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EDITORIAL

Liver transplantation and sleeve gastrectomy in the medically complicated obese: New challenges on the horizon

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Abstract

In the last 30 years, operative, technical and medical advances have made liver transplantation (LT) a life-saving therapy that is used worldwide today. Global industrialization has been a contributor to morbid obesity and this has brought about the metabolic syndrome along with many downstream complications of such. Non-alcoholic steatohepatitis (NASH) has become a recognized hepatic manifestation of the metabolic syndrome and NASH cirrhosis is predicted to be the primary indication for LT in the United States by 2025. Several case series and database reviews have begun analyzing the efficacy of weight reduction surgery in the LT recipient. These data have reasonably demonstrated that weight reduction surgery in the LT recipient is a feasible endeavor. However, several questions have been raised regarding the type of weight reduction surgery, timing of surgery in relation to LT, patient and allograft survival and post-LT maintenance of weight loss to name a few. We look forward to a time when weight reduction surgery will work to improve the technical conduct of LT, improve perioperative benchmarks such as blood transfusions, intensive care unit length of stay and help to prevent recurrence of NASH cirrhosis in the medically complicated obese patient. In the meantime, well-designed prospective clinical trials that focus on the issues highlighted will help guide us in the care of these complicated patients who will soon account for the majority of the patients in our clinics.

Key words: Non-alcoholic steatohepatitis cirrhosis; Liver transplantation; Sleeve gastrectomy; Roux-en-Y gastric bypass; Weight reduction surgery

Core tip: Non-alcoholic steatohepatitis (NASH) has become a recognized hepatic manifestation of the metabolic syndrome and NASH cirrhosis is predicted to be the primary indication for liver transplant (LT) in the United States by 2025. Previous reviews have shown that weight reduction surgery is a feasible endeavor in the liver failure patient. However, our review of the available literature highlights the need for a prospective clinical trial that will focus on the efficacy of sleeve gastrectomy in relation to LT perioperative outcomes, patient and allograft survival and prevention of NASH recurrence in the post-transplant setting.

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TEXT

Nonalcoholic fatty liver disease (NAFLD) encompasses a spectrum of liver injury that is marked by triglyceride accumulation in hepatocytes. The severity of liver injury ranges from benign steatosis that may be found incidentally on ultrasound or cross sectional imaging to nonalcoholic steatohepatitis (NASH), which is characterized by neutrophil infiltration into portal triads. NASH cirrhosis marks the final stage within the spectrum of NAFLD and this has become a leading indication for liver transplant (LT) in the United States[1]. In 1980, Ludwig *et al*[2] first described NASH as a clinical entity when they analyzed the liver biopsies of twenty patients with no history of alcohol abuse and found that the histologic profile was indicative of an inflammatory process as evidenced by hepatic steatosis, lobular hepatitis, focal necrosis with inflammatory infiltrates and Mallory bodies. A common variable for this group of patients was that they had manifestations of metabolic syndrome as most of the patients were female, obese, hypertensive, with diabetes mellitus and hyperlipidemia[2]. This observation has led many to believe that NASH is the hepatic manifestation of the metabolic syndrome.

The prevalence of adult obesity and the metabolic syndrome has reached epidemic proportions affecting an estimated 34% of the adult population in the United States[3-5]. This has led to a parallel trend in the incidence of NASH cirrhosis as the primary indication for LT from 1.2% in 2001 to 9.7% in 2009, making it the third most common indication in the United States[6]. Agopian *et al*[1] have reported the largest single institution series of patients undergoing LT for NASH cirrhosis over an 18-year period. In this retrospective series, they were able to demonstrate graft and patient survivals at 90 d similar to hepatitis C virus (HCV) as well as a retransplant rate for recurrent NASH cirrhosis of 7%, compared to 8% for HCV[1]. Although the short term data are promising, we have yet to understand the long term graft and patient survival, operative complications, immunosuppression-related morbidity and the financial implications of performing liver transplants on patients with NASH cirrhosis.

Historically, surgical procedures in the obese patient have conferred a higher morbidity and mortality compared to those performed in patients with a lower body mass index (BMI)[7-9]. However, only recently have we begun to examine complications in the obese liver transplant recipient. LaMattina *et al*[10] reviewed their series of 306 obese liver transplant recipients over 11 years and they found that patient and graft survival, blood product transfusion, intensive care unit (ICU) length of stay (LOS), and biliary complications requiring intervention were all higher in the obese patients[10]. Specifically, patient survival at 1, 3 and 5 years for Class Ⅱ obese patients (BMI 35.1-40) was 91%, 78%, and 78%, *vs* 94%, 86% and 83% in the non-obese recipients (P = 0.02)[10]. Following a similar trend, allograft survival for Class Ⅱ obesity was 87%, 76%, and 74%, *vs* 91%, 84% and 80% over the same time period (P = 0.04). Comparing the same two groups, blood transfusion use within the first 48 h was significantly higher in the obese group by 5 units (P = 0.002), ICU LOS was 1.5 d longer (P = 0.04) and the need for biliary interventions *via* endoscopic retrograde cholangiopancreatography or percutaneous approach after LT in Class Ⅱ obesity *vs* non-obese counterparts was also elevated (P = 0.003)[10].

Concerns over outcomes in the obese LT recipient have led to the advent of weight reduction surgery in the liver failure patient. Weight reduction surgery has evolved over the past 15 years and these advances have had a significant impact on the metabolic syndrome in the non-transplant obese patient. Of the weight reduction procedures in practice, the gold standard Roux-en-Y gastric bypass (RYGB) has been associated with the most profound sustained weight loss in long term studies[11]. Similarly, cessation of preoperative insulin and antihypertensive medications have been more closely related to RYGB as compared to restrictive procedures such as gastric banding[12]. Despite improved outcomes with RYGB, early approaches towards combined LT with weight reduction surgery have focused on the use of sleeve gastrectomy (SG) as the weight reduction procedure of choice. RYGB has largely been eliminated from the armamentarium in the LT recipient because of increased complexity with this technique as well as the malabsorption associated with RYGB that may adversely affect early post-transplant immunosuppression levels[13,14]. Combined LT and gastric banding has been previously reported. However, this has largely been abandoned due to concerns for having a foreign body in an immunosuppressed patient[15].

When considering approaches for SG in the LT patient, three approaches can be taken. Pretransplant SG, combined liver transplant and SG (LTSG) or SG in

the post-transplant setting. Heimbach *et al*[15] reported on their experience of combined liver transplantation and gastric sleeve resection (LTSG) for patients who had a BMI greater than 35 kg/m^2 along with a MELD score range of 19-32. Although their series contained a total of 44 patients and only 7 patients who underwent combined LTSG, they had two key findings that were important. First, they were able to demonstrate that noninvasive obesity management programs centered on dietary education are very effective at lowering the mean BMI at the time of enrollment from 40 to a mean BMI at the time of transplant of 33. The seven morbidly obese patients (mean BMI 48) who failed to lose weight from dietary modifications went on to get LTSG. The second critical observation is that at 3 years follow-up, the patients who underwent dietary modification and liver transplant alone achieved the target weight loss pretransplant, but were not able to sustain this weight loss after transplant. This resulted in an increase of the mean pretransplant BMI of 33 to 36 in the post-transplant setting when adjusted for ascites and edema. In contrast, the 7 morbidly obese patients who failed the pretransplant dietary modification program and underwent combined LTSG had a mean BMI of 49 at enrollment, 48 at the time of transplant and after 17 mo follow-up had a mean BMI of 29. Of these 7 patients, one gastric staple line leak occurred in a 60-year-old male who had a MELD of 40 at the time of transplant[15]. Although there were no other complications attributable to SG in this group, this very serious complication raises questions regarding the timing of SG within the spectrum of liver disease. Previous reports of weight reduction surgery in the post-transplant setting have demonstrated acceptable outcomes, but were reported to be technically demanding operations due to the altered surgical field[13,16-18]. Performing this operation in the post-transplant setting may offer an advantage in terms of allograft survival if NASH recurrence could be prevented, however, the surgical and perioperative benefits around the time of transplant are lost by taking this approach. Thus, the greatest advantage of weight reduction surgery can potentially come in the pretransplant setting. The timing of such a procedure is critical and must also take into consideration the effect of SG on the technical aspects of the future liver transplant. Namely, adhesion formation subsequent to SG can potentially impact mobilization of the left lobe of the liver due to dense adhesions between the staple line of the stomach and the left lobe of the liver and may similarly impact porta hepatis dissection.

Previous reports based on nationwide admission data, diagnosis and procedure codes have analyzed outcomes for patients who underwent bariatric surgery while having a concomitant diagnosis of compensated *vs* decompensated liver disease or no liver disease at all. Although this data is inherently limited, the expected finding was that patients with decompensated liver disease who underwent bariatric surgery had a higher mortality rate (16.3%) as compared to those patients with compensated (0.9%) or no liver disease at all (0.3%) (P = 0.0002)[19]. By stratifying these groups of patients and focusing on those patients with compensated liver disease, we can potentially identify patients who can tolerate SG prior to LT without progressing to decompensated liver failure. This is a significant barrier that will require increased awareness in order for primary care physicians and hepatologists to identify patients with metabolic syndrome who are at the highest risk of developing NASH cirrhosis.

Weingarten *et al*[20] retrospectively analyzed their prospectively collected data on 340 patients who underwent laparoscopic bariatric operations with morbid obesity as the primary indication for surgery and no known history of liver disease. Liver biopsies were performed intraoperatively and revealed that 44% of the patients had mild NASH with no or minimal fibrosis and 14% had advanced NASH with at least stage 2 fibrosis at the time of their bariatric surgery[20]. The complication rate did not differ significantly across NASH categories when comparing hospital length of stay, 30 d postoperative deaths, or liver failure[20]. This is a critical observation because it implies that we have inherently been operating on patients with advanced, but compensated liver disease who can already be identified as patients who may not recover from their burden of liver disease if left untreated. More importantly, they were able to tolerate a major bariatric operation without any overt decompensation of their newly diagnosed liver disease, as would be expected with this overall minimal degree of liver injury. However, the important observation is that these subsets of patients who have NASH with low grade fibrosis, or perhaps even Child's A cirrhotic patients without any overt evidence of portal hypertension, may be the most appropriate patients who should be considered for SG prior to LT. Although we currently do not have any empiric evidence to support this hypothesis, these observations can be used as preliminary data to help identify the optimal timing for SG in the pretransplant period, while maintaining a low risk for overt decompensation of their liver disease.

CONCLUSION

The future of liver transplant will see a paradigm shift where HCV cirrhosis will become a secondary indication for LT. The advent of direct acting antivirals has changed the playing field when it comes to the treatment of HCV cirrhosis. We can anticipate that NASH cirrhosis will supersede all other indications for LT in the near future if we consider the projection that 25 million Americans will develop NASH by 2025, with 20% progressing to cirrhosis and/or hepatocellular carcinoma that may require LT[3-5]. Our review of the literature summarizes the initial experience with weight reduction surgery in the setting of chronic liver disease and it suggests that we can safely perform SG prior to, in combination with, and in the post-transplant setting. Conventional wisdom would suggest that most centers would consider

patients who have no more than Child's A cirrhosis and a BMI of 35 kg/m^2 for SG in the pretransplant setting. With respect to combined SG and liver transplant in the same setting, we propose that this should be reserved for lower risk patients with low MELD scores or patients who have MELD exceptions and have retained physiologic reserve at the time of transplant. Ultimately, the approach to the timing of SG will likely be center and region specific as centers with very high acuity due to organ constraints may not be able to offer combined SG/liver transplant to their patients as other centers or regions can. Thus, the centers/regions with higher average MELD scores at transplant may be forced to offer this service to their patients in the pretransplant setting, assuming that NASH is the indication for liver transplant and that their liver disease remains compensated. Considering the scope of the problem at hand, a prospective clinical trial that focuses on the timing of SG, long term patient and allograft survival, operative complications, financial implications and NASH recurrence after LT will help guide the future of both of these successful operations.

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EDITORIAL

Innate immune recognition of hepatitis B virus

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Abstract

Hepatitis B virus (HBV) is a hepatotropic DNA virus and its infection results in acute or chronic hepatitis. It is reported that the host innate immune system contributes to viral control and liver pathology, while whether and how HBV can trigger the components of innate immunity remains controversial. In recent years, the data accumulated from HBV-infected patients, cellular and animal models have challenged the concept of a stealth virus for HBV infection. This editorial focuses on the current findings about the innate immune recognition to HBV. Such evaluation could help us to understand HBV immunopathogenesis and develop novel immune therapeutic strategies to combat HBV infection.

Key words: Hepatitis B virus; Pathogen-recognition receptor; Hepatocytes; Interferon; Innate immunity

Core tip: Hepatitis B virus (HBV) infection is prevalent worldwide as a major public health problem and the leading cause of severe liver diseases. A plethora of evidence suggests that innate immune pathways are involved in the cross-talk between HBV components and host immune cells. Many type of cells, including hepatocytes, kupffer cells and circulating monocytes, could sense and be activated by HBV infection through specific pathogen recognition receptors, resulting in the production of pro-inflammatory cytokines and interferons. Understanding of the nature of innate immunity induced by HBV will aid to characterize the immunopathogenesis of HBV infection and to further design novel immune-based therapeutic strategies for HBV infection.

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INTRODUCTION

Hepatitis B virus (HBV) is a hepatotropic DNA virus

belonging to the *Hepadnaviridae* family and causes different outcomes of liver disease in humans, such as acute or chronic hepatitis, liver cirrhosis and hepatocellular carcinoma[1]. Patients with chronic HBV infection are mostly asymptomatic but at risk of developing life-threating complications. Despite the availability of effective prophylactic vaccines, HBV infection is highly epidemic in developing countries and about 1 million people die from HBV-associated severe liver diseases annually[2]. Generally, the pathogenesis and outcomes of HBV infection are mainly determined by the magnitude of host antiviral immune response[3]. It has been experimentally proved that the $CD8^+$ T cells - mediated adaptive immune response is necessary for controlling of HBV infection, and exogenous activation of host innate immune system is able to inhibit HBV replication and gene expression[4]. However, during the occurrence of HBV infection, whether and how HBV trigger the components of innate immunity remains controversial. This review will summarize and evaluate the current findings, some of which are still contradictory, regarding the induction of innate immunity by HBV infection and how innate immune sensors are able to recognize HBV components.

HBV INFECTION ACTIVATES HOST INNATE IMMUNITY

During the early phase of viral infections, the production of pro-inflammatory cytokines and interferons (IFNs), and the activation of natural killer (NK) cells is frequently observed. Previously, HBV was considered as a stealth virus that could establish persistent infection in liver by evading the host innate immune system[5]. Using an experimentally infected chimpanzee model, Wieland *et al*[6] had reported that HBV was unable to interfere host cellular gene transcription significantly and to induce IFN-stimulated genes (ISGs) expression in the liver. However, by quantification of serum cytokines, a study, which was enrolled 21 HBV-infected patients during the pre-symptomatic phase, indicated that HBV infection was unable to elicit a strong production of IFNs and interleukin (IL)-15, but did induce the production of anti-inflammatory cytokine IL-10[7]. In addition to this observation, another study suggested that many cytokines were weakly induced during acute HBV infection. After initiation of viral expansion and before the peak of viremia, IFN-α, tumor necrosis factor (TNF)-α, IL-15, IL-10, IL-6 and IL-1β levels were detectable in serum samples from about half of HBV patients[8]. Interestingly, a longitudinal study performed in woodchuck model demonstrated that NK and NKT cell responses were activated within hours after inoculation with high dose of woodchuck hepatitis virus (WHV)[9]. This result was consistent with the observation in two blood donors developing HBV infection without elevation of alanine aminotransferases at very early stage of infection[10]. Recently, Hong *et al*[11] revealed that HBV exposure *in utero* induced innate immune cell maturation and Th1 response development, which in turn enhanced the responses of cord blood immune cells to bacterial infection *in vitro*. Therefore, rather than being silent, HBV may be efficient in inducing anti-/pro-inflammatory cytokines, but less potent to activate IFN response in patients.

In agreement with the findings above, HBV was shown to be sensed by different types of liver cells with *in vivo* and *in vitro* models. In the chimeric uPA-SCID mice harboring human hepatocytes, a weak activation of ISGs was detected in HBV-infected human hepatocytes, but not in mouse hepatocytes without HBV infection[12]. Further, transduction of liver progenitor cell line HepaRG cells with a baculovirus vector expressing HBV resulted in significant activation of IFN-β and ISGs expression[13]. The possible explanation for activation of IFN pathway in HepaRG cells is that the exceedingly high dose of HBV baculovirus inoculum is able to induce different intracellular pathways. However, when using cultured primary human hepatocytes and non-parenchymal liver cells, it was shown that HBV was recognized by kupffer cells. This recognition led to nuclear factor kappa B pathway activation and IL-6 production, while no induction of type-Ⅰ IFNs[14]. Moreover, circulating monocytes were shown to respond to HBsAg *in vitro*, resulting in strong production of pro-inflammatory cytokines TNF-α and IL-6[15].

Taken together, these data obtained from recent studies suggested that liver cell populations, as well as circulating innate immune cells, could sense and respond to HBV infection, which enables the innate immune system to detect and restrict the invading virus. Then, it is necessary to explore the receptors and the signaling pathways responsible for sensing HBV within the infected hepatocytes or other immune cells.

INNATE IMMUNE RECEPTORS INVOLVED IN RECOGNITION OF HBV

In general, various pathogen-recognition receptors (PRRs) which recognize specific structures and components of pathogens by cells are responsible for activation of host innate immune system. The main PRRs sensing viral infection consist of toll-like receptors (TLRs), NOD-like receptors, retinoic acid inducible gene Ⅰ (RIG-Ⅰ)-like receptors including RIG-Ⅰ and melanoma differentiation associated gene 5 (MDA5). Viral envelope proteins, nucleocapsids and nucleic acids are able to activate special intracellular signaling pathways and induce the production of IFNs, pro-inflammatory cytokines and chemokines[16]. In the case of HBV infection, several PRRs in different cell types were identified to be involved in recognition of HBV. For example, Cooper *et al*[17] demonstrated that HBV nucleocapsids could activate TLR2-mediated signaling pathway in human THP-1 macrophages to induce pro-inflammatory cytokines production. In HBV replicating

hepatocytes, Lu *et al*[18] reported the expression of MDA5 was up-regulated in Huh7 cells transfected with the HBV genotype D replicative plasmid and in the livers of plasmid hydrodynamically injected mice. Further, they found that MDA5, but not RIG-I, was able to associate with HBV-specific nucleic acids, suggesting that MDA5 may sense HBV[18]. In contrast, a recent study suggested that RIG-I was the most important innate immune sensor of HBV in hepatocytes. They demonstrated that IFN-λ but not type-Ⅰ IFNs is predominantly induced in HBV infected primary human hepatocytes and hepatoma cell lines. Moreover, the induction of IFN-λ is dependent on the RIG-Ⅰ-mediated sensing the 5′-ε region of HBV pregenomic RNA[19]. These contradictory results might mainly arise from the usage of different genotype of HBV plasmid and cellular models. In addition, the results also clarified that two previously reported cytosolic DNA sensors, including cyclic GMP-AMP synthase and IFN-γ-inducible protein 16, were not involved in HBV recognition in hepatocytes[19]. In addition, it is worth noting that HBV-induced IFN responses in hepatocytes is relatively weak, as compared with other virus infection, which is consistent with the observations from the studies obtained in chimpanzee[6] and mouse models[14].

PRR ACTIVATION CONTROLS HBV INFECTION

Although the PRR-mediated innate immunity is weakly activated by HBV infection, numerous studies have clarified that HBV replication and gene expression can be inhibited by different PRR agonist stimulation in *vitro* and in *vivo*[4]. For example, Isogawa *et al*[20] firstly reported that intravenous injection of TLR3, TLR4, TLR5, TLR7 or TLR9 ligands resulted in HBV inhibition by type Ⅰ IFN induction in HBV transgenic mice model. This finding was consistent with *in vitro* observation that the culture medium derived from TLR3-activated murine kupffer cells or liver sinusoidal endothelial cells could inhibit HBV replication indirectly by IFN-β induction in immortalized murine hepatocytes[21]. Moreover, in primary woodchuck hepatocytes or hepatoma cell lines, it had been shown that TLR2 or TLR4 ligands were able to inhibit HBV and WHV replication through activation of MAPK-ERK and PI3K-Akt pathways directly[22,23]. Besides TLRs, activation of RIG-Ⅰ in hepatocytes by 5′-triphosphorylated siRNA or HBV 5′-ε region derived RNA also induced a vigorous IFN response against HBV in hepatocytes[19,24]. These studies mentioned above indicated that the PRR-induced anti-HBV response was dependent on the secreted cytokines from immune cells and the intracellular signaling pathways of hepatocytes. It is worth mentioning that recent preclinical studies revealed that oral administration of a TLR7 agonist GS-9620, which was capable of stimulating robust IFN-α responses in plasmacytoid dendritic cells and triggering ISGs expression in PBMCs and liver, resulted in HBV suppression in chronically infected chimpanzees[25] and woodchuck models[26]. Of note, this antiviral activity is also associated with activation of intrahepatic T, NK, and NKT cell responses that produce IFN-γ[25]. Therefore, TLR7 agonist might be a promising drug candidate for immune modulation therapy of chronic HBV infection due to its dual effect on host innate and adaptive immune system[27].

CONCLUSION

The accumulated data highlight that HBV is recognized by host PRRs and thus induces innate immune responses that restrict virus replication and expansion. However, the specific PRRs and intracellular signaling pathways involved in the HBV recognition and inhibition still require further investigation. An in-depth understanding of immune mechanisms induced by distinct components of HBV will provide the opportunity to characterize the immunopathogenesis of HBV infection and develop immune-based therapeutic strategies for HBV infection. Considering the suppressive effect of different viral proteins on innate immune system may contribute to viral persistence in chronic HBV infection[23], the activation of host innate immune system by specific PRR agonists to overcome the immune suppressive effect of HBV, like TLR7 ligand GS-9620[27], may be helpful in clearing HBV infection.

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REVIEW

Hepatitis C virus infection and prisoners: Epidemiology, outcome and treatment

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Abstract

The studies on hepatitis C virus (HCV) infection in prison populations are few and mostly cross-sectional. We analyzed prevalently the articles appearing on PubMed in the last ten years. HCV infection is frequent in prisoners, prevalences ranging from 3.1% to 38% according to the HCV endemicity in the geographical location of the prison and in the countries of origin of the foreign prisoners and to the prevalence of intravenous drug use, which is the most important risk factor for HCV infection, followed by an older age of prisoners and previous prison terms. HCV replication in anti-HCV-positive cases varies from 45% to 90% in different studies, and the most common HCV genotypes are generally 1 and 3. The response to antiviral treatment is similar in prisoners to that of the general population. Unfortunately, treatment is administered less frequently to prisoners because of the difficulties in management and follow-up. The new directly acting antivirals offer a good therapy option for inmates because of their good efficacy, short duration of treatment and low incidence of side effects. The efforts of the prison authorities and medical staff should be focused on reducing the spread of HCV infection in prisons by extending the possibility of follow-up and treatment to more prisoners with chronic hepatitis C.

Key words: Prisoners; Management; Treatment; Care; Chronic hepatitis C

Core tip: Hepatitis C virus (HCV) infection in prisoners is

a social health problem: It is more frequent than in the general population, but access to proper management and treatment is more difficult. In this setting HCV infection can be easily transmitted due to overcrowded conditions, sharing supplies and particularly by drug use. In the past, HCV treatment was rarely administered to prisoners, often because they did not stay in the same structure long enough. Also, the risk of HCV re-infection is high in inmates. New policies should be applied to guarantee prisoners the same care as the general population, particularly in view of the new, shorter and more effective anti-HCV treatments.

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INTRODUCTION

The United Nations Basic Principles for the Treatment of Prisoners state that prisoners "shall have access to the health services available in the country without discrimination on the grounds of their legal situation"[1]. Unfortunately, this basic principle has been infrequently applied in real life and in most countries prisoners have a lesser possibility of assistance and care than other citizens[2].

Hepatitis C virus (HCV) infection is more frequently detected in inmates than in the general population[3,4], the highest prevalence being reported in Central Asia (38%) and Australasia (35%)[3]. These high prevalences are due mostly to unsafe lifestyles and family, psychiatric and social problems, conditions often experienced by prisoners before incarceration. Intravenous drug use (IVDU), tattooing and promiscuous sexual contact[5] are the main risk factors for acquiring HCV infection. Once in prison, overcrowding, violence, separation from family and emotional problems are additional reasons[6] that may induce inmates to start or continue unsafe habits. An estimate of the incidence of new HCV infections in prisons exceeds 30 per 100 persons per year[7,8].

Proper treatment of chronic hepatitis C in prison is rare for social and educational reasons[9,10] and, not least, because most inmates with HCV infection remain unaware of their virological condition. Several other barriers may prevent HCV inmates from being admitted for treatment: Individual problems (drug abuse, stress, fear, lack of confidence) and social problems (stigma, discrimination, difficulty to relate to the health personnel)[11]. Another obstacle may be the lack in a prison of a liver disease specialist, a problem that can be overcome with the use of telemedicine[12].

Although many prisoners are incarcerated for long periods, the average length of stay in the same prison can be weeks or months in several cases[13,14], which makes it difficult to complete the clinical itinerary from screening to post-treatment follow-up.

The prison authorities and physicians should implement strategies to improve the diagnostic and therapeutic approach to HCV in prisoners, general screening for the anti-HCV antibody being the first step in this approach. Prisoners with chronic HCV infection should undergo a full diagnostic procedure and clinical staging before being considered for treatment, since inmates with HCV-related chronic hepatitis can achieve a sustained virological response with the same frequency as free patients[15].

Because of the numerous obstacles mentioned above, only a few studies on HCV infection in prisons have been carried out to date, and directives issued by experts[16] are often not properly followed. Because of complexity of the subject and in order to analyze more recent aspects of the problem, we evaluated prevalently the articles appearing on Pubmed in the last ten years. We used a combination of the following keywords: "prison", "prisoners", "inmate", "HCV infection", "intravenous drug use", "epidemiology", "chronic hepatitis", "cirrhosis", "treatment", "interferon", "ribavirin", "directly acting antivirals (DAA)", "sofosbuvir", "telaprevir", "boceprevir", to find articles focusing on the epidemiology, clinical outcome and treatment of HCV infection in prisons.

EPIDEMIOLOGY OF HCV INFECTION IN PRISONS

Table 1 shows the results of the majority of the studies performed worldwide on the anti-HCV prevalence in prisoners[17-42]. These rates ranged over the years from 3.1% to 38%, in relation to the endemicity of HCV infection in the geographical location of the prison and in the countries of origin of foreign prisoners as well as the prevalence of IVDU in the different studies. The lowest anti-HCV prevalence (3.1%) was reported by Santos *et al*[18] in 422 inmates held in two prisons, one for males and one for females in the State of Sergipe in Brazil, where only 10% of the detainees stated IVDU. In contrast, the highest prevalence of HCV infection was reported by Reekie *et al*[28] in prisoners in Australia investigated in 2004. The same Author found lower rates in subsequent studies evaluating HCV infection in the inmates of all Australian prisons, 33.3% in 2007 and 23.1% in 2010, regardless of IVDU.

Taylor *et al*[23], in a national cross-sectional study conducted in Scotland, showed an overall prevalence of HCV infection of 19% in a population of 4904 inmates, 53% in prisoners with a history of IVDU and 3% in those without. Another national cross-sectional study evaluated 1876 inmates randomly selected among imprisoned individuals aged over 18 in France and in French overseas departments[26] and reported an anti-HCV prevalence of 4.8%. Alvarez *et al*[29] documented a 10.1% prevalence of anti-HCV- positive cases among 2788 inmates held in two prisons in New York State,

Table 1 Hepatitis C virus prevalence in different studies on prisoners

Ref.	Year of screening	Country	Type of study	Number screened/total	Type of screening	HCV prevalence
Adjei *et al*[31]	2004/5	Ghana	C-S 8 prisons; inmates *vs* staff	1336/7652 *vs* 445/2139	C + Q	18.7% *vs* 18.7%
Almasio *et al*[16]		Italy				38%
Alvarez *et al*[29]	2009/13	United States	C-S	2788	C + Q + Clinical records	10.1%
Babudieri *et al*[42]		Italy	C-S 8 prisons	973		38%
Barros *et al*[20]	2007/8	Brazil	C-S	148/150	C + I	6.1%
Brandolini *et al*[17]	2006	Italy	C-S	695/965	HCV History + C	22.4%
Hennessey *et al*[36]	1999/2000	United States	C-S	1292 HIV-positive	Stored blood + medical records	13%
Kazi *et al*[33]	2007/8	Pakistan	C-S	357	C + Q	15.2%
Kheirandish *et al*[37]	2006	Iran	C-S	454/499	C + I	80%
Luciani *et al*[24]	2005/9	Australia	Prospective cohort study	210 HCV Ab -	C + Q + payment+ follow-up	Incidence 14.8 per 100/yr
Macalino *et al*[32]	1998/2000	United States		4269/5390 446 incidence study		23.1% 0.4 per 100/yr
Mahfoud *et al*[30]	2007/8	Lebanon	C-S	580/35500	Random+ C + Q	3.43%
Marco *et al*[41]		Spain	Observational and C-S 18 prisons	371	Q	22.7%
Meyer *et al*[34]	2002	Germany	C-S	1125/1176	C + I post screening	8.6%
Mohamed *et al*[19]		Egypt	C-S	500/1200	Random sampling + C + Q	15.8%
Nokhodian *et al*[40]		Iran	C-S	160	C + I	4.4%
Prasetyo *et al*[21]	2009	Indonesia	C-S 4 prisons	375/375	C + Q	34.1%
Reekie *et al*[28]	2004	Australia	C-S	588	C + Q	33.3%
	2007		C-S	536	C + Q	31.6%
	2010		C-S	618	C + Q	23.2%
Rosa *et al*[27]	2010/11	Brazil	Descriptive study	195/386	Random + C + Q	9.7%
Sagnelli *et al*[38]		Italy	C-S 9 prisons	2241/3468	Peer-to-peer education + C	22.8%
Saiz de la Hoya *et al*[25]	2008	Spain	C-S 18 prisons	378		22.7%
Santos *et al*[18]	2009/10	Brazil	C-S 2 prisons	422/519	C + Q	3.1%
Semaille *et al*[26]	2010	France	C-S 27 prisons	1876	Q + medical records	4.8%
Solomon *et al*[35]	2002	United States	C-S	3914	Educational information, C + or counseling	29.7%
Taylor *et al*[23]	2010/11	Scotland	C-S 14 prisons	4904/6565	C + Q	19% Incidence > 1%
Tresó *et al*[22]	2007/9	Hungary	C-S 20 prisons inmates *vs* staff	4894/14331	C + Q	4.9% *vs* 0.5%

C-S: Cross-sectional; C: Consent; Q: Questionnaire; I: Interview; HCV: Hepatitis C virus.

while Macalino *et al*[32] found a prevalence of 32.1% in a cross-sectional study involving 4260 prisoners incarcerated in Rhode Island correctional facilities. In this study the authors investigated only the inmates detained in the same prison for more than 12 mo and registered an incidence rate of 0.4 per 100 persons per year.

Cross-sectional studies in different Italian prisons published 5 years apart showed anti-HCV positivity of 38%[42] and 22.8%[38] in the inmates investigated.

Most of the studies listed in Table 1 were cross-sectional, performed with different aims, enrolment criteria and statistical analysis. In most studies the information on the prisoners was obtained using a pre-coded questionnaire, less frequently by oral interview[20,34,37,40] and in only one case by doctor-to-patient interview[35]. Some questionnaires gave no information on important socioeconomic factors, which are indicators of the level of awareness of HCV infection[30]. In addition, it cannot be excluded that some inmates may have lied regarding certain questions, in particular those concerning IVDU and sexual behavior, probably because these behaviors are illegal or considered immoral from a social perspective. To have more reliable information from the prisoners, educational programs or peer-to-peer communication[38] could be organized to improve the trust relationship between the patients and medical personnel. In some studies the information was obtained from medical records, with a consequent lack of some important data[26,27,36].

Different results were reported in two interesting studies comparing the prevalences of anti-HCV-positive cases between prisoners and members of the staff. Tresó *et al*[22] performed a multicenter cross-sectional study in Hungary and found a significant difference in the anti-HCV rate between the prisoners (4.9%) and the wardens (0.47%), whereas Adjei *et al*[31] found the same anti-HCV prevalence (18.7%) in prison officers and prisoners in nine prisons in Ghana, possibly reflecting an occupation-related transmission or simply the high prevalence of HCV infection in this country.

RISK FACTORS FOR THE ACQUISITION OF HCV INFECTION IN PRISONERS

The epidemiological impact of various risk factors for acquiring HCV infection has been investigated in

Table 2 Risk factors associated with hepatitis C virus, hepatitis C virus genotype and human immunodeficiency virus and/or hepatitis B virus co-infection

Ref.	HCV prevalence	Risk factors (odds ratio)	HCV genotypes (No. of patients)	Co-infection
Adjei *et al*[31]	18.7% *vs* 18.7%			
Alvarez *et al*[29]	10.1%	IVDU (64.8)[1]; sex with IVDU (8.0)[1]; HIV (4.3)[1]; STD (3.2)[1]; tattoo (2,9)[a]; non-Hispanic black (2.3)[1]		
Babudieri *et al*[42]	38%	IVDU (10.5); tattoo (2.9)		
Barros *et al*[20]	6.1%	IVDU (5.9)[1]; > 6 in prison(4.2)[1]; sex with IVDU(1.4)[1]; age > 40 (4.4)[1]	1a (3) 1b (1) 3a (1)	
Brandolini *et al*[17]	22.4%	HIV +; origin; age 35-52		HIV/HCV 11.6% (60)
Hennessey *et al*[36]	13%	HBV (4.44)[1]; HIV (2.51)[1]; previous imprisonment (2.90)[1]		
Kazi *et al*[33]	15.2%	IVDU (24.32)[1]; surgery (2.41)[1]		
Kheirandish *et al*[37]	80%	History of incarceration (4.35)[1]; tattoo (2.33)[1]; first injection ⩽ 25 years old (2.72)[1]		
Luciani *et al*[24]	Incidence 14.8 per 100/yr	IVDU-related behaviors; origin (2.63)[2]		
Macalino *et al*[32]	23.1% 0.4%/yr	IVDU (32.44)[1]; increasing age > 30		
Mahfoud *et al*[30]	3.43%	IVDU; previous imprisonment; tattoo	1 (5) 3 (1)	
Marco *et al*[41]	22.7%			HIV/HCV 39
Meyer *et al*[34]	8.6%	IVDU; tattoo	1 (34) 2 (5); 3 (24) 4 (3)	HCV/HIV 5 HCV/BcAb 33 B/C 1.2%
Mohamed *et al*[19]	15.8%	IVDU (4.1)[1]; > 10 in prison (3.4)[1]; shared toiletries (3.9)[1]; tattoo (2.8)[1]; dental procedure (4.7)[1]; age > 45 (1.5)[1]; DM (3.9)[1]		
Nokhodian *et al*[40]	4.4%	IVDU (134.44)		
Prasetyo *et al*[21]	34.1%	IVDU (2.5); tattoo (3.2); piercing (3.6)	1a (14) 1c (5) 1b (1) 3a (4) 3k (4) 4a (2)	B/C 4
Reekie *et al*[28]	33.3% ('04) 31.6% ('07) 23.2% ('10)	IVDU; women (1.33)[3] Age ⩾ 25 (1.56)[3] Previous imprisonment (2.15)[3]		HIV/HCV 1 HBV/HCV 6 HBV/HCV 5 HBV/HCV 2
Rosa *et al*[27]	9.7%	IVDU (8.75); tattoo (3.35)		
Saiz de la Hoya *et al*[25]	22.7%	IVDU (24.5)[1]; HIV (8.4)[1]; Spanish (7.5)[1] Prison > 5 yr (5.2)[1]	1a (23) 1b (12) 3 (12) 4 (16)	HIV/HCV 8.5% HBV/HCV 0.3% HBV/HCV/ HIV 1.5%
Santos *et al*[18]	3.1%	IVDU (23.3)[1]; household contact (14.1)[1]; syphilis (9.8)[1]; age > 30 (5.5)[1]	1a (6) 1b (1) 1 (3) 3 (1)	
Semaille *et al*[26]	4.8%	IVDU; women; > age; origin		HIV/HCV 0.08%
Solomon *et al*[35]	29.7%	Increasing age, max > 45 (13.51)[1]; women (1.32)[1]; HIV (4.09)[1]; HBV (2.69)[1]		
Tresó *et al*[22]	4.9%	IVDU		

[1]Adjusted odds ratio; [2]Hazard ratio; [3]IRR. IVDU: Intravenous drug use; HCV: Hepatitis C virus; HBV: Hepatitis B virus; HIV: Human immunodeficiency virus; STD: Sexually transmitted diseases; DM: Diabetes mellitus; IRR: Incidence rate ratio.

several studies on prison populations and the results are summarized in Table 2. The main risk factor associated with HCV infection in the prison populations is IVDU. Although this risky behavior is strictly forbidden in prisons worldwide, nearly half of illicit drug users continue to use these drugs after their imprisonment. In addition, the difficulty to get sterile injecting equipment in prison results in widespread sharing of infected equipment and an increased risk of HCV transmission. A prospective Australian study conducted between 2005 and 2009[24] on 210 anti-HCV-negative subjects with a life-time history of injection drug use observed every 6/12 mo for up to 4 years showed an incidence of HCV infection of 14.8 per 100 persons per year and that imprisonment was associated with high rates of HCV transmission.

In a cross-sectional study including four prisons in Indonesia[21], the general prevalence of inmates with HCV infection was 34.1% (92 in IVDU and 36 in non-IVDU). A cross-sectional study[27] in a rehabilitation center for IVDU in Iran showed that the anti-HCV prevalence reached 80%. Other forms of blood-to-blood contact such as tattooing, sharing toiletries and dental procedures were involved to a lesser extent in the transmission of HCV among prisoners.

Meyer *et al*[34] found an anti-HCV and/or HCV-RNA prevalence of 8.6% in 1125 young prisoners, but 94% of the anti-HCV-positive were intravenous drug users.

In some studies, HCV infection was observed more frequently in female inmates than in males, reflecting the higher rates of females incarcerated for drug-related offences. Solomon *et al*[35] investigated for the anti-HCV

prevalence the inmates entering the Maryland Division of Corrections, which includes one male and one female prison. Overall, 29.7% of 3914 prisoners were infected with HCV and the prevalence was higher in women than in men (37.9% *vs* 28.3%). Semaille *et al*[26] also described a significantly higher anti-HCV prevalence in women than in men (11.8% *vs* 4.5%) in French prisons.

Other risk factors related to HCV infection in prison were an older age and previous imprisonments, factors probably related to an increased exposure over time to the main risk factors. Solomon *et al*[35] found that the HCV prevalence progressively increased with the increase in age, from 7.9% in the age group younger than 25% to 58.5% in that over 45 years. Macalino *et al*[32] and Santos *et al*[18] found a significant association between the presence of HCV infection and an age over 30, and Mohamed *et al*[19] found that an age over 45 and a previous prison term were factors associated with anti-HCV positivity in inmates. A previous imprisonment was registered in the life history of the majority (89%) of anti-HCV-positive inmates in the main prison facility in Lebanon[30].

Prisoners with HIV and/or HBV infection were more likely to be infected with HCV, probably because of the similarity in the routes of transmission of these blood-borne infections. In an Italian prison, the anti-HCV prevalence reached 89.6% in the HCV-human immunodeficiency virus (HIV) co-infected inmates and 15.5% in those without HIV infection[17]. Similar data come from another study showing a higher prevalence of anti-HCV positivity in anti-HIV-positive patients than in the anti-HIV-negative (65.5% *vs* 27.5%), and in those with a present or past HBV infection (47.1%) than in those without any HBV contact (20.2%)[35].

Virological status and clinical outcome

HCV replication in anti-HCV positive cases, as detected by the presence of HCV RNA in serum, has been reported with a rate ranging from 45% to 90% in different studies[17,19-22,25,34].

The HCV genotype distribution varied according to the distribution in the geographical areas of the prisons and to that of the country of origin of the foreign prisoners. Meyer *et al*[34] performed HCV genotyping in 68 young prisoners and found genotype 1 in 50% of cases and genotype 3 in 35%; in this study genotype 1 prevailed in German inmates and genotype 3 in the prisoners from the independent states formerly part of the Soviet Union. HCV-genotype 1 predominated in Indonesian (66%)[21] and Spanish (55%) prisons[25]. Tyczyno *et al*[39] compared the HCV genotyping performed on prisoners in Poland with that of hospital patients in the same country and found that HCV genotype 3 prevailed in the prisoners (60.1%) and genotype 1 in the free patients (79.6%), most probably because genotype 3 is frequent in IVDU.

The severity of the disease associated with HCV infection and the disease progression have been evaluated only in a few studies. Prisoners frequently showed a mild disease[25,34] and liver cirrhosis and progression to cirrhosis were detected with a low frequency[19]. However, most of the patients in the published studies were young and the disease progression was mostly evaluated with surrogate tests (APRI, fibroscan) and infrequently with liver biopsy[25,34]. The mortality risks were estimated to be higher in HCV-infected than in non-infected subjects in the general population[43], a difference that was more evident in prisoners[44].

Treatment

Few studies have been performed to date on the treatment of chronic hepatitis C in prisoners and a sustained viral response (SVR) with standard or pegylated interferon (Peg-IFN) plus ribavirin treatments ranged from 28% to 69%[12,43,45-52]. Encouraging results were observed in an old series in Canadian penitentiaries using standard interferon plus ribavirin, with an overall SVR of 55.9% (31.6% for genotype 1, 100% for genotype 2 and 71.4% for genotype 3)[47]. Maru *et al*[52] showed an overall SVR to Peg-IFN plus ribavirin of 47.1% (43.1% for HCV-genotype 1 and 58.8% for HCV-genotypes 2 and 3), HCV-genotype 1 and liver cirrhosis being identified as predictive factors of a non-response.

Chew *et al*[53] obtained an overall SVR of 28% (18% for genotype 1, 60% for genotype 2 and 50% for genotype 3) with Peg-IFN plus ribavirin.

The use of second generation DAAs to treat HCV chronic infection has substantially reduced the period of treatment and of post-treatment follow-up, thus greatly improving the chances of completing treatment in prisons. A recent study comparing the cost-benefit of treatment with peg-IFN, ribavirin and boceprevir or sofosbuvir found treatment including sofosbuvir cost-effective[54]. However, the rate of HCV re-infection after successful treatment in inmates is high, particularly in IVDU[54,55], a priority situation warranting serious consideration. The high costs of the new DAA treatments are an important issue to be evaluated in order to extend these therapies to prison inmates[56].

Conclusive statements

In most countries, the National Justice and Healthcare Authorities should strive to remove the enormous institutional, bureaucratic and economic barriers hampering an appropriate approach to the management of HCV infection in prisons. These institutions have a great responsibility and a fundamental role in organizing the life of prisoners, particularly of those with chronic diseases who need new costly treatments. More resources should be allocated in each country to reduce the prevalence and incidence of HCV infection in prisons and to treat all inmates already infected. The basic principle underlying this difficult issue is that prisoners in every country deserve the same healthcare treatment as the general population and to deny them this is unjust and immoral. This principle of equivalence is fundamental and is supported by the international

guidelines on prison health and prisoners' rights and the national policies in many countries[57].

Practical advice

Reduce the spread of HCV infection in prisons by: (1) performing screening for anti-HCV as it is cost-effective, which is particularly valid for prisoners with risk factors for HCV infection[58]; The Centers for Disease Control and Prevention recommends screening prisoners born between 1945 and 1965, the age group with the highest prevalence of HCV[59]; (2) defining the prevalence and incidence in prisons of HCV infection; (3) performing educational programs for prisoners and prison personnel on the routes of HCV transmission, prevention measures and management of infected subjects. A successful approach based on peer-to-peer communication[38,60,61] may improve the compliance of inmates and favor their access to screening, clinical evaluation and treatment; (4) performing regular educational programs for prisoners and staff against the discrimination of HCV-infected inmates[62]; (5) improving the conditions of hygiene; (6) supplying the inmates with personal toiletries; (7) heightening vigilance to prevent tattooing and IVDU; and (8) providing opiate replacement therapy for drug users[23].

Improve the access to follow-up and treatment of prisoners with chronic hepatitis C by: (1) defining the clinical condition of all anti-HCV-positive prisoners; (2) avoiding frequent transfers of inmates under treatment from one prison to another to allow the completion of therapy and post-treatment follow-up or permitting continuation treatment in another facility or outside if no longer detained[56]; this is now easier with the introduction of the second generation DAAs, which reduce the duration of treatment and follow-up period; and (3) organizing telematic assistance to benefit from specialist's support in the management of treated patients[56].

Sensitivity, goodwill and a willingness to cooperate by the Healthcare authorities, prison authorities and personnel are necessary.

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MINIREVIEWS

Analgesia after liver transplantation

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Abstract

This article addresses postoperative analgesia in patients with end-stage liver disease who have undergone liver transplantation (LT). Postoperative analgesia determines how patients perceive LT. Although important, this topic is underrepresented in the current literature. With an increased frequency of fast tracking in LT, efficient intra- and postoperative analgesia are undergoing changes. We herein review the current literature, compare the benefits and disadvantages of the therapeutic options, and make recommendations based on the current literature and clinical experience.

Key words: Liver transplant; Analgesia; Fast-track; Opioid; Postoperative

Core tip: Based on several papers published over the last two decades, there is a general assumption that pain following liver transplantation (LT) is less intense than pain following other major abdominal procedures and that the postoperative opioid consumption is lower than for other hepatobiliary procedures. There is also an assumption that patient-controlled opioid analgesia is the only mode of postoperative analgesia for this group of patients. In this paper, we challenged that opinion and addressed the specificity of postoperative pain intensity and treatment in LT patients. We also explored all options in pain control, in addition to patient-controlled analgesia, including epidural analgesia, transversus abdominis plane block and wound catheter infiltration.

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INTRODUCTION

Liver transplantation (LT) is a major surgery performed in very ill patients with end-stage liver disease. In terms of hemodynamic variations, fluid shift and replacement, metabolic derangements, bleeding tendency, duration, and potential complications, it is probably the most challenging abdominal operation. Although there is an abundance of material in the literature on LT and on

certain aspects of anesthesia, there are very few reports regarding postoperative analgesia following LT.

Based on several papers published over the last two decades, there seems to be a general assumption that pain following LT is less intense than pain following other major abdominal procedures and that consequently the postoperative opioid consumption is lower than for other hepatobiliary procedures[1-3]. There is also an assumption that patient-controlled opioid analgesia (PCA) is the only mode of postoperative analgesia for this group of patients. Improvements in perioperative care and fast tracking require changes in intra- and postoperative analgesia[4]. In this paper, we will address the specificity of postoperative pain intensity and treatment in LT. We will also explore all options in pain control.

SPECIFICITY OF PAIN INTENSITY FOLLOWING LT SURGERY

There is a general assumption among LT experts that postoperative pain is not so severe and that analgesia requirements are lower than for other major abdominal procedures; however, several factors have been identified as contributing to a high analgesia requirement following LT. First, the large "Mercedes-Benz incision" that is routinely used for LT is one of the longest and, consequently, most painful incisions[5]. The subcostal component of that incision is particularly painful during deep breaths, coughing, and movement. Second, the long surgical time, the use of surgical retractors, and the pressure applied to the lower ribs with the retractors contribute to an intensely painful sensation following surgery[6]. Third, the hyperdynamic circulation characteristics of end-stage liver disease are associated with a higher distribution clearance of analgesic medications administered intraoperatively[7]. Consequently, the intraoperative analgesia requirement is increased in patients with end-stage liver disease undergoing LT. Fourth, when massive blood loss and transfusion occur during surgery, there is a need for more analgesia simply because some analgesic drugs will be lost with blood loss. Fifth, when the newly transplanted liver is working, analgesic drug metabolism will be higher than that in the pretransplant state. Sixth, some patients undergoing LT experience chronic pain preoperatively. Consequently, management of postoperative pain is as complex as for any other patient with chronic pain. Finally, although less frequent, factors associated with a high analgesia requirement still exist, such as the fact that a small proportion of LT recipients are methadone-maintained and require significantly more intra- and postoperative analgesia[8].

There are also factors that might be expected to contribute to lower analgesia requirements following LT. First, patients with more severe end-stage liver disease generally require less analgesia[9]. Second, during the anhepatic phase, there is no analgesic drug metabolism and thus a decreased need for analgesic medication[10]. Third, when there is primary nonfunction of the transplanted liver or delayed recovery of liver function post-LT, analgesia requirements are decreased. In addition, renal impairment may prolong the action of morphine, in part due to slower excretion of the active metabolites of morphine[11].

Historically, patients undergoing LT were kept sedated and ventilated for at least 12 h, when the pain is the most intense. During that time, they were given generous continuous infusions of opioids that provided sufficient analgesia. When patients woke up, they had already passed the most painful postoperative phase. However, with recent fast tracking in up to 90% of patients undergoing LT, patients are awake within a couple of hours of LT, when postoperative pain is most intense[4].

INTENSITY OF PAIN: THE EVIDENCE

Pain intensity assessed by measuring pain

There are very little data in the literature about pain intensity following LT. No single study has focused on the intensity of postoperative pain. We could only extract data from a control group of a retrospective study on 16 patients who had received morphine PCA for postoperative analgesia, where patients were in the intensive care unit (ICU) and nurses recorded pain scores hourly[12]. The median pain score was 2/(0-3), equivalent to a visual analog scale (VAS) score of 7.5, at 24 h postsurgery[12]. These results were from a transplant center that intended to keep patients asleep for the shortest possible time and that had a track record of fast tracking 25% of patients[13]. This study showed high pain scores in first 24 h following LT. In contrast, another retrospective study by Chen *et al*[3] reported a mean VAS score of 3 on postoperative day 1 and < 3 on postoperative days 2 and 3 following LT.

Pain intensity assessed by opioid consumption

A few retrospective studies have assessed morphine consumption post-LT. One study comparing morphine requirements after liver resection *vs* morphine requirements after LT found slightly lower morphine consumption only on the first postoperative day in the LT group[2]. A small retrospective study of 16 patients who were fast-tracked and then monitored in the ICU revealed that the total amount of morphine consumption over 24 h was 71.8 ± 39.9 mg. Apart from the high morphine consumption, large variation in the morphine dosage was noted[12].

Intraoperative analgesia in LT

One of the many factors that can affect postoperative analgesia following LT surgery is intraoperative analgesia. The type of intraoperative analgesia used depends on the transplantation center or the individual anesthetist's preferences. According to the current literature, most use a continuous infusion or boluses

of fentanyl followed by remifentanil infusion[14]. A small proportion of LT recipients, approximately 10% to 24%, is eligible for intraoperative epidural analgesia[15].

Fentanyl is still the most commonly used intraoperative opioid. The amount of intraoperatively administered fentanyl varies largely from 0.11 μg/kg per minute in Moretti's study[2] to "not to exceed 10 μg/kg" in the Taner study[16] or 100 μg/h until 1 h before surgery in Biancifore's study[17]. Intraoperative fentanyl administration has been reduced for fast tracking post-LT: for example, from 50 μg/kg in the control and 20 μg/kg in the fast-track group[18], with the same analgesic effect.

In the past, a large dose of fentanyl administered intraoperatively delayed the initial request for postoperative analgesia. For example, in Eisenach's study[1], the first request for postoperative analgesia was 725 ± 267 min after the end of surgery. Their patients had 1695 ± 157 μg of fentanyl intraoperatively. When they measured plasma fentanyl levels postoperatively, it took 6 h for plasma fentanyl to be fully eliminated and become undetectable[1]. Such high intraoperative fentanyl administration could explain the low postoperative demand for analgesia in patients undergoing LT before the fast-tracking era.

Although the pharmacokinetic properties of remifentanil are suitable for fast tracking, only a small proportion of LT anesthetists use remifentanil intraoperatively[19]. Changes in anesthetic practices by reducing fentanyl dosing or replacing fentanyl with remifentanil has the potential to facilitate fast tracking following LT[19].

TYPES OF POSTOPERATIVE ANALGESIA FOLLOWING LT

Postoperative analgesia is multimodal, with opioid PCA (fentanyl, remifentanil, morphine, buprenorphine, tramadol, oxycodone) as the main component[20].

Ketamine and clonidine are sometimes used to enhance the opioid effects of PCA. Other components of multimodal analgesia include paracetamol, nonsteroidal anti-inflammatory drugs, and various other analgesics in the transitional period from PCA or epidural analgesia to regular or as-required analgesia. Other options that are rarely used include epidural analgesia or the transversus abdominis plane (TAP) block in addition to PCA[12].

Epidural analgesia and LT

Thoracic epidural analgesia (TEA) has been used as a mode of postoperative pain relief for LT in a select group of patients. It is not widely practiced because of the impaired hemostasis associated with end-stage liver disease and severe unpredictable intraoperative coagulopathy. TEA in LT may not be the technique of choice for routine administration of postoperative analgesia, but can be considered in patients who have normal coagulation profiles preoperatively. Safe conduct of TEA in LT involves anesthetic expertise and stringent monitoring in the postoperative period[6,15].

TAP block and LT

An ultrasound-guided subcostal TAP block can be used as a part of multimodal postoperative analgesia in patients undergoing LT. A retrospective study by Milan *et al*[12] showed a significantly lower 24-h morphine consumption when a TAP block was performed (46 ± 24 mg) than when a TAP block was not performed (72 ± 40 mg), as well as lower pain scores and median times to extubation.

Local anesthetic infiltration via wound catheter infusion

Although there are no reports on the application of wound catheter infiltration for postoperative analgesia in patients undergoing LT, there are some promising results in patients undergoing live donor and live resection. A recent prospective randomized study of 40 patients compared the quality of postoperative analgesia and its side effects when using local anesthetic-based analgesia (PainBuster) with the efficacy of opioid-based analgesia (intrathecal morphine with intravenous fentanyl) in liver donors. The researchers found more satisfactory analgesia with intrathecal opioids and fentanyl than with PainBuster during the first 12 h after surgery and comparable analgesia after that. The side effects were similar. Bowel recovery was faster with PainBuster[21].

Moreover, a recent meta-analysis showed that local anesthetic infiltration *via* wound catheters combined with PCA provided pain relief comparable to continuous epidural analgesia except for the first postoperative day. Both techniques were associated with a similar hospital stay duration, and opioid use with a wound catheter was associated with a lower complication rate[22].

DISCUSSION

There has been a general belief that patients undergoing LT require less postoperative analgesia than do patients undergoing "lesser" hepatobiliary surgery. Everyday practice, however, does not always support this belief. When we reviewed the literature, we found a few publications that had assessed opioid consumption rather than pain intensity[1-3]. Additionally, each publication included no more than 10 patients undergoing LT, and the studies were performed several decades ago[1-3].

Historically, patients undergoing LT received generous intraoperative analgesia with fentanyl. There is evidence that it takes at least 6 h for intraoperatively administered fentanyl to be eliminated from the bloodstream[1]. Additionally, patients were kept asleep for at least 12 h following LT, but sometimes they were kept asleep for days, particularly patients with acute liver failure. By the time the patients were awake, the most severe postoperative pain had resolved, and a significant

proportion of patients had no recollection of any pain or had low pain intensity. Additionally, pain control in sedated and ventilated patients was safe in terms of respiratory depression, which allowed the intensivist to be rather generous with opioid infusion because pain assessment in ventilated and sedated patients is not accurate.

With the relatively recent and expanding trend of fast tracking patients undergoing LT, management of the postoperative pain has changed. First, fast tracking requires a 60% reduction in intraoperative analgesia with fentanyl[18]. Second, intraoperative fentanyl infusion is stopped earlier, approximately 1 h before the end of surgery[18]. Although remifentanil, a shorter-acting synthetic opioid, was supposed to replace fentanyl for intraoperative analgesia, there is no confirmation that this is happening; indeed, more papers describe the intraoperative use of fentanyl than remifentanil[19]. The price of remifentanil for long surgical procedures and its known hyperanalgesic effects may be to blame for this[23].

When it comes to postoperative analgesic methods, little seems to have changed from morphine PCA[19]. There are now more options for PCA, including tramadol, buprenorphine, oxycodone, fentanyl, and, rarely and for short periods of time, remifentanil.

Epidural analgesia should not be ruled out as an option, but only about 10% of patients undergoing LT meet the criteria for normal preoperative clotting results[15]. Logistic issues, such as the lack of competent staff for following patients with epidural catheters, medico-legal issues, and anesthetists' reluctance, are likely the real reasons why epidural analgesia is not popular in LT. Although no publications have addressed epidural hematomas following epidural analgesia for LT, anesthetists have not been proactive in introducing the method for postoperative analgesia. Unknown metabolic pathways of local anesthetics in the anhepatic phase and in patients with deranged liver function are probably additional reasons for anesthetists' reluctance.

There is also modest experience with alternative techniques, such as the TAP block (a small retrospective study on 15 patients and 15 controls)[12] and wound catheter use in postoperative analgesia for LT (unpublished data), which is not likely to motivate LT anesthetists to apply these alternative techniques more often.

In conclusion, it seems that the time has come to reassess pain intensity following LT, the type and quantity of analgesics, and additions to opioid PCA analgesia as part of multimodal analgesia. There is also a need to explore regional anesthesia techniques for postoperative analgesia in patients undergoing LT.

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MINIREVIEWS

Renal failure in cirrhosis: Emerging concepts

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Abstract

Acute renal failure, now termed acute kidney injury (AKI), is frequently found in patients with cirrhosis. The occurrence of AKI, irrespective of the underlying cause, is associated with reduced in-hospital, 3-mo and 1-year survival. Hepatorenal syndrome is associated with the worst outcome among AKI patients with cirrhosis. Several definitions for AKI that have been proposed are outlined and evaluated in this paper. Among these, the International Club for Ascites-AKI criteria substantially strengthen the quality of early diagnosis and intervention according to underlying cause of AKI.

Key words: Renal failure; End-stage liver disease; Acute kidney injury; Hepatorenal syndrome; Liver cirrhosis

Core tip: Acute kidney injury (AKI) is frequently observed in hospitalized patients with cirrhosis and is associated with increased mortality. Recently a new definition for AKI has been proposed by the International Club of Ascites in order to allow early diagnosis and management of AKI in cirrhosis with the purpose of reducing its mortality, particularly with the occurrence of hepatorenal syndrome.

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INTRODUCTION

Renal failure is a common complication of decompensated cirrhosis[1-8]. Acute renal failure, now termed acute kidney injury (AKI), has traditionally been defined by serum creatinine (SCr) levels higher than 1.5 mg/mL. It occurs in 11% of patients with upper gastrointestinal bleeding, in 34% of patients with

spontaneous bacterial peritonitis (SBP), in 27% with bacterial infections other than SBP and in 40% to 49% of critically-ill patients with cirrhosis requiring intensive care support[1,7]. Furthermore, 24% of outpatients with cirrhosis develop some type of renal failure within one year of the first episode of ascites[8]. In most reports, renal failure significantly reduces survival rates[5-8]. In this review, we outline and evaluate the definitions for kidney injury in patients with cirrhosis, particularly the emerging International Club for Ascites-AKI (ICA-AKI) criteria and advances in the management of AKI in cirrhosis.

DIAGNOSIS AND ETIOLOGY OF RENAL FAILURE

The most common causes of renal injury in patients with cirrhosis are: (1) circulatory dysfunction due to bacterial infection; (2) hypovolemia secondary to gastrointestinal bleeding, paracentesis or diuretic use; (3) contrast or drug-induced; (4) chronic kidney diseases (CKD); and (5) hepatorenal syndrome (HRS)[5,7-9].

CKD, such as IgA nephropathy, glomerulonephritis or nephrosclerosis are commonly seen in patients with cirrhosis. In most cases, the underlying causes of both conditions are alcoholic liver disease, hepatitis B and C and non-alcoholic steatohepatitis with associated diabetes and/or hypertension[9]. HRS is a functional type of renal failure[10,11] found only in patients with advanced cirrhosis and ascites[12-14]. It is reversible either with orthotopic liver transplantation (OLT)[11] or with pharmacological treatment with splanchnic vasoconstrictors and albumin[15-18]. HRS is the ultimate result of arterial underfilling due to splanchnic and systemic vasodilation generally with high cardiac output. When the circulatory dysfunction is inadequate to restore hemodynamics, vasoconstrictor mediators are released, resulting in severe renal vasoconstriction[12-14].

HRS diagnosis was initially defined by the ICA based on major and minor criteria to characterize the occurrence of renal failure in a patient with cirrhosis (Table 1)[12]. There are two types of HRS. Type-1 HRS is a rapidly progressive renal failure defined by a doubling of the baseline SCr to a level greater than 2.5 mg/dL in less than 2 wk from baseline. Type-2 HRS is characterized by a steady or slow increase in SCr levels to over 1.5 mg/dL. Type-2 HRS is frequently associated with refractory ascites, while type-1 HRS is usually triggered by infection, particularly SBP. Survival rates of patients with untreated type-1 HRS are extremely low when compared to type-2 HRS, whereas patients with type-2 HRS usually have shorter survival compared to patients with ascites but not HRS[12,13].

In 2007, the ICA revised HRS diagnosis definition (Table 1) to improve accuracy and applicability[13]. Creatinine clearance and all minor criteria were excluded because they are difficult to comply with on a regular basis. Ongoing bacterial infection without septic shock was no longer regarded as among the exclusion criteria, reflecting the fact that bacterial infections are a major cause of HRS. A relevant recommendation of the ICA revised criteria is that albumin infusion should be preferred over the traditional volume expansion with saline. Although simplified, this criteria diagnosed HRS in a lower than expected number of patients with cirrhosis and AKI in different cohorts[5,7,8].

This is important because prognosis is related to the cause of renal failure, as shown by a recent report in which 3-mo survival rates of patients with cirrhosis were 73% for CKD, 46% for hypovolemia, 31% for bacterial infection and 15% for HRS[5].

Renal failure in patients with cirrhosis, defined by abnormally high SCr levels, is clearly associated with increased mortality either in the intensive care unit (ICU) or during hospital stay and reduced 3- and 12-mo survival[5,7,8]. Patients with HRS and bacterial infections requiring renal replacement therapy have the worst prognoses[7].

However, there are several drawbacks to the use of absolute SCr value and creatinine clearance for the assessment of kidney function in patients with cirrhosis[19]. The endogenous production of SCr varies according to muscle mass, which is often markedly decreased in patients with cirrhosis, age, gender and diet. Estimation of kidney function by glomerular filtration rate (GFR) is unreliable because tubular secretion is also involved in SCr elimination, and therefore is a confounding factor[19].

In 2004 the Acute Dialysis Quality Initiative group for the study of AKI proposed the Risk, Injury, Failure, Loss of Kidney Function and End Stage (RIFLE) classification for AKI in patients without cirrhosis. It is based on the dynamic but sustained increase in SCr, GFR assessment by creatinine clearance and urinary output over a 7-d period[20]. RIFLE has three stages of AKI (Risk, Injury and Failure) and two outcomes; loss of kidney function and end-stage kidney disease (Table 2). RIFLE accurately identifies AKI and predicts prognosis, including progression to CKD and higher risk of mortality in the ICU[20,21]. Using the RIFLE criteria, several authors have described a strong correlation between mortality and the presence and severity of AKI in patients with and without cirrhosis[21-24].

However, the RIFLE criteria were difficult to apply in a significant proportion of ICU patients, since it ideally requires the measurement of baseline SCr levels. In the absence of information regarding baseline SCr it can be calculated, using the modification of diet in renal disease equation. This assumes a baseline GFR of 75 mL/min per 1.73 m^2 in the absence of CKD.

Subsequently, the acute kidney injury network (AKIN) revised the RIFLE criteria and proposed their consensus definition, the AKIN criteria[25,26]. The three stages of AKIN are shown in Table 3. Adequate volume expansion and exclusion of urinary tract obstruction are required for establishing the diagnosis of AKI. The diagnostic criteria have been modified to take into

Table 1 The diagnosis of hepatorenal syndrome according to the original (1996) and revised (2007) International Ascites Club criteria

Criteria for HRS-1 (1996)	Revised criteria for HRS-1 (2007)
Major criteria	Presence of cirrhosis with ascites
Chronic or acute liver disease with advanced hepatic failure and portal hypertension	SCr > 1.5 mg/dL
Low GFR: SCr > 1.5 mg/mL or 24 h SCr clearance < 40 mL/min	No improvement of SCr levels after at least 2 d of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/d)
Absence of shock, ongoing bacterial infection or treatment with nephrotoxic drugs or gastrointestinal or renal fluid losses	Absence of shock
No sustained improvement in renal function following diuretic withdrawal and expansion of plasma volume with at least 1500 mL of isotonic saline	No current or recent treatment with nephrotoxic drugs
Proteinuria < 0.5 g/d and no evidence of obstructive nephropathy or parenchymal renal disease on ultrasound	Absence of parenchymal kidney disease as indicated by proteinuria > 500 mg/d, microhaematuria (> 50 red blood cells per high power field) and/or abnormal renal ultrasonography
Additional criteria	
Urinary volume < 0.5 L/d	
Urinary sodium < 10 mmol/L	
Urinary osmolality > plasma osmolality	
Urinary red blood cells < 50 high power field	
Serum sodium concentration < 130 mmol/L	

Adapted from Arroyo *et al*[12] and Salerno *et al*[13]. SCr: Serum creatinine; GFR: Glomerular filtration rate; HRS: Hepatorenal syndrome.

Table 2 Risk, injury, failure, loss of kidney function and end-stage kidney disease classification for acute kidney injury

Class	Baseline SCr levels and GFR within 7 d	Urinary output
Risk	↑ SCr 1.5-1.9 times over baseline or ↓ GFR > 25%	< 0.5 mL/kg per hour for 6 h
Injury	↑ SCr 2.0-2.9 times over baseline or ↓ GFR > 50%	< 0.5 mL/kg per hour for 12 h
Failure	↑ SCr ≥ 3 times over baseline or ↓ GFR > 75% or if baseline SCr ≥ 4 mg/dL: ↑ SCr > 0.5 mg/dL	< 0.3 mL/kg per hour for 24 h or anuria for 12 h
Loss of kidney function	Complete loss of kidney function > 4 wk	
End-stage kidney disease	Complete loss of kidney function > 3 mo	

Adapted from Bellomo *et al*[20]. GFR: Glomerular filtration rate; SCr: Serum creatinine.

Table 3 The Acute Kidney Injury Network classification of acute kidney injury

Stage	Baseline SCr within 48 h	Urinary output
1	↑ SCr ≥ 0.3 mg/dL or ↑ SCr 1.5-1.9 times over baseline	< 0.5 mL/kg per hour for 6 h
2	↑ SCr 2.0-2.9 times over baseline	< 0.5 mL/kg per hour for 12 h
3	↑ SCr ≥ 3 times over baseline or if baseline SCr ≥ 4 mg/dL: ↑ SCr ≥ 0.5 mg/dL	< 0.3 mL/kg per hour for 24 h or anuria for 12 h

Adapted from Khwaja *et al*[30]. SCr: Serum creatinine.

account changes in urinary output and SCr levels within a pre-established time period, allowing early detection of AKI even with modest increases in SCr (Table 3). In AKIN, estimation of creatinine clearance and baseline SCr values are not required for the diagnosis of AKI. AKIN classification allows better identification and grading of AKI than RIFLE criteria in patients hospitalized with cirrhosis[27-29]. Furthermore, AKIN is more effective at identifying adverse prognoses and higher in-hospital and short-term mortality[25,27-29].

Fagundes *et al*[28] found AKI in 47% of the patients either at admission (60%) or during hospitalization (40%). AKIN stages Ⅰ, Ⅱ and Ⅲ were observed in 77%, 11% and 12% of the subjects, respectively. Although AKIN stages were associated with lower 3-mo survival, in stage 1 (mild dysfunction) this was limited to the group with peak SCr levels over 1.5 mg/dL.

Similar results were observed by Piano *et al*[29] who reported AKI in 26% of in-patients with cirrhosis, most of them with AKIN stage Ⅰ. Patients with progression of severity of AKI during hospital stay or peak SCr had increased mortality rates.

The Kidney Disease Improving Global Outcomes (KDIGO) criteria were published in 2012[30]. They differ slightly from AKIN and RIFLE in the following parameters: (1) Increase in SCr by 0.3 mg/dL or more within 48 h; or (2) Increase in SCr to 1.5 times baseline or more within the last 7 d; or (3) Urine output less than 0.5 mL/kg per hour for 6 h.

The new ICA-AKI criteria[14] give a new approach to the definition and staging of AKI, of the definition of AKI progression and response to treatment (Table 4). The major change was the exclusion of urine output as a parameter. Urine output in patients with cirrhosis and ascites is often an unreliable indicator because the GFR may be preserved in spite of the continuous sodium

Table 4 International Club of Ascites-acute kidney injury criteria for diagnosis, grading, assessment of progression and response to treatment of acute kidney injury in patients with cirrhosis

Class	Baseline SCr within 3 mo, most recent prior to hospital admission	Urinary output
Ⅰ	↑ SCr ≥ 0.3 mg/dL or ↑ SCr 1.5-1.9 times over baseline[1]	Not required
Ⅱ	↑ SCr 2.0-2.9 times over baseline[1]	Not required
Ⅲ	↑ SCr ≥ 3 times over baseline or if baseline SCr ≥ 4 mg/dL: ↑ SCr ≥ 0.3 mg/dL[1] or initiation of renal replacement therapy	Not required
Progression of AKI	Progression of AKI to a higher stage and/or need for renal replacement therapy	
Regression of AKI	Regression of AKI to a lower stage	
No response	No regression of AKI	
Partial response	Regression of AKI stage with a reduction of SCr to ≥ 0.3 mg/dL above the baseline value	
Full response	Return of SCr to a value within 0.3 mg/dL of the baseline value	

[1]Which is known, or presumed, to have occurred within the prior 7 d. Adapted from Angeli *et al*[14]. SCr: Serum creatinine; AKI: Acute kidney injury.

Table 5 Updated diagnosis of hepatorenal syndrome type of acute kidney injury according to the International Club of Ascites

Presence of cirrhosis with ascites
Diagnosis of AKI according to ICA-AKI criteria
No improvement of SCr after at least 2 d of diuretic withdrawal and volume expansion with albumin (1 g/kg of body weight per day up to a maximum of 100 g/d)
Absence of shock
No current or recent treatment with nephrotoxic drugs
No macroscopic signs of structural kidney injury: normal findings on renal ultrasonography, absence of proteinuria > 500 mg/d and absence of microhematuria

Adapted from Angeli *et al*[14]. SCr: Serum creatinine; AKI: Acute kidney injury; ICA-AKI: International Club for Ascites-AKI.

retention and oliguria and many patients are under diuretic therapy (Table 5). This requirement is a major disadvantage of RIFLE, AKIN and KDIGO criteria.

MANAGEMENT OF AKI

Management of AKI in cirrhosis has moved towards prioritizing early recognition and intervention, according to the most probable cause of renal failure[14].

Patients with cirrhosis and ascites and AKI grade Ⅰ should be carefully monitored with regards to all risk factors for renal injury. Nephrotoxic agents (including non-steroidal anti-inflammatory, aminoglycoside, contrast agents), vasodilators and beta-blockers should be immediately withdrawn. Diuretics should be decreased or ideally withdrawn. This is particularly true when the patient has refractory ascites because several drugs can induce AKI.

In all patients with clinical and laboratorial signs of hypovolemia, volume expansion with crystalloids, colloids or packed red blood cells should be administered according to clinical need. Patients should always be screened for bacterial infection, and treated as appropriate. If the AKI regresses, patients should be closely followed-up with SCr measurements. In the case of AKI stages Ⅱ or Ⅲ at admission or progression of AKI stage Ⅰ to stages Ⅱ or Ⅲ, in addition to those initial measures, it is recommended to proceed with plasma expansion with albumin 1 g/kg per day to a maximum dose of 100 mg/d for two consecutive days. If not already done, diuretics must be withdrawn. In the absence of AKI regression, the course of treatment is dictated by the underlying cause of renal failure. In patients with type-1 HRS, a course of splanchnic vasoconstrictors and albumin is recommended, particularly if SCr levels are higher than 1.5 mg/mL.

Clinical judgment is crucial to distinguish between those patients with AKI caused by HRS who would benefit from pharmacological therapy from those with acute tubular necrosis or obstructive nephropathy, where the medical therapy would have no effect. In this scenario, biomarkers such as urinary neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 and kidney injury molecule-1, may help differentially diagnose acute tubular necrosis rather than common causes of AKI in patients with cirrhosis. NGAL levels are markedly higher in patients with cirrhosis with ATN compared to patients with AKI caused by hypovolemia, HRS or CKD[31]. However, it has not yet been established whether or not NGAL levels could identify patients with suspected HRS who would benefit from pharmacological therapy with albumin and splanchnic vasoconstrictors.

The diagnosis of type-1 HRS was updated to include patients with ICA-AKI Ⅱ and Ⅲ at admission or subjects who progressed from AKI Ⅰ to AKI Ⅱ or Ⅲ despite volume expansion with albumin[14]. No other previously established criteria were modified (Table 5), but the requirement of SCr threshold levels higher than 2.5 mg/dL for diagnosis of type-1 HRS was abandoned. This high threshold may delay therapy with splanchnic vasoconstrictors and albumin, with a detrimental effect on response to treatment[14].

OLT is considered the best treatment for hepatorenal syndrome[32]. It improves renal function and is the definitive treatment for cirrhosis, which is responsible for severe circulatory dysfunction in patients with type-1 HRS. Due to the poor short-term prognosis for patients with type-1 HRS, OLT was rarely performed in these patients. Nevertheless, after the introduction of MELD score, priority has been given to HRS patients, and many of them reach OLT. While on the waiting list, patients with type-1 HRS must receive bridging

treatments to improve short-term survival.

The hemodynamic and neurohormonal abnormalities associated with type-1 HRS disappear within the first month after OLT and patients regain a normal ability to excrete sodium and free water. The long-term survival of patients with HRS who undergo OLT is good (60% at 3 years)[33]. However, a study by Nair *et al*[34] showed that renal failure is an independent predictor of 30-d and 2-year mortality after OLT. A case-control study showed that patients with type-1 HRS treated with vasoconstrictors before OLT have post-transplantation outcomes similar to OLT patients with normal renal function. These results suggest that in type-1 HRS, treatment with vasoconstrictors before OLT could be an important factor for post-transplantation outcome[35].

Pharmacological treatment of type-1 HRS consists of the infusion of vasoconstrictors and intravenous human albumin[36]. Vasoconstrictors are administered to reverse the splanchnic arterial vasodilation, and albumin for volume expansion. This combination improves venous return and cardiac output.

Several studies have shown that medical treatment is effective in reversing type-1 HRS in 40%-60% of patients[15,16,37-49]. Complete therapeutic response to therapy, as defined by a reduction of SCr to below 1.5 mg/dL, is associated with a marked suppression of plasma renin activity and a significant increase in mean arterial pressure.

Terlipressin, a vasopressin analogue, has been the most frequently used drug to improve splanchnic circulation. In most studies intravenous terlipressin bolus ranged from 0.5 to 2 mg/4-6 h. There are data indicating that the therapeutic response to terlipressin is very poor if not administered with albumin. A recommended dose for albumin administration is 1 g/kg on the first day followed by 20-40 g/d thereafter[45].

A retrospective survey of 99 patients with type-1 HRS treated with terlipressin and albumin showed a rate of improvement in renal function of 58% and increased survival rates[45].

Two randomized, prospective, placebo-controlled trials have been performed in order to evaluate the efficacy and safety of terlipressin for treatment of type-1 HRS[15,16]. Patients were randomly assigned to receive either terlipressin plus albumin or albumin alone (control-group). Compared to controls, the group treated with terlipressin plus albumin had significant improvement in renal function (43.5% compared to 8.7%; $P = 0.017$ in one study and 34% compared to 13%; $P = 0.008$ in the other). In both studies type-1 HRS reversal significantly improved survival. The main conclusions are that: (1) treatment with terlipressin and albumin is effective in improving renal function in patients with cirrhosis; and (2) type-1 HRS reversal significantly improves survival.

Although not often used outside the ICU, norepinephrine has also been successfully used in patients with HRS. Pilot studies suggest that norepinephrine is as effective as terlipressin in the treatment of type-1 HRS[43,46-49].

A recent systematic review and meta-analysis[17] evaluated the efficacy and safety of norepinephrine compared to terlipressin in the management of type-1 HRS. There was no difference between norepinephrine and terlipressin in the reversal of HRS (RR = 0.97; 95%CI: 0.76 to 1.23), mortality at 30 d (RR = 0.89; 95%CI: 0.68 to 1.17) and recurrence of HRS (RR = 0.72; 95%CI: 0.36 to 1.45). Based on these studies, the authors conclude that norepinephrine seems to be an attractive alternative to terlipressin in the treatment of type-1 HRS, particularly in the ICU. Some studies without controls have reported improved renal function in patients with HRS-1 treated with a combination of midodrine and octreotide plus albumin[37]. However, one recent randomized controlled trial demonstrated that terlipressin and albumin were clearly superior treatment options to midodrine, octreotide and albumin in reversal of HRS[50].

Recurrence of type-1 HRS after discontinuation of treatment is observed in approximately 15% of patients. Treatment of recurrent HRS is usually effective. The incidence of ischemic side effects requiring discontinuation of terlipressin is around 5%-10%, although most studies excluded high-risk patients with ischemic heart or artery diseases[15-17].

Data concerning the use of transjugular intrahepatic portosystemic shunts (TIPS) in type-1 HRS are scarce; only three studies have been published as full papers, comprising a total of 30 treated patients[51-53]. These studies showed that GFR improved markedly within 1-4 wk after TIPS. In one study specifically investigating neurohormonal systems, improvement in GFR and SCr was related to a significant suppression of both plasma renin activity and antidiuretic hormone[51]. Survival data were provided in two of the studies[51,52]. In the study by Guevara *et al*[51], 7 patients were included and the mean survival was 4.7 ± 2 mo. In the paper by Brensing *et al*[52], the mean survival was 75 wk, with 3- and 6-mo survival rates of 64% and 50%, respectively. These data sharply contrast with those usually reported in patients with untreated type-1 HRS (median survival of 2 wk)[54].

De novo encephalopathy or deterioration in pre-existing encephalopathy developed in 35%-50% of the patients after TIPS, but most patients were successfully managed with standard treatment. During the first year of follow-up the shunt stenosis rate was 22%[52].

After pharmacological treatment of type-1 HRS, despite marked suppression of renin-angiotensin axis and sympathetic nervous system and normalization of SCr, renal function does not reach normal levels in most cases (GFR ranges between 30 to 50 mL/min).

However, treatment for type-1 HRS with TIPS in patients responding to pharmacological treatment (midodrine or octreotide and albumin) normalizes GFR in most cases[55]. Together these studies strongly suggest that TIPS is useful in the management of type-1 HRS and probably improves survival. Unfortunately the number of treated patients was very low and controlled

studies in larger series must be performed to draw stronger conclusions. Whether the use of covered stents improves outcomes when compared to bare stents is worthy of attention in future studies of TIPS for patients with type-1 HRS.

There are a variety of other treatment options that have been considered for HRS. The beneficial effects of haemodialysis have not been convincingly demonstrated in type-1 HRS. Complications during haemodialysis are common and include arterial hypotension, bleeding, and infections. Extracorporeal albumin dialysis has been reported to improve renal function and survival in a small series of patients with HRS[56]. Further studies are required on this topic.

Survival for patients with type-2 HRS is usually longer compared to type-1, and many survive to OLT. Treatment with vasoconstrictors plus albumin can be used, but recurrence is common after stopping therapy[57]. There are few data on the treatment of type-2 HRS with TIPS. In studies evaluating this issue significant improvement in renal function was observed[52]. However, a low number of patients have been assessed.

Hepatorenal syndrome can be prevented at least in two clinical scenarios; SBP therapy and SBP prophylaxis[2,58]. Sort *et al*[2] randomized 126 patients with cirrhosis and SBP to receive treatment with cefotaxime or cefotaxime plus intravenous albumin (1.5 g/kg at the time of diagnosis, followed by 1 g/kg on day 3). Type-1 HRS was reported in 10% of patients in the group of combination therapy and in 33% of cefotaxime monotherapy. In-hospital mortality (10% compared to 29%) and 3-mo mortality (22% compared to 41%) were also lower in patients who received combination therapy.

Fernández *et al*[58] performed a randomized controlled trial to assess the effectiveness of norfloxacin as primary prophylaxis in patients with cirrhosis and high risk of developing SBP and HRS. These patients had one or more of the following: Protein ascites levels below 15 g/L, Child-Pugh score $\geqslant$ 9 points, serum bilirubin $\geqslant$ 3 mg/dL, SCr $\geqslant$ 1.2 mg/dL, blood urea nitrogen $\geqslant$ 25 mg/dL, or serum sodium $\leqslant$ 130 mEq/L). Norfloxacin reduced the incidence of SBP (7% compared to 61%, $P < 0.001$) and HRS (28% compared to 41%, $P = 0.02$), and improved survival (60% compared to 48%, $P = 0.05$).

CONCLUSION

AKI is a frequent complication of cirrhosis, and has adverse impact on outcomes, particularly in those with decompensated disease requiring hospital or ICU admission. New definitions for AKI, such as RIFLE, AKIN and KDIGO have been introduced to standardize diagnostic criteria as well as to recognize patients at risk or in the early stages of AKI, whose survival rates would improve significantly with early detection and intervention. The ICA revised their definition of AKI and type-1 HRS (ICA-AKI criteria) to propose a new consensus recommendation. Although the impact on outcome of these new criteria needs further exploration, the ICA-AKI criteria substantially strengthen the quality of early diagnosis and intervention of HRS. Use of splanchnic vasoconstrictors, either terlipressin or noradrenaline and high-dose albumin remains the standard treatment for type-1 HRS.

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MINIREVIEWS

Hepatitis B virus reactivation with a rituximab-containing regimen

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Abstract

Rituximab is currently used not only in the treatment of B-cell lymphoma but also for various other diseases, including autoimmune diseases, post-transplant graft *vs* host disease, and rejection following kidney transplants. Due to rituximab's widespread use, great progress has been made regarding research into complications that arise from its use, one of the most serious being the reactivation of hepatitis B virus (HBV), and efforts continue to establish guidelines for preventive treatment against this occurrence. This report discusses preventive measures against rituximab-induced HBV reactivation and future objectives.

Key words: Rituximab; Hepatitis B virus; Reactivation; Nucleoside analog; Non-Hodgkin's lymphoma

Core tip: For preventive measures against hepatitis B virus (HBV) reactivation during rituximab treatment, hepatitis B surface (HBs) antigen positive and HBc antibody positive/HBs antibody negative patients are subject to prophylactic treatment with nucleoside analogs. During rituximab treatment, the HBV-DNA levels of patients who are HBc antibody positive (HBs antibody positive or negative) are ideally monitored with PCR once a month. If the PCR results are positive, the administration of nucleoside analogs is initiated. However, since monitoring HBV-DNA levels is expensive, it might be preferable to follow the HBs antibodies instead. Due to wide differences in the insurance situations in each country, including the follow-up intervals, further research must determine ideal follow-up intervals. However, no standard exists for the timing of this treatment's termination. For HBs antigen negative patients who also receive nucleoside analog treatment, it

will be necessary in the future to evaluate the possibility of switching to a vaccine when a patient becomes HBs antibody positive.

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INTRODUCTION

Rituximab, which improves the prognosis of CD20-positive B-cell lymphoma, is generally indispensable for the treatment of B-cell lymphoma[1-3]. Rituximab inhibits the production of various antibodies by targeting CD20 positive B-cells and is effective for a range of conditions, including diopathic thrombocytopenic purpura, chronic rheumatoid arthritis, multiple sclerosis, and cryoglobulinemic vasculitis with applications to other diseases as well[4-7]. On the other hand, extensive studies have also recently been conducted on rituximab's side effects, which include reports not only of typical infusion reactions but also various infectious diseases due to its immune suppressive effects: Cytomegalovirus, progressive multifocal leukoencephalopathy, parvovirus infection, and Herpes zoster[8-11]. Although hepatitis B virus (HBV) reactivation has been previously reported to be a complication of chemotherapy[12-16], this phenomenon has drawn greater attention due to reports that argue that the frequency of reactivation is higher in patients treated with rituximab than those who only received chemotherapy[17-24]. The best way to deal with HBV reactivation is to prevent it[25,26]. In this review, we describe the prevention and treatment of HBV reactivation based on previous reports and discuss a summary and future objectives.

Principle of HBV reactivation during rituximab treatment

After HBV infection, HBV-DNA synthesis is initially suppressed by cytokine production from NK and other cells. A subsequent cytotoxic T-cell (CTL) reaction occurs due to the presence of CD8-positive T lymphocytes. Because hepatitis is triggered by CTLs, a time lag likely exists between the HBV infection and the manifestation of hepatitis[27,28]. On the other hand, rituximab induces CD4 lymphopenia[29,30]. In a mouse model, B-cell depletion reduced the number and the fraction of CD4 memory T-cells and impaired immunity against virus infection[31]. A reduction in CD20 Bcells shifted the CD4 effector phenotype to that of enhanced interferon-γ, interleukin (IL)-2, and tumor necrosis factor. Perhaps the depletion of CD20 positive B-cells reduces the production of IL-7 and IL-15, both of which are critical for memory T-cell survival, from monocytes or stromal cells[31]. Furthermore, HBV replication is likely accelerated by the indirect effects of B-cell depletion on immune globulin production. It has been reported that rituximab treatment induces a change in CD8 distribution[30]. This might reduce the number of CD8-positive cells and the subsequent acceleration of HBV replication. Once the number of CD8-positive T-cells recovers, cells are produced that specifically target HBV. However, since memory T-cells are impaired by their reduced numbers, CD8-positive T-cells randomly attack HBV, resulting in severe hepatitis[31].

Rituximab not only affects B-cells but T-cells as well and accelerates HBV replication. This is a primary factor in the induction of HBV reactivation by the administration of rituximab alone.

Epidemiology of HBV reactivation

When combined with chemotherapy, the HBV reactivation rate during rituximab treatment has been reported to be 20%-55% overall and 3% in hepatitis B surface antigen (HBsAg) negative patients[32-36]. HBV reactivation can be caused by chemotherapy alone. However, rituximab more easily induces HBV reactivation independently upon combined treatment with chemotherapy or steroid treatment[18,26]. The frequency of HBV reactivation is also higher with combination treatments including rituximab compared to chemotherapy alone or a combination chemotherapy and steroid treatment[18,37]. Risk factors for HBV reactivation in patients receiving chemotherapy include being male, lack of HBs antibody, HBs antigen positivity, presence of a precore mutant, HBV-DNA level, anthracycline/steroid use, transplantation, second/third line treatment, youth, and the presence of lymphoma[35,37-39]. However, when rituximab is used, the risk factors for HBV reactivation are narrowed to a lack of HBs antibody, youth, and being male[37]. All the above reports are retrospective analyses of patients who were HBs antigen positive and who therefore were subject to prophylactic nucleoside analog therapy. In the future, patient groups must be identified who tend to experience reactivation even when receiving such therapy.

Many remaining problems must be addressed. One is whether the attending physician performs antibody or DNA tests before initiating chemotherapy or a rituximab/chemotherapy combination. This issue is rather basic; yet a surprising report by Méndez-Navarro *et al*[40] in 2011 showed that serological screening of HBV is only done in less than 40% of cases before treatment. In some cases, HBV reactivation went undetected because no HBV screening was conducted. Zurawska *et al*[41] analyzed the effect of HBsAg screening by dividing patients into three groups: screening, non-screening, and only screening of high-risk patients. Their results showed that the group that was screened before treatment had the highest prevention rate of HBV reactivation (10-fold); screening the high-risk patient group was the most cost effective measure. When comparing the screening and non-screening groups, the former was more cost effective. Screening prevents HBV reactivation.

Another problem is the screening method. Some patients were diagnosed as HBc antibody negative

when using the EIA method (AxSYM Assay: Abbot Laboratories, Chiba, Japan, 2005), but they were diagnosed as HBc antibody positive with the CLIA method (Architect Assay: Abbott Laboratories, Chiba, Japan, 2013). Thus, in the past, we overlooked an HBV reactivation risk factor since our treatment was based on AxSYM results. Therefore, reports on HBV reactivation cannot be compared since the results were biased by the screening method. This affects the evaluation of risk factors and prophylactic administration. International standardization of screening methods is needed.

The risk factors for HBV reactivation include being male, lack of HBs antibody, HBs antigen positive, presence of precore mutant, HBV-DNA level, anthracycline/steroid combination therapy, transplantation, second/third line treatments, youth, and the presence of lymphoma; When rituximab is used, the risk factors are narrowed down to a lack of HBs antibody, youth, and being male; Currently, the screening rate for HBV is only 30%-40%; Standardization of screening methods is a future task.

HBV-DNA mutations

HBV-DNA mutations must be considered when assessing the potential difficulties in the treatment of HBV using nucleoside analogs. Pelizzari *et al*[42] reported that the mutation rate in HBV-DNA with lamivudine is lower than the rate during treatment for hepatitis B. However, in their study, the observation period was short and they analyzed too few cases. Several mutations were reported in HBV reactivated patients. Main of these mutations were developed in immune-active HBsAg regions, such as M103I-L109I-T118K-P120A-Y134H-S143L-D144E-S171F. In other patients, C48G-V96A-L175S-G185E-V190A mutations were observed whose function escaped the T-cell-mediated responses for HBV. An N-linked glycosylation site was observed in a major hydrophilic loop in HBV reactivated patients without HBsAg[43]. Compared to treatment with standard chemotherapy with or without rituximab, the mutation rate during the prophylactic treatment of HBV-DNA with lamivudine was approximately 15%-20%. Therefore, this indicates no significant difference in the HBV-DNA mutation rate with lamivudine between the prophylactic and standard HBV hepatitis treatment periods[44,45]. A fatal case was also described in which HBV reactivation was caused by HBV-DNA mutation during R-CHOP treatment, although not at an early stage[46]. Recently, encouraging results have been reported on the effectiveness of entecavir in the prevention of HBV reactivation[47]. Due to the low frequency of the emergence of a resistant HBV strain with entecavir use, this is the first choice for the prophylactic treatment of patients with high viral load or patients who require a long prophylactic treatment period[47].

Lamivudine resistance was induced early when a nucleoside analog such as fludarabine was used with rituximab[48]. Similar reports have been noted for the induction of HBV-DNA mutations by nucleoside analogs when steroids or fludarabine were used with rituximab[49]. Note that the combined use of such purine analogs as fludarabine and cladribine with rituximab tends to induce HBV-DNA mutations. A report on HBV reactivation with bendamustine (an alkylating agent) as well as a nucleoside analog has also been published. However, HBV-DNA mutations with these agents were not evaluated and their effectiveness in this regard remains unknown[50].

With regard to HBV-DNA mutations, entecavir is desirable for prophylactic treatment in the event of HBV reactivation due to its poor ability to induce mutations in HBV-DNA. However, its cost is problematic, and measures must be enacted that are suitable for different countries.

The presence of HBV mutations corresponds to the frequency of the emergence of resistant strains with standard nucleoside analogs.

Perhaps HBV mutations will increase with a combination treatment of steroids or anti-cancer drugs such as purine analogs that have a strong immune suppressive effect.

HBs antigen positive cases

There is an international consensus that nucleoside analog administration is necessary in HBs antigen positive patients since prophylactic treatment is effective for the prevention of HBV reactivation and reduces mortality in this group[51-53]. Guidelines for each analog are shown in Table 1. When referring to the guideline treatments for HBs antigen positive chronic hepatitis, entecavir use is desirable when the HBV-DNA concentration exceeds 20000 IU/mL, while lamivudine use is adequate if the HBV-DNA concentration falls under 20000 IU/mL. In addition, in HBV-DNA-positive cases, the possible existence of YMDD mutations must be determined beforehand. If such mutations are detected, using tenofovir or the combined use of two nucleoside analogs might become necessary. As mentioned previously, entecavir is more desirable for the prevention of HBV reactivation due to its low induction of resistant strains during treatment. Ideally, it is desirable to start prophylactic treatment two weeks after the administration of nucleoside analogs since the drugs are most effective during this period. However, there is no standard protocol regarding the starting time for treatment since the specific condition of each individual patient often plays a role. In our clinic, steroids are not used on patients who are HBs antigen positive. A fatality was previously observed in a group of patients who were receiving steroid/rituximab combination therapy that caused HBV-DNA mutation and HBV reactivation even though the patient was HBs antigen negative. We believe that the use of steroids should be avoided, at least in HBs antigen positive patients[47].

For HBs antigen positive patients, treatment with nucleoside analogs is necessary to prevent HBV reactivation.

Although from the point of view of preventing drug

Table 1 Guidelines for chemotherapy or immunosuppressive drug therapy

AASLD	Subject to preventive treatment if HBsAg positive or anti-HBc positive and HBV-DNA positive. If HBV-DNA concentration is less than 20000 IU or for a shortened treatment (< 1 yr), lamivudine or telbivudine is desirable. If HBV-DNA concentration exceeds 20000 IU and long-term treatment is necessary, entecavir or tenofovir is desirable. If HBV-DNA concentration remains less than 2000 IU six months after the completion of treatment, the treatment should be discontinued; otherwise treatment shall continue (2009)
APASL	There are no guidelines (2005)
EASL	HBsAg cases are subject to treatment, and HBV-DNA is measured in these cases, although there is no defined value in which treatment recommendations can be made. Lamivudine is most commonly used; however, it is best used in cases with low HBV-DNA concentration or when resistant strains are less likely to emerge. In high HBV-DNA concentration cases or when there is a high risk of resistance, entecavir is desirable. Careful follow-up of HBV-DNA concentration and liver function is necessary for HBsAg negative, Anti-HBc positive, and HBV-DNA negative cases. Vaccination is recommended in HBV seronegative cases (2009)
JAPAN	Subject to nucleoside analog treatment if HBsAg positive or if HBsAg negative, and anti-HBs or HBc positive plus HBV-DNA positive. If HBV-DNA is negative, HBV-DNA is monitored monthly and nucleoside analogs are administered when HBV-DNA becomes positive. Entecavir is recommended as the nucleoside analog. The timing of the termination of the nucleoside analog treatment shall be determined in accordance with the treatment for type B chronic hepatitis if HBsAg is positive. If the patient is anti-HBs or anti-HBc positive, a nucleoside analog is administered for 12 mo after the completion of immunosuppressive therapy or chemotherapy. During this time, nucleoside analog treatment will be discontinued if HBV-DNA is negative and ALT is normal. Patients are closely observed for 12 mo after treatment with nucleoside analogs (2009)

HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus; ALT: Alanine aminotransferase.

resistant HBV emergence, using entecavir as the initial treatment is advantageous, due to its excessive cost, substitution with lamivudine is acceptable.

Treatment based on the guidelines might be helpful.

HBc antibody positive/HBs antigen negative/HBs antibody negative

The HBc antibody positive/HBs antigen negative serotype is further divided into naïve (HBs antibody positive) and occult types (HBs antibody negative). However, since HBV reactivation is often observed in HBc antibody positive/HBs antigen negative cases, it may be preferable to divide HBc antibody positive/HBs antigen negative cases based on whether they are positive or negative for HBs antibodies. For HBc antibody positive patients, perhaps HBV reactivation is induced by rituximab. Although Hui *et al*[36] reported a 3%-25% reactivation rate, prophylactic treatment may be desirable since the mortality is relatively high (30%-38%) after reactivation occurs[36,54-56]. In 2013, Huang *et al*[47] conducted a randomized controlled trial to evaluate the effect of the prophylactic administration of entecavir on the frequency of HBV reactivation in HBc antibody positive patients. In their report, unlike in retrospective analyses, the prophylactic administration of entecavir was the most important factor, at least for HBc antibody positive patients[47]. Furthermore, Seto *et al*[57] recently reported frequent reactivation of HBV in patients with 10 mIU/mL HBs antibody prior to rituximab treatment. In HBc antibody positive patients, prophylactic treatment is necessary, at least for those who are antibody negative prior to rituximab treatment (occult type). We believe that the prophylactic administration of a nucleic acid analog is preferable in HBc antibody positive/HBs antigen negative/HBs antibody negative cases.

HBc antibody positivity can cause HBV reactivation. Attention is required since mortality is high after reactivation occurs.

Patients who are both HBc antibody positive and HBs antibody negative are subjected to prophylactic treatment with nucleoside analogs.

HBc antibody positive/HBs antigen negative/HBs antibody positive

There are reports of HBV reactivation in HBc-ab negative/HBs-ag positive/HBs-ab positive cases[21,32,36], and reactivation occurred in 6.9% of them[43]. HBV reactivation in HBc antibody negative/HBs antigen negative/HBs antibody positive cases has also been reported (albeit in small numbers)[21,36], and reactivation was reported in 3.4% of them[43].

We previously reported decreased HBs and HBc antibodies as well as induced reactivation after combination rituximab/chemotherapy in HBs antibody positive patients[17,24,25,58-60]. HBs antibody in particular decreased in patients with < 300 mIU/mL and disappeared in patients with < 100 mIU/mL after combination therapy with rituximab and chemotherapy[58-60]. For patients who were originally HBc antibody positive/HBs antibody positive but became HBs antibody negative after continuous treatment with rituximab, perhaps HBV reactivation can be induced by maintenance therapy with rituximab. Therefore, the possibility of HBV reactivation must be evaluated for group receiving maintenance therapy with rituximab. Since a case has been documented in which HBV reactivation occurred even though the patient had an HBs antibody titer of 868 mIU/mL, monthly follow-ups must be conducted during treatment for HBV-DNA positive patients[20]. However, such prophylactic treatment is expensive and HBV reactivation remains a possibility. At present, HBV-DNA follow-up is deemed adequate if the follow-up of HBs and HBc antibodies is extended to once a month. We must identify those who require prophylactic treatment from among HBc antibody positive/HBs antigen negative/HBs antibody positive and HBc antibody negative/HBs antigen negative/HBs antibody positive patients.

Particular attention must be paid to patients with

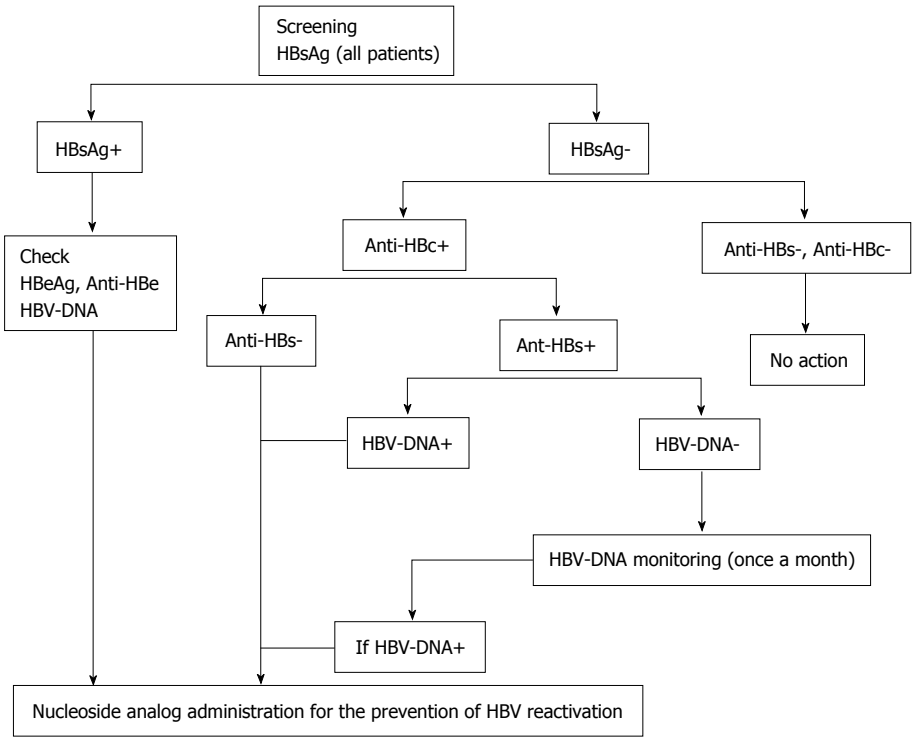

Figure 1 The review is summarized as schematics. The treatment direction described here is based on the assumption that all patients are screened in advance. HBsAg: Hepatitis B surface antigen; HBV: Hepatitis B virus.

< 300 mIU/mL of HBs antibody during maintenance treatment with rituximab since the HBs antibody status might become negative (follow-up of HBs antibody concentration is required).

Since HBV reactivation was reported even in patients with a high HBs antibody titer, HBs antibody follow-up is not sufficient for detecting the occurrence of reactivation. Monthly follow-up for the presence of HBV-DNA is necessary during treatment.

Administration of nucleoside analogs upon HBV reactivation

As for the prophylactic administration to prevent HBV reactivation, low HBV drug resistance is desirable. Although different guidelines exist, 0.5 mg of entecavir might be desirable with regard to both effectiveness and minimizing drug resistance. Depending on the cost of the drug and individual financial circumstances, 100 mg of lamivudine is also acceptable, although drug resistant strains are induced more easily. In this case, various guidelines are helpful in the selection of appropriate prophylactic drugs[51-53]. If HBV reactivation occurs, the patient should be dealt with based on the treatment of acute hepatitis B. Although the first choice for treatment is 0.5 or 100 mg of lamivudine, interferon is usually employed as well for acute hepatitis since nucleoside analogs do not take effect immediately upon HBV reactivation. However, in the case of HBV reactivation, interferon is difficult to apply since reactivation occurs after rituximab or chemotherapy treatment and prolonged bone marrow suppression might occur. Interferon's administration is also undesirable because it can exacerbate liver damage[61]. In our clinic, liver protective drugs (glycyrrhizic and ursodeoxycholic acids) are used together, although they might remain insufficient. If resistance develops to entecavir or lamivudine, 10 mg of adefovir or 200 mg of tenofovir should be used[52,53,61,62]. However, great caution is required since switching treatment drugs may induce further HBV drug resistance[63]. Tenofovir has been reported to be effective for lamivudine as well as adefovir resistant HBV strains[64-66].

We must evaluate whether to discontinue nucleoside analog administration in patients receiving those drugs that promote HBV reactivation. Since HBs antibody might become negative during rituximab treatment, discontinuation should be considered after the treatment's completion. An additional problem exists with regard to determining the duration of the discontinuation period. Cases of HBV reactivation even after long periods of discontinuation have been documented. For example, even after HBs antibody became temporarily positive, it disappeared later and HBV reactivation was induced[60,67]. If nucleoside analog treatment is given to HBs antibody negative patients who later become antibody positive, such treatment can be discontinued[53]. On the other hand, HBV vaccination is unable to suppress HBV reactivation[68]. If rituximab is administered continuously, HBs antibody may not be induced even after HBV vaccination. It is necessary to evaluate not only the induction of HBs antibody after HBV vaccination but also diseases that are appropriate for the discontinuation of nucleoside analog treatment. Based on the above discussion, Figure 1 shows the modified guidelines from

the Ministry of Health, Labour and Welfare.

Although entecavir is the first choice for prophylactic treatment against HBV reactivation, the decision to use it might also be based on financial conditions, and the guidelines should be referred to when selecting the appropriate drug.

When lamivudine resistance emerges, the treatment drug should be switched to adefovir or tenofovir.

Since nucleoside analogs do not take effect immediately upon HBV reactivation, combination treatment with interferon should be considered. However, bone marrow suppression must be considered for patients with hematological disorders.

The discontinuation of nucleoside analogs must be considered in the future. For HBs antigen negative patients, the discontinuation of nucleoside analog treatment may be possible through a vaccine.

CONCLUSION

Regarding the prevention of HBV reactivation, based on results from clinical studies conducted so far, not only HBs antigen positive patients but also those who are HBs antibody negative/HBc antibody positive might be eligible for prophylactic treatment. By employing combination rituximab/chemotherapy, safer treatment for malignant lymphomas is possible. On the other hand, HBV reactivation during maintenance therapy with rituximab must be considered. The discontinuation of nucleoside analog treatment may be possible through combined administration of an HBV vaccine in patients who are receiving nucleoside analogs as a preventive treatment against HBV reactivation (primarily for antibody negative cases).

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MINIREVIEWS

Neurosurgical procedures in patients with liver cirrhosis: A review

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Abstract

Liver cirrhosis, a devastating liver fibrosis caused by hepatitis/inflammation or tumors, is a major comorbid factor in known surgery fields, such as cardiovascular and abdominal surgeries. It is important to review possible comorbid results in neurosurgical procedures in cirrhotic patients. In the reviewed literature, Child-Pugh and model for end-stage liver disease scores are commonly used in the assessment of surgical risks for cirrhotic patients undergoing abdominal, cardiovascular or neurosurgical procedures. The major categories of neurosurgery are traumatic brain injury (TBI), spontaneous intracranial hemorrhage (SICH), brain tumors, and spinal instrumentation procedures. TBI was reported with surgical mortality as high as 34.5% and a complication rate of 87.2%. For SICH, mortality ranged from 22.7% to 47.0%, while complications were reported to be 43.2%. Less is discussed in brain tumor patients; still the postoperative hemorrhage rate approached 26.7%. In spinal fusion instrumentation procedures, the complication rate was as high as 41.0%. Preoperative assessment and correction could possibly decrease complications such as hemorrhage, wound infection and other cirrhosis-related complications (renal, pulmonary, ascites and encephalopathy). In this study, we reviewed the neurosurgical-related literature with regard to liver cirrhosis as a prognostic factor influencing neurosurgical outcomes.

Key words: Neurosurgery; Liver cirrhosis; Traumatic brain injury; Brain tumor; Spine surgery; Complications; Surgical risks; Spontaneous intracranial hemorrhage

Core tip: Liver cirrhosis is a major comorbid factor for surgical patients, including neurosurgery. We reviewed published articles in the field of neurosurgical procedures. For the high incidence of morbidity/mor-

tality rate, in cirrhotic patients, procedures should be carefully assessed and managed aggressively toward the coagulopathy and nutritional status.

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INTRODUCTION

Liver cirrhosis has been identified as a risk factor for increased morbidity and mortality in surgical patients[1-9], trauma patients[3-5,9], and patients undergoing emergent major surgery such as laparotomy, cardiac, and thoracic surgery[1,5,9-12]. A search of the literature found overall mortality rates as high as 45%-50% for patients with liver cirrhosis undergoing emergent nonhepatic surgery[8,13-17] and 40% for trauma surgery[3-5]. Furthermore, liver cirrhosis was also associated with increased postoperative morbidity and longer hospitalization in patients undergoing elective nonhepatic surgery[13-15,18]. Liver cirrhosis, and its associated bleeding tendency, is also a challenge for neurosurgeons in brain and spine surgery. For example, spontaneous intracranial hemorrhage (SICH)[19,20] and traumatic head injury[21,22] in cirrhotic patients have been reported in the literature; however, such reports have been sporadic, and relatively little has been published regarding cirrhotic patients who undergo neurosurgical procedures.

In our previous study[21], we found the overall complication rate for brain surgery with liver cirrhosis was 52.1% and the mortality rate was 24.3%. These high rates emphasize the importance of reviewing the recommendations for patients harboring this devastating systemic disease, including for patients needing neurosurgical procedures. The following study reviewed the risks and outcomes accompanying neurosurgical procedures in patients with liver cirrhosis.

TRAUMATIC BRAIN INJURY IN PATIENTS WITH LIVER CIRRHOSIS

For patients with traumatic brain injury (TBI), liver cirrhosis is a significant risk factor for postoperative complications. Over a 5-year-period, according to the National Trauma Databank in America[22], cirrhotic patients with TBI significantly experienced more ventilator days compared with noncirrhotic patients (2.9 ± 6.4 d *vs* 2.0 ± 6.4 d, $P < 0.001$). In addition, overall mortality was almost two-fold higher for cirrhotic compared with noncirrhotic TBI patients (34.0% *vs* 18.1%, OR = 2.34, 95%CI: 1.05-5.20, $P = 0.035$).

In our previous study[21], we found the complication, rebleeding and mortality rates reached 84.4%, 68.8%, and 37.5%, respectively, in acute TBI patients. According to the Child-Pugh score system (Child), the complication rate increased in a step-wise fashion from 38.7% to 60.0% and then 84.2%, the rebleeding rate from 29.3% to 48.0% and then 63.2%, and the mortality rate from 5.3% to 38.0% and then 63.2% for Child A, B and C patients, respectively. Child classification was significantly associated with higher risk of complication [Child B *vs* A with odds ratio: 2.84 (95%CI: 1.28-6.29), and Child C *vs* A: 5.39 (95%CI: 1.32-22.02)] and risk of mortality [Child C *vs* A: 30.43 (95%CI: 7.71-120.02), and Child B *vs* A: 10.88 (95%CI: 3.42-34.63)].

Notably, in patients undergoing minimally invasive burr holes for chronic subdural hemorrhage, the rebleeding/recurrent rate was 66.7% (10/15 patients) and mortality rate was 33.3% (5/15 patients). Uncontrolled encephalopathy, varices bleeding or associated pneumonia, sepsis and multiple organ failure were hypothesized to be causes of mortality.

SPONTANEOUS INTRACRANIAL HEMORRHAGE/HEMORRHAGIC STROKE IN PATIENTS WITH LIVER CIRRHOSIS

Liver cirrhosis is a well-known risk factor for SICH[19,20,23], despite the relatively rare occurrence of SICH in cirrhotic patients (incidence ranged from 0.7% to 0.8%)[19,20]. However, SICH is life-threatening and is sometimes overlooked due to the similarities of neurologic deficits caused by hepatic encephalopathy; most of the cirrhotic patients who developed SICH were sent to the emergency room for resuscitation and then admitted to the neurosurgery wards for surgical intervention or to the neurology wards for medical treatment if no surgical indication.

Surgical procedures to decrease intracranial pressure in SICH cases, such as craniotomy (hematoma removal) or ventricular drainage (cerebrospinal fluid diversion), were performed only in life-threatening instances. As shown in our previous study, the surgical complication rate was 43.2%, the rebleeding rate was 36.4%, and the mortality rate was 22.7%[21].

Thus, some cirrhotic patients with SICH who underwent medical treatment experienced poor neurologic outcomes even after surgery, including brainstem failure due to delayed medical intervention or severe coagulopathy. The overall mortality rate of cirrhotic patients with SICH, with or without surgery, has been reported as high as 47.0%[20]. Outcomes were associated with the size of the hematoma ($P < 0.005$) and with the initial Glasgow Coma Scale score ($P < 0.05$) and the Child-Pugh classification ($P = 0.05$)[20].

BRAIN TUMOR SURGERY IN PATIENTS WITH LIVER CIRRHOSIS

There is little literature discussing the outcome for cirrhotic patients with brain tumors who underwent

craniotomy. Jiang *et al*[24] reported a median survival of 3 (range 2.2-3.8) mo for 41 cases even with successful intracranial excision of brain metastasis from hepatocellular carcinoma (HCC). We reported 15 cases of brain tumor (meningioma, glioma, pituitary adenoma, lymphoma, and metastasis from breast cancer and HCC) patients who received neurosurgical procedures (craniotomy/biopsy)[21]. Four of these patients (26.7%) had immediate postoperative intracranial hemorrhage.

Despite the lack of clear evidence-based indications nor contraindications for cirrhotic patients with brain tumors, we presumed that the preoperative assessment of neurological deficits, Karnofsky performance scale, and corrections of pre-existing coagulopathy may be crucial for the patients' outcome.

SPINE SURGERY IN PATIENTS WITH LIVER CIRRHOSIS

Spine surgery is a common procedure in some neurosurgery centers (up to 70% of daily practice). Most spine surgeries are elective and less invasive, involving a small amount of intraoperative blood loss. Instrumentations for spinal stability have been widely used in patients with degenerative lumbar and cervical spine diseases to enhance stability and improve clinical results. However, instrumentation inevitably encounters more extensive wound exposure, bony destruction, and intraoperative blood loss. Published literature has shown that the complication rate of lumbar fusion instrumentation ranged from 3% to 15%[25,26]. In a retrospective study of lumbar instrumentation by Liao *et al*[27], patients in the cirrhotic group had significantly more blood loss (P = 0.049) and significantly longer hospitalization (P = 0.023). Complication rate was also significantly higher in the cirrhotic patient group than in the control group (41% *vs* 10%, P = 0.007). Patients with Child Class B score had a significantly higher incidence of complications than those with Child Class A (86% *vs* 27%, P = 0.006). Subanalysis in patients with Child Class A showed that those with a Child score of 6 also had higher complication rates than those with a score of 5 (P = 0.001).

Child score, hypoalbuminemia, ascites, and increased blood loss were identified risk factors for complications, and deteriorated hepatic encephalopathy would contribute to unsatisfactory outcomes. Whenever elective instrumented lumbar surgeries are being considered for cirrhotic patients, preoperative correction could reduce or avoid these postoperative complications.

PREOPERATIVE EVALUATION AND CORRECTION OF COAGULOPATHY

For patients with cirrhotic liver, Child-Pugh[28] and model for end-stage liver disease (MELD)[29] scores are both relied on for the prognosis prediction. The Child system contains serum bilirubin/albumin level, prothrombin time, ascites, and hepatic encephalopathy, while MELD includes serum bilirubin, creatinine, and etiology. Concerns for surgical procedures in cirrhotic patients mostly focused on the impact on coagulopathy, including clotting and the fibrinolytic system. We proposed an algorithm to assess the risk for complications and management of cirrhotic patients receiving regular neurosurgical procedures (Figure 1).

Vitamin K is essential for factor Ⅱ, Ⅶ, Ⅸ and Ⅹ and protein C, S and Z[30]. Liver cirrhosis is a common etiology for vitamin K deficiency due to poor nutrition or cholestasis. In a meta-analysis, intravenous vitamin K supplement from 1 to 5 mg may reverse the excess anticoagulants[31]. Thus, in spontaneous intracranial hemorrhage patients with anticoagulation medications, Degos *et al*[32] suggested 5-10 mg of vitamin K if international normalized ratio > 1.5 preoperatively.

Fresh frozen plasma transfusion could correct almost all coagulation factors. Youssef *et al*[33] suggested higher units (> 6 units) of flash frozen plasma is considered to reverse the prolonged prothrombin time. A concentrated blood product, prothrombin complex concentrate[34], is shown in a clinical trial (phase Ⅲb study) for its superiority and safety in patients with coagulopathy[34,35].

For thrombocytopenia, evidence has shown that platelet counts should be > 50000/μL before implementation of an invasive procedure[36]. However, for patients taking antiplatelet medication who have normal platelet counts, the evidence for platelet transfusion is not as clear. Evidence from a Stage Ⅱb indicates that transfusion with concentrated platelets would be beneficial for patients taking antiplatelet medication[32].

In addition, serum albumin level is possibly related to surgical outcome in patients with liver cirrhosis. In a retrospective study, corrections of pre- and postoperative serum albumin levels in cirrhotic patients who underwent microsurgery for free-flap reconstruction were shown to decrease the intensive care unit stay and complications[37].

Because there was no consensus regarding a standard procedure for emergent neurosurgical interventions, we proposed an algorithm (Figure 2). Emergent, mostly life-threatening, procedures mandate that surgeons make fast and effective decisions. Prospective studies are urgently needed to demonstrate the most essential components to prevent intraoperative bleeding, wound infection, and other associated complications, such as pneumonia, consciousness disturbance, or hepatorenal syndrome.

CONCLUSION

Liver cirrhosis is a diffuse process characterized by fibrosis and conversion of normal liver architecture into structurally abnormal nodules[38]. It was a major chronic devastating disease with high mortality rate (up to 72.7 deaths/10000 population) distributed most frequently in central Asia and the sub-Saharan region[39]. Studies have shown significantly high morbidity/mor-

Table 1 Studies of neurosurgical procedures for cirrhotic patients

Neurosurgical type/ref.	Patient (*n*)	Overall morbidity	Child A	Child B	Child C	Overall mortality	Child A	Child B	Child C
TBI									
Lustenberger *et al*[22]	47	NA	NA	NA	NA	34%	NA	NA	NA
Chen *et al*[21]	32	84.4%	38.7%	60.0%	84.2%	37.5%	5.3%	38.0%	63.2%
SICH									
Chen *et al*[21]	44	43.2%	NA	NA	NA	22.7%	NA	NA	NA
Huang *et al*[20]	36	NA	NA	NA	NA	47%	11.1%	27.7%	8.3%
Brain tumor									
Chen *et al*[21]	15	26.7%	NA	NA	NA	NA	NA	NA	NA
Spine surgery									
Liao *et al*[27]	29	41.0%	27.0%	86.0%	NA	NA	NA	NA	NA

The Child-Pugh score is a classification system used in the prognosis of cirrhosis. NA: Not available; SICH: Spontaneous intracranial hemorrhage; TBI: Traumatic brain injury.

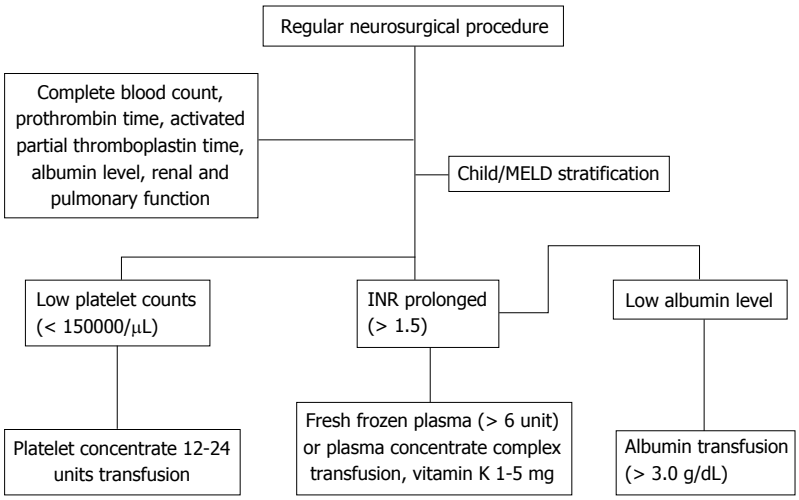

Figure 1 Preoperative assessment and management for patients planned receiving regular neurosurgical procedures. MELD: Model for end-stage liver disease.

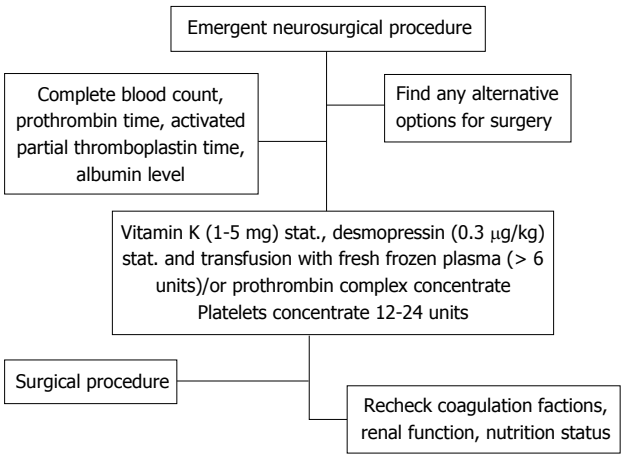

Figure 2 Management for patients receiving emergent neurosurgical procedures.

tality rates in cirrhotic patients undergoing major surgery. Neurosurgical procedures, which have not been researched extensively, have been performed conservatively on cirrhotic patients. However, the need for neurosurgery often precludes the potential cirrhotic complications.

In this review, we discussed the outcome from different etiologies, including TBI, SICH, brain tumor, and spine procedures (Table 1). Preoperative assessment and correction of coagulopathy and nutritional status may be important, despite lack of evidence. Still, the high morbidity/mortality rate in this devastating underlying disease may demand the need to develop evidence-based studies to elucidate the timing and parameters for appropriate correction leading to better surgical outcome in neurosurgical procedures.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Development of risky varices in alcoholic cirrhosis with a well-maintained nutritional status

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Abstract

AIM: To compare the nutritional status between alcoholic compensated cirrhotic patients and hepatitis C virus (HCV)-related cirrhotic patients with portal hypertension.

METHODS: A total of 21 patients with compensated cirrhosis (14 with HCV-related cirrhosis and seven with alcoholic cirrhosis) who had risky esophageal varices were investigated. In addition to physical variables, including the body mass index, triceps skinfold thickness, and arm-muscle circumference, the nutritional status was also assessed using the levels of pre-albumin (pre-ALB), retinol-binding protein (RBP) and non-protein respiratory quotient (NPRQ) measured with an indirect calorimeter.

RESULTS: A general assessment for the nutritional status with physical examinations did not show a significant difference between HCV-related cirrhosis and alcoholic cirrhosis. However, the levels of pre-ALB and RBP in alcoholic compensated cirrhotic patients were significantly higher than those in HCV-related compensated cirrhotic patients. In addition, the frequency of having a normal nutritional status (NPRQ $\geqslant$ 0.85 and ALB value > 3.5 g/dL) in alcoholic compensated cirrhotic patients was significantly higher than that in HCV-related compensated cirrhotic patients.

CONCLUSION: According to our small scale study, alcoholic compensated cirrhotic patients can develop severe portal hypertension even with a relatively well-maintained liver function and nutritional status compared with HCV-related cirrhosis.

Key words: Alcoholic liver cirrhosis; Hepatitis C virus; Rapid-turnover proteins; Albumin; Nutritional status; Esophageal varices; Portal hypertension; Non-protein respiratory quotient

Core tip: We compared the nutritional status between alcoholic compensated cirrhotic patients and hepatitis C virus (HCV)-related cirrhotic compensated patients. The levels of rapid-turnover proteins in alcoholic compensated cirrhotic patients were significantly higher than those in HCV-related compensated cirrhotic patients. When the nutritional status was determined using the albumin level and non-protein respiratory quotient, the frequency of having a normal nutritional status in alcoholic compensated cirrhotic patients was significantly higher than that in HCV-related compensated cirrhotic patients. These findings suggest that alcoholic compensated cirrhotic patients can develop severe portal hypertension even with a relatively well-maintained liver function and nutritional status.

Enomoto H, Sakai Y, Iwata Y, Takata R, Aizawa N, Ikeda N, Hasegawa K, Nakano C, Nishimura T, Yoh K, Ishii A, Takashima T, Nishikawa H, Iijima H, Nishiguchi S. Development of risky varices in alcoholic cirrhosis with a well-maintained nutritional status. *World J Hepatol* 2015; 7(21): 2358-2362 Available from: URL: http://www.wjgnet.com/1948-5182/full/v7/i21/2358.htm DOI: http://dx.doi.org/10.4254/wjh.v7.i21.2358

INTRODUCTION

Chronic liver diseases (CLDs), such as hepatitis virus-related liver diseases and alcoholic liver disease (ALD), cause liver fibrosis and portal hypertension, and the development of gastroesophageal varices is a major complication in patients with advanced liver diseases[1,2]. However, ALD is suggested to have several specific mechanisms which vary from viral hepatitis-related liver diseases and contribute to the progression of liver fibrosis[3,4]. In addition, alcohol intake increases the portal vein pressure by several causes which are independent of the progression of liver fibrosis[5]. For instance, the enlargement of hepatocytes with ballooning was reported to mechanically compress the sinusoid and contribute to increased pressure of the portal vein[6-8]. Therefore, the severity of portal hypertension in alcoholic liver cirrhosis tends to be more remarkable than that in hepatitis virus-related cirrhosis, and patients with alcoholic liver cirrhosis are suggested to develop large varices even with a relatively well-maintained liver function and general clinical conditions[9-11].

Protein energy malnutrition is a major complication of cirrhotic patients, and the presence of energy malnutrition is determined by a low non-protein respiratory quotient (NPRQ) level (< 0.85) which is measured with an indirect calorimeter, and the presence of protein malnutrition was determined by a low level of serological albumin (ALB) (≤ 3.5 g/dL)[12]. Although many cirrhotic patients have nutritional problems, the differences in the nutritional status between alcoholic cirrhotic patients and hepatitis virus-related cirrhotic patients have not yet been investigated in detail.

We previously evaluated cirrhotic patients with high-risk varices and reported the importance of nutritional supporting therapy during the endoscopic treatment for gastroesophageal varices[13]. We herein performed a sub-analysis and investigated clinical variables regarding the nutritional status in compensated cirrhotic patients (Child-Pugh class A) who have portal hypertension and compared those with alcoholic cirrhosis and hepatitis C virus (HCV)-related cirrhosis.

MATERIALS AND METHODS

Of the patients enrolled in our previous study[13] (Clinical Trial Registration: UMIN000001534, https://upload.umin.ac.jp/), a total of 21 patients with compensated cirrhosis (14 with HCV-related cirrhosis and seven with alcoholic cirrhosis with Child-Pugh class A), who were admitted to our department for the treatment of esophageal varices with a high bleeding risk, were analyzed in the present study. Liver cirrhosis as the cause of portal hypertension was diagnosed according to the clinical findings, such as the laboratory data, ultrasonographic findings and endoscopic findings. The characteristics of the study population are summarized in Table 1. All clinical values were obtained on the day of the first-time endoscopic treatment for esophageal varices during hospitalization. The following physical variables were used to evaluate the nutritional status of the patients: body mass index, triceps skinfold thickness (%TSF), and arm-muscle circumference (%AMC). In addition to routine blood tests, pre-albumin (pre-ALB) and retinol-binding protein (RBP) levels were also measured as indicators which correlate the liver synthesis capacity and nutritional status.

The parameters measured by indirect calorimetry were carbon dioxide production per minute and oxygen consumption per minute[12]. The total urinary excretion of nitrogen was measured according to the methods previously reported[14]. According to the study by Tajika *et al*[12], the presence of energy malnutrition and protein malnutrition was determined as a low NPRQ level (< 0.85) and a low ALB level (≤ 3.5 g/dL), respectively. All clinical data were obtained under the fasting condition. The study was reviewed and approved by Hyogo College of Medicine Ethics Committee (Approval No. 650). Written informed consent about personal and

Table 1 Characteristics of enrolled patients with alcoholic compensated cirrhosis or hepatitis C virus-related compensated cirrhosis

Age (yr)	66.0 ± 11.5
Gender (male/female)	18/3
Child-Pugh score	5.4 ± 0.5
AST (IU/L)	43 (16-99)
ALT (IU/L)	26 (10-86)
γ-GTP (IU/L)	41 (12-821)
ALP (IU/L)	289 (191-726)
Total bilirubin (mg/dL)	1.1 ± 0.5
ALB (g/dL)	3.6 ± 0.3
Hemoglobin (g/dL)	11.4 ± 1.7
Platelet count (× 10^3/μL)	110 ± 68
Prothrombin time (%)	83.3 ± 9.1
BCAA treatment (present/absent)	9/12

Quantitative variables were expressed as the mean ± SD or median (range). BCAA: Branched-chain amino acids; AST: Aspartate aminotransferase; ALT: Alanine aminotransferases; γ-GTP: γ-glutamyl transpeptidase; ALB: Albumin; ALP: Alkaline phosphatase.

Table 2 Comparison of the general clinical characteristics between patients with alcoholic compensated cirrhosis and hepatitis C virus-related compensated cirrhosis

	Alcoholic cirrhosis (*n* = 7)	HCV-related cirrhosis (*n* = 14)	*P* value
Age (yr)	63.7 ± 6.8	67.2 ± 13.2	NS
Gender (male/female)	6/1	12/2	NS
Child-Pugh score	5.3 ± 0.5	5.4 ± 0.9	NS
AST (IU/L)	30 (16-99)	47.5 (27-68)	NS
ALT (IU/L)	24 (10-36)	35.5 (18-86)	NS
γ-GTP (IU/L)	113 (24-821)	29.5 (12-159)	< 0.01
ALP (IU/L)	311 (205-726)	281 (191-462)	NS
Total bilirubin (mg/dL)	1.2 ± 0.3	1.0 ± 0.3	NS
ALB (g/dL)	3.7 ± 0.3	3.6 ± 0.3	NS
Prothrombin time (%)	84.5 ± 9.6	82.7 ± 9.1	NS
Platelet (× 10^3/μL)	104 ± 51	112 ± 77	NS
BCAA treatment (+/-)	4/3	5/9	NS

BCAA: Branched-chain amino acids; NS: Not significant; HCV: Hepatitis C virus; AST: Aspartate aminotransferase; ALT: Alanine aminotransferases; γ-GTP: γ-glutamyl transpeptidase; ALB: Albumin; ALP: Alkaline phosphatase.

Table 3 Comparison of nutritional variables between patients with alcoholic compensated cirrhosis and hepatitis C virus-related compensated cirrhosis

	Alcoholic cirrhosis (*n* = 7)	HCV-related cirrhosis (*n* = 14)	*P* value
BMI	25.0 ± 5.8	22.7 ± 3.1	NS
%AMC	102.4 ± 2.3	105.0 ± 12.0	NS
%TSF	142.7 ± 44.3	190.5 ± 75.2	NS
REE/BMR	1.06 ± 0.13	1.02 ± 0.13	NS
FPG (mg/dL)	124 ± 56	105 ± 16	NS
IRI (μU/mL)	9.1 ± 2.6	13.8 ± 8.2	NS
HOMA-IR	2.8 ± 1.7	3.7 ± 2.5	NS
Pre-ALB (mg/dL)	16.3 ± 7.2	9.7 ± 2.7	< 0.01
RBP (mg/dL)	2.4 ± 1.3	1.4 ± 0.3	< 0.05

BMI: Body mass index; AMC: Arm-muscle circumference; TSF: Triceps skinfold thickness; REE/BMR: Resting energy expenditure/basal metabolic rate; FPG: Fasting plasma glucose; Pre-ALB: Pre-albumin; RBP: Retinol-binding protein; HCV: Hepatitis C virus; IRI: Immunoreactive insulin; HOMA-IR: Homeostasis Model Assessment for Insulin Resistance.

medical data collection was obtained from all patients.

Statistical analysis

The data between two groups were compared using Student's *t*-test (normally distributed data) or the Mann-Whitney *U* test (non-normally distributed data). The frequency of having a normal nutritional status between alcoholic compensated cirrhotic patients and HCV-related compensated cirrhotic patients were analyzed using the χ^2 test. A value of $P < 0.05$ was considered to be significant.

RESULTS

Comparison of the clinical data between patients with alcoholic compensated cirrhosis and HCV-related compensated cirrhosis

First, we compared the clinical variables between patients with alcoholic compensated cirrhosis and HCV-related compensated cirrhosis. Since all enrolled patients had a well-maintained liver function (Child-Pugh A), most of the common clinical variables (except for γ-glutamyl transpeptidase), including PT percentage, total bilirubin level, ALB level and platelet count, did not differ between the two groups (Table 2). In addition, the general assessment for nutritional status with physical examinations, such as %AMC and %TSF, did not show any significant differences between the two groups. However, when we compared the levels of pre-ALB and RBP, which are more sensitive indicators for liver synthesis capacity and nutritional status (referred to as "rapid-turnover proteins"), these protein levels were significantly higher in alcoholic compensated cirrhotic patients compared with those in HCV-related compensated cirrhotic patients, suggesting a better maintained liver condition of alcoholic compensated cirrhosis with severe portal hypertension than that of HCV-related compensated cirrhosis (Table 3).

Nutritional status in patients with compensated cirrhosis with risky varices: Comparison between alcoholic compensated cirrhosis and HCV-related compensated cirrhosis

Using the indirect calorimetry in combination with the blood test, we determined the nutritional status of each patient in detail. The frequency of having a normal nutritional status (NPRQ ⩾ 0.85 and ALB value > 3.5 g/dL) in patients with alcoholic compensated cirrhosis (5/7: 71.4%) was significantly higher than that in patients with HCV-related compensated cirrhosis (2/14: 14.2%) (Figure 1). These findings suggest that patients with alcoholic cirrhosis can develop severe portal hypertension even with a relatively well- maintained liver function and nutritional status when compared to patients with HCV-related cirrhosis.

DISCUSSION

ALD leads to an increased intrahepatic and portal

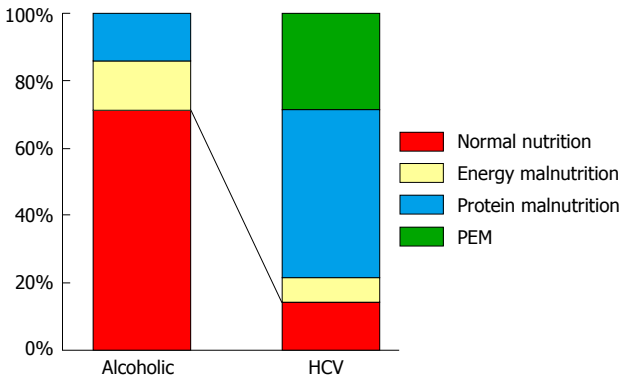

Figure 1 Nutritional status of compensated cirrhosis was determined using the albumin value and non-protein respiratory quotient. The rate of patients with a normal nutritional status (non-protein respiratory quotient level ⩾ 0.85 and albumin level > 3.5 g/dL) was significantly higher in alcoholic compensated cirrhosis than that in HCV-related compensated cirrhosis. HCV: Hepatitis C virus; PEM: Protein energy malnutrition.

pressure and portal hypertension depending on several conditions which vary from hepatitis virus-related CLDs, such as compression of the hepatic sinusoid by enlarged hepatocytes in the form of ballooning[6-8]. In addition, perivenular fibrosis, one of histological characteristics of ALD, is also suggested to contribute to the development of portal hypertension[15-17]. We herein compared several clinical parameters between Child-Pugh grade A patients with alcoholic compensated cirrhosis and those with HCV-related compensated cirrhosis. Although there were no significant differences in the general clinical variables, patients with alcoholic cirrhosis had better liver synthesis capacity and/or nutritional status. These findings suggest that alcoholic cirrhotic patients are prone to develop portal hypertension even under the condition of a well-maintained liver function and nutritional status.

In the present study, the general clinical variables including liver functional tests and physical examinations did not differ between patients with HCV-related compensated cirrhosis and alcoholic compensated cirrhosis. However, we found alcoholic compensated cirrhotic patients showed significantly higher levels of pre-ALB and RBP than HCV-related compensated cirrhotic patients (Table 2). Rapid-turnover proteins, such as pre-ALB and RBP, have shorter life-spans than ALB (pre-ALB: approximately 2 d, RBP: approximately 12 h, and ALB: approximately 3 wk). Therefore, these rapid turnover proteins are able to sensitively reflect the liver synthesis capacity and nutritional status[18-20]. In addition, in HCV-related compensated cirrhotic patients, the levels of ALB and the NPRQ were decreased in 35.7% (5/14) and 78.6% (11/14) of the patients, respectively. Although we did not clarify the role of HCV-infection in the development of malnutrition, our findings suggested that patients with HCV-related cirrhosis potentially had either protein or energy malnutrition, even compensated cirrhotic patients (Child-Pugh A) who did not exhibit cirrhosis-related clinical symptoms. It has been previously reported that cirrhotic patients with either energy malnutrition (NPRQ < 0.85) or protein malnutrition (ALB value ⩽ 3.5) have an unfavorable prognosis[12,21]. Recent advancements in antiviral treatment are expected to lead to a significant decrease in the frequency of HCV infection[22,23]. It would be interesting to evaluate changes in the nutritional status of patients with cirrhosis after the elimination of HCV-related compensated cirrhosis.

In Table 2, the mean value of %TSF was numerically higher in HCV-related cirrhotic patients than that in alcoholic cirrhotic patients, although a statistical significance was not found between the groups. Although physical examinations are generally accepted as a method to assess the nutritional status, measurement errors can easily occur (particularly regarding the levels of TSF and AMC)[13], and therefore we should pay careful attention to the evaluation of the physical variables.

Although the present study is a novel one that focused on the data of rapid-turnover proteins and indirect calorimetry in patients with compensated cirrhosis, there are some limitations associated with our study. First, the number of patients enrolled was small. It would therefore be important to investigate a larger number of patients in order to confirm our results. Second, indirect calorimetry cannot be routinely used in every institute. However, our study is unique in that it investigated compensated cirrhotic patients with similar clinical conditions (Child-Pugh grade A) and determined the differences in the nutritional parameters between patients with different etiologies. Further studies with a greater accumulation of patients and readily available tools for measuring the protein levels are necessary.

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COMMENTS

Background

Although many cirrhotic patients have nutritional problems, the differences in the nutritional status between alcoholic cirrhotic patients and hepatitis virus-related cirrhotic patients have not yet been investigated in detail. The authors herein compared the nutritional status between alcoholic compensated cirrhosis and hepatitis C virus (HCV)-related compensated cirrhosis patients with portal hypertension.

Research frontiers

Assessment of the nutritional statuses in patients with chronic liver diseases has been increasingly important, particularly in cirrhotic patients.

Innovations and breakthroughs

This is the first report to compare the nutritional statuses between alcoholic cirrhosis and HCV-related cirrhosis patients with risky esophageal varices.

Applications

The present study showed that alcoholic compensated cirrhotic patients can develop severe portal hypertension even with a relatively well-maintained liver

function and nutritional status when compared to patients with HCV-related cirrhosis.

Peer-review

This is quite an interesting topic. It focuses on a more realistic field of knowledge.

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