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FRONTIER

Chronic renal dysfunction in cirrhosis: A new frontier in hepatology

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Abstract

Chronic kidney disease (CKD) in patients with liver cirrhosis has become a new frontier in hepatology. In recent years, a sharp increase in the diagnosis of CKD has been observed among patients with cirrhosis. The rising prevalence of risk factors, such as diabetes, hypertension and nonalcoholic fatty liver disease, appears to have contributed significantly to the high prevalence of CKD. Moreover, the diagnosis of CKD in cirrhosis is now based on a reduction in the estimated glomerular filtration rate of < 60 mL/min over more than 3 mo. This definition has resulted in a better differentiation of CKD from acute kidney injury (AKI), leading to its greater recognition. It has also been noted that a significant proportion of AKI transforms into CKD in patients with decompensated cirrhosis. CKD in cirrhosis can be structural CKD due to kidney injury or functional CKD secondary to circulatory and neurohormonal imbalances. The available literature on combined cirrhosis-CKD is extremely limited, as most attempts to assess renal dysfunction in cirrhosis have so far concentrated on AKI. Due to problems related to glomerular filtration rate estimation in cirrhosis, the absence of reliable biomarkers of CKD and technical difficulties in performing renal biopsy in advanced cirrhosis, CKD in cirrhosis can present many challenges for clinicians. With combined hepatorenal dysfunctions, fluid mobilization becomes problematic, and there may be difficulties with drug tolerance, hemodialysis and decision-making regarding the need for liver *vs* simultaneous liver and kidney transplantation. This paper offers a thorough overview of the increasingly known CKD in patients with cirrhosis, with clinical consequences and difficulties occurring in the diagnosis and treatment of such patients.

Key Words: Acute kidney injury; Cirrhosis; Chronic kidney disease; Renal failure; Hepatorenal syndrome; Renal function

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Core Tip: The current definition of chronic kidney disease (CKD) in patients with liver cirrhosis is based on a 3-mo decline in the glomerular filtration rate of < 60 mL/min, and it may be structural or functional CKD, depending on the presence or absence of kidney injury. Emerging data show that the incidence of CKD has risen dramatically in patients with cirrhosis over the last decade. The main reasons behind the increased prevalence of CKD appear to be a growing recognition of this condition and a rising trend in the prevalence of diabetes, hypertension and nonalcoholic fatty liver disease. This paper offers a detailed overview of CKD in patients with cirrhosis, including the clinical implications and difficulties clinicians may face with regard to diagnosis and treatment.

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INTRODUCTION

Most attempts to assess renal impairment in cirrhosis have so far concentrated on acute kidney injury (AKI), and as a result, detailed knowledge of AKI in cirrhosis is now available[1]. However, there is still scarce evidence on the prevalence, clinical impact and treatment of chronic kidney disease (CKD) in cirrhosis. A sharp rise in the diagnosis of CKD among patients with cirrhosis has been observed in recent years. The prevalence of CKD in hospitalized patients with cirrhosis, which used to be approximately 1% in 2005, has now risen to as high as 46.8% in 2019[2,3]. The growing prevalence of CKD in patients with cirrhosis may represent the convergence of several important epidemiological patterns: the continuing increase in the prevalence of metabolic risk factors such as obesity, hypertension and Medicine degree (DM); the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) as a major contributor to the burden of cirrhosis; and the aging cohort of cirrhosis[4-6]. Moreover, some emerging evidence indicates that the risk of developing de novo CKD remains high for AKI survivors[7]. Liver cirrhosis patients are susceptible to developing AKI due to circulatory abnormalities, neurohormonal changes and the involvement of risk factors such as bacterial infection, gastrointestinal bleeding, medication and paracentesis[1,8]. Depending on the severity, length and frequency, AKI increases the risk of developing incident CKD due to decreases in renal mass and nephron number, vascular insufficiency, and maladaptive repair mechanisms[9]. Therefore, rather than separate entities, AKI and CKD may represent a continuum. The term CKD now encompasses both structural CKD due to structural damage to the kidney and functional CKD due to circulatory and neurohormonal imbalances in cirrhosis. The differentiation between various forms of renal dysfunction in cirrhosis is crucial, as each requires a different treatment plan.

DEFINITION AND CLASSIFICATION

The definition of CKD in cirrhosis was originally based on a serum creatinine level of > 1.5 mg/dL until 2011, when an updated definition was introduced by a working group composed of experts from various disciplines[10]. The definition endorsed by kidney disease: Improving global outcomes was largely adopted by this group, and CKD was defined as an estimated glomerular filtration rate (eGFR) of < 60 mL/min for more than 3 mo, measured using the Modification of Diet in Renal Disease-6 (MDRD-6) equation. While the group further agreed that the MDRD-6 equation was not perfect for estimating GFR in patients with cirrhosis, it may still be adopted until better alternatives become available. Currently, the diagnosis of CKD does not require corroborating evidence of kidney damage, such as proteinuria, hematuria, abnormal renal imaging or pathology.

Kidney Disease: Improving Global Outcomes has classified CKD into structural and functional CKD on the basis of the presence or absence of kidney injury. The old entity, type 2 hepatorenal syndrome (HRS), now referred to as HRS-CKD, is essentially a functional CKD[11]. While functional CKD is considered potentially reversible, since biomarkers of renal tubular damage have been found in patients with HRS, this may not exactly be the case[12-14]. Patients with cirrhosis may have several risk factors for developing structural CKD per se, such as DM, NAFLD, and atherosclerosis[4-6]. In addition, persistent renal vasoconstriction in functional CKD can lead to structural changes, transforming it into structural CKD.

THE GROWING PREVALENCE OF CHRONIC KIDNEY DISEASE IN CIRRHOSIS

In recent years, not only has the prevalence of CKD increased significantly in the general population, but an increasing rise in the prevalence of CKD has also been reported in patients with cirrhosis (Table 1)[3,15-17]. The prevalence rates of CKD in cirrhosis, however, vary significantly across studies due to variations in parameters used to describe CKD and differences in the severity of patients with chronic liver disease (CLD).

In a study by Rustgi *et al*[18], although the prevalence of CKD among 94431 patients with cirrhosis collected from the insurance claim database was 3.37%, the proportion of patients with decompensated cirrhosis was higher in the combined CLD-CKD group (27.2% *vs* 11.8%), suggesting that the prevalence of CKD increases with the severity of CLD. In a recent retrospective analysis of a large cohort of patients with cirrhosis (n = 78640) awaiting liver transplantation (LT), while the prevalence of CKD was 7.8% in 2002, it increased to 14.6% in 2017. This is a documented increase in the CKD prevalence rate of 187% in just 15 years. Moreover, among 39719 LT recipients, 6269 (16%) patients met the CKD criteria at the time of last transplant[4]. Another study evaluating the prospectively managed database of the North American Consortium for the End-Stage Liver Disease Study reported a 46.8% prevalence of CKD among 2346 admitted patients with cirrhosis[3]. In an Indian study, the occurrence of CKD was observed in 32.8% of a large prospective cohort (n = 818) of patients with cirrhosis[16]. Functional CKD is considered to be relatively uncommon and accounts for only approximately 3.9% to 15.8% of renal impairments among hospitalized cirrhotic patients; however, new data need to be developed in light of the updated concept of CKD in cirrhosis[2,19].

DETERMINANTS OF INCREASING CHRONIC KIDNEY DISEASE IN CIRRHOSIS

Apart from the aging and the high incidence of AKI in cirrhosis, a rising recognition of this condition and a rising trend in the prevalence of DM, hypertension and NAFLD seem to be the key factors behind the increased prevalence of CKD in cirrhosis (Figure 1).

AKI to CKD transition

AKI is an independent risk factor for developing CKD in the general population. AKI to CKD transition appears to reflect a continuum. In a meta-analysis of 13 studies, the pooled adjusted hazard ratio for developing CKD among patients with AKI was 8.8 (95% confidence interval: 3.1-25.5)[20]. AKI occurs very frequently in patients with decompensated cirrhosis because of pre-existing circulatory abnormalities, neurohormonal changes and the involvement of risk factors such as DM, bacterial infection, gastrointestinal bleeding, medications and therapeutic paracentesis[1,7,10,11]. Emerging data suggest that in patients with decompensated cirrhosis, a large proportion of AKI progresses to CKD. In a recent study, 25% of patients with decompensated cirrhosis with AKI who survived for at least 3 mo developed CKD, compared with only 1% of those without AKI[7]. Moreover, the odds of developing CKD in patients with decompensated cirrhosis with AKI were 31, suggesting that they are more prone to CKD development than general AKI patients. A higher transition from AKI to CKD was seen when the severity of AKI was higher and when it developed after hospitalization. In another study published in India, 32.8% of 818 patients with cirrhosis developed CKD, approximately 80% of patients with CKD had

Table 1 Incidence and prevalence of chronic kidney disease in cirrhosis patients

Ref.	Study subjects (*n*)	Criteria for CKD diagnosis	Incidence or prevalence of CKD
Cullaro *et al*[4], 2020	39719 LT recipient cirrhosis patients	CKD-EPI equation based eGFR < 60 mL/min for 90 d or ≥ 42 d of hemodialysis	16% patients (*n* = 6269) met CKD criteria at the time of LT
Bassegoda *et al*[7], 2020	409 hospitalized cirrhosis patients, 168 with AKI	MDRD-4 equation based eGFR < 60 mL/min > 3 mo	Among survived patients at 3 mo, 9.1% (26/285) developed CKD, Incidence of CKD among cirrhosis-AKI patients was 25% (24/97)
Rustgi *et al*[18], 2020	598455 CLD patients, including 94431 patients with cirrhosis	As per the record, based on International Classification of Disease (ICD-9) code	Among 94431 cirrhosis patients, prevalence of CKD was 3.37%
Wong *et al*[3], 2019	2346 non-electively admitted patients with cirrhosis	MDRD-4 equation based eGFR < 60 mL/min for > 3 mo	Prevalence of CKD was 46.8% (*n* = 1099)
Maiwall *et al*[16], 2020	818 cohort of both hospitalized and outdoor cirrhosis patients	MDRD-6 equation based eGFR < 60 mL/min for > 3 mo and abnormal urine microscopy > 12 wk	Incidence of CKD was 32.8% (*n* = 269)
Chen *et al*[17], 2018	7440 adult patients with cirrhosis	MDRD-6, CKD-EPI and MDRD-4 equation based eGFR < 60 mL/min for > 3 mo	CKD was present in 46.0%, 45.7% and 45.6% of patients using the MDRD-6, CKD-EPI and MDRD-4 equations, respectively
Choi *et al*[19], 2014	643 hospitalized cirrhosis patients	MDRD-6 equation based eGFR < 60 mL/min for > 3 mo	Prevalence of CKD was 3.4% (*n* = 22)
Martín-Llahí *et al*[32] , 2011	463 hospitalized cirrhosis patients with renal impairment	Old criteria for HRS based on serum creatinine: > 1.5 mg/dL	Proportion of CKD-HRS was 3.9% (*n* = 22)
Salerno *et al*[33], 2011	263 hospitalized cirrhosis patients with renal impairment	Old criteria for HRS based on serum creatinine: > 1.5 mg/dL	Proportion of CKD-HRS was 18.5% (*n* = 40)
Péron *et al*[2], 2005	932 hospitalized cirrhosis patients with renal impairment	Old criteria for HRS based on serum creatinine: > 1.5 mg/dL	Proportion of CKD was 10 (1.07%), Proportion of CKD-HRS was 07 (0.75%)

CKD: Chronic kidney disease; LT: Liver transplantation; CKD-EPK: Chronic kidney disease epidemiology collaboration; eGFR: Estimated glomerular filtration rate; AKI: Acute kidney injury; MDRD: Modification of diet and renal disease; CLD: Chronic liver disease; HRS: Hepatorenal syndrome.

at least one episode of AKI, and one-third of patients with AKI had progression to CKD[16]. The mechanisms underlying AKI-CKD progression are still poorly understood. In general, it is believed to be a result of maladaptive repair in the interstitial, vascular and tubular structures of the kidney[9]. However, it is not clear whether the same mechanisms contribute to the development of CKD in cirrhosis. Patients with higher baseline levels of serum creatinine are more likely to develop AKI and less likely to recover from such AKI episodes[21]. Because DM and hypertension patients are more likely to have intrinsic renal disease, such as diabetic nephropathy or hypertensive nephrosclerosis, they are not only at higher risk of developing AKI episodes but also less likely to recover from these episodes due to a lower renal reserve.

Increase in the multiple risk factors

There has been a substantial increase in the multiple shared risk factors for cirrhosis and CKD over the years. NAFLD is independently and significantly associated with an increased incidence and prevalence of CKD[22,23]. In a recent meta-analysis that included nearly 64000 subjects, NAFLD was associated with an approximately 2-fold increased risk of both prevalent and incident CKD[23]. Multiple factors, such as the proinflammatory environment, insulin resistance, oxidative stress, and the activated renin-angiotensin system, may account for the accelerated development and progression of CKD in NAFLD subjects, apart from the common occurrence of DM and hypertension[24]. In addition, NAFLD has been strongly associated with atherosclerosis, as shown by increased intima media thickness or atherosclerotic plaques in the carotid arteries, and atherosclerosis has been associated with glomerulosclerosis, a process that can lead to CKD[25]. In one study, approximately 20%-25% of LT candidates were found to have severe coronary artery disease, suggesting that atherosclerosis in cirrhosis is not uncommon[26]. Over the last 2 decades, the prevalence of NAFLD and NAFLD-related cirrhosis has also increased considerably[27]. In a study, NAFLD accounted for a substantial rise in simultaneous

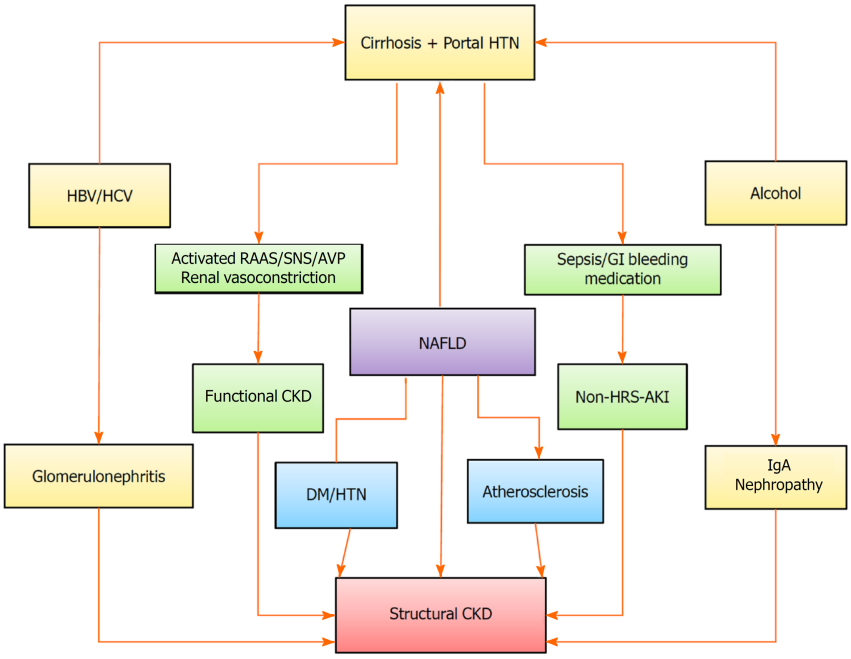

Figure 1 Risk factors associated with chronic kidney disease in patients with liver cirrhosis. A rising trend in the prevalence of medicine degree, hypertension and non-alcoholic fatty liver disease seem to be the key factors behind the increased prevalence of chronic kidney disease in cirrhosis. The risk of developing de-novo chronic kidney disease remains high for acute kidney injury survivors. CKD: Chronic kidney disease; HTN: Hypertension; HBV: Hepatis B virus; HCV: Hepatitis C virus; RAAS: Renin-angiotensin-aldosterone system; SNS: Sympathetic nervous system; AVP: Arginine vasopressin; GI: Gastrointestinal; NAFLD: Non-alcoholic fatty liver disease; HRS: Hepatorenal syndrome; AKI: Acute kidney injury.

liver and kidney transplantation (SLKT), from 8.2% in 2002 to 22% in 2011[28]. In cirrhosis, DM is highly prevalent, with recorded prevalence rates ranging from 35% to 71%, which is far higher than in the general population[29]. Glomerulopathy, which can progress to CKD, may be associated with certain specific causes of cirrhosis, such as hepatitis B virus (HBV) or hepatitis C virus (HCV). Glomerular involvement in patients with viral hepatitis occurs *via* an immune pathogenic mechanism. Circulating immune complexes containing viral antigens have been found in the kidney[30].

CLINICAL IMPLICATIONS OF CHRONIC KIDNEY DISEASE IN CIRRHOSIS

In several ways, CKD can affect the clinical manifestations, complications, therapeutic decisions, and outcomes of patients with cirrhosis.

Impact on clinical manifestations

Anorexia, anemia, ascites, bleeding tendency and encephalopathy can be independently due to both hepatic and renal diseases, so the contributions from individual diseases are often difficult to determine in patients with cirrhosis with CKD. This may create uncertainty about optimal therapeutic choices, such as requirements of renal replacement therapy. In patients with cirrhosis, CKD may contribute to ascites and edema in various ways, such as nephrogenic ascites, chronic fluid overload, hypoproteinemia, and cardiomyopathy[31]. Refractory ascites is almost universal in patients with functional CKD[32,33]. Due to multiple and complex hemostasis abnormalities, patients with concurrent hepatorenal dysfunction may have a higher tendency to bleed. On the other hand, even thrombotic complications are not unusual in such patients[34]. CKD is an independent cardiovascular mortality risk factor, and it can worsen anemia due to cirrhosis[35,36]. Both CKD and cirrhosis can cause immunodepression, leading to an increased risk of infection[37]. Patients with cirrhosis and CKD appear to have an increased risk of developing malignancy[27,38]. In recent years, NAFLD, which is significantly linked to CKD, has also emerged as one of the leading causes of hepatocellular carcinoma (HCC)[27]. Alcohol, HBV infection and HCV infection are other shared risk factors that can be associated with both HCC and CKD. HCC has been found to be associated with a higher prevalence of CKD than any other cancer[39]. After adjustment for many possible confounders, a lower GFR has been

shown to be independently associated with a higher risk of incident renal cell and urothelial cancer[40]. CKD has been shown to be associated with increased mortality from liver, kidney, and urothelial cancers[41].

Impact on complications and outcomes

CKD in cirrhosis is associated with poor outcomes and an increased frequency of complications[3,7]. Wong *et al*[3] found that patients with cirrhosis with CKD had higher rates of superimposed AKI (68% *vs* 21%), need for dialysis (11% *vs* 2%) and 30-d mortality rates (16% *vs* 7%) than patients with cirrhosis without CKD. A 10 mL/min decrease in eGFR was found to be associated with a 13% increase in 30-d mortality in patients with cirrhosis. In a study by Bassegoda *et al*[7], patients with cirrhosis with CKD had a higher frequency of AKI (75% *vs* 45%), refractory ascites (25% *vs* 7%), bacterial infections (58% *vs* 34%) and LT requirement (25% *vs* 10%) compared with those without CKD[7]. In addition, the involvement of cirrhosis is independently related to a poor outcome in patients with CKD[42]. CKD impacts not only waitlist mortality but also worsens post-LT survival. Cullaro *et al*[4] reported that the one-year post-LT mortality rate in patients with CKD was 12%, compared with 9% in those without CKD. In addition, posttransplant renal outcomes may also be affected by the presence of CKD[13].

Impact on health care utilization

Wong *et al*[3] found that cirrhosis patients with CKD had higher rates of hospitalization during the preceding 6 mo (70% *vs* 63%) than those without CKD. Similarly, Bassegoda *et al*[7] reported a higher 3-mo readmission rate (67% *vs* 37%) in cirrhosis-CKD patients compared to cirrhosis alone. A recent study analyzed the usage of health care services and the cost burden associated with CKD in patients with CLD (n = 9869) compared to patients with CLD alone (n = 588586) by using real-world insurance claims data. In a propensity-matched cohort analysis, patients with combined CLD-CKD were found to have substantially greater annual per-person all-cause health care costs than patients with CLD alone[18].

DIAGNOSTIC EVALUATION

The diagnosis of CKD in cirrhosis is based on GFR. Abnormal urine analysis and/or abnormal findings on renal ultrasonography are usually found in advanced CKD and hence are not required for diagnosis. Cirrhosis can be diagnosed in patients with CKD by histopathology or hepatic ultrasound, as well as by clinical manifestations of portal hypertension and/or hepatic decompensation.

Since CKD diagnosis in cirrhosis requires a decrease in GFR to < 60 mL/min for 12 wk, a reliable and reproducible method is required to estimate GFR. The direct iothalamate clearance test is the gold standard for GFR measurement; however, the cumbersome technique and lack of widespread availability limit its usage in clinical practice[43]. Several indirect methods are available to calculate eGFR in clinical practice.

Creatinine-based eGFR

For the assessment of renal function, an eGFR based on the serum creatinine level is commonly used in clinical practice. In patients with cirrhosis, the most commonly used creatinine-based equation is the MDRD. However, serum creatinine levels in patients with cirrhosis may be unreliable due to hepatic dysfunction causing decreased production of creatine, reduced skeletal muscle mass causing decreased creatine-to-creatinine conversion, increased tubular secretion of creatinine, and underestimation of the serum creatinine level by hyperbilirubinemia[44-46]. Therefore, GFR in cirrhosis is typically overestimated by the creatinine-based equation, where a normal serum creatinine level cannot rule out renal dysfunction. In a meta-analysis, the formula based on creatinine was found to overestimate GFR by 18 mL/min[47]. However, despite limitations and until better substitutes become available, the latest creatinine-based MDRD equation (MDRD-6) has been recommended by expert panels to be used in patients with cirrhosis[4,44]. The MDRD-6 equation includes 6 variables: Age, sex, race, serum creatinine, serum albumin, and blood urea nitrogen.

Cystatin-based eGFR

Cystatin C is a protein produced by all nucleated cells in the body that is exclusively removed by glomerular filtration. Hepatic function, muscle mass, sex, hyperbilirubinemia and tubular secretion do not affect the level of cystatin C. Therefore,

cystatin C-based eGFR may be a better alternative to the serum creatinine-based equation for patients with cirrhosis[48-50]. However, the level of cystatin C is affected by hypoalbuminemia, elevated C-reactive protein and leukocytosis, which may limit its role in estimating GFR in cirrhosis[50,51]. Additionally, in patients with cirrhosis, the diagnostic performance of all cystatin C-based GFR equations has been found to be lower than in those without cirrhosis[44]. Combining serum creatinine and cystatin C in an equation appears to predict GFR more accurately than either alone[52]. However, eGFR measurement based on cystatin C has not yet been approved for routine use in patients with cirrhosis.

Biomarkers of kidney damage

The role of conventional urinary markers such as albuminuria is very limited in patients with cirrhosis, which may be because of hypoalbuminemia and relatively increased capillary permeability[44]. In addition, a normal proteinuria or urine examination may not exclude parenchymal changes in the kidney. The recent identification of many urinary biomarkers of renal tubular injury, such as urinary neutrophil gelatinase-associated lipocalin (uNGAL), interleukin-18, liver-type fatty acid-binding protein and kidney injury molecule-1, has revolutionized research into organic renal dysfunction[44,53-55]. These biomarkers have, however, been studied primarily in the context of AKI, and their role in the assessment of CKD is not yet clear. The most extensively assessed biomarker in cirrhotic patients has been uNGAL, an inflammatory biomarker produced by damaged renal tubular cells. The uNGAL levels can help distinguish organic from functional AKI; however, cutoff values for such discrimination lack specificity. In addition, the existence of concomitant infections or prolonged renal vasoconstriction in patients with HRS may significantly increase uNGAL levels, thereby limiting its discriminatory function in patients with cirrhosis[14,53]. In general, uNGAL has a positive correlation with the severity of renal dysfunction in patients with CKD, which indicates its prognostic significance for CKD[53]. However, the prognostic value of uNGAL in patients with cirrhosis with CKD is not known.

The profiles of urinary microRNAs may be an attractive noninvasive tool for future kidney damage assessment[54]. Other biomarkers, such as osteopontin and metalloproteinase-1 tissue inhibitor, are usually elevated in patients with CKD, but their clinical significance has not yet been established[55].

Role of duplex Doppler ultrasonography

Renal duplex Doppler ultrasound is a simple, noninvasive and efficient method that can be used in patients with cirrhosis to study intrarenal hemodynamics (Figure 2). It is a test to assess renal vascular resistance as a vasoconstriction marker, and the renal resistive index (RRI) can be used to detect early renal dysfunction in patients with cirrhosis[56]. In general, there is a progressive increase in RRI as cirrhosis patients move from without ascites to with ascites and then to HRS[57]. Since severe renal vasoconstriction is a feature of HRS, duplex ultrasonography can play a potential role in the assessment of functional CKD in patients with cirrhosis. Furthermore, the RRI can predict CKD progression as it correlates with renal histopathological changes such as glomerular sclerosis, interstitial fibrosis, and arteriolosclerosis[58].

Differentiation between functional and structural CKD

It is important to determine what proportion of CKD in cirrhosis is functional due to HRS and what proportion is associated with structural renal damage. Such differentiation has important therapeutic and prognostic implications. This would assist the clinician in deciding on the use of diuretics, vasoconstrictor treatment and the recommendation of LT *vs* SLKT. Structural CKD patients are more likely to be indolent and have higher survival rates than functional CKD patients[32]. However, in the absence of a renal biopsy, it is often difficult to differentiate a functional CKD from a structural CKD. Abnormal urine analysis (proteinuria > 500 mg/d or hematuria > 50/high power field) and/or abnormal findings on renal ultrasonography (reduced cortical thickness, increased cortical echogenicity and scarring) are features of advanced structural CKD (Figure 2). Currently, no accurate biomarkers are available that can diagnose subclinical renal parenchymal injury or differentiate between reversible and permanent renal injury. Importantly, prolonged renal vasoconstriction in patients with functional CKD may lead to irreversible structural changes in the kidney[32,33]. Studies on the outcome of LT in patients with type 2 HRS have found that 50%-60% of patients develop stage 3 CKD during the posttransplant period, even when HRS reverses[13,59]. Therefore, essentially a long-standing functional CKD can be

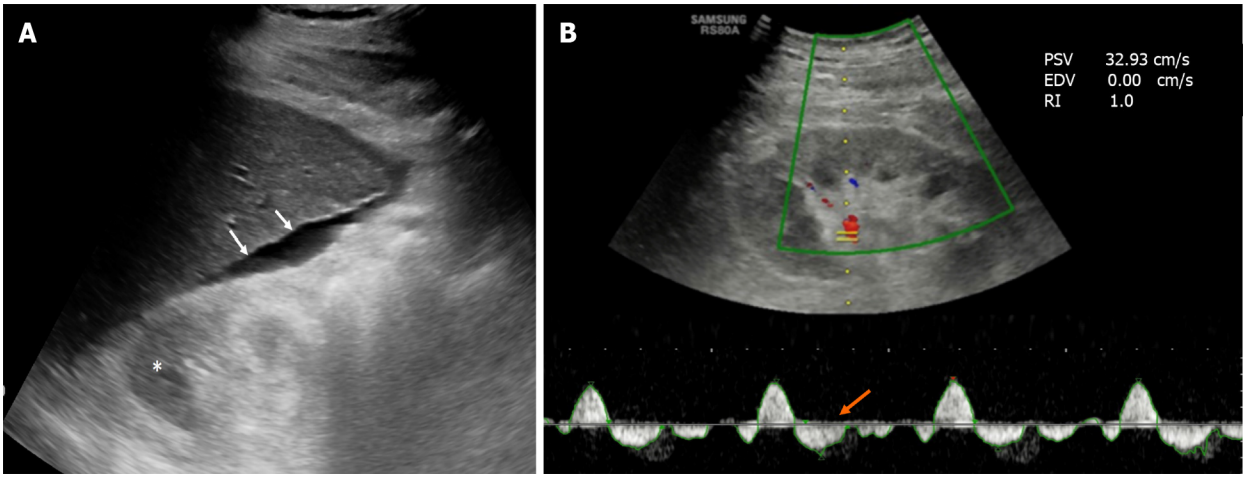

Figure 2 Ultrasonographic image of a 65-year-old diabetic patient with liver cirrhosis and chronic kidney disease. A: The liver outline is irregular (white arrows) and there is ascites around it. The right kidney is small and the parenchymal echogenicity is increased with loss of corticomedullary differentiation (asterisk), suggesting chronic kidney disease; B: Doppler sonogram of the same kidney showed reversal of diastolic flow (orange arrow) with absent end-diastolic velocity, indicating very high resistance vessels.

regarded as structural CKD. In the absence of abnormal early imaging features and reliable biomarkers of CKD, renal biopsy remains the only choice to diagnose and further characterize CKD. However, due to coagulopathy, thrombocytopenia, and the presence of large ascites in cirrhosis, as well as scarred kidneys due to CKD, percutaneous renal biopsy may be technically challenging in patients with decompensated cirrhosis.

Pitfalls in the diagnosis of CKD

A dramatic rise in the diagnosis of CKD in patients with cirrhosis raises some concerns as to whether, in the absence of any corroborating evidence of renal injury, the dependence solely on eGFR leads to overdiagnosis of CKD[60]. An arbitrary single threshold of eGFR < 60 mL/min might have a high propensity to cause overestimation of CKD in elderly subjects. There is a natural steady decrease in GFR with increasing age, and eGFR levels between 50 and 60 mL/min can be insignificant for older individuals, with very little propensity to progress to symptomatic kidney disease[61]. The risks of overdiagnosis of CKD may be significant in patients with cirrhosis since many of them belong to the old age group. In addition, a varying degree of deterioration in GFR may occur in patients with decompensated cirrhosis due to neurohormonal alterations and circulatory dysfunction well before the detection of overt renal disease, which may lead to overdiagnosis of CKD. Therefore, on the basis of a single eGFR threshold and in the absence of any corroborating evidence of kidney damage, caution before labeling CKD in elderly patients with cirrhosis may be needed. Since creatinine-based equations tend to overestimate the GFR, they can underestimate CKD and thus may provide clinicians with false reassurance. Studies need to be performed to determine whether the diagnosis of CKD in patients with decompensated cirrhosis requires a different GFR cutoff.

MANAGEMENT IMPLICATIONS

The presence of CKD in patients with cirrhosis presents many challenges to clinicians with regard to medical care. In particular, fluid mobilization to control ascites and edema becomes a real challenge. The use of diuretic therapy has several limitations. As ascites often reaccumulates rapidly, patients require repeated large volume paracentesis. This puts them at risk of multiple complications, such as worsening circulatory dysfunction, infection and bleeding, in addition to causing discomfort to the patients.

Diuretic therapy

Diuretic therapy is often not prescribed in patients with functional CKD because of the concern that it may further worsen renal failure by causing intravascular volume loss and may precipitate electrolyte imbalance[33]. In patients with structural CKD, the use

of diuretics seems appropriate to manage ascites and edema. However, a varying degree of diuretic resistance is usually present in patients with CKD. This occurs primarily because of decreased renal blood flow, hyperuricemia and organic anion accumulation[62]. The organic anions, uric acid and hypoalbuminemia interfere with the function of loop diuretics. A higher dose of diuretics is therefore required to overcome diuretic resistance in the presence of CKD.

There is a lack of evidence to guide clinicians as to which single or combination diuretic agent is most appropriate for these patients. Furosemide is primarily eliminated by the kidney, while torsemide has predominant hepatic clearance[63]. Therefore, if kidney dysfunction is a predominant issue, torsemide might be preferred over furosemide, while in the case of severe hepatic dysfunction, furosemide may be preferred over torsemide. A recent meta-analysis found that coadministration of albumin with furosemide had a modest effect on overcoming diuretic resistance in hypoalbuminemic patients[64]. Correction of metabolic acidosis and hyperuricemia, adequate restriction of fluid and salt intake, and avoidance of medications that interfere with peritubular diuretic uptake, such as nonsteroidal anti-inflammatory drugs and beta-lactam antibiotics, may be other measures to enhance the diuretic response[62]. Spironolactone should be better avoided in advanced CKD to prevent hyperkalemia.

Vaptans

Vaptan, an antagonist of vasopressin 2 receptor, may be considered in patients with CKD with cirrhosis who are intolerant to or poorly responsive to diuretics. Tolvaptan has been found to be potentially safe with an efficacy rate of 77% for the treatment of refractory ascites in decompensated cirrhosis patients with coexisting type 2 HRS[65]. Tolvaptan significantly increases urine volume in patients with CKD with liver cirrhosis without worsening renal dysfunction[66]. However, its diuretic response gradually diminishes with progression of the CKD stage[67]. Due to the possible risks of hepatocellular damage identified during a clinical trial involving patients with autosomal dominant polycystic kidney disease, the United States Food and Drug Administration issued a warning for tolvaptan use in 2013. However, very high doses of tolvaptan had been used for a long period of time in this study (120 mg/d for 3 years), and no such adverse effects have been reported from the study on patients with cirrhosis where the recommended dose was much lower.

Vasoconstrictor therapy

Midodrine is an orally available α1-agonist that serves as a vasoconstrictor and has been found to have an effect on the systemic hemodynamics of cirrhotic patients. However, midodrine trials in patients with cirrhosis have shown contradictory results. There is insufficient evidence about its use in patients with CKD. In patients with type 2 HRS, midodrine has only a slight beneficial effect on systemic hemodynamics, with no effect on renal hemodynamics[68]. Additionally, treatment with terlipressin or noradrenaline along with albumin appears to have a limited role in patients with CKD. While there are several cases of reversal of type 2 HRS, recurrence after withdrawal of therapy is very common. In addition, evidence on the impact of this treatment on the outcomes of patients is controversial. Few studies have assessed the efficacy of terlipressin in a limited number of patients with type 2 HRS, and the findings have been equivocal[69,70]. In a recent study, 46% of treated patients demonstrated reversal of type 2 HRS; however, nearly half of responders experienced relapse[71]. Furthermore, reversal of type 2 HRS before LT does not appear to provide a major benefit over patients who are untreated or who have failed treatment before LT[13]. Therefore, most of the current guidelines do not recommend vasoconstrictor treatment in functional CKD.

Transjugular intrahepatic portosystemic shunt

Transjugular intrahepatic portosystemic shunt (TIPS) decreases portal pressure, improves kidney function and relieves ascites. While it is being used increasingly to treat patients with refractory ascites and functional renal failure, there is limited evidence on its use in patients with advanced CKD. In a study on TIPS in 17 patients with cirrhosis with CKD, Lakhoo *et al*[72] found that ascites control occurred in 83% of patients but at the expense of a high incidence (47%) of new or worsening hepatic encephalopathy (HE). Michl *et al*[73] reported improvement in renal function and a decrease in the frequency of paracentesis following TIPS in 10 patients with cirrhosis, including three with structural kidney disease. A recent systematic review and meta-analysis found a potential survival benefit of TIPS in patients with HRS but with a

high (49%) incidence of HE. In type 2 HRS, the pooled short-term and 1-year survival rates after TIPS were 86% and 64%, respectively. Moreover, 83% of patients with HRS experienced improvement in renal function after TIPS[74]. In summary, TIPS appears to be very effective in patients with functional CKD, and limited data indicate its effectiveness in structural CKD as well. However, TIPS may increase the incidence of HE, so it should be avoided in patients with encephalopathy, cardiopulmonary disease, and significant hepatic dysfunction.

Cell-free and concentrated ascites reinfusion therapy

Cell-free and concentrated ascites reinfusion therapy (CART) is an apheresis therapy in which ascitic fluid is filtered to remove unwanted cells, sterilely concentrated, and then intravenously reinfused[75]. It was introduced in Japan as a novel treatment for refractory ascites in patients with cirrhosis. The potential advantages of CART include its ability to maintain nutritional status, control ascites, and improve quality of life. Unlike large volume paracentesis, CART is not associated with the risk of hypoproteinemia, hemodynamic instability, renal dysfunction or fatigue. It has been used for both cirrhotic and malignant ascites; however, its safety and efficacy need to be assessed in CLD-CKD patients with refractory ascites. CART has been found to be equally as effective as large volume paracentesis plus albumin infusion[76]. However, its routine use can be limited by the high cost of the CART apparatus[77].

Concerns related to medications

Since the majority of drugs are metabolized and/or excreted by the hepatorenal system, it is a challenging task to prescribe medicines in patients with advanced cirrhosis with renal impairment[78]. There are no evidence-based guidelines for the use of medicines in such patients. Drugs with significant hepatotoxic or nephrotoxic potential or both need to be avoided in such patients. In addition, the dosage of several antibiotics needs to be modified in accordance with GFR. Nonselective β-blockers can increase mortality in patients with advanced cirrhosis with renal dysfunction due to their adverse impact on cardiac compensation[79]. Treatment with hepatitis B nucleos(t)ide analogues can also raise the risk of lactic acidosis if renal dysfunction is present[80].

Treatment modifications according to the etiology of cirrhosis

There are no large controlled studies available to direct appropriate antiviral therapy for patients with CKD with HBV cirrhosis. The use of tenofovir disoproxil fumarate has been associated with a mild risk of CKD progression, but a recent meta-analysis has shown that such a decrease in renal function is inappreciable compared with entecavir[81,82]. Nevertheless, entecavir tends to be the most preferred drug for these patients. However, entecavir therapy may not be as effective in patients with lamivudine resistance, so tenofovir alafenamide, an orally bioavailable tenofovir prodrug with a lower risk of renal toxicity, may be considered in such patients. In patients with HCV-cirrhosis and CKD, high sustained virologic response rates with glecaprevir/pibrentasvir combination in all genotypes and with elbasvir/grazoprevir in genotypes 1 and 4 can be achieved. However, these drugs are largely metabolized in the liver and are therefore not safe in advanced cirrhosis[83]. Patients with advanced decompensated cirrhosis and renal dysfunction are a difficult-to-treat category for which there are no guidelines for treatment; therefore, a treatment decision should be made on a case-by-case basis. While a treatment based on sofosbuvir is not recommended for patients with severe renal impairment, it may be used in patients with mild renal impairment[84]. In patients with nonalcoholic steatohepatitis-CKD, statins have been shown to decrease cardiovascular disease mortality, and sodium-glucose cotransporter-2 inhibitors have been found to slow the progression of CKD and minimize all-cause mortality[85]. However, it is important to determine the role of these drugs in nonalcoholic steatohepatitis-cirrhosis patients with CKD.

Renal replacement therapy

The shared symptoms between the two diseases and overestimation of eGFR make it difficult for patients with cirrhosis with CKD to determine the ideal time for commencing renal replacement therapy. The hemodynamic alterations of cirrhosis pose a challenge to maintaining hemodynamic stability during dialysis, where a sudden decrease in intravascular volume due to ultrafiltration may cause hypotension. A sharp change in blood osmolarity and electrolyte levels increases the risk of developing HE. In addition, thrombocytopenia, platelet dysfunction, and coagulopathy due to combined CKD-cirrhosis may increase the risk of bleeding

complications. In these patients, peritoneal dialysis may be a better choice because it will not only resolve many problems associated with intermittent HD but will also allow ascitic fluid to be regularly evacuated[86,87]. Studies evaluating the survival of cirrhotic patients on peritoneal dialysis have reported a modest survival rate of 8 to 66 mo[88].

LT vs SLKT

Increased post-LT mortality is associated with any form of renal dysfunction. However, most studies evaluating the impact of renal function on post-LT survival do not differentiate between CKD and AKI[4,89,90]. Few studies have reported the progression of CKD, including the development of end-stage renal disease and increased post-LT mortality in cirrhotic patients with CKD receiving LT alone[90-92]. In a recent study, the presence of CKD at the time of LT increased the risk of post-LT mortality by 16%[4]. Thus, there has been a drive to perform more SLKT in patients with combined cirrhosis-CKD. However, in patients with cirrhosis, predicting renal recovery post-LT is difficult, and the degree or severity of CKD that warrants SLKT *vs* LT remains undefined. The 2012 SLKT summit guidelines indicate that SLKT should be considered for cirrhosis-CKD patients with an eGFR of ≤ 40 mL/min measured by the MDRD-6 equation[93]. Once again, however, the use of SLKT is highly variable, and the role of kidney transplantation in nondialysis CKD is controversial. Singh *et al*[94] recently reported the outcome of LT only in nine CKD-cirrhosis patients who had persistently low eGFR < 40 mL/min for ≥ 12 wk but relatively normal kidney biopsy findings. Post-LT, eGFR increased in all nine patients within a week and remained stable afterwards; one patient progressed to ESRD 9 years post-LT, and another patient expired 7 years after LT. While no definite conclusions can be drawn from this small study, there is an indication that, in the absence of other indicators of renal injury, low eGFR alone below an arbitrary cutoff value does not constitute an absolute requirement for SLKT in patients with liver cirrhosis. Functional CKD is potentially reversible after LT[13,52]. However, prolonged renal ischemia can cause permanent tubular or glomerular damage that may not recover with LT, leading to post-LT CKD progression. Because the assessment of renal function may be difficult in patients with advanced cirrhosis, a renal biopsy should be considered whenever possible for identifying parenchymal changes and to decide between LT and SLKT. In patients with low eGFR and kidney biopsy showing > 30% glomerulosclerosis and/or interstitial fibrosis, SLKT should be considered[93]. Future prediction models to assist in decision-making between SLKT and LT should consider integrating kidney injury markers, including new CKD biomarkers.

CONCLUSION

In conclusion, the incidence of CKD in patients with cirrhosis has increased significantly as a result of a rise in risk factors and a change in the diagnostic criteria from a fixed level of serum creatine to a dynamic change in GFR. The available data on this condition are extremely limited. Future studies on this subject are required to explain several contentious issues. Taking into account the problems related to the calculation of GFR in patients with cirrhosis, the main issue to be addressed would be the refining of diagnostic criteria. The other areas that require future research are the identification of reliable biomarkers of chronic kidney damage, the formulation of management strategies based on phenotypic features of CKD in cirrhosis, and the development of prediction models to assist in decision-making between SLKT and LT.

REFERENCES

1 **Bucsics T**, Krones E. Renal dysfunction in cirrhosis: acute kidney injury and the hepatorenal syndrome. *Gastroenterol Rep (Oxf)* 2017; **5**: 127-137 [PMID: 28533910 DOI: 10.1093/gastro/gox009]

2 **Péron JM**, Bureau C, Gonzalez L, Garcia-Ricard F, de Soyres O, Dupuis E, Alric L, Pourrat J, Vinel JP. Treatment of hepatorenal syndrome as defined by the international ascites club by albumin and furosemide infusion according to the central venous pressure: a prospective pilot study. *Am J Gastroenterol* 2005; **100**: 2702-2707 [PMID: 16393223 DOI: 10.1111/j.1572-0241.2005.00271.x]

3 **Wong F**, Reddy KR, O'Leary JG, Tandon P, Biggins SW, Garcia-Tsao G, Maliakkal BJ, Lai JC, Fallon MB, Vargas HE, Subramanian R, Thuluvath PJ, Kamath PS, Thacker L, Bajaj JS. Impact of Chronic Kidney Disease on Outcomes in Cirrhosis. *Liver Transpl* 2019; **25**: 870-880 [PMID:

30908855 DOI: 10.1002/lt.25454]
4 **Cullaro G**, Verna EC, Lee BP, Lai JC. Chronic Kidney Disease in Liver Transplant Candidates: A Rising Burden Impacting Post-Liver Transplant Outcomes. *Liver Transpl* 2020; **26**: 498-506 [PMID: 31785069 DOI: 10.1002/lt.25694]
5 **Solà E**, Ginès P. Chronic Kidney Disease in Cirrhosis: Emerging Complication With Negative Impact in the Liver Transplant Setting. *Liver Transpl* 2020; **26**: 483-484 [PMID: 32031312 DOI: 10.1002/lt.25728]
6 **Younossi ZM**, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Global epidemiology of nonalcoholic fatty liver disease-Meta-analytic assessment of prevalence, incidence, and outcomes. *Hepatology* 2016; **64**: 73-84 [PMID: 26707365 DOI: 10.1002/hep.28431]
7 **Bassegoda O**, Huelin P, Ariza X, Solé C, Juanola A, Gratacós-Ginès J, Carol M, Graupera I, Pose E, Napoleone L, Albertos S, de Prada G, Cervera M, Fernández J, Fabrellas N, Poch E, Solà E, Ginès P. Development of chronic kidney disease after acute kidney injury in patients with cirrhosis is common and impairs clinical outcomes. *J Hepatol* 2020; **72**: 1132-1139 [PMID: 31953138 DOI: 10.1016/j.jhep.2019.12.020]
8 **Parke CY**, Martin P, Bunnapradist S. Renal dysfunction in cirrhosis. *Clin Liver Dis (Hoboken)* 2015; **5**: 150-153 [PMID: 31040973 DOI: 10.1002/cld.485]
9 **Chawla LS**, Kimmel PL. Acute kidney injury and chronic kidney disease: an integrated clinical syndrome. *Kidney Int* 2012; **82**: 516-524 [PMID: 22673882 DOI: 10.1038/ki.2012.208]
10 **Wong F**, Nadim MK, Kellum JA, Salerno F, Bellomo R, Gerbes A, Angeli P, Moreau R, Davenport A, Jalan R, Ronco C, Genyk Y, Arroyo V. Working Party proposal for a revised classification system of renal dysfunction in patients with cirrhosis. *Gut* 2011; **60**: 702-709 [PMID: 21325171 DOI: 10.1136/gut.2010.236133]
11 **Angeli P**, Ginès P, Wong F, Bernardi M, Boyer TD, Gerbes A, Moreau R, Jalan R, Sarin SK, Piano S, Moore K, Lee SS, Durand F, Salerno F, Caraceni P, Kim WR, Arroyo V, Garcia-Tsao G. Diagnosis and management of acute kidney injury in patients with cirrhosis: revised consensus recommendations of the International Club of Ascites. *J Hepatol* 2015; **62**: 968-974 [PMID: 25638527 DOI: 10.1016/j.jhep.2014.12.029]
12 **Trawalé JM**, Paradis V, Rautou PE, Francoz C, Escolano S, Sallée M, Durand F, Valla D, Lebrec D, Moreau R. The spectrum of renal lesions in patients with cirrhosis: a clinicopathological study. *Liver Int* 2010; **30**: 725-732 [PMID: 20040048 DOI: 10.1111/j.1478-3231.2009.02182.x]
13 **Tan HK**, Marquez M, Wong F, Renner EL. Pretransplant Type 2 Hepatorenal Syndrome Is Associated With Persistently Impaired Renal Function After Liver Transplantation. *Transplantation* 2015; **99**: 1441-1446 [PMID: 25643142 DOI: 10.1097/TP.0000000000000557]
14 **Fagundes C**, Pépin MN, Guevara M, Barreto R, Casals G, Solà E, Pereira G, Rodríguez E, Garcia E, Prado V, Poch E, Jiménez W, Fernández J, Arroyo V, Ginès P. Urinary neutrophil gelatinase-associated lipocalin as biomarker in the differential diagnosis of impairment of kidney function in cirrhosis. *J Hepatol* 2012; **57**: 267-273 [PMID: 22521351 DOI: 10.1016/j.jhep.2012.03.015]
15 **Hill NR**, Fatoba ST, Oke JL, Hirst JA, O'Callaghan CA, Lasserson DS, Hobbs FD. Global Prevalence of Chronic Kidney Disease - A Systematic Review and Meta-Analysis. *PLoS One* 2016; **11**: e0158765 [PMID: 27383068 DOI: 10.1371/journal.pone.0158765]
16 **Maiwall R**, Pasupuleti SSR, Bihari C, Rastogi A, Singh PK, Naik V, Singh A, Jain P, Kumar A, Mukund A, Mathur RP, Kumar G, Sarin SK. Incidence, Risk Factors, and Outcomes of Transition of Acute Kidney Injury to Chronic Kidney Disease in Cirrhosis: A Prospective Cohort Study. *Hepatology* 2020; **71**: 1009-1022 [PMID: 31313333 DOI: 10.1002/hep.30859]
17 **Chen CY**, Lin CJ, Lin CS, Sun FJ, Pan CF, Chen HH, Wu CJ. The prevalence and association of chronic kidney disease and diabetes in liver cirrhosis using different estimated glomerular filtration rate equation. *Oncotarget* 2018; **9**: 2236-2248 [PMID: 29416767 DOI: 10.18632/oncotarget.23368]
18 **Rustgi VK**, Li Y, John T, Catalano C, Elsaid MI. Health Care Resource Use and Cost Burden of Chronic Kidney Disease in Patients With Chronic Liver Disease: A Real-World Claims Analysis. *Hepatol Commun* 2020; **4**: 1404-1418 [PMID: 33024912 DOI: 10.1002/hep4.1573]
19 **Choi YJ**, Kim JH, Koo JK, Lee CI, Lee JY, Yang JH, Ko SY, Choe WH, Kwon SY, Lee CH. Prevalence of renal dysfunction in patients with cirrhosis according to ADQI-IAC working party proposal. *Clin Mol Hepatol* 2014; **20**: 185-191 [PMID: 25032185 DOI: 10.3350/cmh.2014.20.2.185]
20 **Coca SG**, Singanamala S, Parikh CR. Chronic kidney disease after acute kidney injury: a systematic review and meta-analysis. *Kidney Int* 2012; **81**: 442-448 [PMID: 22113526 DOI: 10.1038/ki.2011.379]
21 **Cullaro G**, Park M, Lai JC. "Normal" Creatinine Levels Predict Persistent Kidney Injury and Waitlist Mortality in Outpatients With Cirrhosis. *Hepatology* 2018; **68**: 1953-1960 [PMID: 29698588 DOI: 10.1002/hep.30058]
22 **Sinn DH**, Kang D, Jang HR, Gu S, Cho SJ, Paik SW, Ryu S, Chang Y, Lazo M, Guallar E, Cho J, Gwak GY. Development of chronic kidney disease in patients with non-alcoholic fatty liver disease: A cohort study. *J Hepatol* 2017; **67**: 1274-1280 [PMID: 28870674 DOI: 10.1016/j.jhep.2017.08.024]
23 **Musso G**, Gambino R, Tabibian JH, Ekstedt M, Kechagias S, Hamaguchi M, Hultcrantz R, Hagström H, Yoon SK, Charatcharoenwitthaya P, George J, Barrera F, Hafliðadóttir S, Björnsson ES, Armstrong MJ, Hopkins LJ, Gao X, Francque S, Verrijken A, Yilmaz Y, Lindor KD, Charlton M, Haring R, Lerch MM, Rettig R, Völzke H, Ryu S, Li G, Wong LL, Machado M, Cortez-Pinto H, Yasui K, Cassader M. Association of non-alcoholic fatty liver disease with chronic kidney disease: a systematic review and meta-analysis. *PLoS Med* 2014; **11**: e1001680 [PMID: 25050550 DOI:

10.1371/journal.pmed.1001680]
24 **Targher G**, Chonchol MB, Byrne CD. CKD and nonalcoholic fatty liver disease. *Am J Kidney Dis* 2014; **64**: 638-652 [PMID: 25085644 DOI: 10.1053/j.ajkd.2014.05.019]
25 **VanWagner LB**. New insights into NAFLD and subclinical coronary atherosclerosis. *J Hepatol* 2018; **68**: 890-892 [PMID: 29410378 DOI: 10.1016/j.jhep.2018.01.023]
26 **Kalaitzakis E**, Rosengren A, Skommevik T, Björnsson E. Coronary artery disease in patients with liver cirrhosis. *Dig Dis Sci* 2010; **55**: 467-475 [PMID: 19242795 DOI: 10.1007/s10620-009-0738-z]
27 **Kumar R**, Priyadarshi RN, Anand U. Non-alcoholic Fatty Liver Disease: Growing Burden, Adverse Outcomes and Associations. *J Clin Transl Hepatol* 2020; **8**: 76-86 [PMID: 32274348 DOI: 10.14218/JCTH.2019.00051]
28 **Singal AK**, Salameh H, Kuo YF, Wiesner RH. Evolving frequency and outcomes of simultaneous liver kidney transplants based on liver disease etiology. *Transplantation* 2014; **98**: 216-221 [PMID: 24621538 DOI: 10.1097/TP.0000000000000048]
29 **Kumar R**. Hepatogenous Diabetes: An Underestimated Problem of Liver Cirrhosis. *Indian J Endocrinol Metab* 2018; **22**: 552-559 [PMID: 30148106 DOI: 10.4103/ijem.IJEM_79_18]
30 **Venkataseshan VS**, Lieberman K, Kim DU, Thung SN, Dikman S, D'Agati V, Susin M, Valderrama E, Gauthier B, Prakash A. Hepatitis-B-associated glomerulonephritis: pathology, pathogenesis, and clinical course. *Medicine (Baltimore)* 1990; **69**: 200-216 [PMID: 2142748]
31 **Franz M**, Hörl WH. The patient with end-stage renal failure and ascites. *Nephrol Dial Transplant* 1997; **12**: 1070-1078 [PMID: 9175077 DOI: 10.1093/ndt/12.5.1070]
32 **Martín-Llahí M**, Guevara M, Torre A, Fagundes C, Restuccia T, Gilabert R, Solá E, Pereira G, Marinelli M, Pavesi M, Fernández J, Rodés J, Arroyo V, Ginès P. Prognostic importance of the cause of renal failure in patients with cirrhosis. *Gastroenterology* 2011; **140**: 488-496. e4 [PMID: 20682324 DOI: 10.1053/j.gastro.2010.07.043]
33 **Salerno F**, Cazzaniga M, Merli M, Spinzi G, Saibeni S, Salmi A, Fagiuoli S, Spadaccini A, Trotta E, Laffi G, Koch M, Riggio O, Boccia S, Felder M, Balzani S, Bruno S, Angeli P; Italian Association of the Hospital Gastroenterologists (AIGO) investigators. Diagnosis, treatment and survival of patients with hepatorenal syndrome: a survey on daily medical practice. *J Hepatol* 2011; **55**: 1241-1248 [PMID: 21703199 DOI: 10.1016/j.jhep.2011.03.012]
34 **Mannucci PM**, Tripodi A. Hemostatic defects in liver and renal dysfunction. *Hematology Am Soc Hematol Educ Program* 2012; **2012**: 168-173 [PMID: 23233577 DOI: 10.1182/asheducation-2012.1.168]
35 **Thomas R**, Kanso A, Sedor JR. Chronic kidney disease and its complications. *Prim Care* 2008; **35**: 329-344, vii [PMID: 18486718 DOI: 10.1016/j.pop.2008.01.008]
36 **Gkamprela E**, Deutsch M, Pectasides D. Iron deficiency anemia in chronic liver disease: etiopathogenesis, diagnosis and treatment. *Ann Gastroenterol* 2017; **30**: 405-413 [PMID: 28655976 DOI: 10.20524/aog.2017.0152]
37 **Kato S**, Chmielewski M, Honda H, Pecoits-Filho R, Matsuo S, Yuzawa Y, Tranaeus A, Stenvinkel P, Lindholm B. Aspects of immune dysfunction in end-stage renal disease. *Clin J Am Soc Nephrol* 2008; **3**: 1526-1533 [PMID: 18701615 DOI: 10.2215/CJN.00950208]
38 **Wong G**, Hayen A, Chapman JR, Webster AC, Wang JJ, Mitchell P, Craig JC. Association of CKD and cancer risk in older people. *J Am Soc Nephrol* 2009; **20**: 1341-1350 [PMID: 19406977 DOI: 10.1681/ASN.2008090998]
39 **Na SY**, Sung JY, Chang JH, Kim S, Lee HH, Park YH, Chung W, Oh KH, Jung JY. Chronic kidney disease in cancer patients: an independent predictor of cancer-specific mortality. *Am J Nephrol* 2011; **33**: 121-130 [PMID: 21242672 DOI: 10.1159/000323740]
40 **Lowrance WT**, Ordoñez J, Udaltsova N, Russo P, Go AS. CKD and the risk of incident cancer. *J Am Soc Nephrol* 2014; **25**: 2327-2334 [PMID: 24876115 DOI: 10.1681/ASN.2013060604]
41 **Weng PH**, Hung KY, Huang HL, Chen JH, Sung PK, Huang KC. Cancer-specific mortality in chronic kidney disease: longitudinal follow-up of a large cohort. *Clin J Am Soc Nephrol* 2011; **6**: 1121-1128 [PMID: 21511834 DOI: 10.2215/CJN.09011010]
42 **Kim AJ**, Lim HJ, Ro H, Jung JY, Lee HH, Chung W, Chang JH. Liver cirrhosis leads to poorer survival in patients with end-stage renal disease. *Korean J Intern Med* 2016; **31**: 730-738 [PMID: 27017394 DOI: 10.3904/kjim.2014.328]
43 **Hsu CY**, Bansal N. Measured GFR as "gold standard"--all that glitters is not gold? *Clin J Am Soc Nephrol* 2011; **6**: 1813-1814 [PMID: 21784836 DOI: 10.2215/CJN.06040611]
44 **Francoz C**, Nadim MK, Durand F. Kidney biomarkers in cirrhosis. *J Hepatol* 2016; **65**: 809-824 [PMID: 27238754 DOI: 10.1016/j.jhep.2016.05.025]
45 **Papadakis MA**, Arieff AI. Unpredictability of clinical evaluation of renal function in cirrhosis. Prospective study. *Am J Med* 1987; **82**: 945-952 [PMID: 3578363 DOI: 10.1016/0002-9343(87)90156-2]
46 **Woitas RP**, Stoffel-Wagner B, Flommersfeld S, Poege U, Schiedermaier P, Klehr HU, Spengler U, Bidlingmaier F, Sauerbruch T. Correlation of serum concentrations of cystatin C and creatinine to inulin clearance in liver cirrhosis. *Clin Chem* 2000; **46**: 712-715 [PMID: 10794756]
47 **Skluzacek PA**, Szewc RG, Nolan CR 3rd, Riley DJ, Lee S, Pergola PE. Prediction of GFR in liver transplant candidates. *Am J Kidney Dis* 2003; **42**: 1169-1176 [PMID: 14655188 DOI: 10.1053/j.ajkd.2003.08.017]
48 **Demirtaş S**, Bozbaş A, Akbay A, Yavuz Y, Karaca L. Diagnostic value of serum cystatin C for evaluation of hepatorenal syndrome. *Clin Chim Acta* 2001; **311**: 81-89 [PMID: 11566167 DOI:

10.1016/s0009-8981(01)00546-0]
49 **Orlando R**, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, Padrini R, Palatini P. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. *Clin Chem* 2002; **48**: 850-858 [PMID: 12029000]
50 **Mindikoglu AL**, Dowling TC, Weir MR, Seliger SL, Christenson RH, Magder LS. Performance of chronic kidney disease epidemiology collaboration creatinine-cystatin C equation for estimating kidney function in cirrhosis. *Hepatology* 2014; **59**: 1532-1542 [PMID: 23744636 DOI: 10.1002/hep.26556]
51 **Stevens LA**, Schmid CH, Greene T, Li L, Beck GJ, Joffe MM, Froissart M, Kusek JW, Zhang YL, Coresh J, Levey AS. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int* 2009; **75**: 652-660 [PMID: 19119287 DOI: 10.1038/ki.2008.638]
52 **Krones E**, Fickert P, Zitta S, Neunherz S, Artinger K, Reibnegger G, Durchschein F, Wagner D, Stojakovic T, Stadlbauer V, Fauler G, Stauber R, Zollner G, Kniepeiss D, Rosenkranz AR. The chronic kidney disease epidemiology collaboration equation combining creatinine and cystatin C accurately assesses renal function in patients with cirrhosis. *BMC Nephrol* 2015; **16**: 196 [PMID: 26627205 DOI: 10.1186/s12882-015-0188-0]
53 **Bolignano D**, Coppolino G, Campo S, Aloisi C, Nicocia G, Frisina N, Buemi M. Urinary neutrophil gelatinase-associated lipocalin (NGAL) is associated with severity of renal disease in proteinuric patients. *Nephrol Dial Transplant* 2008; **23**: 414-416 [PMID: 17893105 DOI: 10.1093/ndt/gfm541]
54 **Szeto CC**, Wang G, Ng JK, Kwan BC, Mac-Moune Lai F, Chow KM, Luk CC, Lai KB, Li PK. Urinary miRNA profile for the diagnosis of IgA nephropathy. *BMC Nephrol* 2019; **20**: 77 [PMID: 30832601 DOI: 10.1186/s12882-019-1267-4]
55 **Xu TY**, Zhang Y, Li Y, Zhu DL, Gao PJ. The association of serum inflammatory biomarkers with chronic kidney disease in hypertensive patients. *Ren Fail* 2014; **36**: 666-672 [PMID: 24575880 DOI: 10.3109/0886022X.2014.890002]
56 **Mindikoglu AL**, Dowling TC, Wong-You-Cheong JJ, Christenson RH, Magder LS, Hutson WR, Seliger SL, Weir MR. A pilot study to evaluate renal hemodynamics in cirrhosis by simultaneous glomerular filtration rate, renal plasma flow, renal resistive indices and biomarkers measurements. *Am J Nephrol* 2014; **39**: 543-552 [PMID: 24943131 DOI: 10.1159/000363584]
57 **Fouad YM**, Mokarrab H, Elgebaly AF, El-Amin H, Abdel-Raheem EM, Sharawy MA, Shatat ME. Renal duplex Doppler ultrasound in patients with HCV related liver cirrhosis. *Trop Gastroenterol* 2009; **30**: 213-218 [PMID: 20426281]
58 **Spatola L**, Andrulli S. Doppler ultrasound in kidney diseases: a key parameter in clinical long-term follow-up. *J Ultrasound* 2016; **19**: 243-250 [PMID: 27965714 DOI: 10.1007/s40477-016-0201-x]
59 **Rodriguez E**, Henrique Pereira G, Solà E, Elia C, Barreto R, Pose E, Colmenero J, Fernandez J, Navasa M, Arroyo V, Ginès P. Treatment of type 2 hepatorenal syndrome in patients awaiting transplantation: Effects on kidney function and transplantation outcomes. *Liver Transpl* 2015; **21**: 1347-1354 [PMID: 26178066 DOI: 10.1002/lt.24210]
60 **De Broe ME**, Gharbi MB, Zamd M, Elseviers M. Why overestimate or underestimate chronic kidney disease when correct estimation is possible? *Nephrol Dial Transplant* 2017; **32**: ii136-ii141 [PMID: 28380639 DOI: 10.1093/ndt/gfw267]
61 **Wetzels JF**, Kiemeney LA, Swinkels DW, Willems HL, den Heijer M. Age- and gender-specific reference values of estimated GFR in Caucasians: the Nijmegen Biomedical Study. *Kidney Int* 2007; **72**: 632-637 [PMID: 17568781 DOI: 10.1038/sj.ki.5002374]
62 **Wilcox CS**. New insights into diuretic use in patients with chronic renal disease. *J Am Soc Nephrol* 2002; **13**: 798-805 [PMID: 11856788]
63 **Brater DC**. Diuretic therapy. *N Engl J Med* 1998; **339**: 387-395 [PMID: 9691107 DOI: 10.1056/NEJM199808063390607]
64 **Kitsios GD**, Mascari P, Ettunsi R, Gray AW. Co-administration of furosemide with albumin for overcoming diuretic resistance in patients with hypoalbuminemia: a meta-analysis. *J Crit Care* 2014; **29**: 253-259 [PMID: 24268626 DOI: 10.1016/j.jcrc.2013.10.004]
65 **Zhang X**, Wang SZ, Zheng JF, Zhao WM, Li P, Fan CL, Li B, Dong PL, Li L, Ding HG. Clinical efficacy of tolvaptan for treatment of refractory ascites in liver cirrhosis patients. *World J Gastroenterol* 2014; **20**: 11400-11405 [PMID: 25170228 DOI: 10.3748/wjg.v20.i32.11400]
66 **Tanaka A**, Katsuno T, Ozaki T, Sakata F, Kato N, Suzuki Y, Kosugi T, Kato S, Tsuboi N, Sato W, Yasuda Y, Mizuno M, Ito Y, Matsuo S, Maruyama S. The efficacy of tolvaptan as a diuretic for chronic kidney disease patients. *Acta Cardiol* 2015; **70**: 217-223 [PMID: 26148383 DOI: 10.1080/ac.70.2.3073514]
67 **Ikeda S**, Ohshima K, Miyazaki S, Kadota H, Shimizu H, Ogimoto A, Hamada M. Impact of chronic kidney disease on the diuretic response of tolvaptan in acute decompensated heart failure. *ESC Heart Fail* 2017; **4**: 614-622 [PMID: 29154417 DOI: 10.1002/ehf2.12190]
68 **Werling K**, Chalasani N. What is the Role of Midodrine in Patients with Decompensated Cirrhosis? *Gastroenterol Hepatol (N Y)* 2011; **7**: 134-136 [PMID: 21475424]
69 **Ghosh S**, Choudhary NS, Sharma AK, Singh B, Kumar P, Agarwal R, Sharma N, Bhalla A, Chawla YK, Singh V. Noradrenaline vs terlipressin in the treatment of type 2 hepatorenal syndrome: a randomized pilot study. *Liver Int* 2013; **33**: 1187-1193 [PMID: 23601499 DOI: 10.1111/liv.12179]
70 **Alessandria C**, Venon WD, Marzano A, Barletti C, Fadda M, Rizzetto M. Renal failure in cirrhotic patients: role of terlipressin in clinical approach to hepatorenal syndrome type 2. *Eur J Gastroenterol Hepatol* 2002; **14**: 1363-1368 [PMID: 12468959 DOI: 10.1097/00042737-200212000-00013]

71 **Nguyen-Tat M**, Jäger J, Rey JW, Nagel M, Labenz C, Wörns MA, Galle PR, Marquardt JU. Terlipressin and albumin combination treatment in patients with hepatorenal syndrome type 2. *United European Gastroenterol J* 2019; **7**: 529-537 [PMID: 31065370 DOI: 10.1177/2050640619825719]

72 **Lakhoo J**, Gunasekaran SS, Lokken RP, Lipnik AJ, Ray CE Jr, Bui JT, Gaba RC. Does advanced chronic kidney disease impact transjugular intrahepatic portosystemic shunt efficacy and safety? *Acta Gastroenterol Belg* 2017; **80**: 243-248 [PMID: 29560689]

73 **Michl P**, Gülberg V, Bilzer M, Waggershauser T, Reiser M, Gerbes AL. Transjugular intrahepatic portosystemic shunt for cirrhosis and ascites: Effects in patients with organic or functional renal failure. *Scand J Gastroenterol* 2000; **35**: 654-658 [PMID: 10912668 DOI: 10.1080/003655200750023642]

74 **Song T**, Rössle M, He F, Liu F, Guo X, Qi X. Transjugular intrahepatic portosystemic shunt for hepatorenal syndrome: A systematic review and meta-analysis. *Dig Liver Dis* 2018; **50**: 323-330 [PMID: 29422242 DOI: 10.1016/j.dld.2018.01.123]

75 **Ito T**, Hanafusa N. CART: Cell-free and Concentrated Ascites Reinfusion Therapy against malignancy-related ascites. *Transfus Apher Sci* 2017; **56**: 703-707 [PMID: 28916401 DOI: 10.1016/j.transci.2017.08.018]

76 **Graziotto A**, Rossaro L, Inturri P, Salvagnini M. Reinfusion of concentrated ascitic fluid versus total paracentesis. A randomized prospective trial. *Dig Dis Sci* 1997; **42**: 1708-1714 [PMID: 9286238 DOI: 10.1023/a:1018865516168]

77 **Fukui H**, Kawaratani H, Kaji K, Takaya H, Yoshiji H. Management of refractory cirrhotic ascites: challenges and solutions. *Hepat Med* 2018; **10**: 55-71 [PMID: 30013405 DOI: 10.2147/HMER.S136578]

78 **Amarapurkar DN**. Prescribing medications in patients with decompensated liver cirrhosis. *Int J Hepatol* 2011; **2011**: 519526 [PMID: 21994861 DOI: 10.4061/2011/519526]

79 **Sersté T**, Melot C, Francoz C, Durand F, Rautou PE, Valla D, Moreau R, Lebrec D. Deleterious effects of beta-blockers on survival in patients with cirrhosis and refractory ascites. *Hepatology* 2010; **52**: 1017-1022 [PMID: 20583214 DOI: 10.1002/hep.23775]

80 **Kumar R**, Agrawal S. Rapid Onset of Fatal Lactic Acidosis Complicating Tenofovir Therapy in a Diabetic Patient with Cirrhosis: A Cautionary Tale. *J Clin Exp Hepatol* 2017; **7**: 80-81 [PMID: 28348477 DOI: 10.1016/j.jceh.2016.08.010]

81 **Wong GL**, Chan HL, Tse YK, Yip TC, Lam KL, Lui GC, Szeto CC, Wong VW. Chronic kidney disease progression in patients with chronic hepatitis B on tenofovir, entecavir, or no treatment. *Aliment Pharmacol Ther* 2018; **48**: 984-992 [PMID: 30125952 DOI: 10.1111/apt.14945]

82 **Lee HY**, Oh H, Park CH, Yeo YH, Nguyen MH, Jun DW. Comparison of renal safety of tenofovir and entecavir in patients with chronic hepatitis B: Systematic review with meta-analysis. *World J Gastroenterol* 2019; **25**: 2961-2972 [PMID: 31249453 DOI: 10.3748/wjg.v25.i23.2961]

83 **Mücke MM**, Mücke VT, Lange CM, Zeuzem S. Special populations: treating hepatitis C in patients with decompensated cirrhosis and/or advanced renal impairment. *Liver Int* 2017; **37** Suppl 1: 19-25 [PMID: 28052635 DOI: 10.1111/liv.13279]

84 **Kanda T**, Lau GKK, Wei L, Moriyama M, Yu ML, Chuang WL, Ibrahim A, Lesmana CRA, Sollano J, Kumar M, Jindal A, Sharma BC, Hamid SS, Dokmeci AK, Mamun-Al-Mahtab, McCaughan GW, Wasim J, Crawford DHG, Kao JH, Yokosuka O, Sarin SK, Omata M. APASL clinical practice recommendation: how to treat HCV-infected patients with renal impairment? *Hepatol Int* 2019; **13**: 103-109 [PMID: 30539517 DOI: 10.1007/s12072-018-9915-5]

85 **Papademetriou M**, Athyros VG, Geladari E, Doumas M, Tsioufis C, Papademetriou V. The Co-Existence of NASH and Chronic Kidney Disease Boosts Cardiovascular Risk: Are there any Common Therapeutic Options? *Curr Vasc Pharmacol* 2018; **16**: 254-268 [PMID: 28676027 DOI: 10.2174/1570161115666170621081638]

86 **Howard CS**, Teitelbaum I. Renal replacement therapy in patients with chronic liver disease. *Semin Dial* 2005; **18**: 212-216 [PMID: 15934968 DOI: 10.1111/j.1525-139X.2005.18315.x]

87 **Chaudhary K**, Khanna R. Renal replacement therapy in end-stage renal disease patients with chronic liver disease and ascites: role of peritoneal dialysis. *Perit Dial Int* 2008; **28**: 113-117 [PMID: 18332442]

88 **Marcus RG**, Messana J, Swartz R. Peritoneal dialysis in end-stage renal disease patients with preexisting chronic liver disease and ascites. *Am J Med* 1992; **93**: 35-40 [PMID: 1626571 DOI: 10.1016/0002-9343(92)90677-4]

89 **Nair S**, Verma S, Thuluvath PJ. Pretransplant renal function predicts survival in patients undergoing orthotopic liver transplantation. *Hepatology* 2002; **35**: 1179-1185 [PMID: 11981768 DOI: 10.1053/jhep.2002.33160]

90 **Gonwa TA**, McBride MA, Anderson K, Mai ML, Wadei H, Ahsan N. Continued influence of preoperative renal function on outcome of orthotopic liver transplant (OLTX) in the US: where will MELD lead us? *Am J Transplant* 2006; **6**: 2651-2659 [PMID: 16939515 DOI: 10.1111/j.1600-6143.2006.01526.x]

91 **Ruebner R**, Goldberg D, Abt PL, Bahirwani R, Levine M, Sawinski D, Bloom RD, Reese PP. Risk of end-stage renal disease among liver transplant recipients with pretransplant renal dysfunction. *Am J Transplant* 2012; **12**: 2958-2965 [PMID: 22759237 DOI: 10.1111/j.1600-6143.2012.04177.x]

92 **Bloom RD**, Reese PP. Chronic kidney disease after nonrenal solid-organ transplantation. *J Am Soc Nephrol* 2007; **18**: 3031-3041 [PMID: 18039925 DOI: 10.1681/ASN.2007040394]

93 **Nadim MK**, Davis CL, Sung R, Kellum JA, Genyk YS. Simultaneous liver-kidney transplantation: a

survey of US transplant centers. *Am J Transplant* 2012; **12**: 3119-3127 [PMID: 22759208 DOI: 10.1111/j.1600-6143.2012.04176.x]

94 **Singh N**, Ahmadzadeh S, Shokouh-Amiri H, Qazi YA, Sequeira A, Samant H, McMillan R, Zibari GB. Kidney outcomes in patients with liver cirrhosis and chronic kidney disease receiving an orthotopic liver transplant alone. *Clin Transplant* 2017; **31** [PMID: 28504869 DOI: 10.1111/ctr.13008]

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REVIEW

Genotype 3-hepatitis C virus' last line of defense

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Abstract

Chronic infection with hepatitis C virus (HCV) is one of the leading causes of liver disease globally, affecting approximately 71 million people. The majority of them are infected with genotype (GT) 1 but infections with GT3 are second in frequency. For many years, GT3 was considered to be less pathogenic compared to other GTs in the HCV family due to its favorable response to interferon (IFN)-based regimen. However, the growing evidence of a higher rate of steatosis, more rapid progression of liver fibrosis, and lower efficacy of antiviral treatment compared to infection with other HCV GTs has changed this conviction. This review presents the specifics of the course of GT3 infection and the development of therapeutic options for GT3-infected patients in the era of direct-acting antivirals (DAA). The way from a standard of care therapy with pegylated IFN-alpha (pegIFNα) and ribavirin (RBV) through a triple combination of pegIFNα + RBV and DAA to the highly potent IFN-free pangenotypic DAA regimens is discussed along with some treatment options which appeared to be dead ends. Although the implementation of highly effective pangenotypic regimens is the most recent stage of revolution in the treatment of GT3 infection, there is still room for improvement, especially in patients with liver cirrhosis and those who fail to respond to DAA therapies, particularly those containing inhibitors of HCV nonstructural protein 5A.

Key Words: Hepatitis C virus; Genotype 3; Antiviral treatment; Interferon; Direct-acting antivirals; Pangenotypic

Core Tip: Genotype 3 which is second in frequency worldwide, is unique among genotypes of hepatitis C virus in its higher rate of steatosis, accelerated fibrosis progression, and lower cure rates. This paper describes the genotype-specific mechanisms of liver injury and provides an overview of therapeutic options. Currently,

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available highly potent pangenotypic regimens have revolutionized the treatment of genotype 3 infection, however, patients with liver cirrhosis and those who fail to response to direct-acting antiviral therapy still present a therapeutic challenge.

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INTRODUCTION

Chronic infection with hepatitis C virus (HCV) is assumed to be one of the leading causes of liver disease globally, affecting approximately 71 million people[1]. Due to the high genetic diversity of the viral nucleic acid sequence, six major genotypes (GT), differing from each other by 30% at the nucleotide level, comprising multiple subtypes of HCV, have been identified[2]. The majority of patients worldwide are infected with GT1, but infections of GT3 are also common in some regions. GT3 is defined by a higher rate of steatosis, increased risk of liver cirrhosis, and different response to antiviral drugs compared to other GTs. In the era of treatment with pegylated interferon alpha (IFNα) and ribavirin (RBV), patients infected with GT3 were considered "easy to treat" due to an efficacy rate of 70%, compared to less than 50% in GT1 and GT4 infected patients. The introduction of direct-acting antivirals (DAA) has changed the management of HCV infection, allowing a substantial increase in the treatment efficacy, however, the improvement for GT3 infection was not as pronounced as for other GTs, particularly in treatment-experienced patients and those with liver cirrhosis.

THE GLOBAL SPREAD OF GT3

GT3 infections are widely distributed worldwide and are estimated to be the second in frequency accounting for approximately 25%-30% of all HCV cases globally[2]. The distribution of GT3 varies between different countries and continents. The highest global prevalence (exceeding 70%) is found in South Asian countries, while a rate of approximately 20% is reported in Central and Southeast Asia, a few percent in East Asia, and only 0.4% in the Asia-Pacific region. A relatively high frequency of 36% is documented in Australia[3]. GT3 infection accounts for 14.2% of HCV cases in South America, 2.1% in Central America, and 15.7% in North America, ranging from 8.9% in the United States to 22.3% in Canada[3]. In Europe, the distribution of GT3 infections is also heterogeneous with the highest frequency exceeding 40% in Scandinavia and England, over 30% in Ireland, Greece Russia, and Slovenia, and more than 20% of infections in Germany, Switzerland, Montenegro, Belgium, Bosnia, and France[4-6]. The rate of a dozen percent is reported from Spain, Poland, Portugal, Bulgaria, and Croatia, whereas the lowest prevalence, below 10%, are documented in Italy, Albania, Hungary, and Romania[7-10]. The lowest proportional frequency of GT3 infections is found in Africa at an average of 5.3%, with the highest frequency at 7.4% in East Africa through 6.3% in North Africa to 0.8% in the central part of the continent[3].

GOOD OR BAD IN THE HCV FAMILY

For many years, GT3 was considered to be less pathogenic compared to other GTs in the HCV family due to its favorable response to an IFN-based regimen. However, the growing evidence of a higher rate of steatosis and more rapid progression of liver fibrosis compared to infection with other HCV GTs has changed this conviction.

Liver steatosis is a frequent histological finding in patients with chronic hepatitis C (CHC). Although this feature is common among all HCV infected individuals, with an average rate of 50%, the highest prevalence exceeding 70% is observed in patients infected with GT3[11-14]. In in-vitro studies, GT3 is also demonstrated to be much more

likely to induce liver steatosis than other HCV GTs[15]. The pathogenesis of hepatic steatosis is complex and related to host and viral factors, as well as to alcohol consumption. Metabolic steatosis, which is associated with host risk factors including high body mass index, obesity, dyslipidemia, metabolic syndrome, insulin resistance and type 2 diabetes, is commonly found in patients infected with non-GT3 HCV, whereas in the GT3-infected individuals, virus-related hepatic steatosis is described as predominantly being induced by the direct cytopathic effect of the HCV[16-20]. Although the exact mechanism remains unknown, several pathways are linked to the pathogenesis of GT3-induced steatosis. A central role is played by the inhibition of microsomal triglyceride transfer protein function by HCV core protein, resulting in overall decreased hepatocyte lipid export with intracellular triglycerides accumulation. This effect is documented to be amplified with HCV-3 core proteins[21]. Another mechanism through which the virus modulates the host lipid metabolic pathways is inhibition of the peroxisome proliferator associated receptor-α (PPAR-α), a transcription factor inducing hepatic fatty acid oxidation and ketogenesis. A decrease in PPAR-α level leads to hepatic lipid collection. *In vitro* studies document inhibition of PPAR-α observed in the GT3 infections as being more efficient than in infections with GT1 HCV[22]. Viral-induced hepatic steatosis results not only from the reduction of the lipid excretion with subsequent intracellular lipid accumulation but also from the promotion of the neolipogenesis with fatty acid synthesis. This activity is proposed to be a consequence of an increase in function of sterol regulatory element-binding protein-1c activated by the HCV-3 core protein, however, the exact mode of activation is unknown[23]. The hypothesis of a pathogenic link between GT3 infection and steatosis is supported by a significant correlation of the steatosis score and intrahepatic titer of HCV RNA only in patients infected with GT3[16]. The improvement in liver steatosis in GT3-infected patients after successful antiviral therapy, which is not observed in patients infected with GT1, seems to indirectly confirm this association[24,25]. GT3 HCV was also identified as an independent predictor for the accelerated progression of liver fibrosis in addition to established risk factors including the age of infection, male gender, coinfection with hepatitis B virus and human immunodeficiency virus, insulin resistance, iron overload, alcohol and drugs intake[26]. Precise analysis of the influence of HCV GT on the more advanced liver disease is difficult due to the coexistence of the aforementioned predictors and the previously discussed higher prevalence of liver steatosis in GT3 infection, which contributes to more rapid progression of hepatic fibrosis[12,27,28]. However, the pooled analysis confirmed a significantly more severe liver disease in single-biopsy studies and a trend towards the faster progression of fibrosis in GT3 patients compared with the other GTs[29]. The strong association between GT3 infection and end-stage liver disease was documented in HCV-infected drug abusers in France and confirmed by a population-based study in a cohort of native Alaskans with CHC[30,31].

An increased risk not only of liver cirrhosis but also of hepatocellular carcinoma (HCC) among GT3 infected individuals compared to those infected with other GTs was reported in a large cohort (> 110000) of American patients from the Veterans Affairs Registry[32,33]. Consistent results of significantly higher incidence of HCC in GT3 patients were also obtained in French and Korean populations[34,35]. Nevertheless, the effect of HCV GT3 infection on the higher prevalence of liver cancer remains controversial because of the data demonstrated for GT1b as a major risk factor for HCC development[36,37].

IFN AND RBV COUPLE

The standard of care therapy of pegylated (peg) IFNα and RBV established in 2000 has resulted in a sustained virologic response (SVR) of approximately 70% in GT3-infected patients[38-42]. Such a high effectiveness compared to the SVR below 50% achieved by patients with GT1 and GT4 infection was the basis for the GT3 being deemed "easy to treat" and has led to attempts to shorten the treatment course to 16, 14, and even 12 wk. However, the reduction in the SVR rate was reported in patients who did not achieve the so-called rapid virologic response (RVR) defined as undetectability of HCV RNA after 4 wk of therapy[38,39,42-44]. The meta-analysis of twelve clinical trials performed by Andriulli *et al*[45] documented a wide variance in response to pegIFNα and RBV in GT3-infected patients depending on the baseline viral load. Individuals with a high baseline level of HCV RNA demonstrated a significantly lower SVR rate of 58% compared to 75% in those with a low baseline viral load. The strongest predictive factor for treatment response was RVR and this finding provided the basis for the

conclusion that patients without RVR may need a longer therapy duration. The negative impact of cirrhosis on treatment response among subjects infected with GT3, leading to poor antiviral effectiveness was documented by Powis *et al*[46], suggesting that such patients also require an alternative management strategy. However, the extension of the treatment course did not result in higher effectiveness, nor was there an improvement in the SVR rate on increasing the dose of RBV[47-49].

THE COUPLE WITH A LITTLE HELP OF DAA

The registration of the first DAAs in 2011, which were inhibitors of the HCV serine protease (nonstructural protein 3/4A, NS3/4A), started a revolution in the treatment of CHC. The combination of telaprevir or boceprevir with pegIFNα and RBV significantly increased the SVR rate, but only in patients infected with GT1[50,51]. Those infected with other GTs, including GT3, were still treated with pegIFNα and RBV because no significant improvement was demonstrated after the addition of telaprevir or boceprevir[52,53]. Therefore, at the beginning of the DAA era GT3 emerged as a "difficult-to-treat" GT. New hopes for higher effectiveness were raised with the introduction of the next-generation DAAs for possible combination with pegIFNα and RBV. Unfortunately, clinical trials demonstrated that simeprevir, a second-wave protease inhibitor with documented in-vitro pangenotypic activity has limited efficacy in GT3-infected patients, and the effectiveness of daclatasvir (DCV), acting through inhibition of the HCV nonstructural protein 5A (NS5A), has proven to be also disappointing, with SVR rates of 45% and 74% in GT3 patients with and without liver cirrhosis, respectively[54,55]. However, the expectations of a higher response rate among GT3-infected patients have been met by sofosbuvir (SOF), a new DAA class representative, HCV polymerase (NS5B) inhibitor. The addition of SOF to pegIFNα and RBV (SPR) leads to better outcomes when compared to standard of care therapy, regardless of liver fibrosis and history of previous antiviral therapy. Phase 2 clinical trials documented a response of 83% among treatment-experienced patients with liver cirrhosis participating in the LONESTAR-2 study, while non-cirrhotic, treatment-naïve individuals treated in the QUANTUM study responded in 92% of cases[56,57].

Patients included in the BOSON phase 3 clinical trial achieved an SVR of 93%, specifically 88% among individuals with liver cirrhosis and 95% in those without; the lowest efficacy of 86% was demonstrated for patients with liver cirrhosis who failed to respond to previous antiviral therapy[58]. An open-label clinical study evaluating the outcome of SOF-containing treatments reported 100% efficacy among GT3-infected treatment naïve patients without cirrhosis treated with triple therapy[59].

Those results from clinical trials were supported by real-world experience (RWE) data that documented an SVR rate higher than that following dual therapy. The best response of 93% was reported for non-cirrhotics among Americans treated in the Veterans Affairs health care system[60]. Scandinavian patients responded in 96% of cases, an efficacy of 98% was obtained in the Polish EpiTer-2 study and an SVR reached 99% in a German cohort[6,61,62]. The effectiveness of the SPR regimen in cirrhotic individuals in these RWE studies was also promising, reaching 92%, 81%, 91%, and 88%, respectively[6,60-62].

RWE data revealed a failure of previous therapy, with a history of treatment with IFN and RBV shown to be a negative prognostic factor of the response to SPR treatment. This triple regimen was still recommended by the guidelines of the European Association for the Study of the Liver in 2015 for GT3-infected non-cirrhotic patients and those with compensated liver cirrhosis, regardless of treatment history[63]. Irrespective of the high effectiveness of SPR, accompanied by reasonable tolerability due to the short treatment period, any IFN-based therapy was refused by patients[61]. Therefore, further research on the treatment of GT3 infections has focused on highly efficient IFN-free therapeutic options.

DAA HOME ALONE

The first available IFN-free regimen, SOF and RBV, used in GT3-infected patients for 12 wk or 16 wk, did not result in increased efficacy when compared to standard of care therapy, which demonstrated significantly lower response rates in patients with liver cirrhosis, especially in those who had previously failed IFN and RBV therapy (Table 1)[40,58,64].

The extension of treatment duration to 24 wk enabled effectiveness of up to 95%,

Table 1 Efficacy of interferon-free regimens in genotype 3 patients in clinical trials

Ref.	Phase	Number of GT3 participants	Regimen	Treatment duration	SVR			
					Noncirrhotics		Cirrhotics	
					Treatment-naive (%)	Treatment-experienced (%)	Treatment-naive (%)	Treatment-experienced (%)
Lawitz *et al*[40], FISSION	3	173	SOF + RBV	12 wk	61	-	34	-
Jacobson *et al*[64], POSITRON	3	98	SOF + RBV	12 wk	68	-	21	-
Jacobson *et al*[64], FUSION	3	127	SOF + RBV	12 wk	-	37	-	19
				16 wk	-	63	-	61
Foster *et al*[58], BOSON	3	363	SOF + RBV	16 wk	83	76	57	47
				24 wk	90	82	82	77
Zeuzem *et al*[65], VALENCE	3	250	SOF + RBV	24 wk	95	87	92	62
Nelson *et al*[69], ALLY-3	3	152	SOF + DCV	12 wk	97	94	58	69
Leroy *et al*[70], ALLY-3+	3	50	SOF + DCV + RBV	12 wk	100	100	50 (1/2)	93
				16 wk	100	100	100	86
Poordad *et al*[71], ALLY-3C	3	78	SOF + DCV + RBV	24 wk	-	-	93	79
Esteban *et al*[81], NCT02781558	2	204	SOF/VEL	12 wk	-	-	91	
			SOF/VE + RBV	12 wk	-	-	96	
Foster *et al*[80], ASTRAL-3	3	552	SOF + RBV	24 wk	90	73	71	58
			SOF/VEL	12 wk	98	93	91	89
Bourlière *et al*[102], POLARIS-1	3	78	SOF/VEL+ VOX	12 wk	-	100[1]	-	93[1]
Jacobson *et al*[103], POLARIS-2	3	181	SOF/VEL	12 wk	97		-	-
			SOF/VEL+ VOX	8 wk	99		-	-
Jacobson *et al*[103], POLARIS-3	3	219	SOF/VEL	12 wk	-	-	99	91
			SOF/VEL+ VOX	8 wk	-	-	96	97
Bourlière *et al*[102], POLARIS-4	3	106	SOF/VEL	12 wk	-	85[2]	-	85%[2]
			SOF/VEL+ VOX	12 wk	-	96[2]	-	96[2]
Gane *et al*[114], LEPTON	2	41	SOF/VEL+ VOX	6 wk	-	-	83	-
				8 wk	-		100	100
Gane *et al*[115], NCT02378961	2	74	SOF/VEL+ VOX	6 wk	100	-	-	-
				8 wk	-	-	94	-
				12 wk	-	100	-	94
Zeuzem *et al*[92], ENDURANCE-3	3	505	GLE/PIB	8 wk	95	-	-	-
				12 wk	95	-	-	-
			SOF + DCV	12 wk	97	-	-	-
Kwo *et al*[93], SURVEYOR-II (part 2)	3	53	GLE/PIB	8 wk	97	-	-	-
				12 wk	-	92	-	-

Wyles *et al*[94], SURVEYOR-II (part 3)	3	131	GLE/PIB	12 wk	-	91	98	-
				16 wk	-	95	-	96
Brown *et al*[90], EXPEDITION-8	3	124	GLE/PIB	8 wk	-	-	98	-
Wyles *et al*[104], MAGELLAN-3	3	14	GEL/PIB+ SOF + RBV	16 wk	-	100	-	100
Gane *et al*[105], ELECTRON-2	2	101	SOF/LDV	12 wk	64	-	-	-
			SOF/LDV + RBV	12 wk	100	89	-	73
Pawlotsky *et al*[106], VITAL-1	2	181	ALV	24 wk	76	-	-	-
			ALV + RBV	24 wk	93	-	-	-
Lawitz *et al*[109], NAVIGATOR	2	21	OBV/PTV/r	12 wk	40	-	-	-
			OBV/PTV/r + RBV	12 wk	9	-	-	-
Shafran *et al*[110], QUARTZ II-III	2	51	OBV/PTV/r + SOF	12 wk	98	-	-	-
			OBV/PTV/r + SOF + RBV	12 wk	91	-	100	-
Gane *et al*[107], C-WORTHY (part D)	2	41	GZR/EBR + RBV	12 wk	45	-	-	-
				18 wk	57	-	-	-
Lawitz *et al*[111], C-SWIFT	2	41	GZR/EBR + SOF	8 wk	93	-	-	-
				12 wk	100	-	91	-
Foster *et al*[112], C-ISLE	2	100	GZR/EBR + SOF	8 wk	-	-	91	-
				12 wk	-	-	96	100[3]
				16 wk	-	-	-	94
Lawitz *et al*[113], C-CREST-1 and -2	2	337	GZR + EBR + UPR ± RBV	8 wk	95			
				12 wk	97			
				16 wk	96			
Lawitz *et al*[108], C-BREEZE-2	2	61	RZR + UPR	12 wk	80		68	

[1]NS5A-inhibitor-experienced.

[2]No detailed information on the response rate in patients with and without liver cirrhosis.

[3]Recommended by American Association for the Study of Liver Diseases/Infectious Diseases Society of America as an alternative option for pegylated interferon + ribavirin-experienced patients with compensated liver cirrhosis. SVR: Sustained virologic response; GT: Genotype; SOF: Sofosbuvir; RVB: Ribavirin; DCV: Daclatasvir; VEL: Velpatasvir; VOX: Voxilaprevir; GLE: Glecaprevir; PIB: Pibrentasvir; LDV: Ledipasvir; ALV: Alisporivir; OBV: Ombitasvir; PTV/r: Paritaprevir boosted by ritonavir; GZR: Grazoprevir; EBR: Elbasvir; UPR: Uprifosbuvir; RBV: Ribavirin; RZR: Ruzasvir.

however, the difference in response rates between patients without and with liver cirrhosis was significant[58,65]. The results of phase 3 clinical trials confirmed by RWE data became a basis for treatment guidelines, according to which IFN-ineligible GT3-infected patients should receive SOF/RBV for 24 wk. However, this regimen was recognized as suboptimal, due to unsatisfactory effectiveness for those with liver cirrhosis who had previously failed IFN and RBV therapy[66-68].

Searching for the optimal antiviral regimen, the combinations of SOF and another DAA with a different mechanism of action were studied. Promising results were obtained with a SOF and DCV combination administered for 12 wk and 24 wk, with or without RBV[69-71]. Although the difference in response rates with SOF + DCV ± RBV between non-cirrhotic and cirrhotic patients was still noticeable, this regimen was recommended for the treatment for GT3-infected patients regardless of liver fibrosis and history of previous therapy and has been widely used in RWE settings[66,72-74]. High efficacy and good tolerability demonstrated in both clinical trials and real-world cohorts have made this regimen a reasonable choice for therapy for GT3 infection as long as highly potent pangenotypic options became broadly available[75-77].

BETTER IS THE ENEMY OF GOOD ENOUGH

The final stage of the revolution in antiviral treatment which improved the outcome and simplified the management of GT3-infected patients was the implementation of potent pangenotypic regimens (Table 1).

According to the most recent guidelines, two basic options of DAAs are currently approved for the treatment of GT3 infection; a fixed-dose combination of SOF and velpatasvir (VEL), and dual treatment with glecaprevir (GLE), an NS3/4A protease inhibitor, and pibrentasvir (PIB), an NS5A inhibitor (Table 2)[78,79]. A single-tablet regimen containing SOF and VEL was registered based on the results of the ASTRAL-3 study, which confirmed effectiveness exceeding 93% in non-cirrhotic and 89% in cirrhotic patients[80]. The 12-wk regimen is recommended for non-cirrhotics and patients with compensated cirrhosis, regardless of the previous treatment history. The addition of RBV may be considered in compensated individuals.

It is noteworthy that SOF/VEL combined with RBV is the only option recommended for patients with decompensated liver cirrhosis[81,82]. Data on the high efficacy and favorable safety profile of SOF/VEL achieved in clinical trials were supported by RWE studies reporting comparable SVR rates. Prior treatment-experience, as well as advanced liver fibrosis, were significant predictors of reduced effectiveness[83-87]. As resistance-associated substitutions at the NS5A position can be responsible for a reduction in the efficacy of the NS5A inhibitors, the resistance-associated substitutions testing at baseline should be considered for treatment-experienced patients and cirrhotic individuals, irrespective of treatment history, for whom SOF/VEL is being considered. The identification of the Y93H substitution indicates the need for RBV addition or an alternative regimen administration[78,79].

The second potent pangenotypic option is a combination of GLE and PIB, which was approved for the treatment of patients without or with liver cirrhosis irrespective of previous therapy. As protease inhibitors containing regimens carry a risk of decompensation during antiviral treatment, GLE/PIB is not recommended for decompensated cirrhotic patients[88]. This regimen provides the opportunity for shortening therapy to 8 wk in the majority of patients[89]. Based on findings from the ENDURANCE-3, SURVEYOR-II, and EXPEDITION-8 clinical trials, an 8-wk regimen has been registered for all previously untreated patients, including those with compensated liver cirrhosis, whereas treatment-experienced GT3-infected individuals should be treated for 16 wk regardless of liver fibrosis[90-94]. RWE studies reported effectiveness for an 8-wk GLE/PIB regimen, which exceeded 96% in treatment-naïve patients without liver cirrhosis[95-99]. Since the shortening of therapy in previously untreated cirrhotic patients infected with GT3 has been approved very recently, the available RWE data are very limited and only include a small number of patients[100,101]. Therefore, further studies are needed to determine the treatment outcome in this subpopulation. Although the implementation of SOF/VEL and GLE/PIB regimens has resulted in a high efficacy rate among GT3-infected individuals, there is still room for improvement, especially in those who did not achieve SVR, particularly following NS5A containing regimens. For such patients, a 12-wk salvage therapy with a single-tablet combination of SOF/VEL and next-generation NS3/4A protease inhibitor voxilaprevir (VOX) is recommended[102]. Safety and efficacy of SOF/VEL/VOX in GT3-infected patients without and with liver cirrhosis, both treatment-naïve and treatment-experienced were demonstrated in the POLARIS studies (Table 1)[102,103].

The other option to address failed DAA treatment in GT3-infected patients is a combination of GLE/PIB plus SOF and RBV, as investigated in the MAGELLAN-3 study. This demonstrated a 100% SVR rate, however, the small number of patients enrolled may have limited the broad applicability of these findings[104].

SOMETHING WENT WRONG

On the way to developing highly effective pangenotypic regimens against GT3, there were multiple paths that appeared to be dead ends. Some of them were not investigated despite showing encouraging initial results, due to disappointing treatment outcomes in selected subpopulations of GT3 patients. One good example is an open-label study of 12-wk treatment with an NS5A inhibitor—ledipasvir and SOF, plus RBV, which demonstrated a 100% SVR rate among treatment-naïve GT3 infected individuals. Unfortunately, due to limited efficacy in treatment-experienced patients, especially those with liver cirrhosis, as well as low antiviral potency without RBV against GT3, that direction of search has proved a blind alley[105]. Alisporivir, a

Table 2 European Association for the Study of the Liver and American Association for the Study of Liver Diseases/Infectious Diseases Society of America current recommendations on the treatment of genotype 3-infected patients

Recommendations	Genotype/subtype	Cirrhosis status	Prior treatment experience	SOF/VEL	GLE/PIB	SOF/VEL/VOX	GZR/EBR + SOF
European Association for the Study of the Liver[78]	GT3	No cirrhosis	Treatment-naïve	12 wk	8 wk	-	-
			Treatment-experienced		12 wk	-	-
		Compensated cirrhosis	Treatment-naïve	12 wk with RBV[1]	8-12 wk[2]	12 wk	-
			Treatment-experienced		16 wk		-
		Decompensated cirrhosis	Treatment-naïve and experienced	12 wk with RBV or 24 wk	-	-	-
	GT3, subtype b, g or any other subtype naturally harbouring one or several NS5A RASs[3]	No cirrhosis	Treatment-naïve	Unknown	Unknown	12 wk	-
			Treatment-experienced				-
		Compensated cirrhosis	Treatment-naïve				-
			Treatment-experienced				-
AASLD/IDSA (Ghany *et al*[79])	GT3	No cirrhosis	Treatment-naïve	12 wk	8 wk	-	-
			Treatment-experienced	12 wk	16 wk[4]	12 wk[4]	-
			SOF + RBV ± PEGIFN-experienced	-	16 wk	12 wk	-
			DAA-experienced[5]	-	-	12 wk, + RBV for NS5A failures	-
		Compensated cirrhosis	Treatment-naïve	12 wk, + RBV for 12 wk[4]	8 wk	12 wk[4]	-
			PEGIFN + RBV-experienced	+ RBV for 12 wk[4]	16 wk	12 wk	12 wk[4]
			SOF + RBV ± PEGIFN-experienced	-	16 wk	12 wk	-
			DAA-experienced[5]	-	-	12 wk, + RBV for NS5A failures	-
		Decompensated cirrhosis	Treatment-naïve and experienced	12 wk with RBV or 24 wk	-	-	-

[1]If resistance testing is performed, only patients with the nonstructural protein 5A Y93H resistance-associated substitutions at baseline should be treated with sofosbuvir/velpatasvir plus ribavirin or with sofosbuvir/velpatasvir/voxilaprevir, whereas patients without the Y93H resistance-associated substitutions should be treated with sofosbuvir/velpatasvir alone.

[2]In treatment-naïve patients infected with genotype 3 with compensated (Child-Pugh A) cirrhosis, treatment with glecaprevir/pibrentasvir can be shortened to 8 wk, but more data are needed to consolidate this recommendation.

[3]As determined by sequence analysis of the nonstructural protein 5A region by means of population sequencing or deep sequencing (cutoff 15%).

[4]Alternative regimen.

[5]Including nonstructural protein 5A inhibitors except glecaprevir/pibrentasvir failures. NS5A: Nonstructural protein 5A; SOF: Sofosbuvir; VEL: Velpatasvir; GLE: Glecaprevir; PIB: Pibrentasvir; VOX: Voxilaprevir; GZR: Grazoprevir; EBR: Elbasvir; EASL: European Association for the Study of the Liver; GT: Genotype; RBV: Ribavirin; PEGIFN: Pegylated interferon; DAA: Direct-acting antivirals; AASLD/IDSA: American Association for the Study of Liver Diseases/Infectious Diseases Society of America.

cyclophilin inhibitor, applied alone or with RBV in treatment-naïve non-cirrhotic patients has resulted in SVR rates of 76% and 93%, respectively, however, research involving other subgroups of patients was suspended due to a safety issue[106]. Efficacy was observed to be below expectations with the combination of the NS3/4A inhibitor grazoprevir (GZR) and the NS5A inhibitor elbasvir (EBR) with RBV, as well as with a regimen consisting of the NS5A inhibitor ruzasvir and the NS5B inhibitor uprifosbuvir[107,108]. The unsatisfactory outcome of the treatment with NS35A inhibitor ombitasvir, and NS3/4A inhibitor paritaprevir boosted by ritonavir with or without RBV, was subsequently improved by the addition of SOF, but ultimately these regimens were not further evaluated, because there were new potent pangenotypic options on the horizon[109,110]. For this same reason, investigations into a regimen of GZR/EBR combined with uprifosbuvir or SOF were discontinued, despite the high effectiveness demonstrated in phase 2 clinical trials. However, GZR/EBR + SOF is currently recommended by AASLD/IDSA as an alternative option for the specific subpopulation of pegIFNα+RBV-experienced patients with compensated liver cirrhosis[79,111-113].

CONCLUSION

Despite the high efficacy and safety of pangenotypic therapies, that may sooner or later cure all or at least almost all identified HCV infections, including GT3, there will still be many infections that go unrecognized and are therefore impossible to cure with even the best drug. The major problem that remains to be solved worldwide is screening people who are unaware of the risk of liver disease progression from a virus in their body. It is a shame for national governments that, despite having access to the perfect tool to eliminate a dangerous virus and rule out one of the most difficult-to-treat cancers, are not doing enough.

REFERENCES

1 **World Health Organization**. Global Health Sector Strategy on Viral Hepatitis 2016-2021. [cited 31 December 2020]. Geneva, Switzerland: World Health Organization [Internet]. Available from: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf?ua=1

2 **Messina JP**, Humphreys I, Flaxman A, Brown A, Cooke GS, Pybus OG, Barnes E. Global distribution and prevalence of hepatitis C virus genotypes. *Hepatology* 2015; **61**: 77-87 [PMID: 25069599 DOI: 10.1002/hep.27259]

3 **Petruzziello A**, Marigliano S, Loquercio G, Cozzolino A, Cacciapuoti C. Global epidemiology of hepatitis C virus infection: An up-date of the distribution and circulation of hepatitis C virus genotypes. *World J Gastroenterol* 2016; **22**: 7824-7840 [PMID: 27678366 DOI: 10.3748/wjg.v22.i34.7824]

4 **Petruzziello A**, Loquercio G, Sabatino R, Balaban DV, Ullah Khan N, Piccirillo M, Rodrigo L, di Capua L, Guzzo A, Labonia F, Botti G. Prevalence of Hepatitis C virus genotypes in nine selected European countries: A systematic review. *J Clin Lab Anal* 2019; **33**: e22876 [PMID: 30843304 DOI: 10.1002/jcla.22876]

5 **Alberti A**, Lacoin L, Morais E, Lefevre C, Abogunrin S, Iheanacho I. Literature review of the distribution of hepatitis C virus genotypes across Europe. *J Med Virol* 2016; **88**: 2157-2169 [PMID: 27171396 DOI: 10.1002/jmv.24573]

6 **Dalgard O**, Weiland O, Noraberg G, Karlsen L, Heggelund L, Färkkilâ M, Balslev U, Belard E, Øvrehus A, Skalshøi Kjær M, Krarup H, Thorup Røge B, Hallager S, Madsen LG, Lund Laursen A, Lagging M, Weis N. Sofosbuvir based treatment of chronic hepatitis C genotype 3 infections-A Scandinavian real-life study. *PLoS One* 2017; **12**: e0179764 [PMID: 28704381 DOI: 10.1371/journal.pone.0179764]

7 **Flisiak R**, Pogorzelska J, Berak H, Horban A, Orłowska I, Simon K, Tuchendler E, Madej G, Piekarska A, Jabłkowski M, Deroń Z, Mazur W, Kaczmarczyk M, Janczewska E, Pisula A, Smykał J, Nowak K, Matukiewicz M, Halota W, Wernik J, Sikorska K, Mozer-Lisewska I, Rozpłochowski B, Garlicki A, Tomasiewicz K, Krzowska-Firych J, Baka-Ćwierz B, Kryczka W, Zarębska-Michaluk D, Olszok I, Boroń-Kaczmarska A, Sobala-Szczygieł B, Szlauer B, Korcz-Ondrzejek B, Sieklucki J, Pleśniak R, Ruszała A, Postawa-Kłosińska B, Citko J, Lachowicz-Wawrzyniak A, Musialik J, Jezierska E, Dobracki W, Dobracka B, Hałubiec J, Krygier R, Strokowska A, Chomczyk W, Witczak-Malinowska K. Prevalence of HCV genotypes in Poland - the EpiTer study. *Clin Exp Hepatol* 2016; **2**: 144-148 [PMID: 28856279 DOI: 10.5114/ceh.2016.63871]

8 **Palladino C**, Ezeonwumelu IJ, Marcelino R, Briz V, Moranguinho I, Serejo F, Velosa JF, Marinho RT, Borrego P, Taveira N. Epidemic history of hepatitis C virus genotypes and subtypes in Portugal. *Sci Rep* 2018; **8**: 12266 [PMID: 30116054 DOI: 10.1038/s41598-018-30528-0]

9 **Brady Z**, Stoykova Z. Hepatitis C virus genotype analysis in patients with chronic hepatitis in North Eastern Bulgaria. *J Drug Assess* 2019; **8**: 146-149 [PMID: 31552145 DOI: 10.1080/21556660.2019.1654484]

10 **Gervain J**. [Analysis of hepatitis C virus type and subtype distribution in Hungary]. *Orv Hetil* 2018; **159**: 2-8 [PMID: 29847988 DOI: 10.1556/650.2018.31177]

11 **Björnsson E**, Angulo P. Hepatitis C and steatosis. *Arch Med Res* 2007; **38**: 621-627 [PMID: 17613353 DOI: 10.1016/j.arcmed.2006.09.001]

12 **Adinolfi LE**, Gambardella M, Andreana A, Tripodi MF, Utili R, Ruggiero G. Steatosis accelerates the progression of liver damage of chronic hepatitis C patients and correlates with specific HCV genotype and visceral obesity. *Hepatology* 2001; **33**: 1358-1364 [PMID: 11391523 DOI: 10.1053/jhep.2001.24432]

13 **Lonardo A**, Adinolfi LE, Loria P, Carulli N, Ruggiero G, Day CP. Steatosis and hepatitis C virus: mechanisms and significance for hepatic and extrahepatic disease. *Gastroenterology* 2004; **126**: 586-597 [PMID: 14762795 DOI: 10.1053/j.gastro.2003.11.020]

14 **Mihm S**, Fayyazi A, Hartmann H, Ramadori G. Analysis of histopathological manifestations of chronic hepatitis C virus infection with respect to virus genotype. *Hepatology* 1997; **25**: 735-739 [PMID: 9049227 DOI: 10.1002/hep.510250340]

15 **Abid K**, Pazienza V, de Gottardi A, Rubbia-Brandt L, Conne B, Pugnale P, Rossi C, Mangia A, Negro F. An *in vitro* model of hepatitis C virus genotype 3a-associated triglycerides accumulation. *J Hepatol* 2005; **42**: 744-751 [PMID: 15826725 DOI: 10.1016/j.jhep.2004.12.034]

16 **Rubbia-Brandt L**, Quadri R, Abid K, Giostra E, Malé PJ, Mentha G, Spahr L, Zarski JP, Borisch B, Hadengue A, Negro F. Hepatocyte steatosis is a cytopathic effect of hepatitis C virus genotype 3. *J Hepatol* 2000; **33**: 106-115 [PMID: 10905593 DOI: 10.1016/s0168-8278(00)80166-x]

17 **d'Avigdor WMH**, Budzinska MA, Lee M, Lam R, Kench J, Stapelberg M, McLennan SV, Farrell G, George J, McCaughan GW, Tu T, Shackel NA. Virus Genotype-Dependent Transcriptional Alterations in Lipid Metabolism and Inflammation Pathways in the Hepatitis C Virus-infected Liver. *Sci Rep* 2019; **9**: 10596 [PMID: 31332246 DOI: 10.1038/s41598-019-46664-0]

18 **Negro F**. Mechanisms and significance of liver steatosis in hepatitis C virus infection. *World J Gastroenterol* 2006; **12**: 6756-6765 [PMID: 17106922 DOI: 10.3748/wjg.v12.i42.6756]

19 **Asselah T**, Rubbia-Brandt L, Marcellin P, Negro F. Steatosis in chronic hepatitis C: why does it really matter? *Gut* 2006; **55**: 123-130 [PMID: 16344578 DOI: 10.1136/gut.2005.069757]

20 **Fartoux L**, Poujol-Robert A, Guéchot J, Wendum D, Poupon R, Serfaty L. Insulin resistance is a cause of steatosis and fibrosis progression in chronic hepatitis C. *Gut* 2005; **54**: 1003-1008 [PMID: 15951550 DOI: 10.1136/gut.2004.050302]

21 **Mirandola S**, Realdon S, Iqbal J, Gerotto M, Dal Pero F, Bortoletto G, Marcolongo M, Vario A, Datz C, Hussain MM, Alberti A. Liver microsomal triglyceride transfer protein is involved in hepatitis C liver steatosis. *Gastroenterology* 2006; **130**: 1661-1669 [PMID: 16697730 DOI: 10.1053/j.gastro.2006.02.035]

22 **de Gottardi A**, Pazienza V, Pugnale P, Bruttin F, Rubbia-Brandt L, Juge-Aubry CE, Meier CA, Hadengue A, Negro F. Peroxisome proliferator-activated receptor-alpha and -gamma mRNA levels are reduced in chronic hepatitis C with steatosis and genotype 3 infection. *Aliment Pharmacol Ther* 2006; **23**: 107-114 [PMID: 16393287 DOI: 10.1111/j.1365-2036.2006.02729.x]

23 **Jackel-Cram C**, Qiao L, Xiang Z, Brownlie R, Zhou Y, Babiuk L, Liu Q. Hepatitis C virus genotype-3a core protein enhances sterol regulatory element-binding protein-1 activity through the phosphoinositide 3-kinase-Akt-2 pathway. *J Gen Virol* 2010; **91**: 1388-1395 [PMID: 20130133 DOI: 10.1099/vir.0.017418-0]

24 **Castéra L**, Hézode C, Roudot-Thoraval F, Lonjon I, Zafrani ES, Pawlotsky JM, Dhumeaux D. Effect of antiviral treatment on evolution of liver steatosis in patients with chronic hepatitis C: indirect evidence of a role of hepatitis C virus genotype 3 in steatosis. *Gut* 2004; **53**: 420-424 [PMID: 14960527 DOI: 10.1136/gut.2002.009936]

25 **Kumar D**, Farrell GC, Fung C, George J. Hepatitis C virus genotype 3 is cytopathic to hepatocytes: Reversal of hepatic steatosis after sustained therapeutic response. *Hepatology* 2002; **36**: 1266-1272 [PMID: 12395339 DOI: 10.1053/jhep.2002.36370]

26 **Bochud PY**, Cai T, Overbeck K, Bochud M, Dufour JF, Müllhaupt B, Borovicka J, Heim M, Moradpour D, Cerny A, Malinverni R, Francioli P, Negro F; Swiss Hepatitis C Cohort Study Group. Genotype 3 is associated with accelerated fibrosis progression in chronic hepatitis C. *J Hepatol* 2009; **51**: 655-666 [PMID: 19665246 DOI: 10.1016/j.jhep.2009.05.016]

27 **Westin J**, Nordlinder H, Lagging M, Norkrans G, Wejstål R. Steatosis accelerates fibrosis development over time in hepatitis C virus genotype 3 infected patients. *J Hepatol* 2002; **37**: 837-842 [PMID: 12445426 DOI: 10.1016/s0168-8278(02)00299-4]

28 **Rubbia-Brandt L**, Fabris P, Paganin S, Leandro G, Male PJ, Giostra E, Carlotto A, Bozzola L, Smedile A, Negro F. Steatosis affects chronic hepatitis C progression in a genotype specific way. *Gut* 2004; **53**: 406-412 [PMID: 14960525 DOI: 10.1136/gut.2003.018770]

29 **Probst A**, Dang T, Bochud M, Egger M, Negro F, Bochud PY. Role of hepatitis C virus genotype 3 in liver fibrosis progression--a systematic review and meta-analysis. *J Viral Hepat* 2011; **18**: 745-759 [PMID: 21992794 DOI: 10.1111/j.1365-2893.2011.01481.x]

30 **Larsen C**, Bousquet V, Delarocque-Astagneau E, Pioche C, Roudot-Thoraval F; HCV Surveillance Steering Committee; HCV Surveillance Group; Desenclos JC. Hepatitis C virus genotype 3 and the risk of severe liver disease in a large population of drug users in France. *J Med Virol* 2010; **82**: 1647-

1654 [PMID: 20827760 DOI: 10.1002/jmv.21850]
31 **McMahon BJ**, Bruden D, Bruce MG, Livingston S, Christensen C, Homan C, Hennessy TW, Williams J, Sullivan D, Rosen HR, Gretch D. Adverse outcomes in Alaska natives who recovered from or have chronic hepatitis C infection. *Gastroenterology* 2010; **138**: 922-31. e1 [PMID: 19909749 DOI: 10.1053/j.gastro.2009.10.056]
32 **McCombs J**, Matsuda T, Tonnu-Mihara I, Saab S, Hines P, L'italien G, Juday T, Yuan Y. The risk of long-term morbidity and mortality in patients with chronic hepatitis C: results from an analysis of data from a Department of Veterans Affairs Clinical Registry. *JAMA Intern Med* 2014; **174**: 204-212 [PMID: 24193887 DOI: 10.1001/jamainternmed.2013.12505]
33 **Kanwal F**, Kramer JR, Ilyas J, Duan Z, El-Serag HB. HCV genotype 3 is associated with an increased risk of cirrhosis and hepatocellular cancer in a national sample of U.S. Veterans with HCV. *Hepatology* 2014; **60**: 98-105 [PMID: 24615981 DOI: 10.1002/hep.27095]
34 **Nkontchou G**, Ziol M, Aout M, Lhabadie M, Baazia Y, Mahmoudi A, Roulot D, Ganne-Carrie N, Grando-Lemaire V, Trinchet JC, Gordien E, Vicaut E, Baghad I, Beaugrand M. HCV genotype 3 is associated with a higher hepatocellular carcinoma incidence in patients with ongoing viral C cirrhosis. *J Viral Hepat* 2011; **18**: e516-e522 [PMID: 21914071 DOI: 10.1111/j.1365-2893.2011.01441.x]
35 **Lee SS**, Kim CY, Kim BR, Cha RR, Kim WS, Kim JJ, Lee JM, Kim HJ, Ha CY, Kim HJ, Kim TH, Jung WT, Lee OJ. Hepatitis C virus genotype 3 was associated with the development of hepatocellular carcinoma in Korea. *J Viral Hepat* 2019; **26**: 459-465 [PMID: 30516858 DOI: 10.1111/jvh.13047]
36 **Bruno S**, Crosignani A, Maisonneuve P, Rossi S, Silini E, Mondelli MU. Hepatitis C virus genotype 1b as a major risk factor associated with hepatocellular carcinoma in patients with cirrhosis: a seventeen-year prospective cohort study. *Hepatology* 2007; **46**: 1350-1356 [PMID: 17680653 DOI: 10.1002/hep.21826]
37 **Raimondi S**, Bruno S, Mondelli MU, Maisonneuve P. Hepatitis C virus genotype 1b as a risk factor for hepatocellular carcinoma development: a meta-analysis. *J Hepatol* 2009; **50**: 1142-1154 [PMID: 19395111 DOI: 10.1016/j.jhep.2009.01.019]
38 **Mangia A**, Santoro R, Minerva N, Ricci GL, Carretta V, Persico M, Vinelli F, Scotto G, Bacca D, Annese M, Romano M, Zechini F, Sogari F, Spirito F, Andriulli A. Peginterferon alfa-2b and ribavirin for 12 vs. 24 wk in HCV genotype 2 or 3. *N Engl J Med* 2005; **352**: 2609-2617 [PMID: 15972867 DOI: 10.1056/NEJMoa042608]
39 **Mecenate F**, Pellicelli AM, Barbaro G, Romano M, Barlattani A, Mazzoni E, Bonaventura ME, Nosotti L, Arcuri P, Picardi A, Barbarini G, D'Ambrosio C, Paffetti A, Andreoli A, Soccorsi F; Club Epatologi Ospedalieri (CLEO) Group. Short *vs* standard treatment with pegylated interferon alfa-2A plus ribavirin in patients with hepatitis C virus genotype 2 or 3: the cleo trial. *BMC Gastroenterol* 2010; **10**: 21 [PMID: 20170514 DOI: 10.1186/1471-230X-10-21]
40 **Lawitz E**, Mangia A, Wyles D, Rodriguez-Torres M, Hassanein T, Gordon SC, Schultz M, Davis MN, Kayali Z, Reddy KR, Jacobson IM, Kowdley KV, Nyberg L, Subramanian GM, Hyland RH, Arterburn S, Jiang D, McNally J, Brainard D, Symonds WT, McHutchison JG, Sheikh AM, Younossi Z, Gane EJ. Sofosbuvir for previously untreated chronic hepatitis C infection. *N Engl J Med* 2013; **368**: 1878-1887 [PMID: 23607594 DOI: 10.1056/NEJMoa1214853]
41 **Zarębska-Michaluk D**, Lebensztejn D, Chrapek M, Paluch K, Stępień P, Kryczka W. Predictors of sustained virological response in patients with hepatitis C virus genotype 3 infection. *Clin Exp Hepatol* 2016; **2**: 117-124 [PMID: 28856274 DOI: 10.5114/ceh.2016.62526]
42 **Dalgard O**, Bjøro K, Ring-Larsen H, Bjornsson E, Holberg-Petersen M, Skovlund E, Reichard O, Myrvang B, Sundelöf B, Ritland S, Hellum K, Frydén A, Florholmen J, Verbaan H; North-C Group. Pegylated interferon alfa and ribavirin for 14 *vs* 24 wk in patients with hepatitis C virus genotype 2 or 3 and rapid virological response. *Hepatology* 2008; **47**: 35-42 [PMID: 17975791 DOI: 10.1002/hep.21975]
43 **Shiffman ML**, Suter F, Bacon BR, Nelson D, Harley H, Solá R, Shafran SD, Barange K, Lin A, Soman A, Zeuzem S; ACCELERATE Investigators. Peginterferon alfa-2a and ribavirin for 16 or 24 wk in HCV genotype 2 or 3. *N Engl J Med* 2007; **357**: 124-134 [PMID: 17625124 DOI: 10.1056/NEJMoa066403]
44 **von Wagner M**, Huber M, Berg T, Hinrichsen H, Rasenack J, Heintges T, Bergk A, Bernsmeier C, Häussinger D, Herrmann E, Zeuzem S. Peginterferon-alpha-2a (40KD) and ribavirin for 16 or 24 wk in patients with genotype 2 or 3 chronic hepatitis C. *Gastroenterology* 2005; **129**: 522-527 [PMID: 16083709 DOI: 10.1016/j.gastro.2005.05.008]
45 **Andriulli A**, Mangia A, Iacobellis A, Ippolito A, Leandro G, Zeuzem S. Meta-analysis: the outcome of anti-viral therapy in HCV genotype 2 and genotype 3 infected patients with chronic hepatitis. *Aliment Pharmacol Ther* 2008; **28**: 397-404 [PMID: 18549461 DOI: 10.1111/j.1365-2036.2008.03763.x]
46 **Powis J**, Peltekian KM, Lee SS, Sherman M, Bain VG, Cooper C, Krajden M, Deschenes M, Balshaw RF, Heathcote EJ, Yoshida EM; Canadian Pegasys Study Group. Exploring differences in response to treatment with peginterferon alpha 2a (40kD) and ribavirin in chronic hepatitis C between genotypes 2 and 3. *J Viral Hepat* 2008; **15**: 52-57 [PMID: 18088245 DOI: 10.1111/j.1365-2893.2007.00889.x]
47 **Hadziyannis SJ**, Sette H Jr, Morgan TR, Balan V, Diago M, Marcellin P, Ramadori G, Bodenheimer H Jr, Bernstein D, Rizzetto M, Zeuzem S, Pockros PJ, Lin A, Ackrill AM; PEGASYS

International Study Group. Peginterferon-alpha2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. *Ann Intern Med* 2004; **140**: 346-355 [PMID: 14996676 DOI: 10.7326/0003-4819-140-5-200403020-00010]

48 **Shoeb D**, Dearden J, Weatherall A, Bargery C, Moreea S, Alam S, White E, Vila X, Freshwater D, Ryder S, Mills PR, Alexander GJ, Forton D, Foster GR. Extended duration therapy with pegylated interferon and ribavirin for patients with genotype 3 hepatitis C and advanced fibrosis: final results from the STEPS trial. *J Hepatol* 2014; **60**: 699-705 [PMID: 24291239 DOI: 10.1016/j.jhep.2013.11.011]

49 **Jacobson IM**, Brown RS Jr, Freilich B, Afdhal N, Kwo PY, Santoro J, Becker S, Wakil AE, Pound D, Godofsky E, Strauss R, Bernstein D, Flamm S, Pauly MP, Mukhopadhyay P, Griffel LH, Brass CA; WIN-R Study Group. Peginterferon alfa-2b and weight-based or flat-dose ribavirin in chronic hepatitis C patients: a randomized trial. *Hepatology* 2007; **46**: 971-981 [PMID: 17894303 DOI: 10.1002/hep.21932]

50 **Manzano-Robleda Mdel C**, Ornelas-Arroyo V, Barrientos-Gutiérrez T, Méndez-Sánchez N, Uribe M, Chávez-Tapia NC. Boceprevir and telaprevir for chronic genotype 1 hepatitis C virus infection. A systematic review and meta-analysis. *Ann Hepatol* 2015; **14**: 46-57 [PMID: 25536641 DOI: 10.1016/S1665-2681(19)30800-2]

51 **Janczewska E**, Flisiak R, Zarebska-Michaluk D, Kozielewicz D, Berak H, Dobracka B, Librant-Suska M, Lojewski W, Jurczyk K, Musialik J, Postawa-Kłosińska B, Wroblewski J, Augustyniak K, Dudziak M, Olszok I, Ruszala A, Pisula A, Lapinski T, Kryczka W, Horban A, Dobracki W. Effect of Peginterferon or Ribavirin Dosing on Efficacy of Therapy With Telaprevir in Treatment-Experienced Patients With Chronic Hepatitis C and Advanced Liver Fibrosis: A Multicenter Cohort Study. *Medicine (Baltimore)* 2015; **94**: e1411 [PMID: 26402801 DOI: 10.1097/MD.0000000000001411]

52 **European Association for Study of Liver**. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol* 2014; **60**: 392-420 [PMID: 24331294 DOI: 10.1016/j.jhep.2013.11.003]

53 **Foster GR**, Hézode C, Bronowicki JP, Carosi G, Weiland O, Verlinden L, van Heeswijk R, van Baelen B, Picchio G, Beumont M. Telaprevir alone or with peginterferon and ribavirin reduces HCV RNA in patients with chronic genotype 2 but not genotype 3 infections. *Gastroenterology* 2011; **141**: 881-889. e1 [PMID: 21699786 DOI: 10.1053/j.gastro.2011.05.046]

54 **Lenz O**, Vijgen L, Berke JM, Cummings MD, Fevery B, Peeters M, De Smedt G, Moreno C, Picchio G. Virologic response and characterisation of HCV genotype 2-6 in patients receiving TMC435 monotherapy (study TMC435-C202). *J Hepatol* 2013; **58**: 445-451 [PMID: 23142061 DOI: 10.1016/j.jhep.2012.10.028]

55 **Dore GJ**, Lawitz E, Hézode C, Shafran SD, Ramji A, Tatum HA, Taliani G, Tran A, Brunetto MR, Zaltron S, Strasser SI, Weis N, Ghesquiere W, Lee SS, Larrey D, Pol S, Harley H, George J, Fung SK, de Lédinghen V, Hagens P, McPhee F, Hernandez D, Cohen D, Cooney E, Noviello S, Hughes EA. Daclatasvir plus peginterferon and ribavirin is noninferior to peginterferon and ribavirin alone, and reduces the duration of treatment for HCV genotype 2 or 3 infection. *Gastroenterology* 2015; **148**: 355-366. e1 [PMID: 25311593 DOI: 10.1053/j.gastro.2014.10.007]

56 **Lawitz E**, Poordad F, Brainard DM, Hyland RH, An D, Dvory-Sobol H, Symonds WT, McHutchison JG, Membreno FE. Sofosbuvir with peginterferon-ribavirin for 12 wk in previously treated patients with hepatitis C genotype 2 or 3 and cirrhosis. *Hepatology* 2015; **61**: 769-775 [PMID: 25322962 DOI: 10.1002/hep.27567]

57 **Lawitz E**, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, Bernstein DE, Dejesus E, Freilich B, Nelson DR, Dieterich DT, Jacobson IM, Jensen D, Abrams GA, Darling JM, Rodriguez-Torres M, Reddy KR, Sulkowski MS, Bzowej NH, Hyland RH, Mo H, Lin M, Mader M, Hindes R, Albanis E, Symonds WT, Berrey MM, Muir A. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. *Lancet Infect Dis* 2013; **13**: 401-408 [PMID: 23499158 DOI: 10.1016/S1473-3099(13)70033-1]

58 **Foster GR**, Pianko S, Brown A, Forton D, Nahass RG, George J, Barnes E, Brainard DM, Massetto B, Lin M, Han B, McHutchison JG, Subramanian GM, Cooper C, Agarwal K; BOSON Study Group. Efficacy of sofosbuvir plus ribavirin with or without peginterferon-alfa in patients with hepatitis C virus genotype 3 infection and treatment-experienced patients with cirrhosis and hepatitis C virus genotype 2 infection. *Gastroenterology* 2015; **149**: 1462-1470 [PMID: 26248087 DOI: 10.1053/j.gastro.2015.07.043]

59 **Gane EJ**, Stedman CA, Hyland RH, Ding X, Svarovskaia E, Symonds WT, Hindes RG, Berrey MM. Nucleotide polymerase inhibitor sofosbuvir plus ribavirin for hepatitis C. *N Engl J Med* 2013; **368**: 34-44 [PMID: 23281974 DOI: 10.1056/NEJMoa1208953]

60 **Ioannou GN**, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI, Su F, Berry K. Effectiveness of Sofosbuvir, Ledipasvir/Sofosbuvir, or Paritaprevir/Ritonavir/Ombitasvir and Dasabuvir Regimens for Treatment of Patients With Hepatitis C in the Veterans Affairs National Health Care System. *Gastroenterology* 2016; **151**: 457-471. e5 [PMID: 27267053 DOI: 10.1053/j.gastro.2016.05.049]

61 **Zarębska-Michaluk D**, Flisiak R, Jaroszewicz J, Janczewska E, Czauż-Andrzejuk A, Berak H, Horban A, Staniaszek A, Gietka A, Tudrujek M, Tomasiewicz K, Dybowska D, Halota W, Piekarska A, Sitko M, Garlicki A, Orłowska I, Simon K, Belica-Wdowik T, Baka-Ćwierz B, Mazur W, Białkowska J, Socha Ł, Wawrzynowicz-Syczewska M, Laurans Ł, Deroń Z, Lorenc B, Dobracka B,

Tronina O, Pawłowska M. Is Interferon-Based Treatment of Viral Hepatitis C Genotype 3 Infection Still of Value in the Era of Direct-Acting Antivirals? *J Interferon Cytokine Res* 2018; **38**: 93-100 [PMID: 29443655 DOI: 10.1089/jir.2017.0113]

62 **Cornberg M**, Petersen J, Schober A, Mauss S, Böker KH, Link R, Günther R, Serfert Y, Pfeiffer-Vornkahl H, Manns MP, Sarrazin C, Hüppe D, Berg T, Niederau C. Real-world use, effectiveness and safety of anti-viral treatment in chronic hepatitis C genotype 3 infection. *Aliment Pharmacol Ther* 2017; **45**: 688-700 [PMID: 28078723 DOI: 10.1111/apt.13925]

63 **European Association for Study of Liver**. EASL Recommendations on Treatment of Hepatitis C 2015. *J Hepatol* 2015; **63**: 199-236 [PMID: 25911336 DOI: 10.1016/j.jhep.2015.03.025]

64 **Jacobson IM**, Gordon SC, Kowdley KV, Yoshida EM, Rodriguez-Torres M, Sulkowski MS, Shiffman ML, Lawitz E, Everson G, Bennett M, Schiff E, Al-Assi MT, Subramanian GM, An D, Lin M, McNally J, Brainard D, Symonds WT, McHutchison JG, Patel K, Feld J, Pianko S, Nelson DR; POSITRON Study; FUSION Study. Sofosbuvir for hepatitis C genotype 2 or 3 in patients without treatment options. *N Engl J Med* 2013; **368**: 1867-1877 [PMID: 23607593 DOI: 10.1056/NEJMoa1214854]

65 **Zeuzem S**, Dusheiko GM, Salupere R, Mangia A, Flisiak R, Hyland RH, Illeperuma A, Svarovskaia E, Brainard DM, Symonds WT, Subramanian GM, McHutchison JG, Weiland O, Reesink HW, Ferenci P, Hézode C, Esteban R; VALENCE Investigators. Sofosbuvir and ribavirin in HCV genotypes 2 and 3. *N Engl J Med* 2014; **370**: 1993-2001 [PMID: 24795201 DOI: 10.1056/NEJMoa1316145]

66 **AASLD/IDSA HCV Guidance Panel**. Hepatitis C guidance: AASLD-IDSA recommendations for testing, managing, and treating adults infected with hepatitis C virus. *Hepatology* 2015; **62**: 932-954 [PMID: 26111063 DOI: 10.1002/hep.27950]

67 **Wehmeyer MH**, Ingiliz P, Christensen S, Hueppe D, Lutz T, Simon KG, Schewe K, Boesecke C, Baumgarten A, Busch H, Rockstroh J, Schmutz G, Kimhofer T, Berger F, Mauss S, Schulze Zur Wiesch J. Real-world effectiveness of sofosbuvir-based treatment regimens for chronic hepatitis C genotype 3 infection: Results from the multicenter German hepatitis C cohort (GECCO-03). *J Med Virol* 2018; **90**: 304-312 [PMID: 28710853 DOI: 10.1002/jmv.24903]

68 **Feld JJ**, Maan R, Zeuzem S, Kuo A, Nelson DR, Di Bisceglie AM, Manns MP, Sherman K, Frazier LM, Sterling R, Mailliard M, Schmidt M, Akushevich L, Vainorius M, Fried MW. Effectiveness and Safety of Sofosbuvir-Based Regimens for Chronic HCV Genotype 3 Infection: Results of the HCV-TARGET Study. *Clin Infect Dis* 2016; **63**: 776-783 [PMID: 27325691 DOI: 10.1093/cid/ciw387]

69 **Nelson DR**, Cooper JN, Lalezari JP, Lawitz E, Pockros PJ, Gitlin N, Freilich BF, Younes ZH, Harlan W, Ghalib R, Oguchi G, Thuluvath PJ, Ortiz-Lasanta G, Rabinovitz M, Bernstein D, Bennett M, Hawkins T, Ravendhran N, Sheikh AM, Varunok P, Kowdley KV, Hennicken D, McPhee F, Rana K, Hughes EA; ALLY-3 Study Team. All-oral 12-week treatment with daclatasvir plus sofosbuvir in patients with hepatitis C virus genotype 3 infection: ALLY-3 phase III study. *Hepatology* 2015; **61**: 1127-1135 [PMID: 25614962 DOI: 10.1002/hep.27726]

70 **Leroy V**, Angus P, Bronowicki JP, Dore GJ, Hezode C, Pianko S, Pol S, Stuart K, Tse E, McPhee F, Bhore R, Jimenez-Exposito MJ, Thompson AJ. Daclatasvir, sofosbuvir, and ribavirin for hepatitis C virus genotype 3 and advanced liver disease: A randomized phase III study (ALLY-3+). *Hepatology* 2016; **63**: 1430-1441 [PMID: 26822022 DOI: 10.1002/hep.28473]

71 **Poordad F**, Shiffman ML, Ghesquiere W, Wong A, Huhn GD, Wong F, Ramji A, Shafran SD, McPhee F, Yang R, Noviello S, Linaberry M; ALLY-3C study team. Daclatasvir and sofosbuvir with ribavirin for 24 wk in chronic hepatitis C genotype-3-infected patients with cirrhosis: a Phase III study (ALLY-3C). *Antivir Ther* 2019; **24**: 35-44 [PMID: 30382942 DOI: 10.3851/IMP3278]

72 **European Association for the Study of the Liver**. EASL Recommendations on Treatment of Hepatitis C 2016. *J Hepatol* 2017; **66**: 153-194 [PMID: 27667367 DOI: 10.1016/j.jhep.2016.09.001]

73 **American Association for the Study of Liver Diseases and Infectious Diseases Society of America**. HCV Guidance: Recommendations for Testing, Managing, and Treating Hepatitis C. Updated: July 6, 2016. Changes made September 16, 2016. [cited 31 December 2020]. In: AASLD and IDSA [Internet]. Available from: http://www.hcvguidelines.org

74 **Omata M**, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, Lesmana CR, Sollano J, Kumar M, Jindal A, Sharma BC, Hamid SS, Dokmeci AK, Mamun-Al-Mahtab, McCaughan GW, Wasim J, Crawford DH, Kao JH, Yokosuka O, Lau GK, Sarin SK. APASL consensus statements and recommendation on treatment of hepatitis C. *Hepatol Int* 2016; **10**: 702-726 [PMID: 27130427 DOI: 10.1007/s12072-016-9717-6]

75 **Macken L**, Gelson W, Priest M, Abouda G, Barclay S, Fraser A, Healy B, Irving W, Verma S. Efficacy of direct-acting antivirals: UK real-world data from a well-characterised predominantly cirrhotic HCV cohort. *J Med Virol* 2019; **91**: 1979-1988 [PMID: 31329295 DOI: 10.1002/jmv.25552]

76 **Hézode C**, Lebray P, De Ledinghen V, Zoulim F, Di Martino V, Boyer N, Larrey D, Botta-Fridlund D, Silvain C, Fontaine H, D'Alteroche L, Leroy V, Bourliere M, Hubert-Fouchard I, Guyader D, Rosa I, Nguyen-Khac E, Fedchuk L, Akremi R, Bennai Y, Filipovics A, Zhao Y, Bronowicki JP. Daclatasvir plus sofosbuvir, with or without ribavirin, for hepatitis C virus genotype 3 in a French early access programme. *Liver Int* 2017; **37**: 1314-1324 [PMID: 28177199 DOI: 10.1111/liv.13383]

77 **Soria A**, Fava M, Bernasconi DP, Lapadula G, Colella E, Valsecchi MG, Migliorino GM, D'Ambrosio R, Landonio S, Schiavini M, Spinetti A, Carriero C, Degasperi E, Cologni G, Gatti F, Viganò P, Hasson H, Uberti-Foppa C, Pasulo L, Baiguera C, Rossotti R, Vinci M, Puoti M, Giorgini

A, Menzaghi B, Lombardi A, Pan A, Aghemo A, Grossi PA, Boldizzoni R, Colombo S, Viganò M, Rumi MG, Del Poggio P, Valenti L, Giglio O, De Bona A, d'Arminio Monforte A, Colombo A, Spinelli O, Pigozzi MG, Molteni C, Bonfanti P, Terreni N, Perini P, Capretti A, Bella D, Liani C, Polo S, Aimo G, Pagnucco L, Bhoori S, Centenaro R, Graffeo M, Ciaccio A, Dionigi E, Lazzaroni S, Carderi I, Di Marco M, Rizzardini G, Noventa F, Lampertico P, Fagiuoli S. Comparison of three therapeutic regimens for genotype-3 hepatitis C virus infection in a large real-life multicentre cohort. *Liver Int* 2020; **40**: 769-777 [PMID: 31970845 DOI: 10.1111/liv.14386]

78 **European Association for the Study of the Liver**, Clinical Practice Guidelines Panel: Chair, EASL Governing Board representative, Panel members. EASL recommendations on treatment of hepatitis C: Final update of the series☆. *J Hepatol* 2020; **73**: 1170-1218 [PMID: 32956768 DOI: 10.1016/j.jhep.2020.08.018]

79 **Ghany MG**, Morgan TR; AASLD-IDSA Hepatitis C Guidance Panel. Hepatitis C Guidance 2019 Update: American Association for the Study of Liver Diseases-Infectious Diseases Society of America Recommendations for Testing, Managing, and Treating Hepatitis C Virus Infection. *Hepatology* 2020; **71**: 686-721 [PMID: 31816111 DOI: 10.1002/hep.31060]

80 **Foster GR**, Afdhal N, Roberts SK, Bräu N, Gane EJ, Pianko S, Lawitz E, Thompson A, Shiffman ML, Cooper C, Towner WJ, Conway B, Ruane P, Bourlière M, Asselah T, Berg T, Zeuzem S, Rosenberg W, Agarwal K, Stedman CA, Mo H, Dvory-Sobol H, Han L, Wang J, McNally J, Osinusi A, Brainard DM, McHutchison JG, Mazzotta F, Tran TT, Gordon SC, Patel K, Reau N, Mangia A, Sulkowski M; ASTRAL-2 Investigators; ASTRAL-3 Investigators. Sofosbuvir and Velpatasvir for HCV Genotype 2 and 3 Infection. *N Engl J Med* 2015; **373**: 2608-2617 [PMID: 26575258 DOI: 10.1056/NEJMoa1512612]

81 **Esteban R**, Pineda JA, Calleja JL, Casado M, Rodríguez M, Turnes J, Morano Amado LE, Morillas RM, Forns X, Pascasio Acevedo JM, Andrade RJ, Rivero A, Carrión JA, Lens S, Riveiro-Barciela M, McNabb B, Zhang G, Camus G, Stamm LM, Brainard DM, Subramanian GM, Buti M. Efficacy of Sofosbuvir and Velpatasvir, With and Without Ribavirin, in Patients With Hepatitis C Virus Genotype 3 Infection and Cirrhosis. *Gastroenterology* 2018; **155**: 1120-1127. e4 [PMID: 29958855 DOI: 10.1053/j.gastro.2018.06.042]

82 **European Medicines Agency**. Epclusa: Summary of Product Characteristics 2020. [cited 31 December 2020]. In: European Medicines Agency [Internet]. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/epclusa#product-information-section

83 **Wong YJ**, Thurairajah PH, Kumar R, Tan J, Fock KM, Law NM, Li W, Kwek A, Tan YB, Koh J, Lee ZC, Kumar LS, Teo EK, Ang TL. Efficacy and safety of sofosbuvir/velpatasvir in a real-world chronic hepatitis C genotype 3 cohort. *J Gastroenterol Hepatol* 2020 [PMID: 33217040 DOI: 10.1111/jgh.15324]

84 **Belperio PS**, Shahoumian TA, Loomis TP, Mole LA, Backus LI. Real-world effectiveness of daclatasvir plus sofosbuvir and velpatasvir/sofosbuvir in hepatitis C genotype 2 and 3. *J Hepatol* 2019; **70**: 15-23 [PMID: 30266283 DOI: 10.1016/j.jhep.2018.09.018]

85 **Flisiak R**, Zarębska-Michaluk D, Jaroszewicz J, Lorenc B, Klapaczyński J, Tudrujek-Zdunek M, Sitko M, Mazur W, Janczewska E, Pabjan P, Dybowska D, Buczyńska I, Czauż-Andrzejuk A, Belica-Wdowik T, Berak H, Krygier R, Piasecki M, Dobracka B, Citko J, Piekarska A, Socha Ł, Deroń Z, Tronina O, Laurans Ł, Białkowska J, Tomasiewicz K, Halota W, Simon K, Pawłowska M. Changes in patient profile, treatment effectiveness, and safety during 4 years of access to interferon-free therapy for hepatitis C virus infection. *Pol Arch Intern Med* 2020; **130**: 163-172 [PMID: 32031541 DOI: 10.20452/pamw.15181]

86 **von Felden J**, Vermehren J, Ingiliz P, Mauss S, Lutz T, Simon KG, Busch HW, Baumgarten A, Schewe K, Hueppe D, Boesecke C, Rockstroh JK, Daeumer M, Luebke N, Timm J, Schulze Zur Wiesch J, Sarrazin C, Christensen S. High efficacy of sofosbuvir/velpatasvir and impact of baseline resistance-associated substitutions in hepatitis C genotype 3 infection. *Aliment Pharmacol Ther* 2018; **47**: 1288-1295 [PMID: 29536554 DOI: 10.1111/apt.14592]

87 **Wilton J**, Wong S, Yu A, Ramji A, Cook D, Butt ZA, Alvarez M, Binka M, Darvishian M, Jeong D, Bartlett SR, Pearce ME, Adu PA, Yoshida EM, Krajden M, Janjua NZ. Real-world Effectiveness of Sofosbuvir/Velpatasvir for Treatment of Chronic Hepatitis C in British Columbia, Canada: A Population-Based Cohort Study. *Open Forum Infect Dis* 2020; **7**: ofaa055 [PMID: 32154326 DOI: 10.1093/ofid/ofaa055]

88 **European Medicines Agency**. EMA/332999/2020. Maviret: Procedural steps taken and scientific information after the authorization. [cited 31 December 2020]. In: European Medicines Agency [Internet]. Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/maviret-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf

89 **Puoti M**, Foster GR, Wang S, Mutimer D, Gane E, Moreno C, Chang TT, Lee SS, Marinho R, Dufour JF, Pol S, Hezode C, Gordon SC, Strasser SI, Thuluvath PJ, Zhang Z, Lovell S, Pilot-Matias T, Mensa FJ. High SVR12 with 8-week and 12-week glecaprevir/pibrentasvir therapy: An integrated analysis of HCV genotype 1-6 patients without cirrhosis. *J Hepatol* 2018; **69**: 293-300 [PMID: 29551706 DOI: 10.1016/j.jhep.2018.03.007]

90 **Brown RS Jr**, Buti M, Rodrigues L, Chulanov V, Chuang WL, Aguilar H, Horváth G, Zuckerman E, Carrion BR, Rodriguez-Perez F, Urbánek P, Abergel A, Cohen E, Lovell SS, Schnell G, Lin CW, Zha J, Wang S, Trinh R, Mensa FJ, Burroughs M, Felizarta F. Glecaprevir/pibrentasvir for 8 wk in treatment-naïve patients with chronic HCV genotypes 1-6 and compensated cirrhosis: The EXPEDITION-8 trial. *J Hepatol* 2020; **72**: 441-449 [PMID: 31682879 DOI:

10.1016/j.jhep.2019.10.020]

91 **Flamm S**, Mutimer D, Asatryan A, Wang S, Rockstroh J, Horsmans Y, Kwo PY, Weiland O, Villa E, Heo J, Gane E, Ryder SD, Welzel TM, Ruane PJ, Agarwal K, Ng TI, Xue Z, Lovell SS, Krishnan P, Kopecky-Bromberg S, Trinh R, Mensa FJ, Wyles DL. Glecaprevir/Pibrentasvir in patients with chronic HCV genotype 3 infection: An integrated phase 2/3 analysis. *J Viral Hepat* 2019; **26**: 337-349 [PMID: 30421537 DOI: 10.1111/jvh.13038]

92 **Zeuzem S**, Foster GR, Wang S, Asatryan A, Gane E, Feld JJ, Asselah T, Bourlière M, Ruane PJ, Wedemeyer H, Pol S, Flisiak R, Poordad F, Chuang WL, Stedman CA, Flamm S, Kwo P, Dore GJ, Sepulveda-Arzola G, Roberts SK, Soto-Malave R, Kaita K, Puoti M, Vierling J, Tam E, Vargas HE, Bruck R, Fuster F, Paik SW, Felizarta F, Kort J, Fu B, Liu R, Ng TI, Pilot-Matias T, Lin CW, Trinh R, Mensa FJ. Glecaprevir-Pibrentasvir for 8 or 12 Weeks in HCV Genotype 1 or 3 Infection. *N Engl J Med* 2018; **378**: 354-369 [PMID: 29365309 DOI: 10.1056/NEJMoa1702417]

93 **Kwo PY**, Poordad F, Asatryan A, Wang S, Wyles DL, Hassanein T, Felizarta F, Sulkowski MS, Gane E, Maliakkal B, Overcash JS, Gordon SC, Muir AJ, Aguilar H, Agarwal K, Dore GJ, Lin CW, Liu R, Lovell SS, Ng TI, Kort J, Mensa FJ. Glecaprevir and pibrentasvir yield high response rates in patients with HCV genotype 1-6 without cirrhosis. *J Hepatol* 2017; **67**: 263-271 [PMID: 28412293 DOI: 10.1016/j.jhep.2017.03.039]

94 **Wyles D**, Poordad F, Wang S, Alric L, Felizarta F, Kwo PY, Maliakkal B, Agarwal K, Hassanein T, Weilert F, Lee SS, Kort J, Lovell SS, Liu R, Lin CW, Pilot-Matias T, Krishnan P, Mensa FJ. Glecaprevir/pibrentasvir for hepatitis C virus genotype 3 patients with cirrhosis and/or prior treatment experience: A partially randomized phase 3 clinical trial. *Hepatology* 2018; **67**: 514-523 [PMID: 28926120 DOI: 10.1002/hep.29541]

95 **D'Ambrosio R**, Pasulo L, Puoti M, Vinci M, Schiavini M, Lazzaroni S, Soria A, Gatti F, Menzaghi B, Aghemo A, Capelli F, Rumi MG, Morini L, Giorgini A, Pigozzi MG, Rossini A, Maggiolo F, Pan A, Memoli M, Spinelli O, Del Poggio P, Saladino V, Spinetti A, De Bona A, Capretti A, Uberti-Foppa C, Bonfanti P, Terreni N, Menozzi F, Colombo AE, Giglio O, Centenaro R, Borghi M, Baiguera C, Picciotto V, Landonio S, Gori A, Magnani C, Noventa F, Paolucci S, Lampertico P, Fagiuoli S; NAVIGATORE-Lombardia Study Group. Real-world effectiveness and safety of glecaprevir/pibrentasvir in 723 patients with chronic hepatitis C. *J Hepatol* 2019; **70**: 379-387 [PMID: 30472321 DOI: 10.1016/j.jhep.2018.11.011]

96 **Zarębska-Michaluk D**, Jaroszewicz J, Pabjan P, Łapiński TW, Mazur W, Krygier R, Dybowska D, Halota W, Pawłowska M, Janczewska E, Buczyńska I, Simon K, Dobracka B, Citko J, Laurans Ł, Tudrujek-Zdunek M, Tomasiewicz K, Piekarska A, Sitko M, Białkowska-Warzecha J, Klapaczyński J, Sobala-Szczygieł B, Horban A, Berak H, Deroń Z, Lorenc B, Socha Ł, Tronina O, Flisiak R. Is an 8-week regimen of glecaprevir/pibrentasvir sufficient for all hepatitis C virus infected patients in the real-world experience? *J Gastroenterol Hepatol* 2020 [PMID: 33171526 DOI: 10.1111/jgh.15337]

97 **Berg T**, Naumann U, Stoehr A, Sick C, John C, Teuber G, Schiffelholz W, Mauss S, Lohmann K, König B, Pangerl A, Niederau C. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of chronic hepatitis C infection: data from the German Hepatitis C-Registry. *Aliment Pharmacol Ther* 2019; **49**: 1052-1059 [PMID: 30874328 DOI: 10.1111/apt.15222]

98 **Persico M**, Aglitti A, Milella M, Coppola C, Messina V, Claar E, Gentile I, Sogari F, Pierri P, Surace LA, Morisco F, Tundo P, Brancaccio G, Serviddio G, Gatti P, Termite AP, Di Costanzo GG, Caroleo B, Cozzolongo R, Coppola N, Longo A, Fontanella L, Federico A, Rosato V, Terrenato I, Masarone M. Real-life glecaprevir/pibrentasvir in a large cohort of patients with hepatitis C virus infection: The MISTRAL study. *Liver Int* 2019; **39**: 1852-1859 [PMID: 31175707 DOI: 10.1111/liv.14170]

99 **Lampertico P**, Carrión JA, Curry M, Turnes J, Cornberg M, Negro F, Brown A, Persico M, Wick N, Porcalla A, Pangerl A, Crown E, Larsen L, Yu Y, Wedemeyer H. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: A meta-analysis. *J Hepatol* 2020; **72**: 1112-1121 [PMID: 32061651 DOI: 10.1016/j.jhep.2020.01.025]

100 **Flamm SL**, Kort J, Marx SE, Strezewski J, Dylla DE, Bacon B, Curry MP, Tsai N, Wick N. Effectiveness of 8-Week Glecaprevir/Pibrentasvir for Treatment-Naïve, Compensated Cirrhotic Patients with Chronic Hepatitis C Infection. *Adv Ther* 2020; **37**: 2267-2274 [PMID: 32279176 DOI: 10.1007/s12325-020-01301-5]

101 **Lampertico P**, Mauss S, Persico M, Barclay ST, Marx S, Lohmann K, Bondin M, Zhang Z, Marra F, Belperio PS, Wedemeyer H, Flamm S. Real-World Clinical Practice Use of 8-Week Glecaprevir/Pibrentasvir in Treatment-Naïve Patients with Compensated Cirrhosis. *Adv Ther* 2020; **37**: 4033-4042 [PMID: 32754824 DOI: 10.1007/s12325-020-01449-0]

102 **Bourlière M**, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, Ravendhran N, Vierling JM, Tran TT, Pianko S, Bansal MB, de Lédinghen V, Hyland RH, Stamm LM, Dvory-Sobol H, Svarovskaia E, Zhang J, Huang KC, Subramanian GM, Brainard DM, McHutchison JG, Verna EC, Buggisch P, Landis CS, Younes ZH, Curry MP, Strasser SI, Schiff ER, Reddy KR, Manns MP, Kowdley KV, Zeuzem S; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, Velpatasvir, and Voxilaprevir for Previously Treated HCV Infection. *N Engl J Med* 2017; **376**: 2134-2146 [PMID: 28564569 DOI: 10.1056/NEJMoa1613512]

103 **Jacobson IM**, Lawitz E, Gane EJ, Willems BE, Ruane PJ, Nahass RG, Borgia SM, Shafran SD, Workowski KA, Pearlman B, Hyland RH, Stamm LM, Svarovskaia E, Dvory-Sobol H, Zhu Y, Subramanian GM, Brainard DM, McHutchison JG, Bräu N, Berg T, Agarwal K, Bhandari BR, Davis M, Feld JJ, Dore GJ, Stedman CAM, Thompson AJ, Asselah T, Roberts SK, Foster GR. Efficacy of

8 Weeks of Sofosbuvir, Velpatasvir, and Voxilaprevir in Patients With Chronic HCV Infection: 2 Phase 3 Randomized Trials. *Gastroenterology* 2017; **153**: 113-122 [PMID: 28390869 DOI: 10.1053/j.gastro.2017.03.047]

104 **Wyles D**, Weiland O, Yao B, Weilert F, Dufour JF, Gordon SC, Stoehr A, Brown A, Mauss S, Zhang Z, Pilot-Matias T, Rodrigues L Jr, Mensa FJ, Poordad F. Retreatment of patients who failed glecaprevir/pibrentasvir treatment for hepatitis C virus infection. *J Hepatol* 2019; **70**: 1019-1023 [PMID: 30857780 DOI: 10.1016/j.jhep.2019.01.031]

105 **Gane EJ**, Hyland RH, An D, Svarovskaia E, Pang PS, Brainard D, Stedman CA. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 wk in patients with HCV genotype 3 or 6 infection. *Gastroenterology* 2015; **149**: 1454-1461. e1 [PMID: 26261007 DOI: 10.1053/j.gastro.2015.07.063]

106 **Pawlotsky JM**, Flisiak R, Sarin SK, Rasenack J, Piratvisuth T, Chuang WL, Peng CY, Foster GR, Shah S, Wedemeyer H, Hézode C, Zhang W, Wong KA, Li B, Avila C, Naoumov NV; VITAL-1 study team. Alisporivir plus ribavirin, interferon free or in combination with pegylated interferon, for hepatitis C virus genotype 2 or 3 infection. *Hepatology* 2015; **62**: 1013-1023 [PMID: 26118427 DOI: 10.1002/hep.27960]

107 **Gane E**, Nahass R, Luketic V, Asante-Appiah E, Hwang P, Robertson M, Wahl J, Barr E, Haber B. Efficacy of 12 or 18 weeks of elbasvir plus grazoprevir with ribavirin in treatment-naïve, noncirrhotic HCV genotype 3-infected patients. *J Viral Hepat* 2017; **24**: 895-899 [PMID: 28470815 DOI: 10.1111/jvh.12719]

108 **Lawitz E**, Gane E, Feld JJ, Buti M, Foster GR, Rabinovitz M, Burnevich E, Katchman H, Tomasiewicz K, Lahser F, Jackson B, Shaughnessy M, Klopfer S, Yeh WW, Robertson MN, Hanna GJ, Barr E, Platt HL; C-BREEZE-2 Study Investigators. Efficacy and safety of a two-drug direct-acting antiviral agent regimen ruzasvir 180 mg and uprifosbuvir 450 mg for 12 weeks in adults with chronic hepatitis C virus genotype 1, 2, 3, 4, 5 or 6. *J Viral Hepat* 2019; **26**: 1127-1138 [PMID: 31108015 DOI: 10.1111/jvh.13132]

109 **Lawitz E**, Sullivan G, Rodriguez-Torres M, Bennett M, Poordad F, Kapoor M, Badri P, Campbell A, Rodrigues L Jr, Hu Y, Pilot-Matias T, Vilchez RA. Exploratory trial of ombitasvir and ABT-450/r with or without ribavirin for HCV genotype 1, 2, and 3 infection. *J Infect* 2015; **70**: 197-205 [PMID: 25246359 DOI: 10.1016/j.jinf.2014.09.008]

110 **Shafran SD**, Shaw D, Charafeddine M, Agarwal K, Foster GR, Abunimeh M, Pilot-Matias T, Pothacamury RK, Fu B, Cohen E, Cohen DE, Gane E. Efficacy and safety results of patients with HCV genotype 2 or 3 infection treated with ombitasvir/paritaprevir/ritonavir and sofosbuvir with or without ribavirin (QUARTZ II-III). *J Viral Hepat* 2018; **25**: 118-125 [PMID: 28833938 DOI: 10.1111/jvh.12782]

111 **Lawitz E**, Poordad F, Gutierrez JA, Wells JT, Landaverde CE, Evans B, Howe A, Huang HC, Li JJ, Hwang P, Dutko FJ, Robertson M, Wahl J, Barr E, Haber B. Short-duration treatment with elbasvir/grazoprevir and sofosbuvir for hepatitis C: A randomized trial. *Hepatology* 2017; **65**: 439-450 [PMID: 27770561 DOI: 10.1002/hep.28877]

112 **Foster GR**, Agarwal K, Cramp ME, Moreea S, Barclay S, Collier J, Brown AS, Ryder SD, Ustianowski A, Forton DM, Fox R, Gordon F, Rosenberg WM, Mutimer DJ, Du J, Gilbert CL, Asante-Appiah E, Wahl J, Robertson MN, Barr E, Haber B. Elbasvir/grazoprevir and sofosbuvir for hepatitis C virus genotype 3 infection with compensated cirrhosis: A randomized trial. *Hepatology* 2018; **67**: 2113-2126 [PMID: 29473975 DOI: 10.1002/hep.29852]

113 **Lawitz E**, Buti M, Vierling JM, Almasio PL, Bruno S, Ruane PJ, Hassanein TI, Muellhaupt B, Pearlman B, Jancoriene L, Gao W, Huang HC, Shepherd A, Tannenbaum B, Fernsler D, Li JJ, Grandhi A, Liu H, Su FH, Wan S, Dutko FJ, Nguyen BT, Wahl J, Robertson MN, Barr E, Yeh WW, Plank RM, Butterton JR, Yoshida EM. Safety and efficacy of a fixed-dose combination regimen of grazoprevir, ruzasvir, and uprifosbuvir with or without ribavirin in participants with and without cirrhosis with chronic hepatitis C virus genotype 1, 2, or 3 infection (C-CREST-1 and C-CREST-2, part B): two randomised, phase 2, open-label trials. *Lancet Gastroenterol Hepatol* 2017; **2**: 814-823 [PMID: 28802814 DOI: 10.1016/S2468-1253(17)30163-2]

114 **Gane EJ**, Schwabe C, Hyland RH, Yang Y, Svarovskaia E, Stamm LM, Brainard DM, McHutchison JG, Stedman CA. Efficacy of the Combination of Sofosbuvir, Velpatasvir, and the NS3/4A Protease Inhibitor GS-9857 in Treatment-Naïve or Previously Treated Patients With Hepatitis C Virus Genotype 1 or 3 Infections. *Gastroenterology* 2016; **151**: 448-456. e1 [PMID: 27240903 DOI: 10.1053/j.gastro.2016.05.021]

115 **Gane EJ**, Kowdley KV, Pound D, Stedman CA, Davis M, Etzkorn K, Gordon SC, Bernstein D, Everson G, Rodriguez-Torres M, Tsai N, Khalid O, Yang JC, Lu S, Dvory-Sobol H, Stamm LM, Brainard DM, McHutchison JG, Tong M, Chung RT, Beavers K, Poulos JE, Kwo PY, Nguyen MH. Efficacy of Sofosbuvir, Velpatasvir, and GS-9857 in Patients With Hepatitis C Virus Genotype 2, 3, 4, or 6 Infections in an Open-Label, Phase 2 Trial. *Gastroenterology* 2016; **151**: 902-909 [PMID: 27486033 DOI: 10.1053/j.gastro.2016.07.038]

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REVIEW

How to manage inflammatory bowel disease during the COVID-19 pandemic: A guide for the practicing clinician

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Abstract

Managing inflammatory bowel disease (IBD) during the coronavirus disease 2019 (COVID-19) pandemic has been a challenge faced by clinicians and their patients, especially concerning whether to proceed with biologics and immunosuppressive agents in the background of a global outbreak of a highly contagious new coronavirus (severe acute respiratory syndrome coronavirus 2, SARS-CoV-2). The knowledge about the impact of this virus on patients with IBD, although it is still scarce, is rapidly evolving. In particular, concerns surrounding medications' impact for IBD on the risk of acquiring SARS-CoV-2 infection or developing COVID-19, and potentially exacerbate viral replication and the COVID-19 course, are a current thinking of both practicing clinicians and providers caring for patients with IBD. Managing patients with IBD infected with SARS-CoV-2 depends on both the clinical activity of the IBD and the occasional development and severity of COVID-19. In this review, we summarize the current data regarding gastrointestinal involvement by SARS-CoV-2 and pharmacologic and surgical management for IBD concerning this infection, and the COVID-19 impact on both the patient's psychological functioning and endoscopy services, and we concisely summarize the telemedicine roles during the COVID-19 pandemic.

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Core Tip: The knowledge on coronavirus disease 2019 (COVID-19) is rapidly evolving. Although patients with inflammatory bowel disease (IBD) do not appear to be at increased risk for COVID-19, the potential impact of immunosuppressive therapies on patients with IBD infected with severe acute respiratory syndrome coronavirus 2 calls for concern for clinicians and patients. Several recommendations and guidelines have recently been published, including the necessary reorganization of gastroenterology and endoscopy services to attendance of these patients, the growing role played by telemedicine, and the importance of addressing aspects of mental health in this context. We provide an overview and practical guidance for managing patients with IBD medically and surgically in the COVID-19 era.

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INTRODUCTION

Over the past year, the coronavirus disease 2019 (COVID-19) pandemic has evolved as a public health emergency of international concern. The epidemiological panorama is constantly evolving, and the data updated to January 12, 2021 have 191 countries involved, with more than 90947243 confirmed cases and 1947243 confirmed deaths globally[1]. The first opportunity to eradicate the virus over the long term and to protect specific patients from COVID-19 is by introducing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccines[2]. Although efforts to implement mass vaccination programs are currently in place globally, high rates of COVID-19 infections and fatalities are still expected in the months ahead.

Inflammatory bowel disease (IBD), such as ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory conditions of the gastrointestinal (GI) tract affecting millions of people worldwide[3]. Patients with IBD and other immune-mediated diseases often require treatment with corticosteroids, immunomodulators (thiopurines, methotrexate), biologics, and Janus kinase inhibitors, which can increase the risk of infections[4-6]. However, until now, the incidence of SARS-CoV-2 infection in patients with IBD and immunosuppressive therapy did not appear to differ from the general population[7]. Also, based on data from an international registry developed to collect information from patients with IBD from all over the world with confirmed COVID-19 and its outcomes, and the Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD), the evolution of COVID-19 does not seem to be worse in patients with IBD[8].

Notwithstanding, most elective clinical activities involving IBD care were drastically decreased during the pandemic[9-11]. Moreover, as suggested by the most qualified international societies and organizations, outpatient visits, colonoscopies, and non-urgent surgery have been postponed to prevent patient contact with the hospital and to enable patients with IBD to maintain social isolation[12,13].

As the world is gradually attempting to normalize, IBD physicians must face new challenges in terms of both future uncertainty, given the lack of supply of COVID-19 vaccines worldwide, and the ability to reorganize clinical activities for patients with IBD to provide optimal care while avoiding new outbreaks. Facing this scenario, this review aims to critically analyze the evidence on the effect of medications commonly used to treat IBD, as well as the management of the disease in its different degrees of activity, including the setting of SARS-CoV-2 infection.

WHAT IS THE RISK OF SARS-CoV-2 INFECTION IN THE IBD POPULATION?

Data on the incidence of SARS-CoV-2 infection among patients with IBD have been conflicting. Initial evidence suggested that patients with IBD had a lower risk of COVID-19 compared to the general population, as subsequent studies reported that no case of COVID-19 was diagnosed among patients with IBD followed in referral centers in China and Italy[14,15]. However, other studies assessing the risk of COVID-19 among patients with IBD reported incidence rates of 4.9 cases per 1000 patients with IBD in a Spanish cohort[16] and 2.5 cases per 1000 patients with IBD in France and Italy cohorts[17]. In a recent systematic review and meta-analysis by Aziz *et al*[7] comprising six studies that incorporated data from 9177 patients with IBD, the pooled incidence of COVID-19 in the IBD population was approximately 0.3%, which is greatly reassuring, as the incidence is on the lower side compared with the general population (0.2%-4.0%)[7]. Although there is limited evidence available, it seems that patients with IBD are not at greater risk of acquiring COVID-19, and SARS-CoV-2 infection does not seem to be more prevalent in patients with IBD than in the general population. However, this data must be interpreted with caution given that IBD patients might have better adherence to protection, social distancing and hygiene measures, which could explain the lower incidence in this population.

MANAGING IBD MEDICATIONS DURING THE COVID-19 PANDEMIC

Managing IBD medications during SARS-CoV-2 infection and COVID-19

Managing IBD during the COVID-19 pandemic has been a challenge faced by clinicians and their patients, especially concerning whether to carry on with biologics and immunosuppressive agents in the background of a global outbreak of a highly SARS-CoV-2. The knowledge about the impact of this virus on patients with IBD, although it is still scarce, is rapidly evolving[18].

In particular, concerns surrounding medications' impact for IBD on the risk of acquiring SARS-CoV-2 infection or developing COVID-19, and potentially exacerbate viral replication and the COVID-19 course, are a current thinking of both practicing clinicians and providers caring for patients with IBD. Confounding a systematic management strategy reveals that evidence-based data are scarce[19].

Providers caring for patients with IBD during the COVID-19 outbreak are opportune to reduce the burden of COVID-19 by assuming or sharing responsibility for multidisciplinary management of patients with IBD in this common clinical difficulty. The main goal that must be kept in mind is to treat active disease and maintain remission[20].

Fortunately, the worldwide management of patients with IBD during the COVID-19 pandemic presents considerable agreement. Indeed, gastroenterologists, both adult and pediatric, and colorectal surgeons were attending the practical recommendations/guidance and consensus statements from several societies of gastroenterology, endoscopy, surgery, and from the International Organization for the Study of Inflammatory Bowel Disease (IOIBD) with adaptations based on local regional characteristics[18]. For instance, an international survey on this issue showed that most gastroenterologists reduced clinic visits, restricted steroid use, and postponed elective endoscopic procedures and surgery. Also, if a patient was diagnosed with COVID-19, biologics and immunomodulators were mostly held[21].

Understanding the short- and long-term safety of drugs used in patients with IBD remains an important area of research, especially now in the middle of the COVID-19 pandemic. Preliminary evidence specified that except high-dose systemic steroids, using aminosalicylates, budesonide, antibiotics, rectal therapies, nutritional therapy, immunomodulators, and biologics, including anti-tumor necrosis factor (TNF) agents, anti-integrin, or anti-interleukin (IL)-12/23, were well tolerated without an increased risk of unfavorable evolution or duration of viral disease in patients with IBD that develop infection by SARS-CoV-2 and COVID-19[8]. However, recent accumulating evidence from SECURE-IBD registry based on data on over 1400 patients with IBD suggests that compared with anti-TNF monotherapy, thiopurine monotherapy, combotherapy of thiopurines with anti-TNF agent, and, surprisingly, aminosalicylates were associated with significantly increased risk of severe COVID-19, although the association with latter will require further replication in other IBD populations[22]. The authors of this study hypothesized that the influence of combotherapy on increased

COVID-19 severity appears to be guided by thiopurines, as the estimated impact for thiopurines monotherapy and combotherapy compared with anti-TNF monotherapy were similar[22]. Furthermore, this hypothesis followed previous observations that found a higher risk of viral infections in patients during treatment with thiopurines alone or in combotherapy with anti-TNF agents[4]. In line with the British Society of Gastroenterology (BSG) statements[13], these researchers proposed the withdrawal of thiopurine while the ongoing COVID-19 pandemic in high-risk patients with IBD, for instance, those with older age or multiple comorbidities that are in stable remission on combotherapy with anti-TNF agent[22]. Also, in this international registry in progress, there are no significant differences between biological classes (anti-TNF, anti-IL12/23, and integrin antagonists) on the risk of developing severe COVID-19.

Interestingly, some anecdotal reports have shown improvement in pulmonary symptoms and multisystem inflammatory syndrome related to COVID-19 in patients with active IBD treated with infliximab[23,24]. However, whether anti-TNF alpha therapy or other anti-inflammatory agents may protect against cytokine release syndrome in patients with COVID-19 will require further investigation[25]. Moreover, as advances in IBD therapy broaden the therapeutic arsenal, it will be necessary to maintain investigations using collaborative multi-center registries for evaluating the possible impact of novel agents, such as Janus kinase inhibitors, IL-23 antagonists, and others, on SARS-CoV-2 or COVID-19. It should be highlighted that as the knowledge regarding SARS-CoV-2 progresses, it is likely that IBD-specific recommendations in the COVID-19 setting also undergo substantial changes[26].

Managing patients with IBD infected with SARS-CoV-2 depends on both the clinical activity of the IBD and the occasional development and severity of COVID-19[12,27]. For practical purposes, we will present current recommendations for managing drugs for IBD concerning the SARS-CoV-2 infectious status into distinct clinical scenarios: (1) The patient attending outpatient clinic with IBD in remission in the setting of the asymptomatic SARS-CoV-2 infection or confirmed or suspected COVID-19; (2) The patient with active IBD undergoing outpatient follow-up in the setting of the asymptomatic SARS-CoV-2 infection or confirmed or suspected COVID-19; and (3) The patient with IBD hospitalized with asymptomatic SARS-CoV-2 infection or COVID-19.

Management of patient attending outpatient clinic with IBD in remission in the setting of asymptomatic SARS-CoV-2 infection or confirmed or suspected COVID-19 without systemic hyperinflammation syndrome

As the COVID-19 pandemic expands, an increasing number of tests for SARS-CoV-2 are being conducted, including asymptomatic contacts of COVID-19 index cases. Thus, the situation in which an individual tests positive for the virus but remains asymptomatic will be more and more frequent.

The IOIBD recommends for quiescent patients with IBD with asymptomatic SARS-CoV-2 infection — quick withdrawal of prednisone or de-escalating to < 20 mg/d or switch to budesonide or budesonide MMX (Multi Matrix System) when appropriate[12]. Immunomodulators such as thiopurines, methotrexate, and tofacitinib (or other Janus kinase inhibitors) should be temporarily held for 2 wk while monitoring for the appearance of COVID-19 symptoms[12]. Similarly, biologic administration, including anti-TNF drugs, vedolizumab, and ustekinumab, should be postponed for 2 wk if the dose is due, even recognizing that the half-lives of these biologics are relatively long, so that immunosuppressive effects of these drugs will persist for a few additional weeks despite the withdrawal of these agents[26]. Conversely, nonimmune-based anti-inflammatory therapies such as aminosalicylates, antibiotics, budesonide, or rectal therapy may be continued[22,26]. However, for patients with IBD who have had the closest contact with an individual with proven or suspected COVID-19, it is suggested that they isolate themselves and follow local recommendations from health managers. In this situation, European Crohn and Colitis Organization (ECCO) experts recommend that it is unnecessary to hold biologics or immunomodulators based on exposure only[20].

For patient attending outpatient clinic with quiescent IBD but with confirmed or suspected COVID-19, the approach to drug management is like that adopted for patients with asymptomatic infection by SARS-CoV-2. The American Gastroenterology Association (AGA) and IOIBD experts suggest that budesonide, aminosalycilates, antibiotics, and topical therapy may be maintained while systemic corticosteroids (prednisone) should be avoided and withdraw speedily, if possible. Likewise, it is recommended to hold immunomodulators, Janus kinase inhibitors, and biologics until after disappearance of symptoms, usually for 2 wk during the acute disease[12,26].

Management of patient with active IBD undergoing outpatient follow-up in the setting of asymptomatic SARS-CoV-2 infection or confirmed or suspected COVID-19 without systemic hyperinflammation syndrome

Currently, in the COVID-19 era, if a patient with IBD presents an apparent flare, it is important to always question the presence of concomitant symptoms suggestive of COVID-19, such as fever, cough, anosmia, or dyspnea, because GI symptoms including diarrhea, nausea, vomiting, and abdominal pain have been reported in 2%-33% of patients on initial presentation of COVID-19[28]. Moreover, in a few cases, these digestive symptoms may be the only clinical features of COVID-19[29]. This context is a clinical challenge, compounded by the frequent finding of remarkably elevated serum inflammatory biomarkers in patients with COVID-19.

When a patient with IBD presents diarrhea, it is doubtful whether this is secondary to a disease flare or COVID-19, a wait-and-see approach for the next 5-7 d is a reasonable strategy[27], once the diarrhea due to COVID-19 is mostly mild and self-limited, usually with an average duration of 5 d (range, 1 d to 14 d) and a mean frequency of four bowel movements per day[30]. Also, follow-up using interval assessment of fecal calprotectin (FC) may be useful, as FC levels are typically both transiently raised and mildly elevated in patients with diarrhea caused by COVID-19[31]. In contrast, in active IBD, sustained and substantial elevation of FC is commonly seen. In any case, in the current era of COVID-19, the joint expert consensus from ECCO recommends that all patients with a suspected IBD flare be tested to exclude COVID-19 preferably with oropharyngeal and nasopharyngeal swabs reverse transcription polymerase chain reaction (RT-PCR) assays when the first symptoms emerge[20].

In cases where, after initial assessment, diagnostic doubts remain, computed tomography (CT) scans of the chest, abdominal cross-sectional imaging methods, and, more restrictively, ileocolonoscopy assessment can allow the real cause of diarrhea to be established[20]. Another question that remains unknown is whether SARS-CoV-2 can cause a flare of or *de novo* IBD[19]. Moreover, in patients with apparently active IBD (especially colonic IBD), it is important to be aware to exclude enteric superinfections, mainly due to *Clostridioides difficile* (*C. difficile*) and cytomegalovirus (CMV), assess adherence to therapy, and perform therapeutic drug monitoring of biologics[27].

If GI symptoms (including diarrhea) are not caused by COVID-19 and other causes for IBD flare are excluded, such as enteric superinfection, nonsteroidal anti-inflammatory use, and non-adherence to therapy, the drug management for IBD will depend on the equilibrium between the severities of the IBD flare and those of the COVID-19[18-20]. For a flare of mild severity in outpatients with asymptomatic infection by SARS-CoV-2 or with mild to moderate COVID-19 without systemic hyperinflammation syndrome (SHS), it is recommended tapering off prednisone or its equivalent for < 20 mg/d with complete weaning where possible, balancing with the potential for possible adrenal insufficiency in the setting of chronic corticosteroid therapy[12,26,27]. Another option that can be considered in patients using systemic steroids is converting to oral budesonide or budesonide MMX on adequate dosing, provided the patient is in the appropriate clinical setting (*e.g.*, mildly to moderately active ileocecal CD or UC, respectively). Further, it is suggested stopping or avoiding commencing immunomodulators, tofacitinib (or other Janus kinase inhibitors), and biologics for at least 2 wk during viral illness, while budesonide, aminosalycilates, antibiotics, and topical therapy may be initiated or maintained if needed[26,27].

The approach for a IBD flare-up moderate to severe in patients attending outpatient clinic with COVID-19 without SHS may include continuation of current biological therapy for IBD with optimization to rescue a state of remission or starting a new biological agent if needed, preferably in monotherapy and with subcutaneous biologics to reduce the risk of exposure to SARS-CoV-2 in infusion units[20,27].

In this clinical context, if glucocorticosteroids are considered essential, the dose of prednisone (or its equivalent) should be ≤ 40 mg/d limiting the duration of use, if practicable[26]. Also, it is advised to stop if in use or avoid commencing immunomodulators or tofacitinib. If COVID-19 is progressive with significant pulmonary involvement and hospitalization, consultation with infectious diseases experts for possible COVID-19 treatment with antiviral or experimental anticytokine therapy may be interesting[19,20,27]. In Tables 1-3, we present an approach for managing IBD medications in patients attending outpatient clinic who are infected with SARS-CoV-2 with or without COVID-19.

Table 1 Management of patients attending outpatient clinic with quiescent inflammatory bowel disease in the scenario of asymptomatic severe acute respiratory syndrome coronavirus 2 infection or confirmed or suspected coronavirus disease 2019[12,20,26,27]

	Management
Asymptomatic infection with SARS-CoV-2	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be maintained; (2) Hold immunomodulators, tofacitinib, and biologics for 2 wk; (3) Taper or withdraw systemic corticosteroids (prednisone); and (4) Monitoring for 2 wk for COVID-19 symptoms
Mild COVID-19	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be maintained; (2) Hold immunomodulators, tofacitinib, and biologics for 2 wk; and (3) Taper or withdraw systemic corticosteroids (prednisone)
COVID-19 with pulmonary involvement without SHS	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be maintained; (2) Hold immunomodulators, tofacitinib, and biologics for 2 wk; and (3) Taper or discontinue systemic corticosteroids

Immunomodulators refer to thiopurines and methotrexate. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; SHS: Systemic hyperinflammation syndrome.

Table 2 Management of patients attending outpatient clinic with mildly active inflammatory bowel disease in the scenario of the asymptomatic severe acute respiratory syndrome coronavirus 2 infection or confirmed or suspected coronavirus disease 2019[12,20,26,27]

	Management
Asymptomatic infection with SARS-CoV-2	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be used if needed; (2) Hold immunomodulators, tofacitinib, and biologics for 2 wk; (3) Taper or withdraw corticosteroids (prednisone < 20 mg/d); and (4) Monitoring for 2 wk for COVID-19 to present
Mild COVID-19	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be used if needed; (2) Hold immunomodulators, tofacitinib, and biologics for 2 wk; (3) Taper or withdraw systemic corticosteroids); and (4) Monitoring for 2 wk for COVID-19 symptoms to disappear
COVID-19 with pulmonary involvement without SHS	(1) Budesonide, aminosalycilates, antibiotics, and topical therapy may be used if necessary; (2) Hold immunomodulators, tofacitinib, and biologics for at least 2 wk or until COVID-19 resolves; and (3) Taper or withdraw systemic corticosteroids

Immunomodulators refer to thiopurines and methotrexate. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; SHS: Systemic hyperinflammation syndrome.

Table 3 Management of patients attending outpatient clinic with moderately to severely active inflammatory bowel disease in the scenario of asymptomatic severe acute respiratory syndrome coronavirus 2 infection or confirmed or suspected coronavirus disease 2019[12,20,26,27]

	Management
Asymptomatic infection with SARS-CoV-2	(1) Restrict the use of prednisone ≤ 40 mg/d if necessary; (2) Avoid immunomodulators and tofacitinib; (3) Escalate to biologics as necessary (preferably in monotherapy); and (4) Thromboprophylaxis
Mild COVID-19	(1) Restrict the use of prednisone ≤ 40 mg/d if necessary; (2) Avoid starting or stopping, if in use, immunomodulators, and tofacitinib; (3) Escalate to biologics and dose optimization as necessary (preferably in monotherapy); and (4) Thromboprophylaxis
COVID-19 with pulmonary involvement without SHS	(1) Restrict the use of prednisone ≤ 40 mg/d if necessary; (2) Avoid starting or stopping immunomodulators, and tofacitinib; (3) Escalate to biologics and dose optimization as necessary (preferably) in monotherapy based on balance of benefits and risks; consultation with infectious diseases expert for possible COVID-19 treatment with antiviral or experimental anticitokine therapy; and (4) Thromboprophylaxis

Immunomodulators refer to thiopurines and methotrexate. SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; COVID-19: Coronavirus disease 2019; SHS: Systemic hyperinflammation syndrome.

Management of patients with IBD hospitalized with asymptomatic SARS-CoV-2 infection or COVID-19

Although the ongoing COVID-19 pandemic has substantially impacted the management of IBD, with unprecedented restriction of hospitalizations, many patients with IBD will still be hospitalized in the COVID-19 era either because of severely active or complicated IBD, or because they were infected with SARS-CoV-2 and developed progressive or severe COVID-19 with SHS requiring supplemental oxygen or ventilator support, use of vasopressors, or present evidence of end organ damage[19,26]. In fact, hospitalization should be restricted to life-threatening circumstances or complications[20].

For patients hospitalized with severe COVID-19, the priority is life support, while IBD therapy is likely to have less priority. Nonetheless, when possible, therapy for COVID-19 should consider the underlying IBD[12,27]. Ideally, treatment decisions should be personalized and decision-making should include a multidisciplinary approach, involving teams of experts on both conditions. This way, consultation with pulmonary medicine and infectious disease experts is crucial, with discussion involving the possibilities of COVID-19 treatment with experimental antiviral drugs or anticytokine therapy trials, and staying aware of potential interaction with IBD medications[32]. If IBD is mildly active, budesonide, aminosalycilates, and rectal therapies may be initiated while reducing or holding prednisone. Also, stopping biologics, immunomodulators, and tofacitinib throughout the duration of the COVID-19 is appropriate[18,19,26]. For moderately-to-severely active IBD, the limited use of intravenous corticosteroids for IBD is acceptable, if necessary. Topical therapy may be ordered if deemed adequate, while immunomodulators, tofacitinib, or biologics that failed for IBD should be stopped[18,19,27]. Other therapies for IBD should only be used if definitely required. Intravenous cyclosporine may be a reasonable option for severe UC, based on limited evidence of its benefit against coronavirus[26,27].

Interestingly, in a recent trial involving patients without IBD hospitalized with COVID-19, patients were randomized to therapy with oral or intravenous dexamethasone at a dose of 6 mg once daily for up to 10 d or until discharge, whichever was sooner, or to receive usual care only[33]. The group treated with dexamethasone presented significantly lower 28-d mortality in patients receiving either oxygen alone or with invasive mechanical ventilation (23.3% and 29.3% *vs* 26.2% and 41.4% with usual care, respectively). Importantly, the same benefit was not found in subjects receiving no respiratory support[33]. Whether other glucocorticoids like methylprednisolone or hydrocortisone on equivalent doses might also be effective in this setting is unknown and will require future studies. From the perspective of pharmacological effects and on the immune system, there is nothing specific about dexamethasone that other steroids do not offer as well, and so other glucocorticosteroids could in theory be used if dexamethasone is unavailable[34]. If this hypothesis is confirmed in prospective studies, this important therapeutic strategy can help us clarify our approach for suitably managing the challenging and life-threatening scenario of a patient hospitalized that concomitantly presents with a severe flare of IBD and moderate-to-severe COVID-19, where intravenous methylprednisolone or hydrocortisone could be one of the first-line therapies for both conditions.

However, for patients hospitalized due to severe flare of UC and who also have asymptomatic infection with SARS-CoV-2 or mild-moderate COVID-19, priority must be given to address issues pertinent to severe exacerbation of IBD, and usually a standard approach directed to the care of hospitalized patients with IBD should be followed[26,35]. In this clinical setting, expert opinions of the AGA recommend limiting intravenous steroids to three days and then transitioning to infliximab or cyclosporine[20]. Evaluating enteric superinfections, especially those caused by *C. difficile* or CMV, using fecal toxin A/B enzyme immunoassay and/or PCR for detecting toxins A and B genes or for detecting CMV DNA by quantitative PCR should be a routine practice for these patients[27]. In contrast, when CMV superinfection remains suspected despite the results of non-invasive tests, urgent colonoscopy should be reserved for patients in whom the procedure may change or target a specific therapy[12,19,20]; also, colorectal surgery expert consultation in the first days of hospitalization of the patient should also be a standard practice in this context[35]. Foremost, a recent 'RAND appropriateness panel' adapted from the BSG guidelines for managing acute severe UC recommended that regarding the COVID-19 pandemic, prophylactic anticoagulation post-discharge is ordered for patients hospitalized with acute severe colitis that had a positive SARS-CoV-2 testing due to the predisposition to develop thromboembolic complications in both conditions[36]. Indeed, the British Thoracic Society proposes that it is a reasonable approach to consider extended venous thromboembolism prophylaxis on discharge with low molecular weight heparin or direct oral anticoagulant during four weeks in high-risk patients with COVID-19[37]. Table 4 depicts the suggested approach for managing patients with IBD hospitalized with severe COVID-19.

When to restart biological and other immunosuppressive agents in patients with IBD infected with SARS-CoV-2 with or without COVID-19

Considering that patient safety should be a priority in the context of still limited but rapidly expanding knowledge regarding the management of IBD during the COVID-

Table 4 Management of patient with inflammatory bowel disease hospitalized with severe coronavirus disease 2019[12,19,20,26,27]

	Management
Quiescent IBD	(1) Budesonide, aminosalycilates, and rectal therapy may be kept; (2) Taper or withdraw prednisone; (3) Stop immunomodulators, tofacitinib, and biologics; and (4) Prioritize life support; consultation with infectious diseases expert for possible COVID-19 treatment with antiviral or experimental anticitokine therapy; thromboprophylaxis
Mildly active IBD	(1) Budesonide, aminosalycilates, and rectal therapy may be initiated; (2) Taper or withdraw prednisone; (3) Non starting or stopping if in use biologics, immunomodulators, and tofacitinib; and (4) Prioritize life support; consultation with infectious diseases expert for possible COVID-19 treatment with antiviral or experimental anticitokine therapy; thromboprophylaxis
Moderately to severely active IBD	(1) Limited use of intravenous steroids for IBD if necessary; (2) Topical therapy may be initiated if needed; (3) Quit immunomodulators, tofacitinib, or biologics that failed for the IBD; and (4) Consider other therapies for IBD only if absolutely necessary; intravenous cyclosporine may be a reasonable option for ulcerative colitis, based on limited evidence of its benefit against coronavirus. Prioritize life support; consultation with infectious diseases expert for possible COVID-19 treatment with antiviral or experimental anticitokine therapy; thromboprophylaxis

Immunomodulators refer to thiopurines and methotrexate. IBD: Inflammatory bowel disease; COVID-19: Coronavirus disease 2019; Severe COVID-19: Patient with systemic hyperinflammation syndrome needing mechanical ventilation ± vasopressors or evidence of end organ damage.

19 pandemic, most consensus statements and expert opinions recommend temporarily holding biologics and other immunosuppressant drugs in patients with IBD with asymptomatic SARS-CoV-2 infection or in the presence of symptoms suggestive of COVID-19 until a patient recovers[38]. However, if used prolongedly, this practice can lead some patients to both lose the effectiveness of their therapy and present an IBD flare[39]. Therefore, guidance on when to restart IBD medications in this setting is very welcome.

Although the timing for treatment restart is nonconsensual, currently, for decision making, the IOIBD expert panel recommends preferably for most patients a symptoms-based strategy due to the lack of accuracy of current molecular tests available for diagnosing SARS-CoV-2 infection, and also because of the clinical significance still unclear of the prolonged persistence of viral RNA detected by these tests in individuals that had COVID-19[38].

In asymptomatic patients with SARS-CoV-2 infection, some experts advise waiting at least 10 d from the first positive COVID-19 test for restarting immunosuppressive drugs as long as there is no development of symptoms suggestive of COVID-19 in this time interval[12,38]. In patients with COVID-19, the timing of resumed biologics or other immunosuppressants should be guided by the balance between the severity of both viral disease and IBD[38]. Thus, based on updated guidelines from the IOIBD, using a symptom-based strategy, it is recommended to wait at least 10 d since the appearance of the first symptoms of COVID and at least 3 d since recovery, defined as resolution of fever and significant improvement in respiratory symptoms, to re-start these medications[38]. Having two consecutive negative PCR tests in swab specimens, collected at least 24 h apart, is no longer required when this strategy is embraced[38,40]. In severe COVID-19, a longer time frame for re-initiating immunosuppressant may be necessary according to the personalized clinical strategy, if possible awaiting full patient recovery[41]. However, when doctors require a test-based strategy to decide about restarting IBD medications, in addition to the patient having clinically recovered based on the described parameters of the symptom-based strategy, he must have two consecutive negative nasopharyngeal swabs COVID-19 molecular assays collected at least 24 h apart[38].

MONITORING IBD TREATMENT DURING THE PANDEMIC

The outbreak of the COVID-19 infection forced government authorities to impose several restrictions, including lockdown[42]. Hospitals were then forced to rapidly restructure their activities to accommodate this critical and emergent situation. Institutional rearrangements have challenged IBD units worldwide, forcing them to adapt and generate specific approaches to maintain appropriate IBD care[10]. Referral IBD centers and Gastroenterology/IBD Societies published their guidance, helping clinicians tackle this troublesome situation[10,12,13,19,26,42-47]. In common, they advised remote monitoring, drug home delivery whenever possible, infusion unit restrictions, and patient education concerning protective measures (Table 5). Although necessary, all these measures and restrictions may negatively impact patients with IBD. A recent survey among 225 patients with IBD from a referral center showed depressive mood

Table 5 Approach to diminish the spread of coronavirus disease 2019 for patients with inflammatory bowel disease[10]

	Approach to diminish the spread of COVID-19 for patients with IBD
Inpatient clinic	(1) Hospitalized patients with IBD relocated to an isolated area/building, if possible, minimizing exposure to the virus; and (2) Test for coronavirus 2019 with nasopharyngeal swabs (PCR) before hospitalization
Outpatient clinic	(1) Visits rescheduled if possible; (2) Medical staff monitor patients *via* telemedicine (*e.g.*, remote video and telephone call); (3) Laboratory tests strictly limited; use fecal calprotectin (home modality, stool collection kit picked up by express mail services, if possible); (4) Endoscopy and image procedures only for urgent cases; (5) Patients should be advised to keep hygienic measures, avoid nonessential travels, and stay at home or work on a home-office basis; (6) Recommendations to maintain adequate hydration and nutrition status; and (7) Advise patients to continue their therapies, especially if in remission
Infusion center	(1) No accompanying person permitted; (2) Rearrangement of seats allowing a distance of at least 1.5 m in between; (3) Surgical masks for both patients and healthcare professionals; (4) Pre-admission protocol to assess for acute respiratory tract symptoms among patients with IBD and their contacts; (5) Selection of patients that could have their infusion postponed for 1-2 wk to let more space available for rearrangements of seats (those with clinical and endoscopic remission); and (6) Preference, if possible, for those biologics that can be offered subcutaneously, at home, instead of intravenously, to avoid overcrowding in the infusion center

IBD: Inflammatory bowel disease; COVID-19: Coronavirus disease 2019; PCR: Polymerase chain reaction.

as the most prevalent social impact (80.2%), followed by anxiety/fear of death (58.2%), insomnia (51.4%), daily activity impairment (48%), sexual dysfunction (46.2%), and productivity impairment (40%)[11]. These health repercussions in patients with IBD are essential, and healthcare professionals should be aware of them when talking remotely with the patients.

A common feature in the various IBD units is that telemedicine has replaced follow-up visits[48]. Although not the ideal way to follow these patients, that was the best way to do it now. Some authors prefer to term these remote visits video office or telephone office visits[44]. They avoid the term "virtual," which could mistakenly connote that the visits were not "real"[44]. In general, patients found those remote visits worthwhile, but no doubt, this was exhausting for the healthcare professionals that ended up with the well-described "zoom-fatigue"[44]; consequently, the personal visits were reduced by 30%-40%[10,42-44]; for comparison, endoscopic procedures were reduced by 90%-95%[10,42-44] and were indicated in selected cases[42,44,49,50]. Image procedures were also largely deferred and only indicated in cases of intestinal obstruction or suspected abscess[44]. There has been a lack of information on the impact of remote monitoring of patients with IBD during the SARS-CoV-2 pandemic. In a single-center cross-sectional Italian study with 1083 patients with IBD, telemonitoring of patients by phone or videoconference was compared with clinical evaluation in person (control group)[48]. Despite fewer relapses in the control group, there were no statistically significant differences between the groups regarding the quality of life measured by the IBDQ-32 questionnaire[48]. Thus, the possibility of contacting the IBD staff through remote monitoring, although not ideal, partially contributes to maintaining the quality-of-life parameter.

FC has been a valuable tool during this pandemic[27]. Many centers have relied on commercial labs to send an overnight home stool collection kit for FC that can be picked up by express mail services, avoiding the patient from leaving home[44]. A home FC test (IBDoc) was compared with a laboratory test (Quantum Blue® calprotectin test, BÜHLMANN, Schönenbuch, Switzerland) and the correlation between both tests was good ($r = 0.776$, $P < 0.0001$)[51]. Using 250 μg/g as the cutoff, the agreement between the home and laboratory tests was 80%[51]. Diarrhea can be one of the manifestations of COVID-19 or an IBD flare[27]. FC can be particularly useful to differentiate these situations since FC is usually only mildly elevated in patients with COVID-19 with diarrhea, whereas in patients with IBD and active disease, significant and sustained elevation may occur[27].

ENDOSCOPY IN PATIENTS WITH IBD IN THE COVID-19 ERA

Endoscopy is not only one fundamental pillar for diagnosing IBD but also plays an important role in its management, treatment, and colorectal cancer (CRC)/dysplasia surveillance. Differential diagnosis concerning other etiologies and between UC and CD as well as full evaluation of disease extension, activity, response to treatment, and even some therapeutic approaches are some endoscopic indications in a patient with IBD. Ileocolonoscopy, flexible proctosigmoidoscopy, and esophagogastroduodenoscopy are the most commonly used endoscopic methods, but enteroscopy and

videocapsule endoscopy also play a role in IBD management[52,53]. The overcrowded healthcare system worldwide by the COVID-19 pandemic and the need to control the spread of infection required restructuring primary care and hospital activities, including endoscopy units[43,54].

Risk of infection during endoscopy

Regardless of being more contagious than the other coronavirus (SARS-CoV and Middle East respiratory syndrome coronavirus), SARS-CoV-2 has similar ways of infection and complications[55], with aerosolized droplets produced by coughing, sneezing, or breathing as the main route of infection. SARS-CoV-2 infects the GI epithelium, and its RNA can be detected in stool samples, sometimes in high concentrations, even in patients without GI symptoms, lightening the possibility of fecal–oral transmission[55]. Although this route of transmission is controversial, some papers proved the presence of live virus in fecal specimens and even a positive PCR in material collected from the surface of the toilet and sink used by infected patients, thereby corroborating this route of transmission[56].

Both upper and lower GI endoscopies should be considered as aerosol-generating procedures. Upper GI endoscopy can generate respiratory droplets by coughing or gagging induced mainly during endoscopic insertion and lower GI endoscopy by passing flatus or pathogen-containing stools[57]. Therefore, endoscopy can be considered a high-risk procedure for SARS-COV-2 transmission for both patients and healthcare professionals, being reasonable to ration the endoscopic resources.

Indications of endoscopy during COVID-19 pandemic

To minimize the exposure and risk of infection, different Societies of Gastroenterology and Endoscopy worldwide (American Gastroenterological Association[58], BSG[13], European Society of Gastrointestinal Endoscopy and European Society of Gastroenterology and Endoscopy Nurses and Associates[59], Asian Pacific Society for Digestive Endoscopy[60], and Brazilian Society of Digestive Endoscopy[61]) agreed to postpone all the endoscopic procedures during the pandemic period, except for the emergency ones and on a case-by-case basis, some urgent ones. The emergency and urgent endoscopic procedures can be resumed and divided into the following three categories: Emergent, urgent, and elective (Table 6)[62]. The restriction in the indications for GI endoscopy aimed not only to reduce the risk of patients and healthcare professional infection but also to save personal protective equipment (PPE) and other medical supplies[57].

Endoscopy, especially ileocolonoscopy, plays a fundamental role in the diagnosis and management of IBD, ruling out some other diagnoses and providing important information about the extension and activity of the disease, response to treatment, and even a therapeutic approach to stenosis and other complications. During the COVID-19 pandemic, these indications for patients with IBD were reviewed and based on expert opinions, the IOIBD[63] and French Society of Digestive Endoscopy (SFED) recommendations[64], the advice was again to postpone all endoscopic procedures that were not urgent and extremely necessary. However, sometimes, this emergent/urgent indication for endoscopy in patients with IBD is slightly unclear. Thus, next we are going to discuss some possible scenarios[57]:

Confirm IBD diagnosis: In highly suspected cases with moderate-to-severe symptoms and grounded by positive biomarkers and cross-sectional imaging findings (bowel ultrasonography or magnetic resonance enterography) of IBD, lower GI endoscopy (proctosigmoidoscopy or colonoscopy) with biopsies is still indicated[57]. Depending on the clinical situation and the presence of rectal symptoms, proctosigmoidoscopy might be preferable to full colonoscopy, as the former is faster and can be done without sedation (no need for companion) or oral bowel preparation[63]. Cases with mild symptoms can have their endoscopy postponed[57,63,64]. If an isolated small bowel disease is the hypothesis, after negative cross-sectional imaging and in the absence of obstructive symptoms, videocapsule endoscopy should be preferred to enteroscopy for its lower risk[64].

Monitoring IBD treatment: Disease activity monitoring, if possible as mentioned before, should be made by checking patient report outcomes (PROs) and noninvasive tests such as FC, C-reactive protein (CRP), or even cross-sectional imaging[64,65].

Acute severe UC: This is an emergency condition with a high morbimortality. A patient who fulfills the criteria of a stool frequency (≥ 6 per day), with bloody stools, heart rate above 90 bpm, temperature exceeding 37.8 °C, hemoglobin levels below 105

Table 6 Category of endoscopic procedures[13,62]

Emergent endoscopy	Urgent endoscopy	Elective endoscopy
Ascending/acute cholangitis; Foreign body retrieval; GI obstruction; Life-threatening GI bleeding	Cancer staging; Stable GI bleeding; Tumor biopsy; Palliative procedures (stenting, neurolysis); Planned EMR/ESD for complex/high-risk lesions	Biliary stent removal; Clinical trials; Colorectal cancer screening; Percutaneous endoscopic gastrostomy; Post-polypectomy surveillance; Surveillance/follow-up endoscopy (excluding high-risk neoplasia)

GI: Gastrointestinal; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

g/L, and high CRP levels (> 30 mg/L) needs to be hospitalized and undergo investigation to rule out infections other than IBD activity, especially COVID-19, *C. difficile*, and CMV[66,67]. Symptoms such as fever, cough, dysosmia, dysgeusia, and fatigue need to be questioned, and a PCR for SARS-COV-2 asked. If negative, analysis of stool samples should be performed looking for *C. difficile* and parasitological infection and, in this setting, it is advised to perform flexible proctosigmoidoscopy with biopsies to exclude CMV infection[57,63,64].

Postoperative recurrence assessment: Endoscopy plays an important role in the postoperative management of both CD and UC patients. In CD, mainly in cases of ileocecal resection, since endoscopic inflammation precedes biological and clinical activity, ileocolonoscopic findings allow us to tailor therapy. In UC patients, postoperative endoscopy is mainly indicated for pouchitis and surveillance of this segment for dysplasia. However, when we consider the risks and benefits of the procedure during this pandemic period, endoscopy to check postoperative recurrence and dysplasia could be delayed, and for inflammation, patients should be followed noninvasively[63,64,68].

Surveillance colonoscopies: It is known that patients with IBD have twice more risk of CRC than the general population, justifying the importance of its screening and surveillance. Based on ECCO guidelines, surveillance colonoscopy is indicated for all patients with UC, except if the disease is restricted to the rectum eight years after the beginning of the symptoms. Patients with colonic CD with more than 1/3 of the colon affected should follow the same protocol. If primary sclerosing cholangitis (PSC) is present, surveillance is recommended to start immediately when the diagnosis is confirmed and continues yearly. The interval between colonoscopies will depend on the risk factors and the results obtained in the index exam[66]. However, for all the risks listed above, the recommendation is to postpone the colonoscopy in patients without alarming signs. With the extension of the pandemic period, this recommendation needs to be reviewed, and probably the patients will be stratified by risk factors for CRC, as with PSC or previous dysplastic lesions, and will be rescheduled as priorities for endoscopic examination[57,64].

Partial GI obstruction: Patients with IBD are at higher risk of some complications, such as benign or malignant strictures. In cases of a new colonic stricture, a colonoscopy is indicated to exclude malignancy, and if this hypothesis is confirmed, a stent or balloon dilatation might be needed if surgery could not be performed. In CD patients with a known short stricture (< 4 cm) with recurrent obstructive symptoms (nausea, vomiting, weight loss, and abdominal pain), endoscopic dilatation is a therapeutic option to avoid future admission to the emergency room, overloaded during COVID-19 pandemic[57,68].

Upper GI endoscopy: The indications for upper GI endoscopy in patients with IBD during this pandemic period are restricted to acute GI bleeding or dilatation of upper GI strictures[64].

Worsening cholangitis and jaundice in patients with IBD and PSC with a dominant bile duct stricture: Acute cholangitis in a patient with PSC is an emergency, and if there is a dominant bile duct stricture detected on a magnetic resonance cholangiography, an urgent endoscopic retrograde cholangiopancreatography (ERCP) will access the stricture to exclude cholangiocarcinoma and may decompress the bile duct[57].

Endoscopy in industry-sponsored clinical trials: Most of the recruitment of new patients and screening visits for clinical trials have been discontinued during this

pandemic period, but the status of monitoring colonoscopies for participants already recruited should be discussed with trial sponsors and research ethics committees. A case-by-case discussion might be necessary, as for some patients, the investigational product is the only therapeutic option to avoid surgery and/or corticosteroids. Trial visits should occur virtually whenever possible[57,64].

In summary, endoscopy in patients with IBD during the COVID-19 pandemic should be restricted for the indications listed in Table 7.

Safety measures for protection against COVID-19 infection

Aiming to mitigate the risk of the spread of infection from possible COVID-19 patients, reduce the risk of cross-infection, and preserve resources and PPE, some measures are recommended by different GI endoscopy societies[62,69]. The safety recommendations can be targeted to the unit structure, patient safety, healthcare professional safety, and equipment/endoscopy room care.

Unit structure[57,70]**:** Limit the number of patients scheduled; Consider at least a one-hour interval between exams; Select the indications of endoscopy and postpone the others; Remote pre-exam evaluation with a questionnaire about COVID-19 symptoms and contact; Inform the need to wear a mask; Apply social distancing rules in the waiting room; Avoid physical contact; Limit the waiting room time and number of people; Reassure that just exams with sedation or anesthesia require a companion; Relatives and caregivers are forbidden from entering the hospital or endoscopy unit unless required; Medical and nursing students are restricted in the endoscopy units during pandemic crises; Allow only essential staff with proper PPE inside the endoscopic unit; Keep doors closed; Provide information about hand hygiene; Follow-up call one week after endoscopy: As symptoms of COVID-19 can occur after infection, patients undergoing endoscopy could develop symptoms after the procedure if they have contracted the SARS-CoV-2 infection at the community level just before endoscopy. It is a way to verify whether the protective measures at the unit are working[64].

Patient safety[64]**:** Check again for COVID-19 symptoms (fever > 37.5 °C; cough, dysgeusia, dysosmia, and dyspnea) or contact at admission; Access body temperature; Provide the patient alcoholic solution to clean hands; Before entering the endoscopy room, the patient is asked to dress a cotton gown, a hairnet, and a surgical mask; Nasal swabs are not a routine recommendation, as they are not generally available or validated.

Healthcare professionals' safety[64,70,71]**:** AGA and the SFED recommend the use of filtering face piece (FFP) respiratory class 2 or 3 (FFP2 or FFP3) instead of surgical masks to protect Healthcare professionals (HCPs) during upper and lower GI procedures, regardless of the COVID-19 status of the patient. The suggestion for mask changing depends on regional recommendations; Limit the number of endoscopy personnel and operational endoscopy rooms; Endoscopy work teams should comprise a consultant endoscopist, a highly trained endoscopy nurse, and, if possible, a consultant anesthesiologist; HCPs should be checked for COVID-19 symptoms and having their body temperature accessed; HCPs should wear FFP2 mask during the entire time at endoscopy unit as SARS-CoV-2 remained viable in aerosols for at least 3 h; HCPs should be trained in dressing and undressing the PPE, and hand washing is mandatory before both phases; HCPs must remove contact lenses and dress: Hairnet, a long water-resistant gown with back closure, an FFP2 mask, goggles for eye protection, and over-sleeve gloves over the gown. Over the other layers, a single-use gown and another pair of gloves; HCPs should change the disposable gown and the second gloves in each procedure; Hand washing is mandatory before and after every interaction with patient and other HCPs; Conscious sedation remains the most feasible option and can be provided and managed even if the patient is wearing a mask.

Equipment/endoscopy room[62,64,72]**:** Negative-pressure room to prevent generated aerosols from diffusing outside the room is recommended mainly in COVID-19 confirmed or highly suspected cases; Disinfection and decontamination by neutral detergent and virucidal disinfectant using 0.05% sodium hypochlorite or 70% ethanol on surfaces and devices are effective in clearing the virus; All used endoscopes must undergo standardized reprocessing and disinfection; All used accessories must be disposed of; Beds must be cleaned with specific disinfection products and bed sheets changed for each patient.

Table 7 Indications for gastrointestinal endoscopy in patients with inflammatory bowel disease during the coronavirus disease 2019 pandemic[57,63,64]

Recommended	Considered case-by-case	Postpone
Confirm IBD diagnosis in patients with moderate to severe activity; Acute severe ulcerative colitis; Partial GI obstruction; Life-threatening GI bleeding; Worsening cholangitis and jaundice in patients with IBD and PSC with a dominant bile duct stricture	Surveillance colonoscopies of high-risk patients; Specific clinical trials	Confirm IBD diagnosis in patients with mild symptoms; Monitoring IBD treatment; Postoperative recurrence assessment; Surveillance colonoscopies of low-risk patients; Clinical trials

GI: Gastrointestinal; IBD: Inflammatory bowel disease; PSC: Primary sclerosing cholangitis.

Endoscopy post-pandemic phase

When the COVID-19 pandemic ends, endoscopy units must face a dammed demand list with the impossibility of returning to a regular agenda, as the interval between the exams will need to remain longer to prevent new outbreaks. A stratification of priorities will be necessary[73]. Some algorithms based on available point-of-care tests considering epidemiological regional data and an accurate clinical risk assessment are being proposed to stratify the patients[74]. Whatever method is used to prioritize endoscopy, it is important to maintain close contact with patients with IBD by phone or e-mail to monitor for specific symptoms. Planning carefully the post-pandemic phase is primordial, and a case-by-case analysis with reassessments of patients' conditions by both clinician and endoscopist will be demanded, and telemedicine might be a useful tool to help this conversation[73].

SURGICAL INTERVENTIONS IN PATIENTS WITH IBD AND COVID-19

Despite significant advances in the medical management of IBD in recent years, many patients will require surgery. The most common indications for CD surgery include stenosis, fistulae, and abscesses[75]. In UC, the most common indications are acute severe colitis refractory to medical therapy and chronic refractory UC. Other indications of surgery in UC are dysplasia and CRC[76]. Many of these situations are elective or semi-elective surgeries that can be postponed for a few days or weeks in some patients with confirmed COVID-19. However, emergencies, such as perforation, acute severe colitis, and uncontrolled hemorrhage, may occur, and the surgery in these cases cannot be postponed and must be treated promptly. At the peak of the pandemic, one of the collateral effects was that elective surgeries were canceled or temporarily suspended[77]. Elective surgeries in IBD cannot be delayed too long when they are strictly indicated, mainly due to increased morbidity given the patient's weakened condition (*e.g.*, steroids and malnutrition)[78]. It is not recommended to delay surgical treatment for these patients with IBD, regardless of their COVID-19 status.

Conducting emergency surgeries during a pandemic such as COVID-19 is challenging for IBD surgeons and the entire hospital infrastructure[79,80]. The information available on COVID-19 and the possibility of contamination through aerosols and droplets lead to the need for modifications to perform surgery with success, reducing the risk of contaminating hospital facilities and protecting health teams and patients[79]. It is pivotal to protect all surgical teams (*e.g.*, masks, glasses, face shields, and surgical caps) to avoid contagion with COVID-19 when they perform surgery in patients with IBD with suspected or confirmed COVID-19 and protect the patient to prevent him from contracting COVID-19.

There is a concern among surgeons with minimally invasive techniques (*e.g.*, laparoscopy, and robotic surgery) due to a possible risk of viral transmission of the COVID-19 with the creation of pneumoperitoneum[81]. However, minimally invasive surgery (MIS), including laparoscopic surgery, is feasible and safe in IBD and has many advantages, such as reduced length of hospital stay, less pain, reduced trauma, less impact on respiratory movements, reduction of morbidity, and faster postoperative recovery[82].

There is little evidence of viral transmission through laparoscopic or open approaches. As shown by Somashekhar *et al*[79], the risk of infection by COVID-19 for the healthcare team during MIS (laparoscopic or robotic) is considered low. Therefore, in IBD, we should not postpone surgery, even if considered "elective," due to the COVID-19 pandemic. Thus, the care that must be followed by the surgical, nursing,

and anesthesia teams must be standardized at the referred hospital and replicated to other health services referenced in the surgical treatment of IBD.

Precautions to avoid contamination of the surgical team are described in several studies published during the pandemic and include care with airway management during the anesthetic procedure and specific care during laparoscopy[79,81,83-85]. There seems to be a consensus in the literature that intubation and extubation are high-risk healthcare professionals' procedures and that the maximum amount of PPE is needed. However, there is little evidence of the real risk of contamination by healthcare professionals during laparoscopy itself, nor of operating room (OR) pressure, surgical smoke, tissue extraction, or CO_2 deflation[83]. If surgery is considered necessary, the surgeon must minimize the risk of exposure to the virus, involving a minimum number of health professionals and shortening the occupation of the ORs. As said, there are no absolute contraindications to MIS; however, appropriate PPE for the OR team and smoke evacuation/filtration systems are unanimously recommended[85].

If there is a lack of safety measures to allow safe laparoscopy, open surgery should be considered[84]. Nevertheless, previous studies have shown that bacterial and viral aerosols can be detected in both open and laparoscopic surgical operations[86]; then, a surgical aspirator/smoke evacuation device should also be used in open procedures. Electrical instruments and energy devices should be used at the lowest energy level to preclude excessive aerosol and smoke production[87].

There are some tips and tricks to make MIS safer during the COVID-19 pandemic, such as avoid creating a leak for smoke evacuation, use a closed suction system; use leak-free trocars such as balloon trocars, aspirate the entire pneumoperitoneum before retrieving the surgical specimen at the end of a procedure before removing the trocars, or before conversion to open surgery[84]. Hospitals must prepare specific internal protocols and arrange adequate training of the involved personnel[88].

If possible, postpone elective surgery and consider screening every surgical patient for COVID-19 either by RT-PCR swab or CT scan of the thorax[89]. In emergent (< 24 h) surgeries, such as perianal abscess, bowel perforation, toxic megacolon, the surgery must be done without any delay, and all patients must be treated as if they were COVID-19-positive. All surgical teams must strictly follow all rules related to infection against COVID-19. The same rules apply to patients under urgent (< 72 h) situations, such as bowel obstruction (without ischemia). Elective (up to 4 wk to 3 mo) surgeries must have an individualized approach. Seton replacements, "J" pouch confection, can be postponed up to three months. However, colectomy in patients with chronic refractory UC or dysplasia and CRC in UC should be referred to surgery, preferably before this period, so that there will be no worsening of the primary clinical condition.

It is important to emphasize that all known or suspected COVID-19-positive patients requiring surgical intervention must be treated as positive until proven otherwise to minimize infection spread[88]. Besides, whenever possible, dedicate specific OR to patients with COVID-19[83]. Create negative pressure ORs because they are considered ideal; yet, most ORs work at positive pressure, and their use is therefore permitted. An air exchange rate of ≥ 25 cycles/h is considered sufficient to effectively reduce the OR's viral load. Only essential staff members should be admitted into the OR, limiting in/out traffic, and doors should be kept closed. Use level III PPE during intubation and extubation. Use proper filters and closed systems for CO_2 desufflation and do not perform transanal surgery[83].

There are some critical considerations for transanal surgery during the COVID-19 pandemic[90]. Several lines of evidence have supported the possible fecal-oral transmission of the COVID-19[91,92]. It is important to emphasize that positive pressure transanal surgery, such as transanal MIS and transanal endoscopic microsurgery, are aerosol-generating procedures. Hence, it is appropriate to perform routine preoperative fecal testing for SARS-CoV-2, in addition to nasopharyngeal screening, in patients undergoing transanal surgery under positive pressure. For patients with confirmed SARS-CoV-2 infection, conventional open and robotic approaches may be safer alternatives when surgery cannot be postponed.

MENTAL HEALTH AND EDUCATIONAL INITIATIVES

It has been recognized that the pandemic will greatly increase the incidence of severe psychological problems, such as mood disorders, anxiety disorders, or posttraumatic stress disorder (PTSD), as a consequence of isolation, human losses, and financial hardships[93]. For patients with IBD, psychological distress is already a common feature, with studies suggesting that active disease is strongly related to comorbid

anxiety and depression[94]. A recent cross-sectional survey exploring the emotional state, perception, and concerns of Saudi patients with IBD during the pandemic found a diagnosis of anxiety in 48.4% of surveyed patients. In this context, patients with IBD require greater attention, and clinical or cognitive behavioral treatment should be offered to all patients who exhibit psychological distress.

Provided that patients with IBD are experiencing substantial changes to the routine management of their conditions during the pandemic, it seems highly critical to assess patients' perceptions and viewpoints. In the earlier phase of the pandemic, the Federation of Crohn's and Ulcerative Colitis Associations (EFCCA) conducted an anonymous online survey to investigate the concerns, fears, and behaviors of patients with IBD. Based on responses from 3815 participants from 51 countries worldwide, it was shown that about half of respondents reported receiving COVID-19 information or specific recommendations from doctors to prevent infection. However, most patients (60%) would have preferred to receive more recommendations regarding COVID-19 from their physicians[95]. These results emphasized the urgent need for better communication between physicians and patients and for clear and specific recommendations for people with chronic conditions in these unprecedented times. In this context, educational initiatives involving patient associations might play a crucial role in allowing dissemination of the correct messages regarding patient management. Also, patient compliance with healthcare providers' guidelines could be achievable by enhanced collaboration, and long-term, trusted partnerships could also be established.

VACCINATION

The recent availability of vaccines to prevent SARS-CoV-2 infection has raised concerns regarding the safety and efficacy of immunization in patients with IBD. Until now, there has been international agreement among the main international IBD expert groups that the risks of SARS-CoV-2 vaccination in patients with IBD are anticipated to be very low, and it is strongly recommended that patients with IBD should be given a COVID-19 vaccine once it is widely available[2,96-98]. All coronavirus vaccines, which are licensed or in the final stages of testing, are considered suitable for patients on biologics, steroids, and immunosuppressants, as they are not live vaccines. These include the mRNA (Pfizer, Moderna), the non-replicating adenovirus vector (Oxford), and the inactivated SARS-CoV-2 (Coronavac) vaccines. Analogous to other vaccines used for many years, such as influenza and pneumonia vaccines, there is no indication of worsening IBD symptoms or flares following vaccination, and immunization appears improbable to affect IBD activity[99]. SARS-CoV-2 vaccines have also been tested in tens of thousands of patients with safety profiles analogous to other vaccines commonly used in patients with IBD, such as the flu vaccine.

For patients under immunosuppressive treatments, it is anticipated that the vaccine may be slightly less effective, as other studies have shown that immunosuppressant medications may induce some reduction in antibody formation and lower immune response with other common vaccines. For instance, it has been demonstrated that the serologic conversion rate to influenza vaccine is lower in immunosuppressed patients with IBD[99,100] and that the immune response to pneumococcal polysaccharide vaccination is reduced in patients with CD by combining TNF-blockers and immunomodulators[101]. Conversely, treatment with newer biologics, such as ustekinumab or vedolizumab, does not seem to decrease responses to flu vaccine[102,103]. We still do not know which IBD treatments, if any, will reduce the effectiveness of the coronavirus vaccine; however, it is important to emphasize that even if the COVID-19 vaccine works slightly less well in immunosuppressed patients, it will still offer greater protection than not having the vaccine.

It is not advisable that patients should stop their treatments to get vaccinated, as it can induce an exacerbation, putting patients at a greater risk of serious complications of COVID-19. Also, patients should avoid receiving their vaccine on the same day of an infusion/subcutaneous dose of biologic, just in the exceptional circumstance that the patient develops a reaction or adverse effect. It would be important to identify which one (vaccine or biologic) has caused it.

CONCLUSION

In this review, we presented a guide for the practicing clinician for managing IBD during the COVID-19 pandemic. We also reviewed the risk of infection during

endoscopy, highlighting the restricted conditions where we still should indicate GI endoscopy in patients with IBD and the recommendations of the most important endoscopy societies for a safer procedure. All known or suspected COVID-19-positive patients requiring surgical intervention must be treated as positive until proven otherwise to minimize infection spread. It is not advisable that patients should stop their treatments to get vaccinated, as it can induce an exacerbation, putting patients at a greater risk of serious complications of COVID-19. In this time of an unprecedented pandemic, where knowledge about COVID-19 rapidly expands, we suggest that clinicians caring for patients with IBD should periodically check for updates in the SECURE-IBD registry and Gastroenterology Societies statements and guidelines to update knowledge about SARS-CoV-2 and COVID-19 in patients with IBD for better information and follow the approach to manage medications in IBD in this challenging context.

REFERENCES

1 **Dong E**, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**: 533-534 [PMID: 32087114 DOI: 10.1016/S1473-3099(20)30120-1]

2 **Siegel CA**, Melmed GY, McGovern DP, Rai V, Krammer F, Rubin DT, Abreu MT, Dubinsky MC; International Organization for the Study of Inflammatory Bowel Disease (IOIBD). SARS-CoV-2 vaccination for patients with inflammatory bowel diseases: recommendations from an international consensus meeting. *Gut* 2021; **70**: 635-640 [PMID: 33472895 DOI: 10.1136/gutjnl-2020-324000]

3 **Ng SC**, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, Panaccione R, Ghosh S, Wu JCY, Chan FKL, Sung JJY, Kaplan GG. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2017; **390**: 2769-2778 [PMID: 29050646 DOI: 10.1016/S0140-6736(17)32448-0]

4 **Kirchgesner J**, Lemaitre M, Carrat F, Zureik M, Carbonnel F, Dray-Spira R. Risk of Serious and Opportunistic Infections Associated With Treatment of Inflammatory Bowel Diseases. *Gastroenterology* 2018; **155**: 337-346. e10 [PMID: 29655835 DOI: 10.1053/j.gastro.2018.04.012]

5 **Wisniewski A**, Kirchgesner J, Seksik P, Landman C, Bourrier A, Nion-Larmurier I, Marteau P, Cosnes J, Sokol H, Beaugerie L; the Saint-Antoine IBD network. Increased incidence of systemic serious viral infections in patients with inflammatory bowel disease associates with active disease and use of thiopurines. *United European Gastroenterol J* 2020; **8**: 303-313 [PMID: 32529821 DOI: 10.1177/2050640619889763]

6 **Ma C**, Lee JK, Mitra AR, Teriaky A, Choudhary D, Nguyen TM, Vande Casteele N, Khanna R, Panaccione R, Feagan BG, Jairath V. Systematic review with meta-analysis: efficacy and safety of oral Janus kinase inhibitors for inflammatory bowel disease. *Aliment Pharmacol Ther* 2019; **50**: 5-23 [PMID: 31119766 DOI: 10.1111/apt.15297]

7 **Aziz M**, Fatima R, Haghbin H, Lee-Smith W, Nawras A. The Incidence and Outcomes of COVID-19 in IBD Patients: A Rapid Review and Meta-analysis. *Inflamm Bowel Dis* 2020; **26**: e132-e133 [PMID: 32619003 DOI: 10.1093/ibd/izaa170]

8 **Brenner EJ**, Ungaro RC, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Ruemmele FM, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Corticosteroids, But Not TNF Antagonists, Are Associated With Adverse COVID-19 Outcomes in Patients With Inflammatory Bowel Diseases: Results From an International Registry. *Gastroenterology* 2020; **159**: 481-491. e3 [PMID: 32425234 DOI: 10.1053/j.gastro.2020.05.032]

9 **Scaldaferri F**, Pugliese D, Privitera G, Onali S, Lopetuso LR, Rizzatti G, Settanni CR, Pizzoferrato M, Schiavoni E, Turchini L, Amatucci V, Napolitano D, Bernabei T, Mora V, Laterza L, Papa A, Guidi L, Rapaccini GL, Gasbarrini A, Armuzzi A. Impact of COVID-19 pandemic on the daily management of biotechnological therapy in inflammatory bowel disease patients: Reorganisational response in a high-volume Italian inflammatory bowel disease centre. *United European Gastroenterol J* 2020; **8**: 775-781 [PMID: 32438878 DOI: 10.1177/2050640620929133]

10 **Queiroz NSF**, Barros LL, Azevedo MFC, Oba J, Sobrado CW, Carlos AS, Milani LR, Sipahi AM, Damião AOMC. Management of inflammatory bowel disease patients in the COVID-19 pandemic era: a Brazilian tertiary referral center guidance. *Clinics (Sao Paulo)* 2020; **75**: e1909 [PMID: 32321117 DOI: 10.6061/clinics/2020/e1909]

11 **Feitosa MR**, Parra RS, de Camargo HP, Ferreira SDC, Troncon LEA, da Rocha JJR, Féres O. COVID-19 quarantine measures are associated with negative social impacts and compromised follow-up care in patients with inflammatory bowel disease in Brazil. *Ann Gastroenterol* 2021; **34**: 39-45 [PMID: 33414620 DOI: 10.20524/aog.2020.0558]

12 **Rubin DT**, Abreu MT, Rai V, Siegel CA; International Organization for the Study of Inflammatory Bowel Disease. Management of Patients With Crohn's Disease and Ulcerative Colitis During the Coronavirus Disease-2019 Pandemic: Results of an International Meeting. *Gastroenterology* 2020; **159**: 6-13. e6 [PMID: 32272113 DOI: 10.1053/j.gastro.2020.04.002]

13 **Kennedy NA**, Jones GR, Lamb CA, Appleby R, Arnott I, Beattie RM, Bloom S, Brooks AJ, Cooney R, Dart RJ, Edwards C, Fraser A, Gaya DR, Ghosh S, Greveson K, Hansen R, Hart A, Hawthorne

AB, Hayee B, Limdi JK, Murray CD, Parkes GC, Parkes M, Patel K, Pollok RC, Powell N, Probert CS, Raine T, Sebastian S, Selinger C, Smith PJ, Stansfield C, Younge L, Lindsay JO, Irving PM, Lees CW. British Society of Gastroenterology guidance for management of inflammatory bowel disease during the COVID-19 pandemic. *Gut* 2020; **69**: 984-990 [PMID: 32303607 DOI: 10.1136/gutjnl-2020-321244]

14 **Mao R**, Liang J, Shen J, Ghosh S, Zhu LR, Yang H, Wu KC, Chen MH; Chinese Society of IBD, Chinese Elite IBD Union; Chinese IBD Quality Care Evaluation Center Committee. Implications of COVID-19 for patients with pre-existing digestive diseases. *Lancet Gastroenterol Hepatol* 2020; **5**: 425-427 [PMID: 32171057 DOI: 10.1016/S2468-1253(20)30076-5]

15 **Norsa L**, Indriolo A, Sansotta N, Cosimo P, Greco S, D'Antiga L. Uneventful Course in Patients With Inflammatory Bowel Disease During the Severe Acute Respiratory Syndrome Coronavirus 2 Outbreak in Northern Italy. *Gastroenterology* 2020; **159**: 371-372 [PMID: 32247695 DOI: 10.1053/j.gastro.2020.03.062]

16 **Taxonera C**, Alba C, Olivares D. What is the incidence of COVID-19 in patients with IBD in western countries? *Gastroenterology* 2020 [PMID: 32687925 DOI: 10.1053/j.gastro.2020.05.099]

17 **Allocca M**, Fiorino G, Zallot C, Furfaro F, Gilardi D, Radice S, Danese S, Peyrin-Biroulet L. Incidence and Patterns of COVID-19 Among Inflammatory Bowel Disease Patients From the Nancy and Milan Cohorts. *Clin Gastroenterol Hepatol* 2020; **18**: 2134-2135 [PMID: 32360811 DOI: 10.1016/j.cgh.2020.04.071]

18 **Gutin LS**, Lam AY, Velayos FS, Santos SA. Going Viral: Management of IBD in the Era of the COVID-19 Pandemic. *Dig Dis Sci* 2020; **65**: 1571-1575 [PMID: 32363528 DOI: 10.1007/s10620-020-06299-y]

19 **Allez M**, Fleshner P, Gearry R, Lakatos PL, Rubin DT. Care of the Patient With IBD Requiring Hospitalisation During the COVID-19 Pandemic. *J Crohns Colitis* 2020; **14**: S774-S779 [PMID: 32722757 DOI: 10.1093/ecco-jcc/jjaa150]

20 **Magro F**, Rahier JF, Abreu C, MacMahon E, Hart A, van der Woude CJ, Gordon H, Adamina M, Viget N, Vavricka S, Kucharzik T, Leone S, Siegmund B, Danese S, Peyrin-Biroulet L. Inflammatory Bowel Disease Management During the COVID-19 Outbreak: The Ten Do's and Don'ts from the ECCO-COVID Taskforce. *J Crohns Colitis* 2020; **14**: S798-S806 [PMID: 32722754 DOI: 10.1093/ecco-jcc/jjaa160]

21 **Bernstein CN**, Ng SC, Banerjee R, Steinwurz F, Shen B, Carbonnel F, Hamid S, Sood A, Yamamoto-Furusho JK, Griffiths A, Benchimol EI, Travis S, Lopes S, Rubin DT, Kaplan GG, Armstrong D, Gearry R; IBD-Emerging Nations Consortium and the WGO IBD Task Force on COVID-19 . Worldwide Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: An International Survey. *Inflamm Bowel Dis* 2020 [PMID: 32793973 DOI: 10.1093/ibd/izaa202]

22 **Ungaro RC**, Brenner EJ, Gearry RB, Kaplan GG, Kissous-Hunt M, Lewis JD, Ng SC, Rahier JF, Reinisch W, Steinwurz F, Underwood FE, Zhang X, Colombel JF, Kappelman MD. Effect of IBD medications on COVID-19 outcomes: results from an international registry. *Gut* 2021; **70**: 725-732 [PMID: 33082265 DOI: 10.1136/gutjnl-2020-322539]

23 **Bezzio C**, Manes G, Bini F, Pellegrini L, Saibeni S. Infliximab for severe ulcerative colitis and subsequent SARS-CoV-2 pneumonia: a stone for two birds. *Gut* 2021; **70**: 623-624 [PMID: 32554621 DOI: 10.1136/gutjnl-2020-321760]

24 **Dolinger MT**, Person H, Smith R, Jarchin L, Pittman N, Dubinsky MC, Lai J. Pediatric Crohn Disease and Multisystem Inflammatory Syndrome in Children (MIS-C) and COVID-19 Treated With Infliximab. *J Pediatr Gastroenterol Nutr* 2020; **71**: 153-155 [PMID: 32452979 DOI: 10.1097/MPG.0000000000002809]

25 **Sebastian S**, Gonzalez HA, Peyrin-Biroulet L. Safety of Drugs During Previous and Current Coronavirus Pandemics: Lessons for Inflammatory Bowel Disease. *J Crohns Colitis* 2020; **14**: 1632-1643 [PMID: 32520312 DOI: 10.1093/ecco-jcc/jjaa120]

26 **Rubin DT**, Feuerstein JD, Wang AY, Cohen RD. AGA Clinical Practice Update on Management of Inflammatory Bowel Disease During the COVID-19 Pandemic: Expert Commentary. *Gastroenterology* 2020; **159**: 350-357 [PMID: 32283100 DOI: 10.1053/j.gastro.2020.04.012]

27 **Lichtenstein GR**, Rubin DT. Coronavirus and Patients With Inflammatory Bowel Disease: Management Strategies for the Practicing Clinician. *Am J Gastroenterol* 2020; **115**: 1566-1569 [PMID: 32833732 DOI: 10.14309/ajg.0000000000000817]

28 **Yang W**, Cao Q, Qin L, Wang X, Cheng Z, Pan A, Dai J, Sun Q, Zhao F, Qu J, Yan F. Clinical characteristics and imaging manifestations of the 2019 novel coronavirus disease (COVID-19):A multi-center study in Wenzhou city, Zhejiang, China. *J Infect* 2020; **80**: 388-393 [PMID: 32112884 DOI: 10.1016/j.jinf.2020.02.016]

29 **Cha MH**, Regueiro M, Sandhu DS. Gastrointestinal and hepatic manifestations of COVID-19: A comprehensive review. *World J Gastroenterol* 2020; **26**: 2323-2332 [PMID: 32476796 DOI: 10.3748/wjg.v26.i19.2323]

30 **Han C**, Duan C, Zhang S, Spiegel B, Shi H, Wang W, Zhang L, Lin R, Liu J, Ding Z, Hou X. Digestive Symptoms in COVID-19 Patients With Mild Disease Severity: Clinical Presentation, Stool Viral RNA Testing, and Outcomes. *Am J Gastroenterol* 2020; **115**: 916-923 [PMID: 32301761 DOI: 10.14309/ajg.0000000000000664]

31 **Effenberger M**, Grabherr F, Mayr L, Schwaerzler J, Nairz M, Seifert M, Hilbe R, Seiwald S, Scholl-Buergi S, Fritsche G, Bellmann-Weiler R, Weiss G, Müller T, Adolph TE, Tilg H. Faecal

calprotectin indicates intestinal inflammation in COVID-19. *Gut* 2020; **69**: 1543-1544 [PMID: 32312790 DOI: 10.1136/gutjnl-2020-321388]

32 **Al-Ani AH**, Prentice RE, Rentsch CA, Johnson D, Ardalan Z, Heerasing N, Garg M, Campbell S, Sasadeusz J, Macrae FA, Ng SC, Rubin DT, Christensen B. Review article: prevention, diagnosis and management of COVID-19 in the IBD patient. *Aliment Pharmacol Ther* 2020; **52**: 54-72 [PMID: 32348598 DOI: 10.1111/apt.15779]

33 **RECOVERY Collaborative Group**. , Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in Hospitalized Patients with Covid-19. *N Engl J Med* 2021; **384**: 693-704 [PMID: 32678530 DOI: 10.1056/NEJMoa2021436]

34 **Bhimraj A**, Morgan RL, Shumaker AH, Lavergne V, Baden L, Cheng VC, Edwards KM, Gandhi R, Muller WJ, O'Horo JC, Shoham S, Murad MH, Mustafa RA, Sultan S, Falck-Ytter Y. Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19. *Clin Infect Dis* 2020 [PMID: 32338708 DOI: 10.1093/cid/ciaa478]

35 **Kaur M**, Dalal RL, Shaffer S, Schwartz DA, Rubin DT. Inpatient Management of Inflammatory Bowel Disease-Related Complications. *Clin Gastroenterol Hepatol* 2020; **18**: 1346-1355 [PMID: 31927105 DOI: 10.1016/j.cgh.2019.12.040]

36 **Din S**, Kent A, Pollok RC, Meade S, Kennedy NA, Arnott I, Beattie RM, Chua F, Cooney R, Dart RJ, Galloway J, Gaya DR, Ghosh S, Griffiths M, Hancock L, Hansen R, Hart A, Lamb CA, Lees CW, Limdi JK, Lindsay JO, Patel K, Powell N, Murray CD, Probert C, Raine T, Selinger C, Sebastian S, Smith PJ, Tozer P, Ustianowski A, Younge L, Samaan MA, Irving PM. Adaptations to the British Society of Gastroenterology guidelines on the management of acute severe UC in the context of the COVID-19 pandemic: a RAND appropriateness panel. *Gut* 2020; **69**: 1769-1777 [PMID: 32513653 DOI: 10.1136/gutjnl-2020-321927]

37 **British Thoracic Society**. BTS guidance on venous thromboembolic disease in patients with COVID-19. [cited December 23, 2020]. In: British Thoracic Society [Internet]. Available from: https://www.brit-thoracic.org.uk/document-library/quality-improvement/covid-19/bts-guidance-on-venous-thromboembolic-disease-in-patients-with-covid-19/

38 **Siegel CA**, Christensen B, Kornbluth A, Rosh JR, Kappelman MD, Ungaro RC, Johnson DF, Chapman S, Wohl DA, Mantzaris GJ. Guidance for Restarting Inflammatory Bowel Disease Therapy in Patients Who Withheld Immunosuppressant Medications During COVID-19. *J Crohns Colitis* 2020; **14**: S769-S773 [PMID: 33085972 DOI: 10.1093/ecco-jcc/jjaa135]

39 **Grossberg LB**, Pellish RS, Cheifetz AS, Feuerstein JD. Review of Societal Recommendations Regarding Management of Patients With Inflammatory Bowel Disease During the SARS-CoV-2 Pandemic. *Inflamm Bowel Dis* 2020 [PMID: 32619010 DOI: 10.1093/ibd/izaa174]

40 **Hashash JG**, Jabak S, Francis FF, Regueiro M. Should We Be Screening for SARS-CoV-2 in IBD Patients Before Initiation of Biologic Therapy? *Inflamm Bowel Dis* 2021; **27**: 291-294 [PMID: 32619000 DOI: 10.1093/ibd/izaa173]

41 **El Ouali S**, Philpott J, Vargo J, Regueiro M. COVID-19 in patients with IBD and pancreaticobiliary disorders. *Cleve Clin J Med* 2020 [PMID: 32855178 DOI: 10.3949/ccjm.87a.ccc062]

42 **Allocca M**, Fiorino G, Furfaro F, Gilardi D, Radice S, D'Amico F, Zilli A, Danese S. Maintaining the Quality Standards of Care for Inflammatory Bowel Disease Patients During the COVID-19 Pandemic. *Clin Gastroenterol Hepatol* 2020; **18**: 1882-1883 [PMID: 32304737 DOI: 10.1016/j.cgh.2020.04.028]

43 **Fiorino G**, Allocca M, Furfaro F, Gilardi D, Zilli A, Radice S, Spinelli A, Danese S. Inflammatory Bowel Disease Care in the COVID-19 Pandemic Era: The Humanitas, Milan, Experience. *J Crohns Colitis* 2020; **14**: 1330-1333 [PMID: 32211765 DOI: 10.1093/ecco-jcc/jjaa058]

44 **Kornbluth A**, Kissous-Hunt M, George J, Legnani P. Management of Inflammatory Bowel Disease and COVID-19 in New York City 2020: The Epicenter of IBD in the First Epicenter of the Global Pandemic. *Inflamm Bowel Dis* 2020; **26**: 1779-1785 [PMID: 32879978 DOI: 10.1093/ibd/izaa212]

45 **Danese S**, Cecconi M, Spinelli A. Management of IBD during the COVID-19 outbreak: resetting clinical priorities. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 253-255 [PMID: 32214232 DOI: 10.1038/s41575-020-0294-8]

46 **Ungaro RC**, Sullivan T, Colombel JF, Patel G. What Should Gastroenterologists and Patients Know About COVID-19? *Clin Gastroenterol Hepatol* 2020; **18**: 1409-1411 [PMID: 32197957 DOI: 10.1016/j.cgh.2020.03.020]

47 **Martin Arranz E**, Suarez Ferrer C, García Ramírez L, Rueda García JL, Sánchez-Azofra M, Poza Cordón J, Noci J, Zabana Y, Barreiro-de Acosta M, Martín-Arranz MD. Management of COVID-19 Pandemic in Spanish Inflammatory Bowel Disease Units: Results From a National Survey. *Inflamm Bowel Dis* 2020; **26**: 1149-1154 [PMID: 32495826 DOI: 10.1093/ibd/izaa142]

48 **Mastronardi M**, Curlo M, Polignano M, Vena N, Rossi D, Giannelli G. Remote Monitoring Empowerment of Patients with IBDs during the SARS-CoV-2 Pandemic. *Healthcare (Basel)* 2020; **8** [PMID: 33019563 DOI: 10.3390/healthcare8040377]

49 **Ng SC**, Mak JWY, Hitz L, Chowers Y, Bernstein CN, Silverberg MS. COVID-19 Pandemic: Which IBD Patients Need to Be Scoped-Who Gets Scoped Now, Who Can Wait, and how to Resume to Normal. *J Crohns Colitis* 2020; **14**: S791-S797 [PMID: 33085973 DOI: 10.1093/ecco-jcc/jjaa128]

50 **Neumann H**, Emura F, Bokemeyer B, Guda N, Tajiri H, Matsumoto T, Rubin DT. Practical advice for management of inflammatory bowel diseases patients during the COVID-19 pandemic: World

Endoscopy Organization Statement. *Dig Endosc* 2020; **32**: 658-662 [PMID: 32369646 DOI: 10.1111/den.13712]

51 **Wei SC**, Tung CC, Weng MT, Wong JM. Experience of patients with inflammatory bowel disease in using a home fecal calprotectin test as an objective reported outcome for self-monitoring. *Intest Res* 2018; **16**: 546-553 [PMID: 30301339 DOI: 10.5217/ir.2018.00052]

52 **Gomollón F**, Dignass A, Annese V, Tilg H, Van Assche G, Lindsay JO, Peyrin-Biroulet L, Cullen GJ, Daperno M, Kucharzik T, Rieder F, Almer S, Armuzzi A, Harbord M, Langhorst J, Sans M, Chowers Y, Fiorino G, Juillerat P, Mantzaris GJ, Rizzello F, Vavricka S, Gionchetti P; ECCO. 3rd European Evidence-based Consensus on the Diagnosis and Management of Crohn's Disease 2016: Part 1: Diagnosis and Medical Management. *J Crohns Colitis* 2017; **11**: 3-25 [PMID: 27660341 DOI: 10.1093/ecco-jcc/jjw168]

53 **Fiorino G**, Lytras T, Younge L, Fidalgo C, Coenen S, Chaparro M, Allocca M, Arnott I, Bossuyt P, Burisch J, Campmans-Kuijpers M, de Ridder L, Dignass A, Drohan C, Feakins R, Gilardi D, Grosek J, Groß E, Hart A, Jäghult S, Katsanos K, Lönnfors S, Panis Y, Perovic M, Pierik M, Rimola J, Tulchinsky H, Gisbert JP. Quality of Care Standards in Inflammatory Bowel Diseases: a European Crohn's and Colitis Organisation [ECCO] Position Paper. *J Crohns Colitis* 2020; **14**: 1037-1048 [PMID: 32032423 DOI: 10.1093/ecco-jcc/jjaa023]

54 **Gao QY**, Chen YX, Fang JY. 2019 Novel coronavirus infection and gastrointestinal tract. *J Dig Dis* 2020; **21**: 125-126 [PMID: 32096611 DOI: 10.1111/1751-2980.12851]

55 **Montanari Vergallo G**, Ciallella C. Comment on the article by Zaami S, *et al* "Advancements in uterus transplant: new scenarios and future implications". Eur Rev Med Pharmacol Sci 2019; 23: 892-902. *Eur Rev Med Pharmacol Sci* 2019; **23**: 10178-10181 [PMID: 31841169]

56 **Ong SWX**, Tan YK, Chia PY, Lee TH, Ng OT, Wong MSY, Marimuthu K. Air, Surface Environmental, and Personal Protective Equipment Contamination by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) From a Symptomatic Patient. *JAMA* 2020; **323**: 1610-1612 [PMID: 32129805 DOI: 10.1001/jama.2020.3227]

57 **Iacucci M**, Cannatelli R, Labarile N, Mao R, Panaccione R, Danese S, Kochhar GS, Ghosh S, Shen B. Endoscopy in inflammatory bowel diseases during the COVID-19 pandemic and post-pandemic period. *Lancet Gastroenterol Hepatol* 2020; **5**: 598-606 [PMID: 32305075 DOI: 10.1016/S2468-1253(20)30119-9]

58 **Sultan S**, Lim JK, Altayar O, Davitkov P, Feuerstein JD, Siddique SM, Falck-Ytter Y, El-Serag HB; AGA Institute. AGA Rapid Recommendations for Gastrointestinal Procedures During the COVID-19 Pandemic. *Gastroenterology* 2020; **159**: 739-758. e4 [PMID: 32247018 DOI: 10.1053/j.gastro.2020.03.072]

59 **European Society of Gastrointestinal Endoscopy and European Society of Gastroenterology and Endoscopy Nurses and Associates**. ESGE and ESGENA Position Statement on Gastrointestinal Endoscopy and the COVID-19 Pandemic. [cited December 23, 2020]. In: ESGE and ESGENA [Internet]. Available from: https://www.esge.com/esge-and-esgena-position-statement-on-gastrointestinal-endoscopy-and-the-covid-19-pandemic/(2020)

60 **Chiu PWY**, Ng SC, Inoue H, Reddy DN, Ling Hu E, Cho JY, Ho LK, Hewett DG, Chiu HM, Rerknimitr R, Wang HP, Ho SH, Seo DW, Goh KL, Tajiri H, Kitano S, Chan FKL. Practice of endoscopy during COVID-19 pandemic: position statements of the Asian Pacific Society for Digestive Endoscopy (APSDE-COVID statements). *Gut* 2020; **69**: 991-996 [PMID: 32241897 DOI: 10.1136/gutjnl-2020-321185]

61 **Brazilian Society of Digestive Endoscopy**. Recomendações SOBED para Endoscopia Segura durante pandemia por Coronavírus. [cited December 23, 2020]. In: Brazilian Society of Digestive Endoscopy [Internet]. Available from: https://www.sobed.org.br/sobed-comunicacao/noticias-covid19

62 **Aguila EJT**, Cua IHY, Dumagpi JEL, Francisco CPD, Raymundo NTV, Sy-Janairo MLL, Cabral-Prodigalidad PAI, Lontok MAD. COVID-19 and its effects on the digestive system and endoscopy practice. *JGH Open* 2020; **4**: 324-331 [PMID: 32514432 DOI: 10.1002/jgh3.12358]

63 **International Organization for the Study of Inflammatory Bowel Diseases**. IOIBD Update on COVID19 for Patients with Crohn's Disease and Ulcerative Colitis. [cited December 23, 2020]. In: International Organization for the Study of Inflammatory Bowel Diseases [Internet]. Available from: https://www.ioibd.org/ioibd-update-on-covid19-for-patients-with-crohns-disease-and-ulcerative-colitis

64 **Furfaro F**, Vuitton L, Fiorino G, Koch S, Allocca M, Gilardi D, Zilli A, D'Amico F, Radice S, Chevaux JB, Schaefer M, Chaussade S, Danese S, Peyrin-Biroulet L. SFED recommendations for IBD endoscopy during COVID-19 pandemic: Italian and French experience. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 507-516 [PMID: 32528139 DOI: 10.1038/s41575-020-0319-3]

65 **Papa A**, Papa V, Lopetuso LR, Gasbarrini A, Tursi A. Covid-19 and the management of patients with inflammatory bowel disease: a practical decalogue for the post-pandemic phase. *Therap Adv Gastroenterol* 2020; **13**: 1756284820968747 [PMID: 33149764 DOI: 10.1177/1756284820968747]

66 **Magro F**, Gionchetti P, Eliakim R, Ardizzone S, Armuzzi A, Barreiro-de Acosta M, Burisch J, Gecse KB, Hart AL, Hindryckx P, Langner C, Limdi JK, Pellino G, Zagórowicz E, Raine T, Harbord M, Rieder F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017; **11**: 649-670 [PMID: 28158501 DOI:

10.1093/ecco-jcc/jjx008]
67 **Harbord M**, Eliakim R, Bettenworth D, Karmiris K, Katsanos K, Kopylov U, Kucharzik T, Molnár T, Raine T, Sebastian S, de Sousa HT, Dignass A, Carbonnel F; European Crohn's and Colitis Organisation [ECCO]. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 2: Current Management. *J Crohns Colitis* 2017; **11**: 769-784 [PMID: 28513805 DOI: 10.1093/ecco-jcc/jjx009]
68 **Perisetti A**, Gajendran M, Boregowda U, Bansal P, Goyal H. COVID-19 and gastrointestinal endoscopies: Current insights and emergent strategies. *Dig Endosc* 2020; **32**: 715-722 [PMID: 32281689 DOI: 10.1111/den.13693]
69 **European Centre for Disease Prevention and Control**. Disinfection of Environments in Healthcare and Non-healthcare Settings Potentially Contaminated with SARS-CoV2. [cited December 23, 2020]. In: ECDC Technical Report [Internet]. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/Environmental-persistence-of-SARS_CoV_2-virus-Options-for-cleaning2020-03-26_0.pdf
70 **Sinonquel P**, Roelandt P, Demedts I, Van Gerven L, Vandenbriele C, Wilmer A, Van Wijngaerden E, Bisschops R. COVID-19 and gastrointestinal endoscopy: What should be taken into account? *Dig Endosc* 2020; **32**: 723-731 [PMID: 32335962 DOI: 10.1111/den.13706]
71 **World Health Organization**. Rational use of personal protective equipment for coronavirus disease (COVID-19) and considerations during severe shortages. 2020 December 23 [cited December 23, 2020]. In: World Health Organization [Internet]. Available from: https://www.who.int/publications/i/item/rational-use-of-personal-protective-equipment-for-coronavirus-disease-(covid-19)-and-considerations-during-severe-shortages
72 **Kampf G**, Todt D, Pfaender S, Steinmann E. Persistence of coronaviruses on inanimate surfaces and their inactivation with biocidal agents. *J Hosp Infect* 2020; **104**: 246-251 [PMID: 32035997 DOI: 10.1016/j.jhin.2020.01.022]
73 **Manes G**, Repici A, Radaelli F, Bezzio C, Colombo M, Saibeni S. Planning phase two for endoscopic units in Northern Italy after the COVID-19 Lockdown: An exit strategy with a lot of critical issues and a few opportunities. *Dig Liver Dis* 2020; **52**: 823-828 [PMID: 32605868 DOI: 10.1016/j.dld.2020.05.042]
74 **Gupta S**, Shahidi N, Gilroy N, Rex DK, Burgess NG, Bourke MJ. Proposal for the return to routine endoscopy during the COVID-19 pandemic. *Gastrointest Endosc* 2020; **92**: 735-742 [PMID: 32360301 DOI: 10.1016/j.gie.2020.04.050]
75 **Toh JW**, Stewart P, Rickard MJ, Leong R, Wang N, Young CJ. Indications and surgical options for small bowel, large bowel and perianal Crohn's disease. *World J Gastroenterol* 2016; **22**: 8892-8904 [PMID: 27833380 DOI: 10.3748/wjg.v22.i40.8892]
76 **Yamamoto T**, Carvello M, Lightner AL, Spinelli A, Kotze PG. Up-to-date surgery for ulcerative colitis in the era of biologics. *Expert Opin Biol Ther* 2020; **20**: 391-398 [PMID: 31948294 DOI: 10.1080/14712598.2020.1718098]
77 **Søreide K**, Hallet J, Matthews JB, Schnitzbauer AA, Line PD, Lai PBS, Otero J, Callegaro D, Warner SG, Baxter NN, Teh CSC, Ng-Kamstra J, Meara JG, Hagander L, Lorenzon L. Immediate and long-term impact of the COVID-19 pandemic on delivery of surgical services. *Br J Surg* 2020; **107**: 1250-1261 [PMID: 32350857 DOI: 10.1002/bjs.11670]
78 **Seifarth C**, Kreis ME, Gröne J. Indications and Specific Surgical Techniques in Crohn's Disease. *Viszeralmedizin* 2015; **31**: 273-279 [PMID: 26557836 DOI: 10.1159/000438955]
79 **Somashekhar SP**, Acharya R, Saklani A, Parikh D, Goud J, Dixit J, Gopinath K, Kumar MV, Bhojwani R, Nayak S, Rao S, Kothari K, Chandramohan K, Desai S, Gupta A. Adaptations and Safety Modifications to Perform Safe Minimal Access Surgery (MIS: Laparoscopy and Robotic) During the COVID-19 Pandemic: Practice Modifications Expert Panel Consensus Guidelines from Academia of Minimal Access Surgical Oncology (AMASO). *Indian J Surg Oncol* 2020; 1-11 [PMID: 33223748 DOI: 10.1007/s13193-020-01254-9]
80 **Bellato V**, Konishi T, Pellino G, An Y, Piciocchi A, Sensi B, Siragusa L, Khanna K, Pirozzi BM, Franceschilli M, Campanelli M, Efetov S, Sica GS; S-COVID Collaborative Group. Screening policies, preventive measures and in-hospital infection of COVID-19 in global surgical practices. *J Glob Health* 2020; **10**: 020507 [PMID: 33110590 DOI: 10.7189/jogh.10.020507]
81 **Vigneswaran Y**, Prachand VN, Posner MC, Matthews JB, Hussain M. What Is the Appropriate Use of Laparoscopy over Open Procedures in the Current COVID-19 Climate? *J Gastrointest Surg* 2020; **24**: 1686-1691 [PMID: 32285338 DOI: 10.1007/s11605-020-04592-9]
82 **Neumann PA**, Rijcken E. Minimally invasive surgery for inflammatory bowel disease: Review of current developments and future perspectives. *World J Gastrointest Pharmacol Ther* 2016; **7**: 217-226 [PMID: 27158537 DOI: 10.4292/wjgpt.v7.i2.217]
83 **de Leeuw RA**, Burger NB, Ceccaroni M, Zhang J, Tuynman J, Mabrouk M, Barri Soldevila P, Bonjer HJ, Ankum P, Huirne J. COVID-19 and Laparoscopic Surgery: Scoping Review of Current Literature and Local Expertise. *JMIR Public Health Surveill* 2020; **6**: e18928 [PMID: 32406853 DOI: 10.2196/18928]
84 **De Simone B**, Chouillard E, Di Saverio S, Pagani L, Sartelli M, Biffl WL, Coccolini F, Pieri A, Khan M, Borzellino G, Campanile FC, Ansaloni L, Catena F. Emergency surgery during the COVID-19 pandemic: what you need to know for practice. *Ann R Coll Surg Engl* 2020; **102**: 323-332 [PMID: 32352836 DOI: 10.1308/rcsann.2020.0097]
85 **Moletta L**, Pierobon ES, Capovilla G, Costantini M, Salvador R, Merigliano S, Valmasoni M.

International guidelines and recommendations for surgery during Covid-19 pandemic: A Systematic Review. *Int J Surg* 2020; **79**: 180-188 [PMID: 32454253 DOI: 10.1016/j.ijsu.2020.05.061]

86 **Mellor G**, Hutchinson M. Is it time for a more systematic approach to the hazards of surgical smoke? *Workplace Health Saf* 2013; **61**: 265-270 [PMID: 23701005 DOI: 10.3928/21650799-20130516-12]

87 **Flemming S**, Hankir M, Ernestus RI, Seyfried F, Germer CT, Meybohm P, Wurmb T, Vogel U, Wiegering A. Surgery in times of COVID-19-recommendations for hospital and patient management. *Langenbecks Arch Surg* 2020; **405**: 359-364 [PMID: 32385568 DOI: 10.1007/s00423-020-01888-x]

88 **Coccolini F**, Perrone G, Chiarugi M, Di Marzo F, Ansaloni L, Scandroglio I, Marini P, Zago M, De Paolis P, Forfori F, Agresta F, Puzziello A, D'Ugo D, Bignami E, Bellini V, Vitali P, Petrini F, Pifferi B, Corradi F, Tarasconi A, Pattonieri V, Bonati E, Tritapepe L, Agnoletti V, Corbella D, Sartelli M, Catena F. Surgery in COVID-19 patients: operational directives. *World J Emerg Surg* 2020; **15**: 25 [PMID: 32264898 DOI: 10.1186/s13017-020-00307-2]

89 **Chetan MR**, Tsakok MT, Shaw R, Xie C, Watson RA, Wing L, Peschl H, Benamore R, MacLeod F, Gleeson FV. Chest CT screening for COVID-19 in elective and emergency surgical patients: experience from a UK tertiary centre. *Clin Radiol* 2020; **75**: 599-605 [PMID: 32593409 DOI: 10.1016/j.crad.2020.06.006]

90 **Hamid HKS**. Considerations for transanal surgery during COVID-19 pandemic. *J Surg Oncol* 2020; **122**: 995 [PMID: 32668028 DOI: 10.1002/jso.26085]

91 **Xiao F**, Tang M, Zheng X, Liu Y, Li X, Shan H. Evidence for Gastrointestinal Infection of SARS-CoV-2. *Gastroenterology* 2020; **158**: 1831-1833. e3 [PMID: 32142773 DOI: 10.1053/j.gastro.2020.02.055]

92 **Teixeira SC**. Mild and asymptomatic cases of COVID-19 are potential threat for faecal-oral transmission. *Braz J Infect Dis* 2020; **24**: 368 [PMID: 32615073 DOI: 10.1016/j.bjid.2020.06.003]

93 **Taylor S**, Asmundson GJG. Life in a post-pandemic world: What to expect of anxiety-related conditions and their treatment. *J Anxiety Disord* 2020; **72**: 102231 [PMID: 32447204 DOI: 10.1016/j.janxdis.2020.102231]

94 **Choi K**, Chun J, Han K, Park S, Soh H, Kim J, Lee J, Lee HJ, Im JP, Kim JS. Risk of Anxiety and Depression in Patients with Inflammatory Bowel Disease: A Nationwide, Population-Based Study. *J Clin Med* 2019; **8** [PMID: 31083476 DOI: 10.3390/jcm8050654]

95 **D'Amico F**, Rahier JF, Leone S, Peyrin-Biroulet L, Danese S. Views of patients with inflammatory bowel disease on the COVID-19 pandemic: a global survey. *Lancet Gastroenterol Hepatol* 2020; **5**: 631-632 [PMID: 32411920 DOI: 10.1016/S2468-1253(20)30151-5]

96 **Spanish Working Group on Crohn's Disease and Ulcerative Colitis**. Comunicado de GETECCU-GETEII-ACCU en relación a la vacunación frente a SARS-CoV-2 en pacientes con Enfermedad Inflamatoria Intestinal (EII). [cited December 23, 2020]. In: Grupo Español de Trabajo para la Enfermedad de Crohn y Colitis Ulcerosa [Internet]. Available from: https://geteccu.org/comunicado-de-geteccu-geteii-accu-en-relacion-a-la-vacunacion-frente-a-sars-cov-2-en-pacientes-con-enfermedad-inflamatoria-intestinal-eii

97 **British Society of Gastroenterology**. British Society of Gastroenterology Inflammatory Bowel Disease Section and IBD Clinical Research Group position statement on SARS-CoV2 Vaccination. [cited December 23, 2020]. In: British Society of Gastroenterology [Internet]. Available from: https://www.bsg.org.uk/covid-19-advice/british-society-of-gastroenterology-inflammatory-bowel-disease-section-and-ibd-clinical-research-group-position-statement-on-sars-cov2-vaccination

98 **D'Amico F**, Rabaud C, Peyrin-Biroulet L, Danese S. SARS-CoV-2 vaccination in IBD: more pros than cons. *Nat Rev Gastroenterol Hepatol* 2021 [PMID: 33473178 DOI: 10.1038/s41575-021-00420-w]

99 **Lu Y**, Jacobson DL, Ashworth LA, Grand RJ, Meyer AL, McNeal MM, Gregas MC, Burchett SK, Bousvaros A. Immune response to influenza vaccine in children with inflammatory bowel disease. *Am J Gastroenterol* 2009; **104**: 444-453 [PMID: 19174786 DOI: 10.1038/ajg.2008.120]

100 **Cullen G**, Bader C, Korzenik JR, Sands BE. Serological response to the 2009 H1N1 influenza vaccination in patients with inflammatory bowel disease. *Gut* 2012; **61**: 385-391 [PMID: 21757451 DOI: 10.1136/gutjnl-2011-300256]

101 **Melmed GY**, Agarwal N, Frenck RW, Ippoliti AF, Ibanez P, Papadakis KA, Simpson P, Barolet-Garcia C, Ward J, Targan SR, Vasiliauskas EA. Immunosuppression impairs response to pneumococcal polysaccharide vaccination in patients with inflammatory bowel disease. *Am J Gastroenterol* 2010; **105**: 148-154 [PMID: 19755964 DOI: 10.1038/ajg.2009.523]

102 **Caldera F**, Hillman L, Saha S, Wald A, Grimes I, Zhang Y, Sharpe AR, Reichelderfer M, Hayney MS. Immunogenicity of High Dose Influenza Vaccine for Patients with Inflammatory Bowel Disease on Anti-TNF Monotherapy: A Randomized Clinical Trial. *Inflamm Bowel Dis* 2020; **26**: 593-602 [PMID: 31504526 DOI: 10.1093/ibd/izz164]

103 **Doornekamp L**, Goetgebuer RL, Schmitz KS, Goeijenbier M, van der Woude CJ, Fouchier R, van Gorp ECM, de Vries AC. High Immunogenicity to Influenza Vaccination in Crohn's Disease Patients Treated with Ustekinumab. *Vaccines (Basel)* 2020; **8** [PMID: 32824111 DOI: 10.3390/vaccines8030455]

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of endoscopic submucosal dissection for gastric tube cancer: A multicenter retrospective study

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Abstract

BACKGROUND

Recent improvements in the prognosis of patients with esophageal cancer have led to the increased occurrence of gastric tube cancer (GTC) in the reconstructed gastric tube. However, there are few reports on the treatment results of endoscopic submucosal dissection (ESD) for GTC.

AIM

To evaluate the efficacy and safety of ESD for GTC after esophagectomy in a multicenter trial.

METHODS

We retrospectively investigated 48 GTC lesions in 38 consecutive patients with GTC in the reconstructed gastric tube after esophagectomy who had undergone ESD between January 2005 and December 2019 at 8 institutions participating in the Okayama Gut Study group. The clinical indications of ESD for early gastric cancer were similarly applied for GTC after esophagectomy. ESD specimens were evaluated in 2-mm slices according to the Japanese Classification of Gastric Carcinoma with curability assessments divided into curative and non-curative resection based on the Gastric Cancer Treatment Guidelines. Patient characteristics, treatment results, clinical course, and treatment outcomes were analyzed.

RESULTS

The median age of patients was 71.5 years (range, 57-84years), and there were 34 men and 4 women. The median observation period after ESD was 884 d (range, 8-4040 d). The median procedure time was 81 min (range, 29-334 min), the *en bloc* resection rate was 91.7% (44/48), and the curative resection rate was 79% (38/48). Complications during ESD were seen in 4% (2/48) of case, and those after ESD were seen in 10% (5/48) of case. The survival rate at 5 years was 59.5%. During the observation period after ESD, 10 patients died of other diseases. Although there were differences in the procedure time between institutions, a multivariate analysis showed that tumor size was the only factor associated with prolonged procedure time.

CONCLUSION

ESD for GTC after esophagectomy was shown to be safe and effective.

Key Words: Endoscopic submucosal dissection; Gastric tube; Gastric cancer; Esophagectomy; Multicenter study; Retrospective study

Core Tip: Despite increasing occurrence of gastric tube cancer (GTC) after esophagectomy, there are few reports on the treatment results of endoscopic submucosal dissection (ESD) for GTC. This multicenter study showed that treatment results and complications of ESD for GTC were similar to those of standard ESD and there were not significantly difference between institutions except for procedure time. ESD for GTC after esophagectomy is a safe and effective treatment.

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INTRODUCTION

Recently, the survival of patients with esophageal cancer after esophagectomy has improved[1-5]. However, the risk of a subsequent occurrence of primary cancer is high in these patients. The most frequent cancer that overlaps with esophageal cancer is head and neck cancer, while the second most common is gastric cancer, including gastric tube cancer (GTC)[6-9]. Therefore, the improved prognosis of esophageal cancer patients has led to an increase in the occurrence of GTC in the reconstructed gastric tube.

For the treatment of GTC after esophagectomy, total gastric tube resection (TGTR) or partial gastric tube resection (PGTR) has been proposed. However, surgical resection for GTC, being a secondary operation following esophagectomy, may lead to high mortality and morbidity[10,11]. On the other hand, in recent years, endoscopic therapy for early gastric cancer (EGC) has developed and become widespread[12]. Endoscopic submucosal dissection (ESD) enables the treatment of large lesions with a higher rate of *en bloc* resection that cannot be achieved by using conventional endoscopic mucosal resection. In addition, ESD is less invasive than surgery. For this reason, ESD has become widely used as a standard treatment for EGC, and ESD is often performed for GTC.

However, ESD for GTC after esophagectomy is a technically difficult procedure compared with that for an unresected stomach because of the limited working space, unusual fluid-pooling area, food residue, bile reflux, fibrosis, and staples under the suture line[13]. Therefore, a high degree of skill is required for ESD of GTC. There are few reports about ESD for GTC after esophagectomy, and most are case reports and case series of a small number of patients[13-17]. A study by Nonaka *et al*[18] reported the effectiveness and safety of ESD for GTC in a high-volume national center, which had largest number of cases but was nonetheless a single-center study. Therefore, the aim of this study was to evaluate the efficacy and safety of ESD for GTC after esophagectomy in a multicenter context.

MATERIALS AND METHODS

Patients

We retrospectively investigated patients with GTC in the reconstructed gastric tube after esophagectomy for esophageal squamous cell carcinoma who had undergone ESD between January 2005 and December 2019 at 8 institutions participating in the Okayama Gut Study group (O-GUTS). All of the participating institutions in O-GUTS, except Okayama University Hospital (OUH), were considered core hospitals in each area. During the study period, 48 GTC lesions in 38 consecutive patients were treated. The clinical indications of ESD for EGC were based on the Gastric Cancer Treatment Guidelines[19]. These indications were similarly applied for GTC after esophagectomy with gastric tube reconstruction.

Study measurements were as follows: patient characteristics, endoscopic findings, treatment results, adverse events, histopathological results, and clinical courses. In addition, we defined OUH as a high-volume center and compared the patients' background and clinical outcomes between OUH and other facilities.

The institutional review board of each hospital approved this study, and informed consent was obtained from all patients.

Endoscopic procedures

All endoscopic procedures were performed by experts in ESD who had experience with more than 500 clinical cases. There were no restrictions on the scopes and devices used by each endoscopist for ESD. The scopes used were GIF-Q260J or GIF-H260 (Olympus, Tokyo, Japan), and the devices were an insulation-tipped diathermic knife (IT Knife), IT Knife 2, IT Knife nano, or Dual Knife J (Olympus, Tokyo, Japan). Other devices, such as an argon plasma coagulation probe (ERBE, Tubingen, Germany) for marking dots or a needle knife (ZEON MEDICAL, Tokyo, Japan) for the initial incision, were occasionally used.

First, marking dots for the incision lines were placed around the lesion. Next, fructose-added glycerol (Glyceol; TAIYO Pharma CO, Tokyo, Japan) with a minute amount of indigo carmine dye was injected into the submucosal layer. In some cases, 0.4% sodium hyaluronate (MucoUp; Boston Scientific, Tokyo, Japan) was used. After submucosal injection, a precut was made with the Dual Knife J or needle knife, followed by a circumferential mucosal incision around the lesion using the dots as a

landmark and submucosal dissection with the IT Knife, IT Knife 2, IT Knife nano, or Dual Knife J. The resected specimens were evaluated pathologically.

Histopathological assessment of curability

ESD specimens were evaluated in 2-mm slices according to the Japanese Classification of Gastric Carcinoma with curability assessments divided into curative and non-curative resection based on the Gastric Cancer Treatment Guidelines[20]. R0 resection indicated that the lesion was resected *en bloc* with both the horizontal and vertical margins tumor-free histopathologically, but did not include findings regarding lymphovascular infiltration, the type of adenocarcinoma, or an assessment of the depth of invasion for curability. A curative resection was divided into eCura A and eCura B. A non-curative resection was defined as not meeting the criteria of curative resection and was further separated into 2 groups, eCura C-1 and eCura C-2, based on histopathological results per the Gastric Cancer Treatment Guidelines[19].

Statistical analysis

Continuous and categorical variables are expressed as median (range) and *n* (%), respectively. Overall survival was calculated according to the Kaplan-Meier method. Differences in the clinical outcomes of ESD for GTC between institutions were evaluated using the Mann-Whitney *U* test for continuous data and the Chi-squared test for categorical variables. The risk factors for long procedure time were evaluated using logistic regression analysis. All statistical analyses were performed using the statistical analysis software JMP Pro, version 15 (SAS Institute Inc., Cary, NC, United States). *P* values < 0.05 were considered statistically significant.

RESULTS

Patients' characteristics and endoscopic findings

A total of 38 consecutive patients with 48 GTC lesions were treated with ESD between January 2005 and December 2019 (Table 1). The median age of these patients was 71.5 years (range, 57-84 years), and they included 34 men and 4 women. The median period from esophagectomy to the treatment of GTC was 2106 d (range, 38-9523 d). This included patients who had a diagnosis of EGC before surgery for esophageal cancer and had undergone ESD after esophagectomy (5 patients). The reconstruction routes were antethoracic, retrosternal, and posterior mediastinal in 7, 11, and 20 patients, respectively. The location of the GTC lesion was upper, middle, and low in 2, 18, and 28 patients, respectively. Regarding the macroscopic type, there were 21 lesions of 0-IIa, 22 lesions of 0-IIc, 2 lesions of 0-IIb, 1 lesion of 0-III, and 2 combined lesions. The median observation period after ESD was 884 d (range, 8-4040 d).

Treatment results of ESD and histopathological findings

Treatment results of ESD for GTC after esophagectomy and pathological findings are shown in Table 2. The median procedure time was 81 min (range, 29-334 min). *En bloc* resection was performed in 44 of 48 lesions (91.7%). The median tumor size of the resected specimen was 15 mm (range, 4-60 mm). Among the 48 lesions, 43 were differentiated (90%) and 5 were undifferentiated (10%). Regarding the tumor depth, 40 lesions were intramucosal carcinoma (M, 84%), 4 were submucosal superficial carcinoma (SM1, 8%), and 4 were submucosal deep invasive carcinoma (SM2 or deeper, 8%). Ulcerative findings were seen in 6 lesions (13%). Lymphatic infiltration was seen in 3 lesions (6%), and vascular infiltration was seen in 1 lesion (2%). According to the Japanese Gastric Cancer Treatment Guidelines, 38 lesions (79%) achieved curative resection (eCura A) and 10 lesions (21%) were classified as non-curative resection. The reasons for non-curative resection were as follows: 3 lesions were horizontal margin positive (HM1) or cutting into the lesion (eCura C-1), 2 were undifferentiated and showed SM invasion, 2 showed lymphatic infiltration, 2 showed SM invasion with ulcerative findings, and 1 was undifferentiated and showed SM invasion and lymphatic and vascular infiltration (eCura C-2).

Adverse events

Complications during ESD were seen in 2 cases (4%), with 1 case of perforation, and 1 case of bleeding. Complications after ESD were seen in 5 cases (10%), with 2 cases of bleeding, 1 case of subcutaneous abscess, 1 case of liver failure, and 1 case of respiratory failure (Table 2).

Table 1 Patients' characteristics and endoscopic findings

Characteristics	
Patients/lesions, *n*	38/48
Median age, yr (range)	71.5 (57-84)
Sex, *n* (%)	
Male	34 (89)
Female	4 (11)
Median period from esophagectomy to ESD for GTC, d (range)	2106 (38-9523)
Reconstruction route of gastric tube, *n* (%)	
Antethoracic	7 (18)
Retrosternal	11 (29)
Posterior mediastinal	20 (53)
Median observation period after ESD, d (range)	884 (8-4040)
Location of lesion, *n* (%)	
U	2 (4)
M	18 (38)
L	28 (58)
Macroscopic type, *n* (%)	
0-IIa	21 (44)
0-IIb	2 (4)
0-IIc	22 (46)
0-III	1 (2)
Combined	2 (4)

ESD: Endoscopic submucosal dissection; GTC: Gastric tube cancer; U: Upper; M: Medium; L: Lower.

It was the same patient who had perforation during ESD and who formed subcutaneous abscess after ESD (Figure 1). In this case, perforation during ESD was sealed immediately with endoclips. Nevertheless, 20 d after ESD, the patient was admitted to the hospital with redness of the skin in the precordial area and excretion of pus from the skin. Computed tomography showed formation of a subcutaneous abscess around the gastric tube of the antethoracic reconstruction route. The patient was treated conservatively with antibiotics and percutaneous drainage and was discharged on the 16th day after the start of re-admission.

Patients' clinical courses

Of the 38 cases, 2 had local recurrence and 3 had metachronous recurrence. In the 2 cases with local recurrence, 1 received additional surgery and the other received additional ESD. In the 3 cases with metachronous recurrence, 1 received additional surgery and the others received additional ESD. The patients' overall survival curve is shown in Figure 2. The survival rate at 5 years was 59.5%. During the observation period after ESD, no patient died of GTC. However, 10 patients died of other diseases, including pneumonia, which was the most common and occurred in 4 patients, heart failure and hepatocellular carcinoma in 1 patient each, and other unknown diseases.

Comparison of clinical outcomes

A comparison of the patients' background and clinical outcomes between OUH and other hospitals is shown in Table 3. In terms of the patients' backgrounds, the posterior mediastinal route was used as a reconstruction route in more cases at other hospitals. Treatment results were generally similar in both groups; however, procedure time was significantly longer at other hospitals.

Since there were differences in procedure time between institutions, we divided

Table 2 Treatment results of endoscopic submucosal dissection for gastric tube cancer and histopathological findings

Lesions, *n*	48
Median procedure time, min (range)	81 (29-334)
En bloc resection, *n* (%)	44 (91.7)
Adverse events during ESD, *n* (%)	
Bleeding	1(2)
Perforation	1(2)
Adverse events post ESD, *n* (%)	
Bleeding	2 (4)
Subcutaneous abscess	1 (2)
Liver failure	1 (2)
Respiratory failure	1 (2)
Median tumor size, mm (range)	15 (4-60)
Histrogical type, *n*	
Differentiated	43
Undifferentiated	5
Tumor depth, *n*	
M	40
SM1	4
SM2	4
Ulcerative findings, *n*	
Absent	41
Present	7
Lymphatic infiltration, *n*	
Negative	3
Positive	45
Lymphatic infiltration, *n*	
Negative	1
Positive	47
Horizontal margin, *n*	
Negative	45
Positive	3
Vertical margin, *n*	
Negative	47
Positive	1
eCura, *n* (%)	
A	38 (79)
C-1	3 (6)
C-2	7 (15)

ESD: Endoscopic submucosal dissection; M: Intramucosal; SM1: Submucosal superficial; SM2: Submucosal deep invasive.

patients into two groups, a short procedure time group (< 90 min) and a long procedure time group (≥ 90 min), and examined the factors affecting the procedure time. In univariate analysis (Table 4), the treatment institution and tumor size showed

Table 3 Comparison of clinical outcomes between Okayama University Hospital and other hospitals

Institution (patients/lesions)	OUH (17/20)	Other hospitals (21/28)	*P* value
Median age, yr (range)	70 (57-83)	73 (58-84)	0.28
Male, *n* (%)	15 (88)	19 (79)	0.72
Reconstruction route of gastric tube, *n*			< 0.01
Antethoracic	7	0	
Retrosternal	7	4	
Posterior mediastinal	3	17	
Median tumor size, mm (range)	18 (8-60)	15 (4-40)	0.21
depth, M/SM, *n*	16/4	24/4	0.6
Ulcerative findings positive, *n* (%)	3 (15)	4 (14)	0.94
Median procedure time, min (range)	50 (20-180)	108 (32-334)	< 0.01
En bloc resection, *n* (%)	19 (95)	25 (89)	0.48
Curative resection (eCura A or B), *n* (%)	17 (85)	21 (75)	0.4
Adverse events during ESD, *n* (%)	1 (5.0)	1 (3.6)	0.8
Adverse events post ESD, *n* (%)	3 (15)	2 (7.1)	0.37

OUH: Okayama University Hospital; ESD: Endoscopic submucosal dissection; M: Intramucosal; SM: Submucosal.

Table 4 Comparison of short (< 90 min) and long (≥ 90 min) procedure time groups

	< 90 min, *n* = 26	≥ 90 min, *n* = 22	*P* value
Okayama University Hospital/other hospitals, *n*	15/11	5/17	0.01
Reconstruction route of gastric tube, *n*			
Antethoracic/retrosternal/posterior mediastinal	6/11/9	3/4/15	0.06
Location of lesion, *n*			
U/L/M	0/8/18	2/10/10	0.08
Median tumor size, mm (range)	13 (4-26)	15 (6-60)	0.06
Tumor depth, *n*			
M/SM	23/3	17/5	0.30
Ulcerative findings positive, *n*	2	5	0.14

U: Upper; M: Medium; L: Lower; M: Intramucosal; SM: Submucosal.

significant differences between the two groups. However, in multivariate analysis (Table 5), tumor size was the only factor associated with a long procedure time.

DISCUSSION

This study was the first multicenter study on ESD for GTC in the reconstructed gastric tube after esophagectomy, and it included the second largest number of patients. According to a systematic review of GTC after esophagectomy, there are two surgical options for the treatment of GTC: PGTR or TGTR plus lymphadenectomy with colon or jejunal reconstruction[21]. However, surgical treatment for GTC is highly invasive and carries a certain degree of risk. Sugiura *et al*[10] reported that 5 of 7 cases of TGTR had surgical complications (leakage) and 2 died. In addition, 1 of 3 cases of PTGR had fatal complications. Akita *et al*[11] reported that 1 of 5 cases of TGTR died of postoperative complications. On the other hand, in previous studies on ESD for GTC,

Table 5 Multivariate analysis about risk factors for a long procedure time of endoscopic submucosal dissection for gastric tube cancer

	Risk ratio (95%CI)	*P* value
Other hospitals	3.18 (0.59-19.6)	NS
Posterior mediastinal route	3.18 (0.61-19.4)	NS
Location of lesion, U/M	2.12 (0.52-8.84)	NS
Median tumor size ≥ 20 mm	4.90 (1.09-29.6)	0.04

U: Upper; M: Medium; CI: Confidence interval.

the proportions of R0 resection and curative resection were 87.5%-92% and 65%-85%, respectively, and complications were seen in 12.5%-18% of patients[13-18]. In the present study, the proportions of R0 resection and curative resection were 91.7% and 79%, respectively, and complications were seen in 10%. Overall, the treatment results of ESD for GTC in this study were similar to those of previous studies. In a previous study on gastric ESD of the unresected stomach, the proportions of R0 resection, curative resections, and complications were 92%-94.9%, 80.4%-94.7%, and 5.9%-6.3%, respectively[22,23]. Furthermore, in gastric ESD of the remnant stomach after gastrectomy, the proportions of R0 resection, curative resection, and complications were 84.7%-85%, 70.9%-78%, and 2.8%-21.1%, respectively[24,25]. ESD for GTC was considered a minimally invasive, effective, and relatively safe treatment.

There are some points of note in GTC. First, detection of early GTC requires long-term regular endoscopic surveillance after esophagectomy. GTC is often found long after esophagectomy; in some cases, GTC is detected after more than 10 years and the risk of metachronous GTC is high[15-18]. Second, GTC may be difficult to diagnose. The reasons are as follows: Food residue and bile reflux are often seen in the gastric tube, and the lumen of the gastric tube is long and narrow and can constrain endoscopic observation[13]. Therefore, it is necessary to pay attention to these points during endoscopy for patients with gastric tube reconstruction after esophagectomy. Third, when performing ESD for GTC, it is necessary to pay attention to complications specific to GTC. For example, in our study, a subcutaneous abscess formed after treatment in a case with perforation during ESD for GTC in the antethoracic reconstruction route. This case was cured by conservative treatment with antibiotics and percutaneous drainage. Moreover, Miyagi *et al*[26] reported that post-treatment precordial skin burns occurred in 5 of 8 patients with GTC in the antethoracic reconstruction route. In this report, all burns were diagnosed as first-degree burns based on the clinical classification of burn depth, developed on postoperative day 1-2, and took 4-7 d to heal.

In this study, since approximately half of the patients were treated at OUH, we defined it as a high-volume center and compared clinical outcomes with those of other institutions. As a result, there were no significant differences in the clinical outcomes of ESD between institutions. In addition, lesion size was the only factor related to long procedure time in multivariate analysis. We believe these results were attributable to the fact that all of the participating institutions specialized in gastrointestinal diseases with more than 500 cases of ESD for EGC. Moreover, ESD for GTC may have been performed by leading specialists given the relative rarity of GTC. For these reasons, ESD for GTC seems safe if performed by specialists with sufficient ESD experience.

Previously, not a few patients had complications or died of other diseases during the course after esophagectomy[27,28]. However, due to the widespread use of minimally invasive esophagectomy, such as thoracoscopic and laparoscopic surgery, the incidence of postoperative complications, including respiratory complications, has decreased and the general condition of patients after esophagectomy has improved in recent years[29-32]. With continued improvements in the prognosis of esophageal cancer, the number of cases of GTC after esophagectomy will likely increase in the future and the demand for ESD for GTC is expected to increase further.

There were several limitations to this study. First, as this was a retrospective study, the ESD indications and devices used for treatment were not standardized. However, treatment was performed according to the typical standards. Second, since data on *Helicobacter pylori* infection status were missing in some patients, the association between GTC and *Helicobacter pylori* could not be evaluated. Third, as some patients were observed for only a short time, the assessment of long-term prognosis after ESD for GTC was insufficient. Further follow-up studies are needed in the future.

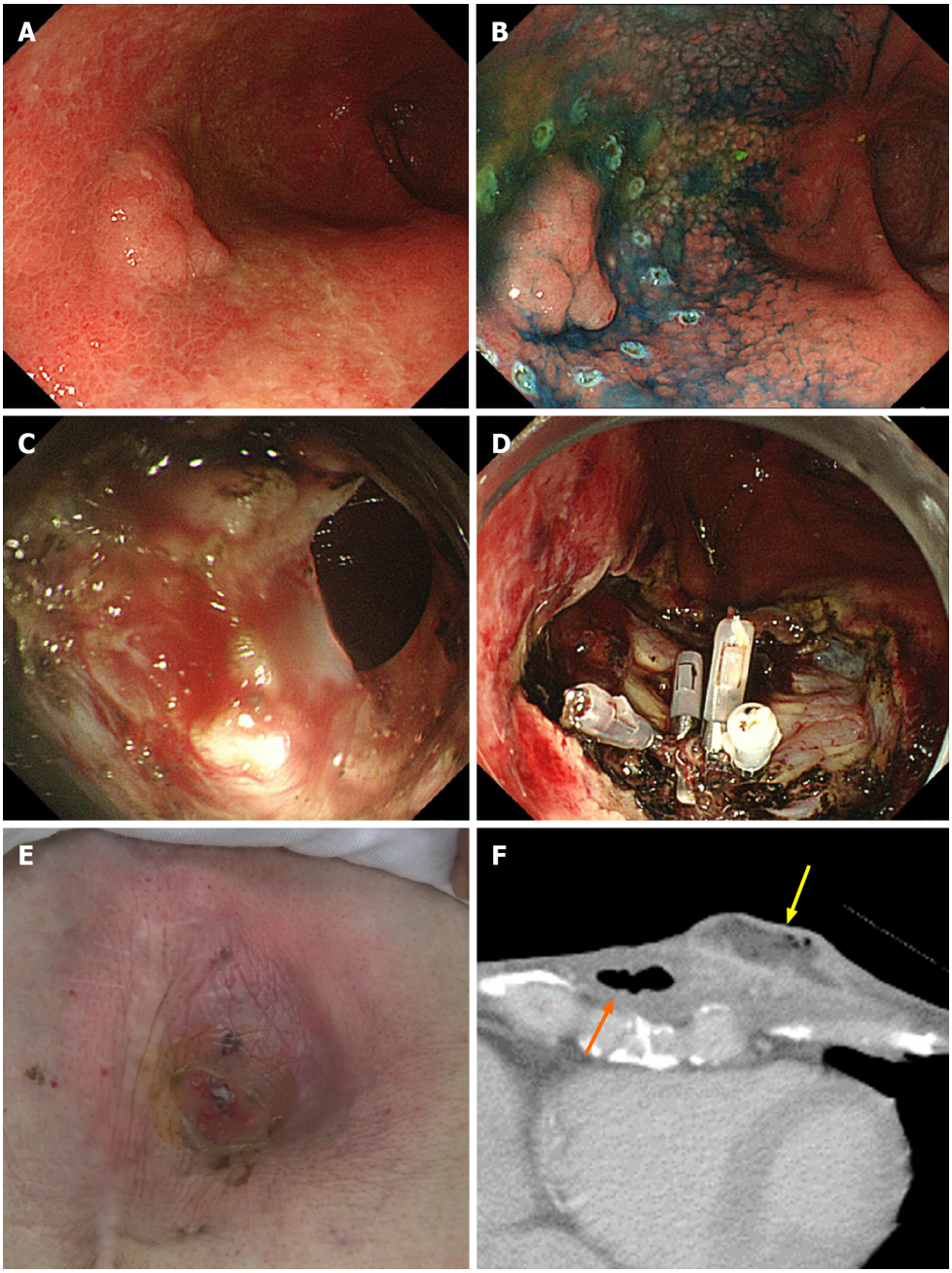

Figure 1 A case of subcutaneous abscess formation after perforation during endoscopic submucosal dissection for gastric tube cancer.
A: Gastric tube cancer located at the anterior wall of gastric body; B: Marking dots were placed around the lesion, and endoscopic submucosal dissection (ESD) was performed as usual; C: Perforation occurred during ESD; D: Perforation was sealed immediately with 4 endoclips; E: Redness of the skin in the precordial area, 20 d after ESD; F: Computed tomography performed 20 d after ESD. A subcutaneous abscess (yellow arrow) had formed around the gastric tube of the antethoracic reconstruction route (orange arrow).

CONCLUSION

In conclusion, ESD for GTC after esophagectomy is a safe and effective treatment that can be performed without significant variability in treatment results at any specialized institution where standard gastric ESD can be performed with sufficient expertise. Further accumulation and follow-up of cases of GTC are necessary in the future.

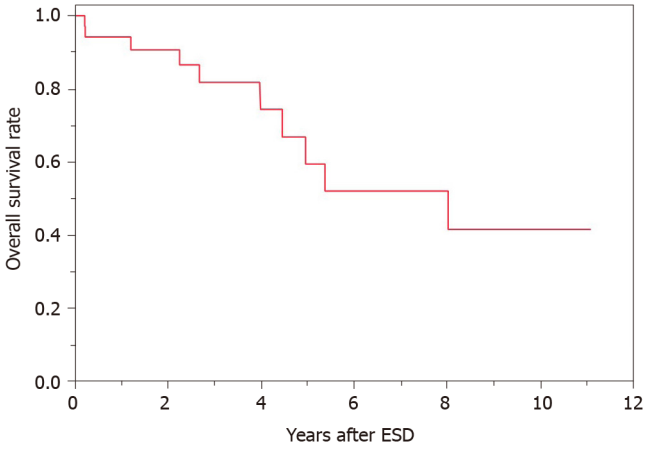

Figure 2 Overall survival curve after endoscopic submucosal dissection for gastric tube cancer. The survival rate at 5 year was 59.5%. ESD: Endoscopic submucosal dissection.

ARTICLE HIGHLIGHTS

Research background

Recent improvements in the prognosis of patients with esophageal cancer have led to the increased occurrence of gastric tube cancer (GTC) in the reconstructed gastric tube.

Research motivation

There are few reports on the treatment results of endoscopic submucosal dissection (ESD) for GTC.

Research objectives

This retrospective study aimed to evaluate the efficacy and safety of ESD for GTC after esophagectomy in a multicenter trial.

Research methods

We retrospectively investigated 48 GTC lesions in 38 consecutive patients with GTC in the reconstructed gastric tube after esophagectomy who had undergone ESD between January 2005 and December 2019 at 8 institutions participating in the Okayama Gut Study group. Patient characteristics, treatment results, clinical course, and treatment outcomes were analyzed.

Research results

The median age of patients was 71.5 years (range, 57-84years), and there were 34 men and 4 women. The median observation period after ESD was 884 d (range, 8-4040 d). The median procedure time was 81 min (range, 29-334 min), the *en bloc* resection rate was 91.7% (44/48), and the curative resection rate was 79% (38/48). Complications during ESD were seen in 4% (2/48) of case, and those after ESD were seen in 10% (5/48) of case. The survival rate at 5 years was 59.5%. During the observation period after ESD, 10 patients died of other diseases. Although there were differences in the procedure time between institutions, a multivariate analysis showed that tumor size was the only factor associated with prolonged procedure time.

Research conclusions

ESD for GTC after esophagectomy was shown to be safe and effective.

Research perspectives

As some patients were observed for only a short time, the assessment of long-term prognosis after ESD for GTC was insufficient. Further accumulation and follow-up of cases of GTC are necessary in the future.

REFERENCES

1 **Medical Research Council Oesophageal Cancer Working Group**. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. *Lancet* 2002; **359**: 1727-1733 [PMID: 12049861 DOI: 10.1016/S0140-6736(02)08651-8]

2 **Allum WH**, Stenning SP, Bancewicz J, Clark PI, Langley RE. Long-term results of a randomized trial of surgery with or without preoperative chemotherapy in esophageal cancer. *J Clin Oncol* 2009; **27**: 5062-5067 [PMID: 19770374 DOI: 10.1200/JCO.2009.22.2083]

3 **Ozawa S**, Tachimori Y, Baba H, Matsubara H, Muro K, Numasaki H, Oyama T, Shinoda M, Takeuchi H, Tanaka O, Teshima T, Udagawa H, Uno T, Barron JP. Comprehensive registry of esophageal cancer in Japan, 2002. *Esophagus* 2010; **7**: 7-22 [DOI: 10.1007/s10388-010-0228-6]

4 **Ando N**, Kato H, Igaki H, Shinoda M, Ozawa S, Shimizu H, Nakamura T, Yabusaki H, Aoyama N, Kurita A, Ikeda K, Kanda T, Tsujinaka T, Nakamura K, Fukuda H. A randomized trial comparing postoperative adjuvant chemotherapy with cisplatin and 5-fluorouracil *vs* preoperative chemotherapy for localized advanced squamous cell carcinoma of the thoracic esophagus (JCOG9907). *Ann Surg Oncol* 2012; **19**: 68-74 [PMID: 21879261 DOI: 10.1245/s10434-011-2049-9]

5 **Toxopeus E**, van der Schaaf M, van Lanschot J, Lagergren J, Lagergren P, van der Gaast A, Wijnhoven B. Outcome of Patients Treated Within and Outside a Randomized Clinical Trial on Neoadjuvant Chemoradiotherapy Plus Surgery for Esophageal Cancer: Extrapolation of a Randomized Clinical Trial (CROSS). *Ann Surg Oncol* 2018; **25**: 2441-2448 [PMID: 29948420 DOI: 10.1245/s10434-018-6554-y]

6 **Kokawa A**, Yamaguchi H, Tachimori Y, Kato H, Watanabe H, Nakanishi Y. Other primary cancers occurring after treatment of superficial oesophageal cancer. *Br J Surg* 2001; **88**: 439-443 [PMID: 11260113 DOI: 10.1046/j.1365-2168.2001.01696.x]

7 **Noguchi T**, Kato T, Takeno S, Wada S, Yanagisawa S, Suzuki M. Necessity of screening for multiple primary cancers in patients with esophageal cancer. *Ann Thorac Cardiovasc Surg* 2002; **8**: 336-342 [PMID: 12517292]

8 **Natsugoe S**, Matsumoto M, Okumura H, Ishigami S, Uenosono Y, Owaki T, Takao S, Aikou T. Multiple primary carcinomas with esophageal squamous cell cancer: clinicopathologic outcome. *World J Surg* 2005; **29**: 46-49 [PMID: 15592914 DOI: 10.1007/s00268-004-7525-y]

9 **Chuang SC**, Hashibe M, Scelo G, Brewster DH, Pukkala E, Friis S, Tracey E, Weiderpass E, Hemminki K, Tamaro S, Chia KS, Pompe-Kirn V, Kliewer EV, Tonita JM, Martos C, Jonasson JG, Dresler CM, Boffetta P, Brennan P. Risk of second primary cancer among esophageal cancer patients: a pooled analysis of 13 cancer registries. *Cancer Epidemiol Biomarkers Prev* 2008; **17**: 1543-1549 [PMID: 18559572 DOI: 10.1158/1055-9965.EPI-07-2876]

10 **Sugiura T**, Kato H, Tachimori Y, Igaki H, Yamaguchi H, Nakanishi Y. Second primary carcinoma in the gastric tube constructed as an esophageal substitute after esophagectomy. *J Am Coll Surg* 2002; **194**: 578-583 [PMID: 12022598 DOI: 10.1016/s1072-7515(02)01135-3]

11 **Akita H**, Doki Y, Ishikawa O, Takachi K, Miyashiro I, Sasaki Y, Ohigashi H, Murata K, Noura S, Yamada T, Eguchi H, Imaoka S. Total removal of the posterior mediastinal gastric conduit due to gastric cancer after esophagectomy. *J Surg Oncol* 2004; **85**: 204-208 [PMID: 14991878 DOI: 10.1002/jso.20017]

12 **Gotoda T**. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1-11 [PMID: 17334711 DOI: 10.1007/s10120-006-0408-1]

13 **Mukasa M**, Takedatsu H, Matsuo K, Sumie H, Yoshida H, Hinosaka A, Watanabe Y, Tsuruta O, Torimura T. Clinical characteristics and management of gastric tube cancer with endoscopic submucosal dissection. *World J Gastroenterol* 2015; **21**: 919-925 [PMID: 25624726 DOI: 10.3748/wjg.v21.i3.919]

14 **Osumi W**, Fujita Y, Hiramatsu M, Kawai M, Sumiyoshi K, Umegaki E, Tokioka S, Yoda Y, Egashira Y, Abe S, Higuchi K, Tanigawa N. Endoscopic submucosal dissection allows less-invasive curative resection for gastric tube cancer after esophagectomy - a case series. *Endoscopy* 2009; **41**: 777-780 [PMID: 19746318 DOI: 10.1055/s-0029-1215024]

15 **Bamba T**, Kosugi S, Takeuchi M, Kobayashi M, Kanda T, Matsuki A, Hatakeyama K. Surveillance and treatment for second primary cancer in the gastric tube after radical esophagectomy. *Surg Endosc* 2010; **24**: 1310-1317 [PMID: 19997933 DOI: 10.1007/s00464-009-0766-y]

16 **Tawaraya S**, Jin M, Matsuhashi T, Suzuki Y, Sawaguchi M, Watanabe N, Onochi K, Koizumi S, Hatakeyama N, Ohba R, Mashima H, Ohnishi H. Advanced feasibility of endoscopic submucosal dissection for the treatment of gastric tube cancer after esophagectomy. *Gastrointest Endosc* 2014; **79**: 525-530 [PMID: 24246794 DOI: 10.1016/j.gie.2013.10.007]

17 **Hirayama Y**, Fujisaki J, Yoshimizu S, Horiuchi Y, Yoshio T, Ishiyama A, Hirasawa T, Imamura Y, Mine S, Watanabe M, Tsuchida T. Efficacy and safety of endoscopic resection for gastric tube cancer after surgical resection of esophageal squamous cell carcinoma. *Esophagus* 2019; **16**: 194-200 [PMID: 30600485 DOI: 10.1007/s10388-018-00653-w]

18 **Nonaka S**, Oda I, Sato C, Abe S, Suzuki H, Yoshinaga S, Hokamura N, Igaki H, Tachimori Y, Taniguchi H, Kushima R, Saito Y. Endoscopic submucosal dissection for gastric tube cancer after esophagectomy. *Gastrointest Endosc* 2014; **79**: 260-270 [PMID: 24060521 DOI: 10.1016/j.gie.2013.07.059]

19 **Japanese Gastric Cancer Association**. Japanese gastric cancer treatment guidelines 2018 (5th edition). *Gastric Cancer* 2021; **24**: 1-21 [PMID: 32060757 DOI: 10.1007/s10120-020-01042-y]

20 **Japanese Gastric Cancer Association**. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]

21 **Gentile D**, Riva P, Da Roit A, Basato S, Marano S, Castoro C. Gastric tube cancer after esophagectomy for cancer: a systematic review. *Dis Esophagus* 2019; **32** [PMID: 31111880 DOI: 10.1093/dote/doz049]

22 **Takenaka R**, Kawahara Y, Okada H, Hori K, Inoue M, Kawano S, Tanioka D, Tsuzuki T, Yagi S, Kato J, Uemura M, Ohara N, Yoshino T, Imagawa A, Fujiki S, Takata R, Yamamoto K. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest Endosc* 2008; **68**: 887-894 [PMID: 18565523 DOI: 10.1016/j.gie.2008.03.1089]

23 **Isomoto H**, Shikuwa S, Yamaguchi N, Fukuda E, Ikeda K, Nishiyama H, Ohnita K, Mizuta Y, Shiozawa J, Kohno S. Endoscopic submucosal dissection for early gastric cancer: a large-scale feasibility study. *Gut* 2009; **58**: 331-336 [PMID: 19001058 DOI: 10.1136/gut.2008.165381]

24 **Nonaka S**, Oda I, Makazu M, Haruyama S, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Kushima R, Saito Y. Endoscopic submucosal dissection for early gastric cancer in the remnant stomach after gastrectomy. *Gastrointest Endosc* 2013; **78**: 63-72 [PMID: 23566640 DOI: 10.1016/j.gie.2013.02.006]

25 **Yabuuchi Y**, Kakushima N, Takizawa K, Tanaka M, Kawata N, Yoshida M, Kishida Y, Ito S, Imai K, Ishiwatari H, Hotta K, Matsubayashi H, Ono H. Short- and long-term outcomes of endoscopic submucosal dissection for early gastric cancer in the remnant stomach after gastrectomy. *J Gastroenterol* 2019; **54**: 511-520 [PMID: 30413872 DOI: 10.1007/s00535-018-1528-1]

26 **Miyagi M**, Yoshio T, Hirasawa T, Ishiyama A, Yamamoto Y, Tsuchida T, Fujisaki J, Igarashi M. Precordial skin burns after endoscopic submucosal dissection for gastric tube cancer. *Dig Endosc* 2015; **27**: 742-746 [PMID: 26012356 DOI: 10.1111/den.12494]

27 **Griffin SM**, Shaw IH, Dresner SM. Early complications after Ivor Lewis subtotal esophagectomy with two-field lymphadenectomy: risk factors and management. *J Am Coll Surg* 2002; **194**: 285-297 [PMID: 11893132 DOI: 10.1016/s1072-7515(01)01177-2]

28 **Ando N**, Ozawa S, Kitagawa Y, Shinozawa Y, Kitajima M. Improvement in the results of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. *Ann Surg* 2000; **232**: 225-232 [PMID: 10903602 DOI: 10.1097/00000658-200008000-00013]

29 **Akaishi T**, Kaneda I, Higuchi N, Kuriya Y, Kuramoto J, Toyoda T, Wakabayashi A. Thoracoscopic en bloc total esophagectomy with radical mediastinal lymphadenectomy. *J Thorac Cardiovasc Surg* 1996; **112**: 1533-40; discussion 1540 [PMID: 8975845 DOI: 10.1016/s0022-5223(96)70012-0]

30 **Osugi H**, Takemura M, Higashino M, Takada N, Lee S, Kinoshita H. A comparison of video-assisted thoracoscopic oesophagectomy and radical lymph node dissection for squamous cell cancer of the oesophagus with open operation. *Br J Surg* 2003; **90**: 108-113 [PMID: 12520585 DOI: 10.1002/bjs.4022]

31 **Luketich JD**, Alvelo-Rivera M, Buenaventura PO, Christie NA, McCaughan JS, Litle VR, Schauer PR, Close JM, Fernando HC. Minimally invasive esophagectomy: outcomes in 222 patients. *Ann Surg* 2003; **238**: 486-94; discussion 494 [PMID: 14530720 DOI: 10.1097/01.sla.0000089858.40725.68]

32 **Zingg U**, McQuinn A, DiValentino D, Esterman AJ, Bessell JR, Thompson SK, Jamieson GG, Watson DI. Minimally invasive *vs* open esophagectomy for patients with esophageal cancer. *Ann Thorac Surg* 2009; **87**: 911-919 [PMID: 19231418 DOI: 10.1016/j.athoracsur.2008.11.060]

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ORIGINAL ARTICLE

Retrospective Study

Study on the characteristics of intestinal motility of constipation in patients with Parkinson's disease

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Abstract

BACKGROUND

Constipation is one of the most important nonmotor symptoms in Parkinson's disease (PD) patients, and constipation of different severities is closely related to the pathogenesis of PD. PD with constipation (PDC) is considered a unique type of constipation, but its mechanism of formation and factors affecting its severity have been less reported. Understanding the gastrointestinal motility characteristics and constipation classification of PDC patients is essential to guide the treatment of PDC. In this study, the colonic transit test and high-resolution anorectal manometry were used to identify the intestinal motility of PDC to provide a basis for the treatment of PDC.

AIM

To investigate the clinical classification of PDC, to clarify its characteristics of colonic motility and rectal anal canal pressure, and to provide a basis for further research on the pathogenesis of PDC.

METHODS

Twenty PDC patients and 20 patients with functional constipation (FC) who were treated at Xuanwu Hospital of Capital Medical University from August 6, 2018 to December 2, 2019 were included. A colonic transit test and high-resolution anorectal manometry were performed to compare the differences in colonic transit time, rectal anal canal pressure, and constipation classification between the two groups.

RESULTS

There were no statistically significant differences in sex, age, body mass index, or

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duration of constipation between the two groups. It was found that more patients in the PDC group exhibited difficulty in defecating than in the FC group, and the difference was statistically significant. The rectal resting pressure, anal sphincter resting pressure, intrarectal pressure, and anal relaxation rate in the PDC group were significantly lower than those in the FC group. The proportion of paradoxical contractions in the PDC group was significantly higher than that in the FC group. There was a statistically significant difference in the type composition ratio of defecatory disorders between the two groups ($P < 0.05$). The left colonic transit time, rectosigmoid colonic transit time (RSCTT), and total colonic transit time were prolonged in PDC and FC patients compared to normal values. The patients with FC had a significantly longer right colonic transit time and a significantly shorter RSCTT than patients with PDC ($P < 0.05$). Mixed constipation predominated in PDC patients and FC patients, and no significant difference was observed.

CONCLUSION

Patients with PDC and FC have severe functional dysmotility of the colon and rectum, but there are certain differences in segmental colonic transit time and rectal anal canal pressure between the two groups.

Key Words: Parkinson's disease; Parkinson's disease with constipation; Colonic transit time; High-resolution anorectal manometry

Core Tip: In this study, we used the colonic transit test and rectal anal manometry to subtype constipation and detect corresponding indicators in patients with Parkinson's disease with constipation (PDC) and functional constipation, with the aim of clarifying the colonic and rectal motility characteristics of PDC and providing a basis for the treatment of PDC. It was found that the segmental colonic transit time and the constituent ratio of types of defecation disorders were statistically different between the two groups.

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INTRODUCTION

Parkinson's disease (PD) is a common neurodegenerative disease, with a prevalence of 1% in the elderly and about 10% in patients before the age of 50[1]. The pathological signs of PD are abnormal deposition of α-synuclein and progressive degeneration and loss of dopamine neurons in the substantia nigra compacta[2]. The main clinical manifestations are resting tremor, myotonia, bradykinesia, and abnormal postural gait. Over the past 15 years, non-motor symptoms (NMS), mainly autonomic dysfunction, have attracted much attention in patients with PD, including gastrointestinal dysfunction (dysphagia, delayed gastric emptying, and constipation), hypo olfaction, and sleep disorders, which are caused by neuronal loss in other areas of the brain[3]. Among them, constipation is one of the most common NMS in patients with PD. Studies have shown that 20%-89% of PD patients experience constipation, and the incidence gradually increases with the progression of the disease[4]. Compared with non-PD subjects, the frequency of constipation in PD patients increased by 2 to 4 times[5], and the degree of constipation was positively correlated with PD. Autopsy of constipated patients revealed a significant decrease in neuronal density in the substantia nigra, which also provided pathological evidence that constipation increased the risk of PD. Constipation can occur more than 10 years earlier than motor symptoms, making it one of the earliest indicators in the process of PD formation;

recently, constipation has been included in the predecessor diagnostic criteria for PD[6]. PD with constipation (PDC) is considered a unique type of constipation, but its mechanism of formation and factors affecting its severity have been less reported, and the conclusions are not uniform[7]. It is likely that there is a causal relationship between PD and constipation, such that they exacerbate one another and form a vicious cycle. To stop constipation, this cycle may be terminated to prevent or delay the occurrence of PD. However, PDC treatment is very difficult and prone to drug resistance[8,9]. Compared with functional constipation (FC), it is not clear whether the clinical characteristics and influencing factors of PDC are unique. Understanding the gastrointestinal motility characteristics and constipation classification of PDC patients is essential to guide the treatment of PDC.

MATERIALS AND METHODS

Patient recruitment

A total of 20 patients with PDC and 20 patients with FC who visited Xuanwu Hospital of Capital Medical University between August 6, 2018 and December 2, 2019 were recruited as test and control groups, respectively. All patients underwent a colonic transit test (CTT) and high-resolution anorectal manometry (HRAM) to compare the differences in colonic transit time, rectal anal canal pressure, and constipation classification between the two groups. Inclusion criteria were: (1) Age older than 18 years; (2) Fulfilled the diagnostic criteria for PD and Rome IV functional constipation; and (3) Symptom onset of more than 6 mo. Exclusion criteria were: (1) Presence of chronic diseases such as hypertension, diabetes mellitus, and coronary heart disease; (2) Organic diseases of the colon; (3) Diseases that may affect gastrointestinal motility function, such as thyroid disease, renal dysfunction, connective tissue disease, mental disorders, *etc*.; (4) History of abdominal surgery; and (5) Taking drugs that affect gastrointestinal motility in the last 2 wk.

Colon functional assessment

HRAM: The ManoScan™ High Resolution Anorectal Manometry System (given, United States) was used for all patients to measure rectal resting pressure, anal sphincter resting pressure, rectal maximum squeeze pressure, anal canal maximum squeeze pressure, intrarectal pressure, anal relaxation rate, residual anal pressure, and rectoanal pressure difference. According to the results, conditions can be divided into either defecatory impetus deficiency, or pelvic floor muscle synergism disorders.

CTT: Radiopaque markers (Sitzmarks, Konsyl Pharmaceuticals, United States) were used for detection. Each capsule contained 24 radiopaque markers, measuring 1 mm × 4.5 mm, of three different shapes: The O-Ring shape, the Double D shape, and the Tri-chamber shape. On day 1, subjects took one capsule containing the Double D shape under supervision, and swallowed the second capsule containing the O-Ring shape and the third capsule containing the Tri-chamber shape after 24 h and 48 h, respectively. After 72 h, a kidney, ureter, and bladder examination of the abdomen was performed. If the transverse colon could not be fully displayed, an X-ray of the upper abdomen was taken. The transit time of the whole colon and segmented colon was then calculated according to Metcalfe's method[10] (Figure 1).

Statistical analysis

IBM SPSS 22.0 was used to analyze all data. Continuous variables were analyzed using a *t*-test (normally distributed) and expressed as mean ± SD. Data with a non-normal distribution were expressed as percentiles, and the Kruskal-Wallis test was used to compare groups. Categorical data were calculated using the Chi-square test and expressed as a ratio (%). A $P < 0.05$ was considered statistically significant.

RESULTS

Twenty patients with PDC and 20 patients with FC were included in the study, and there were no statistically significant differences in sex, age, body mass index (BMI), or duration of constipation between the two groups. The chief complaints of constipation across the two groups were compared, and it was found that more patients in the PDC group exhibited difficulty in defecating than in the FC group, and the difference was

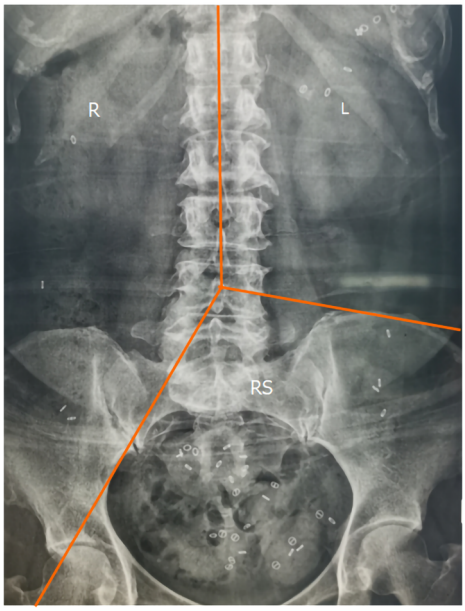

Figure 1 A line is made from the thoracic spinous process to the fifth lumbar spinous process; tangent lines are then made from the fifth lumbar spinous process to both sides of the pelvic outlet. The dashed lines from the fifth lumbar spine to the right pelvic outlet and the left ilium are distinguished as projections into the right colon, left colon, and rectosigmoid colon. R: Right; L: Left; RS: Rectosigmoid colon.

statistically significant (Table 1).

Comparison of HRAM results

The rectal resting pressure and anal sphincter resting pressure in the PDC group were significantly lower than those in the FC group. The intrarectal pressure and anal relaxation rate in the PDC group were significantly lower than those in the FC group. The proportion of paradoxical contractions in the PDC group was significantly higher than that in the FC group. These results are shown in Table 2. The study found that the proportion of defecatory impetus deficiency was 50% (10/20) in the PDC group and 40% (8/20) in the FC group; the proportion of pelvic floor muscle dyssynergia was 35% (7/20) in the PDC group and 20% (4/20) in the FC group. In addition, 10% (2/20) of patients in the PDC group demonstrated inadequate defecatory propulsion combined with pelvic floor muscle dyssynergia. Rectal anal manometry was normal in 40% (8/20) of the FC group and in only 5% (1/20) of the PDC group, with a statistically significant difference in the composition type ratio of defecatory disorders between the two groups ($P < 0.05$) (Table 3).

Comparison of colonic transit time between the two groups

Left colonic transit time (LCTT), rectosigmoid colonic transit time (RSCTT), and total colonic transit time (TCTT) were prolonged in PDC and FC patients when compared with normal values. A comparison of the segmented colonic transit time between the two groups revealed that the patients with FC had a significantly longer right colonic transit time (RCTT) and a significantly shorter RSCTT than the patients with PDC ($P < 0.05$), whereas there were no significant differences in the LCTT and TCTT between the two groups (Table 4).

Comparison of constipation classification between the two groups

Patients with PDC were divided into three subtypes based on CTT and HRAM: (1) Slow transit constipation: Prolonged CTT only (1, 5%); (2) Defecatory disorder: Altered HRAM only (4, 20.0%); and (3) Mixed constipation: Prolonged CTT and altered HRAM (15, 75.0%). Patients with FC were divided into four subtypes: (1) Slow transit constipation: (7, 35.0%); (2) Defecatory disorder: (2, 10.0%); (3) Mixed constipation: (10, 50.0%); and (4) Normal transit constipation: No functional abnormality (1, 5.0%). There were no statistically significant differences in constipation subtypes between the two groups, as seen in Table 5.

Table 1 Comparison of clinical data between the Parkinson's disease with constipation and functional constipation groups

	FC	PDC	*P* value
Male	7 (35.0%)	12 (60.0%)	0.205
Female	13 (65.0%)	8 (40.0%)	
Age, years	70.80 (6.24)	72.32 (4.80)	0.402
BMI	23.32 (2.47)	22.25 (4.32)	0.343
Decreased defecation frequency	10 (50.0%)	16 (80.0%)	0.097
Dry stools	9 (45.0%)	6 (30.0%)	0.514
Defecatory difficulties	13 (65.0%)	20 (100.0%)	0.013
Manual assisted defecation	7 (35.0%)	12 (60.0%)	0.205
Constipation duration, years	10.00 (5.00, 20.00)	5.00 (2.75, 6.50)	0.051

PDC: Parkinson's disease with constipation; FC: Functional constipation; BMI: Body mass index.

Table 2 Comparison of high-resolution anorectal manometry results between the Parkinson's disease with constipation and functional constipation groups

	FC	PDC	*P* value
Rectal resting pressure (mmHg)	82.36 (20.18)	63.98 (30.94)	0.032
Anal sphincter resting pressure (mmHg)	89.55 (16.25)	66.50 (19.35)	< 0.001
Rectal maximum squeeze pressure (mmHg)	189.50 (159.95,250.68)	188.95 (139.60,234.00)	0.516
Anal canal maximum squeeze pressure (mmHg)	222.16 (86.26)	195.25 (63.62)	0.269
Intrarectal pressure (mmHg)	43.08 (20.74)	21.73 (14.61)	0.001
Anal relaxation rate (%)	23.00 (16.00, 42.58)	0.16 (-0.07, 0.22)	< 0.001
Residual anal pressure (mmHg)	75.83 (33.55)	69.70 (30.92)	0.551
Rectoanal pressure difference (mmHg)	-36.77 (36.56)	-47.98 (27.38)	0.279
Paradoxical contraction	1 (5.0%)	8 (40.0%)	0.023

PDC: Parkinson's disease with constipation; FC: Functional constipation.

Table 3 Comparison of the composition type of defecatory disorders between the Parkinson's disease with constipation and functional constipation groups, *n* (%)

	FC	PDC	*P* value
Defecatory impetus deficiency	8 (40.0)	10 (50.0)	0.037
Pelvic floor muscle dyssynergia	4 (20.0)	7 (35.0)	
Inadequate defecatory propulsion combined with pelvic floor muscle dyssynergia	0 (0.0)	2 (10.0)	
Normal	8 (40.0)	1 (5.0)	

PDC: Parkinson's disease with constipation; FC: Functional constipation.

DISCUSSION

Constipation is one of the most important nonmotor symptoms in PD patients, and can occur several years or even decades before the onset of exercise symptoms[11,12]. Taiwanese scholars[5] conducted a follow-up survey of the relationship between the severity of constipation and the risk of PD over 5 years. The study showed that the incidence rate of PD was 1.57/100000 for those without constipation. The incidence

Table 4 Comparison of colonic transit time between the two groups

	FC	PDC	*P* value
RCTT (h)	10.50 (3.12)	8.40 (3.28)	0.045
LCTT (h)	19.50 (6.07)	20.15 (5.07)	0.715
RSCTT (h)	24.45 (4.56)	27.60 (3.68)	0.021
TCTT (h)	55.10 (7.46)	56.00 (8.31)	0.721

Normal reference values: right colon transit time ≤ 17.4 h; left colon transit time ≤ 16.8 h; rectosigmoid transit time ≤ 22.9 h; total colonic transit time ≤ 39 h for men and ≤ 50 h for women. PDC: Parkinson's disease with constipation; FC: Functional constipation; RCTT: Right colonic transit time; LCTT: Left colonic transit time; RSCTT: Rectosigmoid colonic transit time; TCTT: Total colonic transit time.

Table 5 Comparison of constipation classification between the Parkinson's disease with constipation and functional constipation groups, *n* (%)

	FC	PDC	*P* value
Slow transit constipation	7 (35.0)	1 (5.0)	0.067
Defecatory disorder	2 (10.0)	4 (20.0)	
Mixed constipation	10 (50.0)	15 (75.0)	
Normal transit constipation	1 (5.0)	0 (0.0)	

PDC: Parkinson's disease with constipation; FC: Functional constipation.

rate of PD in patients with mild, moderate, and severe constipation increased 5 years later, to 4.04/100000, 5.28/100000, 12.67/100 000, and 12.67/100000, respectively. Therefore, constipation of different severities is closely related to the pathogenesis of PD. Although constipation may be the first symptom of PD, the incidence rate of constipation is high and is influenced by many factors. It is not specific for predicting PD[13]. Thus, this study compared PDC and FC and analyzed the constipation symptoms of the two groups of patients. At the same time, the colonic transit test and HRAM were used to classify constipation and detect the corresponding indicators, in order to find more sensitive and specific indicators to predict which constipation patients will eventually develop PD and to identify the gastrointestinal motility of PDC. It is expected to provide a basis for the treatment of PDC.

The rectal anal manometry classification in this study identified that the incidence of rectoanal dysfunction in the PDC group was 95%, suggesting that anal dysfunction plays an important role in the formation of PDC. In addition, this study compared the rectal and anal dynamics of patients with PDC and FC and found that the resting rectal and anal canal pressures of the PDC group were significantly lower than those of the FC group. This is mainly derived from the internal anal sphincter tension, accounting for about 70%-85% of resting pressure[14], suggesting that patients with PDC have internal sphincter dysfunction. Some previous[14,15] neuropathological studies have found Lewy bodies in the central nervous system, peripheral autonomic system, and enteric nervous system (ENS) of PD patients. The latter can cause neurodegenerative changes in the ENS. It is speculated that neuropathy may involve the autonomic nerves innervating the internal anal sphincter, causing low resting pressure in the rectum and anal canal. In simulated defecation, the rectal defecation pressure and anal relaxation rate of the PDC group were significantly lower than those of the FC group. Rectal defecation pressure is mainly produced by abdominal pressure. Fontana *et al*[16] has found that the increase in abdominal pressure in patients with PD is significantly lower than that in healthy controls. Fontana *et al*[16] believed that the mechanism of impaired abdominal pressure may be due to increased axial muscle tension and decreased contractility. In this study, patients with PDC had an insufficient rectal defecation driving force, such that the anus could not be effectively relaxed resulting in abnormal contraction. This is considered a local dystonia in patients with PD, where rectal contraction is reduced during defecation and the abdominal tension becomes weak. A coordinated movement disorder results due to reduced rectoanal muscle contraction and puborectal and pelvic smooth muscle

dysfunction. The performance of this dystonia is aggravated during the "close" phase of PD and lessened during the "open" phase[17].

Our results showed that the LCTT, RSCTT, and TCTT were significantly prolonged in PDC patients, and the distribution of colonic transmission time in each segment of PDC patients was not uniform, especially in the left semicolon and rectum sigmoid colon, which was consistent with previous studies[18-20]. However, to our knowledge, no study has compared the segmental colon transmission time between PDC and FC patients. Our results suggest that the RSCTT of PDC patients was significantly longer than that of FC patients while the RCTT was significantly shorter than that of FC patients; this revealed the similarities and differences in the mechanism of slow colon transmission between patients with PDC and those with FC. The common mechanism may be explained as follows: (1) Compared with healthy individuals, vasoactive intestinal peptide (VIP) and VIP receptors in the colon mucosa of PDC and FC patients were downregulated[20]. VIP is a non-adrenergic non-cholinergic neuroinhibitory neurotransmitter, and its reduction could increase colon segment peristalsis, weakening the effective promotion of movement. At the same time, through abnormal colon secretion, VIP could reduce the fecal water content and lead to stool sclerosis, thus prolonging colon transmission time; and (2) ENS degeneration, a decrease in the number of intermuscular plexuses of the colonic wall, and the formation of ganglion cell vacuoles may all cause a decrease in the peristaltic function of the colon. The differences between PDC patients and FC patients are as follows: (1) PD leads to the loss of dopaminergic neurons between intestinal muscles, which may lead to decreased colonic transport function[21]. The ENS is rich in cholinergic neurons, including intestinal intermuscular motor neurons, primary transmission neurons, intermediate neurons, and other neurons projecting to the prevertebral sympathetic ganglion. Dopamine is a reactant of tyrosine hydroxylase in 4%-11% of enteric muscle neurons. Therefore, dopamine plays an important role in regulating gastrointestinal motility. Moreover, the innervation of the digestive tract gradually decreases from proximal to distal, and the motor function reduction caused by the loss of dopaminergic neurons is more serious in the distal colon segment[22]; and (2) PDC patients have more abnormal rectal-anal manometry results than FC patients. Some researchers believe that PD patients may have an independent "pelvic floor cooperative motion disorder" which is an element of extrapyramidal disease and a sequelae of neurodegeneration. These are also the reasons why the RSCTT of those with PDC was significantly longer than that of FC patients in this study.

In this study, mixed constipation was dominant in both PDC patients and FC patients, suggesting that both groups of patients had severe functional dyspraxia in the colon and rectum. There was no statistical difference between the two groups. According to the results of HRAM, the rectal sensorimotor dysfunction in patients with PDC was mainly caused by insufficient bowel movement impetus, which may in turn be caused by autonomic neuropathy innervating the rectum. A small number of patients with pelvic floor muscle synergy disorder may also have pelvic floor muscle dystonia caused by PD.

This study has several limitations. The overall sample size of this study was small. In addition, a sample of healthy individuals were not included in the study. Increasing the sample size of patients with PD and including healthy subjects will help us to better understand the pathophysiological mechanism of PDC.

In conclusion, cases of PDC and FC were associated with a prolonged CTT and abnormal HRAM. However, the rectal resting pressure, anal sphincter resting pressure, intrarectal pressure, and anal relaxation rate in the PDC group were significantly lower than those in the FC group. The proportion of paradoxical contractions in the PDC group was significantly higher than that in the FC group. The different segments of the CTT were also significantly different. The RSCTT of PDC patients was significantly longer than that of FC patients, and the RCTT was significantly shorter. The above indexes can be helpful for further studies of the mechanism of PDC and FC and for early diagnosis and treatment of patients with PD.

CONCLUSION

Patients with PDC and FC have severe functional dysmotility of the colon and rectum, but there are certain differences in segmental colonic transit time and rectal anal canal pressure between the two groups.

ARTICLE HIGHLIGHTS

Research background

Parkinson's disease (PD) is a common neurodegenerative disease characterized clinically by typical motor symptoms such as tremor, bradykinesia and myotonia and non motor symptoms such as constipation, depression and dysmetria. Constipation is one of the most common clinical manifestations of PD patients. Investigations have shown that the incidence of constipation among PD patients is up to 88%, and constipation is regarded as one of the independent risk factors for PD. PD constipation (PDC) is considered a unique type of constipation that is clinically inadequately treated, severely affecting patient quality of life. Current studies on the characteristics of intestinal motility in patients with Parkinson's disease with constipation are less frequently reported, and the control groups are mostly healthy subjects, and the conclusions are not uniform.

Research motivation

It is likely that there is a causal relationship between PD and constipation, such that they exacerbate one another and form a vicious cycle. However, PDC treatment is very difficult and prone to drug resistance. Compared with functional constipation, it is not clear whether the clinical characteristics and influencing factors of PDC are unique. Understanding the gastrointestinal motility characteristics and constipation classification of PDC patients is essential to guide the treatment of PDC.

Research objectives

To identify the gastrointestinal motility of PDC and provide a basis for its treatment. Moreover, to find more sensitive and specific indicators to predict which constipation patients will eventually develop PD.

Research methods

A colonic transit test and high-resolution anorectal manometry were performed to compare the differences in colonic transit time, rectal anal canal pressure, and constipation classification between Patients with PDC and functional constipation (FC).

Research results

The study found that the rectal resting pressure, anal sphincter resting pressure, intrarectal pressure, and anal relaxation rate in the PDC group were significantly lower than those in the FC group. The proportion of paradoxical contractions in the PDC group was significantly higher than that in the FC group. The different segments of the colonic transit test (CTT) were also significantly different. The rectosigmoid colonic transit time of PDC patients was significantly longer than that of FC patients, and the right colonic transit time was significantly shorter.

Research conclusions

Cases of PDC and FC were associated with a prolonged CTT and abnormal high-resolution anorectal manometry. There are certain differences in segmental colonic transit time, rectal anal canal pressure and composition type ratio of defecatory disorders between the two groups.

Research perspectives

This study can be helpful for further studies of the mechanism of PDC and FC and for early diagnosis and treatment of patients with PD.

REFERENCES

1 **de Rijk MC**, Tzourio C, Breteler MM, Dartigues JF, Amaducci L, Lopez-Pousa S, Manubens-Bertran JM, Alpérovitch A, Rocca WA. Prevalence of parkinsonism and Parkinson's disease in Europe: the EUROPARKINSON Collaborative Study. European Community Concerted Action on the Epidemiology of Parkinson's disease. *J Neurol Neurosurg Psychiatry* 1997; **62**: 10-15 [PMID: 9010393 DOI: 10.1136/jnnp.62.1.10]

2 **Schulz-Schaeffer WJ**. The synaptic pathology of alpha-synuclein aggregation in dementia with Lewy bodies, Parkinson's disease and Parkinson's disease dementia. *Acta Neuropathol* 2010; **120**: 131-143 [PMID: 20563819 DOI: 10.1007/s00401-010-0711-0]

3 **Pfeiffer RF**. Non-motor symptoms in Parkinson's disease. *Parkinsonism Relat Disord* 2016; **22** Suppl 1: S119-S122 [PMID: 26372623 DOI: 10.1016/j.parkreldis.2015.09.004]

4 **Pfeiffer RF**. Gastrointestinal Dysfunction in Parkinson's Disease. *Curr Treat Options Neurol* 2018; **20**: 54 [PMID: 30361783 DOI: 10.1007/s11940-018-0539-9]

5 **Lin CH**, Lin JW, Liu YC, Chang CH, Wu RM. Risk of Parkinson's disease following severe constipation: a nationwide population-based cohort study. *Parkinsonism Relat Disord* 2014; **20**: 1371-1375 [PMID: 25293395 DOI: 10.1016/j.parkreldis.2014.09.026]

6 **Berg D**, Postuma RB, Adler CH, Bloem BR, Chan P, Dubois B, Gasser T, Goetz CG, Halliday G, Joseph L, Lang AE, Liepelt-Scarfone I, Litvan I, Marek K, Obeso J, Oertel W, Olanow CW, Poewe W, Stern M, Deuschl G. MDS research criteria for prodromal Parkinson's disease. *Mov Disord* 2015; **30**: 1600-1611 [PMID: 26474317 DOI: 10.1002/mds.26431]

7 **Sharma A**, Kurek J, Morgan JC, Wakade C, Rao SSC. Constipation in Parkinson's Disease: a Nuisance or Nuanced Answer to the Pathophysiological Puzzle? *Curr Gastroenterol Rep* 2018; **20**: 1 [PMID: 29350301 DOI: 10.1007/s11894-018-0609-x]

8 **Knowles CH**, Lindberg G, Panza E, De Giorgio R. New perspectives in the diagnosis and management of enteric neuropathies. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 206-218 [PMID: 23399525 DOI: 10.1038/nrgastro.2013.18]

9 **Tateno F**, Sakakibara R, Kishi M, Ogawa E, Yoshimatsu Y, Takada N, Suzuki Y, Mouri T, Uchiyama T, Yamamoto T. Incidence of emergency intestinal pseudo-obstruction in Parkinson's disease. *J Am Geriatr Soc* 2011; **59**: 2373-2375 [PMID: 22188082 DOI: 10.1111/j.1532-5415.2011.03686.x]

10 **Metcalf AM**, Phillips SF, Zinsmeister AR, MacCarty RL, Beart RW, Wolff BG. Simplified assessment of segmental colonic transit. *Gastroenterology* 1987; **92**: 40-47 [PMID: 3023168 DOI: 10.1016/0016-5085(87)90837-7]

11 **Knudsen K**, Krogh K, Østergaard K, Borghammer P. Constipation in parkinson's disease: Subjective symptoms, objective markers, and new perspectives. *Mov Disord* 2017; **32**: 94-105 [PMID: 27873359 DOI: 10.1002/mds.26866]

12 **Stirpe P**, Hoffman M, Badiali D, Colosimo C. Constipation: an emerging risk factor for Parkinson's disease? *Eur J Neurol* 2016; **23**: 1606-1613 [PMID: 27444575 DOI: 10.1111/ene.13082]

13 **Mahlknecht P**, Seppi K, Poewe W. The Concept of Prodromal Parkinson's Disease. *J Parkinsons Dis* 2015; **5**: 681-697 [PMID: 26485429 DOI: 10.3233/JPD-150685]

14 **Lubomski M**, Davis RL, Sue CM. Gastrointestinal dysfunction in Parkinson's disease. *J Neurol* 2020; **267**: 1377-1388 [PMID: 31989280 DOI: 10.1007/s00415-020-09723-5]

15 **Uyar GÖ**, Yildiran H. A nutritional approach to microbiota in Parkinson's disease. *Biosci Microbiota Food Health* 2019; **38**: 115-127 [PMID: 31763115 DOI: 10.12938/bmfh.19-002]

16 **Fontana GA**, Pantaleo T, Lavorini F, Benvenuti F, Gangemi S. Defective motor control of coughing in Parkinson's disease. *Am J Respir Crit Care Med* 1998; **158**: 458-464 [PMID: 9700121 DOI: 10.1164/ajrccm.158.2.9705094]

17 **Yuan ZH**, Wang K, Duan LP, Fan DS, Xu ZJ, Xia ZW, Ge Y. [The characteristics of anorectal manometry in Parkinson's disease with constipation and functional constipation]. *Zhonghua Nei Ke Za Zhi* 2013; **52**: 562-566 [PMID: 24266996]

18 **Jost WH**, Schrank B. Defecatory disorders in de novo Parkinsonians--colonic transit and electromyogram of the external anal sphincter. *Wien Klin Wochenschr* 1998; **110**: 535-537 [PMID: 9782572]

19 **Sakakibara R**, Odaka T, Uchiyama T, Asahina M, Yamaguchi K, Yamaguchi T, Yamanishi T, Hattori T. Colonic transit time and rectoanal videomanometry in Parkinson's disease. *J Neurol Neurosurg Psychiatry* 2003; **74**: 268-272 [PMID: 12531969 DOI: 10.1136/jnnp.74.2.268]

20 **Knudsen K**, Fedorova TD, Bekker AC, Iversen P, Østergaard K, Krogh K, Borghammer P. Objective Colonic Dysfunction is Far more Prevalent than Subjective Constipation in Parkinson's Disease: A Colon Transit and Volume Study. *J Parkinsons Dis* 2017; **7**: 359-367 [PMID: 28157109 DOI: 10.3233/JPD-161050]

21 **Blandini F**, Balestra B, Levandis G, Cervio M, Greco R, Tassorelli C, Colucci M, Faniglione M, Bazzini E, Nappi G, Clavenzani P, Vigneri S, De Giorgio R, Tonini M. Functional and neurochemical changes of the gastrointestinal tract in a rodent model of Parkinson's disease. *Neurosci Lett* 2009; **467**: 203-207 [PMID: 19835930 DOI: 10.1016/j.neulet.2009.10.035]

22 **Knudsen K**, Haase AM, Fedorova TD, Bekker AC, Østergaard K, Krogh K, Borghammer P. Gastrointestinal Transit Time in Parkinson's Disease Using a Magnetic Tracking System. *J Parkinsons Dis* 2017; **7**: 471-479 [PMID: 28759975 DOI: 10.3233/JPD-171131]

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ORIGINAL ARTICLE

Observational Study

Apolipoprotein E polymorphism influences orthotopic liver transplantation outcomes in patients with hepatitis C virus-induced liver cirrhosis

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Abstract

BACKGROUND

Hepatitis C virus (HCV) infection is responsible for a chronic liver inflammation, which may cause end-stage liver disease and hepatocellular carcinoma.

of the manuscript for important intellectual content; and Oriá RB supervised the study.

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Institutional review board statement: All study procedures were in accordance and with the 1964 Helsinki declaration and the study protocol was approved by the Research Ethics Committee of the Federal University of Ceará, protocol No. 2.018.768.

Informed consent statement: All patients were approached by the research team, who explained the study protocol and clarified that failure to participate in the study would not cause discontinuation of care or medical treatment. After that, patients read and signed the informed consent form.

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Apolipoprotein E (protein: ApoE, gene: *APOE*), a key player in cholesterol metabolism, is mainly synthesized in the liver and *APOE* polymorphisms may influence HCV-induced liver damage.

AIM

To determine whether *APOE* alleles affect outcomes in HCV-infected patients with liver cirrhosis following orthotopic liver transplantation (OLT).

METHODS

This was a cohort study in which 179 patients, both genders and aged 34-70 years, were included before or after (up to 10 years follow-up) OLT. Liver injury severity was assessed using different criteria, including METAVIR and models for end-stage liver disease. *APOE* polymorphisms were analyzed by quantitative real-time polymerase chain reaction.

RESULTS

The *APOE3* allele was the most common (67.3%). In inflammation severity of biopsies from 89 OLT explants and 2 patients in pre-transplant, the degree of severe inflammation (A3F4, 0.0%) was significantly less frequent than in patients with minimal and moderate degree of inflammation (≤ A2F4, 16.2%) $P = 0.048$, in patients carrying the *APOE4* allele when compared to non-*APOE4*. In addition, a significant difference was also found (≤ A2F4, 64.4% *vs* A3F4, 0.0%; $P = 0.043$) and (A1F4, 57.4% *vs* A3F4, 0.0%; $P = 0.024$) in *APOE4* patients when compared to *APOE3* carriers. The fibrosis degree of the liver graft in 8 of 91 patients and the lack of the E4 allele was associated with more moderate fibrosis (F2) ($P = 0.006$).

CONCLUSION

Our results suggest that the E4 allele protects against progression of liver fibrosis and degree of inflammation in HCV-infected patients.

Key Words: Apolipoprotein E; Polymorphism; Liver cirrhosis; Hepatitis C virus; Hepatocellular carcinoma; Liver transplantation

Core Tip: Hepatitis C virus (HCV) infection is responsible for a chronic liver inflammation, which may cause end-stage liver disease. Apolipoprotein E (protein: ApoE, gene: *APOE*) is key for lipid metabolism. In this study, the *APOE4* allele, which has been associated with increased risk of acquiring late-onset Alzheimer's disease, was found to have a protective effect against the progression of inflammation and/or fibrosis in liver damage induced by HCV pre- and post-liver transplantation. Further studies are needed to unravel the possible contribution of ApoE from the donor liver to this protection.

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INTRODUCTION

The World Health Organization reported in 2015, that around 71 million people had chronic hepatitis C virus (HCV) infection worldwide, with a global prevalence of 1% and that 399,000 died of hepatocellular carcinoma (HCC) or cirrhosis[1].

HCV infection causes a chronic liver inflammatory condition leading to chronic hepatitis[2,3]. The evolution from acute to chronic hepatitis C occurs in up to 80% of cases when HCV infection lasts for more than six months. Without characteristic

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symptoms, HCV evolves slowly, for years, with approximately 20% of those chronically infected progressing to cirrhosis, and between 1% to 5% to HCC [4,5].

Human apolipoprotein E (protein: ApoE, gene: *APOE*) is a 34-KDa glycoprotein of 299 amino acids. ApoE is an important protein constituent of very-low-density lipoproteins (LDL), high-density lipoproteins, and chylomicrons in plasma, and a ligand for the LDL receptor[6]. ApoE is synthesized mainly in the liver (90%), but also in spleen, kidney, lungs, gonads, monocyte-macrophages, and in the nervous system[7,8].

The human *APOE* gene is polymorphic with three common *APOE* alleles on chromosome 19 (19q13), named E2, E3 and E4, giving six possible genotypes: E2/E2, E2/E3, E2/E4, E3/E3, E3/E4 and E4/E4[9]. These alleles form different ApoE isoforms due to amino acid substitutions at positions 112 and 158: E2 = Cys-112/Cys-158; E3 = Cys-112/Arg-158; and E4 = Arg-112/Arg-158[10].

Several studies have documented the association between ApoE isoforms and chronic illnesses such as Alzheimer's disease[11], atherosclerosis[12], herpes simplex virus infection[13] and early childhood diarrhea[12]. The ApoE4 allele has been recently associated with a high risk for severe coronavirus disease 2019 infection, independent of preexisting cardiovascular disease, type-2 diabetes and dementia[14]. In addition, the *APOE3*/3 genotype is implicated in fibrosis progression in HCV-infected patients, likely through mechanisms of competition for viral entry and replication[15].

Although some studies report that *APOE4* exerts a protective effect in HCV-induced liver damage, no studies have investigated the role of *APOE* genotypes in modifying the natural history of HCV-induced liver injury in liver transplanted patients in a Brazilian setting. Our aim, therefore, was to establish whether *APOE4* genotype recipients were associated with more benign HCV-related liver injuries compared to patients with other *APOE* genotypes.

MATERIALS AND METHODS

Study design

This is a cohort study conducted at the University Hospital Walter Cantídio and the Fortaleza General Hospital (HGF). A total of 179 consecutive patients were enrolled from May 2017 to July 2019 for the collection of buccal cells and medical record data. Medical records from liver transplant recipients before May 2017 were also collected retrospectively and prospectively each year. Patients in the orthotopic liver transplantation (OLT) queue, or liver transplanted from May 2017 onwards, had data collected prospectively and annually during the study period.

The study included 179 patients of both genders and aged 34-70 years, with HCV-related end-stage liver disease, 105 of them complicated with HCC and 74 without HCC, in pre- and/or post-OLT. At enrolment, 143 known HCV-infected patients were on antiviral treatment, 126 with direct-acting antivirals and 17 treated with the combination of interferon & ribavirin or pegylated interferon & ribavirin; 36 patients had not received any treatment. The HCV status of all patients was confirmed by identification of serum HCV-RNA and HCV genotypes. Exclusion criteria were: patient refusal, coinfection with HBV or HIV, and HCC associated with metastases.

The study protocol was approved by the Research Ethics Committee of the Federal University of Ceará, Protocol No 2.018.768 and the HGF, Protocol No 2.062.278. The research team explained the study protocol to all patients and clarified that failure to participate in the study would not cause discontinuation of care or medical treatment. Patients then read and signed the informed consent form. All protocols of this study were in accordance with the Helsinki Declaration.

APOE polymorphisms

Of 179 patients, oral cells for DNA extraction were obtained at single time points from 56 (31.3%) pre-OLT patients, and from 123 (68.7%) who underwent liver transplantation. Oral cell DNA was extracted using the Gentra Puregene system (Qiagen, MD, United States)[12].

APOE genotyping was detected by quantitative real-time polymerase chain reaction (qRT-PCR), through enhancement of a fluorescent signal (SYBR® Green) interspersed in the double strand of the amplified DNA[16]. The primers were combined in three PCR amplification mixtures according to Calero *et al*[16] in a Light Cycler® Nano (Roche) with a 32-well RT-PCR system.

Data and statistical analysis

Demographic, clinical and laboratory data were collected after thorough reviews of medical records during the preoperative period (179 patients) and after OLT with follow-up of the 144 transplanted patients over 10 years (Supplementary Figure 1). Data included serological markers such as anti-HCV antibodies to define the agent and quantitative HCV-RNA; severity markers of liver cirrhosis [models for end-stage liver disease (MELD)]; liver imaging (computed tomography, nuclear magnetic resonance, and ultrasonography) for identification of liver tumor and classification according to the Milan criteria[17]. Out of 144 patients who underwent OLT based on Milan classification, 24 (16.7%) were subjected to one or more sessions of chemoembolization to reduce tumor size before Milan criteria were reached.

Staging the degree of liver damage and hepatic fibrosis

Liver damage severity was categorized into different criteria. Less severe cases were identified by Milan scores (single nodule < 5 cm, or up to 3 nodules < 3 cm), METAVIR (≤ A2 and ≤ F2), and MELD < 25. Patients with more severe liver injury were scored according to the Milan expanded criteria of the University of San Francisco[18] (1 nodule ≤ 6.5 cm; ≤ 3 nodules, each ≤ 4.5 cm with total diameter ≤ 8 cm), METAVIR score (A3 and ≥ F3), and MELD > 25. METAVIR scoring was categorized to assess liver inflammation/fibrosis severity (Supplementary Table 1).

Liver fibrosis was assessed by using aminotransferase-platelet ratio index (APRI) and fibrosis-4 (FIB4) scores. APRI = [AST (U/L)/35 (ULN, the upper limit of normal AST is estimated at 35)]/platelets count (10^9/L) × 100 and FIB4 = AST (U/L) × age (years)/[platelets count (10^9/L) × ALT$^{1/2}$ (U/L)]. The cut-off points of severity are: for significant liver fibrosis (APRI ≥ 1.5, METAVIR F3-F4, and FIB4 ≥ 3.25) and for low-degree fibrosis (APRI ≤ 0.5, METAVIR F0-F1, and FIB4 ≤ 1.45)[19].

Liver biopsy data were obtained from liver explants patients in pre-OLT and of post-OLT liver grafts. Liver biopsies were performed post-transplant in 91 of the 144 transplant recipients, who presented positive HCV viral load, or high risk of viral recurrence or rejection. All recipients had a minimum 1-year follow-up period post-OLT, and donated at least one liver biopsy more than 1 year after their OLT.

Data were analyzed with the SPSS statistical 22.0 software. For normality, D'Agostino and Kolmogorov–Smirnov tests were performed. The absolute and relative frequencies were calculated for the categorical variables and mean ± SD for the numerical variables. Fisher's exact test or the Mann–Whitney test was used to compare frequencies or means, respectively, when appropriate. Multilinear regression and correlation analyses were performed to avoid other potential confounders. Either one-way or two-way ANOVA test followed by Bonferroni's or Kruskal-Wallis, and Dunn's test were used for multiple comparisons. $P < 0.05$ was considered significant.

RESULTS

A total of 179 patients (145 males, 34 females) were enrolled in this study with a median age of 61 (range = 34-70). All patients were diagnosed with HCV-induced chronic liver cirrhosis; 105 of them (58.6%) complicated with HCC.

Analysis of pre-OLT data in the overall population

Demographic and clinical data were collected from all patients only in pre-OLT. Their *APOE* allele stratification is reported in Table 1; no statistical difference was found in any comparisons.

The *APOE* allele frequency according to group, HCV viral load and liver inflammation by the METAVIR score are depicted in Table 2. The *APOE* allele frequencies were 67.3%, 17.1% and 15.6% for E3, E2 and E4, respectively. The most frequent genotype was E3/E3 (51.4%).

APOE allele frequencies were associated with liver inflammation based on METAVIR score, assessed in biopsies of liver explants from 89 patients and from 2 patients in pre-OLT. The degree of severe inflammation (A3F4, 0.0%) was significantly less frequent than in patients with minimal and moderate degree of inflammation (≤ A2F4, 16.2%) $P = 0.048$, in patients carrying the *APOE4* allele when compared to non-*APOE4*. In addition, a significant difference was also found regarding METAVIR score (≤ A2F4, 64.4% *vs* A3F4, 0.0%; $P = 0.043$) and (A1F4, 57.4% *vs* A3F4, 0.0%; $P = 0.024$) in *APOE4* patients compared to *APOE3* carriers (Table 3). All patients with advanced liver inflammation (A3) were treated with antivirals only in the post-OLT period.

Among patients with less severe liver disease (MELD ≤ 25), the degree of severe

Table 1 Demographic and clinical profile of all candidate patients for liver transplant according to E2, E3 and E4 allele stratification

Variables	*APOE2*	*APOE3*	*APOE4*	*P* value
Age (yr) (mean ± SD)	60.8 ± 7.26	60.3 ± 7.19	60.3 ± 7.44	0.956
BMI (mean ± SD)	27.6 ± 4.36	26.4 ± 5.01	27.0 ± 4.81	0.167
Gender (n^1 = 179; n^2 = 358), n^2 (%)				
Male (n^1 = 145; n^2 = 290)	52 (17.9)	193 (66.6)	45 (15.5)	0.650
Female (n^1 = 34; n^2 = 68)	9 (13.2)	48 (70.6)	11 (16.2)	
BMI (n^1 = 179; n^2 = 358), n^2 (%)				
Non-obese (n^1 = 137; n^2 = 274)	49 (17.9)	185 (67.5)	40 (14.6)	0.519
Obese (n^1 = 42; n^2 = 84)	12 (14.3)	56 (66.7)	16 (19.0)	
Etiology (n^1 = 179; n^2 = 358), n^2 (%)				
HCV (n^1 = 74; n^2 = 148)	24 (16.2)	96 (64.9)	28 (18.9)	0.357
HCV + HCC (n^1 = 105; n^2= 210)	37 (17.6)	145 (69.0)	28 (13.3)	
HCC Milan (n^1 = 105; n^2= 210), n^2 (%)				
Within the criteria (n^1 = 83; n^2 = 166)	29 (17.5)	115 (69.3)	22 (13.2)	0.885
Outside the criteria (n^1 = 22; n^2 = 44)	8 (18.2)	29 (65.9)	7 (15.9)	

Of 105 patients complicated with hepatocellular carcinoma. n^1: Number of subjects; n^2: Number of alleles; *APOE*: Apolipoprotein E gene; BMI: Body mass index; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

Table 2 Genotypic and allele distribution of apolipoprotein E according to group, hepatitis C virus serology/viral load and severity of liver inflammation by the METAVIR score of the total population

APOE genotype		Group		HCV-RNA		METAVIR		METAVIR	
	All	HCV	HCV + HCC	Positive	Negative	≤ A2F4	A3F4	A1F4	A3F4
	n^1 (179)	n^1 (74)	n^1 (105)	n^1 (33)	n^1 (146)	n^1 (80)	n^1 (11)	n^1 (27)	n^1 (11)
E2/E2	15 (8.4)	6 (8.1)	9 (8.6)	7 (21.2)	8 (5.5)	9 (11.2)	1 (9.1)	4 (14.8)	1 (9.1)
E2/E3	25 (14.0)	9 (12.2)	16 (15.2)	3 (9.1)	22 (15.1)	11 (13.8)	2 (18.2)	4 (14.8)	2 (18.2)
E2/E4	6 (3.3)	3 (4.1)	3 (2.9)	0 (0.0)	6 (4.1)	2 (2.5)	0 (0.0)	1 (3.7)	0 (0.0)
E3/E3	92 (51.4)	36 (48.6)	56 (53.3)	16 (48.5)	76 (52.0)	39 (48.8)	8 (72.7)	12 (44.5)	8 (72.7)
E3/E4	32 (17.9)	15 (20.3)	17 (16.2)	5 (15.1)	27 (18.5)	14 (17.5)	0 (0.0)	3 (11.1)	0 (0.0)
E4/E4	9 (5.0)	5 (6.7)	4 (3.8)	2 (6.1)	7 (4.8)	5 (6.2)	0 (0.0)	3 (11.1)	0 (0.0)
***APOE* alleles**	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)	n^2 (%)
E2	61 (17.1)	24 (16.2)	37 (17.6)	17 (25.8)	44 (15.1)	31 (19.4)	4 (18.2)	13 (24.1)	4 (18.2)
E3	241 (67.3)	96 (64.9)	145 (69.1)	40 (60.6)	201 (68.8)	103 (64.4)	18 (81.8)	31 (57.4)	18 (81.8)
E4	56 (15.6)	28 (18.9)	28 (13.3)	9 (13.6)	47 (16.1)	26 (16.2)	0(0.0)	10 (18.5)	0 (0.0)
All	358	148	210	66	292	160	22	54	22

METAVIR score of biopsies liver explants from 89 patients and from 2 patients in pre-transplant. n^1: Number of subjects; n^2: Number of alleles; *APOE*: Apolipoprotein E gene; HCV: Hepatitis C virus; HCC: Hepatocellular carcinoma.

inflammation (A3F4, 0.0%) was significantly less frequent in *APOE4* carriers when compared to non-*APOE4* patients with minimal and moderate degree of inflammation (≤ A2F4, 15.7%, P = 0.046), and with minimal degree of inflammation (A1F4, 18.2%, P = 0.044). These results were also significant in *APOE4* patients when compared to *APOE3*, as categorized by their METAVIR scores [≤ A2F4, 65.7% *vs* A3F4, 0.0% (P = 0.042) and A1F4, 61.4% *vs* A3F4, 0.0% (P = 0.040)] (Table 4).

Logistic regression model predicting moderate and severe (A2A3) *vs* minimal (A1)

Table 3 METAVIR scores for liver inflammation in pre-orthotopic liver transplantation patients according to E2, E3 and E4 alleles stratification

METAVIR score	*APOE2*			*APOE3*			*APOE4*		
	Yes	No		Yes	No		Yes	No	
	n^2 (%)	n^2 (%)	*P* value	n^2 (%)	n^2 (%)	*P value*	n^2 (%)	n^2 (%)	*P* value
METAVIR (n^1 = 38; n^2 = 76)									
A1F4 (n^1 = 27; n^2 = 54)	13 (24.1)	41 (75.9)	0.764	31 (57.4)[3]	23 (42.6)	0.064	10 (18.5)	44 (81.5)	0.055
A3F4 (n^1 = 11; n^2 = 22)	4 (18.2)	18 (81.8)		18 (81.8)	4 (18.2)		0 (0.0)[1]	22 (100.0)	
METAVIR (n^1 = 91; n^2 = 182)									
≤ A2F4 (n^1 = 80; n^2 = 160)	31 (19.4)	129 (80.6)	1.000	103 (64.4)[4]	57 (35.6)	0.148	26 (16.2)	134 (83.8)	0.048[a]
A3F4 (n^1 = 11; n^2 = 22)	4 (18.2)	18 (81.8)		18 (81.8)	4 (18.2)		0 (0.0)[2]	22 (100.0)	

n^1: Number of subjects; n^2: Number of alleles.

[3]*APOE3 vs APOE4* allele frequency, $P = 0.024$.

[4]*APOE3 vs APOE4* allele frequency, $P = 0.043$.

[a]$P < 0.05$. METAVIR A1: Minimal degree of inflammation; METAVIR A1A2: Minimal and moderate degree of inflammation; METAVIR A3: High degree of inflammation; *APOE*: Apolipoprotein E gene.

degree of liver inflammation included as significant predictors male-gender ($P = 0.032$), and mean-BMI ($P = 0.017$). In the other analyses, there was no significance without adjustment or with adjustment for potential confounders (MELD, age and BMI) (Table 5).

Analysis of the post-OLT data

With respect to the fibrosis degree, using METAVIR scores, of liver grafts in 91 non-*APOE4* patients undergoing OLT, the frequency of patients with a moderate degree of fibrosis (F2) was significantly higher in up to 1 year when compared to those between 1 and 5 years ($P = 0.006$) (Figure 1D). No other significant differences were found (Figure 1). Of note, patients who progressed to moderate (F2) fibrosis in the post-OLT follow-up were treated with antiviral therapy only in the post-OLT period.

In a 10-year follow-up post-OLT, based on non-invasive tests (APRI and FIB4) of the total transplanted population, a significant higher mean of the 1st year APRI score was found when compared to the 4th and 5th years ($P < 0.001$), as well as between the 1st year FIB4 and the 5th year scores ($P < 0.001$) (Figure 2A). APRI and FIB4 scores over the follow-up time did not significantly change regardless of the E2 and E4 alleles (Figure 2).

DISCUSSION

Increasing evidence associates *APOE* polymorphisms with progression of chronic liver disease[20,21]. Here, we evaluate the impact of ApoE genetic background in patients with HCV-induced liver cirrhosis, with or without HCC, transplanted or non-transplanted, and with positive or negative viral loads; in particular, in a Brazilian population and with a focus on the influence of E2, E3, and E4 alleles. We related E2, E3, and E4 carriers with the degree of liver inflammation, fibrosis and severity of the disease assessed by MELD scores, using liver biopsy and/or non-invasive indices, such as APRI and FIB4, and the METAVIR score. In addition, we also associated *APOE* alleles with co-morbidities and lipid blood levels.

As expected, we found E3 the most common *APOE* allele (67.3%), though slightly lower than the expected 70%-80% seen in the general Brazilian population[22] and in other countries[15,23] The E2 allele frequency was 17.1%, higher than in the Brazilian general population[22] and even greater than the E4 allele (15.6%). This E2 frequency in our study population was also higher than that reported by Wozniak *et al*[24] (7.7%).

Our liver biopsies from 89 liver explants and from 2 pre-OLT patients showed that cirrhotic E4 carriers were less likely to present with severe inflammation. These results were also evident in patients with MELD score ≤ 25. All these patients with severe

Table 4 Association of the models for end-stage liver disease score and variables in pre-orthotopic liver transplantation patients according to E2, E3 and E4 allele stratification

Variables	MELD≤ 25				MELD> 25				MELD≤ 25			MELD> 25		
	APOE2	*APOE3*	*APOE4*		*APOE2*	*APOE3*	*APOE4*		*APOE4*			*APOE4*		
									(Yes)	(No)		(Yes)	(No)	
	n^2 (%)	n^2 (%)	n^2 (%)	*P* value	n^2 (%)	n^2 (%)	n^2 (%)	*P* value	n^2 (%)	n^2 (%)	*P* value	n^2 (%)	n^2 (%)	*P* value
METAVIR (n^1 = 38; n^2 = 76)														
A1F4 (n^1 = 27; n^2 = 54)	9 (20.4)	27 (61.4)[3]	8 (18.2)	0.085	4 (40.0)	4 (40.0)	2 (20.0)	NA	8 (18.2)	36 (81.8)	0.044[a]	2 (20.0)	4 (80.0)	NA
A3F4 (n^1 = 11; n^2 = 22)	4 (18.2)	18 (81.8)	0 (0.0)[3]		0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	22 (100.0)		0 (0.0)	0 (0.0)	
METAVIR (n^1 = 91; n^2 = 182)														
≤ A2F4 (n^1 = 80; n^2 = 160)	26 (18.6)	92 (65.7)[4]	22 (15.7)	0.123	5 (25.0)	11 (55.0)	4 (20.0)	NA	22 (15.7)	118 (84.3)	0.046[a]	4 (20.0)	16 (80.0)	NA
A3F4 (n^1 = 11; n^2 = 22)	4 (18.2)	18 (81.8)	0 (0.0)[4]		0 (0.0)	0 (0.0)	0 (0.0)		0 (0.0)	22 (100.0)		0 (0.0)	0 (0.0)	

n^1: Number of subjects; n^2: Number of alleles.

[3]*APOE3 vs APOE4* allele frequency, $P = 0.040$.

[4]*APOE3 vs APOE4* allele frequency, $P = 0.042$.

[a]$P < 0.05$. METAVIR F4: Cirrhosis; METAVIR A1: Minimal degree of inflammation; METAVIR A1A2: Minimal and moderate degree of inflammation; METAVIR A3: High degree of inflammation; *APOE*: Apolipoprotein E gene; MELD: Model for end-stage liver disease; NA: Not applicable.

hepatic inflammation were treated with antivirals only post-OLT. In agreement, others identified a protective role of *APOE4* against severe HCV-related liver damage, when comparing to patients with mild liver disease[24], while another study found that *APOE4* allele was under-represented in 996 patients chronically infected with HCV[23]. Other researchers have also noted a higher frequency of the E4 allele among patients with chronic non-cirrhotic hepatitis C, suggesting that the E4 allele is protective against severe HCV infection[25] However, somewhat inconsistent with these findings a 2003 report by Mueller *et al*[26] was unable to associate the E4 allele in chronic HCV-infected patients with a strong antiviral treatment response, although a later study by Price *et al*[27] found an association of the E2 and E4 alleles with reduced likelihood of chronic infection in HCV patients.

In 2012, Ahn *et al*[20] suggested that high ApoE serum levels in patients with liver cirrhosis may be due to liver inflammation. ApoE is known to modulate immune function by inhibiting CD4 and CD8 lymphocyte proliferation, reducing lymphocyte-derived production of IL-2, a key cytokine in regulating lymphocyte differentiation[28]. We speculate that a reduction in ApoE plasma levels, which is recognized for *APOE4* carriers[6], could be protective to support OLT and to reduce over-inflammation and fibrosis caused by chronic HCV infection.

Table 5 Logistic regression model predicting moderate and severe (A2A3) degree of liver inflammation

Variables	Odds ratio	95%CI	*P* value
Alcohol consumption	0.636	0.188-2.148	0.466
Gender–male	7.609	1.195-48.447	0.032[a]
Mean MELD	0.932	0.829-1.049	0.244
Mean age	0.969	0.893-1.051	0.446
Mean BMI	0.874	0.782-0.976	0.017[a]
*APOE*2	1.519	0.059-39.334	0.801
*APOE*3	2.850	0.121-66.917	0.516
*APOE*4	2.868	0.112-73.560	0.524

[a]$P < 0.05$. MELD: Model for end-stage liver disease; BMI: Body mass index; *APOE*: Apolipoprotein E gene; CI: Confidence interval.

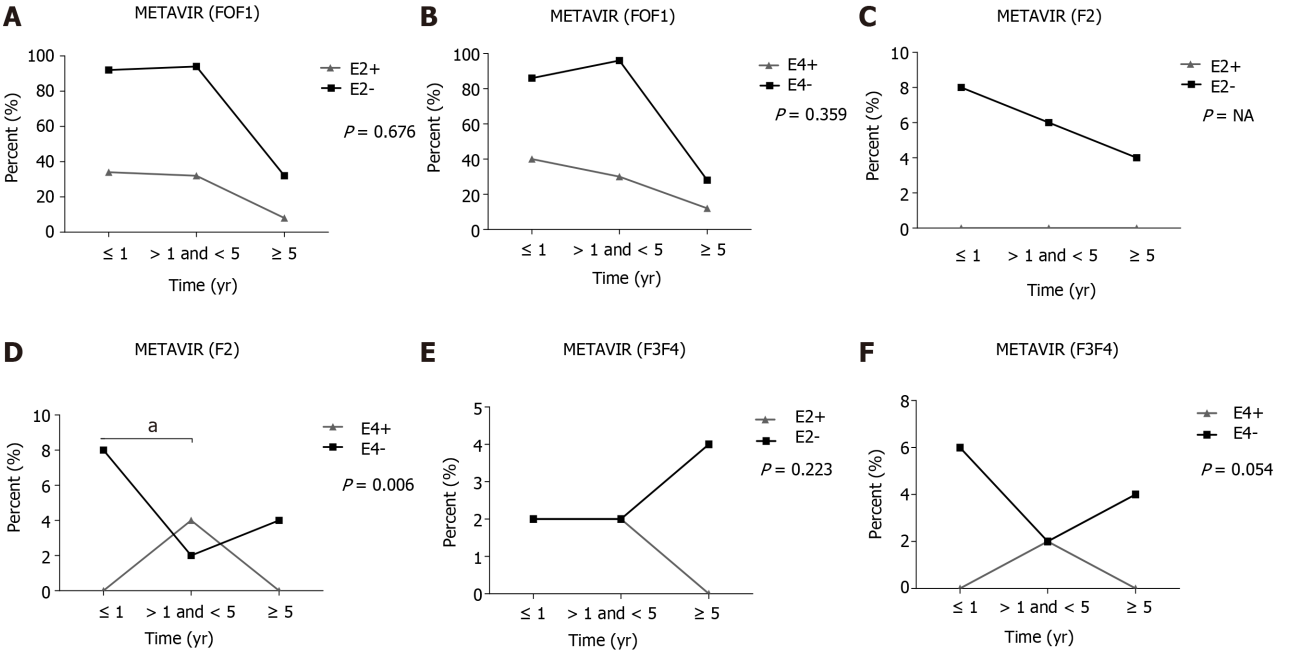

Figure 1 Follow-up of liver fibrosis in liver transplanted patients in the presence or absence of the E2 and E4 allele. A: METAVIR (F0F1) in the presence or absence of the E2 allele; B: METAVIR (F0F1) in the presence or absence of the E4 allele; C: METAVIR (F2) in the presence or absence of the E2 allele; D: METAVIR (F2) in the presence or absence of the E4 allele; E: METAVIR (F3F4) in the presence or absence of the E2 allele; F: METAVIR (F3F4) in the presence or absence of the E4 allele. [a]$P < 0.01$. E2- and E4-: Absence of the respective alleles; E2+ and E4+: Presence of the respective alleles. Fisher chi-square test; F: Degree of fibrosis; NA: Not applicable.

In the follow-up of our 144 liver transplanted patients, we identified the E4 allele as protective against the progression of liver fibrosis in 91 (63.2%) recipients. This protection of *APOE4* against severe HCV-related liver fibrosis agrees with an early report[24]. Other investigators also showed a benefit of the *APOE4* allele against fibrosis progression in liver transplanted patients diagnosed with HCV recurrence. Additionally, it is reported that liver transplanted patients carrying at least one E4 allele may present with reduced graft fibrosis progression during HCV recurrence. Indeed, ApoE polymorphism can be an important tool to monitor fibrosis progression in patients with hepatitis C and normal values of alanine aminotransferase, as there may be competition mechanisms for viral entry and replication in cells[15].

ApoE is a component of several lipoprotein classes and important for lipid transport. ApoE isoforms have several effects on lipoprotein entry into cells, and this mechanism might explain our results, supporting previous investigations in which ApoE4 protects against HCV infection[29,30].

In the follow-up of liver fibrosis progression evaluated between 1 to 10 years post-OLT of our transplanted population, the average score of APRI and FIB4, tended to

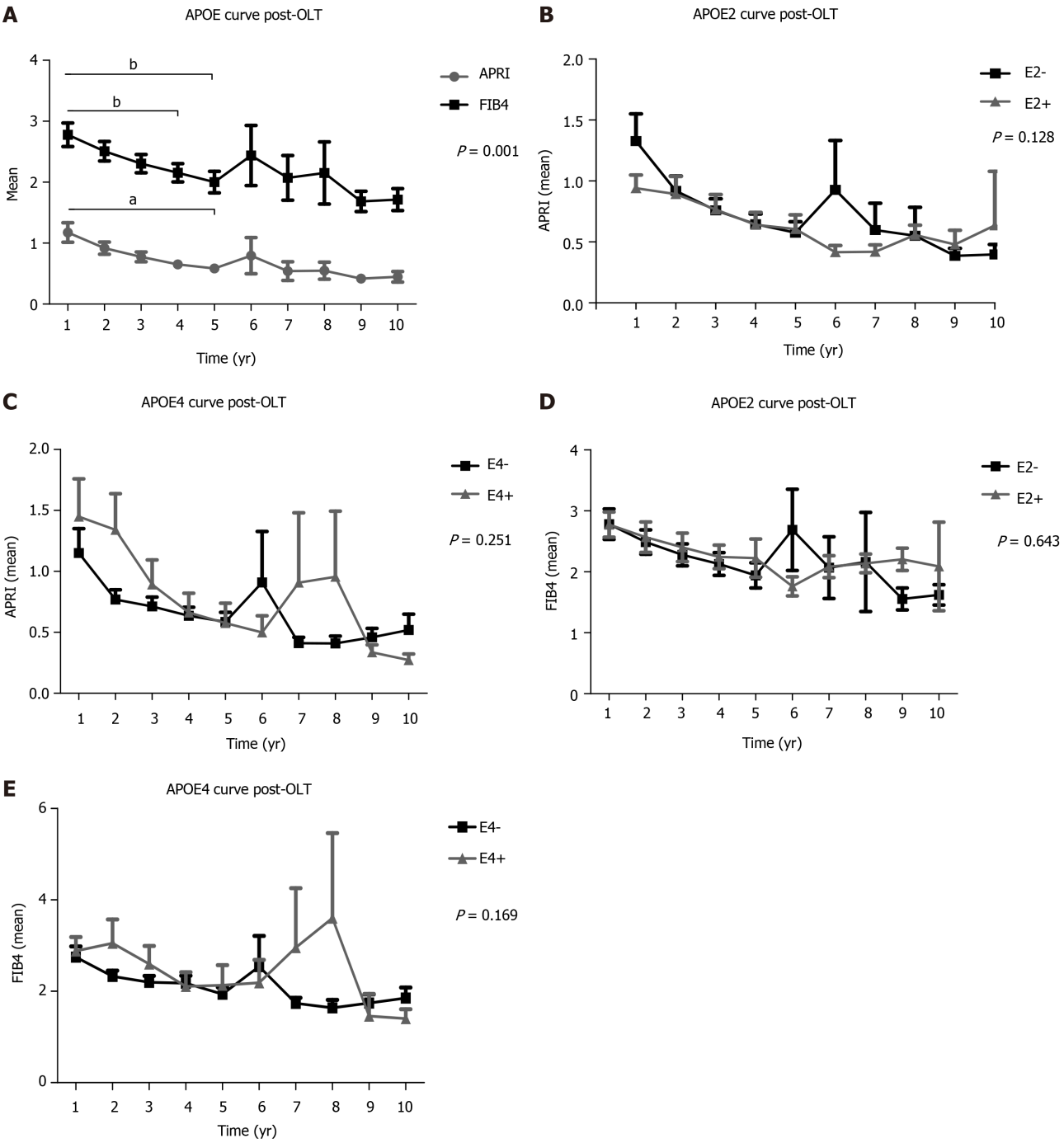

Figure 2 Follow-up using non-invasive methods (aspartate aminotransferase to platelet ratio index and fibrosis 4) of liver transplant patients in the presence or absence of the E2 and E4 alleles. A: Post-orthotopic liver transplantation (OLT) apolipoprotein E gene (*APOE*) curve for mean aspartate aminotransferase to platelet ratio index (APRI) and fibrosis 4 (FIB4); B: Post-OLT curve considering the presence or absence of *APOE2* for mean APRI; C: Post-OLT curve considering the presence or absence of *APOE4* for mean APRI; D: Post-OLT curve considering the presence or absence of *APOE2* for mean FIB4; E: Post-OLT curve considering the presence or absence of *APOE4* for mean FIB4. Two-way ANOVA, results are shown in mean ± SEM. $^{a}P < 0.01$. $^{b}P < 0.01$. E2- and E4-: Absence of the respective alleles; E2+ and E4+: Presence of the respective alleles. *APOE*: Apolipoprotein E gene; OLT: Orthotopic liver transplantation; APRI: Aspartate aminotransferase to platelet ratio index; FIB4: Fibrosis 4.

decrease significantly over the years, implying liver graft survival without progression to fibrosis. Thus, non-invasive methods are now widely used in clinical practice to stage the degree of fibrosis[31,32].

Our findings suggest that *APOE4* can be important tool in the medical management of patients following inflammation and liver fibrosis, since the carriage of *APOE4* may select patients with a more benign clinical course of liver disease. Of note, patients with a degree of severe inflammation and moderate degree of fibrosis (F2) were cured for HCV only in the post-OLT period.

This study has some limitations: Data from liver transplanted patients were

obtained retrospectively from medical records; no data from liver graft donors, including *APOE* genotypes, were collected. The sample size, may have been insufficient to draw strong, robust conclusions. Isoform studies have previously shown that transplanted donor livers supply > 90% of plasma ApoE[10]. The remainder is synthesized by circulating macrophages and immune cells, or by tissues such as kidney, adipose and muscle, and hence retains the phenotype of the recipient. However, to date, there are no reports of how each source, hepatic ApoE or circulating non-liver ApoE, particularly that of macrophages, might affect the inflammation and fibrosis status of the transplanted liver.

CONCLUSION

Our results indicate that *APOE4* genotype may protect against HCV-induced severe hepatic inflammation and fibrosis in pre- and post-OLT patients. Additionally, the *APOE2* allele was over-represented in these patients, suggesting that E2 carriers have increased risk and worse outcomes following HCV infection. Further studies are needed to better understand how ApoE levels *via* liver and extrahepatic derived sources, and biochemical activities, are affected by donor and recipient genetic backgrounds after liver transplantation.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) can cause chronic liver inflammation, end-stage liver disease and hepatocellular carcinoma (HCC). Apolipoprotein E (protein: ApoE, gene: *APOE*) is mainly liver synthesized and *APOE* polymorphisms may affect HCV-induced liver damage after orthotopic liver transplantation (OLT).

Research motivation

Although *APOE4* may protect against HCV-induced liver damage, the role of *APOE* genotypes in modifying HCV-induced liver injury in post-OLT has not been reported.

Research objectives

To establish if *APOE4* genotype OLT recipients have more benign HCV-related liver injuries compared to patients with *APOE2* or *APOE4* genotypes.

Research methods

Patients with HCV-related end-stage liver disease, 105 of 179 complicated with HCC, were assessed pre-OLT (179) and post-OLT (144; with a 1-year follow-up for 132 patients). Liver injury analyses included METAVIR and models for end-stage liver disease scores, while *APOE* genotype was determined by qRT-PCR.

Research results

HCV positive recipients with severe hepatic inflammation had low *APOE4* genotype frequency, compared to those with minimal and moderate inflammation. In addition, liver fibrosis was lower in patients carrying *APOE4* genotype compared to those carrying the most common *APOE3* genotype.

Research conclusions

We found that carriage of *APOE4* genotype protects pre-OLT patients against HCV-induced severe hepatic inflammation, and against fibrosis progression post-OLT.

Research perspectives

We propose that carriage of *APOE*4 genotype protects against progression of inflammation and liver fibrosis in recurrent HCV hepatitis after OLT, but additional studies are needed to assess whether donor-derived ApoE4 protein directly affects these processes.

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REFERENCES

1 **World Health Organization**. Global hepatitis report. 2017. [cited 19 December 2020]. Available from: https://www.who.int/hepatitis/publications/global-hepatitis-report2017/en/
2 **Fauteux-Daniel S**, Larouche A, Calderon V, Boulais J, Béland C, Ransy DG, Boucher M, Lamarre V, Lapointe N, Boucoiran I, Le Campion A, Soudeyns H. Vertical Transmission of Hepatitis C Virus: Variable Transmission Bottleneck and Evidence of Midgestation *In Utero* Infection. *J Virol* 2017; **91** [PMID: 28931691 DOI: 10.1128/JVI.01372-17]
3 **Westbrook RH**, Dusheiko G. Natural history of hepatitis C. *J Hepatol* 2014; **61**: S58-S68 [PMID: 25443346 DOI: 10.1016/j.jhep.2014.07.012]
4 **Mohd Hanafiah K**, Groeger J, Flaxman AD, Wiersma ST. Global epidemiology of hepatitis C virus infection: new estimates of age-specific antibody to HCV seroprevalence. *Hepatology* 2013; **57**: 1333-1342 [PMID: 23172780 DOI: 10.1002/hep.26141]
5 **Toshikuni N**, Arisawa T, Tsutsumi M. Hepatitis C-related liver cirrhosis - strategies for the prevention of hepatic decompensation, hepatocarcinogenesis, and mortality. *World J Gastroenterol* 2014; **20**: 2876-2887 [PMID: 24659879 DOI: 10.3748/wjg.v20.i11.2876]
6 **Mahley RW**. Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders. *J Mol Med (Berl)* 2016; **94**: 739-746 [PMID: 27277824 DOI: 10.1007/s00109-016-1427-y]
7 **Tudorache IF**, Trusca VG, Gafencu AV. Apolipoprotein E - A Multifunctional Protein with Implications in Various Pathologies as a Result of Its Structural Features. *Comput Struct Biotechnol J* 2017; **15**: 359-365 [PMID: 28660014 DOI: 10.1016/j.csbj.2017.05.003]
8 **Mahley RW**, Rall SC Jr. Apolipoprotein E: far more than a lipid transport protein. *Annu Rev Genomics Hum Genet* 2000; **1**: 507-537 [PMID: 11701639 DOI: 10.1146/annurev.genom.1.1.507]
9 **Huebbe P**, Rimbach G. Evolution of human apolipoprotein E (APOE) isoforms: Gene structure, protein function and interaction with dietary factors. *Ageing Res Rev* 2017; **37**: 146-161 [PMID: 28647612 DOI: 10.1016/j.arr.2017.06.002]
10 **Nascimento JCR**, Matos GA, Pereira LC, Mourão AECCB, Sampaio AM, Oriá RB, Toniutto P. Impact of apolipoprotein E genetic polymorphisms on liver disease: An essential review. *Ann Hepatol* 2020; **19**: 24-30 [PMID: 31548169 DOI: 10.1016/j.aohep.2019.07.011]
11 **Saunders AM**, Trowers MK, Shimkets RA, Blakemore S, Crowther DJ, Mansfield TA, Wallace DM, Strittmatter WJ, Roses AD. The role of apolipoprotein E in Alzheimer's disease: pharmacogenomic target selection. *Biochim Biophys Acta* 2000; **1502**: 85-94 [PMID: 10899434 DOI: 10.1016/s0925-4439(00)00035-1]
12 **Pereira LC**, Nascimento JCR, Rêgo JMC, Canuto KM, Crespo-Lopez ME, Alvarez-Leite JI, Baysan A, Oriá RB. Apolipoprotein E, periodontal disease and the risk for atherosclerosis: a review. *Arch Oral Biol* 2019; **98**: 204-212 [PMID: 30503976 DOI: 10.1016/j.archoralbio.2018.11.009]
13 **Linard M**, Letenneur L, Garrigue I, Doize A, Dartigues JF, Helmer C. Interaction between APOE4 and herpes simplex virus type 1 in Alzheimer's disease. *Alzheimers Dement* 2020; **16**: 200-208 [PMID: 31914220 DOI: 10.1002/alz.12008]
14 **Kuo CL**, Pilling LC, Atkins JL, Masoli JAH, Delgado J, Kuchel GA, Melzer D. APOE e4 Genotype Predicts Severe COVID-19 in the UK Biobank Community Cohort. *J Gerontol A Biol Sci Med Sci* 2020; **75**: 2231-2232 [PMID: 32451547 DOI: 10.1093/gerona/glaa131]
15 **Fabris C**, Vandelli C, Toniutto P, Minisini R, Colletta C, Falleti E, Smirne C, Pirisi M. Apolipoprotein E genotypes modulate fibrosis progression in patients with chronic hepatitis C and persistently normal transaminases. *J Gastroenterol Hepatol* 2011; **26**: 328-333 [PMID: 21261723 DOI: 10.1111/j.1440-1746.2010.06403.x]
16 **Calero O**, Hortigüela R, Bullido MJ, Calero M. Apolipoprotein E genotyping method by real time PCR, a fast and cost-effective alternative to the TaqMan and FRET assays. *J Neurosci Methods* 2009; **183**: 238-240 [PMID: 19583979 DOI: 10.1016/j.jneumeth.2009.06.033]
17 **Mazzaferro V**, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, Montalto F, Ammatuna M, Morabito A, Gennari L. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. *N Engl J Med* 1996; **334**: 693-699 [PMID: 8594428 DOI: 10.1056/NEJM199603143341104]
18 **Yao FY**, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, Ascher NL, Roberts JP. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. *Hepatology* 2001; **33**: 1394-1403 [PMID: 11391528 DOI: 10.1053/jhep.2001.24563]
19 **Yen YH**, Kuo FY, Kee KM, Chang KC, Tsai MC, Hu TH, Lu SN, Wang JH, Hung CH, Chen CH. APRI and FIB-4 in the evaluation of liver fibrosis in chronic hepatitis C patients stratified by AST level. *PLoS One* 2018; **13**: e0199760 [PMID: 29953518 DOI: 10.1371/journal.pone.0199760]
20 **Ahn SJ**, Kim DK, Kim SS, Bae CB, Cho HJ, Kim HG, Kim YJ, Lee JH, Lee HJ, Lee MY, Kim KB, Cho JH, Cho SW, Cheong JY. Association between apolipoprotein E genotype, chronic liver disease, and hepatitis B virus. *Clin Mol Hepatol* 2012; **18**: 295-301 [PMID: 23091810 DOI:

10.3350/cmh.2012.18.3.295]

21 **Shen Y**, Li M, Ye X, Bi Q. Association of apolipoprotein E with the progression of hepatitis B virus-related liver disease. *Int J Clin Exp Pathol* 2015; **8**: 14749-14756 [PMID: 26823800]

22 **Fuzikawa AK**, Peixoto SV, Taufer M, Moriguchi EH, Lima-Costa MF. Apolipoprotein E polymorphism distribution in an elderly Brazilian population: the Bambuí Health and Aging Study. *Braz J Med Biol Res* 2007; **40**: 1429-1434 [PMID: 17934638 DOI: 10.1590/s0100-879x2007001100002]

23 **Mueller T**, Fischer J, Gessner R, Rosendahl J, Böhm S, van Bömmel F, Knop V, Sarrazin C, Witt H, Marques AM, Kovacs P, Schleinitz D, Stumvoll M, Blüher M, Bugert P, Schott E, Berg T. Apolipoprotein E allele frequencies in chronic and self-limited hepatitis C suggest a protective effect of APOE4 in the course of hepatitis C virus infection. *Liver Int* 2016; **36**: 1267-1274 [PMID: 26880346 DOI: 10.1111/liv.13094]

24 **Wozniak MA**, Itzhaki RF, Faragher EB, James MW, Ryder SD, Irving WL; Trent HCV Study Group. Apolipoprotein E-epsilon 4 protects against severe liver disease caused by hepatitis C virus. *Hepatology* 2002; **36**: 456-463 [PMID: 12143056 DOI: 10.1053/jhep.2002.34745]

25 **Teama SHH**, Agwa S, Makhlouf M, Nashaat E, Sayed M, Yousry W, Mansour A, Ibrahim W, Elshafie A. Apolipoprotein-E gene polymorphism and possible role of ApoE e4 allele with a lower probability of progression to HCV-related liver cirrhosis in Egyptian patients. *Merit Res J Med Med Sci* 2016; **4**: 440-447

26 **Mueller T**, Gessner R, Sarrazin C, Graf C, Halangk J, Witt H, Köttgen E, Wiedenmann B, Berg T. Apolipoprotein E4 allele is associated with poor treatment response in hepatitis C virus (HCV) genotype 1. *Hepatology* 2003; **38**: 1592; author reply 1592-1592; author reply 1593 [PMID: 14647071 DOI: 10.1016/j.hep.2003.09.042]

27 **Price DA**, Bassendine MF, Norris SM, Golding C, Toms GL, Schmid ML, Morris CM, Burt AD, Donaldson PT. Apolipoprotein epsilon3 allele is associated with persistent hepatitis C virus infection. *Gut* 2006; **55**: 715-718 [PMID: 16299033 DOI: 10.1136/gut.2005.079905]

28 **Kelly ME**, Clay MA, Mistry MJ, Hsieh-Li HM, Harmony JA. Apolipoprotein E inhibition of proliferation of mitogen-activated T lymphocytes: production of interleukin 2 with reduced biological activity. *Cell Immunol* 1994; **159**: 124-139 [PMID: 7994749 DOI: 10.1006/cimm.1994.1302]

29 **Wozniak MA**, Lugo Iparraguirre LM, Dirks M, Deb-Chatterji M, Pflugrad H, Goldbecker A, Tryc AB, Worthmann H, Gess M, Crossey MM, Forton DM, Taylor-Robinson SD, Itzhaki RF, Weissenborn K. Apolipoprotein E-ε4 deficiency and cognitive function in hepatitis C virus-infected patients. *J Viral Hepat* 2016; **23**: 39-46 [PMID: 26306786 DOI: 10.1111/jvh.12443]

30 **Weller R**, Hueging K, Brown RJP, Todt D, Joecks S, Vondran FWR, Pietschmann T. Hepatitis C Virus Strain-Dependent Usage of Apolipoprotein E Modulates Assembly Efficiency and Specific Infectivity of Secreted Virions. *J Virol* 2017; **91** [PMID: 28659481 DOI: 10.1128/JVI.00422-17]

31 **McGoogan KE**, Smith PB, Choi SS, Berman W, Jhaveri R. Performance of the AST-to-platelet ratio index as a noninvasive marker of fibrosis in pediatric patients with chronic viral hepatitis. *J Pediatr Gastroenterol Nutr* 2010; **50**: 344-346 [PMID: 20118806 DOI: 10.1097/MPG.0b013e3181aed725]

32 **Karic U**, Pesic-Pavlovic I, Stevanovic G, Korac M, Nikolic N, Radovanovic-Spurnic A, Barac A, Mitrovic N, Markovic A, Markovic M, Petkovic A, Ostojic I, Perunicic S, Kekic N, Glidzic M, Djonin-Nenezic M, Brmbolic B, Milosevic I. FIB-4 and APRI scores for predicting severe fibrosis in chronic hepatitis C - a developing country's perspective in DAA era. *J Infect Dev Ctries* 2018; **12**: 178-182 [PMID: 31829993 DOI: 10.3855/jidc.10190]

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ORIGINAL ARTICLE

Observational Study

Fatigue in patients with inflammatory bowel disease in Eastern China

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Abstract

BACKGROUND

Fatigue is a very common but relatively neglected problem in patients with inflammatory bowel disease (IBD). The prevalence rate of IBD in China is the highest in Asia, but there is little research on fatigue in patients with IBD. Neither the relationship between fatigue and quality of life (QoL) nor the relationship between fatigue and work productivity (WP) in Chinese IBD patients has been reported.

AIM

To investigate the prevalence of fatigue related to IBD in Eastern China, to identify the risk factors associated with fatigue, to assess the impact of fatigue on QoL, and to evaluate the relationship between fatigue and WP.

METHODS

A cross-sectional study was conducted in a Regional Tertiary IBD Diagnostic and Treatment Center in Eastern China. Clinical data of patients were collected, and disease activity was evaluated. Blood samples were analyzed to assess anemia, albumin, and inflammation. Fatigue was assessed using the multidimensional fatigue inventory. QoL and WP were measured using the short inflammatory bowel disease questionnaire and the work productivity and activity impairment general health questionnaire, respectively. The patients also completed assessments of depression (Patient Health Questionnaire-9) and anxiety (Generalized Anxiety Disorder 7-item Scale).

RESULTS

A total of 311 IBD patients, comprising 168 Crohn's disease patients and 143

ulcerative colitis patients, were enrolled. The prevalence of fatigue in patients with IBD was 60.77%. In a univariate logistic regression analysis, factors such as disease activity, depression, anxiety, anemia, and IBD-related surgery were individually related to a significantly increased risk of fatigue in IBD patients. Multivariate logistic regression analysis indicated that depression [odds ratio (OR) = 8.078, 95% confidence interval (CI): 4.113-15.865], anxiety (OR = 2.373, 95%CI: 1.100-5.119), anemia (OR = 2.498, 95%CI: 1.290-4.834), and IBD-related surgery (OR = 2.035, 95%CI: 1.084-3.819) were related to fatigue in IBD patients. There was a negative correlation between fatigue and QoL (r = -0.831; P < 0.0001) but a positive correlation between fatigue and WP loss.

CONCLUSION

The prevalence of fatigue in IBD patients in Eastern China is remarkably high even in clinical remission. Factors such as depression, anxiety, anemia, and IBD-related surgery are major risk factors for fatigue in IBD patients. In addition, fatigue has a negative impact on QoL and is positively correlated with WP loss.

Key Words: Inflammatory bowel disease; Fatigue; Quality of life; Work productivity; Risk factors; Eastern China

Core Tip: Fatigue is a highly prevalent and burdensome symptom in patients with inflammatory bowel disease (IBD), with an important impact on quality of life and (indirect) health expenditures. The prevalence rate of IBD in China is the highest in Asia, but there is little research on fatigue in patients with IBD. In addition, the relationships of fatigue with quality of life and work productivity in Chinese IBD patients have not been reported.

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INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic, nonspecific inflammation of the gastrointestinal tract with an unknown etiology that can be classified as ulcerative colitis (UC) and Crohn's disease (CD)[1]. IBD has a high prevalence in young adults and is characterized by a long course, high recurrence rate, and severe complications (such as toxic megacolon, intestinal perforation, intestinal obstruction, intestinal bleeding, and cancer)[2]. Mucus-bloody stools, diarrhea, abdominal pain, weight loss, and anemia are the main clinical manifestations of IBD[3], which seriously impact the quality of life (QoL) of patients and increase the financial burden.

Fatigue is expressed as an overwhelming experience of mental and/or physical exhaustion that affects daily living and is unrelieved by rest or sleep[4,5]. Studies in several countries have shown that fatigue is common in patients with IBD[6-10]. Some studies have found that fatigue is associated with active enteritis[11], especially with mucosal healing in patients with IBD[12]. In addition, fatigue also has a negative psychological impact on patients with IBD, exacerbating clinical symptoms and promoting disease progression[13]. Even as a result of fatigue, IBD patients have to adjust their daily activities and work, and some even choose to resign, which seriously affects their QoL[14] and increases their financial burden[15]. Fatigue is a very common but relatively neglected problem in IBD patients, especially in China. The prevalence rate of IBD in China is the highest in Asia[16], but there is little research on fatigue in patients with IBD. In addition, the relationship between fatigue and QoL and work productivity (WP) in Chinese IBD patients has not been reported.

In this study, we aimed to investigate the prevalence and risk factors for fatigue in patients with IBD in Eastern China through a cross-sectional study. We also

guardian, provided informed written consent prior to study enrollment.

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determined the relationships between fatigue and QoL and WP to evaluate the impact of fatigue on IBD patients in Eastern China.

MATERIALS AND METHODS

Study population

This cross-sectional study was conducted at the First Affiliated Hospital of Zhejiang Chinese Medical University, a Regional Tertiary IBD Diagnostic and Treatment Center in Eastern China, from February 2018 to August 2020. The inclusion criteria were a confirmed diagnosis of IBD and signed informed consent. The diagnostic criteria for IBD were based on the Chinese consensus on the diagnosis and treatment of IBD[17]. The exclusion criteria were the inability to understand or complete the questionnaires, refusal to give written informed consent before participation, and concomitant diseases with fatigue as the main symptoms, such as cancer, heart disease, or liver cirrhosis. This study was registered at the Chinese Clinical Trials Registry (ChiCTR1900025890).

Ethics

This study was approved by the ethics committee of the First Affiliated Hospital of Zhejiang Chinese Medical University, and informed consent was obtained from all participants. Patients under the age of 16 were admitted to our study with consent from their parents or guardians.

Clinical and sociodemographic data

The demographic characteristics of the patients were collected, including age, sex, body mass index (BMI), course of the disease, current smoking habits, IBD-related surgery (such as colectomies, other bowel surgery, and perianal surgery), disease activity, type of IBD, location of disease, and current medications. Blood samples were collected (within one week before and after completion of the questionnaires) and analyzed for hemoglobin, albumin, and erythrocyte sedimentation rate.

Definitions

Disease activity and severity were assessed using the following clinical indices: Harvey-Bradshaw activity index[18] was used for CD. Mayo score and Truelove and Witts criteria[19] were used for UC. Anemia was defined as hemoglobin < 130 g/L for males and < 120 g/L for females. Hypoalbuminemia was defined as albumin < 35 g/L. BMI was based on the Chinese criteria of weight for adults[20]. Underweight was defined as BMI < 18.5 kg/m^2; normal weight was defined as 18.5 kg/m^2 ≤ BMI < 24.0 kg/m^2; overweight was defined as 24.0 kg/m^2 ≤ BMI < 28.0 kg/m^2; and obesity was defined as BMI ≥ 28.0 kg/m^2.

The significance level of coefficients is indicated only when they reach the 0.001 criterion. The following cutoffs were used to define the magnitude of the correlation coefficients: < 0.25, low correlation; 0.25 to 0.5, fair correlation; 0.5 to 0.75, moderate-to-good correlation; and > 0.75, good-to-excellent correlation[21].

Questionnaires

Fatigue was analyzed using the multidimensional fatigue inventory (MFI; ranging from 20 to 100, with higher scores indicating more severe fatigue). This questionnaire, previously validated in Chinese and for IBD patients[22], comprises 20 items divided into five subscales: General fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue[23]. The definition of fatigue was complicated by a lack of clear cutoff scores. Several studies have found that scales of general fatigue are more psychometrically useful than the use of numerical rating scales, so the MFI of general fatigue can be called "fatigue"[24-26]. Combining the values reported in a domestic study[27] and foreign studies[28-30] on the MFI, fatigue was defined as general fatigue score ≥ 12.

Depression was analyzed using the Patient Health Questionnaire-9 (PHQ-9), which has been validated in Chinese IBD patients[31]. The PHQ-9 scores each of the 9 DSM-IV criteria on a scale ranging from "0" (not at all) to "3" (nearly every day). The total PHQ-9 score that categorizes depression is as follows: Nondepression as 0 ≤ PHQ-9 ≤ 4, mild depression as 5 ≤ PHQ-9 ≤ 9, moderate depression as 10 ≤ PHQ-9 ≤ 14, moderate-severe depression as 15 ≤ PHQ-9 ≤19, and severe depression as 20 ≤ PHQ-9 ≤ 27[32].

The generalized anxiety disorder 7-item scale was completed to measure symptoms

of anxiety and has been validated in Chinese patients with IBD[31]. The generalized anxiety disorder 7-item scale is a 7-item self-report instrument that is scaled from 0–3 (not at all, several days, more than half the days, and nearly every day), with total scores ranging from 0 to 21, and it is interpreted as follows: The absence of anxiety (0-4), mild anxiety (5-9), moderate anxiety (10-14), and severe anxiety (15-21)[33].

The Short Inflammatory Bowel Disease Questionnaire (SIBDQ) was used to assess IBD-specific QoL[34]. The SIBDQ includes 10 items, each with a score from 1 (worst) to 7 (best), with the total score ranging from 10 to 70 (the higher the score, the better the QoL). Furthermore, the SIBDQ has four domains: Bowel symptoms, systemic symptoms, emotional function, and social function.

The work productivity and activity impairment general health questionnaire[35] measures time missed from work and work impairment because of IBD in the past week. The work productivity and activity impairment general health questionnaire includes four items: Work time missed (absenteeism), impaired productivity at work (presenteeism), overall work impairment (OWI; combined absenteeism and presenteeism), and impairment in non-work-related activities due to health problems (activity impairment). Absenteeism was calculated as [hours missed due to health problems/ (hours missed due to health problems + hours worked)] × 100; presenteeism was calculated as (degree health affected productivity while working/10) × 100; OWI was calculated as absenteeism + [(1-absenteeism) × presenteeism]; and (4) daily activity impairment was calculated as (degree of health affected daily activities/10) × 100.

Statistical analysis

Quantitative variables are expressed as the mean ± SD or as medians and interquartile range (IQR), and qualitative variables are expressed as frequencies and percentages. After transforming fatigue from a quantitative to a qualitative variable (with/without fatigue), logistic regression analyses were performed. Variables with $P < 0.05$ in the univariate analysis were included in the multivariate analysis, and the results are expressed as odds ratios (ORs) with their corresponding 95% confidence intervals (CIs). Correlations between fatigue and QoL and WP were measured with Spearman's rank correlation coefficient. Statistical analyses were performed using Statistic Package for Social Science 24 (Statistic Package for Social Science Inc., Chicago, IL, United States), and $P < 0.05$ was considered statistically significant.

RESULTS

IBD patients' demographic and clinical characteristics

A total of 311 IBD patients, including 168 CD and 143 UC patients, were enrolled in this study. The participants had a median age of 42 (IQR: 31-53) years. Most of the participants had health insurance (90.35%, $n = 281$) and were married (74.28%, $n = 231$). There were 212 (68.17%) patients who had a job, of whom 208 (66.88%) were working full-time. Regarding the duration of disease, the participants reported a median of 5 (IQR: 2-12) years. A total of 51.45% of IBD patients were in the active phase of the disease, and 32.80% of participants had IBD-related surgery. The demographic and clinical characteristics of IBD patients are summarized in Table 1.

Prevalence and score of fatigue in patients with IBD

The prevalence of fatigue in patients with IBD was 60.77%, including 71.88% in patients with active IBD and 49.01% in patients in remission. The median fatigue total score was 43 (IQR: 33-59) in IBD patients, and the median general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation scores were 12 (IQR: 9-15), 8 (IQR: 6-12), 9 (IQR: 6-12), 7 (IQR: 4-9), and 7 (IQR: 4-12), respectively (Figure 1).

Factors associated with fatigue

The univariate analysis showed that disease activity ($P < 0.001$, OR = 2.659; 95%CI: 1.663-4.253), depression ($P < 0.001$, OR = 13.722; 95%CI: 7.608-24.749), anxiety ($P < 0.001$, OR = 8.134; 95%CI: 4.351-15.204), anemia ($P < 0.001$, OR = 3.792; 95%CI: 2.232-6.440), and IBD-related surgery ($P < 0.05$, OR = 1.654; 95%CI: 1.004-2.727) were associated with the presence of fatigue (Figure 2A).

Multivariate logistic regression analysis indicated that depression ($P < 0.001$, OR = 8.078, 95%CI: 4.113-15.865), anxiety ($P = 0.028$, OR = 2.373, 95%CI: 1.100-5.119), anemia ($P = 0.007$, OR = 2.498, 95%CI: 1.290-4.834), and IBD-related surgery ($P = 0.027$, OR =

Table 1 Demographic and clinical characteristics of inflammatory bowel disease patients

	CD (*n* = 168)	UC (*n* = 143)
Age, yr, median (IQR)	39 (IQR: 28-52.75)	45 (IQR: 33-54)
Gender, *n* (%)		
Female	71 (42.26)	64 (44.76)
Male	97 (57.74)	79 (55.24)
BMI, *n* (%)		
Normal	94 (55.95)	81 (56.64)
Thinnish	60 (35.71)	37 (25.88)
Overweight	11 (6.55)	25 (17.48)
Obesity	3 (1.79)	0 (0)
Marital status, *n* (%)		
Unmarried	58 (34.52)	14 (9.79)
Married	105 (62.50)	126 (88.11)
Divorced	3 (1.79)	3 (2.10)
Death of a spouse	2 (1.19)	0 (0)
Employment status, *n* (%)		
No work	16 (9.52)	13 (9.09)
Full time	117 (69.64)	91 (63.64)
Retired	15 (8.93)	35 (24.48)
Long-term sick leave	1 (0.60)	3 (2.10)
Students	19 (11.31)	1 (0.69)
Medical insurance, *n* (%)		
Yes	151 (89.88)	130 (90.91)
No	17 (10.12)	13 (9.09)
Education, *n* (%)		
Primary school or below	14 (8.33)	20 (13.99)
Junior high school	34 (20.24)	36 (25.17)
Senior high school	32 (19.05)	41 (28.67)
Junior college or Undergraduate	81 (48.21)	42 (29.37)
Master degree or above	7 (4.17)	4 (2.80)
Montreal classification, *n* (%)		
L1 ileal	38 (22.62)	
L2 colonic	14 (8.33)	
L3 ileocolonic	72 (42.86)	
L4 upper gastrointestinal tract	11 (6.55)	
L1 + L4	13 (7.74)	
L3 + L4	20 (11.90)	
E1 proctitis		37 (25.88)
E2 left-sided UC		40 (27.97)
E3 extensive UC		66 (46.15)
Disease activity: *n* (%)		
Remission	100 (59.52)	51 (35.66)

Mild activity	26 (15.48)	43 (30.07)
Moderate activity	31 (18.45)	37 (25.88)
Severe activity	11 (6.55)	12 (8.39)
Duration of disease, yr, median (IQR)	5.50 (IQR, 2-11)	5 (IQR, 2.3-13)
Current medication, *n* (%)		
5-ASA	19 (11.31)	88 (61.54)
IS	42 (25)	30 (20.98)
5-ASA + IS	22 (13.09)	8 (5.59)
Biological preparation	45 (26.79)	5 (3.50)
Biological preparation + IS	34 (20.24)	8 (5.59)
Other	6 (3.57)	4 (2.80)
IBD related surgery, *n* (%)		
No	80 (47.62)	129 (90.21)
Yes	88 (52.38)	14 (9.79)

CD: Crohn's disease; UC: Ulcerative colitis; IBD: Inflammatory bowel disease; 5-ASA: 5-aminosalisylic acid; IQR: Interquartile range; IS: Immunosuppressant.

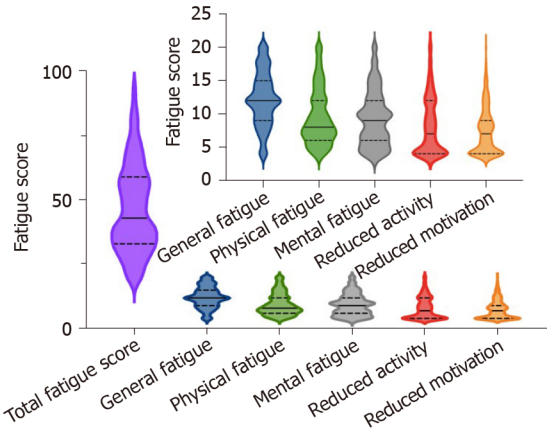


Figure 1 Fatigue score in the inflammatory bowel disease patients. The solid line indicates the median, and the dotted line indicates the interquartile range. The small insert within the graphs in Figure 1 enlarges the scores of the five subscales of multidimensional fatigue inventory (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) in the inflammatory bowel disease patients.

2.035, 95%CI: 1.084-3.819) were related to fatigue in IBD patients (Figure 2B).

Fatigue and QoL

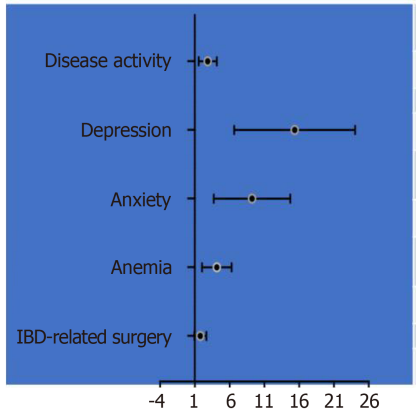
The median QoL total score was 53 (IQR: 44-62), and the median scores of bowel symptoms, social function, emotional function, and systemic symptoms were 17 (IQR: 13-20), 12 (IQR: 9-13), 9 (IQR: 6-12), 15 (IQR: 11-19), and 11 (IQR: 10-13), respectively (Figure 3). Fatigue was negatively correlated with QoL (r = - 0.831; P < 0.0001), particularly with emotional function (r = -0.721; P < 0.0001) (Figure 4A). Further analysis revealed that general fatigue (r = -0.785; P < 0.0001) showed a good-to-excellent correlation with negative QoL, and reduced activity (r = -0.731; P < 0.0001) and psychological fatigue (r = -0.704; P < 0.0001) showed a moderate-to-good correlation with negative QoL (Figure 4B).

Fatigue and WP

There were 208 (66.88%) patients who were working full-time, and their prevalence of fatigue was 58.65%. Further analysis found that their median total fatigue score was 41 (IQR: 32.25-58), with median general fatigue, physical fatigue, mental fatigue, reduced activity, and reduced motivation scores of 12 (IQR: 9-15), 9 (IQR: 7-12), 9 (IQR: 6-11), 6

A

Variables	OR (95%CI)	*P* value
Disease activity	2.659 (1.663-4.253)	< 0.01
Depression	13.722 (7.608-24.749)	< 0.001
Anxiety	8.134 (4.351-15.204)	< 0.001
Anemia	3.792 (2.232-6.440)	< 0.001
IBD-related surgery	1.654 (1.004-2.727)	< 0.05



B

Variables	OR (95%CI)	*P* value
Depression	8.078 (4.113-15.865)	< 0.001
Anxiety	2.373 (1.100-5.119)	0.028
Anemia	2.498 (1.290-4.834)	0.007
IBD-related surgery	2.035 (1.084-3.819)	0.027

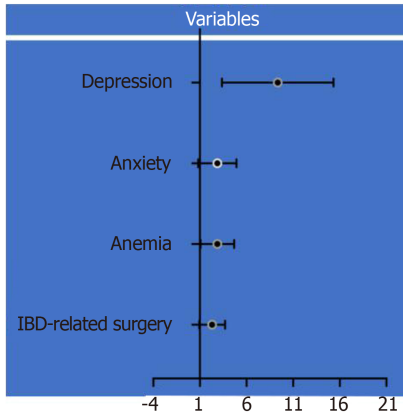


Figure 2 Factors associated with the presence of fatigue. A: Univariate analysis; B: Multivariate analysis. OR: Odds ratio; IBD: Inflammatory bowel disease.

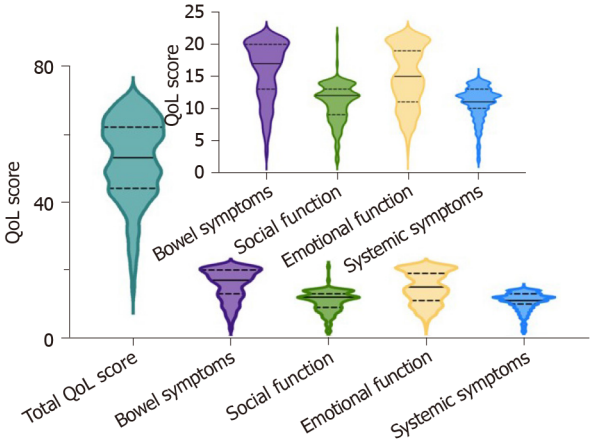


Figure 3 Quality of life score in the inflammatory bowel disease patients. The solid line indicates the median, and the dotted line indicates the interquartile range. The small insert within the graphs in Figure 3 enlarges the scores of the four domains of short inflammatory bowel disease questionnaire (bowel symptoms, systemic symptoms, emotional function, and social function) in the inflammatory bowel disease patients.

(IQR: 4-9), and 6 (IQR: 4-11), respectively (Figure 5). Fatigue had the strongest positive correlation with OWI (r = 0.605; P < 0.0001), followed by activity impairment (r = 0.566; P < 0.0001), presenteeism (r = 0.543; P < 0.0001), and absenteeism (r = 0.480; P < 0.0001) (Figure 6A). Compared with physical fatigue, mental fatigue, reduced activity, and reduced motivation, general fatigue was the most strongly associated with WP loss (OWI: r = 0.552, P < 0.0001; activity impairment: r = 0.549, P < 0.0001; presenteeism: r = 0.519, P < 0.0001; absenteeism: r = 0.442, P < 0.0001) (Figure 6B).

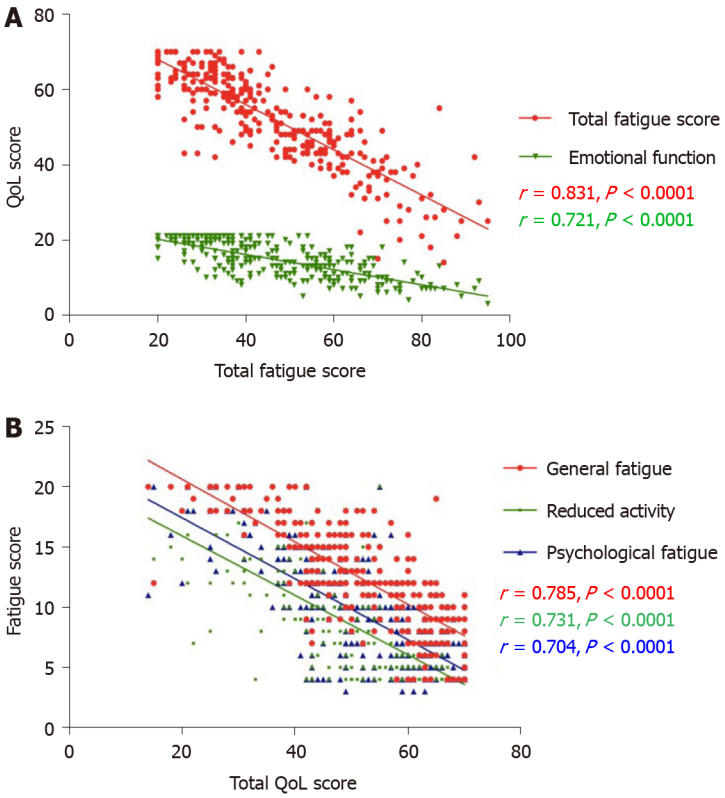


Figure 4 Fatigue and quality of life. A: Correlation between total fatigue scores and quality of life scores (total quality of life scores: Spearman's r = -0.831, P < 0.0001; emotional function: Spearman's r = -0.721, P < 0.0001) in the inflammatory bowel disease patients; B: Correlation between total quality of life scores and fatigue (general fatigue: Spearman's r = -0.785, P < 0.0001; reduced activity: Spearman's r = -0.731, P < 0.0001; psychological fatigue: Spearman's r = -0.704, P < 0.0001) in the inflammatory bowel disease patients.

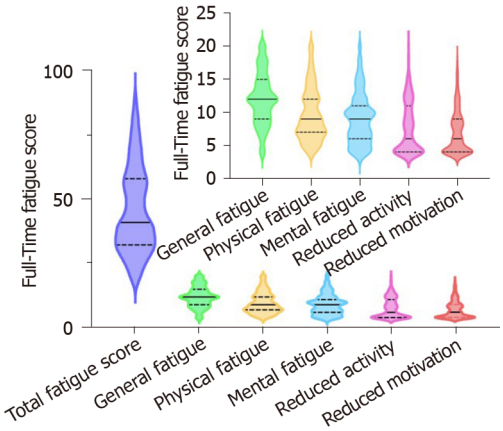


Figure 5 Fatigue score in inflammatory bowel disease patients with full-time jobs. The solid line indicates the median, and the dotted line indicates the interquartile range. The small insert within the graphs in Figure 5 enlarges the scores of the five subscales of multidimensional fatigue inventory (general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue) in the inflammatory bowel disease patients.

DISCUSSION

In the present study, we found that the prevalence of fatigue in patients with IBD in Eastern China was 60.77%, including 71.88% in the active stage and 49.01% in the remission stage. Major factors associated with fatigue were depression, anxiety, anemia, and IBD-related surgery. Female sex, disease activity, and hypoalbuminemia do not increase the risk of fatigue. In addition, fatigue had a negative impact on QoL and was positively correlated with WP loss.

Multifactorial analysis showed that depression and anxiety were risk factors for fatigue, and depression, in particular, is the strongest risk factor for fatigue. Several previous studies are consistent with our findings[36-38]. In chronic diseases, fatigue and

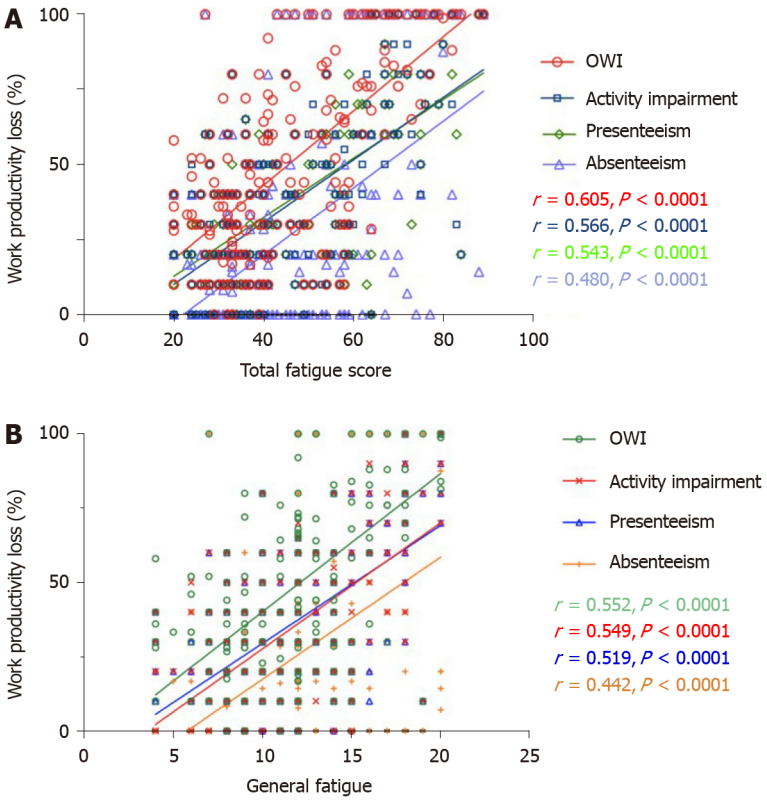


Figure 6 Fatigue and work productivity. A: Correlation between total fatigue scores and work productivity loss [overall work impairment: Spearman's r = 0.605, P < 0.0001; activity impairment: Spearman's r = 0.566, P < 0.0001; presenteeism: Spearman's r = 0.543, P < 0.0001; absenteeism: Spearman's r = 0.480, P < 0.0001] in inflammatory bowel disease patients with full-time jobs; B: Correlation between general fatigue and work productivity loss (overall work impairment: Spearman' s r = 0.552, P < 0.0001; activity impairment: Spearman's r = 0.552, P < 0.0001; presenteeism: Spearman's r = 0.552, P < 0.0001; absenteeism: Spearman's r = 0.552, P < 0.0001) in inflammatory bowel disease patients with full-time jobs. OWI: Overall work impairment.

psychiatric disorders such as depression and anxiety coexist[39,40], including IBD[41]. The immune-inflammatory pathway and gut-brain axis may be possible pathways for the coexistence of fatigue and psychological disorders in IBD[39-42]. One of the reasons for such a high prevalence of fatigue and psychiatric comorbidity in patients with IBD in Eastern China may be due to limited therapeutic drug options. The use of biologics as an effective treatment for IBD in China is very limited. First, the options are limited, with only infliximab entering the Chinese market. When IBD patients fail to respond to infliximab therapy, they are faced with the situation of either having no drugs available or using hormones with more side effects. Second, it is expensive, as only CD is reimbursed by health insurance, which increases the financial burden of patients. The limited availability of medication, the recurrence of disease symptoms, the side effects of hormone therapy, and the heavy financial burden contribute to the development of fatigue and psychiatric disorders in Chinese patients with IBD. Anemia is the most common extraintestinal manifestation of IBD, which occurs in up to 20% of outpatients and up to 68% of inpatients with IBD[43,44]. The major causes of anemia in IBD are iron[45], vitamin B12, and folic acid deficiency[46]. The side effects or complications of some drugs for IBD are anemia. For example, methotrexate can lead to folic acid deficiency and megaloblastic anemia[47]. One of the side effects of azathioprine and 6-mercaptopurine is myelosuppression[48]. Sulfadiazine and 5-aminosalicylate have rare hemolytic complications[49,50]. The relationship between fatigue and IBD-related surgery has rarely been reported. In our study, IBD-related surgery was found to be a risk factor for fatigue in IBD patients, which may be related to postoperative complications, postoperative pain, fear of stoma care, environmental (especially family) reactions, and acceptance of new conditions[29,51,52]. However, a clinical study in Poland that included 60 IBD patients concluded that surgical treatment reduced fatigue symptoms[53], which was contrary to the findings of our study. The difference may be due to different sample sizes, and our study has a larger sample size. In addition, the study in Poland compared the fatigue scores at one day before surgery and three months after surgery. The clinical symptoms of patients at 3 mo after operation were improved, but the postoperative complications were not fully

exposed. Our study included not only patients at 3 mo after the operation but also patients many years after operation and repeated surgery. Postoperative complications, disease activity, the annoyance of anastomotic care, and fear of reoperation were fully exposed. All of these factors will lead to fatigue in IBD patients. Surprisingly, female sex, disease activity, and hypoalbuminemia did not significantly increase fatigue among IBD patients in Eastern China. In previous studies[37,54], female sex was found to be a strong predictor of fatigue, but no good explanation for this association was found. Our study, however, found that female sex was not a risk factor for fatigue. This may have been because of the small sample size in our study. The association between fatigue and disease activity in IBD is controversial. Fatigue scores were higher and more frequent among IBD patients with active disease than in the reference population and among those with quiescent IBD, but contrasts with the findings of others[9,36,55]. In this study, univariate analysis showed that disease activity was a risk factor for fatigue but not in multivariate analyses. Therefore, more research is needed to clarify the relationships between female sex and disease activity and fatigue in Chinese patients with IBD. The common symptom of hypoalbuminemia is fatigue, but our findings suggest that it is not a risk factor for fatigue in patients with IBD in Eastern China. This may have been because of the small number of patients affected (29.3% of all those studied) or because fatigue was strongly associated with other factors, such as depression, anemia, anxiety, or IBD-related surgery.

Risk factors for fatigue, such as depression, anxiety, anemia, and IBD-related surgery, were found to decrease QoL in IBD patients in previous studies[56-59], which explained why fatigue also leads to a decrease in QoL in IBD patients. Our further analysis found that psychological factors are particularly important in the relationship between fatigue and QoL. To improve the QoL of patients with IBD, the risk factors for fatigue should be identified and corrected in time to prevent the occurrence of fatigue. In addition to the impact on the QoL of the patient, fatigue can also lead to WP loss or even unemployment, which has significant economic consequences. Our study found that fatigue had an impact on the OWI, activity impairment, presenteeism, and absenteeism, among which general fatigue had the strongest impact. The appeal conclusion showed that the effect of fatigue on WP loss was also the result of a comprehensive effect, in which physical and psychological factors played an important role.

Although fatigue and its negative consequences are common in patients with IBD, the issue is rarely discussed in China. The underlying cause may be fatigue, especially during remission, which is considered a difficult and frustrating symptom, and the risk factors for fatigue are unclear, so there is little opportunity to help patients. Indeed, in China, there are few studies on the relationship between IBD and fatigue, which cannot provide clinical guidance. It is hoped that our findings will draw the attention of clinicians and patients to the role of fatigue in patients with IBD, improve the QoL of patients with IBD, and reduce the loss of WP by intervening in risk factors that contribute to fatigue. For example, in clinical practice, the joint management of patients' fatigue and psychological disorders is very important. Patients with depression and anxiety should pay close attention to their fatigue through targeted psychological counseling and intervention, such as health lectures, psychological counseling, individual counseling, and other ways to reduce patients' depression and anxiety, improve patients' fatigue, promote patients' health, and improve their QoL. IBD patients with anemia should correct their anemia in time. For IBD patients who have undergone surgery, postoperative complications, postoperative pain, and patients' fear of colostomy nursing should be properly addressed.

There are several limitations to our study. First, the size of the study sample was too small. Further large sample size studies are warranted for a more accurate estimation of the prevalence of fatigue and definitive identification of risk factors for fatigue. Second, our study was a single-center clinical study, which cannot represent the overall situation of IBD patients in China.

CONCLUSION

In conclusion, we have shown that the prevalence of fatigue is considerably high in patients with IBD in Eastern China, even in clinical remission, and the risk factors for fatigue are depression, anxiety, anemia, and IBD-related surgery. Female sex, disease activity, and hypoalbuminemia do not increase the risk of fatigue. In addition, fatigue reduces the QoL of IBD patients in Eastern China and damages WP. The results of our study provide a scientific basis for effectively preventing and improving fatigue in IBD

patients.

ARTICLE HIGHLIGHTS

Research background

Fatigue is frequent and disabling in patients with inflammatory bowel disease (IBD), but the prevalence and risk factors for fatigue in Chinese patients with IBD are unknown. In addition, neither the relationship between fatigue and quality of life (QoL) nor the relationship between fatigue and work productivity (WP) has been reported in Chinese IBD patients.

Research motivation

Fatigue is a very common but relatively neglected problem in patients with IBD. The prevalence rate of IBD in China is the highest in Asia, but there is little research on fatigue in patients with IBD. Neither the relationship between fatigue and QoL nor the relationship between fatigue and WP in Chinese IBD patients has been reported.

Research objectives

Our primary aim was to investigate the prevalence of fatigue related to IBD in Eastern China, and to identify the risk factors associated with fatigue. Our second objective was to assess the impact of fatigue on QoL and to evaluate the relationship between fatigue and WP.

Research methods

A cross-sectional study was conducted in a Regional Tertiary IBD Diagnostic and Treatment Center in Eastern China. Clinical data of patients were collected, and disease activity was evaluated. Blood samples were analyzed to assess anemia, albumin, and inflammation. Fatigue was assessed using the multidimensional fatigue inventory. QoL and WP were measured using the short inflammatory bowel disease questionnaire and the work productivity and activity impairment general health questionnaire, respectively. The patients also completed assessments of depression (Patient Health Questionnaire-9) and anxiety (Generalized Anxiety Disorder 7-item Scale).

Research results

A total of 311 IBD patients were enrolled in this study, 168 of whom were Crohn's disease patients, and 143 of whom were ulcerative colitis patients. The prevalence of fatigue in patients with IBD was 60.77%, including 71.88% in the active stage and 49.01% in the remission stage. The median fatigue total score was 43 (IQR: 33-59) in the full study population. In a univariate logistic regression analysis, factors such as disease activity, depression, anxiety, anemia, and IBD-related surgery were individually related to a significantly increased risk of fatigue in IBD patients. Multivariate logistic regression analysis indicated that depression [odds ratio (OR) = 8.078, 95% confidence interval (CI): 4.113-15.865], anxiety (OR = 2.373, 95%CI: 1.100-5.119), anemia (OR = 2.498, 95%CI: 1.290-4.834), and IBD-related surgery (OR = 2.035, 95%CI: 1.084-3.819) were related to fatigue in IBD patients. There was a negative correlation between fatigue and QoL (r = -0.831; P < 0.0001) but a positive correlation between fatigue and WP loss.

Research conclusions

The prevalence of fatigue in IBD patients in Eastern China is remarkably high even in clinical remission. Factors such as depression, anxiety, anemia, and IBD-related surgery are major risk factors for fatigue in IBD patients. In addition, fatigue has a negative impact on QoL and is positively correlated with WP loss.

Research perspectives

The prevalence of fatigue is considerably high in IBD patients in Eastern China even in clinical remission. In addition, fatigue reduces the QoL of IBD patients in Eastern China and damages WP. Clinicians and patients should be aware of and prevent the incidence of fatigue. The future research direction is to conduct a multicenter study to evaluate the incidence of fatigue in Chinses IBD patients, and more accurately screen out the risk factors leading to the incidence of fatigue in Chinese IBD patients, to effectively prevent the incidence of fatigue.

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REFERENCES

1 **Vanhelst J**, Coopman S, Labreuche J, Dupont C, Bertrand V, Djeddi D, Turck D, Ley D. Protocol of a randomised controlled trial assessing the impact of physical activity on bone health in children with inflammatory bowel disease. *BMJ Open* 2020; **10**: e036400 [PMID: 32430452 DOI: 10.1136/bmjopen-2019-036400]

2 **Kou FS**, Shi L, Li JX, Wang ZB, Shi R, Mao TY, Ke X, Zhang BP, Yang XJ, Wen XL, Zheng WY, Han X, Ding PH, Dong J. Clinical evaluation of traditional Chinese medicine on mild active ulcerative colitis: A multi-center, randomized, double-blind, controlled trial. *Medicine (Baltimore)* 2020; **99**: e21903 [PMID: 32871923 DOI: 10.1097/MD.0000000000021903]

3 **Zeng Z**, Mukherjee A, Zhang H. From Genetics to Epigenetics, Roles of Epigenetics in Inflammatory Bowel Disease. *Front Genet* 2019; **10**: 1017 [PMID: 31737035 DOI: 10.3389/fgene.2019.01017]

4 **Graff LA**, Vincent N, Walker JR, Clara I, Carr R, Ediger J, Miller N, Rogala L, Rawsthorne P, Lix L, Bernstein CN. A population-based study of fatigue and sleep difficulties in inflammatory bowel disease. *Inflamm Bowel Dis* 2011; **17**: 1882-1889 [PMID: 21830266 DOI: 10.1002/ibd.21580]

5 **Bager P**, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, Hjollund NH, Dahlerup JF. Fatigue in out-patients with inflammatory bowel disease is common and multifactorial. *Aliment Pharmacol Ther* 2012; **35**: 133-141 [PMID: 22059387 DOI: 10.1111/j.1365-2036.2011.04914.x]

6 **Zand A**, van Deen WK, Inserra EK, Hall L, Kane E, Centeno A, Choi JM, Ha CY, Esrailian E, D'Haens GR, Hommes DW. Presenteeism in Inflammatory Bowel Diseases: A Hidden Problem with Significant Economic Impact. *Inflamm Bowel Dis* 2015; **21**: 1623-1630 [PMID: 26070004 DOI: 10.1097/MIB.0000000000000399]

7 **Jelsness-Jørgensen LP**, Bernklev T, Henriksen M, Torp R, Moum BA. Chronic fatigue is more prevalent in patients with inflammatory bowel disease than in healthy controls. *Inflamm Bowel Dis* 2011; **17**: 1564-1572 [PMID: 21674713 DOI: 10.1002/ibd.21530]

8 **Grimstad T**, Norheim KB, Isaksen K, Leitao K, Hetta AK, Carlsen A, Karlsen LN, Skoie IM, Gøransson L, Harboe E, Aabakken L, Omdal R. Fatigue in Newly Diagnosed Inflammatory Bowel Disease. *J Crohns Colitis* 2015; **9**: 725-730 [PMID: 25994356 DOI: 10.1093/ecco-jcc/jjv091]

9 **Chavarría C**, Casanova MJ, Chaparro M, Barreiro-de Acosta M, Ezquiaga E, Bujanda L, Rivero M, Argüelles-Arias F, Martín-Arranz MD, Martínez-Montiel MP, Valls M, Ferreiro-Iglesias R, Llaó J, Moraleja-Yudego I, Casellas F, Antolín-Melero B, Cortés X, Plaza R, Pineda JR, Navarro-Llavat M, García-López S, Robledo-Andrés P, Marín-Jiménez I, García-Sánchez V, Merino O, Algaba A, Arribas-López MR, Banales JM, Castro B, Castro-Laria L, Honrubia R, Almela P, Gisbert JP. Prevalence and Factors Associated With Fatigue in Patients With Inflammatory Bowel Disease: A Multicentre Study. *J Crohns Colitis* 2019; **13**: 996-1002 [PMID: 30721954 DOI: 10.1093/ecco-jcc/jjz024]

10 **Yoo S**, Jung YS, Park JH, Kim HJ, Cho YK, Sohn CI, Jeon WK, Kim BI, Park DI. Fatigue severity and factors associated with high fatigue levels in Korean patients with inflammatory bowel disease. *Gut Liver* 2014; **8**: 148-153 [PMID: 24672655 DOI: 10.5009/gnl.2014.8.2.148]

11 **Vogelaar L**, de Haar C, Aerts BR, Peppelenbosch MP, Timman R, Hanssen BE, van der Woude CJ. Fatigue in patients with inflammatory bowel disease is associated with distinct differences in immune parameters. *Clin Exp Gastroenterol* 2017; **10**: 83-90 [PMID: 28496351 DOI: 10.2147/CEG.S123942]

12 **Casellas F**, Barreiro de Acosta M, Iglesias M, Robles V, Nos P, Aguas M, Riestra S, de Francisco R, Papo M, Borruel N. Mucosal healing restores normal health and quality of life in patients with inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2012; **24**: 762-769 [PMID: 22517240 DOI: 10.1097/MEG.0b013e32835414b2]

13 **Jonefjäll B**, Simrén M, Lasson A, Öhman L, Strid H. Psychological distress, iron deficiency, active disease and female gender are independent risk factors for fatigue in patients with ulcerative colitis. *United European Gastroenterol J* 2018; **6**: 148-158 [PMID: 29435325 DOI: 10.1177/2050640617703868]

14 **IsHak WW**, Pan D, Steiner AJ, Feldman E, Mann A, Mirocha J, Danovitch I, Melmed GY. Patient-Reported Outcomes of Quality of Life, Functioning, and GI/Psychiatric Symptom Severity in Patients with Inflammatory Bowel Disease (IBD). *Inflamm Bowel Dis* 2017; **23**: 798-803 [PMID: 28301432 DOI: 10.1097/MIB.0000000000001060]

15 **Holko P**, Kawalec P, Mossakowska M, Pilc A. Health-Related Quality of Life Impairment and Indirect Cost of Crohn's Disease: A Self-Report Study in Poland. *PLoS One* 2016; **11**: e0168586 [PMID: 27992531 DOI: 10.1371/journal.pone.0168586]

16 **Ng SC**, Tang W, Ching JY, Wong M, Chow CM, Hui AJ, Wong TC, Leung VK, Tsang SW, Yu HH, Li MF, Ng KK, Kamm MA, Studd C, Bell S, Leong R, de Silva HJ, Kasturiratne A, Mufeena MNF, Ling KL, Ooi CJ, Tan PS, Ong D, Goh KL, Hilmi I, Pisespongsa P, Manatsathit S, Rerknimitr R, Aniwan S, Wang YF, Ouyang Q, Zeng Z, Zhu Z, Chen MH, Hu PJ, Wu K, Wang X, Simadibrata M, Abdullah M, Wu JC, Sung JJY, Chan FKL; Asia–Pacific Crohn's and Colitis Epidemiologic Study (ACCESS) Study Group. Incidence and phenotype of inflammatory bowel disease based on results

from the Asia-pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013; **145**: 158-165. e2 [PMID: 23583432 DOI: 10.1053/j.gastro.2013.04.007]

17 **Inflammatory Enterology Group**, Chinese Society of Gastroenterology. Consensus on diagnosis and treatment of inflammatory bowel disease (Beijing, 2018). *Zhonghua Xiaohua Zazhi* 2018; **38**: 292-311 [DOI: 10.3760/cma.j.issn.0254-1432.2018.05.002]

18 **Harvey RF**, Bradshaw JM. A simple index of Crohn's-disease activity. *Lancet* 1980; **1**: 514 [PMID: 6102236 DOI: 10.1016/s0140-6736(80)92767-1]

19 **Truelove SC**, Witts LJ. Cortisone in ulcerative colitis; final report on a therapeutic trial. *Br Med J* 1955; **2**: 1041-1048 [PMID: 13260656 DOI: 10.1136/bmj.2.4947.1041]

20 **Hu WB**, Zhang T, Shi JG, Qin W, Tong L, Jin YX, Qiu HQ, Zhou J, Shen YP. Analysis of relationship between dose-response and intensity of BMI and hypertension. *Zhongguo Weisheng Tongji* 2015; **32**: 971-974

21 **Koo TK**, Li MY. A Guideline of Selecting and Reporting Intraclass Correlation Coefficients for Reliability Research. *J Chiropr Med* 2016; **15**: 155-163 [PMID: 27330520 DOI: 10.1016/j.jcm.2016.02.012]

22 **Chuang LL**, Chuang YF, Hsu MJ, Huang YZ, Wong AMK, Chang YJ. Validity and reliability of the Traditional Chinese version of the Multidimensional Fatigue Inventory in general population. *PLoS One* 2018; **13**: e0189850 [PMID: 29746466 DOI: 10.1371/journal.pone.0189850]

23 **Smets EM**, Garssen B, Bonke B, De Haes JC. The Multidimensional Fatigue Inventory (MFI) psychometric qualities of an instrument to assess fatigue. *J Psychosom Res* 1995; **39**: 315-325 [PMID: 7636775 DOI: 10.1016/0022-3999(94)00125-o]

24 **Smets EM**, Garssen B, Cull A, de Haes JC. Application of the multidimensional fatigue inventory (MFI-20) in cancer patients receiving radiotherapy. *Br J Cancer* 1996; **73**: 241-245 [PMID: 8546913 DOI: 10.1038/bjc.1996.42]

25 **Smets EM**, Visser MR, Willems-Groot AF, Garssen B, Oldenburger F, van Tienhoven G, de Haes JC. Fatigue and radiotherapy: (A) experience in patients undergoing treatment. *Br J Cancer* 1998; **78**: 899-906 [PMID: 9764581 DOI: 10.1038/bjc.1998.599]

26 **Minderhoud IM**, Oldenburg B, van Dam PS, van Berge Henegouwen GP. High prevalence of fatigue in quiescent inflammatory bowel disease is not related to adrenocortical insufficiency. *Am J Gastroenterol* 2003; **98**: 1088-1093 [PMID: 12809832 DOI: 10.1111/j.1572-0241.2003.07414.x]

27 **Xia H**, Li Z, Yang J, Liu BZ. Diagnostic value of MFI-20 for post-stroke fatigue (PSF). *Fudan Xuebao* 2020; **47**: 704-708 [DOI: 10.3969/j.issn.1672-8467.2020.05.018]

28 **Aluzaite K**, Al-Mandhari R, Osborne H, Ho C, Williams M, Sullivan MM, Hobbs CE, Schultz M. Detailed Multi-Dimensional Assessment of Fatigue in Inflammatory Bowel Disease. *Inflamm Intest Dis* 2019; **3**: 192-201 [PMID: 31111036 DOI: 10.1159/000496054]

29 **Czuber-Dochan W**, Ream E, Norton C. Review article: Description and management of fatigue in inflammatory bowel disease. *Aliment Pharmacol Ther* 2013; **37**: 505-516 [PMID: 23311461 DOI: 10.1111/apt.12205]

30 **Romberg-Camps MJ**, Bol Y, Dagnelie PC, Hesselink-van de Kruijs MA, Kester AD, Engels LG, van Deursen C, Hameeteman WH, Pierik M, Wolters F, Russel MG, Stockbrügger RW. Fatigue and health-related quality of life in inflammatory bowel disease: results from a population-based study in the Netherlands: the IBD-South Limburg cohort. *Inflamm Bowel Dis* 2010; **16**: 2137-2147 [PMID: 20848468 DOI: 10.1002/ibd.21285]

31 **Ju JY**, Dai YY, Yang JL, Liu CQ, Liu ZJ, Sun XM. Related factors of psychology and quality of life in patients with inflammatory bowel disease. *Zhonghua Xiaohua Zazhi* 2020; **40**: 686-691 [DOI: 10.3760/cma.j.cn311367-20191105-00483]

32 **Kroenke K**, Spitzer RL, Williams JB. The PHQ-9: validity of a brief depression severity measure. *J Gen Intern Med* 2001; **16**: 606-613 [PMID: 11556941 DOI: 10.1046/j.1525-1497.2001.016009606.x]

33 **Spitzer RL**, Kroenke K, Williams JB, Löwe B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006; **166**: 1092-1097 [PMID: 16717171 DOI: 10.1001/archinte.166.10.1092]

34 **Irvine EJ**, Zhou Q, Thompson AK. The Short Inflammatory Bowel Disease Questionnaire: a quality of life instrument for community physicians managing inflammatory bowel disease. CCRPT Investigators. Canadian Crohn's Relapse Prevention Trial. *Am J Gastroenterol* 1996; **91**: 1571-1578 [PMID: 8759664]

35 **Reilly MC**, Zbrozek AS, Dukes EM. The validity and reproducibility of a work productivity and activity impairment instrument. *Pharmacoeconomics* 1993; **4**: 353-365 [PMID: 10146874 DOI: 10.2165/00019053-199304050-00006]

36 **Cohen BL**, Zoëga H, Shah SA, Leleiko N, Lidofsky S, Bright R, Flowers N, Law M, Moniz H, Merrick M, Sands BE. Fatigue is highly associated with poor health-related quality of life, disability and depression in newly-diagnosed patients with inflammatory bowel disease, independent of disease activity. *Aliment Pharmacol Ther* 2014; **39**: 811-822 [PMID: 24612278 DOI: 10.1111/apt.12659]

37 **Keightley P**, Reay RE, Pavli P, Looi JC. Inflammatory bowel disease-related fatigue is correlated with depression and gender. *Australas Psychiatry* 2018; **26**: 508-513 [PMID: 29737197 DOI: 10.1177/1039856218772245]

38 **Artom M**, Czuber-Dochan W, Sturt J, Murrells T, Norton C. The contribution of clinical and psychosocial factors to fatigue in 182 patients with inflammatory bowel disease: a cross-sectional study. *Aliment Pharmacol Ther* 2017; **45**: 403-416 [PMID: 27868215 DOI: 10.1111/apt.13870]

39 **Corfield EC**, Martin NG, Nyholt DR. Co-occurrence and symptomatology of fatigue and depression.

Compr Psychiatry 2016; **71**: 1-10 [PMID: 27567301 DOI: 10.1016/j.comppsych.2016.08.004]
40 **Ormstad H**, Simonsen CS, Broch L, Maes DM, Anderson G, Celius EG. Chronic fatigue and depression due to multiple sclerosis: Immune-inflammatory pathways, tryptophan catabolites and the gut-brain axis as possible shared pathways. *Mult Scler Relat Disord* 2020; **46**: 102533 [PMID: 33010585 DOI: 10.1016/j.msard.2020.102533]
41 **Maes M**, Kubera M, Obuchowiczwa E, Goehler L, Brzeszcz J. Depression's multiple comorbidities explained by (neuro)inflammatory and oxidative & nitrosative stress pathways. *Neuro Endocrinol Lett* 2011; **32**: 7-24 [PMID: 21407167]
42 **Lee CH**, Giuliani F. The Role of Inflammation in Depression and Fatigue. *Front Immunol* 2019; **10**: 1696 [PMID: 31379879 DOI: 10.3389/fimmu.2019.01696]
43 **Artom M**, Czuber-Dochan W, Sturt J, Norton C. Targets for Health Interventions for Inflammatory Bowel Disease-fatigue. *J Crohns Colitis* 2016; **10**: 860-869 [PMID: 26802088 DOI: 10.1093/ecco-jcc/jjw029]
44 **Bager P**, Befrits R, Wikman O, Lindgren S, Moum B, Hjortswang H, Dahlerup JF. The prevalence of anemia and iron deficiency in IBD outpatients in Scandinavia. *Scand J Gastroenterol* 2011; **46**: 304-309 [PMID: 21073374 DOI: 10.3109/00365521.2010.533382]
45 **Bengi G**, Keyvan H, Durmaz SB, Akpınar H. Frequency, types, and treatment of anemia in Turkish patients with inflammatory bowel disease. *World J Gastroenterol* 2018; **24**: 4186-4196 [PMID: 30271083 DOI: 10.3748/wjg.v24.i36.4186]
46 **Gasche C**, Lomer MC, Cavill I, Weiss G. Iron, anaemia, and inflammatory bowel diseases. *Gut* 2004; **53**: 1190-1197 [PMID: 15247190 DOI: 10.1136/gut.2003.035758]
47 **Antwi-Bafour S**, Hammond S, Adjei JK, Kyeremeh R, Martin-Odoom A, Ekem I. A case-control study of prevalence of anemia among patients with type 2 diabetes. *J Med Case Rep* 2016; **10**: 110 [PMID: 27142617 DOI: 10.1186/s13256-016-0889-4]
48 **Zhang R**, Gilbert S, Yao X, Vallance J, Steinbrecher K, Moriggl R, Zhang D, Eluri M, Chen H, Cao H, Shroyer N, Denson L, Han X. Natural compound methyl protodioscin protects against intestinal inflammation through modulation of intestinal immune responses. *Pharmacol Res Perspect* 2015; **3**: e00118 [PMID: 26038694 DOI: 10.1002/prp2.118]
49 **Guagnozzi D**, Lucendo AJ. Anemia in inflammatory bowel disease: a neglected issue with relevant effects. *World J Gastroenterol* 2014; **20**: 3542-3551 [PMID: 24707137 DOI: 10.3748/wjg.v20.i13.3542]
50 **Plikat K**, Rogler G, Schölmerich J. Coombs-positive autoimmune hemolytic anemia in Crohn's disease. *Eur J Gastroenterol Hepatol* 2005; **17**: 661-666 [PMID: 15879729 DOI: 10.1097/00042737-200506000-00011]
51 **Vogelaar L**, van't Spijker A, Timman R, van Tilburg AJ, Bac D, Vogelaar T, Kuipers EJ, van Busschbach JJ, van der Woude CJ. Fatigue management in patients with IBD: a randomised controlled trial. *Gut* 2014; **63**: 911-918 [PMID: 23884638 DOI: 10.1136/gutjnl-2013-305191]
52 **Czuber-Dochan W**, Dibley LB, Terry H, Ream E, Norton C. The experience of fatigue in people with inflammatory bowel disease: an exploratory study. *J Adv Nurs* 2013; **69**: 1987-1999 [PMID: 23215959 DOI: 10.1111/jan.12060]
53 **Bączyk G**, Kozłowska KA, Formanowicz D, Białas E, Karoń J, Krokowicz P. The relationship between the symptom of fatigue and the functioning of patients with inflammatory bowel diseases after surgery. *Prz Gastroenterol* 2019; **14**: 242-249 [PMID: 31988670 DOI: 10.5114/pg.2019.90251]
54 **Villoria A**, García V, Dosal A, Moreno L, Montserrat A, Figuerola A, Horta D, Calvet X, Ramírez-Lázaro MJ. Fatigue in out-patients with inflammatory bowel disease: Prevalence and predictive factors. *PLoS One* 2017; **12**: e0181435 [PMID: 28749985 DOI: 10.1371/journal.pone.0181435]
55 **Huppertz-Hauss G**, Høivik ML, Jelsness-Jørgensen LP, Opheim R, Henriksen M, Høie O, Hovde Ø, Kempski-Monstad I, Solberg IC, Jahnsen J, Hoff G, Moum B, Bernklev T. Fatigue in a population-based cohort of patients with inflammatory bowel disease 20 years after diagnosis: The IBSEN study. *Scand J Gastroenterol* 2017; **52**: 351-358 [PMID: 27852169 DOI: 10.1080/00365521.2016.1256425]
56 **Calixto RP**, Flores C, Francesconi CF. Inflammatory bowel disease: impact on scores of quality of life, depression and anxiety in patients attending a tertiary care center in brazil. *Arq Gastroenterol* 2018; **55**: 202-207 [PMID: 30540078 DOI: 10.1590/S0004-2803.201800000-54]
57 **Diederen K**, de Ridder L, van Rheenen P, Wolters VM, Mearin ML, de Meij TG, van Wering H, Oomen MW, de Jong JR, Sloots CE, Benninga MA, Kindermann A. Quality of life and colorectal function in Crohn's disease patients that underwent ileocecal resection during childhood. *Eur J Pediatr* 2019; **178**: 1413-1421 [PMID: 31327075 DOI: 10.1007/s00431-019-03427-3]
58 **de Alvarenga Antunes CV**, de Alvarenga Nascimento CR, Campanha da Rocha Ribeiro T, de Alvarenga Antunes P, de Andrade Chebli L, Martins Gonçalves Fava L, Malaguti C, Maria Fonseca Chebli J. Treatment of iron deficiency anemia with liposomal iron in inflammatory bowel disease: efficacy and impact on quality of life. *Int J Clin Pharm* 2020; **42**: 895-902 [PMID: 32367457 DOI: 10.1007/s11096-020-01044-x]
59 **Gracie DJ**, Irvine AJ, Sood R, Mikocka-Walus A, Hamlin PJ, Ford AC. Effect of psychological therapy on disease activity, psychological comorbidity, and quality of life in inflammatory bowel disease: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol* 2017; **2**: 189-199 [PMID: 28404134 DOI: 10.1016/S2468-1253(16)30206-0]

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ORIGINAL ARTICLE

Clinical Trials Study

Prospective single-blinded single-center randomized controlled trial of Prep Kit-C and Moviprep: Does underlying inflammatory bowel disease impact tolerability and efficacy?

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Author contributions: Mohsen W and Williams AJ collected data, compiled data, blinded endoscopist (fellow), recruited patients from clinic, organized spreadsheet, developed tables, liaised wrote the manuscript; Wark G collected data and developed the figures; Sechi A inflammatory bowel disease nurse consultant who assisted with education, recruitment of patients and answering patient concerns during the trial process; Koo JH blinded assisted with manuscript review, study design and statistical analysis; Xuan W is statistician from the Ingham institute who assisted with the statistical analysis; Bassan M assisted with the review of the manuscript; Ng W recruited patients, assisted with study design and assisted with review

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Abstract

BACKGROUND

Colonoscopy remains the gold standard for detection of colonic disease. An optimal evaluation depends on adequate bowel cleansing. Patients with inflammatory bowel disease (IBD), require frequent endoscopic assessment for both activity and dysplasia assessment. Two commonly used bowel preparations in Australia are Prep Kit-C (Pc) and Moviprep (Mp). Little is known about tolerability, efficacy and safety of split protocols of Mp and Pc in both IBD and non-IBD patients.

AIM

To primary aim was to compare the tolerability, efficacy and safety of split protocols of Mp and Pc in patients having a colonoscopy. The secondary aim was to compare the efficacy, tolerability and safety of either preparation in patients with or without IBD.

METHODS

Patients were randomized to Pc or Mp bowel preparation. Patients completed a

process and manuscript development; Connor S developed study design and end points for the study, applied for ethics approval, assisted with the development of the manuscript.

Institutional review board statement: Approval was obtained from the Institutional Human Ethics and Research Office (reference HREC/12/LPOOL/108).

Clinical trial registration statement: There was no clinical trial registration for this study.

Informed consent statement: Informed consent form was not required for this study as this was a prospective single blinded single centre study.

Conflict-of-interest statement: All of the authors have no conflict of interest to disclose. We did not receive commercial or government funding for this article.

Data sharing statement: All data included in this study is deidentified.

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questionnaire to assess tolerability. Efficacy was assessed using the Ottawa Bowel Preparation Score. Serum electrolytes and renal function were collected one week prior to colonoscopy and on the day of colonoscopy.

RESULTS

Of 338 patients met the inclusion criteria. Of 168 patients randomized to Mp and 170 to Pc. The efficacy of bowel preparation (mean Ottawa Bowel Preparation Score) was similar between Mp (5.4 ± 2.4) and Pc (5.1 ± 2.1) (P = 0.3). Mean tolerability scores were similar in Mp (11.84 ± 5.4) and Pc (10.99 ± 5.2; P = 0.17). 125 patients had IBD (73 had Crohn's Disease and 52 had Ulcerative colitis). Sixty-four IBD patients were allocated to Mp and 61 to Pc. In non-IBD patients, 104 were allocated to Mp and 109 to Pc. The mean tolerability score in the IBD group was lower than the non-IBD group (mean tolerability scores: IBD: 10.3 ± 5.1 and non-IBD: 12.0 ± 5.3; P = 0.01). IBD patients described more abdominal pain with Mp when compared with Pc; (Mp: 5.7 ± 4.4 *vs* Pc: 3.6 ± 2.6, P = 0.046). Serum magnesium level increased with Pc compared with Mp in all patients (mean increase in mmol/L: Mp: 0.03 ± 0.117 and Pc: 0.11 ± 0.106; P < 0.0001).

CONCLUSION

In this study, the efficacy, tolerability and safety of Mp and Pc were similar in all patients. However, patients with IBD reported lower tolerability with both preparations. Specifically, IBD patients had more abdominal pain with Mp. These results should be considered when recommending bowel preparation especially to IBD patients.

Key Words: Bowel preparation; Inflammatory bowel disease; Tolerability; Efficacy; Moviprep; Prep Kit-C

Core Tip: When comparing Moviprep (Mp) and Prep-Kit C (Pc) in patients with and without inflammatory bowel disease (IBD): (1) Efficacy, tolerability and safety of Mp and Pc are similar; (2) Participants with IBD reported lower tolerability with both preparations; (3) IBD participants described more abdominal pain with Mp. Consideration of these results are important when discussing bowel preparation with IBD patients.

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INTRODUCTION

Colonoscopy remains the gold standard for detection of colonic disease. An optimal evaluation depends on adequate bowel cleansing. Suboptimal preparation occurs in up to 25% of colonoscopies and results in aborted or incomplete examinations in up to 7% of procedures[1,2]. Suboptimal preparation is associated with longer procedural time, increased need for repeat procedures, lower overall polyp detection rates, including detection of flat (non-polypoid) lesions, small polyps (< 10 mm) and large polyps (> 10 mm)[1,3]. The American Society for Gastrointestinal Endoscopy recommends the rate of inadequate bowel preparation should not exceed 15%[4].

Efficacious bowel preparation is not solely dependent on the type of preparation used. Preparation is enhanced when instructions regarding bowel preparation are explained thoroughly, interpreters are used (when required), a split regime is used and when the type of preparation is individualized to the patient's age and comorbidities[5,6].

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Adequate bowel preparation is particularly important in patients with inflammatory bowel disease (IBD). These patients have an increased risk of developing colonic dysplasia and neoplasia. The increasingly adopted technique of chromoendoscopy is also highly dependent on excellent bowel cleansing[7]. With the increasing annual incidence (24 per 100000) and prevalence (345 per 100000) of IBD in Australia[8], efficacious colonoscopy is crucial. Low tolerability of bowel preparation is reported in IBD patients, although this has not been prospectively validated[9]. The exact mechanism driving such low tolerability is unclear. It may relate to abdominal pain, nausea and vomiting[1,9]. Additional factors that have been reported include previous surgery, intestinal stenosis, altered motility, anxiety, or heightened visceral sensitivity and pre-procedure dietary recommendations[1,9].

In the general population, poor bowel preparation is more commonly seen in males, smokers, the elderly, patients with a history of stroke, dementia, diabetes, previous colonic resection and in patients who take opioids, psychotropic drugs and calcium channel blockers[4,10-12]. Tolerability is one of the most significant factors contributing to efficacy of preparation. Efficacy and tolerability are related, and synergistically both contribute to "effectiveness" of a preparation[13]. If the preparation is not well tolerated, even if otherwise efficacious, it will not be consumed, leading to reduced effectiveness.

In Australia, several bowel cleansing agents are available. Bowel preparations are usually based on solutions of polyethylene glycol (PEG)[14,15]. Prep Kit-C (Pc) is a combination of Picoprep (Sodium picosulphate/magnesium citrate) and glycoprep (PEG). Picoprep is a small volume, hyperosmotic solution, primarily exerting its action through osmotically drawing fluid into the intestinal lumen. Moviprep (Mp) is a combination of low volume PEG solution with ascorbic acid. The ascorbic acid has osmotic laxative effects and a pleasant taste[14,16]. Both Pc and Mp are approved for use under the Australian therapeutic goods administration.

At present, there are no prospective studies which examine tolerability, efficacy and safety of Pc when compared with Mp in both the general and IBD populations. This study's primary aim was to compare tolerability, efficacy and safety of split protocols of Mp with Pc in participants having a colonoscopy. The secondary aim was to compare the efficacy and tolerability of either preparation in participants with or without IBD.

MATERIALS AND METHODS

Methods

A prospective, randomized, single blinded trial was conducted at a single tertiary referral center. Recruitment of patients occurred from March 2013 to December 2016. Approval was obtained from the Institutional Human Ethics and Research Office (reference HREC/12/LPOOL/108).

Inclusion criteria

All patients aged between 18-75 years requiring an outpatient colonoscopy were invited to participate in this study. Patients identified as having IBD required histological evidence of Crohn's disease or ulcerative colitis from a previous colonoscopy.

Exclusion criteria

The following were exclusion criteria: non–English speaking, renal insufficiency (defined as an estimated Glomerular Filtration Ratio of less than 50 mL/min), cardiac failure (New York Heart Association Class greater than two), advanced liver disease (Child-Pugh B or C), poorly controlled diabetes mellitus (uninterrupted Hba1c > 8.0% for greater than one year and/or end organ complications from diabetes mellitus), bowel obstruction, total or limited colonic resection, megacolon, dysphagia and pregnancy or planning to become pregnant during the trial period. Patients with IBD who had a preceding colectomy or ileocolonic resection (that involved or extended beyond the hepatic flexure) were also excluded from this study.

Randomization

All participants were randomly allocated to a bowel preparation regime (Mp or Pc) at time of study recruitment in a 1:1 ratio. The allocation sequence was provided by the coordinating investigator. The investigator drew the patient allocated preparation out of an envelope which had equal numbers of both preparations. Patients were provided

with their assigned bowel cleansing preparation at the time of randomization. The cohort was then stratified according to presence of IBD. Patients were unable to be blinded to their allocated preparation due to associated packaging and the differences in administration. Written information about the bowel preparation including appropriate diet and timing of consumption was provided and explained in detail at a clinic review prior to colonoscopy. These instructions are provided in Supplementary material 1 . All assessing endoscopists were blinded to the assigned bowel preparation.

Outcomes

The primary endpoint was the tolerability and efficacy of each bowel preparation in the entire cohort. The secondary endpoints were comparison of the tolerability and efficacy of the allocated bowel preparation in patients with and without IBD, as well as overall safety of bowel preparation.

Tolerability and side effects

Tolerability was assessed using a Tolerability Questionnaire modified from Lawrance *et al*[17] (Supplementary material 2). Patients received the questionnaire at their pre-assessment visit and completed it after finishing their bowel preparation on the day of their colonoscopy. The questionnaire included a five-point Likert scale to assess tolerability (ranging from 0 to 5) and palatability (ranging from 0 to 5) of the preparation. A lower score indicated poorer tolerance. Common side effects (abdominal discomfort, abdominal pain, nausea, vomiting, abdominal distension, dizziness and shortness of breath) were also measured on a five-point Likert scale (ranging from 0 to 5). A higher score indicated worse reported side effects.

Colonoscopy

Patients were provided with written instructions and the bowel preparation explained in detail by the recruiting investigator at the time of study recruitment (full preparation instructions are available in Supplementary material 2). Apart from the preparation agent, preparation was standardized between the two groups including split dosing and 24 h of clear fluids. Colonoscopies were performed by experienced consultant colonoscopists (n = 4) or advanced gastroenterology trainees under the direct supervision of one of the colonoscopists. All procedures were performed using intravenous sedation administered by an anesthetist.

Efficacy

Efficacy of colon cleansing was assessed using the validated Ottawa Bowel Preparation Score (OBPS)[18]. All colonoscopists attended calibrating sessions prior to study commencement. Two colonoscopists were blinded to the allocated bowel preparation, independently assessed the efficacy of bowel cleansing regime during insertion of the colonoscope, prior to washing. The OBPS grades the quality of bowel preparation (0 to 4, with 0 being no fluid and 4 pertaining to fluid/fecal material unable to be cleared) in three colonic segments (right, left, recto-sigmoid) in addition to an overall fluid score. The total score out of 14 was provided for each patient and an average score calculated from both scores. A score of zero represents excellent preparation and 14 represents solid stool in each segment and excessive fluid. Inadequate bowel preparation is defined as an OBPS score equal to or greater than 8[19,20].

Safety: Electrolyte analysis

Safety of each bowel preparation included determination of electrolyte alteration. Blood was collected from each patient within one week before bowel preparation and on the day of colonoscopy prior to the procedure for serum electrolytes. Changes in serum sodium, chloride, potassium, bicarbonate, urea, creatinine, magnesium, calcium and phosphate were measured.

Statistical analyses

For the primary analysis in the entire cohort, an estimated sample size of 127 patients in each group was calculated to detect a 15% difference in the tolerability of bowel preparation between Mp and Pc, with 95% confidence and 90% power. Preliminary data using the same Tolerability Questionnaire which reported the mean tolerability of Moviprep of 13.3 (standard deviation 4.9) in patients undergoing colonoscopy was used to guide the sample size calculation[21]. The difference in tolerability of 15% between bowel preparation regimes was selected as this was also used in another

study assessing tolerability of different bowel preparations[17]. Assuming a completion rate of 80%, a target of at least 159 participants for recruitment in each group was sought, giving a sample size of at least 318. The student *t*-test was used to compare the differences in mean scores of tolerability and efficacy. Associations between categorical variables and outcomes were assessed using Chi-square test. The IBM Statistical Package for the Social Sciences for Windows version 25.0 (IBM corporation, Armonk, NY, United States) was used to analyze the data.

RESULTS

Participant characteristics

From March 2013 to December 2016, 338 patients were enrolled in the study. 168 patients were randomized to Mp and 170 to Pc (Figure 1). One hundred and twenty-five patients had a pre-existing diagnosis of IBD (58% patients with Crohn's disease and 42% with ulcerative colitis). In the IBD group, 64 patients had Mp and 61 had Pc. In the non-IBD group, 104 patients had Mp and 109 had Pc (Figure 1). Within both the IBD and non-IBD groups, there was no difference in age or gender distribution across the allocated bowel preparation groups (Table 1). Forty percent (n = 86) of the non-IBD cohort were male, compared with 52% (n = 65) in the IBD cohort. The mean ages of the IBD and non-IBD groups were 40.3 ± 14.7 and 50.3 ± 13.4 years respectively (P = 0.65).

Tolerability and side effects

Of the 338 patients, 288 (85%) completed the questionnaire assessing tolerability (Figure 1), this proportion was similar in both the Mp and Pc groups. There were no significant differences in the mean scores for tolerability between Mp (11.84 ± 5.4) and Pc groups (10.99 ± 5.2; P = 0.17). Thirty and 20 patients from the IBD and non-IBD groups respectively did not complete the tolerability questionnaire. The tolerability score in the IBD (n = 95) group was significantly lower than the non-IBD group (n = 193) (10.3 ± 5.1 *vs* 12.0 ± 5.3, P = 0.01) (Figure 2), indicating poorer tolerability in this group of patients.

The IBD group reported higher score (indicating worse) for abdominal pain (mean 4.78 *vs* 3.39; P = 0.031) and lower mean score for dizziness (0.37 *vs* 0.78; P = 0.03), and shortness of breath (mean 0.09 *vs* 0.39; P = 0.042) compared with the non-IBD group. The mean scores for nausea/vomiting were similar in both groups (mean 1.15 *vs* 1.65; P = 0.14) (Figure 3). Within the IBD group, patients who had Mp reported more abdominal pain when compared with Pc (mean 5.7 *vs* 3.62; P = 0.046). There were no other significant differences in the mean scores for other symptoms within the non-IBD or IBD group.

When comparing the overall tolerability of Pc (n = 145) with Mp (n = 143) in both the IBD and non-IBD groups, there was no statistically significant difference in mean tolerability scores between the two bowel preparations, although the study may not have been powered to detect a significant difference (Table 2).

Efficacy

Data on efficacy of the bowel preparation was available in 320 patients (95%). There was no difference in the efficacy within the entire group when comparing Mp to Pc [mean OBPS: Mp (n = 158; 5.4 ± 2.4) and Pc (n = 162; 5.1 ± 2.1; P = 0.73)], nor within both the IBD [mean OBPS: Mp (n = 58; 4.8 ± 2.9) and Pc (n = 56; 5.2 ± 3.3; P = 0.53)] and non-IBD [mean OBPS: Mp (n = 100; 5.5 ± 2.4) and Pc (n = 106; 5.4 ± 2.1; P = 0.84)] groups.

Efficacy of bowel preparation when comparing the IBD (n = 114) to the non-IBD (n = 206) group was not significantly different (P = 0.26). Inadequate bowel preparation (defined as an OBPS of greater than or equal to 8)[17,19] was present in 8.9% (n = 29) of all patients: 10.5% (n = 12) of the IBD group and 8% (n = 17) of the non-IBD group.

Safety: Electrolyte analysis

Electrolyte data was available for 256 patients (78%). There was a statistically significant increase in magnesium in patients who received Pc compared with Mp (mean increase in mmol/L: Mp 0.03 ± 0.117 and Pc 0.11 ± 0.106; P < 0.0001) (Figure 4). There were no additional differences detected in the remaining electrolytes. There were no reported clinical concerns attributed to electrolyte abnormalities during the peri-procedural period, such as arrhythmias, exacerbation of congestive cardiac failure or acute pulmonary edema.

Table 1 Baseline characteristics

	IBD cohort (*n* = 125)			Non-IBD cohort (*n* = 213)			*P* value
mean age +/- SD (yr)	40.3 ± 14.7			50.3 ± 13.4			0.65
	Prep Kit -C	Moviprep	*P* value	Prep Kit -C	Moviprep	*P* value	
mean ± SD, age (yr)	39.7 ± 14.27	40.9 ± 15.1	0.65	52.98 ± 12.97	53.65 ± 13.98	0.72	
Male (*n*)	35	30	0.13	39	47	0.93	

SD: Standard deviation; IBD: Inflammatory bowel disease.

Table 2 Tolerability Scores in the inflammatory bowel disease and non-inflammatory bowel disease cohorts

	Prep Kit-C (*n* = 145)	Moviprep (*n* = 143)	*P* value
IBD, *n* = 95	9.67 ± 4.87; *n* = 47	10.89 ± 5.21; *n* = 48	0.25
Non-IBD, *n* = 193	11.61 ± 5.32; *n* = 98	12.32 ± 5.35; *n* = 95	0.36

IBD: Inflammatory bowel disease.

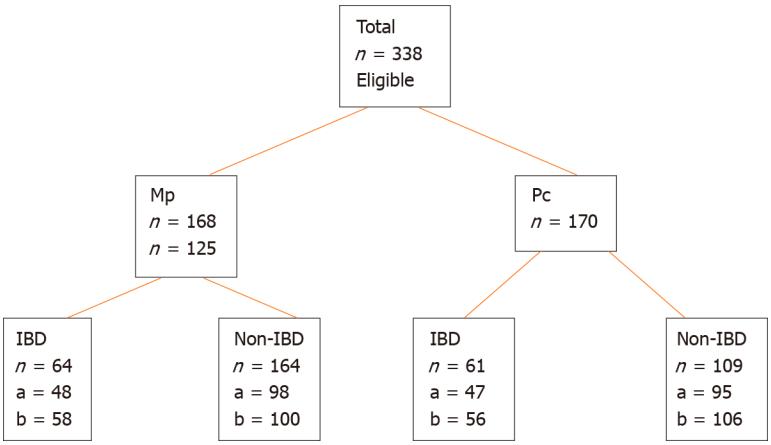

Figure 1 Randomization of bowel preparation. a: Number of patients who completed tolerability questionnaire; b: Number of patients with validated Ottawa Bowel Preparation Scores; Mp: Moviprep; Pc: Prep Kit-C; IBD: Inflammatory bowel disease.

DISCUSSION

This study has demonstrated no significant differences in the tolerability and efficacy of bowel preparation when comparing Mp with Pc. However, subgroup analysis revealed IBD patients were less tolerant of bowel preparation when compared with patients without IBD. IBD patients reported more abdomen pain with both preparations when compared with the non-IBD group. Within the IBD group, Mp produced more abdomen pain compared with Pc. Safety was comparable for IBD and non-IBD patients, although Pc resulted in a higher magnesium level than Mp.

The influence of effective bowel preparation on the quality of colonoscopy is substantial, as recently highlighted by the inclusion of bowel preparation adequacy and safety in the Australian Colonoscopy Care Standards formulated by the Commission on Safety and Quality in Health Care[22]. Systematic reviews have not demonstrated superiority of any specific bowel preparation regimes when assessing efficacy in both the non-IBD population as well as in those with IBD[14,23,24]. At our center, as well as many in Australia, Mp and Pc are commonly recommended bowel preparations. Prior to this study, there have been no prospective studies which compare the efficacy of Pc with Mp in non-IBD or IBD populations. Consistent with systematic reviews for other bowel preparations, our study demonstrated no significant difference in bowel preparation efficacy between Mp and Pc in both IBD and non-IBD populations. Our findings supported both Pc and Mp as suitable choices

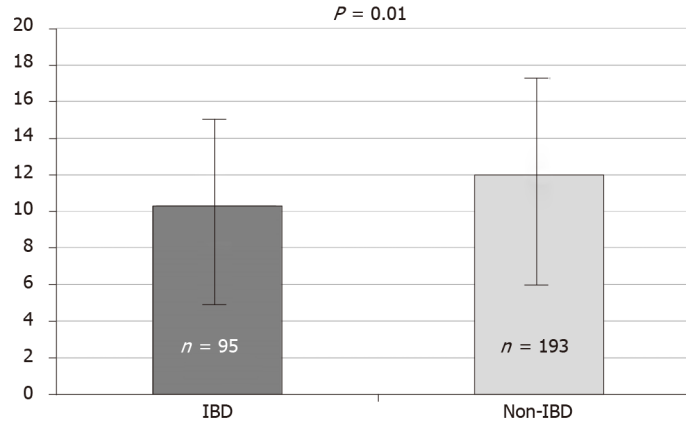

Figure 2 Total tolerability scores when comparing inflammatory bowel disease and non-inflammatory bowel disease cohorts. Of 95 inflammatory bowel disease and 193 non- inflammatory bowel disease participants included. Higher score indicates better tolerability where 0 = poorly tolerated and 5 = well tolerated**.** Total score is out of 20 (0-5 for taste; 0-5 ease of ingestion; 0-5 for palatability; 0-5 for amount). IBD: Inflammatory bowel disease.

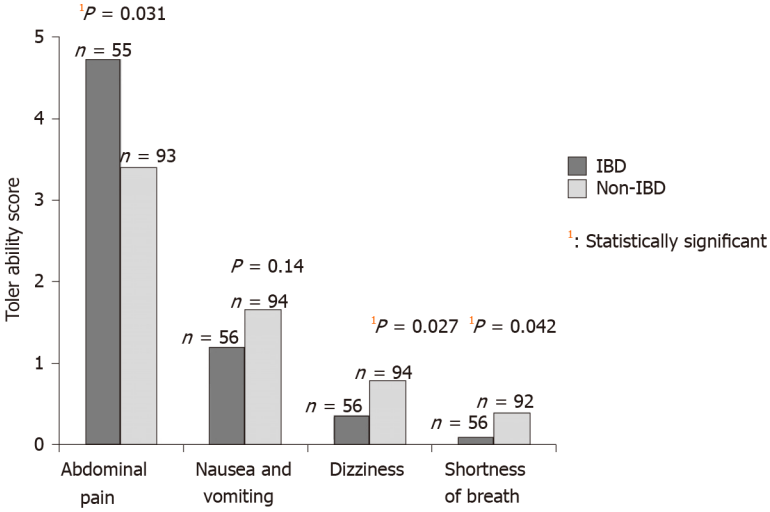

Figure 3 Tolerability scores according to specified symptom. Of 56 inflammatory bowel disease and 93 non-inflammatory bowel disease participants compared. 0 = well tolerated and 5 = poorly tolerated. Maximum score for abdominal pain is 15 (0-5 points abdominal discomfort; 0-5 points for abdominal pain; 0-5 points for abdominal distension). Maximum score for nausea and vomiting is ten (0-5 points for nausea; 0-5 points for vomiting). The maximum points for dizziness or shortness of breath are 5 points. IBD: Inflammatory bowel disease.

when considering efficacy of bowel preparation regimes in patients with and without IBD[1,19,20]. Nine percent of our overall study population had inadequate bowel preparation, which falls within the American Society for Gastrointestinal Endoscopy guidelines for adequate bowel preparation in at least 85% of patients[4].

Our study was unique in that both our IBD and non-IBD patients prospectively completed tolerability questionnaires at the time of bowel preparation ingestion. It was observed that IBD patients were less tolerant of bowel preparation when compared with patients without IBD, though the type of bowel preparation did not affect the total tolerability score when comparing IBD with the non-IBD groups. IBD patients also reported more abdominal pain when compared to non-IBD patients.

Poorer tolerability of bowel preparation within IBD cohorts is consistent with previously published literature. Denters *et al*[25] reported significantly more psychological and physical burden from bowel preparation in patients with IBD when compared with other patient groups. In another study, IBD patients most commonly cited difficulty with bowel preparation as the most important reason for failed compliance with scheduled colonoscopies for colorectal cancer surveillance[9]. Tolerability of bowel preparation in IBD patients may not be entirely related to luminal pathology. In another study, tolerance of bowel preparation was similar when comparing IBD and non-IBD cohorts, however co-morbid anxiety played a role in symptom development during bowel preparation in IBD patients[26].

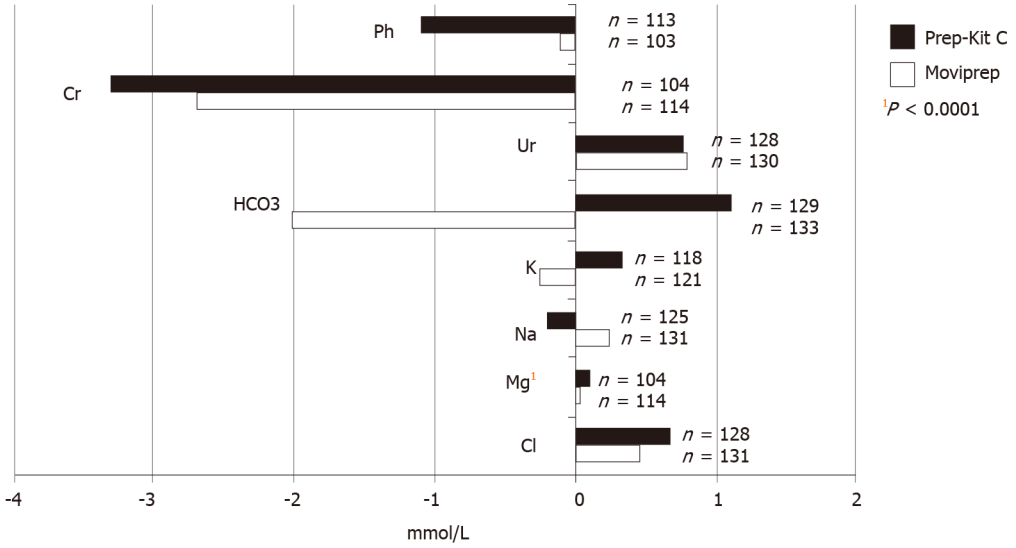

Figure 4 Changes in electrolyte levels (*n* = 256) measured in mmol/L. Levels compared between one week prior to procedure and day of the procedure.

Our study provides further impetus to reinforce the importance of educating IBD patients about bowel preparation, including the possibility for reduced tolerance and more abdomen pain. IBD patient awareness about potentially poor tolerance prior to ingestion may positively impact on the bowel preparation quality and compliance with surveillance protocols. Dietary liberalization, specifically using the white or low residue diet has been shown to be better tolerated and as efficacious as a clear fluid diet[27]. Tolerability of the white diet in comparison with the clear fluid diet, prior to colonoscopy, within the IBD population is a future research area.

Our study supports the safety of both Mp and Pc. There were no reported adverse clinical outcomes. A statistically significant increase in serum magnesium level with the use of Pc when compared with Mp was identified but it was of a small magnitude and unlikely to be clinically significant. Whilst there have been no prospective studies comparing electrolyte changes or adverse outcomes in patients taking Mp compared with Pc, our study is in line with other studies which have shown that Pc can cause electrolyte derangement[24]. Thus, Pc should be avoided in the elderly and patients with renal impairment[24].

Our study has several limitations. In relation to assessment of bowel preparation tolerability, our study utilized a modified, un-validated questionnaire developed by our study team based on an existing questionnaire[17]. Whilst we acknowledge this limitation, the same questionnaire was used in all study arms (Mp and Pc; IBD and non-IBD), and the questionnaire completion rate was equivalent amongst all study arms. Furthermore, tolerability of bowel preparation may have been influenced by the volume of fluid (*e.g.*, water) replacement consumed by each participant in addition to the actual bowel preparation. This was not standardized between groups (Supplementary material 1). The tolerability questionnaire was completed just prior to the colonoscopy. As a result, delayed tolerability side effects from the allocated preparation may have been missed. Lastly, we did not collect data about variables which may influence bowel preparation efficacy. These variables include smoking history, medication history, history of Diabetes Mellitus or disease activity in IBD.

CONCLUSION

Our prospective, randomized controlled study has compared the tolerability, efficacy and safety of Mp and Pc in non-IBD and IBD patients. We demonstrated that both Mp and Pc had similar efficacy of bowel preparation in either the non-IBD or IBD cohorts. However, IBD patients were less tolerant of bowel preparation and reported more abdomen pain compared with patients without IBD. Furthermore, IBD patients reported more abdominal pain with Mp compared with Pc. Future research opportunities in this field include assessing factors contributing to poor bowel preparation tolerability in IBD patients is required.

ARTICLE HIGHLIGHTS

Research background

Colonoscopy remains the gold standard for detection of colonic disease. An optimal evaluation depends on adequate bowel cleansing. Patients with inflammatory bowel disease (IBD), require frequent endoscopic assessment for both activity and dysplasia assessment. Two commonly used bowel preparations in Australia are Prep Kit-C (Pc) and Moviprep (Mp). Little is known about tolerability, efficacy and safety of split protocols of Mp and Pc in both IBD and non-IBD patients.

Research motivation

To determine which bowel preparation is tolerable and effective in both IBD and non-IBD patients. Efficacy and tolerability are related, and both contribute to effectiveness. By maximizing effectiveness we minimise the chances of inadequate bowel cleansing and incomplete colonoscopy. This ensures that hospital and patient resources are not wasted.

Research objectives

This study's primary aim was to compare tolerability, efficacy and safety of split protocols of Mp with Pc in participants having a colonoscopy. The secondary aim was to compare the efficacy and tolerability of either preparation in participants with or without IBD.

Research methods

Patients were randomized to Pc or Mp bowel preparation. Patients completed a questionnaire to assess tolerability. Efficacy was assessed using the Ottawa Bowel Preparation Score. Serum electrolytes and renal function were collected one week prior to colonoscopy and on the day of colonoscopy.

Research results

Of 338 patients met the inclusion criteria. Of 168 patients randomized to Mp and 170 to Pc. The efficacy of bowel preparation (mean Ottawa Bowel Preparation Score) was similar between Mp and Pc. Mean tolerability scores were similar in Mp and Pc. The mean tolerability score in the IBD group was lower than the non-IBD group. IBD patients described more abdominal pain with Mp when compared with Pc. Serum magnesium level increased with Pc compared with Mp in all patients.

Research conclusions

In this study, the efficacy, tolerability and safety of Mp and Pc were similar in all patients. However, patients with IBD reported lower tolerability with both preparations. Specifically, IBD patients had more abdominal pain with Mp.

Research perspectives

These results should be considered when recommending bowel preparation especially to IBD patients. More prospective studies are required in this field.

REFERENCES

1 **Nett A**, Velayos F, McQuaid K. Quality bowel preparation for surveillance colonoscopy in patients with inflammatory bowel disease is a must. *Gastrointest Endosc Clin N Am* 2014; **24**: 379-392 [PMID: 24975529 DOI: 10.1016/j.giec.2014.03.004]

2 **Harewood GC**, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; **58**: 76-79 [PMID: 12838225 DOI: 10.1067/mge.2003.294]

3 **Heron V**, Parmar R, Ménard C, Martel M, Barkun AN. Validating bowel preparation scales. *Endosc Int Open* 2017; **5**: E1179-E1188 [PMID: 29202001 DOI: 10.1055/s-0043-119749]

4 **Rex DK**, Schoenfeld PS, Cohen J, Pike IM, Adler DG, Fennerty MB, Lieb JG 2nd, Park WG, Rizk MK, Sawhney MS, Shaheen NJ, Wani S, Weinberg DS. Quality indicators for colonoscopy. *Am J Gastroenterol* 2015; **110**: 72-90 [PMID: 25448873 DOI: 10.1038/ajg.2014.385]

5 **Sharara AI**, Bou Daher H. Bowel Cleansing Strategies After Suboptimal Bowel Preparation. *Clin Gastroenterol Hepatol* 2019; **17**: 1239-1241 [PMID: 30625406 DOI: 10.1016/j.cgh.2018.12.042]

6 **Australian Commission on Safety and Quality in Health Care**. Colonoscopy Clinical Care Standard. [cited 23 February 2021]. In: Clinical Care Standards, 2020 [Internet]. Available from:

https://www.safetyandquality.gov.au/standards/clinical-care-standards/colonoscopy-clinical-care-standard

7 **Kiesslich R**, Neurath MF. Surveillance colonoscopy in ulcerative colitis: magnifying chromoendoscopy in the spotlight. *Gut* 2004; **53**: 165-167 [PMID: 14724144 DOI: 10.1136/gut.2003.026351]

8 **Studd C**, Cameron G, Beswick L, Knight R, Hair C, McNeil J, Desmond P, Wilson J, Connell W, Bell S. Never underestimate inflammatory bowel disease: High prevalence rates and confirmation of high incidence rates in Australia. *J Gastroenterol Hepatol* 2016; **31**: 81-86 [PMID: 26222770 DOI: 10.1111/jgh.13050]

9 **Friedman S**, Cheifetz AS, Farraye FA, Banks PA, Makrauer FL, Burakoff R, Farmer B, Torgersen LN, Wahl KE. Factors that affect adherence to surveillance colonoscopy in patients with inflammatory bowel disease. *Inflamm Bowel Dis* 2013; **19**: 534-539 [PMID: 23429444 DOI: 10.1097/MIB.0b013e3182802a3c]

10 **Yee R**, Manoharan S, Hall C, Hayashi A. Optimizing bowel preparation for colonoscopy: what are the predictors of an inadequate preparation? *Am J Surg* 2015; **209**: 787-92; discussion 792 [PMID: 25796095 DOI: 10.1016/j.amjsurg.2014.12.018]

11 **Chung YW**, Han DS, Park KH, Kim KO, Park CH, Hahn T, Yoo KS, Park SH, Kim JH, Park CK. Patient factors predictive of inadequate bowel preparation using polyethylene glycol: a prospective study in Korea. *J Clin Gastroenterol* 2009; **43**: 448-452 [PMID: 18978506 DOI: 10.1097/MCG.0b013e3181662442]

12 **Lim SW**, Seo YW, Sinn DH, Kim JY, Chang DK, Kim JJ, Rhee JC, Shim SG, Kim YH. Impact of previous gastric or colonic resection on polyethylene glycol bowel preparation for colonoscopy. *Surg Endosc* 2012; **26**: 1554-1559 [PMID: 22170320 DOI: 10.1007/s00464-011-2068-4]

13 **Rex DK**. Bowel preparation for colonoscopy: entering an era of increased expectations for efficacy. *Clin Gastroenterol Hepatol* 2014; **12**: 458-462 [PMID: 24239858 DOI: 10.1016/j.cgh.2013.11.003]

14 **Barkun A**, Chiba N, Enns R, Marcon M, Natsheh S, Pham C, Sadowski D, Vanner S. Commonly used preparations for colonoscopy: efficacy, tolerability, and safety--a Canadian Association of Gastroenterology position paper. *Can J Gastroenterol* 2006; **20**: 699-710 [PMID: 17111052 DOI: 10.1155/2006/915368]

15 **Munsterman ID**, Cleeren E, van der Ploeg T, Brohet R, van der Hulst R. 'Pico-Bello-Klean study': effectiveness and patient tolerability of bowel preparation agents sodium picosulphate-magnesium citrate and polyethylene glycol before colonoscopy. A single-blinded randomized trial. *Eur J Gastroenterol Hepatol* 2015; **27**: 29-38 [PMID: 25426978 DOI: 10.1097/MEG.0000000000000192]

16 **Bitoun A**, Ponchon T, Barthet M, Coffin B, Dugué C, Halphen M; Norcol Group. Results of a prospective randomised multicentre controlled trial comparing a new 2-L ascorbic acid plus polyethylene glycol and electrolyte solution vs. sodium phosphate solution in patients undergoing elective colonoscopy. *Aliment Pharmacol Ther* 2006; **24**: 1631-1642 [PMID: 17094774 DOI: 10.1111/j.1365-2036.2006.03167.x]

17 **Lawrance IC**, Willert RP, Murray K. A validated bowel-preparation tolerability questionnaire and assessment of three commonly used bowel-cleansing agents. *Dig Dis Sci* 2013; **58**: 926-935 [PMID: 23095990 DOI: 10.1007/s10620-012-2449-0]

18 **Rostom A**, Jolicoeur E. Validation of a new scale for the assessment of bowel preparation quality. *Gastrointest Endosc* 2004; **59**: 482-486 [PMID: 15044882 DOI: 10.1016/s0016-5107(03)02875-x]

19 **Chan M**, Birnstein E, Patel N, Chan L, Kline M. Ottawa Score of 8 or Greater Is an Optimal Cut-off Point for Inadequate Bowel Preparation: 1156. *Am J Gastroenterol* 2011; **106**: S431-S432 [DOI: 10.14309/00000434-201110002-01156]

20 **Parmar R**, Martel M, Rostom A, Barkun AN. Validated Scales for Colon Cleansing: A Systematic Review. *Am J Gastroenterol* 2016; **111**: 197-204; quiz 205 [PMID: 26782820 DOI: 10.1038/ajg.2015.417]

21 **Lee SH**, Lee DJ, Kang JK. A randomized controlled trial of comparison on time and rate of cecal and terminal ileal intubation according to adult-colonoscope length: intermediate versus long. *J Gastroenterol Hepatol* 2014; **29**: 44-46

22 **Australian Commission on Safety and Quality in Health Care**. Colonoscopy Clinical Care Standard 2017. [cited 23 February 2021]. Available from: https://www.safetyandquality.gov.au/standards/clinical-care-standards/colonoscopy-clinical-care-standard

23 **Restellini S**, Kherad O, Bessissow T, Ménard C, Martel M, Taheri Tanjani M, Lakatos PL, Barkun AN. Systematic review and meta-analysis of colon cleansing preparations in patients with inflammatory bowel disease. *World J Gastroenterol* 2017; **23**: 5994-6002 [PMID: 28932092 DOI: 10.3748/wjg.v23.i32.5994]

24 **Belsey J**, Epstein O, Heresbach D. Systematic review: oral bowel preparation for colonoscopy. *Aliment Pharmacol Ther* 2007; **25**: 373-384 [PMID: 17269992 DOI: 10.1111/j.1365-2036.2006.03212.x]

25 **Denters MJ**, Schreuder M, Depla AC, Mallant-Hent RC, van Kouwen MC, Deutekom M, Bossuyt PM, Fockens P, Dekker E. Patients' perception of colonoscopy: patients with inflammatory bowel disease and irritable bowel syndrome experience the largest burden. *Eur J Gastroenterol Hepatol* 2013; **25**: 964-972 [PMID: 23660935 DOI: 10.1097/MEG.0b013e328361dcd3]

26 **Bessissow T**, Van Keerberghen CA, Van Oudenhove L, Ferrante M, Vermeire S, Rutgeerts P, Van Assche G. Anxiety is associated with impaired tolerance of colonoscopy preparation in inflammatory

bowel disease and controls. *J Crohns Colitis* 2013; **7**: e580-e587 [PMID: 23664621 DOI: 10.1016/j.crohns.2013.04.011]

27 **Butt J**, Bunn C, Paul E, Gibson P, Brown G. The White Diet is preferred, better tolerated, and non-inferior to a clear-fluid diet for bowel preparation: A randomized controlled trial. *J Gastroenterol Hepatol* 2016; **31**: 355-363 [PMID: 26250786 DOI: 10.1111/jgh.13078]

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ORIGINAL ARTICLE

Clinical Trials Study

Long-term follow-up of cumulative incidence of hepatocellular carcinoma in hepatitis B virus patients without antiviral therapy

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Author contributions: Tong GD conceived, supervised and guided implementation of the experiments; Jiang XY, Huang B, Huang DP and Wei CS conducted the experiments, collected and organized the data, and analyzed the results; Zhong WC, Peng DT and Huang FR wrote the original draft; all the authors revised the manuscript and approved the final version.

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Abstract

BACKGROUND

China has a high prevalence of hepatitis B virus (HBV), but most chronic hepatitis B (CHB) patients do not receive standardized antiviral therapy. There are few relevant reports addressing the outcomes of the large number of CHB patients who do not receive antiviral therapy.

AIM

To observe the outcomes of long-term follow-up of patients with CHB without antiviral treatment.

METHODS

This study included 362 patients with CHB and 96 with hepatitis B cirrhosis without antiviral treatment and with only liver protection and anti-inflammatory treatment from 1993 to 1998. The median follow-up times were 10 and 7 years, respectively. A total of 203 CHB and 129 hepatitis B cirrhosis patients receiving antiviral therapy were selected as the control groups. The median follow-up times were 8 and 7 years, respectively. Kaplan-Meier curves were used to analyze the cumulative incidence of hepatocellular carcinoma (HCC), and the Cox regression model was used to analyze the risk factors for HCC.

RESULTS

Among the patients in the non-antiviral group, 16.9% had spontaneous decreases

Shenzhen Traditional Chinese Medicine Hospital, The Fourth Clinical Medical College of Guangzhou University of Chinese Medicine.

Clinical trial registration statement: This study was registered at Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx). The registration identification number is ChiCTR2000029281 (1/20/2020).

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: All authors and study participants declare no potential conflicting interests related to this paper.

Data sharing statement: No additional data are available.

CONSORT 2010 statement: The authors have read the CONSORT 2010 statement, and the manuscript was prepared and revised according to the CONSORT 2010 statement.

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Country/Territory of origin: China

Peer-review report's scientific quality classification

in HBV DNA to undetectable levels, and 32.8% showed hepatitis B e antigen (HBeAg) seroconversion. In the antiviral group, 87.2% of patients had undetectable HBV DNA, and 52% showed HBeAg seroconversion. Among CHB and hepatitis B cirrhosis patients, the cumulative incidence rates of HCC were 14.9% and 53.1%, respectively, in the non-antiviral group and were 10.7% and 31.9%, respectively, in the antiviral group. There was no difference between the two groups regarding the CHB patients (P = 0.842), but there was a difference between the groups regarding the hepatitis B cirrhosis patients (P = 0.026). The cumulative incidence rates of HCC were 1.6% and 22.3% (P = 0.022) in the groups with and without spontaneous HBeAg seroconversion, respectively. The incidence rates of HCC among patients with and without spontaneous declines in HBV DNA to undetectable levels were 1.6% and 19.1%, respectively (P = 0.051). There was no difference in the cumulative incidence of HCC between the two groups regarding the patients with drug-resistant CHB (P = 0.119), but there was a significant difference between the two groups regarding the patients with cirrhosis (P = 0.004). The Cox regression model was used for regression of the corrected REACH-B score, which showed that alanine aminotransferase > 400 U/L, history of diabetes, and family history of liver cancer were risk factors for HCC among men aged > 40 years (P < 0.05). Multifactorial analysis showed that a family history of HCC among men was a risk factor for HCC.

CONCLUSION

Antiviral therapy and non-antiviral therapy with liver protection and anti-inflammatory therapy can reduce the risk of HCC. Antiviral therapy may mask the spontaneous serological response of some patients during CHB. Therefore, the effect of early antiviral therapy on reducing the incidence of HCC cannot be overestimated.

Key Words: Chronic hepatitis B; Anti-inflammatory therapy; Hepatoprotective therapy; Cumulative incidence; Hepatocellular carcinoma; Antiviral therapy

Core Tip: According to the status quo of antiviral therapy for chronic hepatitis B (CHB) in China, we conducted long-term follow-up of patients with CHB who were recommended to receive nucleoside antiviral therapy in accordance with the guidelines, but did not receive antiviral therapy. We found that early antiviral therapy in patients with CHB did not yield greater benefits in the incidence of hepatocellular carcinoma than hepatoprotective anti-inflammatory therapy. It is suggested that early antiviral therapy with nucleosides may mask spontaneous viral clearance and hepatitis B e antigen clearance in patients with CHB.

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INTRODUCTION

Approximately 45% of hepatocellular carcinomas (HCCs) in patients worldwide and 80% of HCCs in patients in China are caused by hepatitis B virus (HBV) infection[1]. According to the World Cancer Report published by the World Health Organization in 2014, the number of new cases of and deaths from HCC in China accounted for more than half of the total global number in 2012[2]. The high prevalence of HCC in China is mainly due to HBV infection[3,4].

Early studies suggest that effective antiviral therapy can reduce the incidence of HCC in patients with hepatitis B cirrhosis[5-7]. A clinical study in Hong Kong included

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Grade B (Very good): B, B
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0

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1446 patients with chronic hepatitis B (CHB) (including 482 patients with cirrhosis) who received entecavir treatment. The control group included 424 untreated patients (including 69 with cirrhosis). The cumulative incidence rates of HCC in patients with cirrhosis at 3 and 5 years were reduced in the treatment group[8]. Two studies in Japan showed similar results[9,10].

However, there is no consistent conclusion regarding the effect of antiviral therapy on reducing the incidence of HCC among patients with CHB without cirrhosis who have a low risk of HCC[11,12]. Many studies have found no significant reduction in the incidence of HCC in patients with CHB who benefit from antiviral therapy[13]. A Greek study followed up 818 patients with CHB. The results showed that 49 patients developed HCC and that the cumulative incidence of HCC at 5 years was 3.2%. The incidence rates of HCC among patients aged < 50 years, 50-60 years and > 60 years were 0.7%, 6.7% and 11.7%, respectively. Antiviral therapy did not reduce the incidence of HCC associated with age. Multivariate analysis showed that age, sex and cirrhosis were independent risk factors for HCC, regardless of antiviral therapy[14]. A recent Caucasian study found that among 1666 patients with CHB who received entecavir or tenofovir antiviral therapy, the incidence rates of HCC at 1, 3 and 5 years were 1.3%, 3.4% and 8.7%, respectively[15]. The cumulative incidence of HCC has been increasing even with HBV suppression. With the prolongation of follow-up, the incidence of HCC is predicted to increase.

The occurrence of HCC is related to a high viral load and to a long-term and continuous increase in alanine aminotransferase (ALT). The REVEAL study suggested that HCC is associated with a sustained increase in serum ALT levels[16]. Elevated ALT is an indicator of hepatocyte injury or inflammation. Liver fibrosis and cirrhosis caused by chronic liver inflammation are the pathophysiological and histological bases for HCC progression in patients with hepatitis B[17]. Patients with CHB and persistent or repeated elevations in ALT have significantly higher risks of cirrhosis, hepatic decompensation, and HCC than those with persistently normal ALT levels or with fluctuations that return to normal[18,19].

Anti-inflammatory and hepatoprotective therapy is an important approach for CHB in China[20] and effectively inhibits the inflammatory response of the liver and promotes repair of damaged hepatocytes. Studies have shown that anti-inflammatory and hepatoprotective therapy can delay or even prevent the development of CHB into cirrhosis, indicating its high clinical value[21,22]. Antiviral therapy is also effective in controlling liver inflammation, but the ALT levels of 20% of patients still fail to return to normal afterwards[23]. Abnormal ALT levels during the first year of treatment in patients with CHB are associated with an increased risk of HCC[23].

In China, there are approximately 30 million patients with CHB, but only 11% of these patients receive standardized antiviral therapy[24]. Currently, there are few relevant reports addressing the outcomes of the large number of CHB patients who do not receive antiviral therapy. In our observation group, we included 362 patients with CHB and 96 with hepatitis B cirrhosis who were not treated with antiviral therapy but had been treated with anti-inflammatory and hepatoprotective drugs for a long time. The median follow-up times were 10 and 7 years, respectively. A total of 203 patients with CHB and 129 patients with hepatitis B cirrhosis receiving antiviral therapy were included as the control group. The median follow-up times were 8 and 7 years, respectively.

MATERIALS AND METHODS

Observation group

This study comprised 3500 patients with CHB who were hospitalized for the first time in the Department of Hepatology, Shenzhen Hospital of Traditional Chinese Medicine between January 1993 and December 1998 due to abnormal liver function (ALT ≥ 40 U/L). According to the inclusion and exclusion criteria, we enrolled 362 patients with CHB and 96 patients with cirrhosis who were treated with anti-inflammatory and hepatoprotective drugs without antiviral therapy. The median HBV-DNA (log) load was 7.14, and the median ALT level was 188.62 U/L. These patients should have been treated with antiviral therapy, but for various reasons, they did not receive antiviral therapy.

Control group

We collected data for 3897 patients with CHB who received antiviral therapy when they were admitted to the Department of Shenzhen Hospital of Traditional Chinese

Medicine between January 1999 and December 2007 and who received antiviral therapy at the initial visit. According to the inclusion and exclusion criteria, we enrolled 203 patients with CHB and 129 patients with hepatitis B cirrhosis.

Inclusion criteria

CHB without cirrhosis: (1) Patients were positive for hepatitis B surface antigen (HBsAg) for at least 6 mo; (2) Aged 18-75 years; (3) No treatment with interferon; (4) Patients with anti-inflammatory and hepatoprotective drug treatment had ALT ≥ 2 upper limit of normal, HBV-DNA positivity and follow-up times ≥ 2 years; and (5) Patients with antiviral treatment had voluntary acceptance of nucleoside antiviral therapy, follow-up time of ≥ 2 years, and treatment with anti-inflammatory and hepatoprotective drugs for ≤ 6 mo. Hepatitis B cirrhosis patients: (1) Cirrhosis diagnosed by imaging or histology at enrollment; and (2) Child-Turcotte-Pugh score ≥ 7 points defined as decompensated.

Exclusion criteria

The exclusion criteria were as follows: (1) CHB complicated by drug-induced liver damage, alcoholic liver disease, autoimmune liver disease or other liver diseases; (2) HCC; (3) Liver cancer diagnosed within 1 year after treatment; (4) Patients with anti-inflammatory and hepatoprotective therapy who were followed up for < 2 years after treatment; and (5) Patients with antiviral treatment who were followed up for < 2 years or who received anti-inflammatory and hepatoprotective treatment for > 6 mo.

Study design

This was an ambispective cohort study, with retrospective analyses before December 31, 2007, and prospective cohort analyses thereafter. The study was conducted and reported according to the study protocol, conforming to the ethical guidelines of the 1975 Declaration of Helsinki, which was approved by the Ethics Committee of Shenzhen Hospital of Traditional Chinese Medicine. All of the included patients were required to give signed informed consent.

Treatment

Observation group: Treatment consisted of glycyrrhizin preparation (oral or intravenous injection), glutathione (oral or intravenous injection), schisandra preparation (oral bicyclol, wuzhi capsule or tablet), and Silymarin. Control group: monotherapy consisted of lamivudine (LAM) 100 mg/d (Galans history Ke Pharmaceutical Company), adefovir (ADV) 10 mg/d (GlaxoSmithKline Pharmaceuticals), telbivudine (LDT) 600 mg/d (Beijing Novartis Pharmaceutical Co., Ltd.), or entecavir (ETV) 0.5 mg/d (China-US Shanghai Squibb Pharmaceutical Co., Ltd.), and combination therapy consisted of an initial combination or salvage treatment, namely, LAM + ADV, LDT + ADV, or ETV + ADV.

Follow-up procedure

The starting point was the time when each patient was enrolled for the first time, and the endpoint of follow-up was the time of study discontinuation or last follow-up visit before the patient was lost to follow-up. All patients were followed up at least every 6 mo. The follow-up times of the patients with anti-inflammatory and hepatoprotective treatment were ≥ 2 years. The addition of or switching between antiviral drugs was considered to be the endpoint of follow-up. Patients with antiviral therapy alone were not treated with anti-inflammatory or hepatoprotective therapy for ≥ 6 mo. The anti-inflammatory and hepatoprotective therapy patients were followed up for 2-23 years (1993-2016), and antiviral patients were followed up for 2-17 years (1999-2016) (Figure 1). Follow-up observation indicators were: (1) Liver function: ALT, aspartate aminotransferase (AST), and total bilirubin (TB); (2) HBV-DNA quantification; (3) HBV markers such as HBsAg and hepatitis B e antigen (HBeAg); (4) Routine blood tests; (5) B-mode Doppler imaging, computed tomography (CT) or magnetic resonance imaging (MRI); and (6) a-fetoprotein (AFP) detection.

Laboratory tests

(1) Liver function was tested with an Olympus 2700 automatic biochemical analyzer, and routine analysis of blood was performed with an XS-500i automatic analyzer; (2) HBV marker detection was performed using an ELISA method, with reagents provided by Shanghai Kehua Bioengineering Co., Ltd; (3) HBV-DNA quantitative analysis was performed using real-time fluorescent quantitative polymerase chain reaction (PCR) and COBASTaqMan HBV diagnostic reagents, and the reagents were

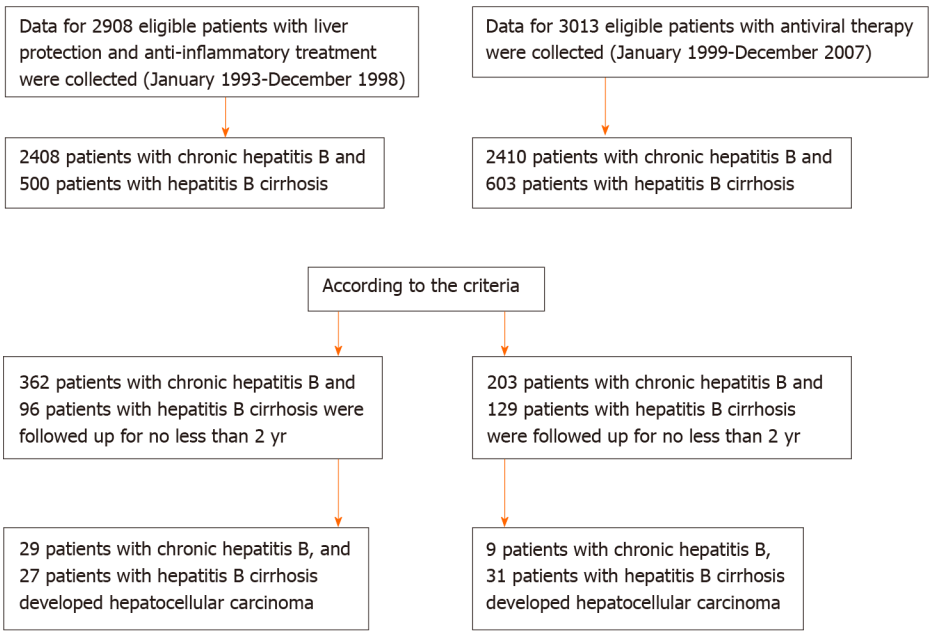

Figure 1 Flow chart of the control group.

provided by Shenzhen Piji Bioengineering Co., Ltd. and Roche Diagnostics Co., Ltd. The instruments used were the ABI PRISM 7000 fluorescence quantitative PCR instrument and COBAS Taqman48analyzer real-time quantitative PCR analyzer; (4) AFP measurements were performed using enzyme immunoassays, with a normal detection value of 20 ng/L; (5) B-mode Doppler imaging was performed using the Fynergy-type color dual-function Doppler produced by the Tyson Corporation. The B-ultrasound diagnostic criteria for cirrhosis were as follows: according to the integral classification standard of liver ultrasound parameters, the score was ≥ 10 points[25]; (6) Lesions in the liver were observed by B-ultrasound, CT and MRI. The CT spiral scanner was the Siemens Picker UltraZ super, and the MRI diagnostic instrument was the Philips intera2.0T, 3.0T high magnetic field superconducting magnetic resonance machine; and (7) For the liver biopsy specimens, the lengths were ≥ 1.5 cm, conventional paraffin sections were prepared for hematoxylin and eosin staining and Masson and reticulum fiber staining, and each specimen contained at least six junction areas.

Statistical analysis

This study used HCC as the endpoint of observation. The study deadline was December 31, 2016. The analysis of all patients with follow-up data and of those who were lost to follow-up was ended with the last clinical datapoints. For statistical analysis of differences between groups, qualitative data were analyzed using the c^2 test or Fisher's exact probability method, and continuous variables were analyzed using the Mann-Whitney test. The cumulative incidence of liver cancer was analyzed by Kaplan-Meier curves, and statistical significance was determined using the log-rank test. The Cox risk regression model was used to analyze the factors influencing liver cancer. All data were analyzed by SPSS version 22.0. $P < 0.05$ was considered statistically significant.

RESULTS

Clinical baseline data of enrolled patients

There were 291 men and 71 women among the 362 patients with CHB in the observation group. There were 175 men and 28 women in the control group. According to the statistical analysis, there were significant differences in sex between the two groups ($P < 0.05$). There were 198 HBeAg-positive patients in the observation group and 123 in the control group. The difference in the proportions of HBeAg-positive patients in the two groups was significant ($P < 0.05$). In the observation group,

the median age was 33 years, and the median follow-up time was 10 years; in the control group, the median age was 39 years, and the median follow-up time was 8 years. There were significant differences in age and follow-up between the two groups ($P < 0.05$). However, there were no significant differences in the remaining indicators (Table 1).

In the observation group, there were 74 men and 22 women among the 96 patients with hepatitis B cirrhosis. In the control group, there were 119 men and 10 women among 129 patients with hepatitis B cirrhosis, and there were significant differences in sex between the two groups ($P < 0.05$). In the observation group, the median TB level was 39.10 mmol/L, and the median platelet count was 99.50 × 10^9/L. In the control group, the median TB level was 37.0 mmol/L, and the median platelet count was 107 × 10^9/L. There were significant differences in the TB and platelet levels between the two groups ($P < 0.05$). There were no significant differences in the other indicators (Table 1).

HBV-DNA, HBeAg, HBsAg and ALT testing at the end of follow-up

At the end of follow-up of the 362 CHB patients, HBV DNA was undetectable in 61 patients (16.6%) and decreased by no less than 2 Log in 216 patients (59.7%). Sixty-five patients (32.8%) were negative for HBeAg, three (0.8%) were negative for HBsAg, and 275 (76.0%) had normal ALT levels. However, among the 203 patients in the control group, 179 were HBV-DNA negative (87.2%), 194 (95.6%) had decreased HBV-DNA levels by no less than 2 Log, 64 (52.0%) were negative for HBeAg, two (0.6%) were negative for HBsAg, and 191 (94.1%) had normal ALT levels (Table 2).

At the end of the follow-up of the 96 patients with hepatitis B cirrhosis, 19 (19.8%) were negative for HBV DNA. Fifty-seven patients (59.37%) showed decreases in HBV-DNA of no less than 2 Log, 12 (40.0%) had HBeAg negative conversion, one had HBsAg negative conversion (1.0%), and 68 patients (70.8%) had normal ALT levels. In the control group of 129 patients, 116 (89.9%) were HBV-DNA negative, 124 (96.1%) had decreases in HBV DNA of no less than 2 Log, 19 (59.4%) had HBeAg negative conversion, one (1.6%) had HBsAg negative conversion, and 110 patients (85.3%) had normal ALT levels (Table 2).

Comparison of cumulative incidence of HCC in CHB patients

Among 362 patients with CHB, the cumulative incidence rates of HCC ($n = 29$) in years 2, 4, 6, 8, 10, 12, 14, 16 and 18 were 0, 0.008, 0.027, 0.045, 0.067, 0.096, 0.111, 0.135 and 0.149, respectively. The cumulative incidence rates of HCC ($n = 9$) among the 203 patients in the control group in years 2, 4, 6, 8, 10, 12, 14 and 16 were 0, 0.005, 0.022, 0.029, 0.066, 0.107, 0.107 and 0.107, respectively. After the Kaplan-Meier log-rank analysis, there was no significant difference in the cumulative incidence of HCC between the two groups ($P = 0.842$) (Figure 2A).

Comparison of cumulative incidence of HCC in patients with hepatitis B cirrhosis

Among the 96 patients with hepatitis B cirrhosis, the cumulative incidence rates of HCC ($n = 27$) in years 2, 4, 6, 8 and 10 in the observation group were 0, 0.065, 0.189, 0.446 and 0.531, respectively. The cumulative incidence rates of HCC ($n = 31$) in years 2, 4, 6, 8, 10, 12 and 14 among the 129 patients with cirrhosis were 0, 0.071, 0.138, 0.264, 0.319, 0.319 and 0.319, respectively. The incidence of HCC accumulation in the control group was lower than that in the observation group, and the results of the Kaplan–Meier log-rank analysis showed that there was a significant difference ($P = 0.026$) (Figure 2B).

Cumulative incidence of HCC after HBeAg negative conversion in HBeAg-positive CHB patients

Among 362 patients with CHB, 198 were HBeAg positive, 65 had HBeAg negative conversion, and one developed HCC after HBeAg negative conversion. The cumulative incidence rates of HCC ($n = 1$) among the 65 patients in years 2, 4 and 6-20 were 0, 0.016 and 0.016-0.016, respectively. Among the 133 patients without HBeAg negative conversion, 12 developed HCC. The cumulative incidence rates of HCC ($n = 12$) in years 2, 4, 6, 8, 10, 12, 14 and 16-20 were 0, 0.050, 0.062, 0.088, 0.104, 0.132, 0.167 and 0.223, respectively. The cumulative incidence rate of HCC in patients with CHB who did not have HBeAg negative conversion was higher than that in patients with HBeAg negative conversion. The cumulative incidence rates of HCC in the two groups were significantly different ($P = 0.022$) (Figure 3A).

Table 1 Data regarding the patients' baseline characteristics

	Chronic hepatitis B patients		Hepatitis B cirrhosis patients	
	Observation group (*n* = 362)	Control group (*n* = 203)	Observation group (*n* = 96)	Control group (*n* = 129)
Sex: Males (%)	291 (80.38)	175 (86.20)[a]	74 (77.08)	119 (92.24)[a]
E antigen-positive patients (%)	198 (54.69)	123 (60.59)[a]	30 (31.25)	32 (24.80)
Age (yr)	33 (25-40)	39 (32-46)[a]	59.50 (48-67)	48 (41-58)
Median follow-up time	10 (7-14)	8 (6-9)[a]	7 (5-8)	7 (6-8)
HBV-DNA (log)	7.14 (5.92-7.70)	6.76 (5.63-7.29)	4.77 (4.37-5.53)	4.92 (4.06-5.57)
ALT	188.62 (141.70-296.55)	185.50 (135.01-260.25)	98.73 (75.91-121.73)	110.00 (78.10-202.00)
AST	132.14 (100.00-173.57)	135.00 (110.00-215.00)	53.15 (40.77-122.58)	76.00 (49.00-105.00)
TB	27.00 (21.30-36.50)	28.50 (21.00-41.25)	39.10 (33.00-45.00)	37.00 (18.00-51.00)[a]
ALB			32.00 (26.00-37.70)	36.00 (33.50-37.00)
PLT			99.50 (58.00-120.00)	107.00 (102.00-119.00)[a]
Diabetes (%)	39 (10.77)	21 (10.34)	21 (21.87)	26 (20.15)
Hypertension (%)	29 (8.01)	18 (8.86)	23 (23.95)	25 (19.37)
Family history of hepatocellular carcinoma (%)	21 (5.80)	10 (4.97)	19 (19.76)	27 (20.93)
REACH-B score	10 (8-12)	10 (8-12)		

[a]$P < 0.05$ compared with the observation group. HBV: Hepatitis B virus; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin; ALB: Albumin; PLT: Platelet.

Table 2 Changes in hepatitis B virus-DNA, hepatitis B e antigen, hepatitis B surface antigen and alanine aminotransferase after anti-inflammatory and hepatoprotective treatment and antiviral therapy in patients with chronic hepatitis B and cirrhosis, *n* (%)

Variable	Chronic hepatitis B		Hepatitis B cirrhosis	
	Observation group (*n* = 362)	Control group (*n* = 203)	Observation group (*n* = 96)	Control group (*n* = 129)
HBV-DNA undetectable	61 (16.85)	179 (87.19)	19 (19.79)	116 (89.92)
HBV-DNA drops no less than 2 log	216 (59.66)	194 (95.56)	57 (59.37)	124 (96.12)
HBeAg negative conversion	65 (32.82)	64 (52.03)	12 (40)	19 (59.37)
HBsAg negative conversion	3 (0.82)	2 (0.55)	1 (1.04)	2 (1.55)
ALT returns to normal	275 (75.96)	191 (94.08)	68 (70.83)	110 (85.27)

Undetectable hepatitis B virus-DNA was defined as hepatitis B virus-DNA < 500 copies/mL; a return of alanine aminotransferase to normal was defined as alanine aminotransferase < 40 mmol/L after treatment. HBV: Hepatitis B virus; ALT: Alanine aminotransferase; HBeAg: Hepatitis B e antigen; HBsAg: Hepatitis B surface antigen.

Cumulative incidence of HCC after spontaneous decreases in HBV DNA to undetectable levels in patients with CHB

Among the 362 patients with CHB, 61 had undetectable HBV DNA, and one developed HCC after undetectable HBV DNA. The cumulative incidence rates of HCC ($n = 1$) in years 2 and 4-20 were 0.016 and 0.016, respectively. A total of 301 patients did not have undetectable HBV DNA, and 28 of them developed HCC. The cumulative incidence rates of liver cancer in years 2, 4, 6, 8, 10, 12, 14 and 16-20 were 0.013, 0.034, 0.047, 0.068, 0.089, 0.135, 0.157 and 0.191, respectively. The incidence of HCC in patients without undetectable HBV DNA was higher than that of HCC in those with HBV-DNA negative conversion. There was no significant difference in the cumulative incidence of liver cancer between the two groups ($P = 0.051$) (Figure 3B).

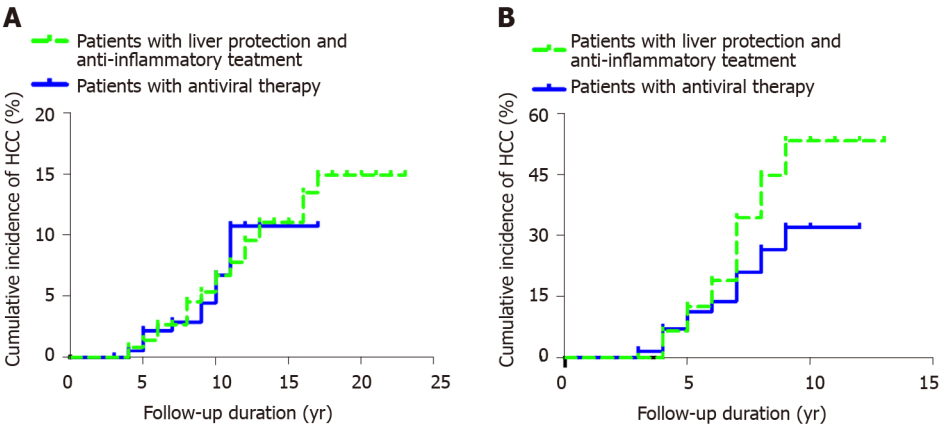

Figure 2 Cumulative incidence of hepatocellular carcinoma. A: Comparison of the incidence of hepatocellular carcinoma over time in two groups of chronic hepatitis B patients (patients with liver protection and anti-inflammatory treatment and patients with antiviral therapy); B: Comparison of the incidence of hepatocellular carcinoma over time in patients with hepatitis B cirrhosis. HCC: Hepatocellular carcinoma.

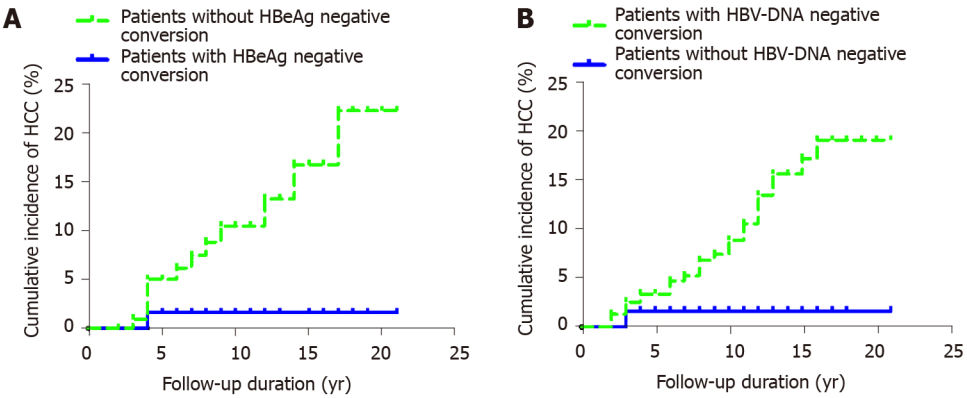

Figure 3 Cumulative incidence of hepatocellular carcinoma. A: Incidence of hepatocellular carcinoma after hepatitis B e antigen negative conversion in hepatitis B e antigen-positive chronic hepatitis B patients; B: Cumulative incidence of hepatocellular carcinoma after hepatitis B virus-DNA negative conversion in patients with chronic hepatitis B. HCC: Hepatocellular carcinoma; HBeAg: Hepatitis B e antigen; HBV: Hepatitis B virus.

Cumulative incidence of HCC among patients with antiviral resistance in CHB

Among the 203 patients with CHB who received direct antiviral therapy, 79 developed antiviral resistance; of whom, 47 received LAM, 22 ADV, and 10 LDT. Seven of 79 patients developed HCC. The cumulative incidence rates of HCC among the 79 patients with drug resistance at years 2, 4, 6, 8, 10 and 12 were 0.000, 0.000, 0.027, 0.043, 0.130 and 0.185, respectively. The cumulative incidence rates of HCC (n = 2) among the 124 nonresistant patients at years 2, 4 and 6-12 were 0.000, 0.008 and 0.018, respectively. There was no significant difference in the cumulative incidence of HCC between the two groups according to the Kaplan-Meier log-rank test (P = 0.119) (Figure 4A).

Cumulative incidence of HCC in patients with antiviral resistance in hepatitis B cirrhosis

Of the 129 patients with direct antiviral cirrhosis, 30 developed antiviral resistance (HCC = 14); 17 of whom received LAM, eight ADV, and five LDT. The cumulative incidence rates of HCC among the 30 patients with drug resistance at years 2, 4, 6 and 8 were 0, 0.033, 0.240 and 0.506, respectively. The cumulative incidence rates of HCC (n = 16) among the 99 patients who did not develop antiviral resistance at years 2, 4, 6, 8 and 10 were 0, 0.083, 0.105, 0.167 and 0.255, respectively. The cumulative incidence of HCC among patients with antiviral-resistant hepatitis B cirrhosis was higher than that among nonresistant patients. The difference was significantly different according to the Kaplan-Meier log-rank test (P = 0.004) (Figure 4B).

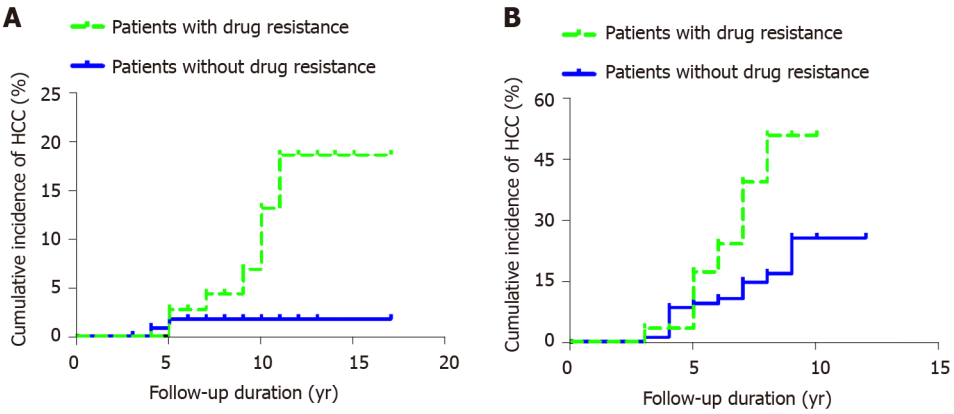

Figure 4 Cumulative incidence of hepatocellular carcinoma. A: Cumulative incidence of hepatocellular carcinoma in patients with antiviral resistance in chronic hepatitis B; B: Cumulative incidence of hepatocellular carcinoma in patients with antiviral resistance in hepatitis B cirrhosis. HCC: Hepatocellular carcinoma.

Cox regression analysis of risk factors for HCC in patients with CHB who were calibrated with REACH-B

We used the Cox regression model of the corrected REACH-B score to determine whether HCC occurred as the endpoint of observation, after adjusting for sex, age, HBeAg, ALT, AST, DNA, and other related parameters. The results showed that men aged > 40 years, ALT > 400 U/L, history of diabetes, and family history of HCC were risk factors for HCC ($P < 0.05$). Multivariate analysis showed that male sex and HCC family history were risk factors for HCC (Table 3).

DISCUSSION

In China, HCC is mainly HBV-associated, and this form of HCC has a worse prognosis than hepatitis-C-virus-associated HCC. Therefore, the effect of antiviral therapy should be discussed based on the incidence of HBV-related HCC rather than on the disappearance of HBV viral markers or serological conversion as the main target of treatment.

The antiviral mechanism of nucleoside analogs (NAs) is propagated mainly through their inhibition of the polymerase of HBV replication, thereby controlling the HBV load in the serum and the circulating pool, thus reducing the pathogenic factors of HBV-related HCC[26]. However, NAs cannot completely eradicate covalently closed circular DNAs, and they cannot block the occurrence of HBV-related HCC. This is mainly related to the carcinogenic mechanism of HBV. It is generally believed that there are three factors contributing to HBV carcinogenesis: the integration of HBV and host genes; accumulation of HBX protein in cells; and the persistence of inflammation. HBV destroys the genes of host cells, and the *trans*-binding carcinogenesis of HBX proteins leads to a series of carcinogenic factors that cannot be countered by NA drugs. It is important to note that persistent liver inflammation is also an important factor in the development of HCC. The causes of HBV inflammation include: (1) Induction of the host immune response by HBV infection; and (2) Uncontrollable inflammatory factors. Specifically, under uncertain conditions, inflammation cannot change from an anti-infection/tissue damage mode to a balanced and stable state[26], leading to continuous progression of inflammation. Proinflammatory cytokines and reactive oxygen species produced in the process of inflammation lead to gene mutations or phenotypic modifications that promote canceration[27].

Antiviral therapy reduces HCC mainly by decreasing the HBV-DNA load, thereby reducing immune-related injury to the body[28-30] and the levels of carcinogenic factors associated with inflammation. NA antiviral therapy can effectively decrease the HBV-DNA load, but it cannot achieve effective immune control. Immunoregulation is generally divided into positive and negative regulation. NA antiviral therapy mainly acts as a negative regulatory factor, but it does not affect positive regulatory factors; thus, it is difficult to achieve true immune functional recovery[31]. Therefore, 50%-70% of patients relapse after stopping drug treatment[32], which confirms the lack of immune recovery.

Current, relevant, long-term follow-up studies that have been published adopted a

Table 3 Cox regression analysis of risk factors for hepatocellular carcinoma in patients with chronic hepatitis B who were calibrated with REACH-B

Variable	Rate ratio (95%CI)	
	Single factor	Multiple factors
Sex		
Female	1.0 (referent)	1.0 (referent)
Male	2.859 (1.835-6.112)[a]	3.076 (1.975-8.437)[a]
Age (yr)		
≤ 40	1.0 (referent)	
> 40	2.677 (1.089-6.579)[a]	
HBeAg		
-	1.0 (referent)	
+	0.614 (0.288-1.310)	
DNA level, IU/L (log)		
≤ 3 (1×10^3 IU/L)	1.0 (referent)	
3-6.30 (2×10^6 IU/L)	1.130 (0.543-1.602)	
> 6.30	2.604 (0.749-3.854)	
ALT level, U/L		
≤ 50	1.0 (referent)	
50-200	1.140 (0.728-6.676)	
200-400	3.310 (0.173-11.112)	
> 400	4.036 (1.678-7.234)[a]	
AST level, U/L		
≤ 40	1.0 (referent)	
40-200	0.592 (0.184-1.904)	
200-400	1.565 (0.124-2.581)	
> 400	8.059 (0.689-11.968)	
TB level, U/L		
≤ 23	1.0 (referent)	
23-46	0.525 (0.211-1.308)	
46-115	1.349 (0.078-1.572)	
> 115	1.605 (0.125-2.936)	
Treatment		
Anti-inflammatory	1.0 (referent)	
Antiviral	0.701 (0.207-1.313)	
Antiviral after anti-inflammatory treatment	0.874 (0.283-1.467)	
Diabetes		
No	1.0 (referent)	
Yes	2.469 (1.079-5.649)[a]	
Hypertension		
No	1.0 (referent)	
Yes	1.932 (0.650-5.748)	
Family history of liver cancer		

No	1.0 (referent)	1.0 (referent)
Yes	30.924 (12.709-75.561)[a]	23.463 (9.372-47.564)[a]

[a]$P < 0.05$ *vs* the observation group. HBeAg: Hepatitis B e antigen; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; TB: Total bilirubin.

retrospective or database observation comparative design, but these studies all had many shortcomings regarding intergroup confounding factors[33]. The present study is a real-world clinical study, lasting 2-23 years, of CHB patients in China. The aim of the study was to evaluate the real clinical outcomes, particularly the occurrence of HCC, in patients who did not receive antiviral therapy but received only anti-inflammatory and hepatoprotective therapy. Notably, a large number of data reported that it generally took 6-12 mo for HCC to be detected by B-ultrasound screening. In order to ensure the reliability and the objectivity of the results, we excluded patients with HCC occurring within 1 year of follow-up. We restricted the follow-up period to at least 2 years, and patients who developed detectable liver cancer within 1 year after enrollment were excluded. Considering that the time to find HCC takes 1-2 years, the follow-up period was determined to be ≥ 2 years. Our results showed that no patient in the CHB group and six patients in the cirrhosis group developed HCC within 1 year and we subsequently excluded these patients in the following observation.

Our results showed that among 362 patients with CHB who were not treated with antiviral therapy but treated only with anti-inflammatory and hepatoprotective therapy, after an average follow-up of 10 years, 16.9% had undetectable HBV DNA, 32.8% had HBeAg seroconversion, and 76.0% had ALT levels that returned to normal. Our results are similar to those of a previous study in Taiwan[34]. In addition, in the antiviral treatment group, 87.2% of patients were HBV-DNA negative, 52.0% had HBeAg seroconversion, and 94.1% had ALT levels that returned to normal. After antiviral treatment, the virological response of patients was significantly higher than that of patients without antiviral treatment; however, neither group showed significant differences.

At present, in China, anti-inflammatory and hepatoprotective drugs, such as glycyrrhizin, glutathione, polyethylene phosphatidylcholine, silymarin, and dicyclol, are classified into multiple categories, including anti-inflammatory, antioxidative and antifibrotic drugs[35,36]. When patients first present with elevated ALT, over the following 5-10 years, approximately 17% of patients may have spontaneous decreases in HBV DNA to undetectable levels, and approximately 33% may have spontaneous HBeAg seroconversion. The results of our study showed that the cumulative incidence of HCC was significantly different between patients with and those without HBeAg seroconversion. As long as the liver inflammatory response is effectively controlled in such patients, once spontaneous HBeAg serological transformation occurs, immune control can be achieved, thereby leading to entry into the inactive HBsAg carrier period, stabilization of the disease for a long time, and a significant reduction of HCC[37]. Although antiviral therapy can significantly inhibit the replication of HBV DNA, 50%-70% of patients relapse after drug withdrawal; even when the serological conversion of HBeAg occurs, it is temporary and unstable, and the cumulative recurrence rate is 44% after a 4-year follow-up period following drug withdrawal[38]. Thus, although these relapsed patients achieve HBV-DNA negative conversion, they do not achieve true immune control, and only 30%-50% of patients have true immune control. There were no significant differences between patients with antiviral therapy who achieved true immune control and spontaneous seroconversion. Therefore, we suggest that antiviral therapy masks the spontaneous relief process of CHB. Several studies have confirmed that the incidence of HCC after interferon therapy is significantly lower than that in patients who benefit from NA antiviral therapy[39-42], which also demonstrates why patients with CHB without cirrhosis who benefit from NA antiviral therapy do not have the advantage of better prevention of HCC. The key is that anti-inflammatory and hepatoprotective treatment can effectively improve the inflammatory response of the liver, slow down the progression of liver fibrosis during spontaneous seroconversion, and thus effectively reduce the incidence of HCC[43].

For patients with CHB complicated by cirrhosis, our results show that effective antiviral therapy can significantly reduce the cumulative incidence of HCC in patients with HBV-related cirrhosis. For hepatitis B cirrhosis patients who are positive for HBV DNA, taking antiviral therapy in a timely manner is important for controlling the persistent inflammatory response in the liver and eliminating the virus[44]. However, the cumulative incidence of HCC in patients with cirrhosis is still increasing with the

prolongation of follow-up, and there is no plateau phase. This shows that antiviral therapy can only delay but not eliminate the occurrence of HCC. Notably, even if patients with cirrhosis are treated with antiviral drugs in a timely manner, the cumulative incidence of HCC is still higher than that of patients with CHB without liver cirrhosis. This indicates that cirrhosis remains the most important factor in the development of HCC[45].

Drug resistance is common in CHB patients receiving antiviral therapy, especially in those treated with LAM and ADV in the early stage. However, will the incidence of HCC be further increased in patients with antiviral resistance? At present, there are still few reports suggesting that drug resistance may offset the benefit of antiviral therapy in patients with cirrhosis[46]. The results of our study showed that there was no significant difference in the cumulative incidence of drug-resistant and nonresistant HCC after antiviral therapy in patients with CHB without cirrhosis. This finding may be related to effective control of the HBV-DNA load in these patients with a low risk of HCC through timely rescue treatment, even when drug resistance occurred. However, in patients with cirrhosis, the incidence of HCC in drug-resistant patients was significantly higher than that in nonresistant patients, and the difference was significantly different. For patients with cirrhosis, the reserve function of the liver decreases, and the effective liver tissue decreases; drug resistance can lead to virological breakthroughs or rebounds, accelerate the progression of the disease, and further aggravate liver injury, thus increasing the risk of cirrhosis and HCC[47]. HBV mutation tends to increase gradually with infection time and disease progression[48], and the selection of antiviral drugs with high resistance barriers is an important factor in preventing viral mutation and reducing the occurrence of HCC in patients with liver cirrhosis.

Taiwanese scholars used data from the Reveal-HBV cohort to quantify HCC risk factors, and they established and preliminarily verified the first HBV-related HCC prediction model, REACH-B. The HCC scoring system includes host factors such as sex, age, family history of HCC, serum ALT levels, and virological indicators such as HBeAg levels, HBV-DNA levels, HBsAg quantification, and HBV genotypes[49]. The optimal cutoff point is 8 points, which is more suitable for the Asian population. Many guidelines recommend this model. The higher the score of this model, the higher the incidence of HCC. In this study, the REACH-B score did not indicate that non-antiviral therapy was an independent factor in the occurrence of HCC, while the occurrence of HCC was closely related to age, sex and family history of HCC.

This study was a single-center, pre-retrospective study, and further prospective cohort studies will be conducted when patients are identified as research subjects. Because antiviral therapy patients were enrolled after 2001 and the enrollment time of each group was different, the results of the study were biased to some extent. In this study, LAM, ADV and other high-resistance and low-potency drugs were used in the early stage of antiviral therapy, which affected the effectiveness of antiviral therapy. The evaluation criteria of the patients with liver cirrhosis were mainly based on B-mode ultrasound, while only 10% of patients were assessed by histopathology, which may have led to an underestimation in diagnosing the degree of liver fibrosis and early cirrhosis.

This study shows that in addition to viruses being the main carcinogenic factor in patients with CHB, inflammation or uncontrollable inflammation of the liver are important carcinogenic factors. Whether it is antiviral therapy or anti-inflammatory and hepatoprotective therapy alone, controlling liver inflammation is one of the mechanisms for improving liver histology. Therefore, once ALT elevation occurs in patients with CHB without cirrhosis, as long as liver inflammation is effectively controlled and immune control is achieved, the incidence of long-term HCC can be reduced to a certain extent. Our results showed that patients with liver cirrhosis had a higher cumulative incidence of HCC, so it was important to prevent patients developing cirrhosis. Patients with cirrhosis must receive antiviral therapy. Antiviral therapy can be implemented at the stage of progressive liver fibrosis to prevent the rapid occurrence of cirrhosis, which will be beneficial to the long-term prevention of HCC. Early NA antiviral therapy for low-HCC-risk patients with CHB without cirrhosis may mask the spontaneous serological response of some patients; therefore, the role of early antiviral therapy in reducing the occurrence of HCC cannot be overestimated.

CONCLUSION

In conclusion, antiviral therapy and non-antiviral therapy with liver protection and anti-inflammatory therapy can reduce the risk of HCC. Antiviral therapy may mask the spontaneous serological response of some patients during CHB. Therefore, the effect of early antiviral therapy on reducing the incidence of HCC cannot be overestimated.

ARTICLE HIGHLIGHTS

Research background

China is one of the leading countries for hepatitis B virus (HBV) prevalence, but most chronic hepatitis B (CHB) patients do not receive standardized antiviral therapy. There are few relevant reports addressing the outcomes of the large number of CHB patients who do not receive antiviral therapy.

Research motivation

The purpose of this study was to provide clinical evidence on the outcomes of CHB patients without antiviral treatment and evaluate the efficacy of antiviral therapy in the development and progression of CHB.

Research objectives

To observe the outcomes of long-term follow-up of patients with CHB without antiviral treatment.

Research methods

This study included 362 patients with CHB and 96 with hepatitis B cirrhosis, without antiviral treatment and with only hepatoprotective and anti-inflammatory treatment in 1993-1998. The median follow-up period was 10 and 7 years, respectively. A total of 203 CHB and 129 hepatitis B cirrhosis patients receiving antiviral therapy were selected as the control groups. The median follow-up period was 8 and 7 years, respectively. Kaplan–Meier curves were used to analyze the cumulative incidence of hepatocellular carcinoma (HCC), and the Cox regression model was used to analyze the risk factors of HCC.

Research results

Among the patients in the non-antiviral group, 16.9% showed spontaneous decreases in HBV DNA to undetectable levels, and 32.8% showed hepatitis B e antigen (HBeAg) seroconversion. In the antiviral group, 87.2% of patients had undetectable HBV DNA, and 52% showed HBeAg seroconversion. Among CHB and hepatitis B cirrhosis patients, the cumulative incidence rates of HCC were 14.9% and 53.1%, respectively, in the non-antiviral group, and were 10.7% and 31.9%, respectively, in the antiviral group. There was no difference between the two groups CHB, but there was a difference between the groups with hepatitis B cirrhosis. The cumulative incidence rates of HCC were 1.6% and 22.3% in the groups with and without spontaneous HBeAg seroconversion, respectively. The incidence rates of HCC among patients with and without spontaneous declines in HBV DNA to undetectable levels were 1.6% and 19.1%, respectively. There was no difference in the cumulative incidence of HCC between the two groups with drug-resistant CHB, but there was a significant difference between the two groups with cirrhosis. The Cox regression model was used for regression of the corrected REACH-B score, and alanine aminotransferase > 400 U/L, history of diabetes, and family history of liver cancer were risk factors for HCC in men aged > 40 years. Multifactor analysis showed that a family history of HCC among men was a risk factor for HCC.

Research conclusions

Antiviral therapy and non-antiviral therapy with hepatoprotective and anti-inflammatory therapy both reduced the risk of HCC. Antiviral therapy may mask the spontaneous serological response of some patients during CHB.

Research perspectives

Our study initially verified the outcomes of patients with CHB without antiviral

treatment. The effect of early antiviral therapy on reducing the incidence of HCC cannot be overestimated. More evidence-based studies are needed to validate the relationship between HCC incidence and antiviral therapy.

REFERENCES

1 **Wang FS**, Fan JG, Zhang Z, Gao B, Wang HY. The global burden of liver disease: the major impact of China. *Hepatology* 2014; **60**: 2099-2108 [PMID: 25164003 DOI: 10.1002/hep.27406]

2 **Ferlay J**, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, Parkin DM, Forman D, Bray F. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer* 2015; **136**: E359-E386 [PMID: 25220842 DOI: 10.1002/ijc.29210]

3 **Chen YC**, Chu CM, Yeh CT, Liaw YF. Natural course following the onset of cirrhosis in patients with chronic hepatitis B: a long-term follow-up study. *Hepatol Int* 2007; **1**: 267-273 [PMID: 19669348 DOI: 10.1007/s12072-007-5001-0]

4 **Koike K**. Hepatitis B virus X gene is implicated in liver carcinogenesis. *Cancer Lett* 2009; **286**: 60-68 [PMID: 19464104 DOI: 10.1016/j.canlet.2009.04.010]

5 **Zoutendijk R**, Zaaijer HL, de Vries-Sluijs TE, Reijnders JG, Mulder JW, Kroon FP, Richter C, van der Eijk AA, Sonneveld MJ, Hansen BE, de Man RA, van der Ende ME, Janssen HL. Hepatitis B surface antigen declines and clearance during long-term tenofovir therapy in patients coinfected with HBV and HIV. *J Infect Dis* 2012; **206**: 974-980 [PMID: 22782950 DOI: 10.1093/infdis/jis439]

6 **Papatheodoridis GV**, Lampertico P, Manolakopoulos S, Lok A. Incidence of hepatocellular carcinoma in chronic hepatitis B patients receiving nucleos(t)ide therapy: a systematic review. *J Hepatol* 2010; **53**: 348-356 [PMID: 20483498 DOI: 10.1016/j.jhep.2010.02.035]

7 **Singal AK**, Salameh H, Kuo YF, Fontana RJ. Meta-analysis: the impact of oral anti-viral agents on the incidence of hepatocellular carcinoma in chronic hepatitis B. *Aliment Pharmacol Ther* 2013; **38**: 98-106 [PMID: 23713520 DOI: 10.1111/apt.12344]

8 **Wong GL**, Tse YK, Wong VW, Yip TC, Tsoi KK, Chan HL. Long-term safety of oral nucleos(t)ide analogs for patients with chronic hepatitis B: A cohort study of 53,500 subjects. *Hepatology* 2015; **62**: 684-693 [PMID: 25973979 DOI: 10.1002/hep.27894]

9 **Kumada T**, Toyoda H, Tada T, Kiriyama S, Tanikawa M, Hisanaga Y, Kanamori A, Niinomi T, Yasuda S, Andou Y, Yamamoto K, Tanaka J. Effect of nucleos(t)ide analogue therapy on hepatocarcinogenesis in chronic hepatitis B patients: a propensity score analysis. *J Hepatol* 2013; **58**: 427-433 [PMID: 23123221 DOI: 10.1016/j.jhep.2012.10.025]

10 **Hosaka T**, Suzuki F, Kobayashi M, Seko Y, Kawamura Y, Sezaki H, Akuta N, Suzuki Y, Saitoh S, Arase Y, Ikeda K, Kumada H. Long-term entecavir treatment reduces hepatocellular carcinoma incidence in patients with hepatitis B virus infection. *Hepatology* 2013; **58**: 98-107 [PMID: 23213040 DOI: 10.1002/hep.26180]

11 **Lok AS**, McMahon BJ, Brown RS Jr, Wong JB, Ahmed AT, Farah W, Almasri J, Alahdab F, Benkhadra K, Mouchli MA, Singh S, Mohamed EA, Abu Dabrh AM, Prokop LJ, Wang Z, Murad MH, Mohammed K. Antiviral therapy for chronic hepatitis B viral infection in adults: A systematic review and meta-analysis. *Hepatology* 2016; **63**: 284-306 [PMID: 26566246 DOI: 10.1002/hep.28280]

12 **Papatheodoridis GV**, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. *J Hepatol* 2015; **62**: 956-967 [PMID: 25595883 DOI: 10.1016/j.jhep.2015.01.002]

13 **Chen HH**, Lin MC, Muo CH, Yeh SY, Sung FC, Kao CH. Combination Therapy of Metformin and Statin May Decrease Hepatocellular Carcinoma Among Diabetic Patients in Asia. *Medicine (Baltimore)* 2015; **94**: e1013 [PMID: 26091447 DOI: 10.1097/MD.0000000000001013]

14 **Papatheodoridis GV**, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, Vasiliadis T, Mimidis K, Gogos C, Ketikoglou I, Manesis EK; HEPNET. Greece Cohort Study Group. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece cohort study. *Gut* 2011; **60**: 1109-1116 [PMID: 21270118 DOI: 10.1136/gut.2010.221846]

15 **Hsu YC**, Ho HJ, Lee TY, Huang YT, Wu MS, Lin JT, Wu CY, El-Serag HB. Temporal trend and risk determinants of hepatocellular carcinoma in chronic hepatitis B patients on entecavir or tenofovir. *J Viral Hepat* 2018; **25**: 543-551 [PMID: 29193536 DOI: 10.1111/jvh.12832]

16 **Chen CJ**, Yang HI. Natural history of chronic hepatitis B REVEALed. *J Gastroenterol Hepatol* 2011; **26**: 628-638 [PMID: 21323729 DOI: 10.1111/j.1440-1746.2011.06695.x]

17 **Lin CL**, Wang Y, Li T, Qu YD, Wang L, Yang BH. Analysis of risk factors for progression of hepatocellular carcinoma in patients with compensatory hepatitis B cirrhosis treated with antiviral therapy. *Shandong Yiyao Zazhi* 2017; **57**: 81-83 [DOI: 10.3969/j.issn.1002-266X.2017.32.026]

18 **Park BK**, Park YN, Ahn SH, Lee KS, Chon CY, Moon YM, Park C, Han KH. Long-term outcome of chronic hepatitis B based on histological grade and stage. *J Gastroenterol Hepatol* 2007; **22**: 383-388 [PMID: 17295771 DOI: 10.1111/j.1440-1746.2007.04857.x]

19 **Wu GC**, Zhou WP, Zhao YR, Guo SH, Wang ZY, Zou SB, Zhang QH, Ren H, Huang AL, Zhang DF. The natural history of chronic hepatitis B: a retrospective study. *Hepatobiliary Pancreat Dis Int*

2003; **2**: 566-570 [PMID: 14627521]
20 **Ge SF**, Ding L, Zhong YB, Xiong Y. Anti-inflammatory and hepatoprotective therapy is one of the effective ways to treat chronic hepatitis B. *Gan Boshi Zazhi* 2018; **1**: 36-37
21 **Peng Y**. Application of anti-inflammatory and liver-protecting drugs in the treatment of chronic hepatitis B. *Heilongjiang Yiyao Zazhi* 2017; **30**: 815-817 [DOI: 10.14035/j.cnki.hljyy.2017.04.052]
22 **Huang CC**, Lin KJ, Cheng YW, Hsu CA, Yang SS, Shyur LF. Hepatoprotective effect and mechanistic insights of deoxyelephantopin, a phyto-sesquiterpene lactone, against fulminant hepatitis. *J Nutr Biochem* 2013; **24**: 516-530 [PMID: 22748804 DOI: 10.1016/j.jnutbio.2012.01.013]
23 **Lok AS**, Lai CL, Leung N, Yao GB, Cui ZY, Schiff ER, Dienstag JL, Heathcote EJ, Little NR, Griffiths DA, Gardner SD, Castiglia M. Long-term safety of lamivudine treatment in patients with chronic hepatitis B. *Gastroenterology* 2003; **125**: 1714-1722 [PMID: 14724824 DOI: 10.1053/j.gastro.2003.09.033]
24 **Polaris Observatory Collaborators**. Global prevalence, treatment, and prevention of hepatitis B virus infection in 2016: a modelling study. *Lancet Gastroenterol Hepatol* 2018; **3**: 383-403 [PMID: 29599078 DOI: 10.1016/S2468-1253(18)30056-6]
25 **Wang BE**. Modern Hepatology. Beijing: Science Press; 2003: 544-545
26 **Wang H**. Cancer Letters special issue hepatobiliary cancer featuring the guest editor. *Cancer Lett* 2016; **379**: 163 [PMID: 26828012 DOI: 10.1016/j.canlet.2016.01.029]
27 **Naik E**, Dixit VM. Mitochondrial reactive oxygen species drive proinflammatory cytokine production. *J Exp Med* 2011; **208**: 417-420 [PMID: 21357740 DOI: 10.1084/jem.20110367]
28 **Ramakrishna G**, Rastogi A, Trehanpati N, Sen B, Khosla R, Sarin SK. From cirrhosis to hepatocellular carcinoma: new molecular insights on inflammation and cellular senescence. *Liver Cancer* 2013; **2**: 367-383 [PMID: 24400224 DOI: 10.1159/000343852]
29 **Chiba T**, Suzuki E, Saito T, Ogasawara S, Ooka Y, Tawada A, Iwama A, Yokosuka O. Biological features and biomarkers in hepatocellular carcinoma. *World J Hepatol* 2015; **7**: 2020-2028 [PMID: 26261691 DOI: 10.4254/wjh.v7.i16.2020]
30 **Lee JS**. The mutational landscape of hepatocellular carcinoma. *Clin Mol Hepatol* 2015; **21**: 220-229 [PMID: 26523267 DOI: 10.3350/cmh.2015.21.3.220]
31 **Chen J**, Wang Y, Wu XJ, Li J, Hou FQ, Wang GQ. Pegylated interferon α-2b up-regulates specific CD8+ T cells in patients with chronic hepatitis B. *World J Gastroenterol* 2010; **16**: 6145-6150 [PMID: 21182232 DOI: 10.3748/wjg.v16.i48.6145]
32 **Liaw YF**, Gane E, Leung N, Zeuzem S, Wang Y, Lai CL, Heathcote EJ, Manns M, Bzowej N, Niu J, Han SH, Hwang SG, Cakaloglu Y, Tong MJ, Papatheodoridis G, Chen Y, Brown NA, Albanis E, Galil K, Naoumov NV; GLOBE Study Group. 2-Year GLOBE trial results: telbivudine Is superior to lamivudine in patients with chronic hepatitis B. *Gastroenterology* 2009; **136**: 486-495 [PMID: 19027013 DOI: 10.1053/j.gastro.2008.10.026]
33 **Lin D**, Yang HI, Nguyen N, Hoang J, Kim Y, Vu V, Le A, Chaung K, Nguyen V, Trinh H, Li J, Zhang J, Hsing A, Chen CJ, Nguyen MH. Reduction of chronic hepatitis B-related hepatocellular carcinoma with anti-viral therapy, including low risk patients. *Aliment Pharmacol Ther* 2016; **44**: 846-855 [PMID: 27549411 DOI: 10.1111/apt.13774]
34 **Yang HI**, Hung HL, Lee MH, Liu J, Jen CL, Su J, Wang LY, Lu SN, You SL, Iloeje UH, Chen CJ; Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer–HBV (REVEAL-HBV) Study Group. Incidence and determinants of spontaneous seroclearance of hepatitis B e antigen and DNA in patients with chronic hepatitis B. *Clin Gastroenterol Hepatol* 2012; **10**: 527-34. e1-2 [PMID: 22178461 DOI: 10.1016/j.cgh.2011.12.019]
35 **Wang H**, Li Y. Protective effect of bicyclol on acute hepatic failure induced by lipopolysaccharide and D-galactosamine in mice. *Eur J Pharmacol* 2006; **534**: 194-201 [PMID: 16487963 DOI: 10.1016/j.ejphar.2005.12.080]
36 **Zhao J**, Chen H, Li Y. Protective effect of bicyclol on acute alcohol-induced liver injury in mice. *Eur J Pharmacol* 2008; **586**: 322-331 [PMID: 18371952 DOI: 10.1016/j.ejphar.2008.02.059]
37 **Hsu YS**, Chien RN, Yeh CT, Sheen IS, Chiou HY, Chu CM, Liaw YF. Long-term outcome after spontaneous HBeAg seroconversion in patients with chronic hepatitis B. *Hepatology* 2002; **35**: 1522-1527 [PMID: 12029639 DOI: 10.1053/jhep.2002.33638]
38 **Reijnders JG**, Perquin MJ, Zhang N, Hansen BE, Janssen HL. Nucleos(t)ide analogues only induce temporary hepatitis B e antigen seroconversion in most patients with chronic hepatitis B. *Gastroenterology* 2010; **139**: 491-498 [PMID: 20381492 DOI: 10.1053/j.gastro.2010.03.059]
39 **Liang KH**, Hsu CW, Chang ML, Chen YC, Lai MW, Yeh CT. Peginterferon Is Superior to Nucleos(t)ide Analogues for Prevention of Hepatocellular Carcinoma in Chronic Hepatitis B. *J Infect Dis* 2016; **213**: 966-974 [PMID: 26582959 DOI: 10.1093/infdis/jiv547]
40 **Cho JY**, Paik YH, Sohn W, Cho HC, Gwak GY, Choi MS, Lee JH, Koh KC, Paik SW, Yoo BC. Patients with chronic hepatitis B treated with oral antiviral therapy retain a higher risk for HCC compared with patients with inactive stage disease. *Gut* 2014; **63**: 1943-1950 [PMID: 24615378 DOI: 10.1136/gutjnl-2013-306409]
41 **Singh R**, Mishra MK, Aggarwal H. Inflammation, Immunity, and Cancer. *Mediators Inflamm* 2017; **2017**: 6027305 [PMID: 29234189 DOI: 10.1155/2017/6027305]
42 **Yu Y**, Gong R, Mu Y, Chen Y, Zhu C, Sun Z, Chen M, Liu Y, Zhu Y, Wu J. Hepatitis B virus induces a novel inflammation network involving three inflammatory factors, IL-29, IL-8, and cyclooxygenase-2. *J Immunol* 2011; **187**: 4844-4860 [PMID: 21957142 DOI: 10.4049/jimmunol.1100998]

43 **Tong DG**, Chen SN, Wei CS, Xing YF, Tang HH, He JS, Zheng YJ, Zhou XZ, Wu QK, Zhou DQ. Long-term follow-up results of anti-inflammatory and hepatoprotective drugs in patients with chronic hepatitis B. *Zhonghua Ganzang Bing Zazhi* 2011; **19**: 701-703 [DOI: 10.3760/cma.j.issn.1007-3418.2011.09.017]

44 **Fu M**, Xue B. Prognosis of antiviral therapy in patients with hepatitis B cirrhosis. *Zhongguo Yiyao Zhinan* 2016: 81

45 **Meng QH**, Hou W. 2015 edition of "Guidelines for the Prevention and Treatment of Chronic Hepatitis B"--Interpretation of the Guidelines for Antiviral Therapy for Chronic Hepatitis B. *Zhongguo Quanke Yixue Zazhi* 2016; **19**: 1613-1615 [DOI: 10.3969/j.issn.1007-9572.2016.14.001]

46 **Yuen MF**, Seto WK, Chow DH, Tsui K, Wong DK, Ngai VW, Wong BC, Fung J, Yuen JC, Lai CL. Long-term lamivudine therapy reduces the risk of long-term complications of chronic hepatitis B infection even in patients without advanced disease. *Antivir Ther* 2007; **12**: 1295-1303 [PMID: 18240869]

47 **Lok AS**, Zoulim F, Locarnini S, Bartholomeusz A, Ghany MG, Pawlotsky JM, Liaw YF, Mizokami M, Kuiken C; Hepatitis B Virus Drug Resistance Working Group. Antiviral drug-resistant HBV: standardization of nomenclature and assays and recommendations for management. *Hepatology* 2007; **46**: 254-265 [PMID: 17596850 DOI: 10.1002/hep.21698]

48 **Lin CL**, Kao JH. Natural history of acute and chronic hepatitis B: The role of HBV genotypes and mutants. *Best Pract Res Clin Gastroenterol* 2017; **31**: 249-255 [PMID: 28774406 DOI: 10.1016/j.bpg.2017.04.010]

49 **Chen TM**, Chang CC, Huang PT, Wen CF, Lin CC. Performance of risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B) score in classifying treatment eligibility under 2012 Asian Pacific Association for the Study of the Liver (APASL) guideline for chronic hepatitis B patients. *Aliment Pharmacol Ther* 2013; **37**: 243-251 [PMID: 23171385 DOI: 10.1111/apt.12144]

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