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REVIEW

Liver transplant in primary sclerosing cholangitis: Current trends and future directions

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Abstract

Primary sclerosing cholangitis (PSC) is a chronic and progressive immune-mediated cholangiopathy causing biliary tree inflammation and scarring, leading to liver cirrhosis and end-stage liver disease. Diagnosis of PSC is challenging due to its nonspecific symptoms and overlap with other liver diseases. Despite the rising incidence of PSC, there is no proven medical therapy that can alter the natural history of the disease. While liver transplantation (LT) is the most effective approach for managing advanced liver disease caused by PSC, post-transplanta-

tion recurrence of PSC remains a challenge. Therefore, ongoing research aims to develop better therapies for PSC, and continued efforts are necessary to improve outcomes for patients with PSC. This article provides an overview of PSC's pathogenesis, clinical presentation, and management options, including LT trends and future aspects. It also highlights the need for improved therapeutic options and ethical considerations in providing equitable access to LT for patients with PSC. Additionally, the impact of liver transplant on the quality of life and psychological outcomes of patients with PSC is discussed. Ongoing research into PSC's pathogenesis and post-transplant recurrence is crucial for improved understanding of the disease and more effective treatment options.

Key Words: Primary sclerosing cholangitis; Liver transplantation; Management; Psychosocial outcomes; Pathogenesis

Core Tip: Despite recent advancements in the field of hepatology, therapeutic options for the medical management of primary sclerosing cholangitis (PSC) are limited. Liver transplantation (LT) remains the primary treatment for patients with end stage liver disease (ESLD) secondary to PSC. Both deceased donor liver transplant and living donor liver transplant have demonstrated successful outcomes in patients with ESLD. Psychosocial patient factors also play a significant role in the outcome LT. Addressing ethical issues is crucial to ensure healthcare equity. Recent developments in digital technology and stem cell therapy suggest a promising future for LT in PSC.

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INTRODUCTION

Primary sclerosing cholangitis (PSC) is a chronic immune-mediated cholangiopathy characterized by inflammation and scarring of the biliary tree, affecting both intrahepatic and extrahepatic bile ducts. Its etiology remains idiopathic and it presents a wide spectrum of symptoms and complications. PSC is a rare condition with a global incidence rate ranging from 0 to 1.58 cases per 100000 per year, and a prevalence bracket of 0 to 31.7 cases per 100000 persons[1]. Recent research northern Europe has shown an increasing frequency of both new cases and overall instances of PSC[1]. As compared to the adult population, the incidence and prevalence of PSC is lower in the pediatric population at 0.2 and 1.5 per 100000 children[2].

Currently, there is no proven no medical therapy to treat effectively or alter the natural history of PSC[3]. As a result, the prognosis of this condition is poor, and it is strongly associated with an elevated risk of developing liver cirrhosis and end-stage liver disease, often necessitating liver transplantation (LT)[4]. The development and progression of PSC involve a combination of genetic susceptibility and environmental factors, although the contribution of genetic factors remains limited[5]. On the other hand, environmental factors, particularly the gut microbiota, have gained increasing attention in PSC development[6]. Additionally, approximately 70% of PSC patients have concomitant inflammatory bowel disease (IBD), which serves as a strong risk factor for colon, bile duct, and gallbladder cancers[7]. The co-occurrence of IBD and PSC is evident, with 2%-7.5% of IBD patients developing PSC[4].

Advancements in noninvasive imaging techniques, such as magnetic resonance cholangiopancreatography (MRCP), have improved the understanding and diagnosis of PSC, including its relationship to LT. PSC accounts for approximately 10% of all liver transplants performed annually[4-8]. However, post-transplant recurrence of PSC has been reported, highlighting the need for a better understanding of its underlying pathogenesis and the development of more comprehensive therapeutic strategies[9]. Despite these challenges, long-term outcomes following transplantation are encouraging, with a 5-year survival rate of 89% and favorable graft survival rates[10].

PSC is a poorly understood domain and has been presented with a huge void in terms of concrete solutions that are yet to be fulfilled. In this review, we discuss the current understanding of PSC's pathogenesis, clinical presentation, management options, the scope of LT, and associated challenges.

DISCUSSION

Pathogenesis of PSC

Inflammation and fibrosis of the bile ducts are two primary processes in the pathogenesis of PSC. However, the mechanism of inflammation and fibrosis in PSC are not fully understood. It is believed that various factors such as Ischemic, traumatic, infectious, autoimmune, or toxic injuries cause damage to cells, leading to the release of "danger-

associated molecular patterns (DAMPs)". These DAMPs activate the innate immune system through "pattern recognition receptors"[11]. Chronic inflammatory response mediated by DAMPs and the recruitment and activation of innate or adaptive immune cells play a critical role in initiating and perpetuating the activation of profibrogenic cells into myofibroblasts through the release of cytokines, chemokines, and reactive oxygen species (ROS). ROS and oxidative stress can induce hepatocyte injury, cell death, and parenchymal cell proliferation, along with altered remodeling and increased expression of tissue inhibitors of metalloproteinases[12]. Additionally, certain cytokines produced by damaged cells, such as interleukin (IL)-1a, IL-33, and others, directly or indirectly promote the development of a Th2 immune response, which is believed to promote fibrosis. Th2 immune response is recognized to have profibrotic properties through the release of IL-4, IL-5, IL-10, and IL-13[11,13]. However, the exact mechanisms and interactions between these processes are still being investigated in the context of PSC pathogenesis.

Role of Bile Ducts in PSC

Cholangiocytes can be activated by various insults such as infections, cholestasis, *etc*., leading to increased proliferation along with pro-fibrotic and pro-inflammatory secretions through pleiotropic autocrine and paracrine mechanisms[14]. Persistent biliary cell damage causes an inflammatory reaction that leads to a pathological reparative reaction with excessive deposition of scar tissue around the injured ducts. The biliary epithelium is exposed to cytokines and chemokines secreted by innate and adaptive immune cells in response to DAMPs. If biliary homeostasis is not restored, there will be a maladaptive chronic inflammatory response stimulating the deposition of connective tissue (Figure 1)[14].

Genetic and Environmental factors in pathogenesis of PSC

Genetic factors play a significant role in PSC pathogenesis. Studies have demonstrated an increased risk of PSC among first-degree relatives of patients with the disease[15]. Genome-wide association studies have identified over 20 susceptibility genes for PSC, with the human leukocyte antigen (HLA) complex on chromosome six showing the strongest association[16-20]. Patients with PSC exhibit chromosomal instability and immunosenescence, as evidenced by higher rates of short telomere length and telomere aggregates compared to patients with IBD[21,22]. It is important to note that genetic findings explain less than 10% of the disease liability, while environmental factors account for over 50% of it[22].

The microbiome has also been implicated in PSC pathogenesis, with bacteria potentially triggering an aberrant immune response and perpetuating inflammation[23]. Studies have shown an enrichment of *Barnesiallaceae* and *Blautia* families and *Barnesiellacaeae* genus in PSC patients. Microbiome shifts associated with PSC are observed in *Clostridiales* and *Bacteroidales* orders, with more than 80% of shifts occurring within the former order. However, the causal relationship between these shifts remain unclear due to limited sample size[24]. Some environmental triggers have been investigated, indicating a higher prevalence of PSC in rural areas and a possible connection to agricultural activities, pesticides, or fertilizers[25]. Close contact with dogs or cats has also been identified as a potential trigger, suggesting the pathogenic role of an unidentified agent such as a toxin or microbiome[26]. Additionally, coffee consumption and smoking have been suggested as protective factors against PSC[27].

Clinical Presentation and Diagnosis of PSC

PSC is characterized by bile duct injury and fibrosis, leading to a variety of symptoms and signs. It is commonly associated with IBD[12]. It typically affects individuals between the ages of 30 and 40, with a higher prevalence in men [28]. PSC patients are identified during general health examinations or the investigation for another disease, and about 50% patients are asymptomatic[29]. When symptoms occur, the most common are pruritus, fatigue, and right upper quadrant pain; less frequent symptoms are weight loss and fever[29,30]. Physical exam often reveals jaundice, hepatomegaly, splenomegaly, and excoriation marks[29,31]. PSC is a progressive cholestatic liver disease associated with complications such as bacterial cholangitis, dominant strictures, gallbladder polyps, adenocarcinoma, and cholangiocarcinoma (CCA)[29,30,32]. Disease progression may differ in children due to absence of other risk factors like alcohol abuse or polypharmacy that can lead to faster progression of the liver disease[33].

Diagnosis of PSC relies on the presence of cholestasis markers [alkaline phosphatase (ALP) and gamma-glutamyl (GGT) transferase], characteristic bile duct changes on imaging and the exclusion of secondary causes[29,20]. The elevation of serum ALP is the commonest marker[29,32]. ALP is not reliable in children as it can be elevated due to high bone turnover. So, GGT transferase is more commonly used as a diagnostic marker in the pediatric population[34]. However, the transient blockage of the strictured bile ducts can create fluctuations in ALP and bilirubin levels. The total serum bilirubin level is usually normal, but an increase or fluctuations in bilirubin levels indicate the presence of dominant strictures or advanced liver disease[32,35]. The dominant strictures are present in around 45% of adult patients at the diagnosis of PSC as compared to < 5% in the pediatric population[34]. Additionally, serum aminotransferases are elevated 2-3 times the upper limit of normal[29]. In cases of a high level of serum aminotransferases, autoimmune hepatitis should be ruled out[36].

PSC is commonly associated with an underlying IBD, with ulcerative colitis (UC) being the most prevalent. Both PSC and UC have an autoimmune component, which is reflected in the presence of autoantibodies. The most frequently reported autoantibodies in PSC and UC are perinuclear antineutrophil cytoplasmic antibodies, found in 26%-94% of PSC cases and 50%-70% of UC cases[37,38]. Additional autoantibodies reported in PSC include antinuclear antibodies (present in 8%-77% of patients) and smooth muscle antibodies (present in 0%-83% of patients)[32,38]. However, it's important to highlight that these autoantibodies lack specificity and are not necessary for a diagnosis of PSC.

Imaging techniques such as abdominal X-ray and ultrasound can reveal abnormal bile ducts and exclude gallstones. However, these techniques are unable to provide a clear view of intrahepatic biliary ducts. Additionally, sclerosis does not dilate the ducts enough to be seen on imaging, resulting in suboptimal assessment in suspected cases of PSC[39]. For

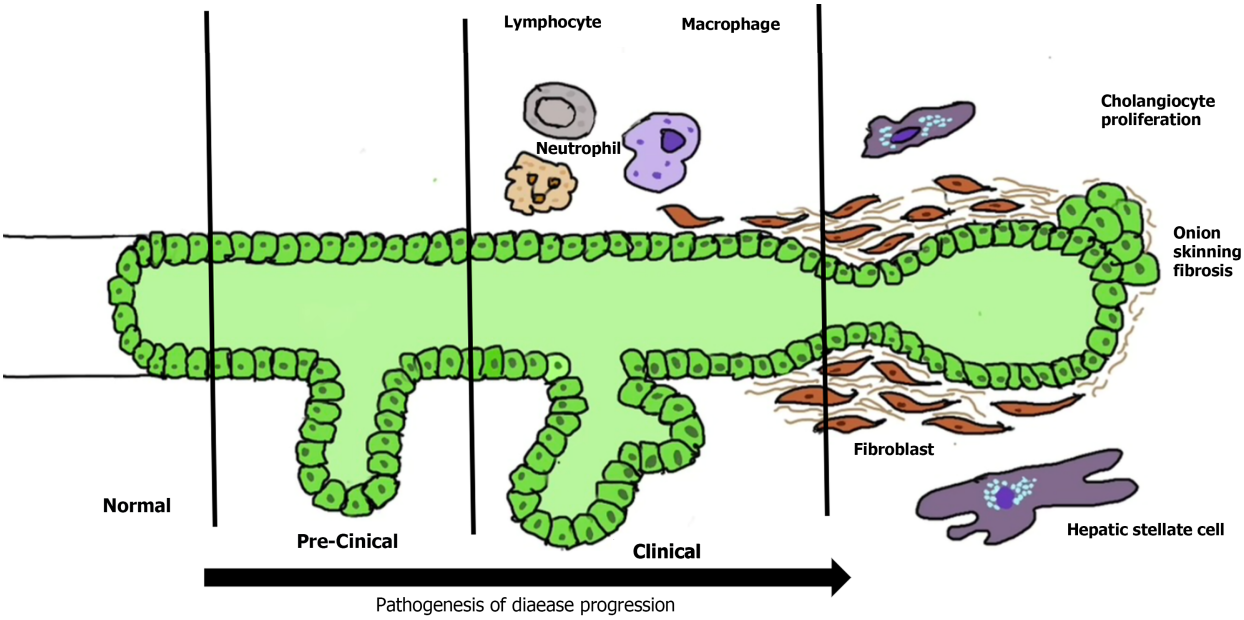

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Figure 1 Pathogenesis of disease progression in primary sclerosing cholangitis.

this reason, cholangiography assessment is essential for the diagnosis of PSC, as the morphological features of PSC mainly involve biliary ductal changes, while liver parenchymal changes develop later[39]. The common imaging findings in PSC seen on MRCP or endoscopic retrograde cholangiopancreatography (ERCP) include intrahepatic and extrahepatic bile duct strictures, which alternate with normal or dilated bile ducts showing a beading appearance (Figure 2)[39-41]. MRCP is preferred as an initial non-invasive imaging method, while ERCP is reserved for therapeutic interventions[30,32,42,43]. The sensitivity and specificity for ERCP in the diagnosis of PSC are 89% and 80% respectively[44]. MRCP has shown a sensitivity of 86% and specificity of 94% for diagnosis of PSC, with superior cost-effectiveness compared to ERCP[45,46].

Staging, Prognosis, and Management of PSC

PSC is staged using a four-stage system first developed by Ludwig *et al*[47] in 1978, which is shown in Table 1. Several good prognostic factors have been identified, including young age, female sex, small duct phenotype, and the presence of Crohn's disease[48]. In early disease, the Mayo PSC risk score can be useful in predicting short-term survival, but it cannot predict the need for LT[49,50]. However, a meta-analysis has shown that the United Kingdom-PSC score and the PSC risk estimate tool are better at predicting long-term risk[51-53]. The components of each prognostic score are listed in Table 2[49,52-57].

The management of PSC focuses on slowing the disease progression and managing its complications. However, there is no definitive treatment to halt the disease process. LT is a viable option for advanced cases and has shown favorable outcomes.

Ursodeoxycholic acid (UDCA), a hydrophilic bile acid, is commonly used in the treatment of cholestatic liver diseases and is extensively studied in PSC[58]. Its mechanisms of action include protecting cholangiocytes against cytotoxic hydrophobic bile acids in early stages, stimulating hepatobiliary secretion in more advanced stages, and protection of hepatocytes against bile acid-induced apoptosis in all stages[59,60]. UDCA has been shown to improve liver function tests, its impact on survival rates, prevention of CCA, or clinical symptoms is inconclusive[61-63]. However, other data has shown that meaningful reductions in ALP levels have been associated with better outcomes in PSC[64-66]. In addition, withdrawing UDCA may be associated with increase in fatigue, pruritus, liver biochemistries, and Mayo PSC risk score[58,67]. American Association for the Study of Liver Diseases (AASLD) updated their guidelines on PSC management in 2022, to suggest a dose of 13-23 mg/kg/d of UDCA, with continued use if there is a reduction or normalization of ALP levels and/or improvement of symptoms after 12 mo of treatment[68].

Immunosuppressive therapies, including glucocorticoids, cyclosporine, tacrolimus, methotrexate, and mycophenolate mofetil, have been explored for PSC treatment. However, a systematic review concluded that these agents, either as monotherapy or in combination do not reduce the risk of mortality or LT, and monotherapy may increase adverse effects [69]. Recent findings from a meta-analysis suggest that immune-modulating therapy may benefit patients with high baseline levels of ALP (> 420 U/L) and aspartate transaminase (> 80 U/L)[70]. Nevertheless, immunosuppressive agents should be reserved for patients with overlap syndromes such as autoimmune hepatitis-PSC or IgG4-associated cholangitis[68]. Ongoing clinical trials are investigating potential treatments options, such as cilofexor (a nonsteroidal farnesoid X receptor agonist), and 24-nor UDCA (a derivative of UDCA), which show promising results[71,72].

Medical management of PSC has several limitations, despite various drugs being investigated, a recent meta-analysis concluded that there is currently insufficient evidence to show differences in effectiveness measures, such as mortality,

Table 1 Staging of primary sclerosing cholangitis based on the four-stage system developed

Primary sclerosing cholangitis stages		Histological finding
Stage I	Portal stage	Presence of portal hepatitis and edema confined to the portal triads with mononuclear infiltration
Stage II	Periportal stage	The inflammation progresses to the periportal space causing periductal fibrosis with dilation of the portal triads. There is absence of bridging necrosis or septal fibrosis
Stage III	Septal stage	Characterized by the presence of fibrous septae and/or bridging fibrosis
Stage IV	Cirrhosis	Established cirrhosis with the presence of fibrous septa and nodular regeneration

Table 2 Overview of the clinical scores for predicting prognosis in primary sclerosing cholangitis and its components that include serum-based biomarkers and clinical features

Clinical scores	Components
Mayo risk score	Age, bilirubin, histological stage, hemoglobin and presence of inflammatory bowel disease
Revised Mayo risk score	Age, bilirubin, albumin, aspartate aminotransferase and variceal bleeding
Amsterdam–Oxford model	Primary sclerosis cholangitis (PSC) subtype, age at PSC diagnosis, albumin, alkaline phosphatase, aspartate aminotransferase, bilirubin and platelets
Short-term United Kingdom-pSC risk score	Bilirubin, albumin, hemoglobin, and platelets count at diagnosis
Long-term United Kingdom-pSC risk score	Age at diagnosis, bilirubin at the second year, alkaline phosphatase at the second year, albumin at the second year, platelets at the second year, presence of extrahepatic biliary disease at diagnosis, and variceal hemorrhage by the second year
Primary sclerosing cholangitis risk estimate tool	Bilirubin, albumin, alkaline phosphatase, platelets, aspartate transaminases, hemoglobin, sodium, PSC duration and age
Model for end stage liver disease	Dialysis at least twice in the past week, creatinine, bilirubin, international normalized ratio and sodium
Child-Pugh score	Bilirubin, albumin, international normalized ratio, ascites and encephalopathy

health-related quality of life, cirrhosis, or LT between any active pharmacological intervention and no intervention[73]. The high risk of bias in most assessed trials further underscores the need for well-designed randomized controlled trials with adequate follow-up in order to improve pharmacological management of patients with PSC. An overview of various clinical trials and meta-analysis assessing the efficacy and adverse effects of medications used in management of PSC is described in Table 3[61-63,69,70,72,74-76].

While most cases of PSC are characterized by multifocal bile duct strictures, a few have a localized high-grade stricture (dominant stricture) superimposed on diffuse disease that can cause jaundice or cholangitis[77]. Furthermore, CCA may appear as a dominant stricture[78,79]. Hence, brush cytology of the biliary tree, endobiliary biopsy, and fluorescence in situ hybridization should be performed to assess it[68]. AASLD recommends ERCP for the evaluation of relevant strictures as well as new-onset or worsening pruritus, unexplained weight loss, worsening serum liver test abnormalities, rising serum cancer antigen 19-9, recurrent bacterial cholangitis, or progressive bile duct dilation[68]. However, it is important to consider that PSC patients undergoing ERCP have an increased risk of bacterial cholangitis and pancreatitis, so antimicrobial prophylaxis should be administered before the procedure[80-84].

Liver Transplant in PSC

Indications for liver transplant in PSC: LT is performed in patients with PSC when medical therapy has reached its limits[85]. PSC is a hepatic condition with a variable clinical course. LT becomes necessary when the patient develops end-stage liver disease and complications related to portal hypertension, such as ascites, hepatic encephalopathy, variceal hemorrhage, or spontaneous bacterial peritonitis[51,85]. In 2006, United Network Of Organ Sharing reported that 6650 patients received liver transplants, while 17221 were on the waiting list[86]. To address the insufficient number of deceased donors and long wait times, living donor liver transplant (LDLT) emerged as an alternative with favorable outcomes for acute and chronic liver diseases, provided appropriate selection criteria[87,88].

In the United States, Model For End Stage Liver Disease (MELD) score is used by Organ Procurement and Transportation in Network (OPTN) to prioritize liver transplant recipients. LT is considered when MELD score is ≥ 15, indicating hepatocellular dysfunction[85]. The MELD score incorporates the patient's serum bilirubin level, international normalized ratio, and serum creatinine level[89]. MELD exceptions for LT are granted to patients with at least two admissions within a 1-year period for acute cholangitis with a documented bloodstream in infection or with evidence of sepsis requiring vasopressors for hemodynamic instability, as well as those with a diagnosis of CCA[90]. The inclusion and exclusion criteria for LT in patients with CCA are detailed in Table 4[68,91]. The LT process involves a multidisciplinary team with different roles, as outlined in Table 5[92].

Table 3 Overview of important clinical trials and meta-analysis assessing medications used in management of primary sclerosing cholangitis

Ref.	Year	Type	Objective	Results							
				Death	Symptoms (fatigue, pruritus)	Liver transplantation	Histological improvement	Marker values (bilirubin, GGT, ALP, ALT or AST)	Cholangiographic changes	Cholangiocarcinoma	Adverse events
Ursodeoxycholic acid											
Shi *et al* [74]	2009	Meta-analysis of RCT (8 RCT, 465 patients)	Evaluate the effect and safety of UDCA in PSC	No significant effect	No significant effect	No significant effect	Significant difference	No significant effect	No significant effect on improvement	No significant difference on incidence	No significant difference on incidence
Othman *et al*[61]	2012	Meta-analysis of RCT (7 RCT, 553 patients)	Investigate the efficacy of UDCA in PSC	No significant effect	No significant effect	No significant effect	No significant effect	Significantly decrease ALP, GGT, bilirubin, ALT or AST	No significant effect on improvement	No significant difference on incidence	No significant difference on incidence
Poropat *et al*[62]	2011	Meta-analysis of RCT (8 RCT, 592 patients)	Assess the beneficial and harmful effects of BA for patients with PSC	No significant effect	No significant effect	No significant effect	No significant effect	Significantly decrease ALP, GGT, bilirubin or AST. Not significant effect on albumin	No significant effect on improvement	No significant difference on incidence	No significant difference on incidence
Triantos *et al*[63]	2011	Meta-analysis of RCT (8 RCT, 567 patients)	Evaluate if UDCA is useful for PSC	No significant effect	No significant effect	No significant effect	No significant effect	Not reported	Not reported	No significant difference on incidence	Not reported
Immunosuppressive therapies: glucocorticoids, cyclosporine, tacrolimus, methotrexate and mycophenolate mofetil											
Peng *et al* [69]	2017	Meta-analysis of RCT (7 RCT, 266 patients)	Evaluate the safety and efficiency of IA for the treatment of PSC	No significant effect	Not reported	No significant effect	Not reported	No significant improvement on liver biochemistry except AST	Not reported	Not reported	Significant increase on incidence
Liu *et al* [70]	2022	Meta-analysis (7 RCT and 14 observational, 737 patients)	Assess the efficacy and adverse effects of immunomodulators in adult patients with PSC	Not reported	Not reported	Not reported	Not reported	Significantly decrease ALP. Not significant effect on bilirubin and AST	Not reported	Not reported	16.1% of patients had severe AEs[1]
Antibiotics											
Shah *et al* [75]	2019	Meta-analysis of clinical trials (3 RCT and 2 open labeled trials, 124 patients)	Assess the effect of antibiotic therapy (vancomycin, metronidazole, rifaximin and minocycline) in PSC with or without inflammatory bowel disease	Not reported	Not reported	Not reported	Not reported	Significant reduction in ALP and bilirubin	Not reported	Not reported	8.9 % of patients had severe AEs[1]
Probiotics											

Vleggaar *et al*[76]	2008	RCT that included 14 patients	Assess potential beneficial effects of probiotics in PSC	Not reported	No significant effect	Not reported	Not reported	No significant effect on bilirubin, ALP, GGT, AST, ALT, prothrombin, albumin or bile salts	Not reported	Not reported	Not reported
Newer drugs											
Fickert *et al*[72]	2017	RCT that included 161 patients	Evaluate the safety and efficacy of three doses of oral nor UDCA compared with placebo in patients with PSC	Not reported	No significant effect	Not reported	Not reported	Significantly decrease ALP, GGT, ALT or AST	Not reported	Not reported	14 patients had severe AE[1]

[1]Results of this outcome were not included in the meta-analysis. It was derived from the assessment of individual studies. GGT: Gamma-glutamyl; ALP: Alkaline phosphatase; AE: Adverse effects; RCT: Randomized controlled trial; AST: Aspartate Aminotransferase; ALT: Alanine transaminase; PSC: Primary sclerosing cholangitis; UDCA: Ursodeoxycholic acid; BA: Bile acids.

Psychosocial evaluation in liver transplant candidates: Patients with PSC may experience anxiety, depression, substance use disorder, or other psychological symptoms due to the chronic and potentially progressive nature of the disease[93]. 35%-65% of transplant candidates meet criteria for an internalizing disorder as a result of waiting and anticipating surgery[94]. Chronic illness can impact the quality of life, especially in case of conditions like PSC where patients may have unpredictable flares of symptoms. The psychological evaluation can also help in identifying coping strategies that patients can use to manage their symptoms and improve their overall well-being[93]. Various psychological instruments used for psychosocial evaluation in transplant candidates are listed in Table 6[93].

Overall, the medical and psychological evaluation in PSC plays a crucial role in assessing the severity of the disease and identifying any associated conditions, as well as addressing psychological factors that may affect the patient's quality of life[93].

Ethical considerations in liver transplant candidates: Organ transplantation raises significant ethical considerations, making it one of the most controversial disciplines in medicine[95]. Key ethical concerns related to organ retrieval include accurately diagnosing brain death, respecting the patient's known wishes regarding organ donation, and upholding the principle of altruism in living organ donation[96]. When it comes to living organ donors, ensuring their understanding of the surgery's risks, benefits and potential complications is crucial, especially during the informed consent process. Comprehensive discussions on short-term and long-term outcomes should take place at this stage[97]. There is notable regional variability in the application and acceptance of MELD exceptions for LT. A study revealed that, despite OPTN's clinical criteria, nearly 80% of exception applications for PSC and cholangitis were approved by regional review boards regardless of the indication[98]. This highlights the need for a standardized national review board to ensure equitable access to LT for patients with PSC and bacterial cholangitis[98].

Sex-based disparities in organ transplantation are also a concern. The MELD score, which relies on creatinine levels, underestimates true renal function in females due to lower muscle mass. Additionally, men face an increased risk of hepatocellular carcinoma, which can lead to MELD exceptions[95]. A analysis of waitlisted candidates from the scientific registry for transplant recipients showed that Hispanics with MELD scores < 20 had an 8% lower deceased donor liver transplant (DDLT) rate compared to Whites[99]. Asian patients with MELD score < 15, on the other hand, had a 24% higher DDLT rate compared to Whites, but this rate dropped by 46% for Asian patients with MELD scores between 30-40 compared to Whites[99]. As the field of LT continues to evolve, addressing ethical concerns requires filling knowledge

Table 4 Inclusion and exclusion criteria for patients with cholangiocarcinoma being considered for Model For End Stage Liver Disease exception points

Inclusion criteria	Exclusion criteria
Evidence of positive tumor cells or cells strongly suspicious for CCA on biopsy	Evidence of extra hepatic disease or lymph node enlargement
Malignant appearing stricture on radiograph and 1 of the following criteria (a or b or c)	Previous malignancy excluding skin or cervical cancer within 5 yr before diagnosis of cholangiocarcinoma
a. Ca 19-19 > 100 U/mL in the absence of acute bacterial cholangitis	History of abdominal radiotherapy
b. Polysomy on fluorescence in-situ hybridization	Uncontrolled infection before treatment
c. Hilar mass < 3 cm in radial diameter on cross-sectional imaging	Prior attempt of surgical tumors reaction and subsequent violation of tumor plane
-	Any medical condition precluding transplantation
-	Any transperitoneal biopsy including percutaneous and/or endoscopic ultrasonographic-guided fine needle aspiration

CCA: Cholangiocarcinoma.

Table 5 Role of multidisciplinary team involved in the process of liver transplantation

Role	Description
Transplant hepatologist	A medical doctor who specializes in liver disease
Liver transplant surgeon	Evaluates the patient and determines whether a liver transplant is the best option by considering surgical contraindications
Transplant nurse coordinator	Serves as the primary contact for the patient throughout the transplant process, ensures that testing is up-to-date, and provides education on the transplant process
Transplant social worker	Focuses on the psychological and social aspects of end-stage liver disease and provides mental health support as needed
Transplant nutritionist	Assesses the patient's nutritional status, including weight patterns and dietary intake, and makes recommendations for an optimal diet
Financial coordinator	Reviews the patient's medical insurance coverage and assists with obtaining adequate coverage for the transplant
Transplant pharmacist	Reviews the patient's medication list for any contraindications before the transplant and provides education on new medications after the transplant

gaps with robust and carefully gathered data that go beyond the informed consent of donors[95].

Outcomes of liver transplant in patients with PSC: The one-year and five-year survival rates were better in patients with LT for impaired quality of life (97.4% and 94.9%) as compared to patients with LT for end-stage liver disease (91.4% and 88.6% respectively) based on a retrospective study on 74 patients with LT[100]. The one-year and five-year survival rates for patients with suspicion of neoplasia prior to the LT were 95.8% and 74.1% respectively[100]. A larger study of 6071 patients had similar outcomes with patient survival rate of 89.7%, 79.8%, 70.7%, 58.3%, 43.8% and 20.4% respectively at 1, 5, 10, 15, 20, and 30 years respectively[101]. Based on a study of 6911 LT patients from the OPTN database, the unadjusted survival rate was significantly higher among the LDLT group as compared to the DDLT group[102]. The most common factors associated with death after LT were infections, malignancies, cardiovascular diseases, graft failure (GF) due to rejection, and hepatic artery thrombosis (HAT)[101,103,104].

Patients with LT for PSC have an acute cellular rejection (ACR) rate of 20-40%, requiring additional immunosuppression[105]. ACR does not affect long-term graft or survival outcomes in patients with LT, as opposed to patients with renal transplant[105]. A retrospective study of patients with a diagnosis of PSC (24 patients) and PSC-autoimmune hepatitis overlap (2 patients) without evidence of CCA at the time of LDLT showed allograft rejection successfully managed by immunosuppression in 11.5% patients, postoperative bile leak in 7.6% patients managed conservatively, and biliary stricture in 11.5% patients with successful ERCP and biliary stent placement[103]. Biliary strictures and bile leaks are other common complications after LT with an incidence of 5%-15% in patients who received DDLT and 28%-32% in recipients of right lobe LDLT[106]. The mean time interval for presentation of biliary strictures after LT is 5-8 mo[106]. Biliary strictures are classified into anastomotic variant and non-anastomotic (NAS) variant. NAS variants may be caused due to HAT and non-HAT etiologies like chronic ductopenic rejection, ABO incompatibility, PSC causing recurrent or ischemic strictures, age of the donors, duration of use of vasopressors, prolonged cold and warm ischemia times, preservative injury, and donation after cardiac deaths[106]. NAS variants related to ischemia usually present within one year and those related to immunological factors present after one year of LT[107].

Table 6 Psychological instruments for psychosocial evaluation of transplant patients

Instrument name	Description	Scoring/rating	Reliability	Validity
Beck depression inventory	Self-report measure of depressive symptoms	21-item scale, higher scores indicate more severe depressive symptoms	High test-retest reliability, internal consistency, and concurrent validity	Established validity in measuring depressive symptoms in various populations
Hamilton depression rating scale	Clinician-rated scale to assess severity of depressive symptoms	17-item scale, higher scores indicate more severe depressive symptoms	High inter-rater reliability, internal consistency, and concurrent validity	Established validity in measuring depressive symptoms in various populations
General health questionnaire	Self-report measure of general mental health	12-item or 28-item scale, higher scores indicate poorer mental health	High internal consistency, test-retest reliability, and concurrent validity	Widely used in assessing mental health in general populations
Primary care evaluation of mental disorders-patient health questionnaire	Self-report measure of common mental disorders	9-item scale, higher scores indicate greater severity of mental disorder symptoms	High sensitivity and specificity, test-retest reliability, and convergent validity	Widely used in primary care settings to screen for mental disorders
Transplant evaluation rating scale	Clinician-rated scale to assess psychosocial functioning in transplant recipients	10 aspects of psychosocial functioning rated on a 5-point scale, higher scores indicate better adjustment	Good inter-rater reliability and validity in liver transplant recipients	Specific to evaluating psychosocial functioning in transplant recipients
Psychosocial assessment of candidates for transplantation	Clinician-rated scale to assess psychosocial acceptability of transplant candidates	8 subscales rated on a 5-point scale, with initial and final overall ratings	Established reliability and validity in evaluating psychosocial acceptability of transplant candidates	Widely used in evaluating transplant candidate suitability
Stanford integrated psychosocial assessment for transplantation	Clinician-rated scale to assess psychosocial functioning in transplant candidates	Comprehensive assessment covering multiple domains of psychosocial functioning	Limited data on reliability and validity, but shows promise in transplant candidate evaluation	Developed specifically for evaluating psychosocial functioning in transplant candidates

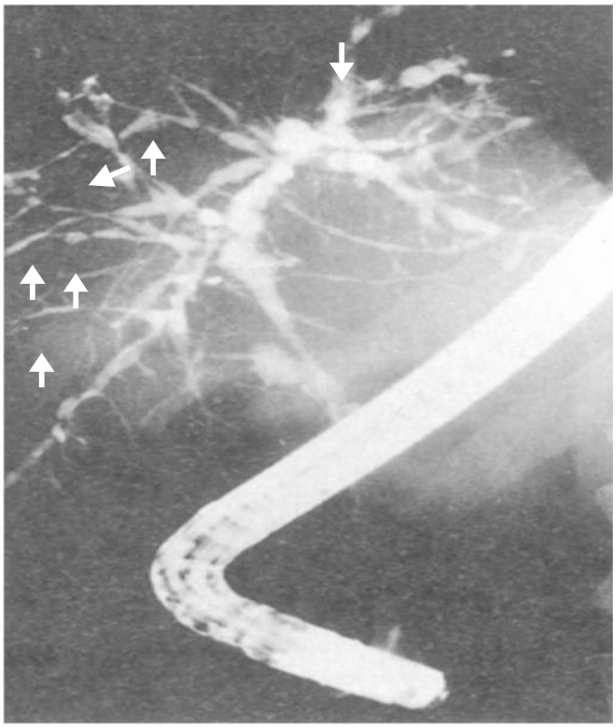

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Figure 2 A cholangiography showing common findings in primary sclerosing cholangitis *i.e* the presence of multiple short narrowings (shown by arrows) and dilatations in the intra and extrahepatic bile ducts, creating a distinctive "beaded pattern".

A study based on the review of 22 publications with a total of 1399 patients who underwent LT for PSC showed that the recurrence rate of PSC was around 18.5%, ranging from 5.7%-59.1%[108]. Another study with a patient population of 230 had a recurrence rate of 23.5% with a median of 4.6 years after LT[108]. Some of the most common factors related to an increased risk of recurrence of PSC are presence of HLA-DRB1*08 in the donor or recipient, absence of donor HLA

DR52, older and younger recipients, male recipients, development of UC after LT, requirement of a longer duration of maintenance therapy with steroids (> 3 mo), steroid resistant ACR, and the presence of CCA or concurrent infection with cytomegalovirus in the donor[108]. Due to a high recurrence rate of PSC in patients and a 4-fold increase in the risk of GF or mortality within 5 years of LT; liver re-transplant (ReLT) is considered to extend survival[109].

Quality of life and psychological outcomes after liver transplant: The health-related quality of life (HRQOL) and employment after LT depends on the etiology of the ESLD. In a cross-sectional study of 356 patients post LT, the return to employment rates within six months were highest amongst patients with PSC (2.4 times) and alcoholic cirrhosis (2.5 times) as compared to patients with primary biliary cirrhosis. However, post LT HRQOL was comparable among different ESLD etiologies[110]. Early retirement was also significantly higher, reaching 83% in patients with PSC[110]. Most commonly reported symptoms of physical distress after LT were fatigue, muscle weakness, increased appetite, headache, backache, and bruising which were higher in females over one year as compared to men[111]. The most commonly reported symptoms of psychological distress at one year were sleeplessness and mood swings, followed by nervousness, depression, and difficulty concentrating[111]. Recipients of LT rated their overall health as 7.17 ± 2.22 out of a possible score of 10 based on a questionnaire adapted from Karnofsky functional performance scale, medical outcomes study short form (SF-36), and psychosocial adjustment to illness scale, with 10 being the best outcome[112]. The greatest benefit reported post LT was "being alive". The worst factor reported about being a LT recipient was dependence on medications and the cost of insurance and medications[112].

Future directions in management of PSC: Recent advancement in digital technology have opened up new possibilities of enhancing the understanding of liver anatomy and vascular structures through the creation of three-dimensional (3D) liver models using data from computed tomography and magnetic resonance imaging scans[113]. PSC often involves the development of strictures and narrowing of the bile ducts, making LT surgery more challenging[114]. The emerging technique of 3D liver transplant offers surgeons assistance in planning surgical procedures, including precise identification of blood vessels and bile ducts, improving the accuracy and efficiency of transplant surgeries[115,116].

Stem cell therapy and gene therapy represent two emerging treatments with potential for managing PSC. Stem cell therapy involves using stem cells to repair and regenerate damaged liver tissue[117]. Various types of stem cells , such as mesenchymal stem cells, induced pluripotent stem cells, and embryonic stem cells, have been investigated for their potential in treating liver diseases, including PSC. Studies indicate that stem cell therapy may reduce inflammation and promote tissue regeneration in PSC cases[117,118]. Gene therapy, on the other hand, utilizes genes to modify the expression of specific proteins involved in the development and progression of the disease. One potential target for gene therapy in PSC is the nuclear factor kappa B (NF-κB) pathway, which plays a role in liver inflammation regulation. Inhibiting the NF-κB pathway has shown promise in reducing inflammation and fibrosis in PSC[119]. Despite the potential benefits of stem cell and gene therapies in PSC, further research is needed to determine their safety and efficacy. Ongoing clinical trials are evaluating the use of these therapies in PSC treatment, and their outcomes will determine their future role in managing the disease[117].

CONCLUSION

LT plays a very crucial role in the management of patients with PSC due to limited options and studies on outcomes with medical management. This review offers a summary of clinical features, diagnosis, medical management and a detailed discussion on the indications, clinical and psychosocial outcomes, ethical dilemmas, and future aspects in the field of liver transplant for management of PSC. The review also highlights the important aspect of pReLT psychosocial evaluation, as well as psychosocial outcomes post-transplant, which plays a pivotal role in preventing mental health crises in the patients. Significant efforts need to be directed towards addressing the ethical issues in liver transplant for equity of the care. Patients with PSC will also greatly benefit from more advances in the medical management of PSC.

FOOTNOTES

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REFERENCES

1 **Mehta TI**, Weissman S, Fung BM, Sotiriadis J, Lindor KD, Tabibian JH. Global incidence, prevalence and features of primary sclerosing cholangitis: A systematic review and meta-analysis. *Liver Int* 2021; **41**: 2418-2426 [PMID: 34224208 DOI: 10.1111/liv.15007]
2 **Cotter JM**, Mack CL. Primary sclerosing cholangitis: Unique aspects of disease in children. *Clin Liver Dis (Hoboken)* 2017; **10**: 120-123 [PMID: 30992770 DOI: 10.1002/cld.672]
3 **Eaton JE**, Talwalkar JA, Lazaridis KN, Gores GJ, Lindor KD. Pathogenesis of primary sclerosing cholangitis and advances in diagnosis and management. *Gastroenterology* 2013; **145**: 521-536 [PMID: 23827861 DOI: 10.1053/j.gastro.2013.06.052]
4 **Karlsen TH**, Folseraas T, Thorburn D, Vesterhus M. Primary sclerosing cholangitis - a comprehensive review. *J Hepatol* 2017; **67**: 1298-1323 [PMID: 28802875 DOI: 10.1016/j.jhep.2017.07.022]
5 **Lazaridis KN**, LaRusso NF. The Cholangiopathies. *Mayo Clin Proc* 2015; **90**: 791-800 [PMID: 25957621 DOI: 10.1016/j.mayocp.2015.03.017]
6 **Qin N**, Yang F, Li A, Prifti E, Chen Y, Shao L, Guo J, Le Chatelier E, Yao J, Wu L, Zhou J, Ni S, Liu L, Pons N, Batto JM, Kennedy SP, Leonard P, Yuan C, Ding W, Hu X, Zheng B, Qian G, Xu W, Ehrlich SD, Zheng S, Li L. Alterations of the human gut microbiome in liver cirrhosis. *Nature* 2014; **513**: 59-64 [PMID: 25079328 DOI: 10.1038/nature13568]
7 **Jussila A**, Virta LJ, Pukkala E, Färkkilä MA. Malignancies in patients with inflammatory bowel disease: a nationwide register study in Finland. *Scand J Gastroenterol* 2013; **48**: 1405-1413 [PMID: 24131389 DOI: 10.3109/00365521.2013.846402]
8 **Staufer K**, Kivaranovic D, Rasoul-Rockenschaub S, Soliman T, Trauner M, Berlakovich G. Waitlist mortality and post-transplant survival in patients with cholestatic liver disease - Impact of changes in allocation policy. *HPB (Oxford)* 2018; **20**: 916-924 [PMID: 29937419 DOI: 10.1016/j.hpb.2018.03.013]
9 **Vera A**, Moledina S, Gunson B, Hubscher S, Mirza D, Olliff S, Neuberger J. Risk factors for recurrence of primary sclerosing cholangitis of liver allograft. *Lancet* 2002; **360**: 1943-1944 [PMID: 12493264 DOI: 10.1016/S0140-6736(02)11861-7]
10 **Kashyap R**, Mantry P, Sharma R, Maloo MK, Safadjou S, Qi Y, Jain A, Maliakkal B, Ryan C, Orloff M. Comparative analysis of outcomes in living and deceased donor liver transplants for primary sclerosing cholangitis. *J Gastrointest Surg* 2009; **13**: 1480-1486 [PMID: 19430850 DOI: 10.1007/s11605-009-0898-3]
11 **Mack M**. Inflammation and fibrosis. *Matrix Biol* 2018; **68-69**: 106-121 [PMID: 29196207 DOI: 10.1016/j.matbio.2017.11.010]
12 **Parola M**, Pinzani M. Liver fibrosis: Pathophysiology, pathogenetic targets and clinical issues. *Mol Aspects Med* 2019; **65**: 37-55 [PMID: 30213667 DOI: 10.1016/j.mam.2018.09.002]
13 **Wynn TA**, Ramalingam TR. Mechanisms of fibrosis: therapeutic translation for fibrotic disease. *Nat Med* 2012; **18**: 1028-1040 [PMID: 22772564 DOI: 10.1038/nm.2807]
14 **Banales JM**, Huebert RC, Karlsen T, Strazzabosco M, LaRusso NF, Gores GJ. Cholangiocyte pathobiology. *Nat Rev Gastroenterol Hepatol* 2019; **16**: 269-281 [PMID: 30850822 DOI: 10.1038/s41575-019-0125-y]
15 **Bergquist A**, Montgomery SM, Bahmanyar S, Olsson R, Danielsson A, Lindgren S, Prytz H, Hultcrantz R, Lööf LA, Sandberg-Gertzén H, Almer S, Askling J, Ehlin A, Ekbom A. Increased risk of primary sclerosing cholangitis and ulcerative colitis in first-degree relatives of patients with primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2008; **6**: 939-943 [PMID: 18674735 DOI: 10.1016/j.cgh.2008.03.016]
16 **Paziewska A**, Habior A, Rogowska A, Zych W, Goryca K, Karczmarski J, Dabrowska M, Ambrozkiewicz F, Walewska-Zielecka B, Krawczyk M, Cichoz-Lach H, Milkiewicz P, Kowalik A, Mucha K, Raczynska J, Musialik J, Boryczka G, Wasilewicz M, Ciecko-Michalska I, Ferenc M, Janiak M, Kanikowska A, Stankiewicz R, Hartleb M, Mach T, Grzymislawski M, Raszeja-Wyszomirska J, Wunsch E, Bobinski T, Mikula M, Ostrowski J. A novel approach to genome-wide association analysis identifies genetic associations with primary biliary cholangitis and primary sclerosing cholangitis in Polish patients. *BMC Med Genomics* 2017; **10**: 2 [PMID: 28056976 DOI: 10.1186/s12920-016-0239-9]
17 **Liu JZ**, Hov JR, Folseraas T, Ellinghaus E, Rushbrook SM, Doncheva NT, Andreassen OA, Weersma RK, Weismüller TJ, Eksteen B, Invernizzi P, Hirschfield GM, Gotthardt DN, Pares A, Ellinghaus D, Shah T, Juran BD, Milkiewicz P, Rust C, Schramm C, Müller T, Srivastava B, Dalekos G, Nöthen MM, Herms S, Winkelmann J, Mitrovic M, Braun F, Ponsioen CY, Croucher PJ, Sterneck M, Teufel A, Mason AL, Saarela J, Leppa V, Dorfman R, Alvaro D, Floreani A, Onengut-Gumuscu S, Rich SS, Thompson WK, Schork AJ, Næss S, Thomsen I, Mayr G, König IR, Hveem K, Cleynen I, Gutierrez-Achury J, Ricaño-Ponce I, van Heel D, Björnsson E, Sandford RN, Durie PR, Melum E, Vatn MH, Silverberg MS, Duerr RH, Padyukov L, Brand S, Sans M, Annese V, Achkar JP, Boberg KM, Marschall HU, Chazouillères O, Bowlus CL, Wijmenga C, Schrumpf E, Vermeire S, Albrecht M; UK-PSCSC Consortium, Rioux JD, Alexander G, Bergquist A, Cho J, Schreiber S, Manns MP, Färkkilä M, Dale AM, Chapman RW, Lazaridis KN; International PSC Study Group, Franke A, Anderson CA, Karlsen TH; International IBD Genetics Consortium. Dense genotyping of immune-related disease regions identifies nine new risk loci for primary sclerosing cholangitis. *Nat Genet* 2013; **45**: 670-675 [PMID: 23603763 DOI: 10.1038/ng.2616]
18 **Karlsen TH**, Franke A, Melum E, Kaser A, Hov JR, Balschun T, Lie BA, Bergquist A, Schramm C, Weismüller TJ, Gotthardt D, Rust C, Philipp EE, Fritz T, Henckaerts L, Weersma RK, Stokkers P, Ponsioen CY, Wijmenga C, Sterneck M, Nothnagel M, Hampe J, Teufel A, Runz H, Rosenstiel P, Stiehl A, Vermeire S, Beuers U, Manns MP, Schrumpf E, Boberg KM, Schreiber S. Genome-wide association analysis in primary sclerosing cholangitis. *Gastroenterology* 2010; **138**: 1102-1111 [PMID: 19944697 DOI: 10.1053/j.gastro.2009.11.046]
19 **Zhang CC**, Voitl R, Hippchen T, Weiss KH, Sauer P, Rupp C. Evaluation of two functional CD24 polymorphisms in primary sclerosing cholangitis. *Scand J Gastroenterol* 2020; **55**: 581-587 [PMID: 32329406 DOI: 10.1080/00365521.2020.1755357]
20 **Alberts R**, de Vries EMG, Goode EC, Jiang X, Sampaziotis F, Rombouts K, Böttcher K, Folseraas T, Weismüller TJ, Mason AL, Wang W,

Alexander G, Alvaro D, Bergquist A, Björkström NK, Beuers U, Björnsson E, Boberg KM, Bowlus CL, Bragazzi MC, Carbone M, Chazouillères O, Cheung A, Dalekos G, Eaton J, Eksteen B, Ellinghaus D, Färkkilä M, Festen EAM, Floreani A, Franceschet I, Gotthardt DN, Hirschfield GM, Hoek BV, Holm K, Hohenester S, Hov JR, Imhann F, Invernizzi P, Juran BD, Lenzen H, Lieb W, Liu JZ, Marschall HU, Marzioni M, Melum E, Milkiewicz P, Müller T, Pares A, Rupp C, Rust C, Sandford RN, Schramm C, Schreiber S, Schrumpf E, Silverberg MS, Srivastava B, Sterneck M, Teufel A, Vallier L, Verheij J, Vila AV, Vries B, Zachou K; International PSC Study Group, The UK PSC Consortium, Chapman RW, Manns MP, Pinzani M, Rushbrook SM, Lazaridis KN, Franke A, Anderson CA, Karlsen TH, Ponsioen CY, Weersma RK. Genetic association analysis identifies variants associated with disease progression in primary sclerosing cholangitis. *Gut* 2018; **67**: 1517-1524 [PMID: 28779025 DOI: 10.1136/gutjnl-2016-313598]

21 **Laish I**, Katz H, Stein A, Liberman M, Naftali T, Kitay-Cohen Y, Biron-Shental T, Konikoff FM, Amiel A. Telomere dysfunction in peripheral blood lymphocytes from patients with primary sclerosing cholangitis and inflammatory bowel disease. *Dig Liver Dis* 2015; **47**: 790-796 [PMID: 26048252 DOI: 10.1016/j.dld.2015.05.002]

22 **Jiang X**, Karlsen TH. Genetics of primary sclerosing cholangitis and pathophysiological implications. *Nat Rev Gastroenterol Hepatol* 2017; **14**: 279-295 [PMID: 28293027 DOI: 10.1038/nrgastro.2016.154]

23 **Allegretti JR**, Kassam Z, Carrellas M, Mullish BH, Marchesi JR, Pechlivanis A, Smith M, Gerardin Y, Timberlake S, Pratt DS, Korzenik JR. Fecal Microbiota Transplantation in Patients With Primary Sclerosing Cholangitis: A Pilot Clinical Trial. *Am J Gastroenterol* 2019; **114**: 1071-1079 [PMID: 30730351 DOI: 10.14309/ajg.0000000000000115]

24 **Torres J**, Bao X, Goel A, Colombel JF, Pekow J, Jabri B, Williams KM, Castillo A, Odin JA, Meckel K, Fasihuddin F, Peter I, Itzkowitz S, Hu J. The features of mucosa-associated microbiota in primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2016; **43**: 790-801 [PMID: 26857969 DOI: 10.1111/apt.13552]

25 **Dyson JK**, Blain A, Foster Shirley MD, Hudson M, Rushton S, Jeffreys Jones DE. Geo-epidemiology and environmental co-variate mapping of primary biliary cholangitis and primary sclerosing cholangitis. *JHEP Rep* 2021; **3**: 100202 [PMID: 33474546 DOI: 10.1016/j.jhepr.2020.100202]

26 **Tenca A**, Färkkilä M, Jalanko H, Vapalahti K, Arola J, Jaakkola T, Penagini R, Vapalahti O, Kolho KL. Environmental Risk Factors of Pediatric-Onset Primary Sclerosing Cholangitis and Autoimmune Hepatitis. *J Pediatr Gastroenterol Nutr* 2016; **62**: 437-442 [PMID: 26465796 DOI: 10.1097/MPG.0000000000000995]

27 **Andersen IM**, Tengesdal G, Lie BA, Boberg KM, Karlsen TH, Hov JR. Effects of coffee consumption, smoking, and hormones on risk for primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2014; **12**: 1019-1028 [PMID: 24076415 DOI: 10.1016/j.cgh.2013.09.024]

28 **Singh S**, Talwalkar JA. Primary sclerosing cholangitis: diagnosis, prognosis, and management. *Clin Gastroenterol Hepatol* 2013; **11**: 898-907 [PMID: 23454027 DOI: 10.1016/j.cgh.2013.02.016]

29 **European Association for the Study of the Liver**. EASL Clinical Practice Guidelines: management of cholestatic liver diseases. *J Hepatol* 2009; **51**: 237-267 [PMID: 19501929 DOI: 10.1016/j.jhep.2009.04.009]

30 **Lindor KD**, Kowdley KV, Harrison ME; American College of Gastroenterology. ACG Clinical Guideline: Primary Sclerosing Cholangitis. *Am J Gastroenterol* 2015; **110**: 646-59; quiz 660 [PMID: 25869391 DOI: 10.1038/ajg.2015.112]

31 **Chapman R**, Fevery J, Kalloo A, Nagorney DM, Boberg KM, Shneider B, Gores GJ; American Association for the Study of Liver Diseases. Diagnosis and management of primary sclerosing cholangitis. *Hepatology* 2010; **51**: 660-678 [PMID: 20101749 DOI: 10.1002/hep.23294]

32 **Rabiee A**, Silveira MG. Primary sclerosing cholangitis. *Transl Gastroenterol Hepatol* 2021; **6**: 29 [PMID: 33824933 DOI: 10.21037/tgh-20-266]

33 **Peeling Back The Layers of Pediatric Primary Sclerosing Cholangitis AASLD**. 2022. Available from: https://www.aasld.org/Liver-fellow-network/core-series/clinical-pearls/peeling-back-layers-pediatric-primary-sclerosing

34 **Deneau MR**, Mack C, Perito ER, Ricciuto A, Valentino PL, Amin M, Amir AZ, Aumar M, Auth M, Broderick A, DiGuglielmo M, Draijer LG, Tavares Fagundes ED, El-Matary W, Ferrari F, Furuya KN, Gupta N, Hochberg JT, Homan M, Horslen S, Iorio R, Jensen MK, Jonas MM, Kamath BM, Kerkar N, Kim KM, Kolho KL, Koot BGP, Laborda TJ, Lee CK, Loomes KM, Martinez M, Miethke A, Miloh T, Mogul D, Mohammad S, Mohan P, Moroz S, Ovchinsky N, Palle S, Papadopoulou A, Rao G, Rodrigues Ferreira A, Sathya P, Schwarz KB, Shah U, Shteyer E, Singh R, Smolka V, Soufi N, Tanaka A, Varier R, Vitola B, Woynarowski M, Zerofsky M, Zizzo A, Guthery SL. The Sclerosing Cholangitis Outcomes in Pediatrics (SCOPE) Index: A Prognostic Tool for Children. *Hepatology* 2021; **73**: 1074-1087 [PMID: 32464706 DOI: 10.1002/hep.31393]

35 **Boberg KM**, Chapman RW, Hirschfield GM, Lohse AW, Manns MP, Schrumpf E; International Autoimmune Hepatitis Group. Overlap syndromes: the International Autoimmune Hepatitis Group (IAIHG) position statement on a controversial issue. *J Hepatol* 2011; **54**: 374-385 [PMID: 21067838 DOI: 10.1016/j.jhep.2010.09.002]

36 **Dyson JK**, Beuers U, Jones DEJ, Lohse AW, Hudson M. Primary sclerosing cholangitis. *Lancet* 2018; **391**: 2547-2559 [PMID: 29452711 DOI: 10.1016/S0140-6736(18)30300-3]

37 **Conrad K**, Roggenbuck D, Laass MW. Diagnosis and classification of ulcerative colitis. *Autoimmun Rev* 2014; **13**: 463-466 [PMID: 24424198 DOI: 10.1016/j.autrev.2014.01.028]

38 **Hov JR**, Boberg KM, Karlsen TH. Autoantibodies in primary sclerosing cholangitis. *World J Gastroenterol* 2008; **14**: 3781-3791 [PMID: 18609700 DOI: 10.3748/wjg.14.3781]

39 **Khoshpouri P**, Habibabadi RR, Hazhirkarzar B, Ameli S, Ghadimi M, Ghasabeh MA, Menias CO, Kim A, Li Z, Kamel IR. Imaging Features of Primary Sclerosing Cholangitis: From Diagnosis to Liver Transplant Follow-up. *Radiographics* 2019; **39**: 1938-1964 [PMID: 31626561 DOI: 10.1148/rg.2019180213]

40 **Ito K**, Mitchell DG, Outwater EK, Blasbalg R. Primary sclerosing cholangitis: MR imaging features. *AJR Am J Roentgenol* 1999; **172**: 1527-1533 [PMID: 10350284 DOI: 10.2214/ajr.172.6.10350284]

41 **Prokopič M**, Beuers U. Management of primary sclerosing cholangitis and its complications: an algorithmic approach. *Hepatol Int* 2021; **15**: 6-20 [PMID: 33377990 DOI: 10.1007/s12072-020-10118-x]

42 **Schramm C**, Eaton J, Ringe KI, Venkatesh S, Yamamura J; MRI working group of the IPSCSG. Recommendations on the use of magnetic resonance imaging in PSC-A position statement from the International PSC Study Group. *Hepatology* 2017; **66**: 1675-1688 [PMID: 28555945 DOI: 10.1002/hep.29293]

43 **Angulo P**, Pearce DH, Johnson CD, Henry JJ, LaRusso NF, Petersen BT, Lindor KD. Magnetic resonance cholangiography in patients with biliary disease: its role in primary sclerosing cholangitis. *J Hepatol* 2000; **33**: 520-527 [PMID: 11059855 DOI: 10.1034/j.1600-0641.2000.033004520.x]

44 **Berstad AE**, Aabakken L, Smith HJ, Aasen S, Boberg KM, Schrumpf E. Diagnostic accuracy of magnetic resonance and endoscopic

retrograde cholangiography in primary sclerosing cholangitis. *Clin Gastroenterol Hepatol* 2006; **4**: 514-520 [PMID: 16616358 DOI: 10.1016/j.cgh.2005.10.007]

45 **Dave M**, Elmunzer BJ, Dwamena BA, Higgins PD. Primary sclerosing cholangitis: meta-analysis of diagnostic performance of MR cholangiopancreatography. *Radiology* 2010; **256**: 387-396 [PMID: 20656832 DOI: 10.1148/radiol.10091953]

46 **Talwalkar JA**, Angulo P, Johnson CD, Petersen BT, Lindor KD. Cost-minimization analysis of MRC versus ERCP for the diagnosis of primary sclerosing cholangitis. *Hepatology* 2004; **40**: 39-45 [PMID: 15239084 DOI: 10.1002/hep.20287]

47 **Ludwig J**, Dickson ER, McDonald GS. Staging of chronic nonsuppurative destructive cholangitis (syndrome of primary biliary cirrhosis). *Virchows Arch A Pathol Anat Histol* 1978; **379**: 103-112 [PMID: 150690 DOI: 10.1007/BF00432479]

48 **Weismüller TJ**, Trivedi PJ, Bergquist A, Imam M, Lenzen H, Ponsioen CY, Holm K, Gotthardt D, Färkkilä MA, Marschall HU, Thorburn D, Weersma RK, Fevery J, Mueller T, Chazouillères O, Schulze K, Lazaridis KN, Almer S, Pereira SP, Levy C, Mason A, Naess S, Bowlus CL, Floreani A, Halilbasic E, Yimam KK, Milkiewicz P, Beuers U, Huynh DK, Pares A, Manser CN, Dalekos GN, Eksteen B, Invernizzi P, Berg CP, Kirchner GI, Sarrazin C, Zimmer V, Fabris L, Braun F, Marzioni M, Juran BD, Said K, Rupp C, Jokelainen K, Benito de Valle M, Saffioti F, Cheung A, Trauner M, Schramm C, Chapman RW, Karlsen TH, Schrumpf E, Strassburg CP, Manns MP, Lindor KD, Hirschfield GM, Hansen BE, Boberg KM; International PSC Study Group. Patient Age, Sex, and Inflammatory Bowel Disease Phenotype Associate With Course of Primary Sclerosing Cholangitis. *Gastroenterology* 2017; **152**: 1975-1984.e8 [PMID: 28274849 DOI: 10.1053/j.gastro.2017.02.038]

49 **Kim WR**, Therneau TM, Wiesner RH, Poterucha JJ, Benson JT, Malinchoc M, LaRusso NF, Lindor KD, Dickson ER. A revised natural history model for primary sclerosing cholangitis. *Mayo Clin Proc* 2000; **75**: 688-694 [PMID: 10907383 DOI: 10.4065/75.7.688]

50 **Ponsioen CY**, Vrouenraets SM, Prawirodirdjo W, Rajaram R, Rauws EA, Mulder CJ, Reitsma JB, Heisterkamp SH, Tytgat GN. Natural history of primary sclerosing cholangitis and prognostic value of cholangiography in a Dutch population. *Gut* 2002; **51**: 562-566 [PMID: 12235081 DOI: 10.1136/gut.51.4.562]

51 **Schmeltzer PA**, Russo MW. Systematic Review of Prognostic Models Compared to the Mayo Risk Score for Primary Sclerosing Cholangitis. *J Clin Med* 2021; **10** [PMID: 34640494 DOI: 10.3390/jcm10194476]

52 **Goode EC**, Clark AB, Mells GF, Srivastava B, Spiess K, Gelson WTH, Trivedi PJ, Lynch KD, Castren E, Vesterhus MN, Karlsen TH, Ji SG, Anderson CA, Thorburn D, Hudson M, Heneghan MA, Aldersley MA, Bathgate A, Sandford RN, Alexander GJ, Chapman RW, Walmsley M; UK-PSC Consortium, Hirschfield GM, Rushbrook SM. Factors Associated With Outcomes of Patients With Primary Sclerosing Cholangitis and Development and Validation of a Risk Scoring System. *Hepatology* 2019; **69**: 2120-2135 [PMID: 30566748 DOI: 10.1002/hep.30479]

53 **Eaton JE**, Vesterhus M, McCauley BM, Atkinson EJ, Schlicht EM, Juran BD, Gossard AA, LaRusso NF, Gores GJ, Karlsen TH, Lazaridis KN. Primary Sclerosing Cholangitis Risk Estimate Tool (PREsTo) Predicts Outcomes of the Disease: A Derivation and Validation Study Using Machine Learning. *Hepatology* 2020; **71**: 214-224 [PMID: 29742811 DOI: 10.1002/hep.30085]

54 **Wiesner RH**, Grambsch PM, Dickson ER, Ludwig J, MacCarty RL, Hunter EB, Fleming TR, Fisher LD, Beaver SJ, LaRusso NF. Primary sclerosing cholangitis: natural history, prognostic factors and survival analysis. *Hepatology* 1989; **10**: 430-436 [PMID: 2777204 DOI: 10.1002/hep.1840100406]

55 **de Vries EM**, Wang J, Williamson KD, Leeflang MM, Boonstra K, Weersma RK, Beuers U, Chapman RW, Geskus RB, Ponsioen CY. A novel prognostic model for transplant-free survival in primary sclerosing cholangitis. *Gut* 2018; **67**: 1864-1869 [PMID: 28739581 DOI: 10.1136/gutjnl-2016-313681]

56 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]

57 **Child CG**, Turcotte J. Surgery and portal hypertension. *Clinics in Gastroenterology* 1979; **8**: 525-541 [DOI: 10.1016/S0300-5089(21)00439-9]

58 **Wunsch E**, Trottier J, Milkiewicz M, Raszeja-Wyszomirska J, Hirschfield GM, Barbier O, Milkiewicz P. Prospective evaluation of ursodeoxycholic acid withdrawal in patients with primary sclerosing cholangitis. *Hepatology* 2014; **60**: 931-940 [PMID: 24519384 DOI: 10.1002/hep.27074]

59 **Paumgartner G**, Beuers U. Ursodeoxycholic acid in cholestatic liver disease: mechanisms of action and therapeutic use revisited. *Hepatology* 2002; **36**: 525-531 [PMID: 12198643 DOI: 10.1053/jhep.2002.36088]

60 **Beuers U**. Drug insight: Mechanisms and sites of action of ursodeoxycholic acid in cholestasis. *Nat Clin Pract Gastroenterol Hepatol* 2006; **3**: 318-328 [PMID: 16741551 DOI: 10.1038/ncpgasthep0521]

61 **Othman MO**, Dunkelberg J, Roy PK. Urosdeoxycholic acid in primary sclerosing cholangitis: a meta-analysis and systematic review. *Arab J Gastroenterol* 2012; **13**: 103-110 [PMID: 23122450 DOI: 10.1016/j.ajg.2012.06.011]

62 **Poropat G**, Giljaca V, Stimac D, Gluud C. Bile acids for primary sclerosing cholangitis. *Cochrane Database Syst Rev* 2011; **2011**: CD003626 [PMID: 21249655 DOI: 10.1002/14651858.CD003626.pub2]

63 **Triantos CK**, Koukias NM, Nikolopoulou VN, Burroughs AK. Meta-analysis: ursodeoxycholic acid for primary sclerosing cholangitis. *Aliment Pharmacol Ther* 2011; **34**: 901-910 [PMID: 21883323 DOI: 10.1111/j.1365-2036.2011.04822.x]

64 **Hilscher M**, Enders FB, Carey EJ, Lindor KD, Tabibian JH. Alkaline phosphatase normalization is a biomarker of improved survival in primary sclerosing cholangitis. *Ann Hepatol* 2016; **15**: 246-253 [PMID: 26845602 DOI: 10.5604/16652681.1193721]

65 **Al Mamari S**, Djordjevic J, Halliday JS, Chapman RW. Improvement of serum alkaline phosphatase to <1.5 upper limit of normal predicts better outcome and reduced risk of cholangiocarcinoma in primary sclerosing cholangitis. *J Hepatol* 2013; **58**: 329-334 [PMID: 23085647 DOI: 10.1016/j.jhep.2012.10.013]

66 **Stanich PP**, Björnsson E, Gossard AA, Enders F, Jorgensen R, Lindor KD. Alkaline phosphatase normalization is associated with better prognosis in primary sclerosing cholangitis. *Dig Liver Dis* 2011; **43**: 309-313 [PMID: 21251891 DOI: 10.1016/j.dld.2010.12.008]

67 **Black DD**, Mack C, Kerkar N, Miloh T, Sundaram SS, Anand R, Gupta A, Alonso E, Arnon R, Bulut P, Karpen S, Lin CH, Rosenthal P, Ryan M, Squires RH, Valentino P, Elsea SH, Shneider BL. A Prospective Trial of Withdrawal and Reinstitution of Ursodeoxycholic Acid in Pediatric Primary Sclerosing Cholangitis. *Hepatol Commun* 2019; **3**: 1482-1495 [PMID: 31701072 DOI: 10.1002/hep4.1421]

68 **Bowlus CL**, Arrivé L, Bergquist A, Deneau M, Forman L, Ilyas SI, Lunsford KE, Martinez M, Sapisochin G, Shroff R, Tabibian JH, Assis DN. AASLD practice guidance on primary sclerosing cholangitis and cholangiocarcinoma. *Hepatology* 2023; **77**: 659-702 [PMID: 36083140 DOI: 10.1002/hep.32771]

69 **Peng X**, Luo X, Hou JY, Wu SY, Li LZ, Zheng MH, Wang LY. Immunosuppressive Agents for the Treatment of Primary Sclerosing Cholangitis: A Systematic Review and Meta-Analysis. *Dig Dis* 2017; **35**: 478-485 [PMID: 28478443 DOI: 10.1159/000471874]

70 **Liu X**, Wang H, Liu X, Bridle K, Crawford D, Liang X. Efficacy and safety of immune-modulating therapy for primary sclerosing cholangitis: A systematic review and meta-analysis. *Pharmacol Ther* 2022; **237**: 108163 [PMID: 35271884 DOI: 10.1016/j.pharmthera.2022.108163]

71 **Trauner M**, Gulamhusein A, Hameed B, Caldwell S, Shiffman ML, Landis C, Eksteen B, Agarwal K, Muir A, Rushbrook S, Lu X, Xu J, Chuang JC, Billin AN, Li G, Chung C, Subramanian GM, Myers RP, Bowlus CL, Kowdley KV. The Nonsteroidal Farnesoid X Receptor Agonist Cilofexor (GS-9674) Improves Markers of Cholestasis and Liver Injury in Patients With Primary Sclerosing Cholangitis. *Hepatology* 2019; **70**: 788-801 [PMID: 30661255 DOI: 10.1002/hep.30509]

72 **Fickert P**, Hirschfield GM, Denk G, Marschall HU, Altorjay I, Färkkilä M, Schramm C, Spengler U, Chapman R, Bergquist A, Schrumpf E, Nevens F, Trivedi P, Reiter FP, Tornai I, Halilbasic E, Greinwald R, Pröls M, Manns MP, Trauner M; European PSC norUDCA Study Group. norUrsodeoxycholic acid improves cholestasis in primary sclerosing cholangitis. *J Hepatol* 2017; **67**: 549-558 [PMID: 28529147 DOI: 10.1016/j.jhep.2017.05.009]

73 **Saffioti F**, Gurusamy KS, Hawkins N, Toon CD, Tsochatzis E, Davidson BR, Thorburn D. Pharmacological interventions for primary sclerosing cholangitis: an attempted network meta-analysis. *Cochrane Database Syst Rev* 2017; **3**: CD011343 [PMID: 28417463 DOI: 10.1002/14651858.CD011343.pub2]

74 **Shi J**, Li Z, Zeng X, Lin Y, Xie WF. Ursodeoxycholic acid in primary sclerosing cholangitis: meta-analysis of randomized controlled trials. *Hepatol Res* 2009; **39**: 865-873 [PMID: 19467021 DOI: 10.1111/j.1872-034X.2009.00527.x]

75 **Shah A**, Crawford D, Burger D, Martin N, Walker M, Talley NJ, Tallis C, Jones M, Stuart K, Keely S, Lewindon P, Macdonald GA, Morrison M, Holtmann GJ. Effects of Antibiotic Therapy in Primary Sclerosing Cholangitis with and without Inflammatory Bowel Disease: A Systematic Review and Meta-Analysis. *Semin Liver Dis* 2019; **39**: 432-441 [PMID: 31315136 DOI: 10.1055/s-0039-1688501]

76 **Vleggaar FP**, Monkelbaan JF, van Erpecum KJ. Probiotics in primary sclerosing cholangitis: a randomized placebo-controlled crossover pilot study. *Eur J Gastroenterol Hepatol* 2008; **20**: 688-692 [PMID: 18679073 DOI: 10.1097/MEG.0b013e3282f5197e]

77 **May GR**, Bender CE, LaRusso NF, Wiesner RH. Nonoperative dilatation of dominant strictures in primary sclerosing cholangitis. *AJR Am J Roentgenol* 1985; **145**: 1061-1064 [PMID: 3876737 DOI: 10.2214/ajr.145.5.1061]

78 **Stiehl A**, Rudolph G, Klöters-Plachky P, Sauer P, Walker S. Development of dominant bile duct stenoses in patients with primary sclerosing cholangitis treated with ursodeoxycholic acid: outcome after endoscopic treatment. *J Hepatol* 2002; **36**: 151-156 [PMID: 11830325 DOI: 10.1016/s0168-8278(01)00251-3]

79 **Björnsson E**, Lindqvist-Ottosson J, Asztely M, Olsson R. Dominant strictures in patients with primary sclerosing cholangitis. *Am J Gastroenterol* 2004; **99**: 502-508 [PMID: 15056092 DOI: 10.1111/j.1572-0241.2004.04106.x]

80 **Bangarulingam SY**, Gossard AA, Petersen BT, Ott BJ, Lindor KD. Complications of endoscopic retrograde cholangiopancreatography in primary sclerosing cholangitis. *Am J Gastroenterol* 2009; **104**: 855-860 [PMID: 19259076 DOI: 10.1038/ajg.2008.161]

81 **Navaneethan U**, Jegadeesan R, Nayak S, Lourdusamy V, Sanaka MR, Vargo JJ, Parsi MA. ERCP-related adverse events in patients with primary sclerosing cholangitis. *Gastrointest Endosc* 2015; **81**: 410-419 [PMID: 25085336 DOI: 10.1016/j.gie.2014.06.030]

82 **Ismail S**, Kylänpää L, Mustonen H, Halttunen J, Lindström O, Jokelainen K, Udd M, Färkkilä M. Risk factors for complications of ERCP in primary sclerosing cholangitis. *Endoscopy* 2012; **44**: 1133-1138 [PMID: 23108808 DOI: 10.1055/s-0032-1325677]

83 **von Seth E**, Arnelo U, Enochsson L, Bergquist A. Primary sclerosing cholangitis increases the risk for pancreatitis after endoscopic retrograde cholangiopancreatography. *Liver Int* 2015; **35**: 254-262 [PMID: 25041074 DOI: 10.1111/liv.12640]

84 **Gustafsson A**, Enochsson L, Tingstedt B, Olsson G. Antibiotic prophylaxis and its effect on postprocedural adverse events in endoscopic retrograde cholangiopancreatography for primary sclerosing cholangitis. *JGH Open* 2023; **7**: 24-29 [PMID: 36660048 DOI: 10.1002/jgh3.12846]

85 **Martin P**, DiMartini A, Feng S, Brown R Jr, Fallon M. Evaluation for liver transplantation in adults: 2013 practice guideline by the American Association for the Study of Liver Diseases and the American Society of Transplantation. *Hepatology* 2014; **59**: 1144-1165 [PMID: 24716201 DOI: 10.1002/hep.26972]

86 **Müllhaupt B**, Dimitroulis D, Gerlach JT, Clavien PA. Hot topics in liver transplantation: organ allocation--extended criteria donor--living donor liver transplantation. *J Hepatol* 2008; **48** Suppl 1: S58-S67 [PMID: 18308415 DOI: 10.1016/j.jhep.2008.01.013]

87 **Akdur A**, Ayvazoğlu Soy HE, Karakaya E, Yıldırım S, Moray G, Haberal M. Living and Deceased Liver Donation Criteria of Baskent University. *Exp Clin Transplant* 2022; **20**: 80-87 [PMID: 36018028 DOI: 10.6002/ect.DonorSymp.2022.O16]

88 **Sandhu L**, Sandroussi C, Guba M, Selzner M, Ghanekar A, Cattral MS, McGilvray ID, Levy G, Greig PD, Renner EL, Grant DR. Living donor liver transplantation *vs* deceased donor liver transplantation for hepatocellular carcinoma: Comparable survival and recurrence. *Liver Transpl* 2012; **18**: 315-322 [DOI: 10.1002/lt.23490]

89 **Bjøro K**, Schrumpf E. Liver transplantation for primary sclerosing cholangitis. *J Hepatol* 2004; **40**: 570-577 [PMID: 15030971 DOI: 10.1016/j.jhep.2004.01.021]

90 **Update National Liver Review Board Guidance Documents and Policy Clarification-OPTN**. Available from: https://optn.transplant.hrsa.gov/policies-bylaws/public-comment/update-national-liver-review-board-guidance-documents-and-policy-clarification/

91 **Khungar V**, Goldberg DS. Liver Transplantation for Cholestatic Liver Diseases in Adults. *Clin Liver Dis* 2016; **20**: 191-203 [PMID: 26593299 DOI: 10.1016/j.cld.2015.08.011]

92 **Liver Transplant Evaluation-Penn Medicine**. Available from: https://www.pennmedicine.org/for-patients-and-visitors/find-a-program-or-service/transplant-institute/Liver-transplant/treatments-and-procedures/Liver-evaluation

93 **Grover S**, Sarkar S. Liver transplant-psychiatric and psychosocial aspects. *J Clin Exp Hepatol* 2012; **2**: 382-392 [PMID: 25755459 DOI: 10.1016/j.jceh.2012.08.003]

94 **Nghiem DM**, Gomez J, Gloston GF, Torres DS, Marek RJ. Psychological Assessment Instruments for Use in Liver and Kidney Transplant Evaluations: Scarcity of Evidence and Recommendations. *J Pers Assess* 2020; **102**: 183-195 [PMID: 31860362 DOI: 10.1080/00223891.2019.1694527]

95 **The Lancet Gastroenterology Hepatology**. Liver transplantation in the USA: ethical issues. *Lancet Gastroenterol Hepatol* 2020; **5**: 1 [PMID: 31818469 DOI: 10.1016/S2468-1253(19)30386-3]

96 **Sells RA**. Ethical issues in transplantation. *Baillieres Clin Gastroenterol* 1994; **8**: 465-479 [PMID: 8000094 DOI: 10.1016/0950-3528(94)90032-9]

97 **Berg CL**. Being Well Informed Is Critical to Informed Consent for Living Liver Donors. *Transplantation* 2022; **106**: 1103-1104 [PMID: 34560699 DOI: 10.1097/TP.0000000000003959]

98 **Goldberg D**, Bittermann T, Makar G. Lack of standardization in exception points for patients with primary sclerosing cholangitis and bacterial cholangitis. *Am J Transplant* 2012; **12**: 1603-1609 [PMID: 22335632 DOI: 10.1111/j.1600-6143.2011.03969.x]

99 **Mathur AK**, Schaubel DE, Gong Q, Guidinger MK, Merion RM. Racial and ethnic disparities in access to liver transplantation. *Liver Transpl* 2010; **16**: 1033-1040 [PMID: 20818740 DOI: 10.1002/lt.22108]

100 **Andersen IM**, Fosby B, Boberg KM, Clausen OP, Jebsen P, Melum E, Line PD, Foss A, Schrumpf E, Karlsen TH. Indications and Outcomes in Liver Transplantation in Patients With Primary Sclerosing Cholangitis in Norway. *Transplant Direct* 2015; **1**: e39 [PMID: 27500239 DOI: 10.1097/TXD.0000000000000548]

101 **Berenguer M**, Di Maira T, Baumann U, Mirza DF, Heneghan MA, Klempnauer JL, Bennet W, Ericzon BG, Line PD, Lodge PA, Zieniewicz K, Watson CJE, Metselaar HJ, Adam R, Karam V, Aguilera V; all the other contributing centers (www. eltr.org) and the European Liver and Intestine Transplant Association (ELITA). Characteristics, Trends, and Outcomes of Liver Transplantation for Primary Sclerosing Cholangitis in Female Versus Male Patients: An Analysis From the European Liver Transplant Registry. *Transplantation* 2021; **105**: 2255-2262 [PMID: 33196626 DOI: 10.1097/TP.0000000000003542]

102 **Ziogas IA**, Alexopoulos SP, Matsuoka LK, Geevarghese SK, Gorden LD, Karp SJ, Perkins JD, Montenovo MI. Living *vs* deceased donor liver transplantation in cholestatic liver disease: An analysis of the OPTN database. *Clin Transplant* 2020; **34**: e14031 [PMID: 33427333 DOI: 10.1111/ctr.14031]

103 **Jadaun SS**, Mehtani R, Hasnain A, Bhatia S, Moond V, Kumar M, Kuhad V, Singh S, Agarwal S, Gupta S, Saigal S. Good outcomes of living donor liver transplant in primary sclerosing cholangitis: an experience from North India. *Hepatol Int* 2023; **17**: 499-506 [PMID: 36376772 DOI: 10.1007/s12072-022-10442-4]

104 **Emek E**, Serin A, Sahin T, Yazici P, Yuzer Y, Tokat Y, Bozkurt B. Experience in Liver Transplantation Due to Primary Sclerosing Cholangitis: A Single Center Experience. *Transplant Proc* 2019; **51**: 2439-2441 [PMID: 31405746 DOI: 10.1016/j.transproceed.2019.01.156]

105 **Martin EF**, Levy C. Timing, Management, and Outcomes of Liver Transplantation in Primary Sclerosing Cholangitis. *Semin Liver Dis* 2017; **37**: 305-313 [PMID: 29272893 DOI: 10.1055/s-0037-1608655]

106 **Sharma S**, Gurakar A, Jabbour N. Biliary strictures following liver transplantation: past, present and preventive strategies. *Liver Transpl* 2008; **14**: 759-769 [PMID: 18508368 DOI: 10.1002/lt.21509]

107 **Verdonk RC**, Buis CI, van der Jagt EJ, Gouw AS, Limburg AJ, Slooff MJ, Kleibeuker JH, Porte RJ, Haagsma EB. Nonanastomotic biliary strictures after liver transplantation, part 2: Management, outcome, and risk factors for disease progression. *Liver Transpl* 2007; **13**: 725-732 [PMID: 17457935 DOI: 10.1002/Lt.21165]

108 **Fosby B**, Karlsen TH, Melum E. Recurrence and rejection in liver transplantation for primary sclerosing cholangitis. *World J Gastroenterol* 2012; **18**: 1-15 [PMID: 22228965 DOI: 10.3748/wjg.v18.i1.1]

109 **Henson JB**, Patel YA, King LY, Zheng J, Chow SC, Muir AJ. Outcomes of liver retransplantation in patients with primary sclerosing cholangitis. *Liver Transpl* 2017; **23**: 769-780 [PMID: 28027592 DOI: 10.1002/lt.24703]

110 **Aberg F**, Höckerstedt K, Roine RP, Sintonen H, Isoniemi H. Influence of liver-disease etiology on long-term quality of life and employment after liver transplantation. *Clin Transplant* 2012; **26**: 729-735 [PMID: 22404665 DOI: 10.1111/j.1399-0012.2012.01597.x]

111 **Ruppert K**, Kuo S, DiMartini A, Balan V. In a 12-year study, sustainability of quality of life benefits after liver transplantation varies with pretransplantation diagnosis. *Gastroenterology* 2010; **139**: 1619-1629, 1629.e1 [PMID: 20600035 DOI: 10.1053/j.gastro.2010.06.043]

112 **Kizilisik AT**, Grewal HP, Shokouh-Amiri MH, Vera SR, Hathaway DK, Gaber AO. Impact of long-term immunosuppressive therapy on psychosocial and physical well being in liver transplant recipients. *Prog Transplant* 2003; **13**: 278-283 [PMID: 14765720 DOI: 10.1177/152692480301300407]

113 **Gavriilidis P**, Edwin B, Pelanis E, Hidalgo E, de'Angelis N, Memeo R, Aldrighetti L, Sutcliffe RP. Navigated liver surgery: State of the art and future perspectives. *Hepatobiliary Pancreat Dis Int* 2022; **21**: 226-233 [PMID: 34544668 DOI: 10.1016/j.hbpd.2021.09.002]

114 **Murphy SV**, Atala A. 3D bioprinting of tissues and organs. *Nat Biotechnol* 2014; **32**: 773-785 [PMID: 25093879 DOI: 10.1038/nbt.2958]

115 **Thomas J**, Patel S, Troop L, Guru R, Faist N, Bellott BJ, Esterlen BA. 3D Printed Model of Extrahepatic Biliary Ducts for Biliary Stent Testing. *Materials (Basel)* 2020; **13** [PMID: 33120964 DOI: 10.3390/ma13214788]

116 **Vesterhus M**, Karlsen TH. Emerging therapies in primary sclerosing cholangitis: pathophysiological basis and clinical opportunities. *J Gastroenterol* 2020; **55**: 588-614 [PMID: 32222826 DOI: 10.1007/s00535-020-01681-z]

117 **He C**, Yang Y, Zheng K, Chen Y, Liu S, Li Y, Han Q, Zhao RC, Wang L, Zhang F. Mesenchymal stem cell-based treatment in autoimmune liver diseases: underlying roles, advantages and challenges. *Ther Adv Chronic Dis* 2021; **12**: 2040622321993442 [PMID: 33633826 DOI: 10.1177/2040622321993442]

118 **Jalan-Sakrikar N**, De Assuncao TM, Navarro-Corcuera A, Hamdan FH, Loarca L, Kirkeby LA, Resch ZT, O'Hara SP, Juran BD, Lazaridis KN, Rosen CB, Heimbach JK, Taner T, Shah VH, LaRusso NF, Huebert RC. Induced Pluripotent Stem Cells From Subjects With Primary Sclerosing Cholangitis Develop a Senescence Phenotype Following Biliary Differentiation. *Hepatol Commun* 2022; **6**: 345-360 [PMID: 34519176 DOI: 10.1002/hep4.1809]

119 **Somers EB**, O'Shannessy DJ. Folate receptor alpha, mesothelin and megakaryocyte potentiating factor as potential serum markers of chronic kidney disease. *Biomark Insights* 2014; **9**: 29-37 [PMID: 24932099 DOI: 10.4137/BMI.S15245]

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MINIREVIEWS

Prognostic and diagnostic scoring models in acute alcohol-associated hepatitis: A review comparing the performance of different scoring systems

Jad Mitri, Mohammad Almeqdadi, Raffi Karagozian

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Abstract

Alcohol-associated hepatitis (AAH) is a severe form of liver disease caused by alcohol consumption. In the absence of confounding factors, clinical features and laboratory markers are sufficient to diagnose AAH, rule out alternative causes of liver injury and assess disease severity. Due to the elevated mortality of AAH, assessing the prognosis is a radical step in management. The Maddrey discriminant function (MDF) is the first established clinical prognostic score for AAH and was commonly used in the earliest AAH clinical trials. A MDF > 32 indicates a poor prognosis and a potential benefit of initiating corticosteroids. The model for end stage liver disease (MELD) score has been studied for AAH prognostication and new evidence suggests MELD may predict mortality more accurately than MDF. The Lille score is usually combined to MDF or MELD score after corticosteroid initiation and offers the advantage of assessing response to treatment a 4-7 d into the course. Other commonly used scores include the Glasgow Alcoholic Hepatitis Score and the Age Bilirubin international normalized ratio Creatinine model. Clinical AAH correlate adequately with histologic severity scores and leave little indication for liver biopsy in assessing AAH prognosis. AAH presenting as acute on chronic liver failure (ACLF) is so far prognosticated with ACLF-specific scoring systems. New artificial intelligence-generated prognostic models have emerged and are being studied for use in AAH. Acute kidney injury (AKI) is one possible complication of AAH and is significantly associated with increased AAH mortality. Predicting AKI and alcohol relapse are important steps in the management of AAH. The aim of this review is to discuss

the performance and limitations of different scoring models for AAH mortality, emphasize the most useful tools in prognostication and review predictors of recurrence.

Key Words: Alcohol-associated hepatitis; Prognostic scores; Mortality; Maddrey discriminant function; Model for end stage liver disease; Acute kidney injury

Core Tip: Clinical prognostic scores for alcohol-associated hepatitis (AAH) are reliable and commonly minimize the need for histological assessment. Model for end stage liver disease (MELD) score is recently showing superiority compared to the commonly used Maddrey Discriminant function for AAH prognostication. Combining MELD at diagnosis with day 4 (or day 7) Lille score when managing severe AAH would be interesting to validate as a superior mean of assessing AAH prognosis. Acute kidney injury is a complication of AAH with significant impact on mortality. It is therefore important to account for when managing AAH.

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INTRODUCTION

Alcohol consumption could result in numerous liver diseases, the most severe one being alcohol-associated hepatitis (AAH). AAH, otherwise known as alcoholic hepatitis, is clinically characterized by rapidly progressing jaundice, malaise, tender hepatomegaly, and discreet systemic inflammatory response syndrome (SIRS) features[1]. While the burden of this disease is well known, little improvement in survival has been noted over the years[2]. Therefore, research and development for AAH are desperately needed to improve patients' outcomes and reduce its morbidity and mortality. In fact, since the coronavirus disease 2019 pandemic, the incidence of AAH has increased by over 50%, with a subsequent increase in referrals to liver transplant centers for patients with AAH[3,4]. Additionally, liver transplant waiting list additions increased by 105.6% and liver transplant recipients increased by 411.8% in patients with AAH[5]. The mortality of AAH may be as high as 30% at 28 d and surpass 50% at 1 year[1]. Several prognostic scores have been created and studied throughout the years in an attempt to predict the mortality of AAH. For instance, the Maddrey discriminant function (MDF), conceived in 1978, has been the first[6] and the most discussed score for the assessment of disease severity and guidance of treatment initiation. However, emerging data has supported other prognostic scores such as the model for end stage liver disease (MELD) score. Among others scores, the dynamic Lille score is renowned for its ability to assess the response of AAH to therapy as the disease progresses. There is no consensus regarding the superiority of one score compared to the other. This review aims to discuss the most recent evidence regarding the clinical relevance and performance of the available AAH prognostic scores.

DIAGNOSIS AND SEVERITY OF ALCOHOL-ASSOCIATED HEPATITIS: CLINICAL, BIOLOGICAL AND HISTOLOGICAL FEATURES

AAH is a potentially fatal complication of chronic alcohol abuse that commonly occurs after a sudden increase in alcohol consumption. Although AAH may present abruptly, it most often progresses insidiously over days or weeks with patients complaining of fatigue and malaise followed by anorexia, nausea and vomiting before developing ascites or jaundice[7]. While the latter are the most important symptoms for diagnosis in clinical practice settings, other signs and symptoms may be seen including tender hepatomegaly, low-grade fever, and abdominal pain[8]. The diagnosis is mainly clinical, however abdominal imaging should also be performed to rule out obstructive biliary disease. Additional workup should rule out acute viral hepatitis, severe autoimmune liver disease and Wilson disease[9,10]. The gold-standard diagnostic test remains liver biopsy. The decision of performing biopsy should be guided by the pre-test probability of AAH and should consider the risk of complications such as bleeding. As per the AAH consortia in 2016 outlining the consensus criteria for the diagnosis of AAH[9], the clinical diagnosis of AAH is based on the presence of typical clinical features as well as laboratory tests that help rule out other causes of liver injury and guide treatment decisions. The most important clinical feature is the onset of jaundice within 8 wk of heavy alcohol consumption overlying a daily consumption that is superior to 40 g/d in women and 60 g/d in men for at least 6 mo. Serum bilirubin level is typically above 3 mg/dL. Other important features include elevated transaminases (aspartate aminotransferase AST > 50, AST to alanine aminotransferase ratio ALT ratio > 1.5) that do not surpass 400 IU/L[9].

The diagnosis of definite, probable, or possible AAH depends on the presence of those typical clinical features as well as laboratory tests that help rule out other causes of liver injury and guide treatment decisions (Table 1)[9,11]. While histological confirmation remains the gold standard, this approach not always necessary when other clinical and laboratory features are clearly suggestive of AAH. Liver biopsy may also help guide treatment decisions in some cases, for example, when there is uncertainty about the severity of liver injury or if drug-induced liver injury is suspected[10]. Histological features of AAH include microvesicular steatosis, periportal Mallory-Denk bodies, and neutrophilic infiltration in the portal areas. Altamirano *et al*[12] proposed an AAH histologic scoring system that included degree of fibrosis, neutrophil infiltration, type of bilirubinostasis, and presence mega-mitochondria. The authors were able to demonstrate that this scoring system was correlated with severity of liver dysfunction as well as mortality. However, this scoring system has not yet been validated in large cohorts and thus not yet routinely used clinically.

While histologic scoring systems may help to assess the severity of AAH, practically, clinical features remain the most important practical determinant of prognosis[8]. Patients with more severe disease are more likely to require hospitalization and have a higher mortality rate. Multiple clinical scoring systems that assess the severity of liver disease of any cause exist, including MELD, Child-Turcotte-Pugh and Chronic Liver Failure Consortium-C (CLIF-C) ACLF (acute-on-chronic liver failure) scores[13]. Some scores were particularly aimed at predicting outcomes in AAH and are widely used including MDF and Age Bilirubin international normalized ratio (INR) Creatinine model (ABIC). Scoring criteria, clinical application and interpretation of relevant AAH prognostic scores are detailed in Table 2. While all these scoring systems have some value, they are far from perfect and need to be interpreted with caution. Head-to-head comparisons of these scores are lacking and it is unclear which, if any, is superior.

Patients with severe AAH have increased short-term mortality rates, causes include portal hypertension complications, multiorgan failure (liver, kidney) and infections[14]. Assessment of the severity of AAH remains a complex task that requires careful clinical evaluation as well as consideration of multiple laboratory and imaging tests. The relevance of clinical prognostic scores to AAH pathophysiology is explained and illustrated in Figure 1.

PROGNOSTIC SCORING SYSTEMS

Maddrey discriminant function

MDF was the first prognostic score found for AAH. It was found through the discriminant analysis of biologic parameters associated with mortality in AAH. This was how, in an early clinical trial, Maddrey *et al*[6] found an independent association with death from AAH between the increase in prothrombin time (PT) and total bilirubin levels at the start of their study.

Discriminant Function = 4.6 × (Pt's PT-control PT) + TBili.

Data on MDF sets the cutoff for severe AAH at 32, where patients with a score lower than 32 have a proven survival rate of 90% at 30 d without steroid therapy, which defines AAH as mild to moderate when MDF < 32. On the other hand, patients with MDF 32 or higher showed mortality exceeding 20%-30% at 30 d (severe AAH = MDF ≥ 32), and can be used as a threshold for initiation steroid therapy if no contraindications exist[15].

MDF was largely used in randomized controlled trials evaluating benefit of steroid therapy in AAH, which reported heterogenous results. In a meta-analysis of 418 patients with AAH, decreased 1-mo mortality after corticosteroid therapy *vs* placebo was proven only in severe AAH (defined as MDF > 32) or in patients with hepatic encephalopathy (relative risk reduction of 36%)[16].

In a post-hoc multivariate analysis of the STOPAH trial (a large study that studied the effect of prednisolone *vs* pentoxifylline on 28-d mortality), treatment with prednisolone displayed significantly improved survival at 28 d, which was limited to short term mortality when MDF > 32. No significant difference in mortality at 90 d or 1 year was found. Of note, the original STOPAH trial did not show any benefit with prednisolone *vs* placebo on 28-d mortality[17]. Because the trial was stopped prematurely (difficult to follow patients out long-term), 33 individuals were not included in 90 d or 1 year follow up and another 159 could not be followed for a full year. Even though the investigators met their goal enrollment of 1026 patients, the lower mortality than expected and use of MDF without liver biopsy probably led to many misclassifications. Furthermore, no taper was used in prednisolone treatment which may have caused harm to patients when they stopped taking the medication.

The above evidence elicits the role of MDF in AAH severity assessment and treatment decisions since it was commonly applied in the concerned trials. However, it has some drawbacks which give grounds for studies on evaluating potential superiority of other scores. MDF is calculated using PT and bilirubin. Despite its wide use in mortality prediction, the MDF lacks some important components which would strongly predict prognosis, such as serum creatinine[18]. Moreover, PT is dependent on the control subject measurement, which creates variability among laboratories. These drawbacks make it mandatory to review research on other scores that might display better performance in AAH mortality prediction than MDF. There have been increasing reports that the MELD can exhibit superiority in AAH mortality prediction compared to MDF[18,19].

MELD score

The MELD is based on INR, bilirubin and creatinine. The new MELD-Na score also encompasses sodium levels. It is a widely used tool in prognostic and severity assessment of AAH. MELD score demonstrates comparable performance to MDF in mortality prediction at 1 mo (Se = 86%, Sp = 86%)[20,21] and at 90 d (Se = 75%, Sp = 75%). For example, a MELD score above 20 predicts 20% mortality at 90 d[22]. Concerning the initiation of corticosteroid therapy in patients with AAH, benefit was proven for patients with MELD > 20, with evidence being the strongest in the range 25 to 39[23]. MELD

Table 1 Alcohol-associated hepatitis diagnosis probability in clinically suspected Alcohol-associated hepatitis[11]

Category	Potential confounding factors[1]	Biopsy indication
Definite AAH	N/A	AAH clinically diagnosed and biopsy proven. Biopsy may inform of the mechanism of injury
Probable AAH	No confounding factors	AAH clinically diagnosed, biopsy not indicated
Possible AAH	Potential confounding factor present	AAH clinically diagnosed but biopsy is indicated for confirmation

[1]Potential confounding factors: (1) Possible ischemic hepatitis (hypotension, severe upper gastrointestinal bleed, cocaine use within 7 d); (2) Possible metabolic liver disease (Wilson disease, alpha 1 antitrypsin deficiency); (3) Hepatotoxic medication within 30 d of onset of jaundice (drug-induced liver injury); (4) Uncertain alcohol intake (if the patient denies excessive alcohol use); (5) Atypical liver function test pattern (aspartate aminotransferase < 50 or > 400 IU/L, aspartate aminotransferase/alanine aminotransferase < 1.5); and (6) positive antinuclear antibody ANA > 1:160 or smooth muscle antibody SMA > 1:80; AAH: Alcohol-associated hepatitis.

Table 2 Alcohol-associated hepatitis prognostic scores: Components, purpose, clinical application and interpretation

Clinical score	Components	Purpose	Clinical application	Interpretation
MELD	INR, bilirubin (total), Creatinine, Sodium	Assess severity of liver disease and predict short-term mortality	Calculate on initial presentation	MELD ≥ 20 = severe AAH
Maddrey Discriminant function	PT (measured and control), bilirubin (total)	Assess severity and prognosis of alcoholic hepatitis	Calculate on initial presentation	MDF ≥ 32 = severe AAH
GAHS	Age, WBC, BUN, Bilirubin, PT (measured and control)	Assess severity and prognosis of alcoholic hepatitis	Calculate on initial presentation	GAHS ≥ 9 = severe AAH
ABIC	Age, bilirubin, INR, PT (measured and control)	Assess prognosis of alcoholic hepatitis in patients on steroid therapy	Use in patients on steroid therapy	< 6.71 low mortality risk; 6.71-8.99 intermediate mortality risk; ≥ 9.00 high mortality risk
Lille score	Age, bilirubin (initial, and day 4 OR day 7), albumin, creatinine, PT	Assess response to corticosteroid therapy in patients with alcoholic hepatitis	Use in patients on steroid therapy, at day 4 and/or day 7 to assess response and indication to continue steroids	< 0.45 at day 4-7 = favorable response to steroid therapy; > 0.45 at day 4-7 = little/no response to steroid therapy
Alcoholic hepatitis histological score	Histologic features of liver injury	Assess severity and prognosis of alcoholic hepatitis	Calculate on biopsy based on: Fibrosis stage, bilirubinostasis, polymorpho-nuclear infiltration, and megamito-chondria	0-3: Mild AAH; 4-5: Moderate AAH; 6-9: Severe AAH

MELD: Model for end-stage liver disease; INR: International normalized ratio; BUN: Blood urea nitrogen; WBC: White blood cells; MDF: Maddrey discriminant function; AAH: Alcohol-associated hepatitis; PT: Prothrombin time; GAHS: Glasgow alcoholic hepatitis score; ABIC: Age-bilirubin-INR-creatinine score.

score is widely used in prioritizing transplant receipt in patients with cirrhosis, that includes patients with severe AAH who are considered to have acute-on-chronic liver failure.

Limitations of MELD score are related to elevated creatinine levels accentuating predicted mortality even when liver function is recovering. Acute kidney injury (AKI) is only one potential complication of AAH, the others (such as portal hypertension, infections, multiorgan failure) are not accounted for in the MELD score. Also, creatinine levels have interpersonal variability with factors such as sex, nutrition, and age, which could also create heterogeneity in MELD score profiles among individuals with similar degrees of hepatic injury, which might not correlate adequately with mortality levels. Sodium levels are also prone to fluctuation related to diuretic/free water administration rather than liver disease. Moreover, it is documented that MELD score for the same individual could differ depending on laboratory measurement of its variables (INR+++ > creatinine > bilirubin)[24-27].

MELD vs MDF: Which score is superior?

Multiple studies have compared MELD and MDF scores in predicting outcomes in AAH. A recent multinational retrospective analysis by Morales-Arráez *et al*[18](n = 2581), proved MELD superiority to MDF with a significant difference in the area under the curve in predicting mortality at 1 mo and 3 mo. The studied population was diversified by recruiting patients throughout 85 tertiary centers in 11 different countries from 3 different continents. The diversity of the population in the study of Morales-Arráez *et al*[18] reinforces findings by a previous analysis of the STOPAH trial by Forrest *et al*[28] in terms of MELD score superiority to MDF in AAH mortality/severity prediction, a finding reflected by

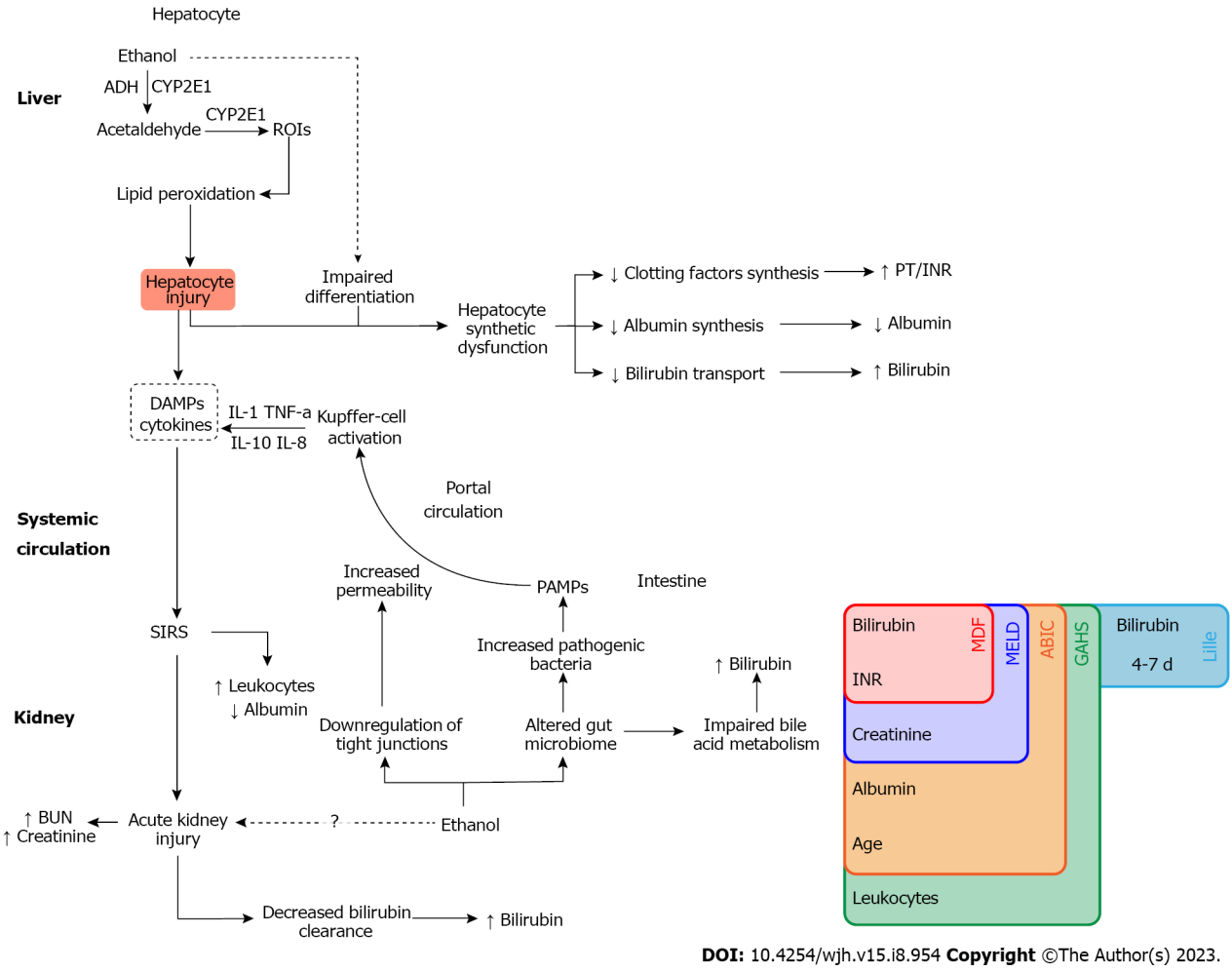

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Figure 1 Pathophysiology of alcohol-associated hepatitis and correlation with prognostic scores. As hepatocytes metabolize ethanol, reactive oxygen species are generated and mediate hepatocyte injury through lipid peroxidation. Injured hepatocytes become unable to adequately perform their functions, this includes albumin and clotting factor synthesis as well as bilirubin transport. Damaged hepatocytes release inflammatory molecules such as danger-associated molecular patterns known as "DAMPs" which favor a systemic inflammatory response system (SIRS). With systemic inflammation, white blood cell count rises, and albumin concentration decreases. SIRS also precipitates acute kidney injury, resulting in a rise in serum creatinine and body urea nitrogen concentrations and causes decreased bilirubin clearance. Large amounts of ethanol alter the gut microbiome and increase intestinal permeability through the downregulation of tight junctions which impairs bile acid metabolism. Furthermore, there is favored growth of pathogenic bacteria that pathogen-associated molecular patterns (PAMPs). PAMPs reach the portal circulation through increased intestinal permeability and activate Kupffer cells in the liver. Which in turn amplifies systemic inflammation and the resulting consequences through cytokine secretion[8]. PAMP: Pathogen-associated molecular patterns; SIRS: Systemic inflammatory response system; BUN: Blood urea nitrogen; MDF: Maddrey discriminant function; INR: International normalized ratio; MELD: Model for end-stage liver disease; GAHS: Glasgow alcoholic hepatitis score; PT: Prothrombin time.

multiple other database analyses of more homogeneous populations around the world[29-31]. More details on the advantages and disadvantages of both scores as well as differences in scoring criteria are listed in Table 3. To analyze the evidence mentioned above: Despite the disadvantages of including creatinine levels in the MELD score and the abundance of MDF use and validation in early AAH trials, accounting for AKI in AAH prognosis is a large advantage of the MELD score over MDF as it addresses an important determinant of AAH mortality. Furthermore, using INR minimizes laboratory-dependent differences in PT values which provides a notable advantage to using MELD over MDF.

A glimpse of other prognostic scores

Glasgow alcoholic hepatitis score: It is based on total bilirubin, age, blood urea nitrogen (BUN), PT and leukocyte count (white blood cell count; WBC). WBC and BUN are variables unique to GAH. GAH has demonstrated superior specificity and accuracy in predicting mortality in comparison to MDF or MELD, however GAH sensitivity to 1- and 3-mo mortality is inferior to MDF or MELD[32]. While the concern for short-term mortality of AAH is substantial, a test with high sensitivity is preferred. GAH adds benefit in clinical decision making by complementing MDF: If MDF > 32, a GAHS 9 or greater is more accurate in predicting mortality, therefore in filtering steroid treatment indications. GAHS was only studied in a relatively homogenous population from one country, population, thus making it solely validated in the United Kingdom[33].

The ABIC model: Age, bilirubin, INR and serum creatinine level classifies patients into categories according to their survival risk. Risk groups are low, medium, and high, with respective survival rates of 100%-70%-25%. ABIC model is

Table 3 Alcohol-associated hepatitis prognostic scores advantages and limitations

Clinical score	Components	Advantages	Limitations
MELD	INR, bilirubin (total), creatinine, sodium	MELD or MELD-Na ≥ 20 predicts high mortality at 30 d, consider corticosteroid therapy	(1) Mortality overestimation with elevated creatinine levels; (2) interpersonal variability of creatinine levels; (3) extrahepatic causes of sodium fluctuations; and (4) does not account for markers of AAH complications other than kidney and liver failure
Maddrey discriminant function	PT (measured and control), bilirubin (total)	MDF ≥ 32 predicts high mortality at 30 d, consider corticosteroid therapy. Oldest, most commonly used score	(1) AKI and other AAH complications not reflected in MDF; (2) PT use instead of INR; and (3) low specificity
GAHS	Age, WBC, BUN, bilirubin, PT (measured and control)	GAHS ≥ 9 is in favor of high mortality, helpful for selecting candidates for steroid treatment	(1) Only studied on the British population; and (2) lower sensitivity for short-term mortality compared to MELD/MDF
ABIC	Age, Bilirubin, INR, PT (measured and control)	Score < 6.71 has high negative predictive value to detect patients with low risk	(1) Not used for deciding on steroid initiation; and (2) low accuracy for predicting mortality in severe group
Lille score	Age, bilirubin (initial, and day 4 OR day 7), albumin, creatinine, and PT	Lille score ≤ 0.45 at day 7 (or 4) implies good response to corticosteroids	(1) Complex to calculate; (2) uses PT instead of INR; and (3) bias secondary to elevated creatinine levels and interpersonal variability of creatinine
Alcoholic hepatitis histological score	Histologic features of liver injury	Can be combined with clinical prognostic scores for more accurate mortality risk stratification	(1) Requires liver biopsy (invasive); and (2) static

MELD: Model for end-stage liver disease; INR: International normalized ratio; BUN: Blood urea nitrogen; AKI: Acute kidney injury; WBC: White blood cells; MDF: Maddrey discriminant function; AAH: Alcohol-associated hepatitis; PT: Prothrombin time; GAHS: Glasgow alcoholic hepatitis score; ABIC: Age-bilirubin-INR-creatinine score.

helpful in prognosticating patients with AAH who were initiated on steroid treatment. However, ABIC model is not commonly used in assessing the indications for treatment initiation[34].

Static vs dynamic scores

As stativity brings bias into prognostic scoring for multiple reasons, some of which are mentioned above, dynamic scoring has been proposed and studied. Lille score adds dynamicity through the incorporation of bilirubin levels at 2 points in time: baseline levels and levels at day 7 of steroid therapy. Lille score is based on the concept that a decrease in bilirubin levels at the first week of treatment is a sign of good prognosis meaning that a score lower than 0.45 is suggestive of steroid treatment benefits outweighing the risks[35]. On the other hand, a Lille score higher than 0.45 reflects a lack of response to steroids and therefore a low likelihood of benefiting from additional days of treatment[36]. New studies are in favor of calculating Lille score at day 4 with comparable performance to day 7, this reduces the limitation of having to wait for 7 d[37].

Despite recent studies favoring MELD over MDF, combining MELD score (static) with Lille score (dynamic) would be interesting to evaluate on large populations in future studies on this matter given fluctuating course of disease, need for treatment response assessment and superior performance of combinations compared to single scores.

One limitation of clinical prognostic scores is performance in the long term. Few studies evaluate long term performance. In one of the studies, mortality of AAH patients at 1 year was found to be significantly lower when MELD < 20, 10.4% *vs* 31.4% MELD > 20 (P < 0.001)[38]. In another retrospective study, patients with MDF < 32 had a 50% mortality at 5 years, but the study did not feature any comparison to patients with MDF > 32[39]. In a comparison of the most commonly used scores in 44 patients with biopsy proven AAH: GAHS, MDF, MELD, and ABIC scores all performed poorly in survival prediction after the 6-mo mark[40].

Prognostication of AAH presenting as acute on chronic liver failure

Alcohol is an important trigger for decompensation of chronic liver disease, including ACLF. The AAH scores mentioned above fail to encompass multiple organ failure beyond acute kidney injury. ACLF prognostic scores are applied to patients with severe AAH complicated by organ failure as mortality rates are similar in ACLF whether infection or AAH are incriminated. Notable prognostic scores for ACLF are: CLIF-C (European) ACLF, Asian Pacific Association for the Study of the Liver acute-on-chronic liver failure Research Consortium (AARC), North American Consortium for the Study of End-Stage Liver Disease (NACSELD)[41].

Clinical score correlation with histologic severity

As previously discussed, clinical data is the cornerstone of AAH prognostication. Histologic severity has been studied, with AHHS (alcoholic hepatitis histological score) being proposed by Altamirano *et al*[12] to predict 90-d mortality through the combination of histological parameters that were most strongly associated to death. Overall, no statistical difference was found among MELD, ABIC and AHHS in 90-d mortality prediction. However, there are cases with added

benefit to combining clinical and histological scores. In patients with MELD < 21, 90-d survival was higher when AHHS was < 5 compared to 5 or higher (94% *vs* 72%; *P* = 0.001). Similarly, patients with ABIC B (medium risk) and AHHS < 5 have shown a potentially lower risk of death at 90 d, *vs* a moderate risk of death at 90 d (95% *vs* 70% survival, *P* = 0.003) for ABIC B patients with AHHS 5 or higher[12,42].

Role of artificial intelligence in AAH prognostication

As artificial intelligence (AI) has been more commonly incorporated in health care, there have been attempts of optimizing AAH prognostication through AI. Of note, a multicenter retrospective cohort by Kezer *et al*[43] validated a new 30-d mortality scoring system based on age, BUN, albumin, bilirubin and INR. The score was derived through AI: The Mortality Index for Alcohol-Associated Hepatitis. Performance showed comparable accuracy to clinical scores, however superiority was only demonstrated compared to MDF but not to MELD[43].

In a recent abstract by Dunn *et al*[44], a new AI-generated score was created with the aim of predicting 90-d survival in AAH and validated in a multicenter international retrospective cohort. The score incorporates age, INR, bilirubin, creatinine, albumin, blood urea nitrogen and neutrophil to lymphocyte ratio. The abstract reports statistical superiority to MDF, MELD, MELD-Na, MELD 3.0. ABIC, GAHS. Steroid use showed decreased mortality at 30 d in those with ALCHAIN score 0.30-0.70.

ROLE OF SCORING SYSTEMS IN PREDICTING KIDNEY INJURY

As previously discussed, AAH elevated short-term mortality correlates with numerous complications, developing AKI is one of them. AKI is an important prognostic determinant in AAH, which makes predicting AKI risk in a patient with AAH an important step in management. It has been demonstrated that patients with liver failure and/or fulfillment of the SIRS criteria in addition to the nephrotoxic effects of alcohol are linked to the occurrence of AKI[45-47].

In a multicentric prospective cohort conducted by Sujan *et al*[48], AAH with AKI were more likely to have hepatic encephalopathy, SIRS criteria upon admission, higher MELD, baseline bilirubin, creatinine and INR. In a second phase, the study developed a risk score for AKI. AUROC was 0.74 (95%CI: 0.69-0.80; *P* < 0.001). AKI risk score incorporates SIRS, hepatic encephalopathy presence and MELD score on admission. The score stratifies AKI risk to three categories: Low (< 3), moderate (3-4), and high (> 4). Patients with AKI risk score classified as high had significantly higher short-term mortality compared to those with moderate and low AKI risk scores (90-d survival respectively 47% *vs* 68% *vs* 88%, *P* value < 0.001)[48].

PREDICTING ALCOHOL RECIDIVISM

Treating AAH includes minimizing the risk for recurrence. Alcohol recidivism prediction is routinely done when evaluating patients for liver transplant. In the United States, 6 mo of alcohol abstinence are usually required for liver transplant (LT) consideration in most centers. This period is useful in terms of observing patients with AAH for clinical improvement/adherence to the treatment plan (abstinence), and even possibly the dissipation of the need for LT. However, the pitfall of the 6-month abstinence condition involves depriving patients with overall poor prognosis and high mortality rates from receiving a curative intervention[49].

Parallel to AAH severity scoring tools, Sustained alcohol use post-liver transplantation score, Stanford Integrated Psychosocial Assessment for Transplantation, Alcohol Relapse Risk Assessment, and High-Risk Alcoholism Relapse are all scores developed to be used when considering patients with AAH for LT. So far, these scores have not formally been used alone for selecting LT candidates given the high stakes. More studies are required to optimize our understanding of their reliability[50].

CONCLUSION

The mortality of patients with severe AAH emphasizes the need for accurate prognostication when managing cases of AAH. Many clinical scores have been studied and used, the most common notable being MELD, MDF and Lille score. While MDF is the oldest and the most popularly used score (MDF > 32) to determine the indication for corticosteroid initiation in AAH, MELD score has been increasingly showing superiority in assessing AAH severity. Dynamic prognostication is superior to static. Therefore, initiating steroids for a MELD of 20 or above and continuing them for a day 7 Lille score < 0.45 (favorable response to steroids) is the logical approach towards managing severe AAH. However, more research on AAH is necessary to improve our understanding of the major driving factors that will lead the way to improving our prediction models.

FOOTNOTES

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REFERENCES

1 **Seitz HK**, Bataller R, Cortez-Pinto H, Gao B, Gual A, Lackner C, Mathurin P, Mueller S, Szabo G, Tsukamoto H. Alcoholic liver disease. *Nat Rev Dis Primers* 2018; **4**: 16 [PMID: 30115921 DOI: 10.1038/s41572-018-0014-7]
2 **Hughes E**, Hopkins LJ, Parker R. Survival from alcoholic hepatitis has not improved over time. *PLoS One* 2018; **13**: e0192393 [PMID: 29444123 DOI: 10.1371/journal.pone.0192393]
3 **Sohal A**, Khalid S, Green V, Gulati A, Roytman M. The Pandemic Within the Pandemic: Unprecedented Rise in Alcohol-related Hepatitis During the COVID-19 Pandemic. *J Clin Gastroenterol* 2022; **56**: e171-e175 [PMID: 34653062 DOI: 10.1097/MCG.0000000000001627]
4 **Yeo YH**, He X, Ting PS, Zu J, Almario CV, Spiegel BMR, Ji F. Evaluation of Trends in Alcohol Use Disorder-Related Mortality in the US Before and During the COVID-19 Pandemic. *JAMA Netw Open* 2022; **5**: e2210259 [PMID: 35507347 DOI: 10.1001/jamanetworkopen.2022.10259]
5 **Bittermann T**, Mahmud N, Abt P. Trends in Liver Transplantation for Acute Alcohol-Associated Hepatitis During the COVID-19 Pandemic in the US. *JAMA Netw Open* 2021; **4**: e2118713 [PMID: 34323988 DOI: 10.1001/jamanetworkopen.2021.18713]
6 **Maddrey WC**, Boitnott JK, Bedine MS, Weber FL Jr, Mezey E, White RI Jr. Corticosteroid therapy of alcoholic hepatitis. *Gastroenterology* 1978; **75**: 193-199 [PMID: 352788 DOI: 10.1016/0016-5085(78)90401-8]
7 **Trabut JB**, Thépot V, Sogni P, Pol S. [Alcoholic hepatitis]. *Rev Med Interne* 2012; **33**: 311-317 [PMID: 22425133 DOI: 10.1016/j.revmed.2012.02.002]
8 **Bataller R**, Arab JP, Shah VH. Alcohol-Associated Hepatitis. *N Engl J Med* 2022; **387**: 2436-2448 [PMID: 36577100 DOI: 10.1056/NEJMra2207599]
9 **Crabb DW**, Bataller R, Chalasani NP, Kamath PS, Lucey M, Mathurin P, McClain C, McCullough A, Mitchell MC, Morgan TR, Nagy L, Radaeva S, Sanyal A, Shah V, Szabo G; NIAAA Alcoholic Hepatitis Consortia. Standard Definitions and Common Data Elements for Clinical Trials in Patients With Alcoholic Hepatitis: Recommendation From the NIAAA Alcoholic Hepatitis Consortia. *Gastroenterology* 2016; **150**: 785-790 [PMID: 26921783 DOI: 10.1053/j.gastro.2016.02.042]
10 **Singal AK**, Bataller R, Ahn J, Kamath PS, Shah VH. ACG Clinical Guideline: Alcoholic Liver Disease. *Am J Gastroenterol* 2018; **113**: 175-194 [PMID: 29336434 DOI: 10.1038/ajg.2017.469]
11 **Crabb DW**, Im GY, Szabo G, Mellinger JL, Lucey MR. Diagnosis and Treatment of Alcohol-Associated Liver Diseases: 2019 Practice Guidance From the American Association for the Study of Liver Diseases. *Hepatology* 2020; **71**: 306-333 [PMID: 31314133 DOI: 10.1002/hep.30866]
12 **Altamirano J**, Miquel R, Katoonizadeh A, Abraldes JG, Duarte-Rojo A, Louvet A, Augustin S, Mookerjee RP, Michelena J, Smyrk TC, Buob D, Leteurtre E, Rincón D, Ruiz P, García-Pagán JC, Guerrero-Marquez C, Jones PD, Barritt AS 4th, Arroyo V, Bruguera M, Bañares R, Ginès P, Caballería J, Roskams T, Nevens F, Jalan R, Mathurin P, Shah VH, Bataller R. A histologic scoring system for prognosis of patients with alcoholic hepatitis. *Gastroenterology* 2014; **146**: 1231-9.e1 [PMID: 24440674 DOI: 10.1053/j.gastro.2014.01.018]
13 **Barosa R**, Roque Ramos L, Patita M, Nunes G, Fonseca J. CLIF-C ACLF score is a better mortality predictor than MELD, MELD-Na and CTP in patients with Acute on chronic liver failure admitted to the ward. *Rev Esp Enferm Dig* 2017; **109**: 399-405 [PMID: 28467096 DOI: 10.17235/reed.2017.4701/2016]
14 **Jinjuvadia R**, Liangpunsakul S; Translational Research and Evolving Alcoholic Hepatitis Treatment Consortium. Trends in Alcoholic Hepatitis-related Hospitalizations, Financial Burden, and Mortality in the United States. *J Clin Gastroenterol* 2015; **49**: 506-511 [PMID: 25198164 DOI: 10.1097/MCG.0000000000000161]
15 **Lucey MR**, Mathurin P, Morgan TR. Alcoholic hepatitis. *N Engl J Med* 2009; **360**: 2758-2769 [PMID: 19553649 DOI: 10.1056/NEJMra0805786]
16 **Louvet A**, Thursz MR, Kim DJ, Labreuche J, Atkinson SR, Sidhu SS, O'Grady JG, Akriviadis E, Sinakos E, Carithers RL Jr, Ramond MJ, Maddrey WC, Morgan TR, Duhamel A, Mathurin P. Corticosteroids Reduce Risk of Death Within 28 Days for Patients With Severe Alcoholic Hepatitis, Compared With Pentoxifylline or Placebo-a Meta-analysis of Individual Data From Controlled Trials. *Gastroenterology* 2018; **155**: 458-468.e8 [PMID: 29738698 DOI: 10.1053/j.gastro.2018.05.011]
17 **Thursz MR**, Richardson P, Allison M, Austin A, Bowers M, Day CP, Downs N, Gleeson D, MacGilchrist A, Grant A, Hood S, Masson S, McCune A, Mellor J, O'Grady J, Patch D, Ratcliffe I, Roderick P, Stanton L, Vergis N, Wright M, Ryder S, Forrest EH; STOPAH Trial. Prednisolone or pentoxifylline for alcoholic hepatitis. *N Engl J Med* 2015; **372**: 1619-1628 [PMID: 25901427 DOI: 10.1056/NEJMoa1412278]
18 **Morales-Arráez D**, Ventura-Cots M, Altamirano J, Abraldes JG, Cruz-Lemini M, Thursz MR, Atkinson SR, Sarin SK, Kim W, Chavez-

Araujo R, Higuera-de la Tijera MF, Singal AK, Shah VH, Kamath PS, Duarte-Rojo A, Charles EA, Vargas V, Jager M, Rautou PE, Rincon D, Zamarripa F, Restrepo-Gutiérrez JC, Torre A, Lucey MR, Arab JP, Mathurin P, Louvet A, García-Tsao G, González JA, Verna EC, Brown RS Jr, Argemi J, Fernández-Carillo C, Clemente A, Alvarado-Tapias E, Forrest E, Allison M, Bataller R. The MELD Score Is Superior to the Maddrey Discriminant Function Score to Predict Short-Term Mortality in Alcohol-Associated Hepatitis: A Global Study. *Am J Gastroenterol* 2022; **117**: 301-310 [PMID: 34962498 DOI: 10.14309/ajg.0000000000001596]

19 **Srikureja W**, Kyulo NL, Runyon BA, Hu KQ. MELD score is a better prognostic model than Child-Turcotte-Pugh score or Discriminant Function score in patients with alcoholic hepatitis. *J Hepatol* 2005; **42**: 700-706 [PMID: 15826720 DOI: 10.1016/j.jhep.2004.12.022]

20 **Sheth M**, Riggs M, Patel T. Utility of the Mayo End-Stage Liver Disease (MELD) score in assessing prognosis of patients with alcoholic hepatitis. *BMC Gastroenterol* 2002; **2**: 2 [PMID: 11835693 DOI: 10.1186/1471-230x-2-2]

21 **Mathurin P**, O'Grady J, Carithers RL, Phillips M, Louvet A, Mendenhall CL, Ramond MJ, Naveau S, Maddrey WC, Morgan TR. Corticosteroids improve short-term survival in patients with severe alcoholic hepatitis: meta-analysis of individual patient data. *Gut* 2011; **60**: 255-260 [PMID: 20940288 DOI: 10.1136/gut.2010.224097]

22 **Dunn W**, Jamil LH, Brown LS, Wiesner RH, Kim WR, Menon KV, Malinchoc M, Kamath PS, Shah V. MELD accurately predicts mortality in patients with alcoholic hepatitis. *Hepatology* 2005; **41**: 353-358 [PMID: 15660383 DOI: 10.1002/hep.20503]

23 **Arab JP**, Díaz LA, Baeza N, Idalsoaga F, Fuentes-López E, Arnold J, Ramírez CA, Morales-Arraez D, Ventura-Cots M, Alvarado-Tapias E, Zhang W, Clark V, Simonetto D, Ahn JC, Buryska S, Mehta TI, Stefanescu H, Horhat A, Bumbu A, Dunn W, Attar B, Agrawal R, Haque ZS, Majeed M, Cabezas J, García-Carrera I, Parker R, Cuyàs B, Poca M, Soriano G, Sarin SK, Maiwall R, Jalal PK, Abdulsada S, Higuera-de la Tijera MF, Kulkarni AV, Rao PN, Guerra Salazar P, Skladaný L, Bystrianska N, Prado V, Clemente-Sanchez A, Rincón D, Haider T, Chacko KR, Cairo F, de Sousa Coelho M, Romero GA, Pollarsky FD, Restrepo JC, Castro-Sanchez S, Toro LG, Yaquich P, Mendizabal M, Garrido ML, Narvaez A, Bessone F, Marcelo JS, Piombino D, Dirchwolf M, Arancibia JP, Altamirano J, Kim W, Araujo RC, Duarte-Rojo A, Vargas V, Rautou PE, Issoufaly T, Zamarripa F, Torre A, Lucey MR, Mathurin P, Louvet A, García-Tsao G, González JA, Verna E, Brown RS, Roblero JP, Abraldes JG, Arrese M, Shah VH, Kamath PS, Singal AK, Bataller R. Identification of optimal therapeutic window for steroid use in severe alcohol-associated hepatitis: A worldwide study. *J Hepatol* 2021; **75**: 1026-1033 [PMID: 34166722 DOI: 10.1016/j.jhep.2021.06.019]

24 **Lisman T**, van Leeuwen Y, Adelmeijer J, Pereboom IT, Haagsma EB, van den Berg AP, Porte RJ. Interlaboratory variability in assessment of the model of end-stage liver disease score. *Liver Int* 2008; **28**: 1344-1351 [PMID: 18482269 DOI: 10.1111/j.1478-3231.2008.01783.x]

25 **Al-Saeedi M**, Yassein T, Schultze D, Nickkholgh A, Bruns H, Zorn M, Hinz U, Ganten TM, Schemmer P. Impact of Inter-Laboratory Variability on Model of End-Stage Liver Disease (MELD) Score Calculation. *Ann Transplant* 2016; **21**: 675-682 [PMID: 27799654 DOI: 10.12659/aot.899241]

26 **Trotter JF**, Olson J, Lefkowitz J, Smith AD, Arjal R, Kenison J. Changes in international normalized ratio (INR) and model for endstage liver disease (MELD) based on selection of clinical laboratory. *Am J Transplant* 2007; **7**: 1624-1628 [PMID: 17511686 DOI: 10.1111/j.1600-6143.2007.01822.x]

27 **Cholongitas E**, Marelli L, Kerry A, Senzolo M, Goodier DW, Nair D, Thomas M, Patch D, Burroughs AK. Different methods of creatinine measurement significantly affect MELD scores. *Liver Transpl* 2007; **13**: 523-529 [PMID: 17323365 DOI: 10.1002/Lt.20994]

28 **Forrest EH**, Atkinson SR, Richardson P, Masson S, Ryder S, Thursz MR, Allison M; STOPAH trial Management Group. Application of prognostic scores in the STOPAH trial: Discriminant function is no longer the optimal scoring system in alcoholic hepatitis. *J Hepatol* 2018; **68**: 511-518 [PMID: 29175535 DOI: 10.1016/j.jhep.2017.11.017]

29 **Kadian M**, Kakkar R, Dhar M, Kaushik RM. Model for end-stage liver disease score versus Maddrey discriminant function score in assessing short-term outcome in alcoholic hepatitis. *J Gastroenterol Hepatol* 2014; **29**: 581-588 [PMID: 24117536 DOI: 10.1111/jgh.12400]

30 **Goyal SK**, Dixit VK, Jain AK, Mohapatra PK, Ghosh JK. Assessment of the Model for End-stage Liver Disease (MELD) Score in Predicting Prognosis of Patients with Alcoholic Hepatitis. *J Clin Exp Hepatol* 2014; **4**: 19-24 [PMID: 25755531 DOI: 10.1016/j.jceh.2014.02.006]

31 **Louvet A**, Labreuche J, Artru F, Boursier J, Kim DJ, O'Grady J, Trépo E, Nahon P, Ganne-Carrié N, Naveau S, Diaz E, Gustot T, Lassailly G, Cannesson-Leroy A, Canva-Delcambre V, Dharancy S, Park SH, Moreno C, Morgan TR, Duhamel A, Mathurin P. Combining Data From Liver Disease Scoring Systems Better Predicts Outcomes of Patients With Alcoholic Hepatitis. *Gastroenterology* 2015; **149**: 398-406.e8; quiz e16 [PMID: 25935634 DOI: 10.1053/j.gastro.2015.04.044]

32 **Forrest EH**, Evans CD, Stewart S, Phillips M, Oo YH, McAvoy NC, Fisher NC, Singhal S, Brind A, Haydon G, O'Grady J, Day CP, Hayes PC, Murray LS, Morris AJ. Analysis of factors predictive of mortality in alcoholic hepatitis and derivation and validation of the Glasgow alcoholic hepatitis score. *Gut* 2005; **54**: 1174-1179 [PMID: 16009691 DOI: 10.1136/gut.2004.050781]

33 **Forrest EH**, Morris AJ, Stewart S, Phillips M, Oo YH, Fisher NC, Haydon G, O'Grady J, Day CP. The Glasgow alcoholic hepatitis score identifies patients who may benefit from corticosteroids. *Gut* 2007; **56**: 1743-1746 [PMID: 17627961 DOI: 10.1136/gut.2006.099226]

34 **Dominguez M**, Rincón D, Abraldes JG, Miquel R, Colmenero J, Bellot P, García-Pagán JC, Fernández R, Moreno M, Bañares R, Arroyo V, Caballería J, Ginès P, Bataller R. A new scoring system for prognostic stratification of patients with alcoholic hepatitis. *Am J Gastroenterol* 2008; **103**: 2747-2756 [PMID: 18721242 DOI: 10.1111/j.1572-0241.2008.02104.x]

35 **Mathurin P**, Abdelnour M, Ramond MJ, Carbonell N, Fartoux L, Serfaty L, Valla D, Poupon R, Chaput JC, Naveau S. Early change in bilirubin levels is an important prognostic factor in severe alcoholic hepatitis treated with prednisolone. *Hepatology* 2003; **38**: 1363-1369 [PMID: 14647046 DOI: 10.1016/j.hep.2003.09.038]

36 **Louvet A**, Naveau S, Abdelnour M, Ramond MJ, Diaz E, Fartoux L, Dharancy S, Texier F, Hollebecque A, Serfaty L, Boleslawski E, Deltenre P, Canva V, Pruvot FR, Mathurin P. The Lille model: a new tool for therapeutic strategy in patients with severe alcoholic hepatitis treated with steroids. *Hepatology* 2007; **45**: 1348-1354 [PMID: 17518367 DOI: 10.1002/hep.21607]

37 **Garcia-Saenz-de-Sicilia M**, Duvoor C, Altamirano J, Chavez-Araujo R, Prado V, de Lourdes Candolo-Martinelli A, Holanda-Almeida P, Becerra-Martins-de-Oliveira B, Fernandez-de-Almeida S, Bataller R, Caballeria J, Duarte-Rojo A. A Day-4 Lille Model Predicts Response to Corticosteroids and Mortality in Severe Alcoholic Hepatitis. *Am J Gastroenterol* 2017; **112**: 306-315 [PMID: 27922027 DOI: 10.1038/ajg.2016.539]

38 **Samala N**, Gawrieh S, Tang Q, Lourens SG, Shah VH, Sanyal AJ, Liangpunsakul S, Chalasani N. Clinical Characteristics and Outcomes of Mild to Moderate Alcoholic Hepatitis. *GastroHep* 2019; **1**: 161-165 [PMID: 32952446 DOI: 10.1002/ygh2.353]

39 **Degré D**, Stauber RE, Englebert G, Sarocchi F, Verset L, Rainer F, Spindelboeck W, Njimi H, Trépo E, Gustot T, Lackner C, Deltenre P, Moreno C. Long-term outcomes in patients with decompensated alcohol-related liver disease, steatohepatitis and Maddrey's discriminant function <32. *J Hepatol* 2020; **72**: 636-642 [PMID: 31954208 DOI: 10.1016/j.jhep.2019.12.023]

40 **Palaniyappan N**, Subramanian V, Ramappa V, Ryder SD, Kaye P, Aithal GP. The utility of scoring systems in predicting early and late

mortality in alcoholic hepatitis: whose score is it anyway? *Int J Hepatol* 2012; **2012**: 624675 [PMID: 22988517 DOI: 10.1155/2012/624675]

41 **Ballester MP**, Sittner R, Jalan R. Alcohol and Acute-on-Chronic Liver Failure. *J Clin Exp Hepatol* 2022; **12**: 1360-1370 [PMID: 36157143 DOI: 10.1016/j.jceh.2021.12.010]

42 **Liangpunsakul S**, Kleiner DE. The alcoholic hepatitis histologic score: structured prognostic biopsy evaluation comes to alcoholic hepatitis. *Gastroenterology* 2014; **146**: 1156-1158 [PMID: 24680970 DOI: 10.1053/j.gastro.2014.03.016]

43 **Kezer CA**, Buryska SM, Ahn JC, Harmsen WS, Dunn W, Singal AK, Arab JP, Díaz LA, Arnold J, Kamath PS, Shah VH, Simonetto DA. The Mortality Index for Alcohol-Associated Hepatitis: A Novel Prognostic Score. *Mayo Clin Proc* 2022; **97**: 480-490 [PMID: 35181163 DOI: 10.1016/j.mayocp.2021.10.026]

44 **Dunn W**, Yanming L, Pablo J. An Artificial Intelligence-Generated Model From A Global Cohort To Predict 90-Day Survival In Alcohol-Associated Hepatitis. *Hepatology* 2022; **76**: 125 [DOI: 10.1016/j.aohep.2023.101035]

45 **Maiwall R**, Chandel SS, Wani Z, Kumar S, Sarin SK. SIRS at Admission Is a Predictor of AKI Development and Mortality in Hospitalized Patients with Severe Alcoholic Hepatitis. *Dig Dis Sci* 2016; **61**: 920-929 [PMID: 26470868 DOI: 10.1007/s10620-015-3921-4]

46 **Michelena J**, Altamirano J, Abraldes JG, Affò S, Morales-Ibanez O, Sancho-Bru P, Dominguez M, García-Pagán JC, Fernández J, Arroyo V, Ginès P, Louvet A, Mathurin P, Mehal WZ, Caballería J, Bataller R. Systemic inflammatory response and serum lipopolysaccharide levels predict multiple organ failure and death in alcoholic hepatitis. *Hepatology* 2015; **62**: 762-772 [PMID: 25761863 DOI: 10.1002/hep.27779]

47 **Bagshaw SM**, Laupland KB, Doig CJ, Mortis G, Fick GH, Mucenski M, Godinez-Luna T, Svenson LW, Rosenal T. Prognosis for long-term survival and renal recovery in critically ill patients with severe acute renal failure: a population-based study. *Crit Care* 2005; **9**: R700-R709 [PMID: 16280066 DOI: 10.1186/cc3879]

48 **Sujan R**, Cruz-Lemini M, Altamirano J, Simonetto DA, Maiwall R, Axley P, Richardson T, Desai V, Cabezas J, Vargas V, Kamath PS, Shah VH, Sarin SK, Bataller R, Singal AK. A Validated Score Predicts Acute Kidney Injury and Survival in Patients With Alcoholic Hepatitis. *Liver Transpl* 2018; **24**: 1655-1664 [PMID: 30153377 DOI: 10.1002/lt.25328]

49 **Bhatti S**, Kim D, Ahmed A, Cholankeril G. Current Trends in Liver Transplantation for Alcoholic Hepatitis. *Clin Liver Dis* 2021; **25**: 625-634 [PMID: 34229844 DOI: 10.1016/j.cld.2021.04.002]

50 **Shenoy A**, Dienstag A, Dienstag P, Ford L, Schubert E, Wankoff M, Mohan K, Mirza O, Bhardwaj M, Im G. Scoring systems to assess relapse risk in alcohol use disorder presenting for early liver transplantation: A systematic review. *Gen Hosp Psychiatry* 2021; **72**: 23-30 [PMID: 34229280 DOI: 10.1016/j.genhosppsych.2021.06.012]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Tenofovir alafenamide significantly increased serum lipid levels compared with entecavir therapy in chronic hepatitis B virus patients

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Abstract

BACKGROUND

Tenofovir alafenamide (TAF) has a serum lipid-raising effect in patients with HIV; however, its effect on serum lipids and nonalcoholic fatty liver disease (NAFLD) risk in patients with chronic hepatitis B (CHB) is unclear.

AIM

To compare the effects of TAF and entecavir (ETV) on serum lipid levels in patients with CHB.

METHODS

In this retrospective cohort study, the data including the clinical features, serum lipids, and metabolic factors of patients with CHB at baseline and approximately 1 year after TAF or ETV treatment were collected and analyzed. We used propensity score-matched models to assess the effects on high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol (TCHO).

RESULTS

A total of 336 patients (75.60% male) were included; 63.69% received TAF and 36.31% received ETV. Compared with the ETV group, the TAF group had significantly higher TCHO levels after treatment (4.67 ± 0.90 *vs* 4.36 ± 1.05, $P = 0.006$). In a propensity score-matched model for body mass index, age, sex, smoking, drinking, presence of comorbidities such as NAFLD, cirrhosis, diabetes mellitus, and hypertension, TAF-treated patients had significantly increased TCHO levels compared to that at baseline ($P = 0.019$). There was no difference for the ETV group. Body mass index, sex, hypertension, baseline TCHO, and creatine kinase-MB isoenzyme levels were significantly associated with elevated TCHO levels in logistic regression analysis. However, 1-year TAF treatment did not increase the incidence of NAFLD.

CONCLUSION

A greater increase in TCHO was observed in patients with CHB receiving TAF compared to those receiving ETV. However, TAF-induced dyslipidemia did not increase the incidence of NAFLD.

Key Words: Tenofovir alafenamide; Entecavir; Hepatitis B virus; Serum lipid; Metabolic factor

Core Tip: This study compared the effects of tenofovir alafenamide (TAF) and entecavir on serum lipid levels in chronic hepatitis B patients. The results suggested that TAF-treated patients had significantly increased triglycerides, and total cholesterol levels compared to that at baseline, while there was no difference in the entecavir group. However, dyslipidemia caused by TAF therapy did not increase the incidence of nonalcoholic fatty liver disease. Our findings indicated that the potential impact of anti-viral therapy on the lipid profile may be an important consideration in the treatment choices for chronic hepatitis B patients with abnormal metabolic factors.

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INTRODUCTION

Hepatitis B virus (HBV) infects approximately 240 million people worldwide, including approximately 86 million people in China[1]. Chronic hepatitis B (CHB) may lead to decompensation of cirrhosis and hepatocellular carcinoma (HCC), which are the leading causes of mortality in patients with CHB[2]. Nonalcoholic fatty liver disease (NAFLD) is a hepatic manifestation of metabolic syndrome (MetS), with a cumulative prevalence of 24% worldwide[3]. In recent decades, the prevalence of NAFLD has significantly increased in China, leading to the coexistence of NAFLD and CHB. Dyslipidemia, which is characterized by high triglyceride (TG), high total cholesterol (TCHO), low high-density lipoprotein (HDL), and high low-density lipoprotein levels, is strongly associated with NAFLD and MetS[4].

Interferon and nucleoside analog therapies cannot completely eradicate HBV infection[5]. Many patients require long-term anti-HBV therapy with potent oral drugs tenofovir alafenamide (TAF) and entecavir (ETV), which are recommended as first-line treatment in HBV clinical practice guidelines[6]. TAF has also recently been incorporated into antiretroviral regimens for people with HIV, and we observed its impact on serum lipid levels in these individuals. A prospective cohort study showed that patients with HIV infection treated with a TAF-containing regimen had significantly worse blood lipid levels, especially those with higher LDL and TCHO[7]. In a recent real-world study, switching from tenofovir disoproxil fumarate (TDF) to a TAF-containing regimen in HIV-infected patients resulted in a significant increase in serum lipid profiles[8]. However, data on the effects of TAF on serum lipid levels in patients with HIV may be limited by the potentially confounding effects of concomitant antiretroviral HIV drugs.

The effect of ETV on serum lipid profiles has not yet been reported in postmarketing studies. A retrospective cohort study showed greater reductions in TCHO, LDL, and HDL levels in patients with CHB treated with TDF than in those treated with ETV[9]. TAF is considered the successor of TDF; however, no studies have compared the effects of TAF and ETV on lipid profiles in HBV-treated patients. Meanwhile, there are limited data on the effects of TAF on metabolism-related complications in real-world settings. Therefore, this retrospective cohort study aimed to characterize the effect of TAF on serum lipid levels and NAFLD risk in patients with CHB, and we compared the pretreatment and post-treatment serum lipid profile changes after initiation of either TAF or ETV anti-viral therapy.

MATERIALS AND METHODS

Eligibility/study subjects

This study included all patients with CHB older than 18 years who visited the outpatient department of the Hepatology Research Institute of the First Affiliated Hospital of Fujian Medical University between January 2020 and January 2021. Information such as patient demographics, treatment history, laboratory data, and comorbidities was extracted from the electronic medical record system. CHB was defined according to the Guidelines for the Prevention and Treatment of Chronic Hepatitis B (2019) of China[10]. Diagnosis of decompensated cirrhosis was confirmed by ultrasonography or imaging for inclusion in the study. Finally, the study included 336 participants (Figure 1) who were taking TAF or ETV and had a pretreatment serum lipid profile and repeated serum lipid assessment after initiating anti-viral therapy for 1 year. Exclusion criteria were as follows: (1) Less than 1 year of anti-viral therapy; (2) Use of other oral anti-viral drugs during the study period; (3) Use of lipid-lowering drugs; (4) Complicated with other liver disease or pregnancy; (5) Heavy alcohol intake (amounting to ethanol consumption of ≥ 40 g/day for males and ≥ 20 g/day for females).

Measurement of parameters /data collection

The collected clinical and demographic data included age, sex, body mass index (BMI), drinking and smoking habits, date of anti-viral treatment initiation, cirrhosis, and comorbidities [diabetes mellitus (DM), hypertension, and NAFLD]. A fatty liver was identified using ultrasonography. Clinical laboratory information included HBV-DNA, hepatitis B surface antigen, aspartate aminotransferase, alanine aminotransferase, glomerular filtration rate, uric acid, creatinine, creatine kinase (CK), CK-MB isoenzyme, fasting serum lipid profiles (TCHO, TG, HDL, and LDL), and baseline fasting blood glucose levels. The parameters were measured by the clinical laboratory of the First Affiliated Hospital of Fujian Medical University, and data were collected before and 1 year after the initiation of anti-viral therapy. This retrospective study was approved by the Ethics Committee of the First Affiliated Hospital of Fujian Medical University, China.

Statistical analysis

Statistical analyses were performed using SPSS 23.0. Normally distributed continuous variables were presented as mean ± standard deviation, which were further evaluated by Student's *t*-test for the different treatment groups. Categorical variables were described using frequencies and proportions, and Pearson's χ^2 test was used to compare categorical variables. The paired *t*-test and McNemar's test were used to assess the differences between the levels before and after treatments in the same treatment group. We calculated the pretreatment and post-treatment differences in each lipid profile component in order to evaluate the impact of anti-viral therapy on lipid profile.

Propensity score-matched models were used to assess the effect of treatment type (TAF *vs* ETV) on lipid profile component changes. All propensity score-matched models were adjusted for BMI, age, sex, fatty liver disease, cirrhosis, DM, hypertension, smoking, and drinking. We presented the average changes in the model coefficients. Finally, logistic regression analysis was used to estimate the odds ratio of the association between baseline factors and elevated TCHO levels. Statistical *P* values less than 0.05 were considered significant.

RESULTS

Summary of baseline clinical and demographic data of TAF-treated and ETV-treated CHB patients

Overall, 336 CHB patients receiving anti-viral therapy (TAF, n = 214 *vs* ETV, n = 122) were included in the study. The mean age was 46.67 years, 75.60% were male, and 30.95% were cirrhotic at baseline. Patients were older in the ETV group (P = 0.001), but the two groups had a similar rate of NAFLD (TAF: 35.05% *vs* ETV: 26.23%, P = 0.122) and BMI (TAF: 22.97 *vs* ETV: 23.78, P = 0.152). However, hypertension and cirrhosis were more prevalent in the ETV group (17.21% *vs* 7.94%, P = 0.016 and 40.98% *vs* 25.23%, P = 0.004, respectively). TAF and ETV had similar levels of hepatitis B surface antigen (3.07 *vs* 3.04, P = 0.787) and HBV-DNA (1.94 *vs* 1.86, P = 0.560) (Table 1) as well as no statistically significant differences in serum alanine aminotransferase and aspartate aminotransferase levels.

Comparison of serum lipid profiles before and after anti-viral therapy in TAF-treated vs ETV-treated CHB patients

TCHO, TG, LDL, and HDL values in the TAF-treated and ETV-treated individuals were comparable at baseline (prior to anti-viral medication). In the TAF-treated group, post-treatment serum lipoprotein levels were considerably higher than the pretreatment levels for TCHO (4.51 ± 0.93 *vs* 4.67 ± 0.90, P = 0.001) and TG (1.25 ± 0.67 *vs* 1.37 ± 0.81, P = 0.014), whereas HDL and LDL levels did not change in the TAF group over the duration of our study. Further, the TAF group showed significantly higher post-treatment TCHO levels compared with that in the ETV group (4.67 ± 0.90 *vs* 4.36 ± 1.05, P = 0.006). However, TAF treatment did not increase the incidence of NAFLD after 1 year of follow-up (Table 2). In the ETV cohort, there was no significant difference between the pretreatment and post-treatment serum lipoprotein levels.

TAF as an independent predictor of TCHO level change

Using propensity score-matched models for BMI, age, sex, smoking, drinking, and presence of comorbidities such as NAFLD, cirrhosis, DM, and hypertension, we assessed the impact of TAF compared to ETV on achieving an increase in the levels of the serum lipid profile (Table 3). Patients treated with TAF had a statistically significant increase in TCHO levels (P = 0.019), which was 5% higher than that in the baseline lipid profile.

Table 1 Summary of demographic and clinical characteristics at baseline of chronic hepatitis B patients on tenofovir alafenamide or entecavir therapy

Characteristic	TAF, *n* = 214	ETV, *n* = 122	*P* value
Age in yr	43.38 ± 10.42	49.96 ± 11.82	0.001
Male	158 (73.83)	96 (78.69)	0.387
BMI in kg/m^2	22.97 ± 2.93	23.78 ± 3.30	0.152
Smoking	16 (7.48)	15 (12.30)	0.203
Drinking	13 (6.07)	14 (11.48)	0.123
ALT in U/L	36.60 ± 36.87	30.44 ± 20.00	0.089
AST in U/L	28.01 ± 26.41	24.50 ± 13.58	0.172
logHBsAg in ng/mL	3.07 ± 0.92	3.04 ± 0.84	0.787
logDNA in IU/mL	1.94 ± 1.23	1.86 ± 1.05	0.56
CREA in μmol/L	73.68 ± 15.87	74.82 ± 16.78	0.535
UA in μmol/L	353.52 ± 89.10	357.23 ± 84.29	0.708
GFR in mL/min	103.48 ± 15.01	97.86 ± 14.17	0.001
CK in U/L	157.23 ± 444.75	122.91 ± 71.31	0.401
FBG in mmol/L	5.18 ± 0.80	5.52 ± 1.61	0.011
Concurrent diseases			
Hypertension	17 (7.94)	21 (17.21)	0.016
DM	20 (9.35)	13 (10.66)	0.844
NAFLD	75 (35.05)	32 (26.23)	0.122
Cirrhosis	54 (25.23)	50 (40.98)	0.004

Data are presented as *n* (%). ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; CK: Creatine kinase; CREA: Creatinine; DM: Diabetes mellitus; ETV: Entecavir; FBG: Fasting blood-glucose; GFR: Glomerular filtration rate; HBsAg: Hepatitis B surface antigen; NAFLD: nonalcoholic fatty liver disease; TAF: Tenofovir alafenamide; UA: Uric acid.

Table 2 Comparison of serum lipid profile before and after 1 year of anti-viral therapy either tenofovir alafenamide or entecavir

Characteristic	TAF, *n* = 214, statistic	*P* value[1]	ETV, *n* = 122, statistic	*P* value[1]	*P* value[2]
Pre-Tx TCHO in mmol/L	4.51 ± 0.93	0.001	4.41 ± 1.03	0.275	0.376
Post-Tx TCHO in mmol/L	4.67 ± 0.90		4.36 ± 1.05		0.006
Pre-Tx TG in mmol/L	1.25 ± 0.67	0.014	1.33 ± 0.75	0.052	0.35
Post-Tx TG in mmol/L	1.37 ± 0.81		1.24 ± 0.61		0.126
Pre-Tx HDL in mmol/L	1.32 ± 0.40	0.794	1.26 ± 0.40	0.879	0.246
Post-Tx HDL in mmol/L	1.32 ± 0.36		1.27 ± 0.41		0.285
Pre-Tx LDL in mmol/L	3.12 ± 0.90	0.785	3.06 ± 1.01	0.078	0.543
Post-Tx LDL in mmol/L	3.14 ± 0.92		3.15 ± 1.00		0.906
Pre-Tx NAFLD	75 (35.05)	0.125	32 (26.23)	1	0.122
Post-Tx NAFLD	70 (32.71)		31 (25.41)		0.16

[1]Comparing the pretreatment and post-treatment variables (paired) in each therapy type.
[2]Comparing the same variable (either pretreatment or post-treatment) according to type of therapy. ETV: Entecavir; HDL: High density lipoprotein; LDL: Low-density lipoprotein; NAFLD: Nonalcoholic fatty liver disease; TAF: Tenofovir alafenamide; TCHO: Total cholesterol; TG: Triglycerides; Tx: Treatment.

Table 3 Impact of tenofovir alafenamide on achieving a higher level of total cholesterol in chronic hepatitis B patients

Characteristic	TCHO, increased change (%) by using TAF compared with ETV[1,2], OR (95%CI)	*P* value
5% higher than baseline	1.88 (1.11, 3.16)	0.019
10% higher than baseline	1.70 (0.94, 3.09)	0.081
15% higher than baseline	2.07 (0.99, 4.34)	0.055

[1]All propensity score-matched models were adjusted for body mass index, age, sex, nonalcoholic fatty liver disease, cirrhosis, diabetes mellitus, hypertension, smoking, and drinking. The increased percentage change was presented by using tenofovir alafenamide (TAF) compared with entecavir (ETV).

[2]The increased change was transformation of the treatment effect coefficients in propensity score-matched models. CI: Confidence interval; OR: Odds ratio; TCHO: Total cholesterol.

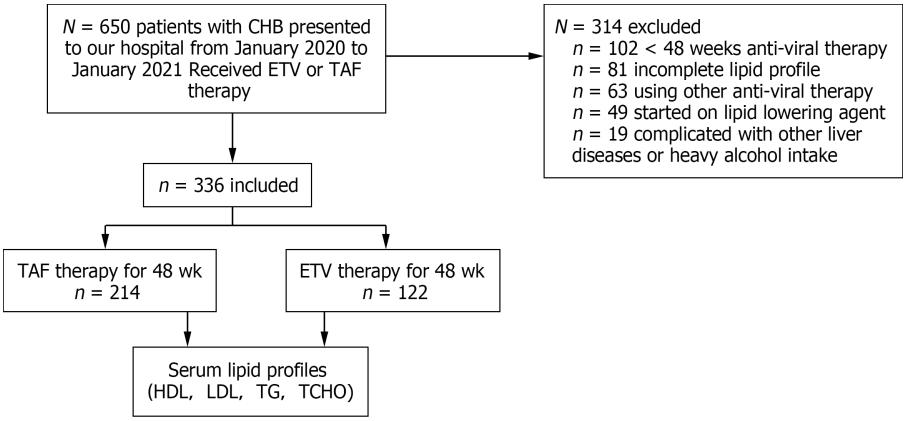

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Figure 1 Flowchart of study participants. CHB: Chronic hepatitis B; TAF: Tenofovir alafenamide; ETV: Entecavir; TCHO: Total cholesterol; HDL: High density lipoprotein; LDL: Low-density lipoprotein; TG: Triglycerides.

Risk factors were associated with elevated TCHO levels in CHB patients with 1-year TAF therapy

Logistic regression analysis was used to evaluate the risk factors associated with the worsening of TCHO levels (Figure 2). BMI, sex, hypertension, the baseline TCHO, and CK-MB levels were significantly associated with elevated TCHO levels. Furthermore, a nomogram incorporating statistically significant parameters in the logistic regression analysis was constructed, and the total points predicted the probability of elevated TCHO levels in individual patients.

DISCUSSION

In this real-life retrospective cohort study of 336 patients with CHB who received anti-viral therapy for 1 year, we compared fasting serum lipid profiles before and after initiation of either TAF or ETV treatment. In the TAF-treated cohort, we found a significant increase in the serum TCHO and TG levels compared with no difference in patients who received ETV. However, there were no concomitant significant changes in serum HDL or LDL levels in TAF-treated patients. Recent data have demonstrated that MetS increased the risk of progression of liver fibrosis independent of viral factors in patients with CHB[11,12]. Elevated TCHO and TG levels as MetS risk factors were related to a high risk of cirrhotic events in patients with CHB; thus, the results of this investigation may affect the decision regarding anti-viral therapy in CHB patients with cirrhotic risk factors.

TAF has been used as first-line therapy for CHB and HIV infections. Dyslipidemia and metabolic disorders have been linked to the prolonged use of TAF to treat HIV infection. Previous studies found that the serum lipid profile increased in HIV patients switching from TDF to TAF therapy, and the effect of increased serum lipids on the risk of cardiovascular events cannot be ignored[13-15]. Therefore, whether dyslipidemia due to TAF treatment in patients with CHB would lead to an increased risk of NAFLD is also a concern. Studies have reported that patients with CHB and NAFLD have better liver-related outcomes and overall mortality than those with CHB alone[16]. It is increasingly recognized that metabolic factors, which are precursors of NAFLD, can also be used to evaluate the risk of HCC in patients with CHB[17,18].

In our study, patients who received TAF therapy for 1 year did not have a significantly increased risk of developing NAFLD. However, owing to the short follow-up period of our study, the effect of TAF on increasing the incidence of NAFLD still needs to be evaluated over a longer follow-up period, and more data are required to better elucidate this.

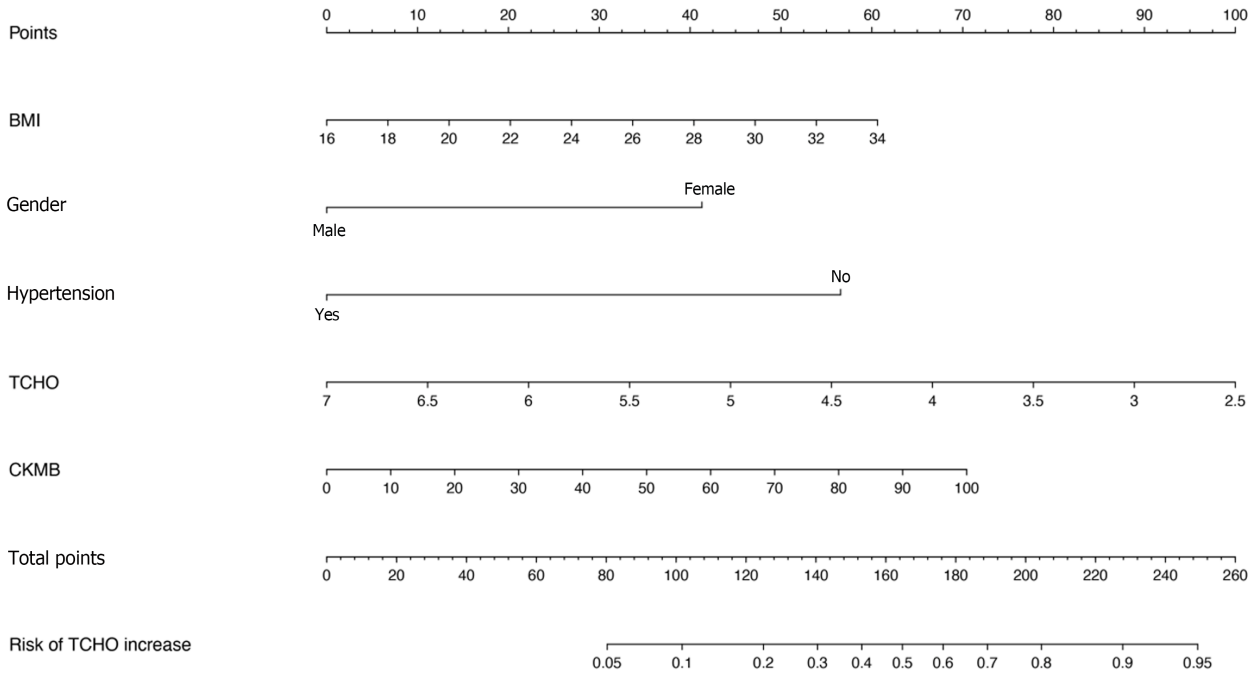

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Figure 2 Nomogram plot predicted the probability of the elevated total cholesterol level for individual patients receiving tenofovir alafenamide therapy. BMI: Body mass index; CK-MB: Creatine kinase-MB isoenzyme; TCHO: Total cholesterol.

It was unclear how TAF increased lipid concentrations, but the mechanism was independent of the patient's HIV status because a similar effect of TAF has been reported in HIV-negative patients receiving CHB therapy. Notably, a higher proportion of TAF-treated CHB patients experienced higher levels of LDL than the TDF group at the 48-wk follow-up[19,20]; however, the use of lipid-lowering agents was not described. In our study, the increased TCHO levels with TAF treatment represented a small change in the propensity score-matched model (5% higher than baseline, $P = 0.019$), but we did not find a significant change in the LDL profile compared to the ETV treatment group. Regular serum lipid measurements might not accurately capture the intricate alterations in lipid metabolism brought on by anti-viral medication. A recent study showed that TDF modulates lipid metabolism by upregulating hepatic CD36 *via* PPAR-a activation in patients with HBV infection[21]. However, the mechanism by which TAF increases serum lipid profiles remains unclear, and further studies are required.

In addition, in multivariate logistic regression analysis, metabolic factors, including BMI, hypertension, baseline TCHO, and CK-MB levels, were significantly associated with elevated TCHO levels, demonstrating an important impact of metabolic factors in terms of the elevated lipid profile caused by TAF. Previous studies have reported the effects of MetS on the adverse outcomes of fibrosis in patients with CHB[22,23]. Furthermore, some studies have confirmed that metabolic factors positively affected the risk of HCC in patients with HBV infection[17,24]. Based on the results mentioned above, the treatment options for patients with CHB who have the aforementioned aberrant metabolic variables may need to consider the potential effects of TAF medication on blood lipid levels.

Our study had some limitations. First, not all relevant clinical data were obtained from the treatment databases, and important data elements, such as lifestyle risk factors (*i.e.* exercise and diet) and family history, were not fully documented. Second, this was not a multicenter study, and we adjusted for baseline factors through a propensity score-matched model. Therefore, the observed increase in the TCHO profile may be due to the effect of anti-viral treatment. Third, the effect of TAF on the incidence of NAFLD cannot be elucidated well because of the short follow-up time. However, this study provided real-world data from China regarding the relationship between TAF-treated patients with CHB and changes in serum lipid levels. Large-scale multicenter prospective studies should be conducted in the future to further evaluate the effects of CHB and anti-HBV therapies on the risk of dyslipidemia, NAFLD, cirrhosis, and HCC.

CONCLUSION

In this real-life retrospective cohort study in China, we found that TAF was significantly associated with higher TCHO levels, whereas ETV had no effect in patients with CHB treated for 1 year. Risk factors (BMI, sex, baseline TCHO and CK-MB levels) were significantly associated with elevated TCHO levels. In the future, we will focus on increased NAFLD risk and not just changes in serum lipid profiles. Further studies will help elucidate the effect of TAF on long-term metabolic-related complications in patients with CHB.

ARTICLE HIGHLIGHTS

Research background

In recent decades, the prevalence of nonalcoholic fatty liver disease (NAFLD) has significantly increased in China, leading to the coexistence of NAFLD and chronic hepatitis B (CHB). Many patients require long-term anti-hepatitis B virus (HBV) therapy with potent oral drugs tenofovir alafenamide (TAF) and entecavir (ETV), which are recommended as first-line treatment in HBV clinical practice guidelines. However, no studies have compared the effects of TAF and ETV on lipid profiles in HBV-treated patients. Meanwhile, there are limited data on the effects of TAF on metabolism-related complications in real-world settings.

Research motivation

Many patients require long-term anti-HBV therapy with the potent oral drugs TAF and ETV, which are recommended as first-line treatment in HBV clinical practice guidelines. TAF has a serum lipid-raising effect in patients with HIV; however, its effect on serum lipids and NAFLD risk in patients with CHB is unclear.

Research objectives

This retrospective cohort study aimed to characterize the effect of TAF on serum lipid levels and NAFLD risk in patients with CHB, and we compared the pretreatment and post-treatment serum lipid profile changes after initiation of either TAF or ETV anti-viral therapy.

Research methods

The data including the clinical features, serum lipids, and metabolic factors of patients with CHB at baseline and approximately 1 year after TAF or ETV treatment were collected and analyzed. We used propensity score-matched models to assess the effects on high-density lipoprotein, low-density lipoprotein, triglycerides, and total cholesterol (TCHO).

Research results

Compared with the ETV group, the TAF group had significantly higher TCHO levels after treatment (4.67 ± 0.90 *vs* 4.36 ± 1.05, P=0.006). In a propensity score-matched model, TAF-treated patients had significantly increased TCHO levels compared to that at baseline (P = 0.019), while there was no difference for the ETV group. Body mass index, sex, hypertension, baseline TCHO, and creatine kinase-MB isoenzyme levels were significantly associated with elevated TCHO levels in logistic regression analysis. However, 1-year TAF treatment did not increase the incidence of NAFLD.

Research conclusions

Our study found that a greater increase in TCHO was observed in patients with CHB receiving TAF than in those receiving ETV; however, TAF-induced dyslipidemia did not increase the incidence of NAFLD.

Research perspectives

This was not a multicenter study, and most of patients with CHB in this study were Asians. Large-scale multicenter prospective studies should be conducted in the future to further evaluate the effects of CHB and anti-HBV therapies on the risk of dyslipidemia, NAFLD, cirrhosis, and hepatocellular carcinoma.

FOOTNOTES

Author contributions: Lai RM and Lin S contributed equally to this work; Lai RM and Lin S conceived and designed the study; Chen TB and Zhou JH contributed to the data analysis and manuscript feedback; Li N and Wang MM collected clinical data of the patients; Lai RM and Zheng Q wrote the manuscript; All authors approved the final version of the manuscript.

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REFERENCES

1 **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]
2 **Nguyen MH**, Wong G, Gane E, Kao JH, Dusheiko G. Hepatitis B Virus: Advances in Prevention, Diagnosis, and Therapy. *Clin Microbiol Rev* 2020; **33** [PMID: 32102898 DOI: 10.1128/CMR.00046-19]
3 **Younossi Z**, Anstee QM, Marietti M, Hardy T, Henry L, Eslam M, George J, Bugianesi E. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. *Nat Rev Gastroenterol Hepatol* 2018; **15**: 11-20 [PMID: 28930295 DOI: 10.1038/nrgastro.2017.109]
4 **Lozano-Bartolomé J**, Llauradó G, Rodriguez MM, Fernandez-Real JM, Garcia-Fontgivell JF, Puig J, Maymó-Masip E, Vendrell J, Chacón MR. Reduced circulating levels of sTWEAK are associated with NAFLD and may affect hepatocyte triglyceride accumulation. *Int J Obes (Lond)* 2016; **40**: 1337-1345 [PMID: 27121253 DOI: 10.1038/ijo.2016.73]
5 **Isorce N**, Lucifora J, Zoulim F, Durantel D. Immune-modulators to combat hepatitis B virus infection: From IFN-α to novel investigational immunotherapeutic strategies. *Antiviral Res* 2015; **122**: 69-81 [PMID: 26275801 DOI: 10.1016/j.antiviral.2015.08.008]
6 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *J Hepatol* 2017; **67**: 370-398 [PMID: 28427875 DOI: 10.1016/j.jhep.2017.03.021]
7 **Lacey A**, Savinelli S, Barco EA, Macken A, Cotter AG, Sheehan G, Lambert JS, Muldoon E, Feeney E, Mallon PW, Tinago W; UCD ID Cohort Study. Investigating the effect of antiretroviral switch to tenofovir alafenamide on lipid profiles in people living with HIV. *AIDS* 2020; **34**: 1161-1170 [PMID: 32310899 DOI: 10.1097/QAD.0000000000002541]
8 **Kauppinen KJ**, Kivelä P, Sutinen J. Switching from Tenofovir Disoproxil Fumarate to Tenofovir Alafenamide Significantly Worsens the Lipid Profile in a Real-World Setting. *AIDS Patient Care STDS* 2019; **33**: 500-506 [PMID: 31742421 DOI: 10.1089/apc.2019.0236]
9 **Shaheen AA**, AlMattooq M, Yazdanfar S, Burak KW, Swain MG, Congly SE, Borman MA, Lee SS, Myers RP, Coffin CS. Tenofovir disoproxil fumarate significantly decreases serum lipoprotein levels compared with entecavir nucleos(t)ide analogue therapy in chronic hepatitis B carriers. *Aliment Pharmacol Ther* 2017; **46**: 599-604 [PMID: 28707319 DOI: 10.1111/apt.14218]
10 **Chinese Society of Infectious Diseases**; Chinese Medical Association; Chinese Society of Hepatology, Chinese Medical Association. [The guidelines of prevention and treatment for chronic hepatitis B (2019 version)]. *Zhonghua Gan Zang Bing Za Zhi* 2019; **27**: 938-961 [PMID: 31941257 DOI: 10.3760/cma.j.issn.1007-3418.2019.12.007]
11 **Wong GL**, Chan HL, Yu Z, Chan AW, Choi PC, Chim AM, Chan HY, Tse CH, Wong VW. Coincidental metabolic syndrome increases the risk of liver fibrosis progression in patients with chronic hepatitis B--a prospective cohort study with paired transient elastography examinations. *Aliment Pharmacol Ther* 2014; **39**: 883-893 [PMID: 24612251 DOI: 10.1111/apt.12658]
12 **Lemieux I**, Després JP. Metabolic Syndrome: Past, Present and Future. *Nutrients* 2020; **12** [PMID: 33202550 DOI: 10.3390/nu12113501]
13 **Squillace N**, Ricci E, Menzaghi B, De Socio GV, Passerini S, Martinelli C, Mameli MS, Maggi P, Falasca K, Cordier L, Celesia BM, Salomoni E, Di Biagio A, Pellicanò GF, Bonfanti P; CISAI Study Group. The Effect of Switching from Tenofovir Disoproxil Fumarate (TDF) to Tenofovir Alafenamide (TAF) on Liver Enzymes, Glucose, and Lipid Profile. *Drug Des Devel Ther* 2020; **14**: 5515-5520 [PMID: 33364747 DOI: 10.2147/DDDT.S274307]
14 **Mills A**, Arribas JR, Andrade-Villanueva J, DiPerri G, Van Lunzen J, Koenig E, Elion R, Cavassini M, Madruga JV, Brunetta J, Shamblaw D, DeJesus E, Orkin C, Wohl DA, Brar I, Stephens JL, Girard PM, Huhn G, Plummer A, Liu YP, Cheng AK, McCallister S; GS-US-292-0109 team. Switching from tenofovir disoproxil fumarate to tenofovir alafenamide in antiretroviral regimens for virologically suppressed adults with HIV-1 infection: a randomised, active-controlled, multicentre, open-label, phase 3, non-inferiority study. *Lancet Infect Dis* 2016; **16**: 43-52 [PMID: 26538525 DOI: 10.1016/S1473-3099(15)00348-5]
15 **Milinkovic A**, Berger F, Arenas-Pinto A, Mauss S. Reversible effect on lipids by switching from tenofovir disoproxil fumarate to tenofovir alafenamide and back. *AIDS* 2019; **33**: 2387-2391 [PMID: 31764103 DOI: 10.1097/QAD.0000000000002350]
16 **Choi HSJ**, Brouwer WP, Zanjir WMR, de Man RA, Feld JJ, Hansen BE, Janssen HLA, Patel K. Nonalcoholic Steatohepatitis Is Associated With Liver-Related Outcomes and All-Cause Mortality in Chronic Hepatitis B. *Hepatology* 2020; **71**: 539-548 [PMID: 31309589 DOI: 10.1002/hep.30857]
17 **Lee YB**, Ha Y, Chon YE, Kim MN, Lee JH, Park H, Kim KI, Kim SH, Rim KS, Hwang SG. Association between hepatic steatosis and the development of hepatocellular carcinoma in patients with chronic hepatitis B. *Clin Mol Hepatol* 2019; **25**: 52-64 [PMID: 30360031 DOI: 10.3350/cmh.2018.0040]
18 **Chan AW**, Wong GL, Chan HY, Tong JH, Yu YH, Choi PC, Chan HL, To KF, Wong VW. Concurrent fatty liver increases risk of hepatocellular carcinoma among patients with chronic hepatitis B. *J Gastroenterol Hepatol* 2017; **32**: 667-676 [PMID: 27547913 DOI: 10.1111/jgh.13536]
19 **Chan HL**, Fung S, Seto WK, Chuang WL, Chen CY, Kim HJ, Hui AJ, Janssen HL, Chowdhury A, Tsang TY, Mehta R, Gane E, Flaherty JF, Massetto B, Gaggar A, Kitrinos KM, Lin L, Subramanian GM, McHutchison JG, Lim YS, Acharya SK, Agarwal K; GS-US-320-0110 Investigators. Tenofovir alafenamide versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive chronic hepatitis B virus infection: a randomised, double-blind, phase 3, non-inferiority trial. *Lancet Gastroenterol Hepatol* 2016; **1**: 185-195 [PMID: 28404091 DOI:

10.1016/S2468-1253(16)30024-3]

20 **Agarwal K**, Brunetto M, Seto WK, Lim YS, Fung S, Marcellin P, Ahn SH, Izumi N, Chuang WL, Bae H, Sharma M, Janssen HLA, Pan CQ, Çelen MK, Furusyo N, Shalimar D, Yoon KT, Trinh H, Flaherty JF, Gaggar A, Lau AH, Cathcart AL, Lin L, Bhardwaj N, Suri V, Mani Subramanian G, Gane EJ, Buti M, Chan HLY; GS-US-320-0110; GS-US-320-0108 Investigators. 96 weeks treatment of tenofovir alafenamide vs. tenofovir disoproxil fumarate for hepatitis B virus infection. *J Hepatol* 2018; **68**: 672-681 [PMID: 29756595 DOI: 10.1016/j.jhep.2017.11.039]

21 **Suzuki K**, Suda G, Yamamoto Y, Furuya K, Baba M, Nakamura A, Miyoshi H, Kimura M, Maehara O, Yamada R, Kitagataya T, Yamamoto K, Shigesawa T, Ohara M, Kawagishi N, Nakai M, Sho T, Natsuizaka M, Morikawa K, Ogawa K, Ohnishi S, Sakamoto N; NORTE Study Group. Tenofovir-disoproxil-fumarate modulates lipid metabolism *via* hepatic CD36/PPAR-alpha activation in hepatitis B virus infection. *J Gastroenterol* 2021; **56**: 168-180 [PMID: 33211179 DOI: 10.1007/s00535-020-01750-3]

22 **Lanthier N**, Horsmans Y, Leclercq IA. The metabolic syndrome: how it may influence hepatic stellate cell activation and hepatic fibrosis. *Curr Opin Clin Nutr Metab Care* 2009; **12**: 404-411 [PMID: 19474722 DOI: 10.1097/MCO.0b013e32832c7819]

23 **Yoon H**, Lee JG, Yoo JH, Son MS, Kim DY, Hwang SG, Rim KS. Effects of metabolic syndrome on fibrosis in chronic viral hepatitis. *Gut Liver* 2013; **7**: 469-474 [PMID: 23898389 DOI: 10.5009/gnl.2013.7.4.469]

24 **Yu MW**, Lin CL, Liu CJ, Yang SH, Tseng YL, Wu CF. Influence of Metabolic Risk Factors on Risk of Hepatocellular Carcinoma and Liver-Related Death in Men With Chronic Hepatitis B: A Large Cohort Study. *Gastroenterology* 2017; **153**: 1006-1017.e5 [PMID: 28711626 DOI: 10.1053/j.gastro.2017.07.001]

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ORIGINAL ARTICLE

Retrospective Cohort Study

Stages of care for patients with chronic hepatitis C at a hospital in southern Brazil

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Abstract

BACKGROUND

Hepatitis C virus (HCV) is defined as a public health problem by the World Health Organization (WHO) and since then has defined targets through the HCV elimination. The HCV cascade of care highlights the progress towards these goals and essential interventions that need to be delivered along this continuum care.

AIM

To document the treatment cascade for patients with HCV infection at the Hospital Nossa Senhora da Conceição (HNSC), defining the percentage of antibody-positive patients who collected molecular biology tests (polymerase

chain reaction), attended outpatient clinic assistance, underwent treatment, and achieved a virologic cure termed sustained virologic response (SVR).

METHODS

With the retrospective cohort design, patients diagnosed with HCV infection in the period between January 1, 2015 and December 31, 2020 were included. Data from HCV notification forms, electronic medical records, Computerized Laboratory Environment Manager System, and Medicine Administration System (evaluation of special medications) were collected in 2022 and all information up to that period was considered. The data were analyzed with IBM SPSS version 25, and Poisson regression with robust simple variance was performed for analysis of variables in relation to each step of the cascade. Variables with $P < 0.20$ were included in the multivariate analysis with $P < 0.05$ considered significant. Pearson's chi-square test was applied to compare the groups of patients who persisted in follow-up at the HNSC and who underwent follow-up at other locations.

RESULTS

Results were lower than expected by the WHO with only 49% of candidates receiving HCV treatment and only 29% achieving SVR, despite the 98% response rate to direct acting antivirals documented by follow-up examination. The city of origin and the place of follow-up were the variables associated with SVR and all other endpoints. When comparing the cascade of patients who remained assisted by the HNSC *vs* external patients, we observed superior data for HNSC patients in the SVR. Patients from the countryside and metropolitan region were mostly assisted at the HNSC and the specialized and continuous care provided at the HNSC was associated with superior results, although the outcomes remain far from the goals set by the WHO.

CONCLUSION

With the elaboration of the HCV cascade of care using local data, it was possible to stratify and evaluate risk factors associated with losses between each step of the cascade, to inform new strategies to guide elimination efforts in the future.

Key Words: Cascade of care; Elimination; Hepatitis C virus; Sustained virologic response

Core Tip: Hepatitis C virus (HCV) is defined as a public health problem by the World Health Organization and since then has defined targets through the HCV elimination. The present study aimed to document the treatment cascade for patients with HCV infection at a hospital in southern Brazil. With the retrospective cohort design, patients diagnosed with HCV infection between 2015 and 2020 were included to create the HCV cascade of care described as five exposure columns according to the stages of HCV care. Variables were related to each step of the cascade to identify obstacles for patients to reach the last step. With the elaboration of the HCV cascade of care using local data, it was possible to stratify and evaluate risk factors associated with losses between each step of the cascade, to inform new strategies to guide elimination efforts in the future.

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INTRODUCTION

The World Health Organization (WHO) set the goal of diagnosing 90% of cases of viral hepatitis and treating 80% of diagnosed cases with the aim of reducing the incidence by 90% and mortality attributable to hepatitis by 65% by 2030[1]. The hepatitis C virus (HCV) care cascade represents the care that patients receive in the respective health services and consequently illustrates the basic indicators of the WHO targets[2]. In the first stage are people with HCV infection, in the second are the patients aware of the diagnosis of HCV, in the third, those who underwent treatment, and in the fourth stage, those who achieved cure with viral suppression from 12 wk to 24 wk after the end of treatment[2-4]. Other stages can be added, such as retention in care and after cure monitoring, but it is difficult to standardize the criteria, hindering the possibility of later comparison[3].

The elaboration of the treatment cascade facilitates the identification of barriers and groups of risks which we must work with[3,5]. The correlation between sociodemographic variables and results between stages is an important tool for the analysis of the HCV cascade of care[6]. Mental health problems, change in follow-up location, and restriction of information about the disease were detected as causes of failures in the stages of chronic HCV treatment in a study by health professionals[7]. Therefore, the construction of local cascades is necessary for the understanding of gaps in current practices and the elaboration of changes[8].

Brazil joined the Hepatitis C Elimination Plan in 2017[9]. Since then, the country has been developing and implementing guidelines of care and prevention to guarantee a greater access to diagnostic tests and the treatment for all patients with chronic HCV infection and acute hepatitis C and children with infection by HCV[9]. Retreatment is also possible, especially after the availability of new direct-acting antivirals (DAAs)[9]. Despite the measures instituted in Brazil, there are no data available for the elaboration of a local cascade of care, which determines the need to qualify national databases to monitor the hepatitis elimination policy[10].

The South region of Brazil is responsible for the highest detection rate of confirmed HCV infection in the country and also for the highest mortality rate, with higher rates than national data[11]. Within this region, the city of Porto Alegre, in 2020 was the second capital with the highest HCV detection rate, and in 2021 the first, even higher than the national rate [11]. The Hospital Nossa Senhora da Conceição (HNSC) in Porto Alegre is a tertiary hospital that has an infectology service which is a reference in treatment services for patients with human immunodeficiency virus (HIV) infection and viral hepatitis[12]. The objective of this study was to define the continuity of care or treatment cascade for patients with chronic HCV infection at the HNSC and to define sociodemographic variables that influence follow-up between each step of the cascade.

MATERIALS AND METHODS

This referred retrospective cohort study included patients diagnosed with chronic HCV infection between 2015 and 2020 at the HNSC. All hospitalized patients and outpatients above 16 years of age notified by the HNSC epidemiological center for viral hepatitis with positive anti-HCV or HCV-polymerase chain reaction (PCR) results detectable during this period were analyzed. Patients under 16 years of age were excluded, as they would be followed up at a pediatric hospital attached to the HNSC. Patients who died, who were not connected with the HNSC, or who were not located in the electronic medical records of the hospitals were excluded.

The Information System for Notifiable Diseases (SINAM) for Viral Hepatitis, electronic medical records from the HNSC, computerized Laboratory Environment Management System (GAL), and Medicine Administration System (AME) provided data such as age, gender, race, education level, history of pregnancy and drug use, profession, city of origin, institutionalization situation, and co-infection with HIV and hepatitis B virus (HBV). Specific data of the disease under study were also obtained, such as date of diagnosis of HCV infection (anti-HCV test), history of consultation with a specific outpatient clinic for the treatment of hepatitis, initial quantitative HCV-PCR and final quantitative HCV-PCR (after the 12th wk since the end of treatment), genotyping, history of cirrhosis or hepatocellular carcinoma, specific regimen, and date of treatment prescribed for HCV. Data were collected in 2022 and all information up to that period was considered.

Regarding the HCV cascade of care, five exposure columns were built according to the stages of HCV care. The first stage covers all people diagnosed with chronic HCV infection, that is, patients with positive anti-HCV or detectable quantitative HCV-PCR in the analyzed period. The second includes patients who underwent some quantitative PCR collection, and the third includes patients who underwent consultation at a specialized outpatient clinic for monitoring hepatitis C. The fourth step integrates all who underwent treatment with specific antivirals for chronic HCV infection according to the established protocol. The fifth step ends with all patients who achieved a sustained virological response, that is, those who obtained an undetectable quantitative HCV-PCR test after the 12th wk since the end of treatment. Patients who did not collect this exam after treatment were not included in the fifth step, being presented in the cascade as "missing" and subsequently analyzed within the group of those who were not cured. The percentages were then calculated using the "*n*" of the first step and the "*n*" of the previous step as denominator, thus obtaining two percentages for analysis, being represented using a series of unidirectional columns.

Using the IBM SPSS version 25 program, Poisson regression with robust simple variance was performed to estimate the incidence ratio (IR) at a 95% confidence interval (95%CI) for the variables of gender, age group, race, education, city of residence, place of follow-up, presence of cirrhosis, institutionalization, year of diagnosis, and co-infection with HIV/HBV related to each step of the cascade: PCR-HCV collection, bond, treatment, and sustained virologic response (SVR). All variables that had a value of $P < 0.20$ in the simple analyzes were included in the multivariable model, and in this model only variables with $P < 0.05$ were considered significant.

Two more cascades were also built, discriminating between patients who underwent treatment at the HNSC and those who underwent treatment at other locations after the diagnosis. The comparison of the sociodemographic characteristics between the groups, HNSC and external, was performed using Pearson's chi-square test and results with $P < 0.05$ were considered significant. The study was approved by the research ethics committee of the Hospitalar Conceição Group, under number 51462421.8.0000.5530, and informed consent was waived, subject to the patient's commitment to confidentiality.

RESULTS

By searching the HNSC viral hepatitis notification database between 2015 and 2020 at the HNSC, 2498 patients were identified. A total of 487 patients who died, with decompensated cirrhosis, hepatocellular carcinoma, renal failure, and sepsis as the main etiologies reported, were excluded. Another 1232 patients were also excluded because they had a diagnosis of other viral hepatitis, an HCV diagnosis prior to 2015, a false anti-HCV test result, no attachment to the HNSC, or being younger than 16 years old. A total of 779 patients diagnosed with HCV infection during the analyzed

period were included, but of these 70 had spontaneous cure and, as they did not require treatment, were disregarded for further analyses.

For the HCV cascade of care, 709 patients were analyzed, showing a sociodemographic profile of being predominantly male (54.3%), white (76.6%), and from Porto Alegre (44.7%), and just having had completed elementary education (67.4%). The mean age of the patients was 53 years. Only 22 patients had a history of pregnancy, 13% co-infection with the HIV, 10.3% co-infection with HBV, 17.8% had a history of cirrhosis, and only 2% a diagnosis of hepatocellular carcinoma. It was identified that 24.9% had a history of drug use and 33 patients of institutionalization. Regarding the genotype, 44.5% of the patients did not have an identified genotype and, among the available genotypes, genotype 1 was the most prevalent (60%), followed by genotype 3 (34.6%) and finally genotype 2 (5.3%).

Regarding the total of 709 patients, 534 (75.3%) collected quantitative PCR, 461 (65%) consulted at a specialized clinic, 344 (48.5%) underwent treatment for HCV infection, and 204 (28.7%) reached SVR. When considering the previous column as the denominator, the percentages would be, respectively, 75% with RT-PCR collection, 86% consulted, 75% treated, and 59% with SVR confirmed by post-treatment examination. Both percentages are represented in Figure 1. The results of the simple and multivariate analyzes of the variables in relation to each step of the cascade are described in Tables 1 and 2, respectively.

Patients with incomplete primary education had lower rates of HCV-PCR collections after the diagnosis of HCV infection in the simple analysis ($P < 0.20$), as well as patients who underwent diagnosis in 2018; however, these variables were not significant in multivariate analysis. Patients living in the metropolitan area and countryside regions, who consulted at an outpatient clinic at the HNSC, co-infected with HIV and HBV, with a history of cirrhosis, and who were diagnosed in 2016 and in 2020, had higher collections of PCR-HCV in the first analysis ($P < 0.20$). In the second analysis, patients from the metropolitan area and countryside regions, patients from the HNSC, and those diagnosed in 2020 were more likely to obtain HCV-PCR ($P < 0.05$).

Despite linkage being the subsequent step in the cascade, there were 22 patients who consulted and did not collect any HCV-PCR test. The variables that showed a difference in favor of creating a link to a specialized outpatient clinic were female gender, living outside the city of Porto Alegre, having cirrhosis, and consulting at the HNSC. The diagnoses in 2018 and in 2019, as well as having only elementary school, were factors contrary to consulting with specialists. In the multivariate analysis, only being from the countryside or metropolitan area and consulting the HNSC were significant ($P < 0.05$). Through the records in the GAL and AME, we identified that 121 patients were followed up in other places after the diagnosis in the hospital.

Being female, having a history of cirrhosis, living outside the city of Porto Alegre, and consulting at the HNSC were protective factors in the simple analysis for undertaking the treatment. As risk factors for not undergoing HCV treatment, co-infection with HIV, being institutionalized, being non-white, having had only completed elementary school, and having been diagnosed in 2019 were identified. Consulting at the HNSC and being from the countryside remained significant protective factors ($P < 0.05$). The mean time between diagnosis and initiation of treatment was approximately 2 years. The DAAs most used in treatment were sofosbuvir and ledispasvir (26.0%), sofosbuvir and velpatasvir (22.0%), sofosbuvir and daclatasvir (17.0%), and sofosbuvir, daclatasvir, and ribavirin (15.0%). Only eight patients (1.1%) underwent more than one treatment. Among the 22 pregnant women in the study, only nine underwent treatment, but timing of treatment before or after pregnancy was unknown. No history of vertical transmission was found in these cases, since the GAL system evaluated the newborns of the respective pregnant women.

Out of all 344 patients who underwent treatment, only 204 reached SVR; however, 136 patients had no record in the GAL of collection of HCV-PCR control after the 12th wk since the end of treatment. Only four had SVR failure, resulting in a documented DAA response rate of 98%. The risk factors in the simple analysis for not achieving documented SVR were being of non-white race and having only elementary education. As variables favorable to SVR, living in the metropolitan area, in the countryside, and consultation at the HNSC were found, in addition to having been diagnosed with HCV infection in 2015 and in 2016. In the multivariate analysis, only the places of residence (countryside and metropolitan area) and consultation at the HNSC were significant ($P < 0.05$).

Because significance was found in all stages of HCV care regarding the place of follow-up, we constructed two separate cascades of care: One for patients who remained under follow-up at the HNSC and another for patients who chose to be assisted in other places. As previously mentioned, 340 patients remained at the HNSC, of whom 70% underwent treatment and 49% achieved SVR, 1% showed failure, and 20% did not collect a PCR test after treatment. Among 121 outpatients, 88% underwent treatment and 31% had SVR, but 55% did not perform a control PCR collection and 2% had SVR failure (Figure 2). As variables favorable to SVR, living in the metropolitan area, in the countryside, and consultation at the HNSC were found, in addition to having been diagnosed with HCV infection in 2015 and in 2016. In the multivariate analysis, only the places of residence (countryside and metropolitan area) and consultation at the HNSC were significant ($P < 0.05$) (Table 3).

DISCUSSION

We conducted this study in our local hospital to identify the HCV care cascade and relevant characteristics for progressing from diagnosis to successful cure, to provide representative data from Rio Grande do Sul and mainly from the city of Porto Alegre[11,13]. The highest prevalence of HCV infection was found in patients who are male, white, and aged over 40 years, consistent with both data from the state of Rio Grande do Sul and national statistics[11,14]. Also, higher prevalence of HCV was observed in patients with only elementary education[11]. Regarding co-infection with HIV, we present data that are very close to those of the South region in 2021 (10.1%)[11]. Groups most vulnerable to

Table 1 Analysis of variables with absolute number and relative percentage (%) and Poisson regression with robust simple variance of each variable in relation to steps of cascade of care of patients diagnosed with hepatitis C virus infection at the Hospital Nossa Senhora da Conceição between 2015 and 2020

	Total (%)	PCR-HCV collection	*P* value	Specialized assistance	*P* value	Treatment	*P* value	SVR	*P* value
Total	709	534 (75.3%)		461 (65.0%)		344 (48.5%)		204 (28.7%)	
Gender									
Female	324 (45.7%)	238 (73.5%); 0.95 (0.87-1.04)	0.295	221 (68.2%); 1.09 (0.98-1.21)	0.101	175 (54.0%); 1.23 (1.05-1.43)	0.007	109 (62.3%); 1.10 (0.92-1.32)	0.253
Male	385 (54.3%)	296 (76.9%); 1.0		240 (62.3%); 1.0		169 (43.9%); 1.0		95 (56.2%); 1.0	
Age (yr)									
17-39	118 (16.6%)	90 (76.3%); 1.0		79 (66.9%); 1.0	0.420	52 (44.1%); 1.0		27 (51.9%); 1.0	
40-59	348 (49.1%)	267 (76.7%); 1.00 (0.89-1.13)	0.920	225 (64.7%); 0.96 (0.83-1.12)	0.646	170 (48.9%); 1.10 (0.88-1.39)	0.380	103 (60.6%); 1.16 (0.87-1.55)	0.294
> 60	243 (34.3%)	177 (72.8%); 0.95 (0.84-1.08)	0.479	157 (64.6%); 0.96 (0.82-1.12)	0.657	122 (50.2%); 1.13 (0.89-1.44)	0.284	74 (60.7%); 1.16 (0.86-1.57)	0.307
Race									
White	543 (76.6%)	405 (74.6%); 1.0		353 (65.0%); 1.0		269 (49.5%); 1.0		164 (61.0%); 1.0	
Non-white	154 (21.7%)	118 (76.6 %); 1.02 (0.92-1.13)	0.598	97 (63.0%); 0.96 (0.84-1.11)	0.649	65 (42.2%); 0.85 (0.69-1.04)	0.123	32 (49.2%); 0.80 (0.62-1.05)	0.113
Education									
Illiterate	39 (5.5%)	28 (71.8%); 0.88 (0.71-1.08)	0.238	26 (66.7%); 0.95 (0.74-1.22)	0.741	20 (51.3%); 0.96 (0.68-1.35)	0.834	13 (65.0%); 0.95 (0.66-1.36)	0.804
Elementary school	478 (67.4%)	344 (72%); 0.88 (0.80-0.97)	0.011	301 (63.0%); 0.90 (0.79-1.03)	0.134	219 (45.8%); 0.86 (0.71-1.03)	0.110	120 (54.8%); 0.80 (0.66-0.98)	0.031
High school and university	141 (19.9%)	115 (81.6%); 1.0		98 (69.5%); 1.0		75 (53.2%); 1.0		51 (68.0%); 1.0	
City of origin									
Porto Alegre	317 (44.7%)	215 (67.8%); 1.0		174 (54.9%); 1.0		121 (38.2%); 1.0		49 (40.5%); 1.0	
Metropolitan region	247 (34.8%)	190 (76.9%); 1.13 (1.02-1.25)	0.016	166 (67.2%); 1.22 (1.07-1.39)	0.003	126 (51.0%); 1.33 (1.11-1.60)	0.002	81 (64.3%); 1.58 (1.23-2.04)	0
Countryside	134 (18.9%)	118 (88.1%); 1.29 (1.17-1.43)	0	112 (83.6%); 1.52 (1.34-1.72)	0	91 (67.9%); 1.77 (1.48-2.13)	0	68 (74.7%); 1.84 (1.44-2.36)	0
Follow-up site									
HNSC	341 (48.1%)	320 (93.8%); 1.61 (1.47-1.76)	0	340 (99.7%); 3.03 (2.62-3.50)	0	237 (69.5%); 2.39 (2.00-2.84)	0	166 (70.0%); 1.97 (1.50-2.58)	0
External	121 (17.1%)	214 (58.2%); 1.0		121 (32.9%); 1.0		107 (29.1%); 1.0		38 (35.5%); 1.0	
Institutionalized									
Yes	33 (4.7%)	25 (75.8%); 1.0		18 (54.5%); 1.0		12 (36.4%); 0.74 (0.46-1.17)	0.198	8 (66.7%); 1.12 (0.74-1.70)	
No	676 (95.3%)	509 (75.3%); 1.00 (0.82-1.22)	0.952	443 (65.5%); 0.83 (0.60-1.14)	0.255	332 (49.1%); 1.0		196 (59.0%); 1.0	0.561
Co-infection with HBV									
Yes	73 (10.3%)	61 (83.6%); 1.12 (1.00-1.25)	0.041	43 (58.9%); 1.0		30 (41.1%); 0.83 (0.62-1.10)	0.208	18 (60.0%); 1.01 (0.74-1.37)	0.935
No	636 (89.7%)	473 (74.4%); 1.0		418 (65.7%); 0.89 (0.73-1.09)	0.282	314 (49.4%); 1.0		186 (59.2%); 1.0	0.935

Co-infection with HIV									
Yes	93 (13.1%)	75 (80.6%); 1.08 (0.97-1.20)	0.158	63 (67.7%); 1.04 (0.90-1.22)	0.541	35 (37.6%); 0.75 (0.57-0.98)	0.039	17 (48.6%); 0.80 (0.56-1.14)	0.222
No	616 (86.9%)	459 (74.5%); 1.08		398 (64.6%); 1.0		309 (50.2%); 1.0		187 (60.5%); 1.0	
Cirrhosis									
Yes	126 (17.8%)	112 (88.9%); 1.22 (1.13-1.33)	0	106 (84.1%); 1.38 (1.25-1.52)	0	82 (65.1%); 1.44 (1.23-1.69)	0	60 (73.2%); 1.33 (1.12-1.57)	0.001
No	583 (82.2%)	422 (72.4%); 1.0		355 (60.9%); 1.0		262 (44.9%); 1.0		144 (55.0%); 1.0	
Date of diagnosis									
2015	149 (21.0%)	111 (74.5%); 1.0		102 (68.5%); 1.0		76 (51%); 1.0		42 (55.3%); 1.0	
2016	136 (19.2%)	113 (83.1%); 1.11 (0.98-1.25)	0.076	101 (74.3%); 1.08 (0.93-1.25)	0.278	72 (52.9%); 1.03 (0.83-1.29)	0.744	51 (70.8%); 1.28 (0.99-1.64)	0.052
2017	121 (17.1%)	92 (76.0%); 1.02 (0.89-1.17)	0.771	84 (69.4%); 1.01 (0.86-1.19)	0.865	68 (56.2%); 1.10 (0.88-1.37)	0.393	45 (66.2%); 1.19 (0.91-1.56)	0.181
2018	121 (17.1%)	80 (66.1%); 0.88 (0.75-1.04)	0.140	72 (59.5%); 0.86 (0.72-1.04)	0.133	53 (43.8%); 0.85 (0.66-1.10)	0.244	30 (56.6%); 1.04 (0.75-1.39)	0.880
2019	128 (18.1%)	90 (70.3%); 0.94 (0.81-1.09)	0.440	67 (52.3%); 0.76 (0.62-0.93)	0.008	49 (38.3%); 0.75 (0.57-0.98)	0.038	22 (44.9%); 0.81 (0.56-1.17)	0.272
2020	54 (7.6%)	48 (88.9%); 1.19 (1.04-1.36)	0.009	35 (64.8%); 0.94 (0.75-1.18)	0.634	26 (48.1%); 0.94 (0.68-1.29)	0.723	14 (53.8%); 0.97 (0.64-1.46)	0.901

P value < 0.20 was considered significant. HNSC: Hospital Nossa Senhora da Conceição; HCV: Hepatitis C virus; HBV: Hepatitis B virus; SVR: Sustained virologic response.

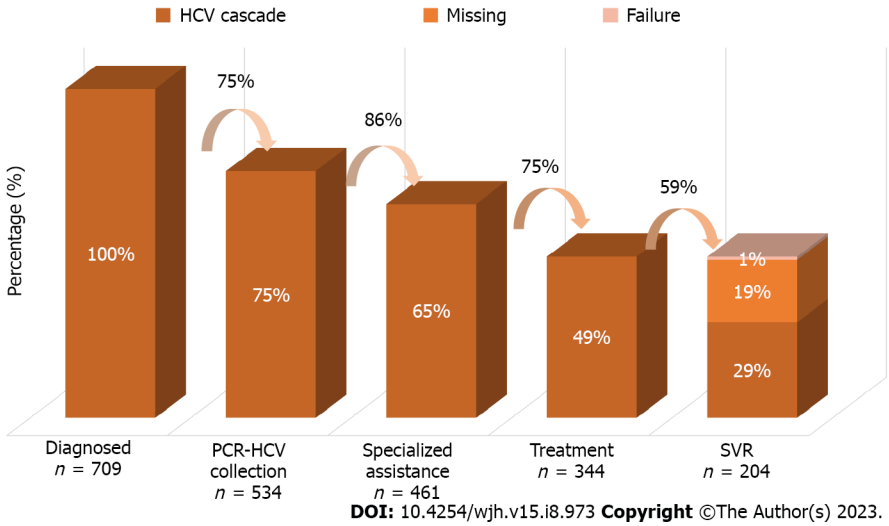

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Figure 1 Cascade of care of hepatitis C virus infected patients diagnosed at the Hospital Nossa Senhora da Conceição between 2015 and 2020. HCV: Hepatitis C virus; SVR: Sustained virologic response.

infection by the HCV, such as people living with HIV, institutionalized people, and drug users, were considerably represented, corroborating the importance of focusing on testing and preventive actions for these particular subpopulations[9,14]. Genotypes 1 and 3 were the most prevalent, as expected according to national and local data[14].

According to the WHO, the second step of the HCV cascade of care would be represented by patients aware of their diagnosis, with a target of 90%[1]. However, in this study, we did not carry out this estimate and included patients from the diagnosis of chronic HCV infection which we performed at the HNSC. Overall, the WHO target of patients on treatment (80%) was not reached. But when analyzing the cascade broken down by place of follow-up, patients being followed up outside the HNSC reached the goal. This can be explained by a possible data collection bias, where all patients with prescriptions for treatment in the AME system from other locations were linked to other services. In addition, HNSC patients may have even started treatment due to the lack of clinical conditions, such as neoplasms or

Table 2 Poisson regression analysis with multivariable robust variance of significant variables in relation to steps of cascade of care of patients diagnosed with hepatitis C virus infection at the Hospital Nossa Senhora da Conceição between 2015 and 2020

	PCR-HCV collection	*P* value	Specialized assistance	*P* value	Treatment	*P* value	SVR	*P* value
Gender								
Female			0.06 (0.97-1.16)	0.148	1.20 (1.03-1.40)	0.014		
Male			1.00		1.00			
Race								
White					1.0		1.0	
Non-white					0.99 (0.81-1.21)	0.931	0.95 (0.72-1.25)	0.734
Education								
Illiterate	0.83 (0.67-1.03)	0.103	0.87 (0.73-1.04)	0.152	0.76 (0.53-1.09)	0.145	0.63 (0.35-1.12)	0.120
Elementary school	0.89 (0.81-0.97)	0.014	0.94 (0.85-1.04)	0.244	0.85 (0.72-1.02)	0.082	0.79 (0.65-0.95)	0.014
High school and university	1.0		1.0		1.0		1.0	
City of origin								
Porto Alegre	1.0		1.0		1.0		1.0	
Metropolitan region	1.11 (1.00-1.23)	0.033	1.12 (1.00-1.24)	0.034	1.19 (0.98-1.45)	0.074	1.54 (1.19-1.98)	0.001
Countryside	1.19 (1.08-1.33)	0.001	1.14 (1.03-1.25)	0.009	1.38 (1.14-1.68)	0.001	1.62 (0.24-2.12)	0.000
Follow-up site								
HNSC	1.58 (1.43-1.75)	0.000	3.00 (2.58-3.50)	0.000	2.19 (1.80-2.65)	0.000	1.59 (1.20-2.09)	0.001
External	1.0		1.0		1.0		1.0	
Institutionalized								
Yes					0.70 (0.42-1.17)	0.178		
No					1.0			
Co-infection with HBV								
Yes	1.11 (0.97-1.27)	0.121						
No	1.0							
Co-infection with HIV								
Yes	1.11 (0.97-1.27)	0.121			0.80 (0.59-1.08)	0.156		
No	1.0				1.0			
Cirrhosis								
Yes	1.02 (0.94-1.11)	0.504	0.96 (0.90-1.03)	0.327	1.07 (0.91-1.62)	0.363	1.18 (0.91-1.36)	0.275
No	1.0		1.0		1.0		1.0	
Date of diagnosis								
2015	1.0		1.0		1.0		1.0	1.000
2016	1.02 (0.90-1.16)	0.662	0.90 (0.80-1.01)	0.083	0.82 (0.65-1.03)	0.102	1.05 (0.80-1.37)	0.701
2017	0.97 (0.84-1.12)	0.711	0.93 (0.81-1.06)	0.311	0.96 (0.76-1.20)	0.730	1.06 (0.80-1.41)	0.652
2018	0.90 (0.77-1.05)	0.213	0.92 (0.79-1.07)	0.321	0.83 (0.64-1.07)	0.153	0.93 (0.67-	0.685

							1.30)	
2019	1.02 (0.88-1.19)	0.717	0.88 (0.76-1.03)	0.118	0.81 (0.62-1.05)	0.125	0.81 (0.57-1.16)	0.267
2020	1.27 (1.09-1.48)	0.002	1.03 (0.86-1.25)	0.698	1.02 (0.75-1.39)	0.879	0.96 (0.66-1.40)	0.862

P value < 0.05 was considered significant. HCV: Hepatitis C virus; SVR: Sustained virologic response; HNSC: Hospital Nossa Senhora da Conceição.

Table 3 Comparison between patients with hepatitis C virus infection who underwent follow-up at the Hospital Nossa Senhora da Conceição and external ones using Pearson's chi-square test

	HNSC	External	*P* value
Total	340 (73.8%)	121 (26.2%)	
Gender			0.654
Female	161 (47.2%)	60 (49.6%)	
Age (yr)			0.854
< 40	60 (17.6%)	19 (15.7%)	
40-59	167 (49.0%)	59 (48.8%)	
> 60	114 (33.4%)	43 (35.5%)	
Race			0.450
White	262 (79.2%)	91 (75.8%)	
Education			0.411
Illiterate	22 (7.1%)	4 (3.5%)	
Elementary school	218 (69.9%)	83 (73.5%)	
High school and university	72 (23.1%)	26 (23.0%)	
City of origin			0.006
Porto Alegre	121 (36.4%)	53 (43.8%)	
Metropolitan region	116 (34.9%)	51 (42.1%)	
Countryside	95 (28.6%)	17 (14.0%)	
Cirrhosis			0.000
Yes	100 (29.3%)	7 (5.8%)	

P value < 0.05 was considered significant. HNSC: Hospital Nossa Senhora da Conceição.

serious comorbidities. Not having genotyping or HCV-PCR test within a year are also bureaucratic reasons that interfere with the delay in starting HCV therapy, which is unfortunate given the possibility of simplified protocols with pangenotypic regimens[15,16].

About 90% of patients with HCV infection are cured with the new DAAs, resulting in a markedly decreased risk of liver-related morbidity and mortality and also a drastic reduction of onward transmission[5]. Despite the high response rate to DAAs, the SVR percentages are surprisingly low in this study, which represents the biggest "gap" among all the cascade steps. This is due to the large number of patients with missing data after treatment, making it impossible to confirm SVR. In addition to the collection of HCV-PCR control outside the Brazilian Unified Health System (SUS), another reason for the ignored data would be the loss to follow-up of the patients after the completion of the treatment, identifying the importance of implementing a strategy to enhance the rate of return of the patients after the exams[17]. The coronavirus disease 2019 pandemic had an important impact on the follow-up of these patients after treatment[18]. HNSC patients had a higher SVR and a lower number of ignored HCV-PCR tests, possibly due to less loss to follow-up.

RT-PCR collection

National data and data from the state of Rio Grande do Sul have shown a progressive decrease in reported cases of viral hepatitis with anti-HCV reagents and concomitant HCV-PCR reagents, which may demonstrate an increase in notifications of cases of serological cure, or even less access to confirmatory HCV-PCR tests[11,13]. Patients who were connected to the hospital collected significantly more PCR-HCV, which may have been facilitated by the logistics of collecting the

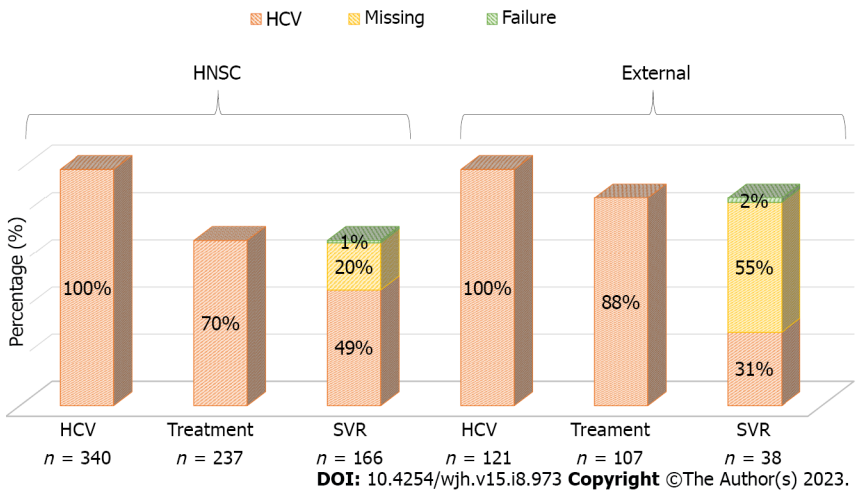

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Figure 2 Cascade care of hepatitis C virus infected patients diagnosed between 2015 and 2020 at the Hospital Nossa Senhora da Conceição and who underwent follow-up at the Hospital Nossa Senhora da Conceição and elsewhere (external). HNSC: Hospital Nossa Senhora da Conceição; HCV: Hepatitis C virus; SVR: Sustained virologic response.

test inside the hospital under study, after the diagnosis was made. This can also be explained by the greater severity of the patients, as patients with comorbidities, such as HBV and HIV infections and cirrhosis, were shown to have greater access to the test. Living in the countryside and in the metropolitan area were also significant protective factors in this analysis for HCV-PCR collection, as most of these patients have consultations at the HNSC, possibly due to less access to confirmatory HCV-PCR tests outside the capital Porto Alegre[13]. Patients ended up collecting more exams in 2020, demonstrating more accessibility to the exam that year or even greater concern for investigating the disease of patients throughout the pandemic.

Bond

Gaps occur at all stages of HCV care, with dropouts in care occurring before and after linking to specialized care[19]. Consultation at a specialized outpatient clinic is recommended in the treatment lines established in the country; however, more recent guidelines describe the intention of training non-specialist physicians[10,14]. HNSC patients may have found it easier to create a bond with an infectology or gastroenterology outpatient clinic because they were diagnosed in the same hospital. On the other hand, patients from the countryside and metropolitan area, who mostly have consultations at the HNSC, sought this service possibly due to a shortage or lack of specialized professionals in their cities of origin.

Treatment

Having hepatocellular carcinoma, decompensated cirrhosis, or other neoplasms interfere with the assessment of the patient's profile and with the recommendation of treatment[14]. Cirrhosis was shown to be a positive factor in the simple analysis, which is justified by the recent finding that having advanced cirrhosis was a necessary criterion for undertaking treatment[14]. On the other hand, co-infection with HIV and institutionalized individuals proved to be risk factors for not undergoing treatment, and it should be noted that they are vulnerable groups[14]. The non-white race in the simple analysis also proved to be a vulnerable group for not undergoing treatment, which reminds us of the need to consider race in the implementation of public policies[20]. In the final analysis, the female sex obtained higher data in the performance of treatment; however, this data contradicts the results seen previously where women, mainly young people, tend to face barriers to engaging in any form of health care[21]. Furthermore, HCV infection rates in women of childbearing potential have increased, making prenatal diagnosis a priority[22]. Being connected to the HNSC was associated with a significantly higher rate of undergoing treatment, which may be related to the maintenance of follow-up at a specialized outpatient clinic for gastroenterology and infectology services.

SVR

Having a low level of education, only elementary school, proved to be an obstacle to collecting HCV-RNA and achieving SVR, indicating the importance of education for the perception of their health status. Counterintuitively, it is possible that having more knowledge about the natural history of the disease is associated with greater stigma of HCV infection, another barrier to be addressed in the continuous care of patients. The patients at the HNSC were mostly from the countryside and metropolitan area and had cirrhosis inferring the need and demand for specialized care. Despite these results, the training of primary care professionals is able to increase the rate of treatment of patients, with HCV cure results in the decentralization of care similar to specialty outpatient clinics[22].

CONCLUSION

Among the limitations of the study is our inability to determine the true rate of SVR due to the high number of missing follow-up HCV-PCR data. Furthermore, other missing data from the HNSC medical records and external sites, important for a thorough analysis of sociodemographic variables, are also a considerable limitation of the referred study. This study identified that the sociodemographic characteristics of patients diagnosed with HCV infection at the HNSC are similar to regional and national data. It was also possible to stratify relevant risk factors for patients failing to proceed along the treatment cascade, thereby elucidating potential targeted strategies to improve care. According to the results of the hepatitis treatment at the HNSC, the importance of specialized care was highlighted. To make hepatitis treatment more accessible to patients in the countryside and metropolitan area, teams need to be properly trained. Given that we are far from the goals defined by the WHO necessary for elimination of HCV as a public health problem, it is critical to strengthen the treatment lines and facilitate care for patients not only at the HNSC, but also throughout the South region.

ARTICLE HIGHLIGHTS

Research background

Hepatitis C virus (HCV) is defined as a public health problem by the World Health Origination (WHO) and since then has defined targets through the HCV elimination.

Research motivation

The South region of Brazil is responsible for the highest detection rate of confirmed HCV infection in the country and also for the highest mortality rate, with higher rates than national data. Within this region, the city of Porto Alegre, in 2020 was the second capital with the highest HCV detection rate, and in 2021 the first, even higher than the national rate.

Research objectives

To define the continuity of care or treatment cascade for patients with chronic HCV infection at the Hospital Nossa Senhora da Conceição (HNSC) and to define sociodemographic variables that influence follow-up between each step of the cascade.

Research methods

With the retrospective cohort design, patients diagnosed with HCV infection in the period between January 1, 2015 and December 31, 2020 were included. Data from HCV notification forms, electronic medical records, Computerized Laboratory Environment Manager System and Medicine Administration System (evaluation of special medications) were collected in 2022 and all information up to that period was considered. The data were analyzed with IBM SPSS version 25, and Poisson regression with robust simple variance was performed for analysis of variables in relation to each step of the cascade. Variables with $P < 0.20$ were included in the multivariate analysis with $P < 0.05$ considered significant. Pearson's chi-square test was applied to compare the groups of patients who persisted in follow-up at the HNSC and who underwent follow-up at other locations.

Research results

Results were lower than expected by the WHO with only 49% of candidates receiving HCV treatment and only 29% achieving sustained virologic response (SVR), despite the 98% response rate to direct acting antivirals documented by follow-up examination. The city of origin and the place of follow-up were the variables associated with SVR and all other endpoints. When comparing the cascade of patients who remained assisted by the HNSC *vs* external patients, we observed superior data for HNSC patients in the SVR. Patients from the countryside and metropolitan region were mostly assisted at the HNSC and the specialized and continuous care provided at the HNSC was associated with superior results, although the outcomes remain far from the goals set by the WHO.

Research conclusions

This study identified that the sociodemographic characteristics of patients diagnosed with HCV infection at the HNSC are similar to regional and national data. It was also possible to stratify relevant risk factors for patients failing to proceed along the treatment cascade, thereby elucidating potential targeted strategies to improve care. According to the results of the hepatitis treatment at the HNSC, the importance of specialized care was highlighted. To make hepatitis treatment more accessible to patients in the countryside and metropolitan area, teams need to be properly trained.

Research perspectives

We have the perspective that other places carry out their HCV cascade of care for stratification of local risk factors, thus helping to eliminate hepatitis C.

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FOOTNOTES

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REFERENCES

1 **World Health Organization**. Global Health Sector Strategy on Viral Hepatitis, 2016–2021: towards ending viral hepatitis. April 26, 2018. [cited 1 June 2023]. Available from: http://apps.who.int/iris/bitstream/10665/246177/1/WHO-HIV-2016.06-eng.pdf
2 **World Health Organization**. Global Hepatitis Report 2017. 2017. [cited 1 June 2023]. Available from: https://www.who.int/publications-detail-redirect/9789241565455
3 **Safreed-Harmon K**, Blach S, Aleman S, Bollerup S, Cooke G, Dalgard O, Dillon JF, Dore GJ, Duberg AS, Grebely J, Boe Kielland K, Midgard H, Porter K, Razavi H, Tyndall M, Weis N, Lazarus JV. The Consensus Hepatitis C Cascade of Care: Standardized Reporting to Monitor Progress Toward Elimination. *Clin Infect Dis* 2019; **69**: 2218-2227 [PMID: 31352481 DOI: 10.1093/cid/ciz714]
4 **World Health Organization**. Global reporting system for hepatitis (GRSH)–project description. 2018. [cited 1 June 2023]. Available from: https://www.who.int/teams/global-hiv-hepatitis-and-stis-programmes/hepatitis/strategic-information/global-reporting-system
5 **World Health Organization**. Progress report on access to hepatitis C treatment: focus on overcoming barriers in low- and middle-income countries. March 2018. [cited 1 June 2023]. Available from: https://apps.who.int/iris/bitstream/handle/10665/260445/WHO-CDS-HIV-18.4-eng.pdf?sequence=1
6 **Balakrishnan M**, Kanwal F. The HCV Treatment Cascade: Race Is a Factor to Consider. *J Gen Intern Med* 2019; **34**: 1949-1951 [PMID: 31342332 DOI: 10.1007/s11606-019-04962-3]
7 **Hawks L**, Norton BL, Cunningham CO, Fox AD. The Hepatitis C virus treatment cascade at an urban postincarceration transitions clinic. *J Viral Hepat* 2016; **23**: 473-478 [PMID: 26856967 DOI: 10.1111/jvh.12512]
8 **Yehia BR**, Schranz AJ, Umscheid CA, Lo Re V 3rd. The treatment cascade for chronic hepatitis C virus infection in the United States: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e101554 [PMID: 24988388 DOI: 10.1371/journal.pone.0101554]
9 **Brazil Ministry of Health**. Secretary of Health Surveillance. Prevention and Control of Sexually Transmitted Infections, HIV/AIDS and Viral Hepatitis. Plan for the Elimination of Hepatitis C in Brazil. Brasília: Ministry of Health, 2018. [cited 1 June 2023]. Available from: https://bvsms.saude.gov.br/bvs/publicacoes/protocolo_clinico_hiv_sifilis_hepatites.pdf
10 **Coalition for Global Hepatitis Elimination**. Perfil Nacional De Eliminação. Das Hepatites Virais. Julho, 2021. [cited 1 June 2023]. Available from: https://www.globalhep.org/sites/default/files/content/news/files/2021-07/National%20Hepatitis%20Elimination%20Profile_Brazil_July%2028.pdf
11 **BRAZIL**. Ministry of Health. Secretary of Health Surveillance. Department of Surveillance, Prevention and Control of STIs, HIV/AIDS and Viral Hepatitis. Epidemiological Bulletin of Viral Hepatitis. Brasilia: Ministry of Health, 2022. [cited 1 June 2023]. Available from: https://www.gov.br/saude/pt-br/centrais-de-conteudo/publicacoes/boletins/epidemiologicos/especiais/2022/boletim-epidemiologico-de-hepatites-virais-2022-numero-especial

12 **Grupo Hospitalar Conceição**. Letter of Services to the Citizen. 2017. [cited 1 June 2023]. Available from: https://www.ghc.com.br/files/cartacidadao.pdf.

13 **Government of the State of Rio Grande do Sul**. State Health Surveillance Center. Epidemiological Bulletin Viral Hepatitis, Rio Grande do Sul. July, 2022. [cited 1 June 2023]. Available from: https://saude.rs.gov.br/upload/arquivos/202207/25120953-boletim-epidemiologico-hepatites-virais-2022.pdf

14 **Capraru C**, Feld JJ. Remaining challenges in HCV elimination. *J Hepatol* 2021; **74**: 964-965 [PMID: 33589319 DOI: 10.1016/j.jhep.2020.11.051]

15 **Solomon SS**, Wagner-Cardoso S, Smeaton L, Sowah LA, Wimbish C, Robbins G, Brates I, Scello C, Son A, Avihingsanon A, Linas B, Anthony D, Nunes EP, Kliemann DA, Supparatpinyo K, Kityo C, Tebas P, Bennet JA, Santana-Bagur J, Benson CA, Van Schalkwyk M, Cheinquer N, Naggie S, Wyles D, Sulkowski M. A minimal monitoring approach for the treatment of hepatitis C virus infection (ACTG A5360 [MINMON]): a phase 4, open-label, single-arm trial. *Lancet Gastroenterol Hepatol* 2022; **7**: 307-317 [PMID: 35026142 DOI: 10.1016/S2468-1253(21)00397-6]

16 **Kamali I**, Shumbusho F, Barnhart DA, Nyirahabihirwe F, Gakuru JP, Dusingizimana W, Nizeyumuremyi E, Habinshuti P, Walker S, Makuza JD, Serumondo J, Nshogoza Rwibasira G, Ndahimana JD. Time to complete hepatitis C cascade of care among patients identified during mass screening campaigns in rural Rwanda: a retrospective cohort study. *BMC Infect Dis* 2022; **22**: 272 [PMID: 35313817 DOI: 10.1186/s12879-022-07271-z]

17 **Romero-Hernández B**, Martínez-García L, Rodríguez-Dominguez M, Martínez-Sanz J, Vélez-Díaz-Pallarés M, Pérez Mies B, Muriel A, Gea F, Pérez-Elías MJ, Galán JC. The Negative Impact of COVID-19 in HCV, HIV, and HPV Surveillance Programs During the Different Pandemic Waves. *Front Public Health* 2022; **10**: 880435 [PMID: 35937266 DOI: 10.3389/fpubh.2022.880435]

18 **Blanding DP**, Moran WP, Bian J, Zhang J, Marsden J, Mauldin PD, Rockey DC, Schreiner AD. Linkage to specialty care in the hepatitis C care cascade. *J Investig Med* 2021; **69**: 324-332 [PMID: 33203787 DOI: 10.1136/jim-2020-001521]

19 **Pawlotsky JM**, Ramers CB, Dillon JF, Feld JJ, Lazarus JV. Simplification of Care for Chronic Hepatitis C Virus Infection. *Semin Liver Dis* 2020; **40**: 392-402 [PMID: 32725611 DOI: 10.1055/s-0040-1713657]

20 **Pearce ME**, Bartlett SR, Yu A, Lamb J, Reitz C, Wong S, Alvarez M, Binka M, Velásquez Garcia H, Jeong D, Clementi E, Adu P, Samji H, Wong J, Buxton J, Yoshida E, Elwood C, Sauve L, Pick N, Krajden M, Janjua NZ. Women in the 2019 hepatitis C cascade of care: findings from the British Columbia Hepatitis Testers cohort study. *BMC Womens Health* 2021; **21**: 330 [PMID: 34511082 DOI: 10.1186/s12905-021-01470-7]

21 **Luetkemeyer AF**, Wyles DL. CROI 2019: highlights of viral hepatitis. *Top Antivir Med* 2019; **27**: 41-49 [PMID: 31137002]

22 **Saine ME**, Szymczak JE, Moore TM, Bamford LP, Barg FK, Forde KA, Schnittker J, Holmes JH, Mitra N, Lo Re V 3rd. The impact of disease-related knowledge on perceptions of stigma among patients with Hepatitis C Virus (HCV) infection. *PLoS One* 2021; **16**: e0258143 [PMID: 34610030 DOI: 10.1371/journal.pone.0258143]

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ORIGINAL ARTICLE

Observational Study

Impact renaming non-alcoholic fatty liver disease to metabolic associated fatty liver disease in prevalence, characteristics and risk factors

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Abstract

BACKGROUND

Recently, a group of hepatologists proposed to rename non-alcoholic fatty liver disease (NAFLD) as metabolic associated fatty liver disease (MAFLD) with modified diagnostic criteria. It is important to note, however, that there are some differences between the diagnostic criteria used for NAFLD and MAFLD. Since the research on MAFLD is just beginning, however, evidence on its incidence and prevalence in the general population and in specific subpopulations remains limited.

AIM

To assess epidemiology of fatty liver in new definition and compare MAFLD with NAFLD. Exploring risk factors of MAFLD individuals.

METHODS

This was a retrospective, cross-sectional study. A total of 85242 adults were selected from the Chinese health management database in 2017–2022. The data of general information, laboratory indicators, lifestyle management and psychological status were obtained. MAFLD was diagnosed as ultrasound diagnosis of fatty liver and at least one between these three conditions: Overweight/obesity, type 2 diabetes mellitus (T2DM) or metabolic dysregulation. Metabolic factors were not considered in NAFLD diagnosis standard. The clinical characteristics of MAFLD and NAFLD were analysed using descriptive statistics. Continuous

variables normally distributed were expressed as means ± SD. Categorical variables were expressed as frequencies and proportions. Binary logistic regression was used to determine risk factors of the MAFLD.

RESULTS

The prevalence of MAFLD and NAFLD was 40.5% and 31.0%, respectively. The MAFLD or NAFLD population is more likely to be older (M: 47.19 ± 10.82 *vs* 43.43 ± 11.96; N: 47.72 ± 11.17 *vs* 43.71 ± 11.66), male (M: 77.21% *vs* 44.43%; N: 67.90% *vs* 53.12%) and high body mass index (M: 26.79 ± 2.69 *vs* 22.44 ± 2.48; N: 26.29 ± 2.84 *vs* 23.29 ± 3.12) than the non-MAFLD or non-MAFLD population. In multivariate analysis, general information (*e.g.*, ≥ 2 metabolic abnormalities OR = 3.38, (95%CI: 2.99-3.81), $P < 0.001$; diastolic blood pressure OR = 1.01, (95%CI: 1.00–1.01), $P = 0.002$), laboratory results [*e.g.*,total bilirubin (TBIL) OR = 0.98, (95%CI: 0.98-0.99), $P < 0.001$; serum uric acid(SUA) OR = 1.01, (95%CI: 1.01-1.01), $P < 0.001$], and lifestyle factors [*e.g.*, drink beverage OR = 0.32, (95%CI: 0.17-0.63), $P = 0.001$] were influence factors for MAFLD. Our study results offer new insight into potential risk factors associated with fatty liver disease, including SUA, TBIL and creatinine, all of which are related to chronic renal disease (CKD).

CONCLUSION

MAFLD is more prevalent than NAFLD, with two-fifths of individuals meeting the diagnosis criteria. MAFLD and NAFLD populations have different clinical characteristics. CKD may be related with MAFLD.

Key Words: Metabolic (dysfunction)-associated fatty liver disease; Non-alcoholic fatty liver disease; Epidemiology; Risk factors; Characteristics; Cross-section study

Core Tip: This study explores the epidemiological characteristics, risk factors and draws reliable conclusions based on the new diagnostic criteria for metabolic associated fatty liver disease, using a large sample of data, and provides evidence for subsequent studies.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is associated with excessive lipid accumulation in the liver resulting from disordered hepatic lipid metabolism that is stimulated by non-alcohol-related factors[1]. In 2019, the global prevalence of NAFLD was approximately 30.6%[2]. In China, the prevalence is as high as 32.3%[3], making it the number one cause of chronic liver disease and abnormal liver biochemical indicators during routine physical examination. These findings indicate that NAFLD imposes a heavy disease burden on patients and society. As its disease mechanism has become better understood, the limitations of the NAFLD nomenclature have become more apparent. These include: (1) The lack of a uniform standard for calculating alcohol intake, which has led to an underestimation of the role of alcohol consumption in disease pathogenesis; and (2) a failure to recognize the influence of metabolic factors in disease etiology [4]. In 2020, Eslam *et al*[5] suggested renaming NAFLD as 'metabolic (dysfunction) associated fatty liver disease' (MAFLD). A diagnosis of MAFLD includes the presence of hepatic steatosis and one or more of the following features: (1) Overweight based on body mass index (BMI); (2) type 2 diabetes mellitus; or (3) lean or normal weight with evidence of metabolic dysregulation[6]. The new nomenclature aims to reflect the close relationship between fatty liver and overnutrition, sedentary lifestyle, and metabolic conditions such as type 2 diabetes, hypertension, dyslipidemia, and obesity[7]. Adopting a positive diagnosis like MAFLD recognizes the impact of metabolic conditions and fatty liver on the natural history of different liver diseases such as chronic viral hepatitis and alcohol-related liver disease[8].

It is important to note, however, that there are some differences between the diagnostic criteria used for NAFLD and MAFLD. Study indicates that[6] some NAFLD patients are excluded under the proposed MAFLD definition, based on disparate characteristics included in each definition. The rates of diabetes, hypertriglyceridemia, hypertension, and fibrosis risk are significantly higher among MAFLD than NAFLD patients. The proposed MAFLD definition challenges the current understanding of the prevalence and associated factors of fatty liver. Meanwhile, MAFLD is shown to be a better predictor of cardiovascular disease risk among asymptomatic individuals than NAFLD[9]. Since the research on MAFLD is just beginning, however, evidence on its incidence and prevalence in the general population and in specific subpopulations remains limited. The few studies are based on small sample sizes and do not directly compare the characteristics of NAFLD and MAFLD[10]. Thus, our study aims to conduct an updated analysis of the prevalence and factors associated with MAFLD. A more comparative analysis of the clinical characteristics of patients with NAFLD and MAFLD

is also performed in order to identify MAFLD-specific risk factors.

MATERIALS AND METHODS

Study design

A cross-sectional study was conducted by recruiting participants from the health management center of the general tertiary hospital of Southern China between August 1, 2017 and October 31, 2022. Patients who were ≥ 18 years of age, had received a fatty liver color Doppler ultrasonography result, blood lipid examination, exercise and dietary evaluation, and were voluntary participants in this study were included. Patients who lacked imaging or laboratory data for a MAFLD diagnosis, had incomplete Diet and Exercise Health Check survey responses, or were pregnant at the time of examination due to different waist circumference and BMI measurements caused by pregnancy, were excluded from the study. This study was reviewed and approved by the Central South University Ethics Review Board (IRB2022-S217). All patients provided their written informed consent to participate in the study.

Diagnostic criteria and group definitions

Definition of hepatic steatosis: Hepatic steatosis was defined in NHANES III participants using the Hepatic Steatosis Ultrasound Examination. Adult patients received a hepatic ultrasound at a mobile examination center using a Toshiba Sonolayer SSA-90A ultrasound machine (Toshiba America Medical Systems, Inc., Tustin, CA, United States)[11]. Board-certified radiologists used five different parameters to assess hepatic steatosis: parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, bright vessel walls, and gallbladder wall definition. Ultrasonographic assessments were reported as normal, mild, moderate, or severe hepatic steatosis. Abiding by quality control procedures, reliability results (intra-rater and inter-rater) were calculated. The intra-rater and inter-rater reliabilities were 91.3% (kappa 0.77) and 88.7% (kappa 0.70), respectively[12].

Definition of MAFLD: MAFLD was defined[13] as the presence of hepatic steatosis by liver ultrasound plus one or more of the following conditions: (1) overweight/obesity (BMI>23 kg/m^2); (2) type 2 diabetes mellitus (T2DM); (3) at least two metabolic risk abnormalities. Metabolic risk abnormalities included: (1) A waist circumference ≥ 90 cm in males or ≥ 80 cm in females; (2) a blood pressure ≥ 130/85 mmHg or specific drug treatment; (3) plasma triglycerides ≥ 150 mg/dL (≥ 1.70 mmol/L) or specific drug treatment; (4) plasma high density lipoprotein cholesterol(HDL-C) < 40 mg/dL (< 1.0 mmol/L) for males and < 50 mg/dL (< 1.3 mmol/L) for females or specific drug treatment; (5) prediabetes [fasting glucose levels of 100–125 mg/dL (5.6–6.9 mmol/L) or HbA1c (5.7%–6.4%) 39–47 mmol/L]; (6) homeostasis model assessment of insulin resistance (HOMA-IR) score ≥ 2.5; (7) a plasma high sensitivity C-reactive protein level > 2 mg/L.

Definition of NAFLD: NAFLD was diagnosed according to the EASL-European Association for the Study of Diabetes-European Association for the Study of Obesity and American Association for the Study of Liver Diseases Clinical Practice Guidelines for the Management of NAFLD: (1) Fatty liver by abdominal ultrasonography; (2) alcohol consumption< £30 g/d for men and <£20 g/d for women; and (3) no competing etiologies for fatty liver or coexisting causes of chronic liver disease[14].

Demographic variables

The following demographic variables were obtained from the patient electronic record database: age, gender, BMI, waist circumference, hip circumference, smoking, alcohol consumption, hypertension, diabetes, and actively acquisition of medical knowledge. BMI was calculated as the weight (in kilograms) divided by the square of the height (in meters). Overweight/obesity was defined as BMI > 23 kg/m^2. Waist and hip circumferences were determined in centimeters using a tape measure. Blood pressure was recorded in the sitting position using standardized equipment. Hypertension was defined as a systolic blood pressure (SBP) ≥ 130 mmHg and a diastolic blood pressure ≥ 85 mmHg or the use of antihypertensive medications. A diagnosis of diabetes was based on a history of diabetes, use of antidiabetic medications, and/or a fasting plasma glucose ≥ 7.0 mmol/L. Information on lifestyle and psychological factors was acquired from the patient self-report questionnaires.

Laboratory parameters

Laboratory measurements included total bilirubin (TBIL), aspartate aminotransferase (AST), alanine transaminase (ALT), albumin/globulin (A/G), fasting plasma glucose (FPG), glycated haemoglobin (HbA1c), total cholesterol (TC), triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), platelet, creatinine, ≥ 2 metabolic abnormalities, blood urea nitrogen (BUN) and serum uric acid (SUA). All biochemical assessments were performed using standard laboratory methods. HDL-C, LDL-C, FPG, BUN, TC and TG were reported in millimoles per liter (mmol/L). The units of TBIL, SUA, total bile acid and creatinine were micromoles per liter(umol/L), HbA1c is expressed in percentage terms, and liver enzymes(AST,ALT) were reported in units per liter (U/L).

Statistical analysis

Continuous variables normally distributed were expressed as means ± SD. Categorical variables were expressed as frequencies and proportions. The prevalence of MAFLD and NAFLD was determined as the number of subjects with the corresponding conditions divided by the total number of subjects. Univariable and multivariable binary logistic regression analyses were also performed to determine factors associated with MAFLD. The univariate and multivariate

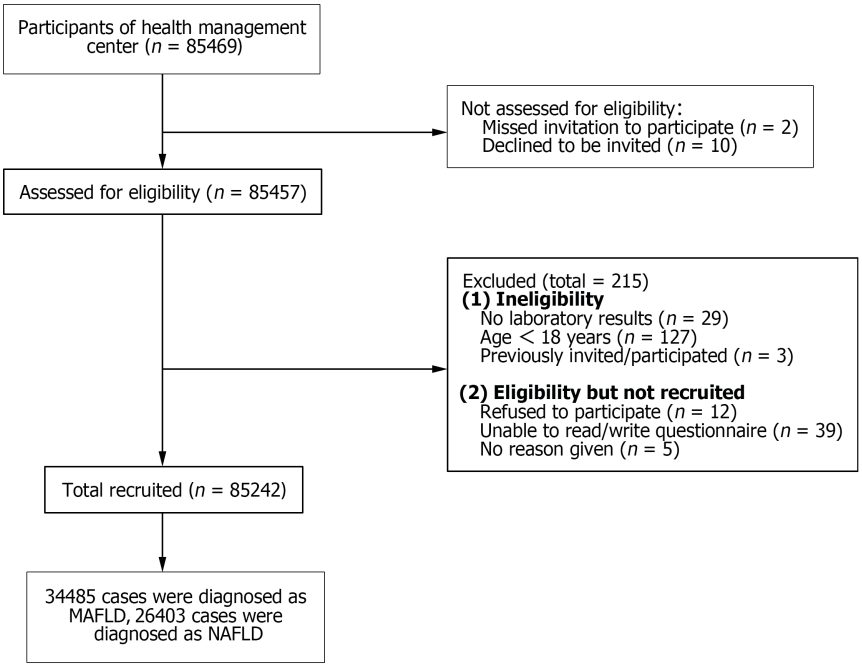

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Figure 1 Flow chart of the study population inclusion process. MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

odd ratios (OR) were reported along with 95% confidence intervals (CI). All tests were two-tail and results with a P value < 0.05 were considered statistically significant. All analyses were conducted using SPSS 24 version.

RESULTS

Of the 85242 recruited participants (Figure 1), 26403 (31.0%) had NAFLD [8476 (32.10%) women, median age 47.72 ± 11.17 years], and 34485 (40.5%) met the criteria for MAFLD [7858 (22.79%) women; median age 47.19 ± 10.82 years] (Figure 2, Table 1). Total 23905 (28.0%) participants diagnosed with both MAFLD and NAFLD [7555 (31.60%) women; median age 47.85 ± 11.18 years]. Patients with MAFLD had a higher BMI than those without [26.79 ± 2.69 kg/m^2 *vs* 22.44 ± 2.48 kg/m^2, respectively]. 5.15% (1775/34485) of patients diagnosed with MAFLD have diabetes, and 79.85% (27536/34485) had two or more metabolic abnormalities. Meanwhile, 2498 patients met the definition of NAFLD but did not meet the MAFLD criteria (Figure 3). The general information , laboratory, lifestyle, and psychological characteristics of the study population are summarized in Table 1. All the patients were ethnic Chinese.

The prevalence of MAFLD was lower among individuals < 30 years of age (approximately 2.56%) and highest among those 50–59 years of age (Figure 4). Disease prevalence was significantly higher among men than women. Changes in age-related prevalence were similar for patients with NAFLD and MAFLD, however, there was a lower overall prevalence of NAFLD than MAFLD (Figure 5). The prevalence of both MAFLD and NAFLD increased with BMI and for patients with a BMI ≥ 25, the risk of NAFLD and MAFLD increased dramatically (Figure 6).

In univariate analysis, male sex, older age, higher BMI, higher diastolic blood pressure, higher waist circumference, lower hip circumference, and alcohol consumption, ≥ 2 metabolic abnormalities, medically knowledgeable, TG, HDL-C, TBIL, AST, ALT, A/G, glycated hemoglobin (HbA1c), SUA, platelet, creatinine, drink beverage, exercise frequency, exercise duration and physical labor intensity were associated with MAFLD. In contrast, systolic blood pressure, smoking, diabetes, TC, LDL-C, blood urea nitrogen (BUN), FPG, total bile acid, inappetence, night snacks, crapulent, food preferences, and psychological characteristics were not significantly associated with this disease (P > 0.05). In multivariate analysis, female sex (OR = 0.67, 95%CI: 0.57–0.80, P = 0.001), older age (OR = 1.01, 95%CI: 1.00–1.02, P = 0.001), higher BMI (OR = 1.45, 95%CI: 1.40–1.51, P < 0.001), diastolic blood pressure (OR = 1.01, 95%CI: 1.00–1.01, P = 0.002), waist circumference (OR = 1.12, 95%CI: 1.11–1.14, P < 0.001), hip circumference (OR = 0.95, 95%CI: 0.93–0.96, P < 0.001), metabolic abnormalities(OR = 3.38, 95%CI: 2.99–3.81, P < 0.001), actively acquire medical knowledge (OR = 1.14, 95%CI: 1.03–1.27, P = 0.014), TG (OR = 1.33, 95%CI: 1.27–1.40, P < 0.001), HDL-C (OR = 0.58, 95%CI: 0.47–0.71, P < 0.001), TBIL(OR = 0.98, 95%CI: 0.98–0.99, P < 0.001), AST OR = 1.01, 95%CI: 1.01–1.01, P < 0.001), ALT (OR = 1.02, 95%CI: 1.02–1.02, P < 0.001), HbA1c (OR = 1.52, 95%CI: 1.47–1.57, P < 0.001), higher SUA level (OR = 1.01, 95%CI: 1.01–1.01, P < 0.001), platelets (OR = 1.00, 95%CI: 1.00–1.00, P < 0.001), creatinine (OR = 0.99, 95%CI: 0.99–0.99, P < 0.001), drink beverages (OR = 0.32, 95%CI: 0.17–0.63, P = 0.001), exercise frequency (OR = 0.82, 95%CI: 0.71–0.95, P = 0.009), exercise duration (OR = 1.24, 95%CI: 1.04-1.47, P = 0.015), and labour intensity (OR = 0.78, 95%CI: 0.65–0.95, P = 0.013) remained as independent variables associated with MAFLD (Table 2).

Table 1 Clinical characteristics of the study participants metabolic associated fatty liver disease & non-alcoholic fatty liver disease, with and without metabolic associated fatty liver disease and non-alcoholic fatty liver disease, *n* (%)

Characteristics	All	MAFLD	Not MAFLD	NAFLD	Not NAFLD	MAFLD & NAFLD
N	85242	34485 (40.5)	50757 (59.5)	26403 (31.0)	58839 (69.0)	23905 (28.0)
General information						
Age, yr		47.19 ± 10.82	43.43 ± 11.96	47.72 ± 11.17	43.71 ± 11.66	47.85 ± 11.18
Sex						
Male	49177	26627 (77.21)	22550 (44.43)	17927 (67.90)	31259 (53.12)	16350 (68.40)
Female	36065	7858 (22.79)	28207 (55.57)	8476 (32.10)	27589 (46.88)	7555 (31.60)
BMI, kg/m^2		26.79 ± 2.69	22.44 ± 2.48	26.29 ± 2.84	23.29 ± 3.12	26.64 ± 2.71
Systolic blood pressure, mmHg		128.50 ± 15.42	118.67 ± 15.13	127.40 ± 15.67	120.52 ± 15.68	128.21 ± 15.69
Diastolic blood pressure, mmHg		79.97 ± 11.06	72.17 ± 10.42	78.49 ± 10.96	73.91 ± 11.24	79.06 ± 10.96
Waist circumference, cm		90.41 ± 7.68	76.78 ± 8.01	88.57±8.03	79.51 ± 10.03	89.43 ± 7.74
Hip circumference, cm		97.81 ± 5.52	91.53 ± 5.03	96.92 ± 5.63	92.80 ± 5.83	97.42 ± 5.55
Smoke						
Never	57452	19713 (57.18)	37739 (74.36)	17589 (66.63)	39863 (67.76)	15824 (66.21)
Always	20951	11443 (33.19)	9508 (18.73)	6663 (25.24)	14288 (24.29)	6127 (25.64)
Smoke in the past	3106	1666 (4.83)	1440 (2.84)	1047 (3.97)	2059 (3.50)	956 (4.00)
Passive exposure to secondhand smoke	3720	1655 (4.80)	2065 (4.07)	1098 (4.16)	2622 (4.46)	992 (4.15)
Alcohol consumption						
Yes	27567	14899 (44.10)	12668 (25.31)	5546 (21.31)	22021 (38.09)	5042 (21.41)
No	56275	18882 (55.90)	37393 (74.69)	20478 (78.69)	35797 (61.91)	18506 (78.59)
Diabetes						
Yes	2596	1775 (5.15)	821 (1.62)	1287 (5.12)	1309 (2.22)	1287 (5.38)
No	82645	32710 (94.85)	49935 (98.38)	25116 (94.88)	57529 (97.78%)	22618 (94.61)
Inappetence						
Never	57298	24017 (69.66)	33281 (65.57)	18671 (70.73)	38627 (65.65)	16988 (71.08)
Occasionally	24989	9446 (27.40)	15543 (30.62)	6976 (26.43)	18013 (30.62)	6232 (26.08)
Often	2947	1016 (2.95)	1931 (3.80)	751 (2.84)	2196 (3.73)	680 (2.85)
Take the initiative to acquire medical knowledge						
Yes	48284	19268 (55.88)	29016 (57.17)	14989 (56.78)	33295 (56.59)	13534 (56.63)
No	36946	15210 (44.12)	21736 (42.83)	11409 (43.22)	25537 (43.41)	10366 (43.37)
Laboratory inspection						
TG, mmol/L		2.67 ± 2.40	1.32 ± 1.00	2.38 ± 2.07	1.63 ± 1.67	2.47 ± 2.14
TC, mmol/L		5.24 ± 1.04	4.89 ± 0.92	5.19 ± 1.00	4.96 ± 0.97	5.19 ± 1.01
LDL-C, mmol/L		2.88 ± 0.89	2.86 ± 0.78	2.94 ± 0.87	2.84 ± 0.80	2.92 ± 0.88
HDL-C, mmol/L		1.18 ± 0.24	1.42 ± 0.30	1.19 ± 0.24	1.38 ± 0.31	1.18 ± 0.23
TBIL, μmol/L		13.38 ± 5.15	13.52 ± 5.28	13.24 ± 5.15	13.56 ± 5.26	13.21 ± 5.16
AST, U/L		26.83 ± 18.10	22.55 ± 17.75	25.76 ± 13.67	23.74 ± 19.70	26.00 ± 14.07
ALT, U/L		35.73 ± 27.93	21.28 ± 21.60	33.86 ± 25.81	24.09 ± 24.57	34.59 ± 26.44
A/G		1.76 ± 0.29	1.76 ± 0.31	1.75 ± 0.28	1.77 ± 0.31	1.74 ± 0.28
FPG, mmol/L		5.96 ± 1.68	5.32 ± 1.77	5.88 ± 1.62	5.44 ± 1.81	5.93 ± 1.65

HbA1c (%)		5.91 ± 0.96	5.52 ± 0.63	5.90 ± 0.95	5.59 ± 0.72	5.92 ± 0.95
BUN, mmol/L		4.97 ± 1.23	4.71 ± 1.31	4.95 ± 1.23	4.75 ± 1.31	4.97 ± 1.23
SUA, μmol/L		385.23 ± 85.79	312.61 ± 79.14	372.25 ± 85.03	328.43 ± 87.85	375.02 ± 85.10
Platelets ($\times 10^9$/L)		227.84 ± 54.33	225.02 ± 55.02	229.55 ± 54.92	224.64 ± 54.61	229.55 ± 55.11
Total bile acid, μmol/L		4.36 ± 5.89	3.96 ± 5.25	4.24 ± 5.13	4.07 ± 5.71	4.29 ± 5.25
Creatinine, μmol/L		77.32 ± 16.64	78.80 ± 43.80	75.62 ± 17.34	72.46 ± 41.16	75.84 ± 17.52
≥ 2 metabolic abnormalities						
Yes	38399	27536 (79.85)	10863 (21.40)	19018 (72.03)	19381 (32.94)	19018 (79.56)
No	46843	6949 (20.15)	39894 (78.60)	7385 (27.97)	39458 (67.06)	4887 (20.44)
Lifestyle management						
Do you often eat late night snacks						
Never	56798	23097 (66.99)	33701 (66.40)	19221 (72.81)	37577 (63.87)	17377(72.70)
Occasionally	25624	10204 (29.59)	15420 (30.38)	6579 (24.92)	19045 (32.37)	5971 (24.98)
Often	2811	1179 (3.42)	1632 (3.22)	600 (2.27)	2211 (3.76)	554 (2.32)
Crapulent						
Yes	5750	3175 (9.21)	2575 (5.07)	1799 (6.81)	3951 (6.72)	1706 (7.14)
No	79484	31305 (90.79)	48179 (94.93)	24600 (93.19)	54884 (93.28)	22195 (92.86)
Food preference						
Light	35389	12278 (35.61)	23111 (45.54)	10875 (41.20)	24514 (41.67)	9665 (40.44)
Briny	26194	12755 (36.99)	13439 (26.48)	8694 (32.93)	17500 (29.74)	8014 (33.53)
Unclear	23649	9446 (27.40)	14203 (27.98)	6829 (25.87)	16820 (28.59)	6221 (26.03)
Drink beverage						
Never	46065	18399 (82.24)	27666 (82.51)	13920 (81.90)	32145 (82.27)	12602 (81.58)
Occasionally	9198	3653 (16.33)	5545 (16.54)	2830 (16.65)	6368 (16.30)	2624 (16.99)
Often	806	320(1.43)	320 (0.95)	246 (1.45)	560 (1.43)	222 (1.44)
Exercise frequency						
1-2 times/wk	21380	8441 (39.52)	12939 (41.37)	6477 (39.69)	14903 (41.04)	5820 (39.48)
3-5 times/wk	21162	8672 (40.60)	12490 (39.94)	6503 (39.85)	14659 (40.36)	5887 (39.93)
> 5 times/wk	10093	4247 (19.88)	5846 (18.69)	3338 (20.46)	6755 (18.60)	3036 (20.59)
Exercise training						
Yes	52829	21444 (62.20)	31385 (61.84)	16404 (62.15)	36425 (61.91)	14825 (62.03)
No	32400	13033 (37.80)	19367 (38.16)	9991 (37.85)	22409 (38.09)	9073 (37.97)
Exercise duration						
< 30 min	12701	4950 (23.17)	7751 (24.78)	4085 (25.03)	8616 (23.72)	3662 (24.84)
30-60 min	30669	12575 (58.87)	18094 (57.85)	9475 (58.06)	21194 (58.36)	8568 (58.12)
> 60 min	9266	3836 (17.96)	5430 (17.36)	2758 (16.90)	6508 (17.92)	2513 (17.05)
Labour intensity						
Light physical labor	77907	31651 (91.78)	46256 (91.13)	24186 (91.60)	53721 (91.30)	21844 (91.38)
Moderate physical labor	6282	2463 (7.14)	3819 (7.52)	1940 (7.35)	4342 (7.38)	1808 (7.56)
Heavy physical labor	1053	371 (1.08)	682 (1.34)	277 (1.05)	776 (1.32)	253 (1.06)
Psychological states						
Irritability						

Never	43964	18836 (54.63)	25128 (49.51)	14745 (55.85)	29219 (49.67)	13428 (56.18)
Occasionally	35294	13631 (39.53)	21663 (42.68)	10152 (38.46)	25142 (42.74)	9103 (38.09)
Often	5973	2012 (5.84)	3961 (7.80)	1502 (5.69)	4471 (7.60)	1370 (5.73)
Tense and unrelaxed						
Never	54907	22753 (65.99)	31154 (61.38)	17813 (67.47)	36094 (61.35)	16156 (67.59)
Occasionally	26438	10081 (29.24)	16357 (32.23)	7379 (27.95%)	19059 (32.39)	6638 (27.77%)
Often	4890	1647 (4.78)	3243 (6.39)	1208 (4.58)	3682 (6.26)	1108 (4.64)
Anxious						
Never	55837	23594 (68.43)	32243 (63.53)	18363 (69.56)	37474 (63.69)	16670 (69.75)
Occasionally	25399	9578 (27.78)	15821 (31.17)	7059 (26.74)	18340 (31.17)	6337 (26.51)
Often	3999	1307 (3.79)	2692 (5.30)	977 (3.70)	3022 (5.14)	894 (3.74)
Depress						
Never	59871	25192 (73.06)	34679 (68.32)	19610 (74.28)	40261 (68.43)	17811 (74.52)
Occasionally	22155	8306 (24.09)	13849 (27.29)	6040 (22.88)	16115 (27.39)	5410 (22.63)
Often	3210	982 (2.85)	2228 (4.39)	750 (2.84)	2460 (4.18)	681 (2.85)
Sleep						
Well	33017	14188 (41.15)	18829 (37.10)	11027 (41.77)	21990 (37.38)	10043 (42.02)
Moderate	43242	16974 (49.23)	26268 (51.76)	12894 (48.84)	30348 (51.58)	11627 (48.65)
Bad	8974	3318 (9.62)	5656 (11.14)	2478 (9.39)	6496 (11.04)	2231 (9.33)

BMI: Body Mass Index; SUA: Serum uric acid; TG: Triglycerides; TC: Total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TBIL: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; A/G: Albumin/globulin; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; HbA1c: Glycated hemoglobin.

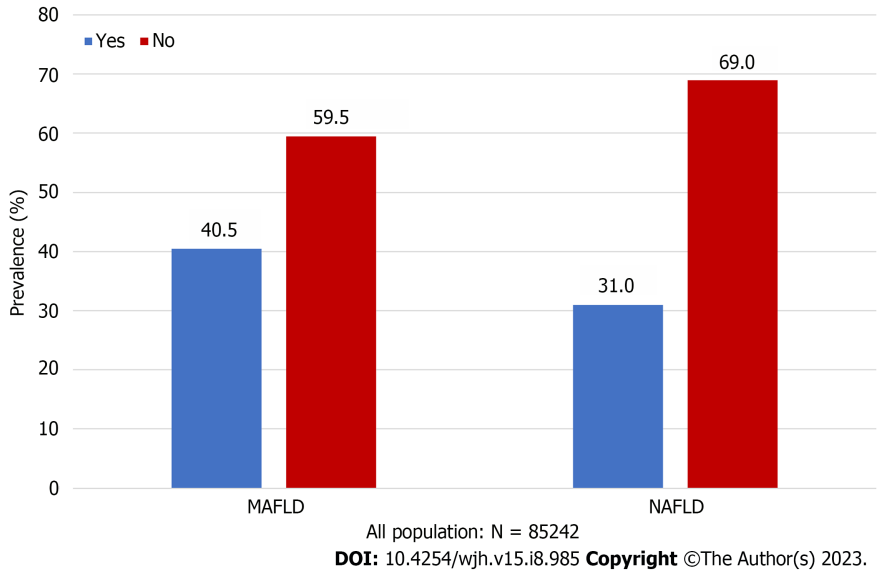

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Figure 2 Prevalence of metabolic associated fatty liver disease and non-alcoholic fatty liver disease. MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

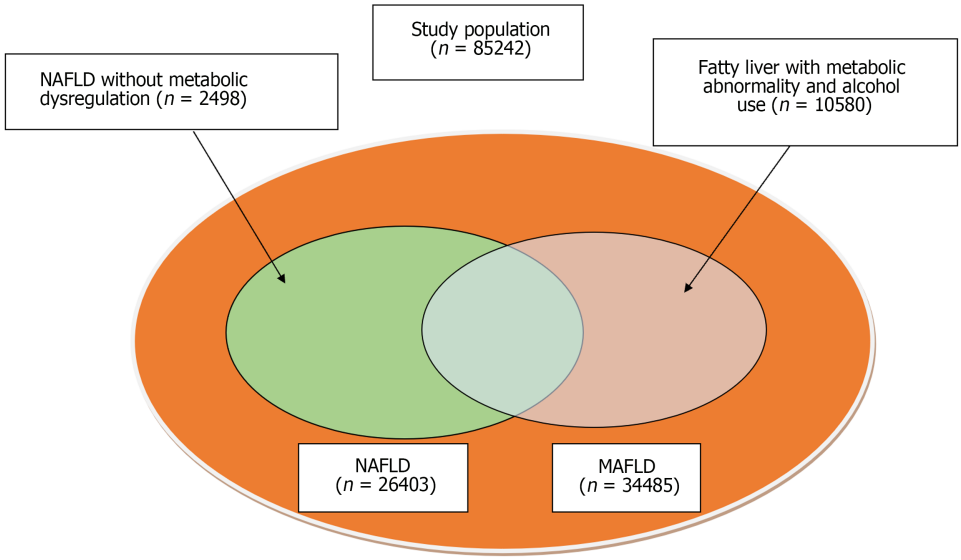

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Figure 3 Participants with metabolic associated fatty liver disease, non-alcoholic fatty liver disease, and those excluded by the two definitions. MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease.

DISCUSSION

This study found that the prevalence of fatty liver disease was higher when the MAFLD definition was used for diagnosis rather than the NAFLD definition (40.5% *vs* 31.0%, respectively). In addition, a higher number of factors were associated with MAFLD, including general information (*e.g.*, 8 items such as metabolic abnormalities, diastolic blood pressure), laboratory (*e.g.*, 9 items such as TBIL, SUA), and lifestyle (*e.g.*, 4 items such as drink beverage) characteristics. In contrast, psychological factors were not significantly correlated with MAFLD. Among these significant indicators, we have an interesting finding that three indicators are associated with CKD. Participants with CKD may have elevated SUA levels [15], low TBIL levels[16] and abnormal creatinine values, which may suggest that there is an association between CKD and MAFLD, the exact mechanism need to further analysis.

MAFLD prevalence

The prevalence of MAFLD in this study was 40.5%. Several studies have assessed the epidemiology of MAFLD, however, the reported prevalence of this condition varies. While the study[17] demonstrated a lower prevalence of MAFLD (25%-37.3%), a meta-analysis of 2667052 individuals estimated that the global prevalence[18] of this disease was 50.7%. A study using 2017-2018 NHANES data[19] indicated that MAFLD prevalence was 39.1%, a finding similar to that reported here. Consistent with the our study, prior reports have also found that MAFLD[20] is more prevalent in males. Reported[21] variations in the prevalence of MAFLD may be the result of ethnic disparities and environment factors. Differences in the methods used to estimate steatosis (liver ultrasound, elastography, diagnostic scores) may account for some of the heterogeneity.

NAFLD prevalence

The prevalence of NAFLD (31.0%) was lower than the prevalence of MAFLD in this study. A total of 23905 participants had overlapping diagnostic criteria for NAFLD and MAFLD. While 2498 patients had NAFLD without metabolic dysregulation, 10580 patients had fatty liver with metabolic abnormalities and alcohol use. A recent study by Lee *et al*[22] identified a similar number of cases using the MAFLD and NAFLD criteria on population-based data (*n* = 8962813) from National Health and Nutrition Examination surveys (37.3% *vs* 28.0%, respectively), a result similar to our findings. It is probable that the high MAFLD prevalence in the current study was primarily caused by the high prevalence of overweight and metabolic dysfunction.

Comparison of MAFLD and NAFLD disease characteristics

Regardless of age, the prevalence of MAFLD and NAFLD was much higher in males than females, a finding consistent with a study by Ito *et al*[23]. This may be because males are more prone to poor lifestyle habits, such as smoking and alcohol consumption. The current study also found that the peak prevalence of MAFLD occurred earlier among men (40–49 years) than women (50–59 years), a finding reported previously[24]. Women enter menopause and begin to lose estrogen after they are ≥ 50 years of age. Estrogen is thought to suppress visceral fat accumulation and increase subcutaneous fat accumulation. A higher BMI is linked to a higher prevalence of MAFLD and NAFLD. Thus, individuals with high BMI should be appropriately educated about these conditions.

Table 2 Univariate and multivariate logistic regression analysis of factors associated with metabolic associated fatty liver disease, *n* (%)

Variable	Category	Univariate analysis		Multivariable analysis	
		Odds ratio (95%CI)	*P* value	Odds ratio (95%CI)	*P* value
General information					
Sex	Male(ref)				
	Female	0.69 (0.58-0.84)	**< 0.001**	0.67 (0.57-0.80)	**0.001**
Age		1.01 (1.01-1.02)	**0.001**	1.01 (1.00–1.02)	**0.001**
BMI, kg/m^2		1.46 (1.41-1.52)	**< 0.001**	1.45 (1.40-1.51)	**< 0.001**
Systolic blood pressure, mmHg		1.00 (0.99-1.00)	0.360	None	
Diastolic blood pressure, mmHg		1.01 (1.00-1.02)	**0.007**	1.01 (1.00–1.01)	**0.002**
Waist circumference, cm		1.12 (1.11-1.14)	**< 0.001**	1.12 (1.11-1.14)	**< 0.001**
Hip circumference, cm		0.95 (0.93-0.96)	**< 0.001**	0.95 (0.93-0.96)	**< 0.001**
Smoke	Never (ref)		0.409	None	
	Always	1.18 (0.90-1.56)	0.236	None	
	Smoke in the past	1.07 (0.80-1.43)	0.667	None	
	Passive exposure to secondhand smoke	1.15 (0.80-1.65)	0.464	None	
Alcohol consumption	No(ref)				
	Yes	0.89 (0.78-1.01)	**0.061**	1.11 (0.99-1.26)	0.082
Diabetes	No(ref)				
	Yes	1.16 (0.91-1.49)	0.231	None	
≥ 2 metabolic abnormalities	No(ref)				
	Yes	3.38 (3.00-3.82)	**< 0.001**	3.38 (2.99-3.81)	**< 0.001**
Take the initiative to acquire medical knowledge	No(ref)				
	Yes	1.14 (1.02-1.26)	**0.017**	1.14 (1.03-1.27)	**0.014**
Laboratory inspection					
TG, mmol/L		1.31 (1.15-1.49)	**< 0.001**	1.33 (1.27-1.40)	**< 0.001**
TC, mmol/L		1.09 (0.81-1.45)	0.578	None	
LDL- C, mmol/L		1.00 (0.74-1.35)	0.997	None	
HDL-C, mmol/L		0.50 (0.33-0.73)	**< 0.001**	0.58 (0.47-0.71)	**< 0.001**
TBIL, μmol/L		1.01 (1.00-1.02)	**0.044**	0.98 (0.98-0.99)	**< 0.001**
AST, U/L		0.98 (0.97-0.98)	**< 0.001**	1.01 (1.01-1.01)	**< 0.001**
ALT, U/L		1.02 (1.02-1.03)	**< 0.001**	1.02 (1.02-1.02)	**< 0.001**
A/G		1.85 (1.53-2.25)	**< 0.001**	0.99 (0.92-1.08)	0.884
BUN, mmol/L		0.98 (0.94-1.02)	0.388	None	
FPG, mmol/L		0.97 (0.91-1.04)	0.426	None	
HbA1c (%)		1.35 (1.20-1.52)	**< 0.001**	1.52 (1.47-1.57)	**< 0.001**
Total bile acid, μmol/L		1.00 (1.00-1.01)	0.395	None	
SUA, μmol/L		1.00 (1.00-1.01)	**< 0.001**	1.01 (1.01-1.01)	**< 0.001**
Platelets (×10^9/L)		1.00 (1.00-1.00)	**< 0.001**	1.00 (1.00-1.00)	**< 0.001**
Creatinine, μmol/L		0.99 (0.99-1.00)	**< 0.001**	0.99 (0.99-0.99)	**< 0.001**
Lifestyle management					

Inappetence	Never(ref)		0.597	None	
	Occasionally	1.13 (0.84-1.52)	0.409	None	
	Often	1.16 (0.86-1.57)	0.322	None	
Do you often eat late night snacks	Never(ref)		0.529	None	
	Occasionally	1.33 (0.78-2.28)	0.288		
	Often	1.37 (0.79-2.35)	0.260		
Crapulent	No(ref)				
	Yes	0.93 (0.73-1.20)	0.586	None	
Food preference	Light (ref)		0.868	None	
	Briny	0.97 (0.85-1.10)	0.617		
	Unclear	0.99 (0.85-1.14)	0.874		
Drink beverage	Never (ref)		**0.015**		**0.004**
	Occasionally	2.66 (1.37-5.18)	**0.004**	1.01 (0.85-1.20)	0.917
	Often	2.69 (1.36-5.32)	**0.004**	0.32 (0.17-0.63)	**0.001**
Exercise frequency	1-2 times/wk (ref)		**0.048**		**0.025**
	3-5 times/wk	1.20 (1.03-1.40)	**0.017**	0.95 (0.84-1.08)	0.429
	> 5 times/wk	1.14 (1.00-1.30)	**0.049**	0.82 (0.71-0.95)	**0.009**
Exercise training		0.39 (0.04-3.58)	0.404	None	
Exercise duration	< 30 min (ref)		**0.049**		**0.045**
	30-60 min	0.81 (0.68-0.96)	**0.017**	1.07 (0.94-1.22)	0.283
	> 60 min	0.87 (0.76-1.00)	**0.045**	1.24 (1.04-1.47)	**0.015**
Labor intensity	Light physical labor (ref)		**0.049**		**0.026**
	Moderate physical labor	0.80 (0.66-0.97)	**0.024**	0.78 (0.65-0.95)	**0.013**
	Heavy physical labor	0.79 (0.51-1.21)	0.273	0.77 (0.50-1.18)	0.226
Psychological states					
Irritability	Never (ref)		0.637	None	
	Occasionally	1.01 (0.89-1.15)	0.851		
	Often	1.14 (0.87-1.50)	0.346		
Tense and unrelaxed	Never (ref)		0.806	None	
	Occasionally	0.95 (0.820-1.11)	0.351		
	Often	0.96 (0.69-1.35)	0.828		
Anxious	Never (ref)		**0.076**		0.091
	Occasionally	0.92 (0.78-1.08)	0.290	0.96 (0.85-1.07)	0.447
	Often	1.38 (0.91-2.08)	0.127	1.31 (1.00-1.73)	0.052
Depress	Never (ref)		0.211	None	
	Occasionally	1.09 (0.92-1.29)	0.320		
	Often	0.77 (0.49-1.21)	0.264		
Sleep	Well (ref)		0.221	None	
	Moderate	0.98 (0.82-1.16)	0.791		
	Bad	0.89 (0.74-1.07)	0.225		

BMI: Body Mass Index; SUA: Serum uric acid; TG: Triglycerides; TC: Total cholesterol; LDL-C: low density lipoprotein cholesterol; HDL-C: high density lipoprotein cholesterol; TBIL: Total bilirubin; AST: Aspartate aminotransferase; ALT: Alanine transaminase; A/G: Albumin/globulin; FPG: Fasting plasma glucose; BUN: Blood urea nitrogen; HbA1c: Glycated hemoglobin.

Independent risk factors for MAFLD

General information: This study found that as hip circumference increase (OR = 0.95, 95CI%: 0.93–0.96), the risk of MAFLD decreases, a finding consistent with Lin *et al*[25]. Indeed, fat accumulation on the hips may be beneficial to metabolic health and reduce the risk of metabolic-related diseases[26]. The risk of MAFLD was also 1.14 times higher among those who actively acquired medical knowledge than those who did not. This may be because individuals who are willing to actively acquire knowledge are more likely to attend medical check-ups for early detection and diagnosis. Meanwhile, people who aren't willing to acquire medical knowledge lack an understanding of self-health management and may be less likely to attend medical check-ups. This could cause an illusion of low MAFLD prevalence.

Laboratory indicators: After correcting for sex, age and BMI confounders, multivariate logistic regression analysis found that TG, HDL-C, TBIL, AST, ALT, glycated hemoglobin, SUA, platelets, and creatinine were associated factors for MAFLD. The risk of MAFLD increases by 1.33 times for each unit increase in TG value, which is consistent with the findings of previous studies[27]. Therefore, regular screening of TG levels and attention to dynamic changes in TG should be performed during routine medical examinations to facilitate screening of people at risk of MAFLD. A high HDL-C level indicates that the body is using cholesterol well and is a sign of good health. The OR value of 0.58 in our study, which suggests that elevated HDL-C may be an important protective factor for MAFLD. ALT and AST are indicators of hepatocellular damage, with ALT being the most sensitive. A number of studies have shown that ALT is an independent risk factor for the development of MAFLD in both obese and non-obese people[28]. In this study, ALT and AST were significantly increased in patients with MAFLD, and they were independent risk factors for the development of MAFLD. The increase in free fatty acids in the liver cells of MAFLD patients led to an increased susceptibility of the liver to inflammatory reactions and the production of oxygen free radicals, which led to hepatocyte degeneration and necrosis, resulting in an increase in serum ALT and AST.

Platelets[29] are elevated during inflammation, and previous studies have found a linear correlation between platelet count and the severity of liver fibrosis[30] in individuals with MAFLD. In our study, we also found that platelet count was mild correlated with MAFLD, consistent with the results of Zeng *et al*[31], indicating that platelet count may be used as a reference indicator of MAFLD development and the resulting liver fibrosis. And our study found that high glycated hemoglobin values were also strongly associated with a high risk of MAFLD (OR = 1.52, 95%CI: 1.47-1.57), suggesting that glycated hemoglobin is an important reference indicator for screening for MAFLD, and there is previous evidence that patients with MAFLD have significantly higher glycated haemoglobin values compared to the healthy population [32].

In addition to above indicators, we have an interesting finding, SUA, TBIL and creatinine have significance in the multifactorial regression analysis of this study. Participants with CKD may have elevated SUA levels, low TBIL levels and abnormal creatinine values, which may suggest that there is an association between CKD and MAFLD, the exact mechanism need to further analysis. Longitudinal studies[33] have also shown an increased incidence of CKD among NAFLD patients. Despite these findings, however, there is little awareness about CKD in NAFLD, and evidence on the relationship between MAFLD and CKD is even rarer. The current study found that SUA was significantly correlated with MAFLD. While the mechanisms remain unclear, there are a few hypotheses. First, SUA may act as an oxidant and elevated levels may increase oxidative stress, thereby promoting the development of MAFLD. Second, SUA[34] induces adipogenesis through the production of endoplasmic reticulum, activating fatty acid synthase and acetyl coenzyme A carboxylase and leading to the accumulation of fat in hepatocytes. Indeed, low TBIL[35] and creatinine levels may be associated with MAFLD risk. The descend creatinine levels in MAFLD are consistent with the findings of Liu *et al*[36]. The reduction in creatinine associated with MAFLD may be the result of sarcopenia, which is linked to low skeletal muscle mass and reduced function. MAFLD patients maybe follow lower skeletal muscle mass, especially in lean MAFLD patients. There are differing views on the relationship between TBIL and the risk of MAFLD. Our study showed a mild negative correlation. This may be because TBIL activates toll-like receptor 4 signaling and promotes inflammation.

Lifestyle indicators: Previous studies[37] have shown that consuming sugary beverages may increase the risk of MAFLD, while drinking coffee and tea may reduce the risk. The current study found that individuals who regularly consumed beverages were 0.32 times more likely to develop MAFLD than those who never drank beverages. This may be because coffee and tea, which contain biologically active compounds with anti-oxidant and anti-fibrotic potential, were the most consumed beverages in this population[38]. Our study found that the risk of developing MAFLD when exercising > 5/wk was only 0.82 times that of exercising 1-2/wk. Meanwhile, prior studies have indicated that < 2/wk maybe no effect[39]. However, these findings do not necessarily mean that more frequent exercise is beneficial. It is also important to consider frequency in relation to exercise intensity and length. The risk of MAFLD was found to be 1.24 times higher following exercise lasting > 60 min than exercise lasting < 30 min, suggesting that the benefit of exercise doesn't increase after a certain length, perhaps due to fatigue that reduces long-term adherence. Finally, labor intensity was a protective factor, with moderate labor intensity is 0.78 times risk incidence of MAFLD than light labor intensity. This finding is consistent with a study by Chen *et al*[40] and suggests that moderate physical labor is beneficial to health.

Limitations

To our knowledge, this is the first largest sample study to assess the new nomenclature of MAFLD in the Mid-South region of China. The study has some limitations, however. First, lifestyle information was self-reported by the participants, which may cause recall bias. Second, all the participants were recruited from one medical facility so the findings may not be generalizable to the Chinese population. Additional studies are needed to assess the prevalence and features of MAFLD in other regions of the country. Third, this study lacked histological information on steatosis and fibrosis diagnoses. While ultrasound imaging is highly sensitive and specific for liver fibrosis and steatosis, this technique

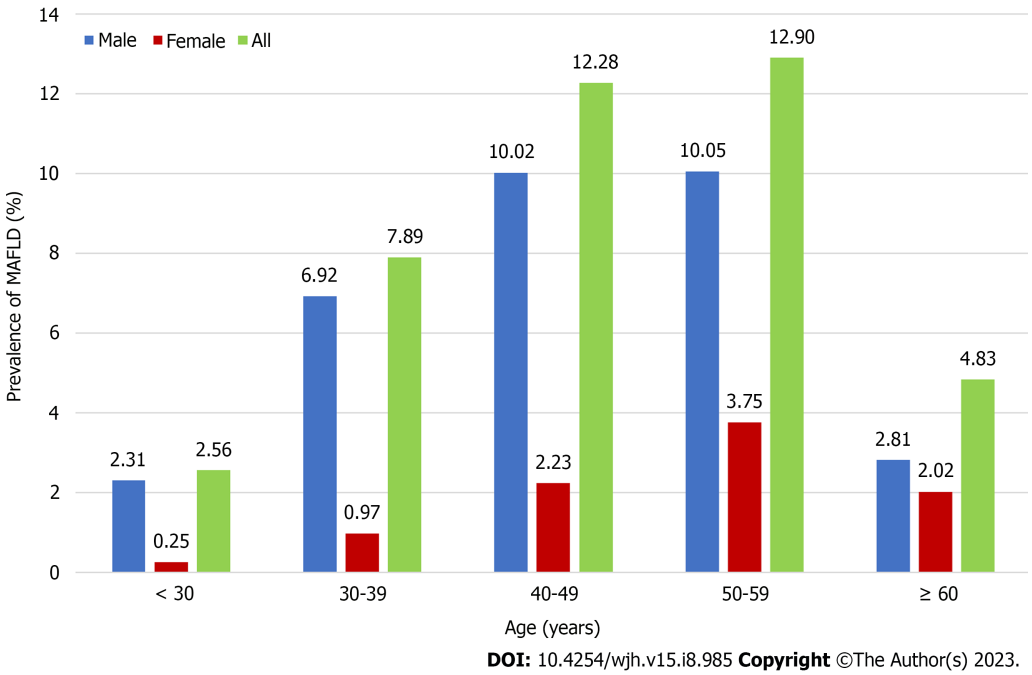

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Figure 4 Prevalence of metabolic associated fatty liver disease by gender and age group. MAFLD: Metabolic associated fatty liver disease.

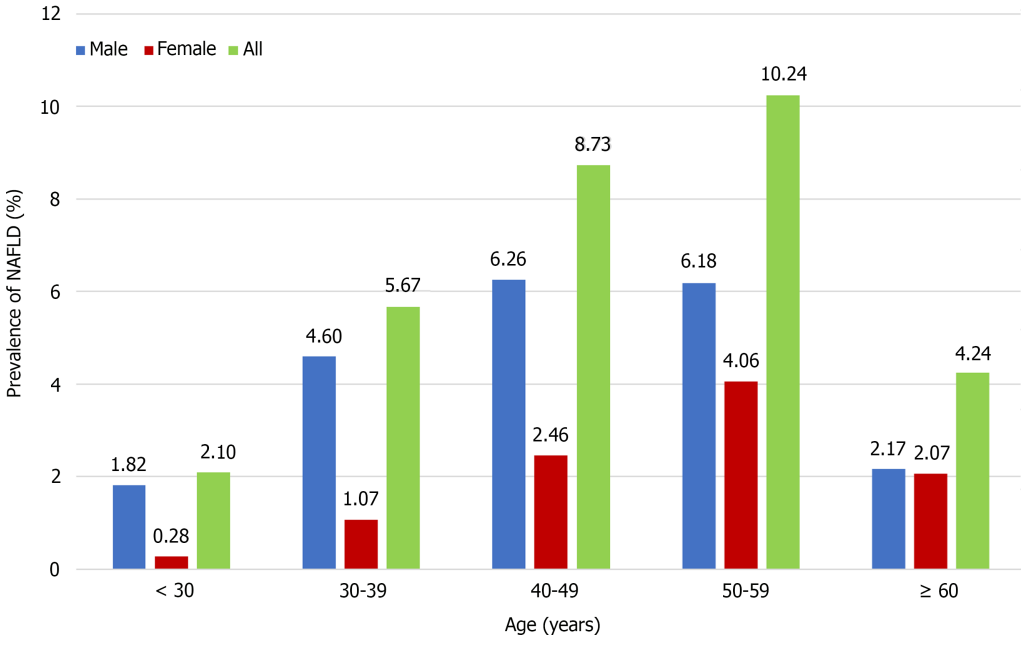

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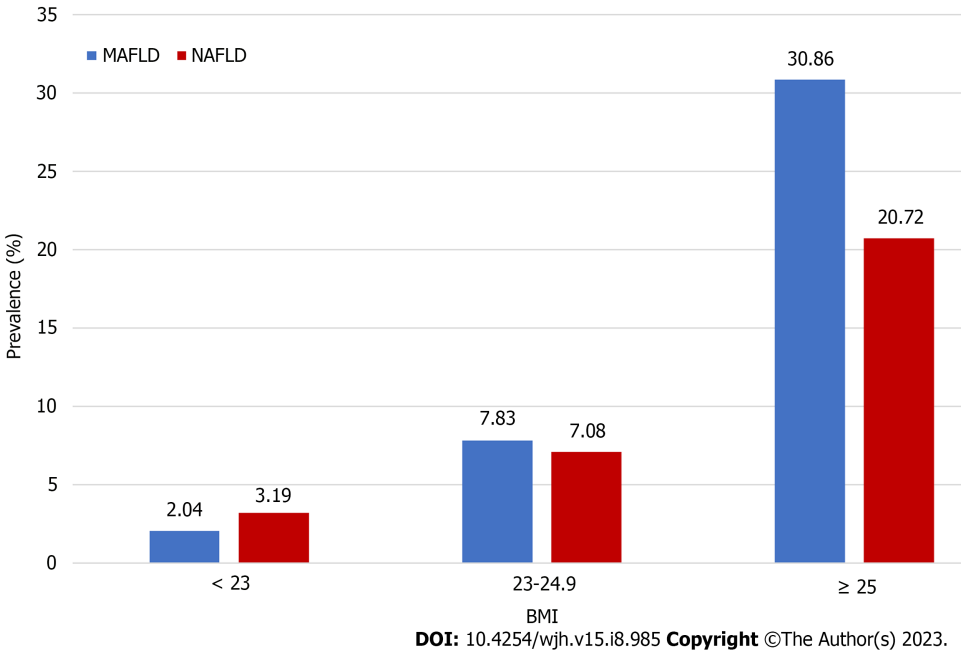
Figure 5 Prevalence of non-alcoholic fatty liver disease by gender and age group. NAFLD: Non-alcoholic fatty liver disease.

is not the gold standard for diagnosis. In addition, vibration controlled transient elastography (VCTE) also been recommended for a wide range of studies related to NAFLD[41-45], and VCTE has good diagnostic performance in assessing steatosis. However, there are certain shortcomings that limit its use and make it less widespread than ultrasound, such as high dependence on operator experience, limited sampling range, large overlap in liver fibrosis staging data, and inconsistent delineation of Cut off values.

CONCLUSION

This study found that MAFLD was significantly more prevalent than NAFLD in our study population. In addition to the usual risk factors, our results suggest that CKD may be related with MAFLD. More research is needed to determine the



DOI: 10.4254/wjh.v15.i8.985

Figure 6 Non-alcoholic fatty liver disease and metabolic associated fatty liver disease prevalence by body mass index zone. MAFLD: Metabolic associated fatty liver disease; NAFLD: Non-alcoholic fatty liver disease; BMI: Body mass index.

potential mechanisms underlying the occurrence of MAFLD and to develop interventions to prevent and treat this disease.

ARTICLE HIGHLIGHTS

Research background

Metabolic associated fatty liver disease (MAFLD) is renamed from non-alcoholic fatty liver disease (NAFLD), but there are differences in diagnostic criteria. Since the research on MAFLD is just beginning, however, evidence on its incidence and prevalence in the general population and in specific subpopulations remains limited.

Research motivation

MAFLD proposal is not only a change in nomenclature. On one hand, MAFLD includes patients with concomitant liver diseases and secondary causes of fatty liver. On the other hand, patients with hepatic steatosis but not fulfilling the metabolic criteria are not classified as MAFLD. How these criteria affect our understanding of the epidemiology of MAFLD is unclear. The clinical characteristics and risk factors between MAFLD and NAFLD has not been adequately explored. We aimed to further clarify a possible link and difference between the two diagnostic criteria.

Research objectives

We sought to assess the impact of the new definition on the epidemiology of fatty liver disease and compare MAFLD with NAFLD in a general population. Potential risk factors of MAFLD-diagnosed individuals were also explored.

Research methods

A total of 85242 adults were selected from the Chinese health management database in 2017–2022. Specifically, the participants were divided into MAFLD group, NAFLD group and MAFLD & NAFLD group for analysis and comparison. Several elements were included such as prevalence, disease characteristics, and risk factors.

Research results

We found a higher prevalence of MAFLD than NAFLD. There are differences in clinical features between MAFLD, NAFLD and MAFLD & NAFLD. In addition to the common risk factors, we identified CKD may be related with MAFLD.

Research conclusions

MAFLD was more prevalent than NAFLD in the study population, with two-fifths of individuals meeting the diagnosis criteria. Compared to NAFLD, MAFLD has its own disease characteristics and risk factors. Intervention program should address the risk factors for MAFLD and regular screening for the disease is recommended.

Research perspectives

Some of the risk factors for MAFLD have been initially identified, but cross-sectional studies of causality are weak. In the future, multi-centre, multi-regional longitudinal studies could be conducted to elucidate disease characteristics, disease trajectory and risk factors in depth.

FOOTNOTES

Author contributions: All authors on this manuscript made significant contributions to the study; Xinjuan Huang and Chunxiang Qin were primarily involved in the study design; Huang XJ, Zhou BQ, and Yin M were responsible for the analysis and interpretation of data, as well as drafting the manuscript; Tan XY and Xia YQ were involved in the acquisition of data; all authors read and approved the final manuscript.

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REFERENCES

1 The diagnosis and management of nonalcoholic fatty liver disease: Practice guidance from the American Association for the Study of Liver Diseases. *Clin Liver Dis (Hoboken)* 2018; **11**: 81 [PMID: 30992795 DOI: 10.1002/cld.722]
2 **Le MH**, Yeo YH, Li X, Li J, Zou B, Wu Y, Ye Q, Huang DQ, Zhao C, Zhang J, Liu C, Chang N, Xing F, Yan S, Wan ZH, Tang NSY, Mayumi M, Liu X, Rui F, Yang H, Yang Y, Jin R, Le RHX, Xu Y, Le DM, Barnett S, Stave CD, Cheung R, Zhu Q, Nguyen MH. 2019 Global NAFLD Prevalence: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2022; **20**: 2809-2817.e28 [PMID: 34890795 DOI: 10.1016/j.cgh.2021.12.002]
3 **Wang Z**, Zhao X, Chen S, Wang Y, Cao L, Liao W, Sun Y, Wang X, Zheng Y, Wu S, Wang L. Associations Between Nonalcoholic Fatty Liver Disease and Cancers in a Large Cohort in China. *Clin Gastroenterol Hepatol* 2021; **19**: 788-796.e4 [PMID: 32407969 DOI: 10.1016/j.cgh.2020.05.009]
4 **Yilmaz Y**, Byrne CD, Musso G. A single-letter change in an acronym: signals, reasons, promises, challenges, and steps ahead for moving from NAFLD to MAFLD. *Expert Rev Gastroenterol Hepatol* 2021; **15**: 345-352 [PMID: 33270482 DOI: 10.1080/17474124.2021.1860019]
5 **Eslam M**, George J. Reply to: correspondence regarding "A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement": Bringing evidence to the NAFLD-MAFLD debate. *J Hepatol* 2020; **73**: 1575 [PMID: 32933781 DOI: 10.1016/j.jhep.2020.07.045]
6 **Tilg H**, Effenberger M. From NAFLD to MAFLD: when pathophysiology succeeds. *Nat Rev Gastroenterol Hepatol* 2020; **17**: 387-388 [PMID: 32461575 DOI: 10.1038/s41575-020-0316-6]
7 **Lee HW**, Wong GL, Kwok R, Choi KC, Chan CK, Shu SS, Leung JK, Chim AM, Luk AO, Ma RC, Chan HL, Chan JC, Kong AP, Wong VW. Serial Transient Elastography Examinations to Monitor Patients With Type 2 Diabetes: A Prospective Cohort Study. *Hepatology* 2020; **72**: 1230-1241 [PMID: 31991487 DOI: 10.1002/hep.31142]
8 **Younossi ZM**, Golabi P, de Avila L, Paik JM, Srishord M, Fukui N, Qiu Y, Burns L, Afendy A, Nader F. The global epidemiology of NAFLD

and NASH in patients with type 2 diabetes: A systematic review and meta-analysis. *J Hepatol* 2019; **71**: 793-801 [PMID: 31279902 DOI: 10.1016/j.jhep.2019.06.021]

9 **Kim H**, Lee CJ, Ahn SH, Lee KS, Lee BK, Baik SJ, Kim SU, Lee JI. MAFLD Predicts the Risk of Cardiovascular Disease Better than NAFLD in Asymptomatic Subjects with Health Check-Ups. *Dig Dis Sci* 2022; **67**: 4919-4928 [PMID: 35579799 DOI: 10.1007/s10620-022-07508-6]

10 **Wong VW**, Wong GL, Woo J, Abrigo JM, Chan CK, Shu SS, Leung JK, Chim AM, Kong AP, Lui GC, Chan HL, Chu WC. Impact of the New Definition of Metabolic Associated Fatty Liver Disease on the Epidemiology of the Disease. *Clin Gastroenterol Hepatol* 2021; **19**: 2161-2171.e5 [PMID: 33137486 DOI: 10.1016/j.cgh.2020.10.046]

11 Survey. NHaNE. Third National Health and Nutrition Examination Survey: Hepatic/Gallbladder Ultrasound and Hepatic Steatosis (HGUHS). 2021; Accessed Aug 23, 2021. Available from: https://wwwn.cdc.gov/nchs/Data/Nhanes3/34A/HGUHS.htm

12 National Health and Nutrition Examination Survey (NHANES) III, Hepatic Steatosis Ultrasound Images Assessment Procedures Manual 2010. Accessed Aug 23, 2021. Available from: https://www.cdc.gov/nchs/data/nhanes/nhanes3/hepatic_steatosis_ultrasound_procedures_manual.pdf

13 **Boccatonda A**, Andreetto L, D'Ardes D, Cocco G, Rossi I, Vicari S, Schiavone C, Cipollone F, Guagnano MT. From NAFLD to MAFLD: Definition, Pathophysiological Basis and Cardiovascular Implications. *Biomedicines* 2023; **11** [PMID: 36979861 DOI: 10.3390/biomedicines11030883]

14 **European Association for the Study of the Liver (EASL)**; European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. *Diabetologia* 2016; **59**: 1121-1140 [PMID: 27053230 DOI: 10.1007/s00125-016-3902-y]

15 **Bartáková V**, Kuricová K, Pácal L, Nová Z, Dvořáková V, Švrčková M, Malúšková D, Svobodová I, Řehořová J, Svojanovský J, Olšovský J, Bělobrádková J, Kaňková K. Hyperuricemia contributes to the faster progression of diabetic kidney disease in type 2 diabetes mellitus. *J Diabetes Complications* 2016; **30**: 1300-1307 [PMID: 27324705 DOI: 10.1016/j.jdiacomp.2016.06.002]

16 **Wang J**, Wang B, Liang M, Wang G, Li J, Zhang Y, Huo Y, Cui Y, Xu X, Qin X. Independent and combined effect of bilirubin and smoking on the progression of chronic kidney disease. *Clin Epidemiol* 2018; **10**: 121-132 [PMID: 29391834 DOI: 10.2147/CLEP.S150687]

17 **Li H**, Guo M, An Z, Meng J, Jiang J, Song J, Wu W. Prevalence and Risk Factors of Metabolic Associated Fatty Liver Disease in Xinxiang, China. *Int J Environ Res Public Health* 2020; **17** [PMID: 32168920 DOI: 10.3390/ijerph17061818]

18 **Liu J**, Ayada I, Zhang X, Wang L, Li Y, Wen T, Ma Z, Bruno MJ, de Knegt RJ, Cao W, Peppelenbosch MP, Ghanbari M, Li Z, Pan Q. Estimating Global Prevalence of Metabolic Dysfunction-Associated Fatty Liver Disease in Overweight or Obese Adults. *Clin Gastroenterol Hepatol* 2022; **20**: e573-e582 [PMID: 33618024 DOI: 10.1016/j.cgh.2021.02.030]

19 **Ciardullo S**, Perseghin G. Prevalence of NAFLD, MAFLD and associated advanced fibrosis in the contemporary United States population. *Liver Int* 2021; **41**: 1290-1293 [PMID: 33590934 DOI: 10.1111/liv.14828]

20 **Lin S**, Huang J, Wang M, Kumar R, Liu Y, Liu S, Wu Y, Wang X, Zhu Y. Comparison of MAFLD and NAFLD diagnostic criteria in real world. *Liver Int* 2020; **40**: 2082-2089 [PMID: 32478487 DOI: 10.1111/liv.14548]

21 **Chan KE**, Koh TJL, Tang ASP, Quek J, Yong JN, Tay P, Tan DJH, Lim WH, Lin SY, Huang D, Chan M, Khoo CM, Chew NWS, Kaewdech A, Chamroonkul N, Dan YY, Noureddin M, Muthiah M, Eslam M, Ng CH. Global Prevalence and Clinical Characteristics of Metabolic-associated Fatty Liver Disease: A Meta-Analysis and Systematic Review of 10 739 607 Individuals. *J Clin Endocrinol Metab* 2022; **107**: 2691-2700 [PMID: 35587339 DOI: 10.1210/clinem/dgac321]

22 **Lee H**, Lee YH, Kim SU, Kim HC. Metabolic Dysfunction-Associated Fatty Liver Disease and Incident Cardiovascular Disease Risk: A Nationwide Cohort Study. *Clin Gastroenterol Hepatol* 2021; **19**: 2138-2147.e10 [PMID: 33348045 DOI: 10.1016/j.cgh.2020.12.022]

23 **Ito T**, Ishigami M, Zou B, Tanaka T, Takahashi H, Kurosaki M, Maeda M, Thin KN, Tanaka K, Takahashi Y, Itoh Y, Oniki K, Seko Y, Saruwatari J, Kawanaka M, Atsukawa M, Hyogo H, Ono M, Ogawa E, Barnett SD, Stave CD, Cheung RC, Fujishiro M, Eguchi Y, Toyoda H, Nguyen MH. The epidemiology of NAFLD and lean NAFLD in Japan: a meta-analysis with individual and forecasting analysis, 1995-2040. *Hepatol Int* 2021; **15**: 366-379 [PMID: 33580453 DOI: 10.1007/s12072-021-10143-4]

24 **Huang YP**, Zhang S, Zhang M, Wang Y, Wang WH, Li J, Li C, Lin JN. Gender-specific prevalence of metabolic-associated fatty liver disease among government employees in Tianjin, China: a cross-sectional study. *BMJ Open* 2021; **11**: e056260 [PMID: 34911725 DOI: 10.1136/bmjopen-2021-056260]

25 **Lin S**, Xian Y, Liu Y, Cai W, Song J, Zhang X. Risk factors and community intervention for nonalcoholic fatty liver disease in community residents of Urumqi, China. *Medicine (Baltimore)* 2018; **97**: e0021 [PMID: 29489647 DOI: 10.1097/MD.0000000000010021]

26 **Stefan N**. Causes, consequences, and treatment of metabolically unhealthy fat distribution. *Lancet Diabetes Endocrinol* 2020; **8**: 616-627 [PMID: 32559477 DOI: 10.1016/S2213-8587(20)30110-8]

27 **Tong C**, Li Q, Kong L, Ni X, Halengbieke A, Zhang S, Wu Z, Tao L, Han Y, Zheng D, Guo X, Yang X. Sex-specific metabolic risk factors and their trajectories towards the non-alcoholic fatty liver disease incidence. *J Endocrinol Invest* 2022; **45**: 2233-2245 [PMID: 35896944 DOI: 10.1007/s40618-022-01848-w]

28 **Lee JH**, Kim D, Kim HJ, Lee CH, Yang JI, Kim W, Kim YJ, Yoon JH, Cho SH, Sung MW, Lee HS. Hepatic steatosis index: a simple screening tool reflecting nonalcoholic fatty liver disease. *Dig Liver Dis* 2010; **42**: 503-508 [PMID: 19766548 DOI: 10.1016/j.dld.2009.08.002]

29 **Ozhan H**, Aydin M, Yazici M, Yazgan O, Basar C, Gungor A, Onder E. Mean platelet volume in patients with non-alcoholic fatty liver disease. *Platelets* 2010; **21**: 29-32 [PMID: 19947902 DOI: 10.3109/09537100903391023]

30 **Pitisuttithum P**, Chan WK, Piyachaturawat P, Imajo K, Nakajima A, Seki Y, Kasama K, Kakizaki S, Fan JG, Song MJ, Yoon SK, Dan YY, Lesmana L, Ho KY, Goh KL, Wong VWS, Treeprasertsuk S. Predictors of advanced fibrosis in elderly patients with biopsy-confirmed nonalcoholic fatty liver disease: the GOASIA study. *BMC Gastroenterol* 2020; **20**: 88 [PMID: 32252638 DOI: 10.1186/s12876-020-01240-z]

31 **Zeng J**, Yang RX, Sun C, Pan Q, Zhang RN, Chen GY, Hu Y, Fan JG. Prevalence, clinical characteristics, risk factors, and indicators for lean Chinese adults with nonalcoholic fatty liver disease. *World J Gastroenterol* 2020; **26**: 1792-1804 [PMID: 32351294 DOI: 10.3748/wjg.v26.i15.1792]

32 **Huang H**, Wang Q, Shi X, Chen Y, Shen C, Zhang J, Xu C. Association between Monocyte to High-Density Lipoprotein Cholesterol Ratio and Nonalcoholic Fatty Liver Disease: A Cross-Sectional Study. *Mediators Inflamm* 2021; **2021**: 6642246 [PMID: 34916874 DOI: 10.1155/2021/6642246]

33 **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]

34 **Chao G**, Chen L. Study on the independent effect of thyroid hormone based on uric acid level on NAFLD. *J Health Popul Nutr* 2021; **40**: 21 [PMID: 33941292 DOI: 10.1186/s41043-021-00247-w]

35 **Liang C**, Yu Z, Bai L, Hou W, Tang S, Zhang W, Chen X, Hu Z, Duan Z, Zheng S. Association of Serum Bilirubin With Metabolic Syndrome and Non-Alcoholic Fatty Liver Disease: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne)* 2022; **13**: 869579 [PMID: 35937795 DOI: 10.3389/fendo.2022.869579]

36 **Liu L**, Shi X, Gao J, Xu C, Liu X. Predictive Risk Factors of Nonalcoholic Fatty Liver Disease in a Lean Chinese Population. *J Pers Med* 2022; **12** [PMID: 36556179 DOI: 10.3390/jpm12121958]

37 **Chhimwal J**, Patial V, Padwad Y. Beverages and Non-alcoholic fatty liver disease (NAFLD): Think before you drink. *Clin Nutr* 2021; **40**: 2508-2519 [PMID: 33932796 DOI: 10.1016/j.clnu.2021.04.011]

38 **Kennedy OJ**, Roderick P, Poole R, Parkes J. Coffee, caffeine and non-alcoholic fatty liver disease? *Therap Adv Gastroenterol* 2016; **9**: 417-418 [PMID: 27134669 DOI: 10.1177/1756283X16636765]

39 **Zheng YC**, Wen J. Research progress of exercise prescription for non-alcoholic fatty liver disease. Occupation and Health 2020 36: 569-572, 576 Available from: https://docs.qq.com/pdf/DQmZPS3Z3cE1NZmVU

40 **Chen SJ**, Zhang H, Chang XL, Fu JP, Li HY, Yang HY, Guo YH, Wei M, Wang HL, Song JD. Analysis of new risk factors for metabolic syndrome in Han Chinese population in urban health check-ups in northern China. *Zhongguo Quanke Yixue Zazhi* 2010; **13**: 980-983,985 [DOI: 10.3969/j.issn.1007-9572.2010.09.022]

41 **Xie R**, Liu M. Relationship Between Non-Alcoholic Fatty Liver Disease and Degree of Hepatic Steatosis and Bone Mineral Density. *Front Endocrinol (Lausanne)* 2022; **13**: 857110 [PMID: 35360054 DOI: 10.3389/fendo.2022.857110]

42 **Blank V**, Petroff D, Boehlig A, Heinze A, Karlas T, Berg T, Wiegand J. Clinical implications of hepatic structure and function evaluation based on vibration-controlled transient elastography and liver maximum function capacity test in patients with nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2022; **34**: 686-692 [PMID: 35102112 DOI: 10.1097/MEG.0000000000002347]

43 **Xie R**, Zhang Y. Associations between dietary flavonoid intake with hepatic steatosis and fibrosis quantified by VCTE: Evidence from NHANES and FNDDS. *Nutr Metab Cardiovasc Dis* 2023; **33**: 1179-1189 [PMID: 36964061 DOI: 10.1016/j.numecd.2023.03.005]

44 **Tang M**, Liu M, Zhang Y, Xie R. Association of family income to poverty ratio and vibration-controlled transient elastography quantified degree of hepatic steatosis in U.S. adolescents. *Front Endocrinol (Lausanne)* 2023; **14**: 1160625 [PMID: 37033220 DOI: 10.3389/fendo.2023.1160625]

45 **Xie R**, Xiao M, Li L, Ma N, Liu M, Huang X, Liu Q, Zhang Y. Association between SII and hepatic steatosis and liver fibrosis: A population-based study. *Front Immunol* 2022; **13**: 925690 [PMID: 36189280 DOI: 10.3389/fimmu.2022.925690]

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SYSTEMATIC REVIEWS

Emerging therapeutic options for non-alcoholic fatty liver disease: A systematic review

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Abstract

BACKGROUND

Non-alcoholic fatty liver disease (NAFLD) has become a prevalent cause of chronic liver disease and ranks third among the causes of transplantation. In the United States alone, annual medical costs are approximately 100 billion dollars. Unfortunately, there is no Federal Drug Administration (FDA)-approved medication for its treatment. However, various clinical trials are investigating several therapeutic classes that could potentially treat NAFLD. It is valuable to have a compilation of the data available on their efficacy.

AIM

To assess the efficacy of cyclophilin inhibitors, fibroblast growth factor 21 analogs (FGF21), and dual and pan peroxisome proliferator-activated receptor (PPAR) agonists for treating NAFLD.

METHODS

A comprehensive literature search using keywords including cyclophilin inhibitor, FGF agonist, pan-PPAR agonists, dual-PPAR agonist, NAFLD, non-alcoholic steatohepatitis, and fatty liver was conducted on October 29, 2022, in PubMed, EMBASE, Cochrane Library, Scopus and Web of Science. Animal and human research, case reports, and published articles in English from all countries with patients aged 18 and above were included. Only articles with a National Institutes of Health (NIH) Quality Assessment score of five or higher out of eight points were included. Articles that were narrative or systematic reviews,

abstracts, not in English, focused on patients under 18 years old, did not measure outcomes of interest, were inaccessible, or had a low NIH Quality Assessment score were excluded. Each article was screened by two independent researchers evaluating relevance and quality. Resources were scored based on the NIH Quality Assessment Score; then, pertinent data was extracted in a spreadsheet and descriptively analyzed.

RESULTS

Of the 681 records screened, 29 met the necessary criteria and were included in this review. These records included 12 human studies and 17 animal studies. Specifically, there were four studies on cyclophilin inhibitors, four on FGF agonists/analogs, eleven on pan-PPAR agonists, and ten on dual-PPAR agonists. Different investigational products were assessed: The most common cyclophilin inhibitor was NV556; FGF agonists and analogs was Efruxifermin; pan-PPAR agonists was Lanifibranor; and dual-PPAR agonists was Saroglitazar. All classes were found to be statistically efficacious for the treatment of NAFLD, with animal studies demonstrating improvement in steatosis and/or fibrosis on biopsy and human studies evidencing improvement in different metabolic parameters and/or steatosis and fibrosis on FibroScan ($P < 0.05$).

CONCLUSION

The data analyzed in this review showed clinically significant improvement in individual histological features of NAFLD in both animal and human trials for all four classes, as well as good safety profiles ($P < 0.05$). We believe this compilation of information will have positive clinical implications in obtaining an FDA-approved therapy for NAFLD.

Key Words: Non-alcoholic fatty liver disease; Non-alcoholic steatohepatitis; Cyclophilin inhibitors; Fibroblast growth factor 21 analogs; Dual peroxisome proliferator-activated receptor agonists; Pan peroxisome proliferator-activated receptor agonists

Core Tip: Non-alcoholic fatty liver disease (NAFLD) has become a significant global health issue. There is no medication approved by the Federal Drug Administration for the treatment of NAFLD. However, there are several therapeutic classes currently being studied in clinical trials. In this systematic review, we analyze the scientific data of cyclophilin inhibitors, fibroblast growth factor 21 analogs, and dual and pan peroxisome proliferator-activated receptor agonists for the treatment of NAFLD.

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INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is a prevalent chronic liver disease affecting approximately 30% of the world's population[1]. It is characterized by the buildup of more than 5% of fat in hepatocyte histology[1]. NAFLD encompasses a range of conditions, such as non-alcoholic fatty liver (NAFL), non-alcoholic steatohepatitis (NASH), and cirrhosis[2]. NAFL is defined as hepatic steatosis without inflammation, based on liver biopsy histology[2].

Approximately 20% of patients with NAFL will develop NASH, which is the presence of hepatic steatosis, lobular inflammation, and hepatocyte ballooning[1,2]. This persistent liver cell injury leads to progressive fibrosis and cirrhosis in approximately 10%–20% of patients, converting NAFLD into the quickest-growing cause of hepatocellular carcinoma (HCC)[1,3]. NAFLD is currently liver transplantation's third most common cause[1]. Unlike other causes of HCC, which start with fibrosis, up to one-third of patients with NASH and HCC are non-cirrhotic and are more advanced, making treatment difficult[3].

NAFLD is a liver condition that is closely linked with metabolic syndrome[1]. It is often seen in people who have type 2 diabetes, are insulin resistant, have high levels of triglycerides and cholesterol, and are obese[1]. The main risk factors for developing NAFLD are a diet high in fats and sugars and a sedentary lifestyle[1]. Some experts have started using metabolic-associate fatty liver disease to describe this condition because of its strong link with metabolic dysfunction. Still, for clarity purposes, we will stick with the NAFLD nomenclature throughout this review[4].

Approximately 70% of diabetics, overweight patients, and 90% of patients with dyslipidemia and morbid obesity will develop NAFLD[1,4]. NAFLD is also associated with systemic pathologies such as chronic kidney disease, cardiovascular disease, and reduced mineral density[1]. Cardiovascular disease is the most common cause of death in NAFLD patients; however, they also have an increased overall mortality rate compared to the general population[1]. It is of utmost concern that there is an increase in the prevalence of adolescents with NAFLD, leading to earlier end-stage liver disease[5].

In the United States alone, $100 billion of annual medical costs are attributed to NAFLD. Searching for an approved medical therapy for NAFLD is a pressured race[4]. The lack of an authorized agent could be secondary to the limited understanding of a multifactorial disease process and the absence of dependable non-invasive biomarkers[4]. Due to the acknowledgment of an increasing epidemic and the severity of NAFLD, several trials are ongoing to identify possible pharmacologic agents[3]. Most of the agents target the known metabolic associations with NAFLD, such as adipose tissue dysfunction, insulin resistance, de novo lipogenesis, lipid exportation in the liver, and imbalance between energy intake and expenditure[5].

There is growing interest in future combined medications targeting multiple critical pathways involved in developing NAFLD[5]. Precise identification of the drivers of this disease is crucial for developing new agents, and it is hoped that registered therapy for NAFLD will become available in the next few years[2]. Clinicians must be aware of the emerging agents for the treatment of NAFLD and the need for further human research to characterize better the efficacy, dosage, length of treatment, *etc.* This systematic review will delve into the scientific data behind four innovative therapeutic classes currently being studied for treating NAFLD: Cyclophilin inhibitors, fibroblast growth factor 21 analogs (FGF21), and dual and pan peroxisome proliferator-activated receptor (PPAR) agonists.

MATERIALS AND METHODS

This review analyzed animal and human research, case reports, and published articles in English from all countries with patients aged 18 and above. Only articles with a five or higher National Institutes of Health (NIH) Quality Assessment score were included. Articles that were narrative or systematic reviews, abstracts, not in English, focused on patients under 18 years old, did not measure outcomes of interest, were inaccessible, or had a low NIH Quality Assessment score were excluded.

A comprehensive literature search using broad search criteria was conducted in five databases: PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science (October 29, 2022). Our search terms were as follows: (rencofilstat OR "cyclophilin inhibitor" OR "cyclophilin inhibition" OR lanifibranor OR "PPAR agonist" OR "peroxisome proliferator activated receptor agonist" OR "pan-ppar agonist" OR "pan-peroxisome proliferator activated receptor agonist" OR efruxifermin OR "FGF-21 inhibitor" OR "fibroblast growth factor-21 inhibitor" OR "fibroblast growth factor 21 inhibitor" OR "FGF21 inhibitor" OR "FGF21 inhibition" OR "FGF-21 inhibition") AND (NASH or "fatty liver" or "hepatic steatosis" or steatohepatitis OR NAFLD OR "non-alcoholic fatty liver disease" OR "Non-alcoholic Fatty Liver Disease" OR "Fatty Liver, Non-alcoholic" OR "Fatty Livers, Non-alcoholic" OR "Liver, Non-alcoholic Fatty" OR "Non-alcoholic Fatty Liver" OR "Non-alcoholic Fatty Livers" OR "Non-alcoholic Steatohepatitis" OR "Non-alcoholic Steatohepatitides" OR "Steatohepatitides, Non-alcoholic" OR "Steatohepatitis, Non-alcoholic" OR "liver, fatty" OR "steatosis of liver" OR "visceral steatosis" OR "steatosis, visceral" OR "steatoses, visceral" OR "visceral steatosis" OR "liver steatosis" OR "liver steatoses" OR "steatosis, liver" OR "steatoses liver").

For the study selection process, Covidence was used, a platform that facilitates the importation of citations and screening of titles, abstracts, and full text. Each article was initially screened by title and abstract by two independent researchers (J.T. and N.B.) to exclude studies irrelevant to our aim. Next, each article was screened by full text by the same two independent researchers (J.T. and N.B.) to exclude studies that were finally irrelevant to our aim. Once both researchers completed all screening stages, any conflicts were registered in Covidence, and the discrepancies were reviewed and resolved.

The following data were collected separately by J.T. and N.B. from all eligible studies and recorded in Excel: First author, digital object identifier, study design, number of participants, name of therapy, mechanism of action, side effects, and statistical data about liver enzymes, cholesterol panels, weight reduction, NAFLD activity score (NAS), Fibroscan controlled attenuation parameter (CAP) and kPa, fibrosis stage, fibrotic markers, and quality assessment scores. J.T. and N.B. resolved all discrepancies in the collected data. The quality of included studies was assessed by the NIH Quality Assessment tool. We included articles with a score greater than or equal to five out of eight points.

RESULTS

Records were identified from 5 databases: PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science. One hundred twenty-two duplicate records were removed before the screening. Six hundred eighty-one records were screened, out of which eighty-two were excluded by an automation tool. Five hundred fifty-nine reports were sought for retrieval, out of which three hundred were not retrieved. Two hundred fifty-nine reports were assessed for eligibility, out of which two hundred and thirty were excluded. The most common reason for exclusion was review articles (156) followed by irrelevant articles (31), abstracts (18), duplicates (16), foreign language (5), and unable to be accessed (4). Twenty-nine of the two hundred and fifty-nine records assessed for eligibility were included (Figure 1). Most studies, including human and animal participants, were small (n < 100). Some studies enrolled patients with NAFLD and others with NASH. Articles were included when the NIH Quality Assessment Score was greater than or equal to five points. The majority of articles included were scored as six or seven points. Reasons for lower scores included unknown publication bias and no rating by two independent reviewers. Most studies did not report harmful outcomes.

Four studies evaluated cyclophilin inhibitors (Table 1), four evaluated FGF analogs (Table 2), eleven evaluated pan-PPAR agonists (Table 3), and ten evaluated dual-PPAR agonists (Table 4). Different investigational products were assessed; the most common for cyclophilin inhibitors was NV556, for FGF agonists/analogs was Efruxifermin (EFX), for

Table 1 Studies of cyclophilin inhibitors in the treatment of non-alcoholic fatty liver disease

Ref.	Human or animal	Study design	Number of participants	Key inclusion criteria	Investigational product/dose	Study end points	Key findings
Harrison *et al*[9], 2022	Human	Randomized, single-blind, placebo-controlled, phase 2a study; Duration: 4 wk	n = 49	Patients with presumed F2/F3 NASH	Rencofilstat Placebo *vs* Rencofilstat (75 or 225 mg daily)	Evaluate the effect of Rencofilstat on ALT, Pro-C3, liver steatosis, and fibrosis measured by FibroScan	ALT in the placebo *vs* 75 *vs* 225 mg group was 70.67 *vs* 42.5 *vs* 30.56 IU/L. Pro-C3 was reduced in stratified patients with Pro-C3 > 15 (P < 0.01). Fibrosis was 22 *vs* 14 *vs* 12 kPa. Steatosis was 351 *vs* 337 *vs* 329 dB/m
Kuo *et al* [6], 2019	Animal	Duration: 30 wk	n = 10	High-fat diet-induced NASH mouse model (n = 10)	CRV431: Control *vs* 50 mg/kg daily	Evaluate the effect of CRV431 on liver fibrosis measured by Sirius red staining in liver biopsy sections	Fibrosis levels were 37%–46% lower in the treatment *vs* control group (P < 0.05)
Kuo *et al* [8], 2019	Animal	Duration: 6 wk	n = 9	CCL4-induced liver fibrosis mouse model (n = 9)	CRV431: Control *vs* 50 mg/kg daily	Evaluate the effect of CRV431 on liver fibrosis measured by Sirius red staining in liver biopsy sections	Liver fibrosis was lowered by 43% in the treatment *vs* control group (P < 0.01)
Kuo *et al* [8], 2019	Animal	Duration: 6 wk	n = 8	High-fat diet-induced NASH mouse model	NV556: Control *vs* 50 mg/kg daily	Evaluate the effect of NV556 on liver collagen and fibrosis measured by Sirius red staining in liver biopsy sections	Fibrosis was reduced by 60% in the treatment *vs* control group (P = 0.0281)
Simón Serrano *et al*[7], 2019	Animal	Duration: 7 wk	n = 20	Choline-deficient high-fat diet-induced model of NASH in mice (n = 10 per group)	NV556: Control *vs* 100 mg/kg daily	Effect of NV556 on liver fibrosis and collagen production measured by Sirus red staining	Reduction of liver fibrosis by 25% (2% in control *vs* 1.5% in treatment group P < 0.01)

ALT: Alanine transaminase; AST: Aspartate aminotransferase; NASH: Non-alcoholic steatohepatitis; NAFLD: Non-alcoholic fatty liver disease; CCL4: Carbon tetrachloride; IU: International units.

pan-PPAR agonists was Lanifibranor, and for dual-PPAR agonists was Saroglitazar.

In terms of cyclophilin inhibitors, four animal studies demonstrated significant improvement in fibrosis on liver biopsy weeks after product use (P < 0.05). The randomized controlled trial (RCT) performed in humans (n = 49) noted similar results, with a reduction in ALT and Pro-C3 levels (P < 0.01), as well as steatosis and fibrosis as measured on FibroScan (P < 0.01).

The three animal studies using FGF analogs demonstrated significant improvement in both steatosis and fibrosis measured on liver biopsy (P < 0.05). The RCT performed in humans (n = 80) measured the change in hepatic fat fraction (HFF) on magnetic resonance imaging at 12 wk of treatment. It noted a greater than 50% reduction in HFF in all treatment dosage groups (P < 0.0001).

Eight animal studies using pan-PPAR agonists evidenced a significant reduction in steatosis on biopsy as measured by the decrease in triglyceride or lipid accumulation in hepatocytes (P < 0.05). There was also a reduction in fibrosis and collagen deposition on liver biopsy (P < 0.05). The human studies included three RCTs that examined the metabolic effects and/or steatosis markers (steatosis activity score) and concluded improved metabolic function, resolution of steatosis, and fibrosis improvement (P < 0.05).

In terms of dual-PPAR agonists, six animal studies reported improvement in steatosis, reduction in fibrosis or progression to fibrosis, and improvement in lipid metabolism and insulin sensitivity (P < 0.05). Two human in-vitro studies on hepatic cells were performed, which demonstrated a reduction in hepatic lipid accumulation, secretion of inflammatory chemokines, and profibrotic gene expression. Four additional human studies, including prospective design and RCTs, showed improved metabolic parameters such as insulin sensitivity, hemoglobin A1c, and lipid profiles (P < 0.05). Additionally, FibroScan results showed improved liver stiffness and steatosis (P < 0.05).

DISCUSSION

Cyclophilin inhibitors

Cyclophilins are thought to contribute to the development of liver fibrosis and cancer. Among these, Cyclophilin B is known to play a role in collagen production, leading to fibrosis. To treat NASH, several investigational products have

Table 2 Studies of fibroblast growth factor analogs/agonists in the treatment of non-alcoholic fatty liver disease

Ref.	Human or animal	Study design	Number of participants	Key inclusion criteria	Investigational product/dose	Study endpoints	Key findings
Harrison *et al*[10], 2021	Human	Randomized, double-blind, placebo-controlled, phase 2a BALANCED study. Duration: 16 wk	n = 80	Patients with biopsy-confirmed NASH (F1-F3)	Efruxifermin: Placebo *vs* EFX (28, 50, 70 mg)	Absolute change from baseline in HFF measured as MRI-proton density fat fraction at 12 wk of EFX	The mean relative change in HFF at week 12 was -63.2% - 70.9%, and -72.3%, respectively, in the treatment groups of 28, 50, and 70 mg (P < 0.0001)
Bao *et al* [12], 2018	Animal	Duration: 15 d	n = 10	Choline-deficient high-fat diet-induced model of NASH in mice (n = 5 per group)		Effect of PSTag600 on attenuation of the development of NASH measured by NAS and oil red O staining	Decrease in NAS in control *vs* treatment group of 5 *vs* 1 and area of oil red O of 26% *vs* 3%, respectively (P < 0.05)
Le *et al* [11], 2018	Animal	Duration: 4 wk	n = 8	MCD diet-induced NASH mouse model		Evaluate the attenuation of fibrosis with the administration of LY2405319 by measuring levels of a-SMA and GPR91 (cells and receptors involved in hepatic fibrogenesis) on liver biopsy after 8 wk	The expression of α-SMA and GPR91 in the liver of mice fed with MCD diet was increased. The treatment group had an attenuated increase of collagen type 1, α-SMA, and GPR91 protein levels (P < 0.05). LY2405319 intraperitoneal administration for 4 wk daily ameliorated hepatic steatosis and fibrosis that was induced by MCD diet
Puengel *et al*[13], 2022	Animal	Duration: 6 wk	n = 12	Choline-deficient high-fat diet-induced model of NASH in mice (n = 6 per group)	BMS-986171: Control *vs* 0.6 mg/kg twice weekly	Effect of BMS-986171 on liver steatosis and fibrosis measured NAS on biopsy	NAS of the control vs. treatment group was 5 *vs* 4 (P < 0.05), hepatic steatosis 2.5 *vs* 1.5 (P < 0.01), inflammation 3.5 *vs* 2.5 and ballooning 1.2 *vs* 0.75 (P < 0.001) respectively

NASH: Non-alcoholic steatohepatitis; n: Number; NAS: NAFLD activity score; EFX: Efruxifermin; HFF: Hepatic fat fraction; MRI: Magnetic resonance imaging; α-SMA: Alpha-smooth muscle actin; MCD: Methionine and choline-deficient.

been developed to target Cyclophilins[6]. The main cyclophilin inhibitors reviewed here are CRV431[6], NV556[7,8], and Rencofilstat[9].

Studies conducted on animals, mainly mice that were administered a cyclophilin inhibitor, have shown positive results in improving liver fibrosis during biopsy[6-8]. In particular, Kuo *et al*'s research indicated a reduction of over 37% in liver fibrosis with CRV431 treatment compared to control on various mouse models[6,8]. Likewise, NV556 also demonstrated a significant decrease in collagen production and liver fibrosis[7,8].

Due to these promising results, researchers conducted a phase 2a RCT with 49 patients who received Rencofilstat (75, 225 mg) or a placebo[9]. The results showed that patients with high baseline Pro-C3 levels (> 15) experienced a decrease in collagen biomarkers, which are predictors for collagen deposition (P < 0.01)[9]. This aligns with previous animal studies, suggesting that cyclophilin inhibitor treatment may reduce liver fibrosis. The patients generally tolerated Rencofilstat well, with only mild side effects reported, such as constipation, diarrhea, back pain, dizziness, and headache [9]. Animal and human studies have shown that various investigational products that inhibit cyclophilin effectively treat patients with NASH. These agents are also well-tolerated and have anti-fibrotic properties that are beneficial.

FGF21 analogs or agonists

FGF21 is an active component of organ metabolism. Different variants have been studied for treating fatty liver disease, diabetes, and obesity due to their effect on glucose and lipid metabolism[10]. The main FGF21 analogs and agonists reviewed here are LY2405319[11], PsTag600[12], BMS-986171[13], and EFX[10]. Multiple animal studies involving FGF21 analogs and agonists have demonstrated improved glucose metabolism and reductions in markers of liver injury and fibrosis[11,12]. Le *et al*[11] performed an animal study using LY2405319 (FGF21 analog), which attenuated increased collagen type 1, alpha-smooth muscle actin, and GPR91 protein levels[11]. These results align with research on PsTag600 (long-acting FGF21) and BMS-986171 (FGF21 agonist)[12,13].

A phase 2a study included 80 patients treated with a placebo or EFX 28 mg, 50 mg, or 70 mg (FGF21 analog) for 12 wk [10]. The results indicated a significant decrease in HFF, with 78% of patients showing a positive response to NAS with an increase of at least 2 points and 48% of patients showing a resolution of NASH[10]. There was also a statistically

Table 3 Studies of pan peroxisome proliferator-activated receptor agonists in the treatment of non-alcoholic fatty liver disease

Ref.	Human or animal	Study design	Number of participants	Key inclusion criteria	Investigational product/dose	Study endpoints	Key findings
Abitbol *et al*[21], 2016	Human	Double-blind, randomized, placebo-controlled, parallel-group study. Duration: 4 wk		Patients with biopsy-confirmed NASH and type 2 diabetes on stable doses of metformin	IVA337 (Lanifibranor). Placebo *vs* IVA337 (400, 800, or 1200 mg daily)		Reduction in triglycerides by 32% and ALT by 10% ($P < 0.05$)
Cooreman *et al*[14], 2022	Human	Post-hoc analysis of the phase 2b NATIVE study. Duration: 24 wk	$n = 247$	Patients with non-cirrhotic biopsy-confirmed NASH	Lanifibranor Placebo *vs* Lanifibranor (800 or 1200 mg daily)	Effect of Lanifibranor on glycemic control and NASH markers. Efficacy in NASH was measured with SAF score and fibrosis staging	NASH resolution and fibrosis improvement in the treatment group *vs* placebo was 26% *vs* 7%, respectively, and a 41% reduction of HbA1c from baseline ($P < 0.001$)
Francque *et al*[18], 2021	Human	Randomized, double-blind, placebo-controlled, phase 2b trial. Duration: 24 wk	$n = 247$	Patients with noncirrhotic, highly active NASH (SAF ≥ 1 or higher for steatosis, hepatocellular ballooning, and lobular inflammation on liver biopsy)	Lanifibranor Placebo *vs* Lanifibranor (800 or 1200 mg daily)	Decrease of at least 2 points in the SAF score without worsening of fibrosis	48% of patients in the 800 mg group and 55% in the 1200 mg group had a decrease of at least 2 points in the SAF score *vs* 33% in the placebo group ($P = 0.007$)
An *et al* [22], 2017	Animal	Duration: 3 wk	$n = 5$	Genetically obese mice	MHY2013: Control *vs* 5 mg/kg daily	Reduction of hepatic steatosis measured *via* liver triglycerides on biopsy	Liver triglycerides were 10 mg/100 mg of protein in the control *vs* 7 mg/100 mg of protein in the treatment group ($P < 0.05$)
An *et al* [25], 2018	Animal	Duration: 3 wk	$n = 6$	Aged model mice	MHY2013: Control *vs* MHY2013 (1 or 3-5 mg/kg daily)	Evaluate the attenuation of hepatic lipid accumulation measured by liver biopsy	The ratio of liver weight/body weight was 0.035, 0.03, and 0.025 in control, 1 and 3-5 mg/kg groups, respectively ($P < 0.01$)
Barbosa-da-Silva *et al*[16], 2015	Animal	Duration: 4 wk	$n = 20$	High-fat diet mice ($n = 10$ per group)	Bezafibrate: Control *vs* 100 mg/kg daily	Effect of Bezafibrate on hepatic lipid metabolism measured by liver TG and steatosis on biopsy	Reduction in TG levels and liver steatosis of 30% and 50%, respectively, in the treatment group ($P < 0.0001$)
Boubia *et al* [19], 2018	Animal	Duration: 3 wk	$n = 16$	CCl4-induced liver fibrosis in mice ($n = 8$ per group)	Lanifibranor: Control *vs* 30 mg/kg daily	Efficacy of Lanifibranor in reducing fibrosis in NASH measured by hepatic collagen on biopsy	Reduction in hepatic collagen deposition from 0.6% of the area to 0.3% in the control *vs* treatment group ($P < 0.01$)
Lefere *et al* [15], 2020	Animal	Duration: 6 wk	$n = 16$	Choline-deficient high-fat diet-induced NASH mouse model ($n = 8$). Isolated hepatic macrophages ($n = 8$)		Effect on NAFLD measured by the NAFLD activity score, fibrosis by the Sirus red staining, and hepatic macrophages assessed by IHC	Reduction of NAFLD activity score from 6 to 2 in the treatment *vs* control group ($P < 0.0001$), collagen by 5% to 3% ($P < 0.01$), and liver macrophages from 22% to 8% ($P < 0.0001$)
Møllerhøj *et al*[20], 2022	Animal	Duration: 12 wk	$n = 13$	Gubra-Amylin NASH diet-induced obese mouse with biopsy-confirmed NASH	Lanifibranor: Control *vs* 30 mg/kg daily	Change in NAS and fibrosis stage measured on biopsy	At least a 2-point improvement in the steatosis score, and only 20% of hepatocytes had lipid droplets *vs* 80% in the control group ($P < 0.001$). 50% of mice had a 1-point improvement in fibrosis ($P < 0.05$)

Nagasawa *et al*[17], 2006	Animal	Duration: 5 wk	$n = 7$	Choline-deficient high-fat diet-induced NASH mouse model	Benzafibrate: Control *vs* Benzafibrate (50, 100 mg/kg daily)	Effect on hepatic lipid content and histopathological changes measured on biopsy by the number of activated hepatic stellate cells	Liver TG was 25, 20, and 55 mg/g in the 50, 100 mg/kg *vs* placebo groups, respectively ($P < 0.01$). The activated hepatic stellate cells were 11 number/15 fields *vs* 1 number/15 fields, respectively
Wettstein *et al*[24], 2017	Animal	Duration: 3 wk	$n = 20$	Choline-deficient high-fat diet-induced model of NASH in mice ($n = 10$ per group)	IVA337 (Lanifibranor) Control *vs* 30 mg/kg daily	Evaluate the effects of IVA337 on hepatic features associated with NASH measured by hepatic lipid droplet count and lobular inflammation foci count	Prevention of steatosis in 98% of mice and inflammation in 75% of mice ($P < 0.001$)

ALT: Alanine transaminase; NASH: Non-alcoholic steatohepatitis; n: Number; TG: Triglycerides; CCL4: Carbon tetrachloride; SAF: Steatosis activity fibrosis; NAFLD: Non-alcoholic fatty liver disease; NAS: NAFLD activity score; IHC: Immunohistochemistry.

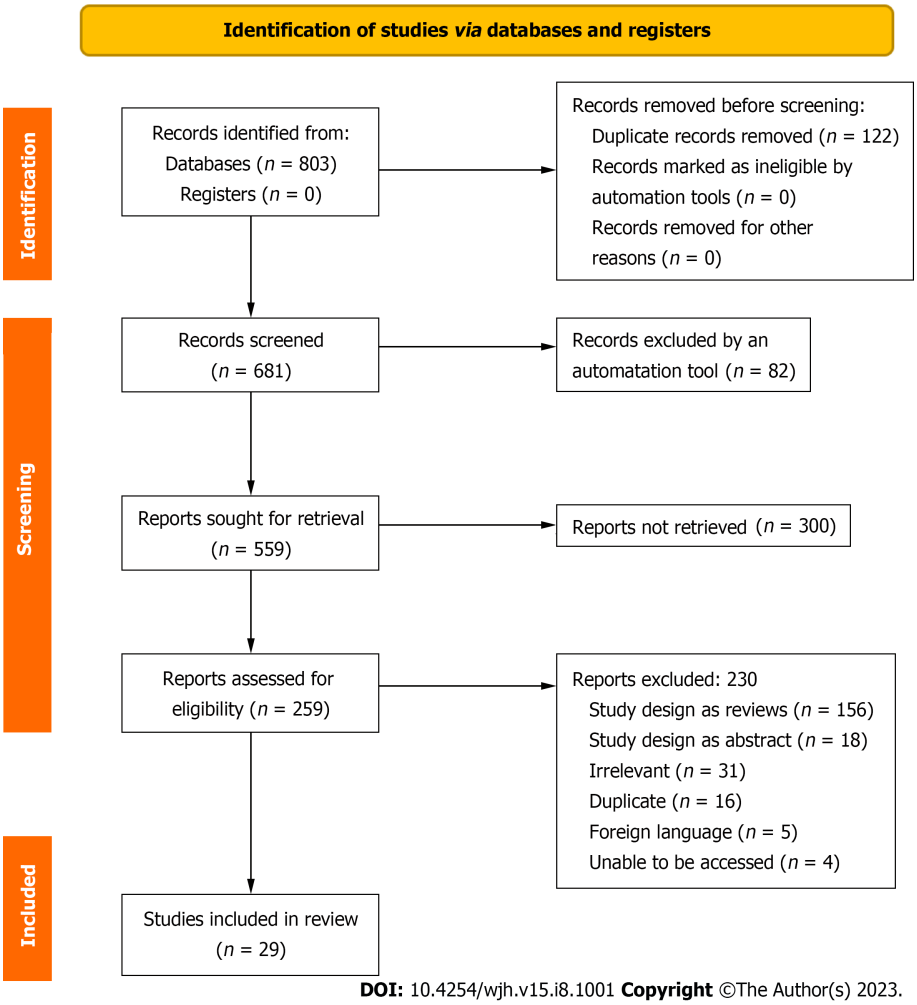

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Figure 1 PRISMA flow diagram.

significant reduction in alanine transaminase (ALT), aspartate aminotransferase (AST), and total cholesterol levels[10]. Compared to Resmetirom, a selective thyroid hormone receptor-β agonist in phase 3 trials, FGF21 analogs/agonists showed similar reductions in HFF and fibrosis[10]. The side effects reported for EFX were mild and included diarrhea, nausea, vomiting, abdominal pain, frequent bowel movements, and fatigue[10]. In conclusion, FGF21 analogs and agonists have numerous benefits for NAFLD, including improved glucose and lipid metabolism, reduced markers of liver injury, and liver fibrosis. They effectively reduce hepatic steatosis and fibrosis, making them a promising treatment for NAFL and NASH.

Table 4 Studies of dual-pan peroxisome proliferator-activated receptor agonists in the treatment of non-alcoholic fatty liver disease

Ref.	Human or animal	Study design	Number of participants	Key inclusion criteria	Investigational product/dose	Study endpoints	Key findings
Boeckmans *et al*[34], 2019	Human		N/A	Hepatic cells generated from human skin-derived precursors with induced NASH	Elafibranor	Effect on hepatic steatosis and inflammatory chemokines	Reduction in hepatic lipid load, as well as the expression and secretion of inflammatory chemokines, which are responsible for the recruitment of immune cells
Boeckmans *et al*[33], 2021	Human	*In vitro* study. Duration: N/A	N/A	Hepatic cells generated from human skin-derived precursors with induced NASH	Elafibranor	Effect on hepatic steatosis, inflammatory chemokines, and pro-fibrotic gene expression	Attenuated lipid accumulation, inflammatory chemokine secretion, and pro-fibrotic gene expression
Cariou *et al* [27], 2013	Human	Multicenter, randomized, single-blind, placebo-controlled, crossover study. Duration: 8 wk	n = 22	Abdominally obese insulin-resistant males	GFT505: Placebo *vs* 80 mg daily	Effect on peripheral and hepatic insulin sensitivity with improvement in GIR	Improved peripheral insulin sensitivity with a 21% increase of the GIR (P = 0.048) and enhanced hepatic insulin sensitivity with a 44% increase in insulin suppression of endogenous glucose production (P = 0.006)
Chaudhuri *et al*[32], 2023	Human	Single-center, prospective, observational, open-label, single-arm study. Duration: 52 wk	n = 76	Patients with NAFLD and elevated ALT levels along with liver stiffness value ≥ 6 kPa and/or liver steatosis CAP > 290 dB/m	Saroglitazar 4 mg daily	Effect on liver stiffness and steatosis measured by LSM and CAP on FibroScan at baseline, 24 and 54 wk	There was significant improvement of LSM from baseline (11.03 ± 7.19 kPa) to 24-wk (9.29 ± 6.39 kPa) and 52-wk (8.59 ± 6.35 kPa) values, respectively (P < 0.001). There was a significant improvement in median CAP at 24 wk 281 dB/m, (P < 0.001) and 52 wk 287 dB/m, (P < 0.001) as compared with the baseline 328 dB/m
Hassan *et al* [29], 2019	Animal	Duration: 5 wk	n = 12	Mice with induced NASH by a high-fat emulsion diet (n = 6 per group)	Saroglitazar: Control *vs* 4 mg/kg daily	Histopathological effects of Saroglitazar by using light microscopy	In the control *vs* treatment group, steatosis score was 3 *vs* 0.5, hepatic ballooning was 2 *vs* 0.5, lobar hepatitis was 3 *vs* 1, and portal hepatitis was 3 *vs* 0.25, respectively (P < 0.05)
Padole *et al* [31], 2022	Human		n = 91	Patients with BMI > 23 kg/m^2 diagnosed with NAFLD (CAP > 248 dB/m)	Saroglitazar 4 mg daily	Change from baseline of liver biomarker, hepatic steatosis, and fibrosis in patients who lost > 5% of the weight	Patients with > 5% of weight loss had a median AST of 36 *vs* 40 at baseline (P = 0.038), ALT 44 *vs* 53 (P < 0.01), kPa 5.9 *vs* 6.8 (P = 0.336) and CAP 265 *vs* 311 (P = 0.128)
Rajesh *et al* [28], 2022	Human		n = 85	Patients with NAFLD (US, CT, or MRI) and type 2 diabetes mellitus, and dyslipidemia	Saroglitazar 4 mg daily	Evaluate the effect of Saroglitazar on liver function test, liver fibrosis score by FibroScan, lipid profiles, and HbA1c	From baseline, there was a reduction in ALT from 49 u/L to 48 (P < 0.05), fibrosis score 10 kPa to 6 (P < 0.0001), TG 359.89 to 103.04 (P = 0.0001), HbA1c 10.29% to 9.85% (P = 0.002)
Jain *et al* [30], 2018	Animal	Duration: 12 wk	n = 18	CDHFD-induced model of NASH in mice (n = 9 per group)	Saroglitazar: Control *vs* 3 mg/kg daily	Reversal of CDHFD-induced NASH after 8 wk	In control vs. treatment, respectively, steatosis score was 2.6 *vs* 0, ballooning 1.4 *vs* 0, inflammation 3 *vs* 1.1 (P < 0.1)
Jain *et al* [30], 2018	Animal	Duration: 12 wk	n = 16	CCL4-induced fibrosis model in mice (n = 8 per group)	Saroglitazar: Control *vs* 4 mg/kg daily	Reversal of CCl4-induced liver fibrosis after 4 wk	Saroglitazar protected mice from CCl4-induced liver fibrosis measured *via* Hematoxylin and Eosin stains
Staels *et al* [26], 2013	Animal	Duration: 7 wk	n = 16	Choline-deficient high-fat diet-	GFT505: Control *vs* 10 mg/kg	Evaluate the prevention of the	The percentage of animals with macrosteatosis in

				induced model of NASH in mice (*n* = 8 per group)	daily	development of NASH in CDHFD mice	control *vs* treatment was 100% to 0%, inflammation was 100% to 0%, and the percentage of fibrosis was 1.3% to 0.8% ($P < 0.01$)
Staels *et al* [26], 2013	Animal	Duration: 7 wk	*n* = 12	CCl4-induced liver fibrosis in mice (*n* = 6 per group)	GFT505: Control *vs* 30 mg/kg daily	Evaluate the prevention of the development of NASH in CCL4 mice	The fibrotic surface of control *vs* treatment was 8% *vs* 4% in CCL4 mice ($P < 0.001$)
Ye *et al*[23], 2003	Animal	Duration: 2 wk	*n* = 6	High fat-fed rats	Ragaglitazar: 3 mg/kg-1 daily	Evaluate the benefits of Ragaglitazar on insulin sensitivity and lipid metabolism.	Enhanced insulin suppressibility of hepatic glucose output by 79% ($P < 0.001$), decrease in liver TG from baseline of 23 μmol/g to 7 μmol/g ($P < 0.01$)

N/A: Not applicable; NASH: Non-alcoholic steatohepatitis; n: Number; TG: Triglycerides; CCL4: Carbon tetrachloride; NFS: NAFLD fibrosis score; CAP: Controlled attenuation parameter; HbA1c: Hemoglobin A1c; NAFLD: Non-alcoholic fatty liver disease; GIR: Glucose infusion rate; CDHFD: Choline-deficient high-fat diet; BMI: Body mass index; ALT: Alanine transaminase; AST: Aspartate aminotransferase; US: Ultrasound; MRI: Magnetic resonance imaging; CT: Computerized tomography.

Pan-PPAR agonists

There are three different isoforms of PPAR, α, γ, δ[14]. PPARα mainly regulates genes that participate in lipid transport, beta-oxidation, gluconeogenesis, and ketogenesis[15]. PPARγ regulates adiponectin, glucose metabolism, adipocyte differentiation, and lipogenesis[15]. PPARδ limits inflammation and regulates hepatic fatty acid oxidation[15]. Single PPAR agonists have had unwanted adverse effects and less effective results, for which investigational products that act on several isoforms have been attractive[15].

The main pan-PPAR agonists reviewed here are Benzafibrate[16,17], Lanifibranor[14,15,18-21], and MHY2013[22,23]. Multiple animal studies involving pan-PPAR agonists have demonstrated increased plasma adiponectin, improvement in hepatic steatosis, and markers of liver injury[15,17,19,20,22-24]. In alignment with the mechanism of pan-PPAR agonists, MHY2013[22,25] and Lanifibranor[19,20,24] also led to a decrease in hepatic steatosis, hepatic inflammation, serum triglycerides, profibrotic and fibrotic genes. In addition to the previously mentioned effects of Lanifibranor, Møllerhøj *et al*[20] revealed that Lanifibranor resulted in progressive weight loss, a 23% decrease at eight weeks and a 30% decrease at 12 wk [20].

In line with results from animal studies, a study of 45 patients using Lanifibranor (400 mg, 800 mg, or 1200 mg) or placebo for four weeks revealed an increase in adiponectin, a decrease in triglycerides, and ALT[25]. Shortly after, a more significant phase 2b trial was performed on 247 patients with NASH that were randomly assigned to Lanifibranor (800 or 1200 mg) or a placebo daily for 24 wk[18]. Participants had at least a 2-point decrease in the Steatosis, Activity, and Fibrosis score[18]. A comparison of pan-PPAR agonists *vs* single agents revealed that pan-PPAR agonists were more potent in counteracting fibrosis by combining specific mechanisms of single PPAR agonists[15]. Lanifibranor was generally well tolerated with mild reported side effects, including diarrhea, nausea, peripheral edema, anemia, and weight gain[18]. Based on initial data, pan-PPAR agonists are more effective in improving the histological features of fatty liver disease with fewer adverse side effects than single PPAR agonists. This makes them a desirable option for the treatment of fatty liver disease.

Dual-PPAR agonists

Like pan-PPAR agonists, these agents act on two isoforms of PPAR, allowing for a more targeted effect. Saroglitazar has already been Federal Drug Administration (FDA)-approved for diabetic dyslipidemia and hypertriglyceridemia and has been shown to improve NAFLD, which piqued interest.

The main dual-PPAR agonists reviewed here are Ragaglitazar (α/γ)[23], GFT505 (α/δ)[26,27], Saroglitazar (α/γ)[28-32] and Elafibranor (α/δ)[33,34]. Multiple animal studies involving dual-PPAR agonists have demonstrated promising results, including reduced triglycerides and liver injury markers[23,29]. Ragaglitazar revealed an 88% reduction in triglycerides, increased adiponectin, counteracted an increase in visceral fat mass, and enhanced insulin suppressibility of hepatic glucose output[23]. These outcomes correlate with results seen with GFT505[26] and Saroglitazar[20,29]. Furthermore, Saroglitazar completely normalized AST and ALT, reduced serum TNF-α level by 47.6% and leptin by 58.6%[29].

Human research showed promising results in line with the aforementioned animal studies. GFT505 80 mg/day revealed a statistically significant reduction of fasting plasma triglycerides, LDL, and liver enzyme levels[27]. However, the most studied investigational product is Saroglitazar. A more extensive study in 85 patients revealed reduced ALT and triglycerides[28]. Furthermore, a study of Saroglitazar in 91 patients showed that 57 patients (63%) could reduce ≥ 5% of their weight[31]. There has been discussion regarding pan-PPAR agonists *vs* dual agents; Boeckmans *et al*[33] compared Elafibranor *vs* Lanifibranor (pan-PPAR agonist), which identified Elafibranor as having higher anti-NASH properties[33]. In general, dual-PPAR agonists are safe and effective in treating NAFLD and obesity. Research suggests that Elafibranor may be more effective than pan-PPAR agonists in treating these conditions.

CONCLUSION

NAFLD has become one of the most common causes of chronic liver disease globally. It's troubling that no FDA-approved treatments are currently available for this condition. Patients are limited to lifestyle changes and managing any concurrent diseases associated with fatty liver. However, there are promising developments in the form of investigational products that are being studied through clinical trials. These products include cyclophilin inhibitors, FGF21 agonists, and pan and dual PPAR agonists. The data analyzed in this review show clinically significant improvement in individual histological features of NAFLD in both animal and human trials for all four classes. These agents were generally well tolerated, with minimal side effects. We believe this compilation of information will have positive clinical implications in obtaining an FDA-approved therapy for NAFLD. However, more extensive trials are needed to further determine their efficacy, proper dosage, duration of therapy, and potential side effects for patients with NAFLD, including those with hepatic steatosis and fibrosis.

ARTICLE HIGHLIGHTS

Research background

Non-alcoholic fatty liver disease (NAFLD) has become a global health issue with significant medical costs. The lack of a Federal Drug Administration (FDA)-approved medication for the treatment of NAFLD has prompted the investigation of several potential therapeutic classes. It is valuable to have a compilation of the data available on their efficacy.

Research motivation

Due to the absence of an approved medication by the FDA for the treatment of NAFLD, several therapeutic classes have been investigated in clinical trials. It is important to understand the mechanisms and statistical significance of the agents being investigated, as NAFLD is extremely prevalent.

Research objectives

To assess the efficacy of cyclophilin inhibitors, fibroblast growth factor 21 analogs (FGF21), and dual and pan peroxisome proliferator-activated receptor (PPAR) agonists as possible therapeutic classes for treating NAFLD.

Research methods

We searched PubMed, EMBASE, Cochrane Library, Scopus, and Web of Science using keywords including cyclophilin inhibitor, FGF agonist, pan-PPAR agonists, dual-PPAR agonist, NAFLD, non-alcoholic steatohepatitis, and fatty liver. Articles with a National Institutes of Health Quality Assessment score of five or higher were included. Each article was screened by two independent researchers evaluating relevance and quality. Pertinent data were extracted in a spreadsheet and descriptively analyzed.

Research results

We identified 29 studies that met the necessary criteria and were included in this review. These records included 12 human studies and 17 animal studies. Specifically, there were four studies on cyclophilin inhibitors, four on FGF analogs, 11 on pan-PPAR agonists, and ten on dual-PPAR agonists. All classes were found to be efficacious for the treatment of NAFLD with statistical significance ($P < 0.05$).

Research conclusions

We found that cyclophilin inhibitors, fibroblast growth factor 21 analogs, and dual and pan PPAR agonists are not only statistically efficacious for the treatment of NAFLD but also generally well tolerated. We recommend more extensive human clinical research to further delineate therapy's efficacy, dosage, and duration.

Research perspectives

It is to be expected that additional human clinical trials of the therapeutic classes assessed in this review, as well as additional novel agents, will be conducted in the near future. An FDA-approved agent for the treatment of NAFLD is of utmost importance.

FOOTNOTES

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REFERENCES

1 **Filipovic B**, Lukic S, Mijac D, Marjanovic-Haljilji M, Vojnovic M, Bogdanovic J, Glisic T, Filipovic N, Al Kiswani J, Djokovic A, Kapor S, Bukumiric Z, Starcevic A. The New Therapeutic Approaches in the Treatment of Non-Alcoholic Fatty Liver Disease. *Int J Mol Sci* 2021; **22** [PMID: 34948020 DOI: 10.3390/ijms222413219]

2 **Rowe IA**, Wong VW, Loomba R. Treatment Candidacy for Pharmacologic Therapies for NASH. *Clin Gastroenterol Hepatol* 2022; **20**: 1209-1217 [PMID: 33711479 DOI: 10.1016/j.cgh.2021.03.005]

3 **Lee YA**, Friedman SL. Inflammatory and fibrotic mechanisms in NAFLD-Implications for new treatment strategies. *J Intern Med* 2022; **291**: 11-31 [PMID: 34564899 DOI: 10.1111/joim.13380]

4 **Nassir F**. NAFLD: Mechanisms, Treatments, and Biomarkers. *Biomolecules* 2022; **12** [PMID: 35740949 DOI: 10.3390/biom12060824]

5 **Ratziu V**, Francque S, Sanyal A. Breakthroughs in therapies for NASH and remaining challenges. *J Hepatol* 2022; **76**: 1263-1278 [PMID: 35589249 DOI: 10.1016/j.jhep.2022.04.002]

6 **Kuo J**, Bobardt M, Chatterji U, Mayo PR, Trepanier DJ, Foster RT, Gallay P, Ure DR. A Pan-Cyclophilin Inhibitor, CRV431, Decreases Fibrosis and Tumor Development in Chronic Liver Disease Models. *J Pharmacol Exp Ther* 2019; **371**: 231-241 [PMID: 31406003 DOI: 10.1124/jpet.119.261099]

7 **Simón Serrano S**, Grönberg A, Longato L, Rombouts K, Kuo J, Gregory M, Moss S, Elmér E, Mazza G, Gallay P, Pinzani M, Hansson MJ, Massoumi R. Evaluation of NV556, a Novel Cyclophilin Inhibitor, as a Potential Antifibrotic Compound for Liver Fibrosis. *Cells* 2019; **8** [PMID: 31717385 DOI: 10.3390/cells8111409]

8 **Kuo J**, Serrano SS, Grönberg A, Massoumi R, Hansson MJ, Gallay P. Cyclophilin Inhibitor NV556 Reduces Fibrosis and Hepatocellular Carcinoma Development in Mice With Non-Alcoholic Steatohepatitis. *Front Pharmacol* 2019; **10**: 1129 [PMID: 31611801 DOI: 10.3389/fphar.2019.01129]

9 **Harrison SA**, Mayo PR, Hobbs TM, Canizares C, Foster EP, Zhao C, Ure DR, Trepanier DJ, Greytok JA, Foster RT. Rencofilstat, a cyclophilin inhibitor: A phase 2a, multicenter, single-blind, placebo-controlled study in F2/F3 NASH. *Hepatol Commun* 2022; **6**: 3379-3392 [PMID: 36271849 DOI: 10.1002/hep4.2100]

10 **Harrison SA**, Ruane PJ, Freilich BL, Neff G, Patil R, Behling CA, Hu C, Fong E, de Temple B, Tillman EJ, Rolph TP, Cheng A, Yale K. Efruxifermin in non-alcoholic steatohepatitis: a randomized, double-blind, placebo-controlled, phase 2a trial. *Nat Med* 2021; **27**: 1262-1271 [PMID: 34239138 DOI: 10.1038/s41591-021-01425-3]

11 **Le CT**, Nguyen G, Park SY, Choi DH, Cho EH. LY2405319, an analog of fibroblast growth factor 21 ameliorates α-smooth muscle actin production through inhibition of the succinate-G-protein couple receptor 91 (GPR91) pathway in mice. *PLoS One* 2018; **13**: e0192146 [PMID: 29444136 DOI: 10.1371/journal.pone.0192146]

12 **Bao L**, Yin J, Gao W, Wang Q, Yao W, Gao X. A long-acting FGF21 alleviates hepatic steatosis and inflammation in a mouse model of non-alcoholic steatohepatitis partly through an FGF21-adiponectin-IL17A pathway. *Br J Pharmacol* 2018; **175**: 3379-3393 [PMID: 29859019 DOI: 10.1111/bph.14383]

13 **Puengel T**, Lefere S, Hundertmark J, Kohlhepp M, Penners C, Van de Velde F, Lapauw B, Hoorens A, Devisscher L, Geerts A, Boehm S, Zhao Q, Krupinski J, Charles ED, Zinker B, Tacke F. Combined Therapy with a CCR2/CCR5 Antagonist and FGF21 Analogue Synergizes in Ameliorating Steatohepatitis and Fibrosis. *Int J Mol Sci* 2022; **23** [PMID: 35743140 DOI: 10.3390/ijms23126696]

14 **Cooreman MP**, Francque S, Dzen L, Huot-Marchand P, Junien JL, Broqua P, Abdelmalek MF. 830-P: The Pan-PPAR Agonist Lanifibranor Improves Nonalcoholic Steatohepatitis (NASH) and Glycemic Control. *Diabetes* 2022; **71** (Supp 1): 830-P [DOI: 10.2337/db22-830-P]

15 **Lefere S**, Puengel T, Hundertmark J, Penners C, Frank AK, Guillot A, de Muynck K, Heymann F, Adarbes V, Defrêne E, Estivalet C, Geerts A, Devisscher L, Wettstein G, Tacke F. Differential effects of selective- and pan-PPAR agonists on experimental steatohepatitis and hepatic macrophages(☆). *J Hepatol* 2020; **73**: 757-770 [PMID: 32360434 DOI: 10.1016/j.jhep.2020.04.025]

16 **Barbosa-da-Silva S**, Souza-Mello V, Magliano DC, Marinho Tde S, Aguila MB, Mandarim-de-Lacerda CA. Singular effects of PPAR agonists on nonalcoholic fatty liver disease of diet-induced obese mice. *Life Sci* 2015; **127**: 73-81 [PMID: 25748419 DOI: 10.1016/j.lfs.2015.02.003]

17 **Nagasawa T**, Inada Y, Nakano S, Tamura T, Takahashi T, Maruyama K, Yamazaki Y, Kuroda J, Shibata N. Effects of bezafibrate, PPAR pan-agonist, and GW501516, PPARdelta agonist, on development of steatohepatitis in mice fed a methionine- and choline-deficient diet. *Eur J Pharmacol* 2006; **536**: 182-191 [PMID: 16574099 DOI: 10.1016/j.ejphar.2006.02.028]

18 **Francque SM**, Bedossa P, Ratziu V, Anstee QM, Bugianesi E, Sanyal AJ, Loomba R, Harrison SA, Balabanska R, Mateva L, Lanthier N, Alkhouri N, Moreno C, Schattenberg JM, Stefanova-Petrova D, Vonghia L, Rouzier R, Guillaume M, Hodge A, Romero-Gómez M, Huot-

Marchand P, Baudin M, Richard MP, Abitbol JL, Broqua P, Junien JL, Abdelmalek MF; NATIVE Study Group. A Randomized, Controlled Trial of the Pan-PPAR Agonist Lanifibranor in NASH. *N Engl J Med* 2021; **385**: 1547-1558 [PMID: 34670042 DOI: 10.1056/NEJMoa2036205]

19 **Boubia B**, Poupardin O, Barth M, Binet J, Peralba P, Mounier L, Jacquier E, Gauthier E, Lepais V, Chatar M, Ferry S, Thourigny A, Guillier F, Llacer J, Amaudrut J, Dodey P, Lacombe O, Masson P, Montalbetti C, Wettstein G, Luccarini JM, Legendre C, Junien JL, Broqua P. Design, Synthesis, and Evaluation of a Novel Series of Indole Sulfonamide Peroxisome Proliferator Activated Receptor (PPAR) α/γ/δ Triple Activators: Discovery of Lanifibranor, a New Antifibrotic Clinical Candidate. *J Med Chem* 2018; **61**: 2246-2265 [PMID: 29446942 DOI: 10.1021/acs.jmedchem.7b01285]

20 **Møllerhøj MB**, Veidal SS, Thrane KT, Oró D, Overgaard A, Salinas CG, Madsen MR, Pfisterer L, Vyberg M, Simon E, Broermann A, Vrang N, Jelsing J, Feigh M, Hansen HH. Hepatoprotective effects of semaglutide, lanifibranor and dietary intervention in the GAN diet-induced obese and biopsy-confirmed mouse model of NASH. *Clin Transl Sci* 2022; **15**: 1167-1186 [PMID: 35143711 DOI: 10.1111/cts.13235]

21 **Abitbol JL**, Broqua P, Junien JL. Metabolic effects and good tolerance of IVA337 a Pan-PPAR agonist in diabetic patients warrant further investigation in NASH. *J Hepatol* 2016; **64**: S189

22 **An HJ**, Lee B, Kim DH, Lee EK, Chung KW, Park MH, Jeong HO, Kim SM, Moon KM, Kim YR, Kim SJ, Yun HY, Chun P, Yu BP, Moon HR, Chung HY. Correction: Physiological characterization of a novel PPAR pan agonist, 2-(4-(5,6-methylenedioxybenzo[d]thiazol-2-yl)-2-methylphenoxy)-2-methylpropanoic acid (MHY2013). *Oncotarget* 2017; **8**: 45030 [PMID: 28693125 DOI: 10.18632/oncotarget.18922]

23 **Ye JM**, Iglesias MA, Watson DG, Ellis B, Wood L, Jensen PB, Sørensen RV, Larsen PJ, Cooney GJ, Wassermann K, Kraegen EW. PPARalpha /gamma ragaglitazar eliminates fatty liver and enhances insulin action in fat-fed rats in the absence of hepatomegaly. *Am J Physiol Endocrinol Metab* 2003; **284**: E531-E540 [PMID: 12556350 DOI: 10.1152/ajpendo.00299.2002]

24 **Wettstein G**, Luccarini JM, Poekes L, Faye P, Kupkowski F, Adarbes V, Defrêne E, Estivalet C, Gawronski X, Jantzen I, Philippot A, Tessier J, Tuyaa-Boustugue P, Oakley F, Mann DA, Leclercq I, Francque S, Konstantinova I, Broqua P, Junien JL. The new-generation pan-peroxisome proliferator-activated receptor agonist IVA337 protects the liver from metabolic disorders and fibrosis. *Hepatol Commun* 2017; **1**: 524-537 [PMID: 29404476 DOI: 10.1002/hep4.1057]

25 **An HJ**, Lee B, Kim SM, Kim DH, Chung KW, Ha SG, Park KC, Park YJ, Kim SJ, Yun HY, Chun P, Yu BP, Moon HR, Chung HY. A PPAR Pan Agonist, MHY2013 Alleviates Age-Related Hepatic Lipid Accumulation by Promoting Fatty Acid Oxidation and Suppressing Inflammation. *Biol Pharm Bull* 2018; **41**: 29-35 [PMID: 29311481 DOI: 10.1248/bpb.b17-00371]

26 **Staels B**, Rubenstrunk A, Noel B, Rigou G, Delataille P, Millatt LJ, Baron M, Lucas A, Tailleux A, Hum DW, Ratziu V, Cariou B, Hanf R. Hepatoprotective effects of the dual peroxisome proliferator-activated receptor alpha/delta agonist, GFT505, in rodent models of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. *Hepatology* 2013; **58**: 1941-1952 [PMID: 23703580 DOI: 10.1002/hep.26461]

27 **Cariou B**, Hanf R, Lambert-Porcheron S, Zaïr Y, Sauvinet V, Noël B, Flet L, Vidal H, Staels B, Laville M. Dual peroxisome proliferator-activated receptor α/δ agonist GFT505 improves hepatic and peripheral insulin sensitivity in abdominally obese subjects. *Diabetes Care* 2013; **36**: 2923-2930 [PMID: 23715754 DOI: 10.2337/dc12-2012]

28 **Rajesh NA**, Drishya L, Ambati MMR, Narayanan AL, Alex M, R KK, Abraham JJ, Vijayakumar TM. Safety and Efficacy of Saroglitazar in Nonalcoholic Fatty Liver Patients With Diabetic Dyslipidemia-A Prospective, Interventional, Pilot Study. *J Clin Exp Hepatol* 2022; **12**: 61-67 [PMID: 35068786 DOI: 10.1016/j.jceh.2021.03.012]

29 **Hassan NF**, Nada SA, Hassan A, El-Ansary MR, Al-Shorbagy MY, Abdelsalam RM. Saroglitazar Deactivates the Hepatic LPS/TLR4 Signaling Pathway and Ameliorates Adipocyte Dysfunction in Rats with High-Fat Emulsion/LPS Model-Induced Non-alcoholic Steatohepatitis. *Inflammation* 2019; **42**: 1056-1070 [PMID: 30737662 DOI: 10.1007/s10753-019-00967-6]

30 **Jain MR**, Giri SR, Bhoi B, Trivedi C, Rath A, Rathod R, Ranvir R, Kadam S, Patel H, Swain P, Roy SS, Das N, Karmakar E, Wahli W, Patel PR. Dual PPARα/γ agonist saroglitazar improves liver histopathology and biochemistry in experimental NASH models. *Liver Int* 2018; **38**: 1084-1094 [PMID: 29164820 DOI: 10.1111/liv.13634]

31 **Padole P**, Arora A, Sharma P, Chand P, Verma N, Kumar A. Saroglitazar for Nonalcoholic Fatty Liver Disease: A Single Centre Experience in 91 Patients. *J Clin Exp Hepatol* 2022; **12**: 435-439 [PMID: 35535066 DOI: 10.1016/j.jceh.2021.06.015]

32 **Chaudhuri S**, Dutta A, Chakraborty SBD. Efficacy and safety of saroglitazar in real-world patients of non-alcoholic fatty liver disease with or without diabetes including compensated cirrhosis: A tertiary care center experience. *JGH Open* 2023; **7**: 215-220 [PMID: 36968568 DOI: 10.1002/jgh3.12878]

33 **Boeckmans J**, Natale A, Rombaut M, Buyl K, Cami B, De Boe V, Heymans A, Rogiers V, De Kock J, Vanhaecke T, Rodrigues RM. Human hepatic in vitro models reveal distinct anti-NASH potencies of PPAR agonists. *Cell Biol Toxicol* 2021; **37**: 293-311 [PMID: 32613381 DOI: 10.1007/s10565-020-09544-2]

34 **Boeckmans J**, Buyl K, Natale A, Vandenbempt V, Branson S, De Boe V, Rogiers V, De Kock J, Rodrigues RM, Vanhaecke T. Elafibranor restricts lipogenic and inflammatory responses in a human skin stem cell-derived model of NASH. *Pharmacol Res* 2019; **144**: 377-389 [PMID: 31028903 DOI: 10.1016/j.phrs.2019.04.016]

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