

# World Journal of *Hepatology*

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2014-2017

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- 1327** Liver resection for early hepatocellular cancer: Comparison of centers in 3 different countries

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**ABOUT COVER**

Editorial Board Member of *World Journal of Hepatology*, Dr. Yu-Bao Zheng, MD, PhD, Associate Professor, Chief Doctor, Teacher, Department of Infectious Diseases, the Third Affiliated Hospital, Sun Yat-sen University, Guangzhou 510630, Guangdong Province, China

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## Alcohol use disorder and its impact on chronic hepatitis C virus and human immunodeficiency virus infections

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### Abstract

Alcohol use disorder (AUD) and hepatitis C virus (HCV) infection frequently co-occur. AUD is associated with greater exposure to HCV infection, increased HCV infection persistence, and more extensive liver damage due to interactions between AUD and HCV on immune responses, cytotoxicity, and oxidative stress. Although AUD and HCV infection are associated with increased morbidity and mortality, HCV antiviral therapy is less commonly prescribed in individuals with both conditions. AUD is also common in human immunodeficiency virus (HIV) infection, which negatively impacts proper HIV care and adherence to antiretroviral therapy, and liver disease. In addition, AUD and HCV infection are also frequent within a proportion of patients with HIV infection, which negatively impacts liver disease. This review summarizes the current knowledge regarding pathological interactions of AUD with hepatitis C infection, HIV infection, and HCV/HIV co-infection, as well as relating to AUD treatment interventions in these individuals.

**Key words:** Hepatitis C virus; Human immunodeficiency virus; Hepatitis C virus/human immunodeficiency virus co-infection; Liver; Alcohol

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**Core tip:** The present review is focused on alcohol use disorder and hepatitis C virus (HCV) and human immunodeficiency virus (HIV) infection, as well as HCV/

## HIV co-infection.

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## INTRODUCTION

Alcohol abuse is a major cause of preventable liver disease worldwide, and alcohol use disorder (AUD) is associated with substantial disease burden in western countries<sup>[1]</sup>. According to 5<sup>th</sup> edition of the Diagnostic and Statistical Manual of Mental Disorders<sup>[2]</sup>, AUD encompasses both alcohol abuse and alcohol dependence. Table 1 presents the diagnostic criteria for AUD and other definitions of unhealthy alcohol use, such as the recommendations of the United States National Institute on Alcohol Abuse and Alcoholism.

In the United States, almost 9% of the adult population meets the AUD criteria and alcohol contributes to 79000 deaths annually<sup>[3]</sup>. Within the European Union, alcohol misuse causes 14% of deaths in men and nearly 8% of deaths in women, with alcohol-related mortality disproportionately impacting young people<sup>[4]</sup>. In Spain, unhealthy alcohol use is exhibited by 5% of the population between 15 and 64 years old, and 15% report at least one binge drinking episode within the prior year<sup>[5]</sup>. Moreover, the pattern of binge drinking is becoming increasingly prevalent, mainly among young individuals.

Per capita alcohol consumption is strongly correlated with liver cirrhosis mortality rates globally<sup>[6]</sup>. However, the short- and long-term impacts of binge drinking with regards to the development and severity of alcoholic liver disease (ALD) are not yet known. Per capita alcohol consumption is strongly correlated with liver cirrhosis mortality rates across countries<sup>[5]</sup>. Notably, the medical literature reveals wide heterogeneity in the methods used to assess alcohol exposure, and it can be challenging to analyze time-varying exposures like alcohol consumption over time<sup>[7]</sup>.

### Epidemiology of AUD in hepatitis C virus and human immunodeficiency virus infection

Addressing alcohol use is critical in the management of hepatitis C virus (HCV)-infected patients, as AUD is associated with poor clinical outcomes and liver-related deaths in this patient group<sup>[8]</sup>. Compared to the general population, HCV-infected adults tend to consume greater amounts of ethanol<sup>[9]</sup>, being over twice as likely to consume more than one alcoholic drink per day (34% vs 14%) and almost 8 times more likely to consume over three drinks per day (19% vs 2%)<sup>[10]</sup>.

Moreover, alcohol abuse is associated with concomitant use of illegal substances, and 30% to 50% of patients with a history of substance abuse consume alcohol<sup>[11]</sup>. This is highly important since 2/3 of new HCV infections in the western world are associated with drug injection<sup>[12]</sup>. Accordingly, the prevalence of HCV infection is higher among patients with AUD who are current or past injecting drug users<sup>[13]</sup>. Within a cohort of patients with AUD admitted for hospital detoxification in the Barcelona area, HCV prevalence was as high as 20%<sup>[14]</sup>. However, other researchers in Spain reported a much lower prevalence of 3.5%<sup>[13]</sup>, possibly due to differences in patient selection.

The prevalence of HCV infection is confounded by the degree of liver disease. Cross-sectional studies performed in hepatology clinics showed that HCV prevalence was higher among patients with advanced liver fibrosis, and almost universal among HCV-infected patients with hepatocellular carcinoma<sup>[15,16]</sup>. On the other hand, HCV prevalence ranged from 1% to 10% in community-oriented studies of individuals with AUD but without clinically apparent liver disease<sup>[17,18]</sup>. A recent meta-analysis including 24 studies reported that the average weighted prevalence of HCV infection among patients with AUD was 16.3%<sup>[13]</sup>.

AUD may also be common among human immunodeficiency virus (HIV)/AIDS patients, with a prevalence ranging from 30% to 50%<sup>[19]</sup>. High prevalences of alcohol consumption have been reported in HIV/AIDS cohort studies from the United States<sup>[20,21]</sup>, Europe<sup>[22-24]</sup>, South Africa<sup>[25]</sup>, and other parts of the world<sup>[26]</sup>. In the Women's Interagency HIV Study, 14%-24% of female HIV/AIDS participants reported hazardous alcohol use within the past year<sup>[27]</sup>. On the other hand, patients with AUD show a lower prevalence of HIV infection than HCV infection<sup>[14]</sup>, which is confounded by prevalence of injection drug use.

## AUD AND CHRONIC HCV INFECTION

### Effect of alcohol on HCV replication

Alcohol metabolites apparently enhance viral protein expression as well as the heterogeneity of HCV quasispecies<sup>[28]</sup>. Some authors describe RNA-HCV increases among patients who use alcohol<sup>[29]</sup>. However, a meta-analysis performed by Anand *et al*<sup>[30]</sup> in 2005 showed no association between RNA-HCV and alcohol consumption.

### Impact of alcohol on HCV infection persistence

Spontaneous resolution of HCV infection requires an early and wide immune response against HCV viral proteins<sup>[31]</sup>. Once acute HCV infection is controlled, the presence of memory T-cell populations is associated with reduced persistence of infection in re-exposed individuals<sup>[32]</sup>. HCV infection persistence is also associated with loss of specific T-cell proliferation, and reduced migration of effector T cells to the liver<sup>[33]</sup>. HCV-infected patients with AUD show functional impairment of dendritic cells<sup>[34]</sup>, which partly explains the association between alcohol use

**Table 1** Diagnostic criteria for alcohol use disorder and other definitions of unhealthy alcohol use

## AUD (DSM-5)

In the past year<sup>[2]</sup>, have you<sup>1</sup>

Had times when you ended up drinking more, or longer than you intended?

More than once wanted to cut down or stop drinking, or tried to, but couldn't?

Spent a lot of time drinking? Or being sick or getting over the aftereffects?

Experienced craving - a strong need, or urge, to drink?

Found that drinking or being sick from drinking often interfered with taking care of your home or family? Or caused job troubles? Or school problems?

Continued to drink even though it was causing trouble with your family or friends?

Given up or cut back on activities that were important or interesting to you, or gave you pleasure, in order to drink?

More than once gotten into situations while or after drinking that increased your chances of getting hurt (such as driving, swimming, using machinery, walking in a dangerous area, or having unsafe sex)?

Continued to drink even though it was making you feel depressed or anxious or adding to another health problem? Or after having had a memory blackout?

Had to drink much more than you once did to get the effect you want? Or found that your usual number of drinks had much less effect than before?

Found that when the effects of alcohol were wearing off, you had withdrawal symptoms, such as trouble sleeping, shakiness, irritability, anxiety, depression, restlessness, nausea, or sweating? Or sensed things that were not there?

Risky alcohol use<sup>[178]</sup>

Drinking more than the recommended amount by the National Institute on Alcohol Abuse and Alcoholism

&gt; 14 drinks per week or &gt; 4 drinks on any day for men

&gt; 7 drinks per week or &gt; 3 drinks on any day for women or men &gt; 65 yr

## Problem drinking

Use of alcohol accompanied by alcohol-related consequences but not meeting criteria for AUD

<sup>1</sup>Meeting any two of the 11 criteria during the same 12-mo period is consistent with AUD. The severity of an AUD-mild, moderate, or severe-is based on the number of criteria met. AUD: Alcohol use disorder; DSM-5: Diagnostic and statistical manual of mental disorders.

and lower odds of spontaneous HCV resolution<sup>[35,36]</sup>.

**Effect of alcohol on HCV-related immunity**

Mice that are chronically exposed to ethanol exhibit diminished immune responses to HCV-core protein, mainly due to impaired maturation of dendritic cells<sup>[34]</sup>. In HCV-infected patients, dendritic cells present impaired allostimulation capacity, which is more apparent in the presence of alcohol<sup>[34]</sup>. Alcohol and HCV infection exert synergistic effects, suppressing major histocompatibility complex class II<sup>[37]</sup> *via* functional impairment of the proteasome (intracellular protein complexes that degrade unnecessary or damaged proteins) and alterations in interferon signaling<sup>[38]</sup>. This could partly explain the lower efficacy of interferon-based HCV treatment regimens among patients with AUD<sup>[39]</sup>.

**Effect of alcohol on cytotoxicity**

Enhanced hepatocyte apoptosis is observed in HCV infection, which is apparently associated with impaired immune responses rather than directly attributable to the viral infection<sup>[40]</sup>. Hepatocyte apoptosis is mediated by cytotoxic T cells and natural killer cells *via* caspase activity<sup>[40]</sup>. BCL-2 protein is associated with mitochondrial permeability, and its expression is reduced in HCV-infected hepatocytes<sup>[41]</sup>. Alcohol seems to enhance hepatocyte apoptosis through down-regulation of BCL-2 expression<sup>[40]</sup>.

**Alcohol and oxidative stress**

The HCV core viral protein is associated with higher oxidative stress. It binds the mitochondrial wall, facilitating calcium entrance, electron transport, and increased

reactive oxygen species, which results in increased oxidative stress that damages the cell<sup>[42]</sup>. This protein also targets microsomal triglyceride transfer protein activity, thus modifying hepatic very-low-density lipoprotein particle assembly and secretion, which leads to liver steatosis<sup>[43]</sup>. Moreover, the HCV core viral protein alters the oxidant/antioxidant state of the liver in the absence of inflammation, consequently producing mitochondrial DNA damage<sup>[44]</sup>.

In HCV-core transgenic mice, chronic ethanol administration is associated with higher lipid peroxidation and synergic induction of TGF- $\beta$ 1 and hepatic stellate cells<sup>[45]</sup>. The HCV-core protein cooperates with ethanol to activate some p38 mitogen-activated protein kinase pathways, resulting in polygene modulation, and contributing to liver disease pathogenesis<sup>[46]</sup>. In alcohol-fed NS5A transgenic mice, the synergistic effect between HCV infection and alcohol is dependent on mechanisms involving Toll-like receptor 4, which belongs to the innate immune system<sup>[47]</sup>. Alcohol consumption and HCV infection impact FOXO3 expression, thus impairing antioxidant capacity in the liver<sup>[48]</sup>.

In humans, indirect evidence suggests that oxidative stress is associated with more extensive liver injury in patients with AUD and HCV infection, as they tend to show higher serum levels of malondialdehyde (a lipid peroxidation product), poor glutathione peroxidase activity, and stimulation of Th1 response cytokines<sup>[49]</sup>. Moreover, patients with AUD present major lipid peroxidation, and the loss of antioxidant capacity is associated with liver fibrosis<sup>[50]</sup>. Among HCV-infected patients who drink alcohol, liver fibrosis is independently associated with liver steatosis, oxidative stress, age, and iron

deposits in the liver<sup>[51]</sup>.

### **Alcohol and progression of HCV-related liver disease**

Alcohol consumption is associated with more extensive progression of HCV-related liver damage<sup>[52,53]</sup>. No safe level of alcohol consumption has been described, as even HCV-infected patients who drink moderate amounts of alcohol (30 g/d) experience progressive liver fibrosis<sup>[54-56]</sup>. A meta-analysis assessed 20 studies that were published between 1995 and 2004, and found that the relative risk of progression to liver cirrhosis or decompensated liver disease among HCV-infected patients was 2.3 times higher, with a 95%CI of 1.7-3.3, among those who drank alcohol compared to abstainers<sup>[52]</sup>. However, the majority of included studies were performed in liver units, and thus might be biased towards patients with more severe forms of liver disease<sup>[52]</sup>. Alcohol consumption is also associated with higher risks of cirrhosis decompensation and liver-related death<sup>[57]</sup>. Moreover, alcohol consumption has a synergistic effect with chronic hepatitis C, increasing the risk of liver cancer<sup>[58]</sup>.

### **Assessment of liver disease in patients with AUD and HCV infection**

In both HCV infection and ALD, liver fibrosis is the main prognostic factor of liver disease progression<sup>[59,60]</sup>. Although liver biopsy is the gold standard for liver fibrosis assessment<sup>[61]</sup>, it is associated with several rare complications and is not usually performed in patients with substance use disorders<sup>[62]</sup>. Recent reports describe the estimation of liver fibrosis using several non-invasive biological markers derived from laboratory parameters routinely used in clinical practice, including aspartate aminotransferase (AST), alanine aminotransferase (ALT), and platelet count.

Of these potential markers, FIB-4<sup>[63]</sup> and the aspartate aminotransferase/platelet ratio index (APRI)<sup>[64]</sup> have been validated against the gold standard of liver biopsy in HCV-monoinfected patients as well as HCV/HIV-coinfected patients<sup>[65-68]</sup>. These markers perform better for detecting either the absence of liver fibrosis or the presence of advanced liver fibrosis<sup>[63,64]</sup>. However, clinical experience using these markers in patients with AUD is limited<sup>[69]</sup>, and concerns have been raised about the possibility of overestimating liver fibrosis in patients with alcoholic steatohepatitis. Moreover, ALD is a formal contraindication for the use of Pohl's score<sup>[70]</sup>-an index that uses aminotransferase levels and platelet count. Transient elastography has also been used to assess liver fibrosis in ALD<sup>[71]</sup>, but the presence of severe liver steatosis may distort results, leading to overestimation of advanced liver fibrosis<sup>[72]</sup>.

In prior studies, we have defined alcohol-related liver disease (ARLD) as the presence of any two of the following criteria: Elevated AST to between 74 and 300 U/L, AST/ALT  $\geq 2$ , and total bilirubin  $> 1.2$  mg/dL<sup>[73,74]</sup>. Within a cohort of AUD patients admitted for hospital detoxification in metropolitan Barcelona, Spain, 14.6%

met those criteria, and ARLD was associated with mid-term mortality<sup>[75]</sup>.

### **Impact of HCV infection on hospitalizations and mortality of patients with AUD**

As previously mentioned, alcohol use is associated with worse prognosis in HCV-related liver disease. It is estimated that 36% of liver cirrhosis among HCV-infected individuals is attributable to alcohol use<sup>[76]</sup>. HCV infection also has a deleterious impact on clinical outcomes among patients with AUD<sup>[77-80]</sup>. Tsui *et al.*<sup>[77]</sup> identified 6354 AUD-related hospital admissions, and reported that the HCV-positive patients were twice as likely to die (4.4% vs 2.4%,  $P < 0.01$ ), and showed significantly longer hospital stays (19% longer, 95%CI: 12%-27%). Another study included patients from the United States Nationwide Inpatient Sample Dataset who had a primary or a secondary discharge diagnosis of alcoholic hepatitis, and reported that HCV-positive patients had higher mortality with an odds ratio (OR) of 1.29 (95%CI: 1.12-1.49,  $P < 0.01$ )<sup>[78]</sup>.

Patients with AUD who are exposed to HCV infection probably differ from those who are not exposed with regards to co-morbidities or behaviors associated with poorer survival, such as the use of illicit drugs<sup>[81]</sup>. However, even in studies that have accounted for various lifestyle factors, HCV infection remains associated with both overall mortality, showing a hazard ratio (HR) of 2.55 (95%CI: 1.50-4.33,  $P < 0.01$ ), and liver-related mortality (HR = 3.24, 95%CI: 1.18-8.94,  $P = 0.02$ )<sup>[79]</sup>.

In our study of 675 AUD patients admitted for hospital detoxification, we examined the impact of HCV infection on mortality. Our results showed that HCV infection was associated with higher mortality, and that this effect was more apparent in patients with younger ages at admission (HR = 3.1, 95%CI: 1.3-7.3,  $P < 0.01$ ) and those who were co-infected with HCV/HIV (HR = 3.9, 95%CI: 2.1-7.1,  $P < 0.01$ )<sup>[80]</sup>. In the same Barcelona cohort, we recently reported that AUD patients with HCV mono-infection showed an increased risk of liver-related death in comparison to AUD patients without HCV-infection (HR = 3.92, 95%CI: 2.03-7.59)<sup>[82]</sup>.

### **Interferon-based treatment of HCV infection in patients with AUD**

In the era of HCV antiviral therapy including interferon, infection treatment was challenging in individuals who consumed alcohol<sup>[8]</sup>. In fact, alcohol use was a major reason for a lack of HCV treatment<sup>[83,84]</sup>. Several researchers analyzed strategies to extend HCV treatment to patients with unhealthy alcohol use. Le Lan *et al.*<sup>[85]</sup> performed an observational study of HCV treatment in alcohol-drinking patients, in which drinking in moderation was encouraged but not required. Of the study population, 30% continuously abstained, 34% consumed low-risk amounts of alcohol, and 36% continued to drink risky amounts. The overall sustained viral response (SVR) rate was 48% with no difference observed between

**Table 2 Treatment interventions for unhealthy alcohol use and alcohol use disorder**

Condition	Intervention
Unhealthy alcohol use	Brief intervention
AUD	Motivational interviewing
	Hospital detoxification
	Individual and group therapy
	Approved pharmacological treatments:
	Disulfiram
	Acamprosate
	Naltrexone
	Nalmefene
	Investigational treatments:
	Baclofene
	Topiramate
	Gabapentin

AUD: Alcohol use disorder.

abstainers and low-risk drinkers<sup>[85]</sup>, confirming prior results in a Swiss HCV cohort<sup>[86]</sup>.

Evon *et al.*<sup>[87]</sup> performed a randomized clinical trial in the United States, which included 9-mo intervention comprising counseling, case management, and motivational interviewing for patients ineligible for HCV treatment (31% due to alcohol abuse). The intervention was associated with a 2.38 relative risk of being deemed eligible (95%CI: 1.21-4.68). The groups did not differ with regards to the proportion of patients that eventually received HCV antiviral therapy<sup>[87]</sup>.

### **Interferon-free treatment of HCV infection in patients with AUD**

The advent of direct-acting antivirals and interferon-free regimens has dramatically changed the landscape of HCV treatment, with most registration trials and pilot real-life experiences reporting SVR rates of over 90%<sup>[88]</sup>. Although treatment is now more feasible for patients with substance use disorders<sup>[89,90]</sup>, to date, very few patients with AUD have been included in clinical trials<sup>[91-93]</sup>.

The current American Association for the Study of Liver Diseases - Infectious Diseases of America guidelines for HCV treatment advocate abstinence from alcohol<sup>[94]</sup>. When appropriate, these guidelines suggest interventions to facilitate the cessation of alcohol consumption, ranging from brief interventions for patients with low alcohol intake<sup>[94]</sup>, to referral to mutual help groups and specialty treatment for patients with established AUD<sup>[94]</sup>. While alcohol consumption is not a formal contraindication for HCV treatment, a year of abstinence from alcohol is thought to be necessary to achieve adequate treatment adherence<sup>[95]</sup>.

There remains a need for a change in the provision of HCV treatment such that patients with AUD and HCV infection can benefit from viral eradication. Expansion of the capacity of primary care clinics or addiction clinics to provide HCV treatment has been successfully tested in several areas of the United States<sup>[96]</sup> and Australia<sup>[90]</sup>. These experiences should be replicated worldwide to

more effectively treat difficult-to-reach populations<sup>[97]</sup>.

### **AUD treatment in patients with HCV infection**

Brief interventions involving feedback and discussion of the negative consequences of alcohol abuse are efficacious at motivating reduced alcohol consumption among among patients with unhealthy alcohol use<sup>[98]</sup>, but not patients with alcohol dependence. Such brief interventions can be targeted towards patients with HCV infection, with delivery at the primary care level or in hepatology clinics<sup>[94,99]</sup>. More intensive treatments, such as motivational enhancement therapy, can also reduce the number of drinking days among patients with chronic HCV infection<sup>[100]</sup>. Other type of interventions, such as group therapy, can reportedly motivate abstinence from alcohol in 44% of patients in an HCV clinic<sup>[101]</sup>.

Table 2 summarizes the various treatment strategies for patients with AUD. Specialty treatment should be favored in such cases, and patients should be offered detoxification; specific pharmacotherapy including disulfiram, acamprosate, naltrexone, or nalmefene; and psychosocial support<sup>[3]</sup>. Some researchers have reported satisfactory results with baclofene in patients with overt end-stage liver disease<sup>[102]</sup>.

## **AUD AND HIV INFECTION**

### **Effect of alcohol on the immune system**

The combined effects of alcohol and HIV on the immune system have been investigated in simian models<sup>[103]</sup>. Alcohol and HIV infection show a synergistic impact on gastrointestinal tract integrity, causing initial depletion of intestinal CD4 cells<sup>[104,105]</sup>. Loss of intestinal wall integrity is associated with increased permeability, microbial translocation, and immune activation<sup>[106]</sup>. Immune activation is crucial for HIV disease progression<sup>[107]</sup>, and is reportedly a better predictor of disease progression than HIV viral load<sup>[106,108]</sup>. While alcohol seems to impact the adaptive immune responses to HIV infection in animal models, the results in humans are mixed<sup>[103]</sup>. In a study of HIV-infected patients, blood alcohol levels relative to alcohol intake were higher before antiretroviral treatment compared to after treatment<sup>[109]</sup>.

### **Alcohol and HIV disease progression**

Prior to widespread use of antiretroviral therapy (ART), epidemiological data suggested that alcohol use was not associated with HIV disease progression<sup>[110,111]</sup>. However, following the advent of ART, several authors have reported reduced ART effectiveness among patients with AUD<sup>[19,112]</sup>. In 2003, Samet *et al.*<sup>[113]</sup> investigated a cohort of HIV-infected patients, and reported cross-sectional data suggesting that alcohol consumption negatively impacted HIV disease progression. Alcohol consumption was associated with lower CD4 cell counts and higher HIV viral loads in patients receiving ART. A later longitudinal study of the same cohort demonstrated that heavy alcohol use in patients not receiving ART was

associated with lower CD4 cell counts but not with HIV viral load<sup>[114]</sup>.

Chander *et al.*<sup>[115]</sup> at John Hopkins University reported that heavy alcohol consumption was associated with reduced viral suppression of HIV infection and lower treatment adherence. Wu *et al.*<sup>[116]</sup> investigated 325 subjects receiving ART and found that, after adjusting for adherence, daily drinkers showed a nearly four-fold increase in the odds of detectable HIV viral load. This association was non-significant for regular drinkers. Their results further showed that alcohol use was not associated with CD4 cell count, and that alcohol consumption was not associated with HIV viral load among patients not receiving ART<sup>[116]</sup>. On the other hand, Baum *et al.*<sup>[117]</sup> investigated HIV-infected patients receiving ART, and reported that alcohol use was associated with lower CD4 cell counts, greater risk of showing a CD4 cell count of < 200, and an increased HIV viral load over time.

More recent studies indicate that the benefits of ART seem to outweigh the detrimental effects of alcohol use, reinforcing the importance of initiating ART and ensuring adequate treatment adherence<sup>[118]</sup>. A study in a Swiss HIV cohort revealed no effect of alcohol consumption on either virological failure or CD4 cell count, both among ART-receiving and ART-naïve patients<sup>[119]</sup>. That study also demonstrated that heavy drinkers were more likely to interrupt ART; however, only 2.8% of participants were heavy drinkers<sup>[119]</sup>. A recent French study of HIV/AIDS patients reported that low levels of alcohol consumption (< 10 g/d) were associated with higher CD4 counts compared to in abstainers<sup>[120]</sup>. However, the beneficial effects of such low levels of alcohol consumption may be confounded by other healthier behaviors exhibited by moderate drinkers<sup>[121]</sup>.

Overall, evidence acquired during the first decade of ART use suggested that AUD may impact HIV disease progression; however, more recent studies do not support those findings. These contradictory results may be partly explained by poor adherence to treatment and barriers to proper medical care associated with AUD.

### **Alcohol and comorbidities**

Alcohol use is associated with unprotected sex and syringe sharing, thus elevating the risks of HIV acquisition and transmission<sup>[122-124]</sup>. Moreover, alcohol use is associated with higher prevalence of depressive symptoms<sup>[125]</sup>, which can influence ART initiation<sup>[126]</sup>, treatment adherence<sup>[127]</sup>, treatment discontinuation<sup>[128]</sup>, and disease progression<sup>[129,130]</sup>. Other substance use disorders frequently co-exist in patients who exhibit alcohol abuse<sup>[11]</sup>, which is also associated with poorer treatment adherence, reduced HIV viral suppression, and lower retention in care<sup>[112,131]</sup>.

Heavy alcohol use is related to liver disease among patients with HIV infection<sup>[132,133]</sup>, and is also associated with cardiovascular disease<sup>[134]</sup> and exacerbations of chronic obstructive pulmonary disease<sup>[135]</sup>. A systematic review of 13 studies reported that heavy alcohol use was associated with elevated risk of cardiovascular

disease, with a risk ratio of 1.78 (95%CI: 1.09-2.93)<sup>[134]</sup>.

### **Alcohol and mortality in HIV infection**

Alcohol is commonly regarded as an underappreciated modifiable risk factor in individuals with HIV infection, with or without HCV co-infection<sup>[116]</sup>. A retrospective study from northern California evaluated data from between 1996 and 2005, and found that higher mortality rates were associated with diagnosis of a substance use disorder (alcohol only, drug only, or alcohol and drug)<sup>[136]</sup>. In the HIV-LIVE cohort of HIV-positive patients with alcohol problems, short-term mortality was associated with homelessness and drug use<sup>[137]</sup>, and long-term mortality was associated with HCV infection and high levels of inflammation markers<sup>[79,138]</sup>. A study from the VACS cohort revealed that even non-hazardous levels of alcohol consumption were associated with decreased survival<sup>[139]</sup>. Recent data from the same VACS cohort shows that among HIV-positive participants, alcohol use was associated with greater physiological injury. Moreover, within this cohort, a greater risk of mortality was associated with an Alcohol Use Disorders Identification Test value of  $\geq 4$  drinks/mo (HR = 1.25, 95%CI: 1.09-1.44), and of  $\geq 30$  drinks/mo (HR = 1.30, 95%CI: 1.14-1.50)<sup>[140]</sup>.

### **HIV treatment in patients with AUD**

Alcohol use co-existing with other substance use is associated with lower quality of HIV care<sup>[141]</sup> and poor retention in care<sup>[131]</sup>. A systematic review of 53 studies published between 2010 and 2015 showed that 77% of studies revealed that alcohol use was negatively associated with the HIV treatment cascade, *i.e.*, access to care, ART prescription, and treatment adherence<sup>[142]</sup>. This suggests that unhealthy alcohol use should be targeted to increase the proportion of HIV/AIDS patients who achieve viral suppression.

Even modest alcohol consumption has been associated with poor ART adherence<sup>[139]</sup>. Hendershot *et al.*<sup>[143]</sup> performed a meta-analysis of 40 studies, and showed that patients who drank relatively more were 50%-60% less likely to adhere to ART compared with those who abstained or drank relatively less. Alcohol consumption appears to be dose-dependently related to ART adherence<sup>[115]</sup>, and shows a temporal relationship to missed ART treatments<sup>[144]</sup>.

### **AUD treatment in HIV-infected patients**

Among HIV/AIDS patients who drink alcohol, brief interventions are reportedly efficacious for reducing the frequency of alcohol use and the frequency of unprotected sex<sup>[145,146]</sup>. However, patients abusing alcohol might need more intensive treatment. Some authors report that the addition of motivational interviewing<sup>[147]</sup> and problem solving therapy may be necessary to improve ART adherence<sup>[148]</sup>. An intervention called retention through enhanced personal contact has also been tested to improve retention among HIV-positive patients with alcohol use or mental illness<sup>[149]</sup>.

**Table 3** Non-invasive methods for analyzing liver fibrosis in patients with alcohol use disorder, hepatitis C virus infection and hepatitis C virus - human immunodeficiency virus co-infection

Ref.	Setting	Non-invasive method	Method for detecting alcohol consumption	Finding
Lieber <i>et al</i> <sup>[69]</sup>	VA studies (2) of alcoholic liver disease	APRI <sup>1</sup>	Average alcohol intake	Low sensitivity and specificity of APRI in comparison to liver biopsy, especially in subjects with HCV
Chaudhry <i>et al</i> <sup>[169]</sup>	HIV Hopkins clinical cohort	APRI	Past 6-mo hazardous drinking	No effect of alcohol on APRI values in HCV/HIV co-infection
Blackard <i>et al</i> <sup>[170]</sup>	WIHS cohort	FIB-4 <sup>2</sup>	Recent drinking	No association between alcohol intake and FIB-4 values in HCV/HIV co-infection
Muga <i>et al</i> <sup>[171]</sup>	AUD patients admitted for detoxification	FIB-4	Past 6-mo unhealthy drinking	No association between FIB-4 and alcohol use in HCV/HIV co-infection
Fuster <i>et al</i> <sup>[173]</sup>	HIV-live cohort	FIB-4 and APRI	LDH	No association between LDH and liver fibrosis measured with FIB-4 or APRI
Lim <i>et al</i> <sup>[174]</sup>	VACS cohort	FIB-4	AUDIT-C <sup>3</sup>	Advanced liver fibrosis correlated with alcohol use

<sup>1</sup>APRI: AST to platelet ratio index= {[AST/AST upper limit of normal (IU/L)]/platelet count (10<sup>9</sup>/L)} × 100<sup>[64]</sup>; <sup>2</sup>FIB-4 = age × AST (IU/L)/platelet count (10<sup>9</sup>/L) × ALT (IU/L)<sup>1/2</sup><sup>[63]</sup>; <sup>3</sup>AUDIT-C: Alcohol Use Disorders Identification Test<sup>[79]</sup>. HIV: Human immunodeficiency virus; AUD: Alcohol use disorder; APRI: Aminotransferase/platelet ratio index; HCV: Hepatitis C virus; LDH: Lifetime drinking history; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; VA: United States Department of Veteran Affairs; WIHS: Women's Interagency HIV study; VACS: Veterans Aging Cohort study.

Chander *et al*<sup>[150]</sup> recently performed a cross-sectional survey among HIV care providers, and found that although the majority reported that they usually screen for alcohol use, only 10% used a formal screening tool. Moreover, knowledge of pharmacotherapy for AUD was low, and most care providers referred patients to outside resources for treatment<sup>[150]</sup>.

## AUD AND HCV/HIV CO-INFECTION

A proportion of patients with both AUD and HCV infection also have HIV infection. In fact, HCV/HIV co-infection is clinically relevant among individuals with history of injection drug use<sup>[151]</sup>. HIV infection is associated with faster progression of HCV-related liver fibrosis<sup>[152,153]</sup> as well as earlier occurrence of decompensated liver disease<sup>[154,155]</sup>, liver cancer<sup>[156]</sup>, and liver-related death<sup>[157]</sup>. During the interferon era, co-infection with HIV compromised HCV treatment response<sup>[158,159]</sup>. However, interferon-free regimens have greatly increased the efficacy of HCV antiviral treatment among co-infected patients, both in clinical trials<sup>[160]</sup> and in real-life scenarios<sup>[161,162]</sup>. On the other hand, HCV infection is associated with increased risk of ART-related liver toxicity<sup>[163]</sup>, which is even higher with concurrent alcohol use<sup>[164]</sup>. In cases of HCV/HIV co-infection, alcohol use is also associated with poorer treatment adherence<sup>[165]</sup>, and seems to increase HCV RNA levels<sup>[166,167]</sup>.

Until recently, the impact of alcohol use on HCV-related liver disease in HIV-infected patients had not received much attention in the literature. Older studies suggest that alcohol use is associated with biopsy-proven liver fibrosis in cases of co-infection<sup>[152,168]</sup>. However, studies using non-invasive methods have produced mixed results, highlighting the shortcomings of non-invasive methods-including methods relying on ALT, AST, and platelets-in patients with ALD<sup>[70,69]</sup>. Table 3

summarizes the different studies that have used non-invasive methods to evaluate liver fibrosis in patients with AUD and HCV infection or HCV/HIV co-infection.

A cross-sectional study in an urban HIV/AIDS cohort revealed that heavy alcohol use was associated with advanced liver fibrosis measured using the APRI score<sup>[169]</sup>. However, when the patients were stratified by HCV infection, high APRI score was associated with hazardous alcohol use only among patients without HCV infection<sup>[169]</sup>. Blackard *et al*<sup>[170]</sup> investigated a cohort of women, and demonstrated that alcohol use was not associated with FIB-4 values among HCV/HIV co-infected patients. Within our cohort of AUD patients, FIB-4 was significantly higher among HCV/HIV co-infected patients compared to in HCV mono-infected patients<sup>[171]</sup>. In the HIV-LIVE cohort, lifetime alcohol consumption<sup>[172]</sup> was not associated with the absence of liver fibrosis (FIB-4 < 1.45), and similar results were found for the presence of advanced liver fibrosis (FIB-4 ≥ 3.25) and among patients with HCV infection<sup>[173]</sup>. A study in the VACS cohort-which included a larger number of patients and a different measure of alcohol consumption-reported greater risks of advanced liver fibrosis (measured based on FIB-4) among co-infected patients who exhibited nonhazardous drinking (OR = 14.2, 95%CI: 5.91-34.0) or hazardous/binge drinking (OR = 18.9, 95%CI: 7.98-44.8), or who had alcohol-related diagnoses (OR = 25.2, 95%CI: 10.6-59.7) relative to uninfected individuals who were nonhazardous drinkers<sup>[174]</sup>. The somewhat discordant results among studies may be partly due to differences in the methods used to describe alcohol use and other characteristics of the study population<sup>[169-174]</sup>.

French researchers investigating HCV/HIV co-infected patients recently found that advanced liver fibrosis (measured with transient elastography) was more common among those with an alcohol-related diagnosis (OR = 3.06, 95%CI: 1.42-6.60) compared

to non-hazardous drinkers<sup>[175]</sup>. Elastography may be more reliable than laboratory markers for assessing liver fibrosis in HCV/HIV co-infected patients with AUD. Additionally, the combination of HCV infection and alcohol use is associated with greater mortality within HIV/AIDS cohorts<sup>[79,176]</sup>, highlighting the need to further address alcohol use in co-infection. Although it can be challenging, it is feasible to reduce alcohol use in the setting of HCV/HIV co-infection<sup>[177]</sup>.

## CONCLUSION

To reduce the impact of HCV, HIV and ethanol on liver disease, patients with AUD should be screened for HCV and HIV infection, and interventions should focus on both reducing alcohol consumption and treating viral infections. Moreover, patients with HCV infection or HCV/HIV co-infection should be screened for unhealthy alcohol use to prevent end-stage liver disease. Several treatment interventions are efficacious for reducing alcohol consumption among individuals with HCV infection or HCV/HIV co-infection.

In settings where AUD often coexists with other substance use and viral co-infections, higher levels of co-morbidities are expected. Health care facilities for treatment interventions and multidisciplinary approaches must be widely accessible for managing AUD and associated diseases.

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## Prophylactic liver transplantation for high-risk recurrent hepatocellular carcinoma

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### Abstract

Hepatocellular carcinoma (HCC) is the second most common cause of cancer-related death in the world. Radical treatment of HCC in early stages results in a long disease-free period and improved overall survival. The choice of optimal management strategy for HCC mainly depends on the severity of the underlying liver disease. For patients with decompensated liver cirrhosis and HCC within Milan criteria (MC), liver transplant (LT) is the choice of treatment. However, for patients with good residual liver reserve and HCC within MC, selection of other curative treatments such as liver resection (LR) or radiofrequency ablation may be a reasonable alternative. For patients without cirrhosis, LR can result in an overall survival similar to that provided by LT. Therefore, it is an accepted alternative to LT especially in areas with organ shortage. However, the cumulative 5-year recurrence rate of HCC post LR might be as high as 70%. For initial transplant-eligible (within MC) patients with recurrent HCC post LR, salvage liver transplant (SLT) was first proposed in 2000. However, most patients with recurrent HCC considered for SLT are untransplantable cases due to HCC recurrence beyond MC or comorbidity. Thus, the strategy of opting for SLT results in the loss of the opportunity of LT for these patients. Some authors proposed the concept of "de principe liver transplant" (*i.e.*, prophylactic LT before HCC recurrence) to prevent losing the chance of LT for these potential candidates. Factors associated with the failure of SLT will be dissected and discussed in three parts: Patient, tumor, and underlying liver disease. Regarding patient-related factors, the rate of transplantability depends on patient compliance. Patients without regular follow-up tend to develop HCC recurrence beyond MC at the time of tumor detection. Advancing age is another factor related to severe comorbidities when LT is considered for HCC recurrence, and these elderly candidates become ineligible as time goes by. Regarding tumor-related factors, histopathological features of the resected specimen are used mostly for determining the prognosis of early HCC recurrences. Such

prognostic factors include the presence of microvascular invasion, poor tumor differentiation, the presence of microsatellites, the presence of multiple tumors, and the presence of the gene-expressing signature associated with aggressive HCC. These prognostic factors might be used as a selection tool for SLT or prophylactic LT, while remaining mindful of the fact that most of them are also prognostic factors for post-transplant HCC recurrence. Regarding underlying liver disease-related factors, progression of chronic viral hepatitis and high viral load may contribute to the development of late (*de novo*) HCC recurrence as a consequence of sustained inflammatory reaction. However, correlation between the severity of liver fibrosis and tumor recurrence is still controversial. Some prognostic scoring systems that integrate these three factors have been proposed to predict recurrence patterns after LR for HCC. Theoretically, after excluding patients with high risk of post-transplant HCC recurrence, either by observation of a cancer-free period or by measurement of biological factors (such as alpha fetoprotein), prophylactic LT following curative resection of HCC could be considered for selected patients with high risk of recurrence to provide longer survival.

**Key words:** Liver transplant; Hepatocellular carcinoma; Salvage; Risk factor; Resection; Microvascular invasion; Recurrence; Prophylactic

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**Core tip:** In this minireview, we discuss about the strategy of prophylactic liver transplant after liver resection for patients with a high risk of recurrence. Prognostic risk factors and scoring systems for recurrence are also analyzed.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) is the most common primary liver cancer. It has a high prevalence in Asia and sub-Saharan Africa due to the high incidence of chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections in these regions. It is much more common in men than in women. In men, HCC is the second leading cause of cancer-related death in developing countries and worldwide<sup>[1]</sup>.

It is well established that liver transplant (LT) is the treatment of choice for patients with early HCC and decompensated liver disease<sup>[2]</sup>. The most notable criteria for transplant in HCC cases is the Milan criteria (MC)

described by Mazzaferro *et al*<sup>[3]</sup> in 1996. In selected patients with a single tumor less than 5 cm in diameter, or no more than 3 tumors each 3 cm or less in diameter, LT can offer a > 70% 5-year survival and a < 10% 5-year recurrence rate<sup>[4]</sup>. However, for patients with early HCC and cirrhotic liver with preserved function, the choice between liver resection (LR) and LT has been an issue of debate<sup>[5]</sup>. Donor organ shortage is the major problem with using LT for this group of patients<sup>[6]</sup>. Primary LR can achieve comparable 5-year overall survival rates (> 70%) with proper patient selection and application of advanced surgical techniques over the last decades<sup>[7-10]</sup>. However, the intrahepatic recurrence rate within 5 years of LR in cirrhotic patients is > 70%<sup>[11]</sup>. In the era of organ shortage, Majno *et al*<sup>[12]</sup> first proposed a treatment strategy that involves performing LR as the first-line treatment for patients with single small HCC and preserved liver function and reserving LT for patients with recurrent HCC within MC. This is the so-called "salvage liver transplant (SLT)" strategy. Most patients with HCC recurrence cannot benefit by this strategy in the real-world clinical setting due to recurrent HCC beyond MC at detection or poor general condition unsuitable for LT. We speculate whether early LT before the development of untransplantable recurrence can save their lives and eradicate the cancer. This concept of prophylactic LT for high-risk recurrent HCC before the development of recurrence is also called "de principe LT"<sup>[13]</sup>. Recently, some authors suggested the use of the histopathological features of the specimen of the resected tumor as the selection tool for LT to improve the outcome of cases with high recurrence rate after LR<sup>[13-16]</sup>. However, most of these histopathological features are also prognostic factors of post-transplant HCC recurrence. This review will discuss the treatment strategy of LT before HCC recurrence (de principe) and at recurrence (salvage) for initial transplant-eligible patients developing recurrent tumors after LR. Poor prognostic clinicopathological factors associated with early and late HCC recurrence are also reviewed in three parts, "patient", "tumor", and "underlying liver disease". At last, we introduce some scoring systems for predicting HCC recurrence after LR.

## LT AT HCC RECURRENCE: SALVAGE LT

LR as the first-line treatment for primary small HCC in compensated cirrhotic liver is widely adopted with an acceptable survival rate but a high recurrence rate. No treatment guidelines exist for recurrent HCC after LR. Salvage curative treatment for recurrent HCC following primary LR includes SLT, repeat LR, and radiofrequency ablation (RFA). In our group, Lee *et al*<sup>[17]</sup> first reported in 1995 that the cumulative 5-year survival rates in patients undergoing repeated hepatic resection after the first operation was 65.1%, and according to Ho *et al*<sup>[18]</sup>, the latest 5-year survival rates after recurrence in patients receiving repeat hepatectomy was 72%,

which is similar to that of patients who have undergone primary resection and have no recurrence. Chan *et al.*<sup>[19]</sup> report comparable survival rates and tumor-free survival rates in SLT and repeat LR, but RFA yields poorer outcome than SLT and repeat LR (5-year survival rates in SLT, repeat LR, and RFA: 50.0%, 48.0%, 11.4%, respectively; 5-year tumor-free survival rates in SLT, repeat LR, and RFA: 57.9%, 49.3%, 10.6%, respectively). RFA is associated with poor survival rates but can be considered for patients not suitable for LR. In another series by Yamashita *et al.*<sup>[20]</sup> which compared the outcomes between repeat LR and SLT, the perioperative outcomes including the operation time, intraoperative blood loss, the length of hospital stay, and post-operative morbidity, were all significant worse in the SLT group. No significant difference was observed in the overall survival between these two groups, but patients who underwent SLT had better disease-free survival<sup>[20,21]</sup>. The difference between the results of these two salvage treatments is similar to the difference between primary LT and initial LR for early HCC in compensated liver. However, in areas without sufficient donors, repeat LR is the only treatment for patients with recurrent HCC and enough remnant liver that can provide an overall survival comparable to SLT. Mise *et al.*<sup>[22]</sup> report the result of third or more repeat hepatectomies for recurrent HCC. The 5- and 10-year overall survival rates from the initial hepatectomy are 91.4% and 75.5% respectively, and the 5-year disease-free survival rate after the second hepatectomy is 17.9%.

Comparison of primary LT and SLT for HCC within MC in recent studies revealed similar perioperative course, morbidity, overall survival, and disease-free survival<sup>[16,23-28]</sup>, while a previous study showed the association of LT after resection and higher operative mortality, an increase of recurrence, and poorer outcomes<sup>[29]</sup>. In the systemic review by Chan *et al.*<sup>[30]</sup> the median 5-year overall and disease-free survival rates in SLT are 62% and 67%, respectively. In the era of organ shortage, LR should be considered as the primary curative treatment for resectable tumors in compensated livers, and SLT is a safe and effective strategy for initial transplant-eligible patients when recurrent HCC or hepatic function deterioration occur<sup>[12]</sup>.

The SLT strategy is widely acceptable for patients with previous transplant-eligible HCC. However, some authors also advocate the strategy of performing LR as one of the locoregional therapies for tumor downstaging in patients with initial HCC beyond LT criteria and performing LT after HCC recurrence<sup>[31]</sup>. The results of this downstaging strategy showed better survival outcomes as compared with patients with HCC recurrence who undergo LR without SLT. However, for post-LR recurrent HCC beyond MC, the results of SLT are not beneficial and not recommended in a recent report<sup>[22]</sup>. Prospective studies are needed to examine the long-term outcomes of extending the criteria of LT for intermediate-advanced HCC either before or after tumor recurrence.

## LT BEFORE RECURRENCE: CONCEPT OF PROPHYLACTIC LT

As previous study stated, SLT has been proven effective for patients with recurrent HCC within the criteria of the following: Tumor recurrence within MC, patient adherence to a regular follow-up with imaging to detect early recurrence, and good general patient condition for LT. However, the intention-to-treat analysis by Fuks *et al.*<sup>[32]</sup> showed that nearly half of the patients with recurrent HCC following LR did not undergo LT, including one-third due to recurrence beyond MC. Other studies also report that 20% to 80% of the patients considered for SLT are not transplantable due to recurrence beyond transplant criteria or advanced age with significant comorbidity<sup>[8,15,29,33,34]</sup>. This means that with the strategy of SLT, we lose the chance of LT in originally transplantable patient. Sala *et al.*<sup>[13]</sup> first reported four cases of prophylactic LT, performed based on the expectation of early recurrence according to the gross and microscopic features of the resected specimen, including microvascular invasion and additional nodules. Patients with high risk of recurrence as identified by histopathological findings were enlisted for LT. Scatton *et al.*<sup>[14]</sup> predicted the risk of HCC recurrence after LR on the basis of the histological features of the resected specimen (including Edmondson score, vascular invasion, nuclear grade, and architectural growth pattern), which are used as the selection tool for LT. In this series, six patients were enlisted and underwent prophylactic LT without evidence of residual disease. However, the population of this study was heterogeneous, with three of the six patients in this study having HCC beyond MC at resection, and the other three patients having resected HCC within MC. These six patients are all alive without recurrence with mean follow-up of 55 mo.

Tribillon *et al.*<sup>[34]</sup> report the largest series of prophylactic LT in intention-to-treat analysis of 63 patients with intermediate or bad pathological factors (microvascular invasion and/or moderate/poor differentiation) in the resected specimen being enlisted for LT prior to recurrence (de principe group). The overall survival of this group was compared to 48 patients with favorable pathological features being enlisted for LT at the time of HCC recurrence (salvage group). The 5-year survival rate since primary LR was significantly better in the de principe group as compared with the salvage group (84.6% vs 74.8%), and the 5-year disease survival rate was also better in the de principe group (79.3% vs 72.3%).

This active attitude of enlisting patients for LT prior to recurrence can treat both potential recurrent HCC and underlying liver disease. However, literature about this strategy is scarce. The most important viewpoint discussed in the literature about this prophylactic strategy is preventing original transplant-eligible patients from developing beyond MC at recurrence and provide longer survival. However, if more stringent follow-ups and increased accuracy of imaging studies lead to

**Table 1 Comparison between prophylactic liver transplant and wait-and-see before hepatocellular carcinoma recurrence**

The strategy	Prophylactic LT	Wait-and-see
Immunosuppressant exposure	Life-long	Nil
Surgical morbidity and mortality	Present	Nil
Long-term HCC recurrence	Lower <sup>[32]</sup>	Higher <sup>[11]</sup>
Survival benefit (5-year survival rate)	84.6% <sup>[32]</sup>	Around 70% <sup>[7-10]</sup>
Further management after recurrence	Hepatectomy, RFA, TACE, Sorafenib, Yttrium-90	SLT, repeat hepatectomy, RFA, TACE, Sorafenib, Yttrium-90

LT: Liver transplant; RFA: Radiofrequency ablation; TACE: Transcatheter arterial chemoembolization; HCC: Hepatocellular carcinoma.

**Table 2 Prognostic factors of early hepatocellular carcinoma recurrence after liver resection and after liver transplantation**

Risk factor of HCC recurrence	After liver resection	After liver transplantation
Serological		
AFP	> 400 ng/mL <sup>[49]</sup>	> 1000 ng/mL <sup>[34,35]</sup>
Tumor gross		
Tumor size	> 3 cm <sup>[30]</sup> or > 5 cm <sup>[37,41,65]</sup>	> 6 cm <sup>[35]</sup>
Tumor number	> 3 <sup>[65]</sup>	≥ 4 <sup>[35]</sup>
Satellite nodules	Yes <sup>[30,63,66]</sup>	Yes <sup>[33]</sup>
Tumor microscopic		
Tumor differentiation	Intermediate, or poor differentiation, or undifferentiation <sup>[30,49,65]</sup>	Poor differentiation, or undifferentiation <sup>[33]</sup>
Microvascular invasion	Yes <sup>[30,37,41,49,64-66]</sup>	Yes <sup>[33,34]</sup>
Liver parenchyma		
Severity of cirrhosis	Controversial <sup>[67-69]</sup>	No
Milan criteria	Yes <sup>[68]</sup> (predict recurrence within/beyond MC)	Yes <sup>[3]</sup>

HCC: Hepatocellular carcinoma; AFP: Alpha-fetoprotein; MC: Milan criteria.

early detection of recurrent tumor for these patients, does the result still justify this novel strategy? Salvage treatment after detection of recurrent HCC includes LT, repeat hepatectomy, RFA, transcatheter arterial chemoembolization, sorafenib, and trans-arterial radio-rembolization (Yttrium-90). The choice of these salvage treatment depends on the extent of underlying liver disease, the aggressiveness of tumor at recurrence, and the general condition of the patient. LT has been proven to be correlated with better overall survival and disease-free survival rates with careful patient selection as a curative method, as compared with other salvage treatments previously stated<sup>[17-19]</sup>. However, for cases without evidence of recurrence, it is unclear if we should choose prophylactic LT for patients with a high risk of recurrence or just close follow-ups and salvage treatment at recurrence. The accompanying morbidity and mortality with prophylactic LT and the limited number of organs also hinder this aggressive strategy. The comparison of the benefits and risks between prophylactic LT and the wait-and-see strategy followed by salvage treatment is listed in Table 1.

On the other hand, is a higher probability of recurrence after initial hepatectomy equivalent to a shorter disease-free survival after salvage or prophylactic LT? If HCC recurs easily after salvage or prophylactic LT, this strategy became meaningless. Most prognostic factors associated with recurrence after LR are also relevant to post-transplant recurrence, including microvascular invasion of HCC, larger tumor size, higher tumor number, poorer differentiation of the tumor, and higher level of alpha-fetoprotein (AFP)<sup>[35-37]</sup> (Table 2). It is difficult to

distinguish patients with higher recurrence after hepatectomy from those with possible post-transplant HCC recurrence. A period of observation should be considered after primary LR to identify the aggressiveness of occult HCC in the absence of specific predicting factors. Further investigation is needed to stratify patients for better application of treatment after hepatectomy.

## CLINICOPATHOLOGICAL FACTORS ASSOCIATED WITH HIGH-RISK RECURRENCE

The most important issue in adopting prophylactic LT is the identification of prognostic factors associated with high-risk recurrence. Tumor dissemination from primary tumor before resection and new lesion development in underlying oncogenic cirrhotic parenchyma are two major pathways leading to recurrence<sup>[38-42]</sup>. The former is associated with early recurrence within 2 years after primary resection, while the latter is more likely associated with late recurrence<sup>[42-45]</sup>. We summarize the recent data in the literature on the clinicopathological factors linked with HCC recurrence.

## PATIENT-RELATED FACTORS: DEMOGRAPHIC AND BIOCHEMICAL FACTORS

The age factor associated with recurrence after resection remains controversial. Older age at resection may be

suggestive of long-standing chronic liver disease and higher susceptibility to HCC recurrence over time. Older age (65 years or more) is an independent risk factor for tumor recurrence, as shown in the recent major series by Fan *et al.*<sup>[46]</sup> and Pompili *et al.*<sup>[47]</sup>. However, in the series of HBV-related HCC by Mathews *et al.*<sup>[48]</sup> younger age (40 years or less) was closely associated with more aggressive disease and shorter disease-free survival after resection. The other major series by Hung *et al.*<sup>[49]</sup> does not show old age (60 years or more) to be a poor independent factor for tumor recurrence.

Serum AFP level has been conventionally used as a simple and effective tool for routine surveillance of HCC and for monitoring recurrence following treatment<sup>[50]</sup>. Elevated serum AFP level at the time of resection has been frequently reported to predict the risk of post-resection recurrence of HCC<sup>[51-56]</sup>. Many studies have proposed the relationship between the pretreatment AFP level and tumor-free survival using different cut-off values of AFP level (for example, 20, 100, 400 or 1000 ng/mL)<sup>[44,49,57,58]</sup>. Higher pretreatment serum AFP level is associated with shorter disease-free period. Ho *et al.*<sup>[51]</sup> proposed the value of 400 ng/mL as the cut-off AFP level to predict untransplantable recurrence after primary curative resection of HCC. However, in another study by Shim *et al.*<sup>[59]</sup> the result of a test based on propensity score, included 525 patients who underwent HCC resection and showed no correlation between preoperative serum AFP level and the risk of recurrence. Serum AFP level can also be abnormally high in chronic hepatitis C and advanced cirrhotic liver without HCC<sup>[60]</sup>. It is controversial to use serum AFP level as the predictor of HCC recurrence. Instead of predicting the risk of recurrence, the higher level of serum AFP should be considered as the consequence of aggressive tumor features such as microvascular invasion and poorer tumor differentiation, which indicate worse prognosis<sup>[61]</sup>. Serum AFP level > 1000 ng/mL is also reported to be associated with higher post-transplant recurrence due to the correlation with more aggressive tumor biology<sup>[35-37]</sup>.

## TUMOR-RELATED FACTORS: HISTOPATHOLOGICAL FACTORS

It is well known that early recurrence after HCC resection is related to tumor dissemination prior to operation<sup>[42]</sup>. The histopathological profile obtained from the resected specimen has been used to predict the risk of tumor dissemination and as an objective selection tool for LT in the last decade<sup>[13,14,32,34]</sup>. Among these factors, microvascular invasion of the tumor is the most critical factor in disease dissemination. As seen in most cancers, angiogenesis, or new vessel formation, is essential for HCC growth<sup>[62]</sup>. In advanced stages of tumor progression, HCC cells develop the ability to invade adjacent blood vessels and potentially begin to metastasize. The presence of microvascular invasion is the hallmark of aggressive tumor behavior

and associated with high recurrence rate after curative resection<sup>[63]</sup>. Sumie *et al.*<sup>[64]</sup> report 3-year recurrence-free survival rates in HCC with and without microvascular invasion to be 27.7% and 67.5%, respectively. Other poor histopathological features, like the presence of satellite nodules and poor tumor differentiation, are also recognized, along with microvascular invasion, to predict early recurrence<sup>[32,39,43,65-68]</sup>. Most of these poor histopathological factors associated with early recurrence after LR are also predictors of recurrence after LT, including larger tumor size, larger tumor number, satellite nodules, poorer tumor differentiation, and microvascular invasion (Table 2). These features are linked to the aggressiveness of the tumor biology and predict the recurrence both after LR and LT. Patients with a tendency of post-LR recurrence may also develop a risk of post-LT recurrence. While considering prophylactic LT for patients with these poor histopathological features, cut-off criteria should be made to exclude those with more aggressive HCC and also potentially easy recurrence after LT.

## UNDERLYING LIVER DISEASE-RELATED FACTORS: VIROLOGICAL FACTORS

The preneoplastic status of underlying liver disease is considered to relate with elevated carcinogenesis and de novo tumor development in late phase recurrence (2 years after resection)<sup>[42]</sup>. The correlation between stage of liver fibrosis and disease-free survival is controversial. Grazi *et al.*<sup>[69]</sup> and Taura *et al.*<sup>[70]</sup> showed that HCC without cirrhosis has better disease-free survival compared with HCC with cirrhosis after curative resection in Asia, while Beard *et al.*<sup>[71]</sup> showed the reverse results for western countries. Instead of the severity of liver cirrhosis, the sustained necroinflammatory reaction resulting from higher hepatitis activity may play a more important role in the development of secondary primary HCC two years after resection. Initial high HBV viral loads > 2000 IU/mL<sup>[72]</sup> or 10<sup>6</sup> copies/mL<sup>[45]</sup> at the time of HBV-related HCC resection or one month post resection HBV DNA > 20000 IU/mL<sup>[49]</sup> are all proven to be independent risk factors for tumor recurrence. Ongoing HBV replication can induce active hepatitis and subsequent inflammation in oncogenic liver parenchyma leading to *de novo* recurrent HCC. Regarding Hepatitis C, patients with HCV infection tend to have higher hepatitis activity, which is related to elevated carcinogenesis, than patients with HBV infection<sup>[42]</sup>. However, the difference in recurrence-free survival is not significant between patients with HBV infection or those with HCV infection<sup>[73,74]</sup>. A recent national study of 11950 patients in Japan by Utsunomiya *et al.*<sup>[75]</sup> showed that patients without viral hepatitis have a significant lower risk of HCC recurrence than those with HBV or HCV infection.

## SCORING SYSTEM

Some authors propose the scoring system that integrated

**Table 3** Scoring systems for predicting hepatocellular carcinoma recurrence

Ref.	Basis of scoring system	Prognostic factors	Discriminated scores
Pan <i>et al</i> <sup>[76]</sup>	Glasgow prognostic score	Preoperative CRP > 10 mg/L (1 point) Albumin < 3.5 g/L (1 point)	0, 1, 2
Fuks <i>et al</i> <sup>[32]</sup>	Histological features	Microscopic vascular invasion Presence of satellite nodules Tumor size > 3 cm Poor differentiated tumor Cirrhosis	< 3 factors ≥ 3 factors
Roayaie <i>et al</i> <sup>[66]</sup>	Degree of vascular invasion	Invasion of a vessel with a muscular wall (1 point) Invasion of a vessel ≥ 1 cm from the tumor capsule (1 point)	0, 1, 2
Lee <i>et al</i> <sup>[68]</sup>	Clinical risk score	Initial disease beyond Milan criteria Microsatellites or multiple tumors Lymphovascular invasion (1 point for each factor)	0, 1, 2, 3

Higher scores indicate higher recurrence rate. CRP: C-reactive protein.

clinical, biochemical, and histopathological factors to classify the risk of HCC recurrence after resection<sup>[32,66,68,76]</sup> (Table 3). Most scoring systems consist of the extent of tumor invasiveness, while the Glasgow prognostic score originally used in the prediction of outcomes among non-small-cell lung cancer patients<sup>[77]</sup> is composed of the serum levels of C-reactive protein (CRP) and albumin. The higher serum level of CRP and lower serum level of albumin present in the systemic inflammatory response is associated with a more active viral hepatitis in the remnant liver parenchyma<sup>[76]</sup>. The higher scores in each system indicate shorter disease-free period and poorer outcome. The clinical risk score system by Lee *et al*<sup>[68]</sup> uses pathological factors to predict the likelihood of recurrence after LR, and it can be used to identify patients who may lose the chance of SLT at recurrence. Whether this strategy system applies to prophylactic liver transplantation needs further validation.

## CONCLUSION

Prophylactic LT is a novel concept for patients with high-risk recurrent HCC after primary resection before recurrence. Microvascular invasion, larger tumor size, larger tumor number, and poor tumor differentiation are all predictors for recurrence after LR and LT, while serum AFP level > 1000 ng/mL is the unique feature for predicting recurrence after LT. The length of observation after prophylactic LT should be established to examine the occult aggressiveness of the HCC resulting in recurrence after LT. It is safe and effective when patients who fulfilled MC at the time of resection are carefully selected. Large prospective studies are required to clarify the long-term results of this strategy.

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## Retrospective Cohort Study

# Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment

Lydia Shuk Yee Tang, Jack Masur, Zayani Sims, Amy Nelson, Anu Osinusi, Anita Kohli, Sarah Kattakuzhy, Michael Polis, Shyam Kottlil

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**Institutional review board statement:** Each study was approved by the institutional review board of NIAID and was conducted in compliance with the Good Clinical Practice guidelines, the Declaration of Helsinki and regulatory requirements. An independent safety monitor participated in the interim safety and efficacy analysis for SPARE. The Regulatory Compliance and Human Participants Protection Branch of NIAID served as the study sponsor and medical monitor.

**Informed consent statement:** All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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## Abstract

### AIM

To study impact of baseline mental health disease on hepatitis C virus (HCV) treatment; and Beck's Depression Inventory (BDI) changes with sofosbuvir- and

interferon-based therapy.

## METHODS

This is a retrospective cohort study of participants from 5 studies enrolled from single center trials conducted at the Clinical Research Center of the National Institutes of Health, Bethesda, MD, United States. All participants were adults with chronic HCV genotype 1 infection and naïve to HCV therapy. Two of the studies included HCV mono-infected participants only (SPARE, SYNERGY-A), and 3 included human immunodeficiency virus (HIV)/HCV co-infected participants only (ERADICATE, PFINPK, and ALBIN). Patients were treated for HCV with 3 different regimens: Sofosbuvir and ribavirin in the SPARE trial, ledipasvir and sofosbuvir in SYNERGY-A and ERADICATE trials, and pegylated interferon (IFN) and ribavirin for 48 wk in the PIFNPK and ALBIN trials. Participants with baseline mental health disease (MHD) were identified (defined as either a DSM IV diagnosis of major depression, bipolar disorder, schizophrenia, generalized anxiety, and post-traumatic stress disorder or requiring anti-depressants, antipsychotics, mood stabilizers or psychotropics prescribed by a psychiatrist). For our first aim, we compared sustained virologic response (SVR) and adherence (pill counts, study visits, and in 25 patients, blood levels of the sofosbuvir metabolite, GS-331007) within each study. For our second aim, only patients with HIV coinfection were evaluated. BDI scores were obtained pre-treatment, during treatment, and post-treatment among participants treated with sofosbuvir-based therapy, and compared to scores from participants treated with interferon-based therapy. Statistical differences for both aims were analyzed by Fisher's Exact, and *t*-test with significance defined as a *P* value less than 0.05.

## RESULTS

Baseline characteristics did not differ significantly between all participants with and without MHD groups treated with sofosbuvir-based therapy. Among patients treated with sofosbuvir-based therapy, the percentage of patients with MHD who achieved SVR was the same as those without (SPARE: 60.9% of those MHD compared to 67.6% in those without, *P* = 0.78; SYNERGY-A: 100% of both groups; ERADICATE: 100% compared to 97.1%). There was no statistically significant difference in pill counts, adherence to study visits between groups, nor mean serum concentrations of GS-331007 for each group at week 2 of treatment (*P* = 0.72). Among patients with HIV co-infection, pre-treatment BDI scores were similar among patients treated with sofosbuvir, and those treated with interferon (sofosbuvir-based 5.24, IFN-based 6.96; *P* = 0.14); however, a dichotomous effect on was observed during treatment. Among participants treated with directly acting antiviral (DAA)-based therapy, mean BDI scores decreased from 5.24 (pre-treatment) to 3.28 during treatment (1.96 decrease, *P* = 0.0034) and 2.82 post-treatment. The decrease in mean score from pre- to post-treatment was statistically significant (-2.42, *P* = 0.0012). Among participants treated with IFN-based therapy, mean BDI

score increased from 6.96 at pre-treatment to 9.19 during treatment (an increase of 2.46 points, *P* = 0.1), and then decreased back to baseline post-treatment (mean BDI score 6.3, *P* = 0.54). Overall change in mean BDI scores from pre-treatment to during treatment among participants treated with DAA-based and IFN-therapy was statistically significant (-1.96 and +2.23, respectively; *P* = 0.0032). This change remained statistically significant when analysis was restricted to participants who achieved SVR (-2.0 and +4.36, respectively; *P* = 0.0004).

## CONCLUSION

Sofosbuvir-based therapy is safe and well tolerated in patients with MHD. A decline in BDI associated with sofosbuvir-based HCV treatment suggests additional MHD benefits, although the duration of these effects is unknown.

**Key words:** Sofosbuvir; Direct acting antivirals; Directly acting antiviral; Hepatitis C; Mental health disease; Depression; Interferon; Beck's Depression Inventory

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**Core tip:** The prevalence of mental health disease (MHD) among patients with chronic hepatitis C virus (HCV) can be high. However, patients with MHD may be marginalized with respect to HCV therapy and MHD is one of the most frequently cited reason for exclusion from HCV therapy. HCV therapy has evolved from interferon-based to directly acting antiviral (DAA)-based therapy with excellent tolerability and efficacy. Our study found that baseline MHD did not impact efficacy nor treatment adherence to sofosbuvir-based therapy. Furthermore, we found that Beck's Depression Inventory scores improved with sofosbuvir-based therapy, suggesting that HCV treatment with the newer DAA therapies may have additional mental health benefits.

Tang LSY, Masur J, Sims Z, Nelson A, Osinusi A, Kohli A, Kattakuzhy S, Polis M, Kottitil S. Safe and effective sofosbuvir-based therapy in patients with mental health disease on hepatitis C virus treatment. *World J Hepatol* 2016; 8(31): 1318-1326 Available from: URL: <http://www.wjgnet.com/1948-5182/full/v8/i31/1318.htm> DOI: <http://dx.doi.org/10.4254/wjh.v8.i31.1318>

## INTRODUCTION

An estimated 185 million people worldwide are currently infected with chronic hepatitis C virus (HCV), and approximately 3 to 4 million new infections occur each year<sup>[1]</sup>. Chronic infection with HCV is a leading cause of progressive liver disease, end-stage liver disease, hepatocellular cancer, and remains the leading indication for liver transplantation in the United States<sup>[2-4]</sup>.

A complex interplay exists between mental health

disorders (MHD) and HCV infection<sup>[5-9]</sup>. In some cohorts, 30%-44% of all patients with HCV have an active psychiatric-most frequently depression-disorder<sup>[7,10-14]</sup>. MHD is one of the most frequently cited reason for exclusion from HCV therapy, contributing to 44% of exclusions in one study<sup>[13]</sup>. Exacerbation of psychiatric complications, adherence, concurrent substance abuse, and concern for reinfection are just some of the barriers to treatment<sup>[5]</sup>. These concerns are primarily related to interferon-based therapies, which require long treatment durations of 24 to 48 wk, high pill burdens, and multiple associated dose-limiting neuropsychiatric side effects<sup>[8,14-16]</sup>. Recent reports, however, suggest that patients with MHD can successfully achieve sustained virologic response (SVR, considered cure) rates with interferon-based regimens comparable to those without MHD<sup>[8,14,17]</sup>.

Treatment has shifted to combination all-oral, interferon-free directly acting antiviral (DAA) therapy characterized by short treatment durations of 8-24 wk<sup>[18-22]</sup>, low pill burdens, improved tolerability, and achieving SVR rates of over 90% for both treatment naïve and interferon treatment experienced<sup>[20-24]</sup>. In this study, we present data from five National Institute of Allergy and Infectious Diseases (NIAID) trials - SPARE<sup>[19]</sup> (using sofosbuvir and ribavirin), SYNERGY-A<sup>[18]</sup>, and ERADICATE<sup>[25]</sup> (both using ledipasvir and sofosbuvir), and PIFNPK<sup>[26]</sup> and ALBIN<sup>[27]</sup> [studies of interferon (IFN)-ribavirin-based therapy among patients with human immunodeficiency virus (HIV)/HCV co-infection]. This study has two aims. Firstly, we address the impact of baseline MHD on SVR and adherence to sofosbuvir-based, interferon-free therapy. Secondly, we characterize the change in Beck's Depression Inventory (BDI) scores among patients with HIV/HCV co-infection treated with sofosbuvir-based therapy and with interferon-based therapy. For our first aim we present data from three NIAID trials - SPARE<sup>[19]</sup> (using sofosbuvir and ribavirin), SYNERGY-A<sup>[18]</sup>, and ERADICATE<sup>[25]</sup> (both using ledipasvir and sofosbuvir). For our second aim, BDI scores were obtained from patients enrolled in ERADICATE, PIFNPK and ALBIN.

## MATERIALS AND METHODS

### Patients

Patients for all studies were enrolled from single center trials conducted at the Clinical Research Center of the National Institutes of Health, Bethesda, MD, United States. Adult patients with chronic HCV genotype 1 (GT-1) infection naïve to HCV therapy were included. Written or oral informed consent approved by the NIAID Institutional Review Board was obtained from all patients. Full eligibility criteria for all 5 studies are as previously published<sup>[18,19,25-28]</sup>.

### Baseline MHD and impact on SVR and adherence

SPARE was a 2-part, randomized controlled trial from October 2011 through April 2012<sup>[19]</sup>. Patients with early

to moderate liver fibrosis were treated for 24 wk with 400 mg/d of sofosbuvir and weight-based ribavirin, 400 mg in the morning, 600 mg in the evening if < 75 kg or 600 mg twice a day if > 75 kg). A second cohort of patients with all stages of fibrosis (including compensated cirrhosis) was randomized to receive 400 mg/d of sofosbuvir in combination with either weight-based ribavirin or low-dose (600 mg/d) ribavirin for 24 wk<sup>[19]</sup>.

SYNERGY-A was a phase 2a cohort study<sup>[18]</sup>. From January 2013 to December 2013, twenty GT-1 HCV-infected patients were treated for 12 wk with ledipasvir 90 mg and sofosbuvir 400 mg administered as a single combination pill (ledipasvir-sofosbuvir) taken once daily. Neither patient nor investigators were blinded<sup>[18]</sup>.

ERADICATE was an open-label phase 2b trial of ledipasvir-sofosbuvir once daily to non-cirrhotic GT-1 HCV-infected patients with stable HIV-disease<sup>[25]</sup>. From June 2013 to February 2014, fifty HCV GT-1 patients were treated for 12 wk with ledipasvir and sofosbuvir.

### Identification of baseline mental health disorders

In all three clinical trials of sofosbuvir-based therapy, patients with MHD were included. We retrospectively identified patients with baseline MHD defined as either: (1) a DSM IV diagnosis of major depression, bipolar disorder, schizophrenia, generalized anxiety, and post-traumatic stress disorder; or (2) requiring anti-depressants, anti-psychotics, mood stabilizers or psychotropics prescribed by a psychiatrist.

### Efficacy assessment

SVR, defined as undetectable HCV RNA 12 wk post completion of treatment, was the primary outcome. Plasma HCV RNA levels were measured using the real time HCV assay (Abbott), with a lower limit of quantification (LLOQ) of 12 IU/mL, and COBAS TaqMan HCV RNA assay version 2.0 (Roche), with an LLOQ of 43 IU/mL.

### Adherence assessment

For all 3 studies, we performed pill counts at set time points: Sofosbuvir and ribavirin counts in SPARE; ledipasvir-sofosbuvir counts in SYNERGY-A and ERADICATE. Sofosbuvir adherence was documented during 11 time points based on participant recall and pill counts. Missed doses were recorded only through the time of treatment discontinuation in patients who stopped treatment early. We compared the percentage of patients who completed treatment with 3 or less missed pills to those who missed more than 3. For SYNERGY-A and ERADICATE, the average number of sofosbuvir-ledipasvir pills taken by patients in each group was also calculated.

In SPARE, attendance at study visits for all participants was monitored. In addition, pharmacokinetics and pharmacodynamics of sofosbuvir and its metabolite GS-331007 were obtained and calculated on 25 participants. Levels in serum were measured at 0, 1, 2, 4, 8, 12, 24, 36 h and at 14 d after administration of sofosbuvir and ribavirin using a high-performance liquid

**Table 1** Baseline demographics of participants with mental health disease treated with ledipasvir-sofosbuvir *n* (%)

	SPARE ( <i>n</i> = 23)	SYNERGY A ( <i>n</i> = 7)	ERADICATE ( <i>n</i> = 15)	<i>P</i> value
Demographic				
Age, mean ± SD	54 ± 6	52 ± 10	56 ± 8	0.44
Male gender	14 (61)	5 (71)	9 (60)	0.86
Race or ethnicity				0.68
White	4 (17)	2 (29)	2 (13)	-
Black	19 (83)	5 (71)	13 (87)	-
Hispanic	0	0	0	-
HCV genotype 1 subtype				0.46
1A	18 (78)	4 (57)	12 (80)	-
1B	5 (22)	3 (43)	3 (20)	-
HIV +	0 (0)	0 (0)	15 (100)	< 0.0001
Mental health disorder				
Depression	14 (61)	4 (57)	8 (53)	0.89
Anxiety	4 (17)	3 (43)	1 (7)	0.12
Bipolar disorder	4 (17)	3 (43)	5 (33)	0.32
Post-traumatic stress disorder	2 (7)	1 (14)	3 (20)	0.60
Schizophrenia	0	1 (14)	0	-

HCV: Hepatitis C virus; HIV: Human immunodeficiency virus.

chromatography mass spectrometry bioanalytical technique (QPS LLC) as previously described<sup>[19]</sup>.

### Change in BDI among patients with HIV/HCV coinfection

PIFNPK and ALBIN were open label, non-randomized studies designed to look at the safety, toxicity, pharmacokinetics, and efficacy of interferon in combination with ribavirin. In the PIFNPK study, peginterferon alfa-2a 180 µg twice weekly (Pegasys; Roche Laboratories, Palo Alto, CA), was evaluated. In the ALBIN study, Alb-interferon (albumin/interferon alfa 2b fusion protein 900 µg subcutaneous injection every two weeks, Peg-Intron; Schering-Plough) was evaluated. Eligibility criteria as previously published<sup>[26-28]</sup>.

BDI scores were collected prior to treatment (baseline), during treatment, and one to eight weeks post-end of treatment on participants with HIV/HCV co-infection from ERADICATE, PIFNPK, and ALBIN. BDI scores for all participants, and those who achieved SVR were evaluated.

### Statistical analysis

Statistical differences in mean and observed frequencies for both aims were analyzed by Fisher's Exact, and *t*-test with significance defined as a *P* value less than 0.05. Changes in observed frequencies in SVR and adherence between participants with MHD and those without for aim 1 were analyzed by Fisher's Exact test within each study. Analyses were performed using PRISM 6.0 (GraphPad).

## RESULTS

### SVR and adherence among patients with MHD treated with sofosbuvir-based therapy

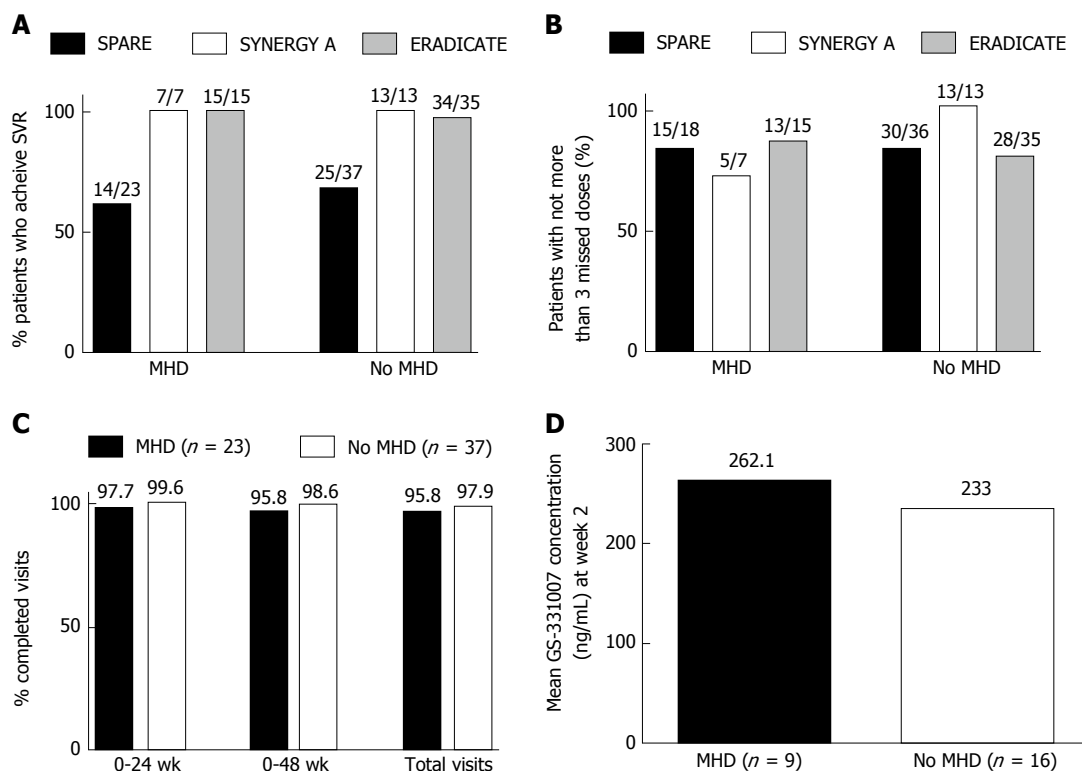
**Baseline demographics:** In all 3 studies, differences in baseline characteristics were not statistically significant between treatment groups (Table 1). The average age

was 50-60 years, and participants were predominantly African American males with GT-1a genotype.

**Mental health disease:** Thirty-eight percent of participants in SPARE, 35% in SYNERGY-A, and 30% in ERADICATE were classified as having baseline MHD. The prevalence of disorders for each study is shown in Table 1. Depression was the most common disorder and many participants had more than one diagnosis.

**Treatment outcome:** In all 3 studies the percentage of patients with MHD who achieved SVR was not statistically different from those without MHD (Figure 1A). In SPARE, 60.9% of those with MHD achieved SVR compared to 67.6% in those without (*P* = 0.78). In SYNERGY-A, 100% of both groups achieved SVR and in ERADICATE 100% of those with and 97.1% of those without MHD achieved SVR.

**Patient adherence:** (1) pill counts; in SYNERGY-A those with MHD and those without took, on average, 96.9% and 98.9% of their pills, respectively (*P* = 0.5). Both groups in ERADICATE took, on average, 97.8% of their pills. There was no statistically significant difference between groups with respect to the numbers that completed treatment with no more than 3 missed pills (Figure 1B): In SPARE, 83% in both groups completed treatment with no more than 3 missed pills. In SYNERGY-A, 5 of the 7 patients (71%) with MHD missed no more than 3 pills compared to 13 out of 13 (100%) among those without MHD (*P* = 0.11). In ERADICATE 13 out of 15 (87%) of those with MHD compared to 28 out of 35 (80%) of those without completed treatment with no more than 3 missed pills (*P* = 0.7); (2) adherence to study visit-SPARE; there was no difference in the proportion of patients with MHD and those without who completed the total required visits (95.8% vs 97.9%,



**Figure 1 Sustained virologic response and measures of adherence among participants with and without mental health disease.** A: Sustained virologic response (SVR) achieved (ERADICATE, SYNERGY-A, SPARE). The comparisons of achieved SVR between groups within each study showed no significant differences for those with mental health disease (MHD) from those without MHD; B: Patients with not more than 3 missed doses (ERADICATE, SYNERGY-A, SPARE). The comparisons of adherence tracked by number of patients who had 3 or fewer total missed doses by pill count showed no significant differences for those with MHD from those without MHD in each study; C: Visit adherence (SPARE). Comparisons of total numbers of required visits completed showed no difference between those with MHD and those without during treatment (0-24 wk), through SVR24 (0-48 wk) and overall ( $P = 0.12$ ); D: GS-331007 concentration at week 2 (SPARE). Comparisons of mean GS-331007 concentration showed no difference between those with MHD and those without at week 2 of treatment ( $P = 0.72$ ).

$P = 0.12$ ) (Figure 1C); and (3) Serum levels of GS-331007-SPARE; We obtained pharmacodynamic and pharmacokinetic data for GS-331007 from 25 patients. Nine had MHD compared to 16 without. There was no statistically significant difference in the mean serum concentrations of GS-331007 for each group at week 2 of treatment ( $P = 0.72$ ) (Figure 1D).

#### **BDI scores among patients with HIV/HCV co-infection treated with sofosbuvir- and IFN-based therapy**

Table 2 shows the baseline characteristics of the patients treated with ledipasvir-sofosbuvir and IFN-based therapy. Age and sex were similar in both groups; however, the ledipasvir-sofosbuvir-treatment group included more African-American and fewer patients with late stage 2-4 disease. While more participants had baseline MHD in the IFN-based treatment group, baseline BDI scores were similar among the patients of both treatment groups (ledipasvir-sofosbuvir  $5.24 \pm \text{SD } 5.48$ , IFN-based  $6.96 \pm \text{SD } 8.67$ ;  $P = 0.14$ ).

#### **BDI scores among all patients**

**Patients treated with ledipasvir-sofosbuvir:** Mean BDI scores decreased from 5.24 at baseline to 3.28 during treatment (1.96 decrease,  $\pm \text{SD } 4.50$ ,  $P = 0.0034$ ) and 2.82 post-treatment. The decrease in

mean score from baseline to post-treatment was also statistically significant ( $-2.42 \pm \text{SD } 4.99$ ,  $P = 0.0012$ , Figure 2A).

**Patients treated with IFN:** Mean BDI score increased from 6.96 at day zero to 9.19 during treatment. This change was not statistically significant (an increase of  $2.46 \pm \text{SD } 8.96$ ;  $P = 0.1$ ), and then decreased back to baseline post-treatment (mean BDI score  $6.3 \pm \text{SD } 7.91$ ;  $P = 0.54$ , Figure 2A).

**Comparison of change in BDI scores from baseline to during and post-treatment:** The overall change in BDI scores from baseline to during treatment among patients treated with ledipasvir-sofosbuvir ( $-1.96 \pm \text{SD } 4.5$ ) compared to the change among those treated with IFN ( $+2.23 \pm \text{SD } 7.5$ ) was statistically significant ( $P = 0.0032$ , Figure 2A). However, change from baseline to post-treatment was not statistically significant ( $-2.42 \pm \text{SD } 4.99$  vs  $-0.65 \pm \text{SD } 6.24$ ;  $P = 0.18$ ).

#### **BDI scores among patients who achieved SVR**

**Patients treated with ledipasvir-sofosbuvir who achieved SVR:** Forty-nine out of the 50 (98%) patients treated achieved SVR. Baseline BDI was  $5.35 \pm \text{SD } 5.48$ . Mean BDI decreased to  $3.35 \pm \text{SD } 4.75$  during treatment

**Table 2** Baseline demographics of participants with hepatitis C/human immunodeficiency virus coinfection who had baseline, during, and post-treatment Beck's Depression Inventory scoring analyzed *n* (%)

Demographic	Sofosbuvir-based therapy ( <i>n</i> = 50)	Interferon-based therapy ( <i>n</i> = 26)	<i>P</i> value
Age, median	58	47	
Male	37 (74)	22 (84)	0.79
African American	42 (84)	11 (42)	0.0004
Fibrosis			0.00132
F0-1	35 (70)	10 (38)	
F2-4	15 (30)	16 (62)	
SVR	49 (98)	13 (50)	0.0001
Baseline mental health disease	15 (30)	15 (58)	0.0264

SVR: Sustained virologic response.

(an overall change of  $-2 \pm \text{SD } 4.45$ ,  $P = 0.0034$ ), and further decreased to  $2.88 \pm \text{SD } 5$  post-treatment. The change in mean BDI from baseline to post-treatment was statistically significant ( $-2.47 \pm \text{SD } 5.03$ ,  $P = 0.0012$ ).

**Patients treated with IFN and achieved SVR:** Eleven out of 26 (42%) patients achieved SVR. Among these participants, mean baseline BDI was  $4.55 \pm \text{SD } 4.48$ . This increased to  $8.91 \pm \text{SD } 7.67$  during treatment ( $P = 0.07$ ) and then returned to baseline of  $5.81 \pm \text{SD } 6.4$ .

#### Comparison of change in BDI scores from baseline to during and post-treatment among patients who achieved SVR

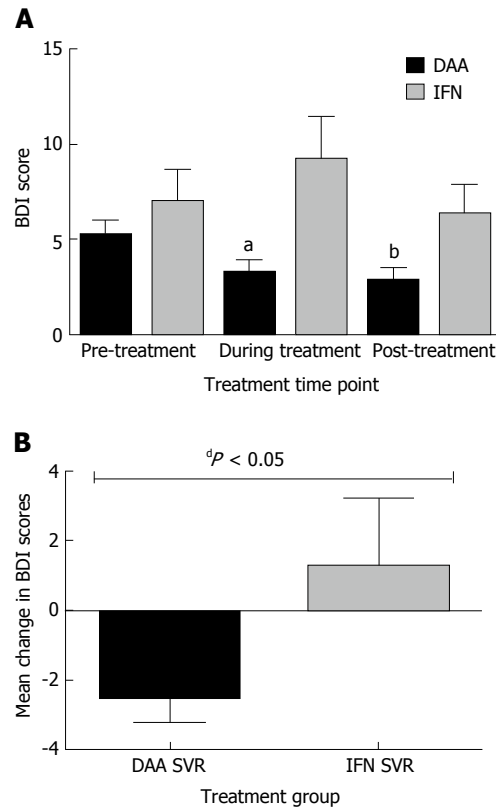
Mean BDI among participants treated with ledipasvir-sofosbuvir decreased  $2 \pm \text{SD } 4.54$  from baseline to during-treatment, whereas among participants treated with IFN-based therapy, mean BDI increased by  $4.36 \pm \text{SD } 7.2$ . This difference in changes in mean BDI scores was statistically significant ( $P = 0.0004$ ).

Similarly, the difference in change in mean BDI from baseline to post-treatment was also statistically significant ( $-2.47 \pm \text{SD } 5.03$ , compared to  $+1.27 \pm \text{SD } 6.36$ ,  $P = 0.038$ ).

## DISCUSSION

Sofosbuvir-based therapy was equally effective among participants with MHD, and among those without MHD. Patients with baseline MHD demonstrated similar levels of adherence with study visits, study drugs, and achieved similar rates of SVR to those who did not have a baseline MHD diagnosis. Furthermore, among participants with HIV/HCV coinfection treated with DAA therapy, we observed a statistically significant improvement in BDI scores during and after the end of treatment time point (post-treatment) compared to baseline (pre-treatment), while participants treated with IFN-based therapy saw no significant change in BDI scores.

In a study of 4084 United States veterans, psychiatric disease was identified as a predictor of non-treatment (odds ratio = 9.45)<sup>[29]</sup>. Furthermore, due to shared



**Figure 2** Beck's Depression Inventory scores among participants with hepatitis C/human immunodeficiency virus coinfection and treated with ledipasvir-sofosbuvir and interferon-based therapy. A: Mean BDI scores pre-, during, and post-treatment among all participants; Decrease in mean score from baseline to during treatment, <sup>a</sup> $P = 0.0034$ , DAA vs IFN; Decrease in mean score from baseline to post-treatment, <sup>b</sup> $P = 0.0012$ , DAA vs IFN; B: Change in mean BDI scores from baseline to post-treatment among participants who achieved SVR, <sup>d</sup> $P = 0.0004$ , DAA vs IFN. SVR: Sustained virologic response; BDI: Beck's Depression Inventory; DAA: Directly acting antiviral; IFN: Interferon.

transmission routes, HIV/HCV coinfection can be high among certain cohorts. A cross sectional study of a large cohort of patients with HIV found that 21% were coinfecting with HCV. Among these patients with HIV/HCV coinfection, depression severity scores were higher, and antidepressant medications were more often prescribed, compared to patients with HIV mono-infection<sup>[30]</sup>. Concern for emergent or worsening of neuropsychiatric side effects associated with interferon-based HCV therapy resulted in treatment deferment even for patients with stable MHD<sup>[14,31,32]</sup>. The treatment of chronic HCV, however, has evolved to interferon-free, all-oral, DAA regimens. Concerns regarding adherence to and subsequent success with DAA regimens among patients with MHD remains to be addressed.

This study has 2 aims: Firstly, to address the impact of baseline MHD on adherence to and subsequent success with DAA regimens among patients with MHD; and secondly, to describe the change in BDI scores among patients treated with a sofosbuvir-based regimen (ledipasvir-sofosbuvir) and compare this to the change among patients treated with IFN-based therapy.

In the current study, we combined results from three studies using interferon-free regimens. We compared the

effect of MHD on outcome (SVR) and three modalities of adherence (pill count, study visits and serum levels of GS-331007). The prevalence of MHD among the 3 studies (approximately 35%) was comparable to the baseline prevalence reported in other studies<sup>[7,10-14]</sup>. This study demonstrates that patients with MHD can achieve SVR at rates comparable to those without MHD. Six patients from SPARE did not complete treatment, 5 of which were identified as suffering from MHD but only one discontinuation from study could be attributed to MHD as determined by evaluation by the principal investigator. This suggests that these interferon-free regimens did not affect adherence and subsequent efficacy of therapy.

For our second aim, we analyzed baseline pre-treatment, during treatment, and post-treatment BDI scores among HIV/HCV coinfecting participants treated with a sofosbuvir-based regimen (ledipasvir-sofosbuvir) in the ERADICATE study and coinfecting participants treated with IFN-based therapy (PFINPK and ALBIN). Mean changes from baseline to during and to post-treatment were compared within, and between, each treatment group. We demonstrate that despite similar baseline BDI scores in both treatment groups, participants treated with ledipasvir-sofosbuvir saw a decrease in BDI scores during treatment and post-treatment compared to baseline. However, participants treated with IFN-based therapy did not see any change in BDI scores. In fact, when treatment groups were compared to each other and adjusted for participants who achieved SVR, the overall decrease in BDI score from baseline to post-treatment among participants treated with ledipasvir-sofosbuvir was significantly different compared to the overall increase in BDI score among participants treated with IFN-based therapy. It is conceivable that successful treatment of HCV alone should be associated with improvement in mental health. However, our findings suggest that sofosbuvir-based (and possibly any IFN-free) anti-HCV therapy may have additional mental health benefits beyond end of treatment.

This study is strengthened by multiple measures of adherence: Pill counts for all 3 studies; and in SPARE study visits with the additional objective measure of serum levels of the sofosbuvir metabolite GS-331007 at week 2 of therapy. Adherence to oral DAA therapy was high in all 3 studies, regardless of baseline MHD status, with no significant differences in pill counts, study visits, and serum GS-331007 levels between those with and without MHD. Whether the high adherence was a consequence of participant selection and the more intensive adherence interventions and counseling that are inherent to clinical trials, or related to the improved tolerability and ease of administration of the medications cannot be determined.

Limitations of this study include its small sample sizes for the three patient groups analyzed and therefore may not be sufficiently powered to detect differences. This did not allow for addressing the hypothesis that a regimen of fewer pills for shorter duration (1 pill once a day in ERADICATE and SYNERGY-A for 12 wk

compared to several pills a day for 24 wk in SPARE) was associated with significantly higher adherence. Furthermore, combining more than one study did result in a non-homogenous study population, most evident in the difference in baseline fibrosis stage among the participants undergoing BDI evaluation. Finally, this study did not include patients with severe, uncontrolled MHD therefore may have been biased towards those who already had a background of good adherence or lower BDI scores.

We hope that these preliminary findings will open the dialogue to further expand eligibility to those with MHD and lead to further, larger studies involving patients with more challenging characteristics: Not just those with baseline MHD, but also those with substance abuse - two diagnoses which are frequently paired<sup>[5-8]</sup>. Inclusion of these marginalized groups will be necessary if we are to gain an advantage in the battle to eradicate hepatitis C.

In conclusion, our study supports that patients with baseline MHD can be successfully engaged and treated with DAA therapies, and that sofosbuvir-based therapy is associated with improvement in BDI scores.

## COMMENTS

### Background

The treatment of chronic hepatitis C has evolved from interferon-based to direct acting antiviral-based therapy, with high tolerability and efficacy. Much focus has now shifted to increasing access to these new agents. However, the prevalence of mental health disease (MHD) is high among patients with hepatitis C and MHD is one of the most frequently cited reasons for withholding hepatitis C therapy.

### Research frontiers

The author's group focuses on hepatitis C eradication strategies among urban populations with unique patient populations that are predominantly African American, with advanced liver fibrosis, and high prevalence of human immunodeficiency virus co-infection and MHD. The authors believe that patients with MHD can be safely and effectively treated for hepatitis C with direct acting antiviral therapy. The findings of this study supports this hypothesis.

### Innovations and breakthroughs

Patients with mental health diseases may be excluded from hepatitis C therapy due to concerns for exacerbation of psychiatric complications, adherence, concurrent substance abuse, and reinfection due to continued high-risk behaviors. Hepatitis C therapy has evolved from interferon-based to direct acting antiviral agents, which are associated with minimal side effects. However, the high cost of these agents has led to restricted access to these medications. This study addresses the concerns regarding adherence to and subsequent success with directly acting antiviral regimens among patients with MHD. Furthermore, the findings of this study suggest that sofosbuvir-based therapy may be associated with improvements in Beck's Depression Inventory (BDI) scores.

### Applications

The findings of this study supports policy change to increase eligibility and access to hepatitis C therapy with new direct acting antiviral therapies among patients with mental health disease.

### Terminology

Sofosbuvir is a direct acting antiviral nucleotide inhibitor that acts upon the hepatitis C NS5B polymerase, preventing viral replication, and is the backbone to several hepatitis C treatment regimens. BDI is a multiple-choice tool for

measuring the severity of depression.

## Peer-review

Study of mental health in hepatitis C virus treated patients is considered to be a good practical point.

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## Retrospective Study

# Liver resection for early hepatocellular cancer: Comparison of centers in 3 different countries

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**Author contributions:** All the authors contributed to the manuscript.

**Institutional review board statement:** This study was reviewed and approved by the University of Hawaii Institutional Review Board. Data from Shanghai is from a cohort in which the anonymous data is publically available. Data from the Nippon Medical Center did not require Institutional review as it is retrospective anonymous data.

**Informed consent statement:** This is not applicable since this is a retrospective study. Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

**Conflict-of-interest statement:** Dr Wong is a speaker for Bayer Healthcare. The other authors have no conflicts of interest to declare.

**Data sharing statement:** No additional data are available.

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## Abstract

### AIM

To compare patients who underwent resection of early stage hepatocellular cancer (HCC) in three different countries.

### METHODS

This retrospective study characterizes 573 stage I / II HCC patients treated with liver resection in 3 tertiary-referral centers: Tokyo ( $n = 250$ ), Honolulu ( $n = 146$ ) and Shanghai ( $n = 177$ ).

### RESULTS

Shanghai patients were younger, predominantly male, hepatitis-B seropositive (94%) and cirrhotic (93%). Tokyo patients were older and more likely to have hepatitis-C (67%), smaller tumors, low albumin, and normal alpha-fetoprotein. The Honolulu cohort had the largest tumors and 30% had no viral hepatitis. Age-adjusted mortality at 1 and 5-years were lower in the

Tokyo cohort compared to Honolulu and there was no difference in mortality between Shanghai and Honolulu cohorts. Elevated alpha-fetoprotein, low albumin and tumor > 5 cm were associated with increased 1-year mortality. These factors and cirrhosis were independently associated with increased 5-year mortality. Independent risk factors of survival varied when examined separately by center.

## CONCLUSION

The profile of early-stage HCC patients is strikingly different across countries and likely contributes to survival differences. Underlying differences in patient populations including risk factors/comorbidities influencing disease progression may also account for variation in outcomes.

**Key words:** Hepatocellular cancer; Liver resection; Viral hepatitis

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**Core tip:** Treatment for hepatocellular cancer (HCC) depends on stage and liver function. Single-institution studies have characterized resection for HCC but this unique study combines the experience of three large hepatobiliary centers in different countries with 573 resections for stage I / II HCC in Tokyo ( $n = 250$ ), Honolulu ( $n = 146$ ) and Shanghai ( $n = 177$ ). Groups differed in viral hepatitis, tumor size, alpha fetal protein (AFP) and cirrhosis. One and 5-year mortality was lowest in the Tokyo cohort. Elevated AFP, low albumin, tumor > 5 cm and cirrhosis were independently-associated with increased 5-year mortality. The profile of early-stage HCC patients is strikingly different across countries and likely contributes to survival differences.

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## INTRODUCTION

Hepatocellular cancer (HCC) is the fifth most common cancer in males and the ninth in females worldwide and is the second most deadly cancer. In 2012, there were 782000 HCC cases and 745000 deaths. HCC is more prominent in less-developed countries and more than 50% of cases were diagnosed in Asia<sup>[1]</sup>. In the United States, there were 35000 new cases of liver and intrahepatic bile duct cancer in 2015 and HCC is one of the few cancers that is increasing in both incidence and mortality<sup>[2]</sup>. The best treatments for early stage HCC include liver resection for those with adequate liver function and liver transplant for those with decompensated

cirrhosis or tumor that is not amenable to resection. Multiple single center studies have demonstrated success with liver resection and transplant, but patient populations largely differ in underlying risk factors (viral hepatitis, diabetes, obesity, alcohol and smoking) and may differ by technique of resection, indications for resection, patient management, use of adjuvant therapy, and follow-up<sup>[3-8]</sup>. The use of liver resection may also vary depending on the availability of liver transplantation. Countries with relatively limited donor liver availability or new transplant programs may depend more on resection for curative therapy. Because of limited donor livers, some countries, such as Japan, have made great efforts at developing successful surveillance and diagnosis programs that detect more than 60% of HCC at a very early stage<sup>[9]</sup>. Early detection allows more patients to undergo resection or liver-directed therapy such as local ablation with curative intent.

Because of potential differences in surveillance, tumor size, and available therapies, it is difficult to directly compare a particular therapy for HCC in different countries. The aim of the present study is to compare patient and clinical characteristics and survival of early (stage I , II ) HCC patients treated by resection in three different countries. These centers include large tertiary referral centers for HCC in Shanghai (China), Nippon (Japan) and Hawaii, the United States with the highest incidence of HCC.

## MATERIALS AND METHODS

This is a retrospective analysis of 573 liver resections performed in 3 tertiary referral centers for liver disease performed in 3 different countries.

### Honolulu cohort (United States)

The Honolulu cohort consisted of 936 HCC cases referred between 1993 and 2014 to the only liver transplant program in Hawaii and the only referral center for liver disease/surgery for the American territories of the Pacific Basin (including Samoa, Guam, Saipan, and the Marshall Islands). Patients were primarily United States citizen of diverse racial/ethnic backgrounds including Whites, Asians, and Pacific Islanders but also included foreign nationals from Asian countries who sought medical care in the United States. Race/ethnicity and birthplace were assessed as risk factors for HCC were previously shown to vary by these demographic characteristics in this study population<sup>[10]</sup>. This clinic and the transplant center were initially affiliated with Hawaii Medical Center-East (formerly St. Francis Medical Center) and after 2012, the Queens Medical Center. This center sees about 60%-70% of the HCC cases in Hawaii. Liver resections were performed by a single group of hepatobiliary/transplant surgeons, with about 80% of these cases done by a single surgeon (LW).

HCC was confirmed histologically by percutaneous biopsy or at surgery. In the first decade, HCC consistent

with the previous United Network for Organ Sharing policy regarded transplant for HCC patients without biopsy. More recently, the diagnosis of HCC was made with only imaging if a dynamic contrast-enhanced study showed typical arterial enhancement with venous “washout” as described by the American Association for the Study of Liver Disease guidelines<sup>[11,12]</sup>.

Data collected included demographic data (age, sex, birthplace, self-reported ethnicity) and the presence of diabetes mellitus, hyperlipidemia, smoking, viral hepatitis, alcohol abuse, obesity and other chronic liver diseases. Laboratory data collected included bilirubin, albumin, prothrombin time, creatinine, alanine aminotransferase, aspartate aminotransferase, platelet count, Model for End-stage Liver Disease score and alpha fetal protein (AFP). The size, number, and location of the tumor(s) were used to determine the Tumor Node Metastases stage according to the American Joint Commission on Cancer (AJCC) staging manual<sup>[13]</sup>.

After excluding patients who presented with ruptured HCC and underwent embolization prior to resection, 146 HCC cases were included in the study. During this time period, 84 patients underwent liver transplant for HCC. This study was approved by the University of Hawaii Institutional Review Board.

#### **Shanghai cohort (China)**

The Shanghai cohort was comprised of 241 HCC cases diagnosed between 2002–2003 and followed for up to 70 mo. Patients were diagnosed and treated at Zhongshan Hospital (Fudan University) in Shanghai, China. Zhongshan Hospital is a major teaching hospital affiliated with the Ministry of Health of China. This is a 1700 bed medical facility that serves approximately 80000 inpatients and 3 million outpatients/emergency visits annually.

All patients were of Chinese ethnicity and were initially seen by medical organizations in the surrounding areas but the final diagnosis was made in this facility. Patients were diagnosed based on imaging criteria, as well as with a history of chronic viral hepatitis and elevated AFP. Three surgeons including Dr. Zhao-You Tang (author) performed all of the liver resections in this cohort. The diagnosis of HCC was confirmed by two independent pathologists.

The patient enrollment criteria included those with detailed information on clinical presentation and pathological characteristics; and detailed follow-up data for at least 3 years, which included recurrence-free survival, overall survival, as well as the cause of death. The detailed clinical presentation characteristics included but were not limited to sex, age, OKUDA staging, CLIP staging, BCLC staging, Child-Pugh score, TNM staging, multiple nodules, satellite nodule, tumor size, tumor capsule, cirrhosis, tumor thrombosis, lymph node, alanine transaminase, Albumin, international normalized ratio, hepatitis B surface (HBV) Ag, hepatitis C antibody, HBV viral status, pre-treatment AFP, preoperative therapy,

and postoperative other therapies. A majority of patients were long-term carriers of HBV (94%). The updated TNM classification was used in this cohort, and 177 early stage HCC patients (TNM stage I and II) with survival information were therefore chosen to perform comparison analysis in our study. Data for this cohort are publically available and have been used in many HCC translational research studies<sup>[14,15]</sup>.

#### **Tokyo cohort (Japan)**

The Tokyo cohort consisted of 504 HCC cases diagnosed between 1986 and 2014 in the Department of Surgery at Nippon Medical School, which has a primary medical center (1000 beds) and 3 smaller branch hospitals. Decisions on therapy were made by hepatologists and surgeons and all liver resections were performed at the primary medical center by members of a dedicated liver surgery team (10 hepatobiliary surgeons, surgical residents and medical students). Living-donor liver transplantation is done in this medical center, but only 15 cases have been done and no deceased-donor liver transplants were performed during this time period.

Although the treatment strategy has been changing in Japan, decisions on therapy were based on an algorithm for treatment of HCC reported by Makuuchi *et al.*<sup>[16,17]</sup>. This algorithm was based on three factors: Degree of liver damage (Childs A, B or C), number of tumors (single, 2–3 or 4 or more), and tumor diameter ( $\leq 3$  cm or  $> 3$  cm). Indications for surgery were according to modified-Makuuchi criteria incorporating the indocyanine green test<sup>[18]</sup>. The final diagnosis of HCC was histologically confirmed at surgery by a group of expert pathologists. Use of transplantation for HCC was extremely limited because of scarcity of organs from deceased donors. Hepatectomy is generally the first choice for Child-Pugh class A and selected class B cirrhotic patients.

In this cohort of 504 patients with HCC, the vast majority of patients were Japanese. The pre-operative diagnosis of HCC was made primarily with imaging and confirmed at resection. Liver biopsy prior to surgery was rarely performed. Data collected in this cohort included: Age, gender, HBV, hepatitis C virus (HCV), presence of coma, ascites, bilirubin, albumin, protime, AFP, Childs-Pugh class, presence of cirrhosis, stage, tumor size, recurrence and survival. Additional data that were collected but not used in this analysis included ICG (indocyanine green), AFP-LC, PIVKA, tumor differentiation, vascular invasion and details on the segments of liver that were removed. Of the 504 HCC patients in this cohort, 250 diagnosed at TNM stage I and II were included in the present analysis.

#### **Statistical analysis**

All analyses were conducted with SAS version 9.3 (SAS Institute, Inc., Cary NC). All *P*-values were two-sided, and *P* < 0.05 was defined as significant. Characteristics of Honolulu, Tokyo and Shanghai HCC patients were compared using generalized linear models (continuous variables) and  $\chi^2$  tests (categorical variables). Differences

**Table 1** Characteristics of resected stage 1 and 2 hepatocellular cancer patients: Honolulu, Tokyo and Shanghai

Characteristic	Honolulu ( <i>n</i> = 146)	Tokyo ( <i>n</i> = 250)	Shanghai ( <i>n</i> = 177)	<i>P</i> value
	<i>n</i> (%)	<i>n</i> (%)	<i>n</i> (%)	
Mean age in years	62.7 (SD 11.4)	67.0 (SD 8.7)	50.6 (SD 11.1)	< 0.0001
Age < 50 yr	18 (12.3)	8 (3.2)	83 (46.9)	< 0.0001
Males	100 (68.5)	180 (72.0)	145 (81.9)	0.01
Hepatitis B positive	62 (42.5)	35 (14.3)	167 (94.4)	< 0.0001
Hepatitis C positive	39 (26.7)	163 (66.8)	5 (3.3)	< 0.0001
Hepatitis B and C positive	5 (3.4)	4 (1.6)	3 (2.0)	0.50
Stage I	129 (88.4)	68 (27.2)	91 (51.4)	< 0.0001
Childs A	143 (99.3)	224 (89.6)	172 (97.2)	< 0.0001
Cirrhosis	60 (41.1)	133 (56.8)	163 (92.6)	< 0.0001
Mean tumor size (cm)	6.4 (SD 4.6)	3.0 (SD 2.1)	3.9 (SD 2.6)	< 0.0001
Tumor size < 5.0 cm	75 (51.4)	213 (85.2)	137 (77.4)	< 0.0001
AFP < 20 ng/mL	72 (49.3)	144 (57.6)	70 (39.6)	0.0011
Albumin < 3.5 g/dL	23 (15.8)	85 (34)	21 (11.9)	< 0.0001

Hepatitis B surface (*n* = 6); hepatitis C virus (*n* = 32); Child-Pugh (*n* = 2); cirrhosis (*n* = 17); albumin *n* = 17). AFP: Alpha fetal protein.

in HCC mortality among patients treated in Honolulu, Tokyo and Shanghai were examined using Kaplan-Meier estimates and Cox proportional hazards regression. Survival period was computed from the date of HCC diagnosis to the date of death from any cause. Patients alive at the end of the follow-up period were considered censored. The proportional hazard assumption for Cox models was checked by plotting scaled Schoenfeld residuals against time to event<sup>[19]</sup>. There was evidence of non-proportionality of hazards with respect to time. For this reason and due to the uneven follow-up period between the three centers, survival was partitioned into two time periods: Survival at 1 year after diagnosis and at 5 years following diagnosis were modeled separately. Analyses were adjusted for patients' age at time of diagnosis. Predictors of overall survival were also evaluated in 1-year and 5-year models. Univariate analyses were used to model age (< 50 year; ≥ 50 year), sex (male; female); stage (I; II); Child-Pugh Score (A; B); tumor size (< 5 cm; ≥ 5 cm) presence/absence of cirrhosis; AFP (< 20 ng/mL; ≥ 20 ng/mL); albumin levels (< 3.5 g/dL; ≥ 3.5 g/dL), HBV (positive; negative); and HCV (positive; negative). The three center locations were modeled as indicator variables with Honolulu as the reference. Along with age, factors found to be significant at the  $P \leq 0.10$  level in univariate analyses were included in the full multivariate models. A statistical review of the study was performed by a biomedical statistician.

## RESULTS

A total of 573 HCC patients diagnosed at AJCC stage I or II who underwent resection were included in the present analyses. Patients included 146 from Honolulu, 250 from Tokyo, and 177 from Shanghai. Patient and clinical characteristics varied widely across countries (Table 1). Patients were youngest in Shanghai and oldest in Tokyo ( $P < 0.0001$ ). Males comprised 82% of Shanghai patients, 72% of Tokyo cases, and 69% of Honolulu cases ( $P =$

0.01). HBV seropositivity was highest among Shanghai HCC cases (94%), followed by Honolulu (43%) and Tokyo (14%) cases ( $P < 0.0001$ ). Conversely, HCV seropositivity was highest among Tokyo cases (67%), followed by Honolulu (27%) and Shanghai (3%) patients ( $P < 0.0001$ ). Stage I cases were predominant in Honolulu (89%), compared to Shanghai (51%) and Tokyo (27%) cases ( $P < 0.0001$ ). Cirrhosis was present in most Shanghai cases (93%), compared to 57% of Tokyo and 41% of Honolulu cases ( $P < 0.0001$ ). Mean tumor size was largest in Honolulu cases (6.4 cm), compared to Shanghai and Tokyo cases (3.9 cm and 3.0 cm, respectively) ( $P < 0.0001$ ). Elevated AFP levels were present in 60% of Shanghai patients, 51% of Honolulu cases, and 42% of Tokyo patients ( $P = 0.001$ ). Abnormal albumin levels (< 3.5 g/dL) were present in 34% of Tokyo patients compared to 16% and 12% in the Honolulu and Shanghai cohorts, respectively ( $P < 0.0001$ ).

Overall, 1-year and 5-year mortality varied across the three centers (Figure 1). Thirty-day mortality was 2.8%, 1.6% and 0% for Honolulu, Tokyo and Shanghai groups, respectively. Mortality was compared across the three centers with Honolulu as the reference (Table 2). (Estimates adjusted for age at diagnosis only and additionally adjusted for the year of surgery were comparable. Therefore, estimates adjusted for age at diagnosis only are reported). During the 1-year survival and 5-year periods, Tokyo patients had lower mortality than those in Honolulu (age-adjusted HR = 0.28; 95%CI: 0.15-0.51 and age-adjusted HR = 0.70; 95%CI: 0.50-0.98, respectively). One-year and 5-year survival did not differ between the Shanghai and Honolulu cohorts.

Predictors of overall 1-year and 5-year survival were examined (Table 3). For 1-year survival, the multivariate model included age, AFP, tumor size, albumin and center as covariates. In the final multivariate model, the following were positively associated with increased risk of mortality at 1-year: AFP levels ≥ 20 (adjusted HR = 2.27; 95%CI: 1.32-3.90), tumor size ≥ 5 cm

**Table 2 Overall age-adjusted survival in resected stage 1 and 2 hepatocellular cancer patients: Honolulu, United States, Tokyo, Japan and Shanghai, China**

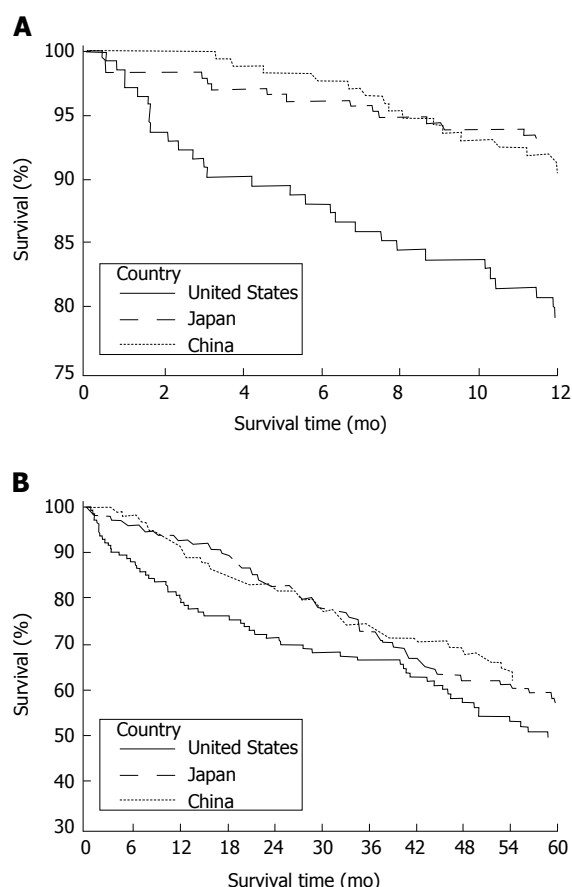
Center		Honolulu	Tokyo	Shanghai
No. patients		146	250	177
No. deaths		29	17	6
Mean follow-up (yr)		4.04	3.75	3.55
Median follow-up (yr)		3.33	2.83	4.36
1-yr survival	Hazard ratio <sup>1</sup>	1	0.28	0.63
	95%CI	Reference	0.15-0.51	0.32-1.21
	P value		< 0.0001	0.17
5-yr survival	Hazard ratio	1	0.7	0.74
	95%CI	Reference	0.50-0.98	0.51-1.09
	P value		0.04	0.13

<sup>1</sup>Age-adjusted.

(adjusted HR = 2.00; 95%CI: 1.17-3.43) and albumin < 3.5 g/dL (adjusted HR = 2.10; 95%CI: 1.20-3.68). The Tokyo cohort had lower 1-year mortality than Honolulu (adjusted HR = 0.33; 95%CI: 0.17-0.65). For 5-year survival, the multivariate model included age, stage, Child-Pugh Score, AFP, albumin, cirrhosis, tumor size, and center as covariates. In the final multivariate model, predictors of 5-year survival were AFP  $\geq$  20 (adjusted HR = 1.57; 95%CI: 1.17-2.10), cirrhosis (adjusted HR = 1.59; 95%CI: 1.12-2.26), tumor size  $\geq$  5 cm (adjusted HR = 1.84; 95%CI: 1.34-2.54), and albumin < 3.5 g/dL (adjusted HR = 1.72; 95%CI: 1.21-2.46). Both Tokyo and Shanghai centers had better 5-year survival than the Honolulu cohort (adjusted HR = 0.51; 95%CI: 0.33-0.78 and adjusted HR = 0.47; 95%CI: 0.31-0.72). Predictors of overall 1-year and 5-year survival were examined separately by center. In Honolulu, predictors of both 1-year and 5-year survival were AFP  $\geq$  20 (1-year: adjusted HR = 3.21; 95%CI: 1.36-7.56; 5-year: adjusted HR = 3.18; 95%CI: 1.35-7.51) and albumin < 3.5 g/dL (1-year: adjusted HR = 4.17; 95%CI: 1.92-9.04; 5-year: adjusted HR = 4.13; 95%CI: 1.90-8.98). In the Tokyo cohort, there were no significant predictors of 1-year survival. Five-year survival was associated with cirrhosis (adjusted HR = 1.90; 95%CI: 1.17-3.09) and tumor size  $\geq$  5 cm (adjusted HR = 2.29; 95%CI: 1.33-3.94). For the Shanghai cohort, 1-year mortality risk was associated with tumor size  $\geq$  5 cm (adjusted HR = 2.99; 95%CI: 1.14-7.80) and 5-year predictors included AJCC stage 2 (vs 1) (adjusted HR = 2.30; 95%CI: 1.35-3.92) and Child-Pugh Score (B vs A) (adjusted HR = 4.51; 95%CI: 1.59-12.81).

## DISCUSSION

Therapy for hepatocellular cancer has evolved and there are current practice guidelines based on Barcelona Clinic Liver Cancer (BCLC) staging<sup>[11,12]</sup>. These guidelines provide a general framework, but what occurs in the real world is likely center and country specific. In developed countries with resources to perform liver transplant, multiple studies have compared outcome between resection



**Figure 1 Overall survival analysis of hepatocellular cancer patients from Honolulu, Tokyo, and Shanghai.** A: Kaplan-Meier survival curves for one-year survival analysis; B: Kaplan-Meier survival curves for five-year survival analysis; A and B: Log-rank test were used for statistical analysis.

and transplant and those treated with transplant have better survival and less recurrence<sup>[7,20-30]</sup>. Nonetheless, widespread use of transplant is constrained by the availability of donor livers. Other reports compared liver resection and local ablation. Although ablation was effective especially for tumors less than 2.0 cm and can be performed with fewer complications, liver resections had better long-term, recurrence free-survival in some series<sup>[3,31-34]</sup>. Good short-term outcomes occur in small tumors, whether resected, ablated or transplanted, but recurrence rates, cost and donor livers are major factors in the decision-making. Worldwide, strategies to treat liver cancer have evolved based on the burden of liver cancer and the available resources in that particular area.

This is the first study that attempts to assess one surgical modality in 3 different countries, each of which has a high burden of disease, but different resources and treatment strategies. We chose liver resection because this was uniformly available and not dependent on technology or donor livers. Rather than comparing data in the form of a meta-analysis or systematic review, we developed a working relationship between the surgeons and scientists in these three centers. In this study, we selected only stage I / II HCC who underwent liver resection, in an attempt to make a comparison in as

**Table 3** Predictors of 1-year and 5-year overall mortality in resected stage 1 and 2 hepatocellular cancer patients in Honolulu, Tokyo and Shanghai

Covariates	Univariate			Multivariate		
	Hazard ratio	Confidence interval	P value	Hazard ratio <sup>1</sup>	Confidence interval	P value
<b>1-yr</b>						
Age (yr, $\geq 50$ vs $< 50$ )	1.29	0.66-2.55	0.46	1.41	0.68-2.92	0.36
Sex (male vs female)	1.39	0.82-2.38	0.22			
AFP (ng/mL, $\geq 20$ vs $< 20$ )	2.28	1.33-3.91	0.003	2.27	1.32-3.90	0.003
Cirrhosis (yes vs no)	1.13	0.65-1.95	0.66			
Tumor size (cm, $\geq 5$ vs $< 5$ )	2.64	1.60-4.34	0.0001	2.00	1.17-3.43	0.01
Albumin (g/dL, $< 3.5$ vs $\geq 3.5$ )	1.72	1.01-2.94	0.045	2.10	1.20-3.68	0.01
AJCC stage (2 vs 1)	0.90	0.55-1.49	0.16			
Childs Pugh (B vs A)	1.27	0.46-3.49	0.64			
Hepatitis B (+ vs -)	0.77	0.47-1.28	0.33			
Hepatitis C (+ vs -)	0.73	0.42-1.25	0.25			
Tokyo vs Honolulu	0.32	0.17-0.58	0.0002	0.33	0.17-0.65	0.001
Shanghai vs Honolulu	0.43	0.23-0.78	0.005	0.54	0.28-1.03	0.06
<b>5-yr</b>						
Age (yr, $\geq 50$ vs $< 50$ )	1.12	0.79-1.60	0.52	1.14	0.77-1.69	0.53
Sex (male vs female)	1.14	0.84-1.56	0.40			
AFP (ng/mL, $\geq 20$ vs $< 20$ )	1.56	1.17-2.06	0.002	1.57	1.17-2.10	0.002
Cirrhosis (yes vs no)	1.32	0.97-1.80	0.08	1.59	1.12-2.26	0.009
Tumor size (cm, $\geq 5$ vs $< 5$ )	1.66	1.24-2.23	0.0007	1.84	1.34-2.54	0.0002
Albumin (g/dL, $< 3.5$ vs $\geq 3.5$ )	1.91	1.41-2.58	$< 0.0001$	1.72	1.21-2.46	0.003
AJCC stage (2 vs 1)	1.30	0.98-1.72	0.07			
Childs Pugh (B vs A)	1.78	1.05-3.02	0.03	1.33	0.73-2.43	0.35
Hepatitis B (+ vs -)	0.87	0.65-1.15	0.31			
Hepatitis C (+ vs -)	1.11	0.83-1.49	0.48			
Tokyo vs Honolulu	0.74	0.53-1.03	0.08	0.51	0.33-0.78	0.002
Shanghai vs Honolulu	0.66	0.46-0.94	0.02	0.47	0.31-0.72	0.0006

<sup>1</sup>Multivariate model adjusted for covariates listed. AFP: Alpha fetal protein; AJCC: American Joint Commission on Cancer.

homogeneous a group as possible. We showed that although the survival outcomes are different in various centers, overall survival is mostly dependent on tumor factors and underlying liver function. Although the patients in each center differ in many respects (mean age, gender, viral risk factor, tumor size, mean tumor size and AFP), all centers had excellent 30-d mortality. Our study showed that tumor size, AFP, and albumin were factors associated with early mortality. By 5 years post-resection, these same factors in addition to the presence of cirrhosis were predictors of mortality. Both the Tokyo and Shanghai cohorts had better 1- and 5-year survival compared to the Honolulu cohort even after adjustment for clinical factors. Differences in patient populations across the centers may account for these differences. Compared to the generally homogeneous Tokyo and Shanghai patients, the Honolulu cohort was comprised of racially and ethnic diverse individuals born within and outside the United States. Many Honolulu patients had comorbidities including those that may contribute to disease progression (obesity, type-2 diabetes, excess alcohol consumption and past intravenous drug use)<sup>[10]</sup>. We were unable to account for these differences in comorbidities and risk factors as this information was not available for the Tokyo and Shanghai cohorts. Differences in the patient populations are further supported by our observation that independent risk factors of survival differed across centers. In Honolulu, elevated AFP and albumin were associated with both 1-year and 5-year

survival. In the Tokyo cohort, cirrhosis large and tumor size were associated with 1-year survival. For the Shanghai cohort, tumor size was a predictor of 1-year survival while AJCC stage and Child-Pugh Score were associated with 5-year mortality risk.

Single-center studies have similarly demonstrated that tumor characteristics (size, vascular invasion) and underlying liver function are predictors of survival<sup>[3,5,21,35,36]</sup>. Kao *et al.*<sup>[3]</sup> examining 1265 liver resections for early stage HCC, showed that low albumin, AFP  $> 20$  ng/mL, and tumor size  $> 3$  cm affected mortality. Kang *et al.*<sup>[34]</sup> studying 353 South Korean patients, found that vascular invasion and thrombocytopenia were risk factors for poor disease-free survival. Many of these studies were large series of liver resections in centers outside the United States. Large United States studies of liver resection for HCC have been primarily based on cancer databases with limited information on underlying liver function<sup>[30,33,37]</sup>, or were conducted in single centers that focused on the comparison between liver transplant and resection<sup>[29-38]</sup>.

A few studies have also compared the outcome of liver resections in patients with HBV vs HCV. Chen *et al.*<sup>[38]</sup> studying 2920 patients in Taiwan, showed that patients with HBV were younger, had higher AFP and larger tumor size and lower mean survival (11.1 mo vs 23.9 mo with HCV). Dohmen *et al.*<sup>[39]</sup> demonstrated that among 692 patients in Japan, HBV patients were younger, presented with more advanced stage and had poorer overall survival. Wu *et al.*<sup>[40]</sup> reported that

among 110 Taiwanese patients who underwent hepatic resection for HCC, neither underlying cirrhosis nor viral status affected operative morbidity or mortality, but the poorer liver reserve in HCV cirrhotic patients resulted in worse survival compared to the HBV patients. Franssen *et al.*<sup>[37]</sup> reported that among 567 United States patients who underwent liver resection, HBV rather than HCV-related HCC had better survival and less recurrence. Our study allowed comparison of a primarily HBV-related HCC group of patients (China), a primarily HCV-related HCC group (Japan) and a mixed group (Hawaii), and when considered together viral hepatitis status had little bearing on overall 1- and 5-year survival as the cirrhosis, tumor size, AFP and underlying liver function had the greatest effect on outcome.

This study is limited in that the time frame was different in the three groups. In the Tokyo and Honolulu cohorts, this study represented a 20+ year experience, whereas the Shanghai cohort underwent liver resection over a 2-year period. Because this study was done retrospectively, each group collected different parameters, so there was limited data collected by all groups that could be directly compared. There are also likely differences in the quality of long-term follow up between the centers. This study also has variable data on recurrence of HCC and treatment of these recurrences, which may affect long-term survival. Survival was also expressed as all-cause survival so it is difficult to determine the contribution of HCC to overall patient outcome. Finally, differences in survival after liver resection may be due to availability of liver transplant and other locoregional therapies in a particular country. The increased availability of liver transplant in the Honolulu group may have prompted fewer resections in those with smaller tumors, leaving liver resections for larger tumors with reasonable liver function. Unfortunately, we would not be able to determine this without information on all HCC referred to each of these centers.

In spite of these differences and limitations, this study represents a large experience of liver resections by expert hepatobiliary surgeons in their respective countries. In the final analysis, the very early outcome after liver resection for HCC is similar in specialized centers in different countries but later survival is better in the Tokyo and Shanghai groups. Tumor factors, underlying liver function, comorbidities and availability of other therapies may be playing a role patient selection for resection and the ultimate outcome. Nevertheless, this study demonstrates that collaborations at an international level will be important for understanding how to better manage and treat HCC.

## COMMENTS

### Background

Treatment for hepatocellular cancer depends on stage and liver function. How liver cancer is treated in different country may also depend on available therapy. Liver transplant has the best long-term disease free survival for early liver cancer, however the availability of liver transplant differs in various countries

and may limit this therapy.

### Research frontiers

Single-institution studies have characterized resection for hepatocellular but this unique study combines the experience of three large hepatobiliary centers in different countries with 573 resections for stage I/II hepatocellular cancer in Tokyo ( $n = 250$ ), Honolulu ( $n = 146$ ) and Shanghai ( $n = 177$ ).

### Innovations and breakthroughs

Groups differed in viral hepatitis, tumor size, alpha fetal protein (AFP) and cirrhosis. One and 5-year mortality was lowest in the Tokyo cohort. Elevated AFP, low albumin, tumor > 5 cm and cirrhosis were independently-associated with increased 5-year mortality. The profile of early-stage hepatocellular patients is strikingly different across countries and likely contributes to survival differences.

### Applications

This study is important as it demonstrates the importance of collaboration between centers in different countries so that we can better diagnose and manage hepatocellular cancer.

### Terminology

Liver resection is a surgical procedure involving removal of a portion of liver that has a malignant cancer. Liver transplantation is performed for those patients with hepatocellular cancer and poor underlying liver function.

### Peer-review

The authors of this paper observed excellent early outcomes after liver resection for early stage hepatocellular cancer. Differences in longer term survival were likely related to tumor size, albumin, AFP and the presence of cirrhosis.

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## Prospective Study

# Mortality and rebleeding following variceal haemorrhage in liver cirrhosis and periportal fibrosis

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## Abstract

### AIM

To investigate mortality and rebleeding rate and identify associated risk factors at 6 wk and 5 d following acute variceal haemorrhage in patients with liver cirrhosis and schistosomal periportal fibrosis.

### METHODS

This is a prospective study conducted during the period from March to December 2014. Patients with portal hypertension presenting with acute variceal haemorrhage secondary to either liver cirrhosis (group A) or schistosomal periportal fibroses (group B) presenting within 24 h of the onset of the bleeding were enrolled in the study and followed for a period of 6 wk. Analysis of data was done by Microsoft Excel and comparison between groups was done by Statistical Package of Social Sciences version 20 to calculate means and find the levels of statistical differences and define the mortality rates, the *P* value of < 0.05 was considered to be significant.

### RESULTS

A total of 94 patients were enrolled in the study. Thirty-two patients (34%) had liver cirrhosis (group A) and

62 (66%) patients had periportal fibrosis (group B). Mortality: The 6-wk and 5-d mortality were 53% and 16% respectively in group A compared to 10% and 0% in group B ( $P$  value  $< 0.000$  and  $< 0.004$ ). In group A; a Child-Turcotte-Pugh class C and rebleeding within 5 d were significantly associated with 5-d mortality ( $P$  value  $< 0.029$  and  $< 0.049$  respectively) and Child-Turcotte-Pugh class C was also a significant risk factor for 6-wk mortality ( $P$  value  $< 0.018$ ). In group B; mortality was significantly associated with rebleeding within the 6-wk follow-up period and requirement for blood transfusion on admission ( $P$  value  $< 0.005$  and  $< 0.049$ ). Rebleeding: The 6-wk and 5-d rebleeding rate in group A were 56% and 25% respectively compared to 32% and 3% in group B ( $P$  value  $< 0.015$  and  $< 0.002$ ). Clinical presentation with encephalopathy was a significant risk factor for 5 d rebleeding in group A ( $P$  value  $< 0.005$ ) while grade III periportal fibrosis and requirement for blood transfusion on admission were significant risk factors for 6-wk rebleeding in group B ( $P$  value  $< 0.004$  and  $< 0.02$ ).

### CONCLUSION

The 6-wk and 5-d mortality and rebleeding rate were significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

**Key words:** Variceal haemorrhage; Periportal fibrosis; Liver cirrhosis; Mortality; Rebleeding

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**Core tip:** This study was conducted to investigate the rate and risk factors associated with rebleeding and mortality at 6 wk and 5 d following acute variceal haemorrhage in patients with liver cirrhosis and schistosomal periportal fibrosis (PPF). The 6-wk and 5-d mortality in cirrhosis were 56% and 16% compared to 10% and 0% in patients with schistosomal PPF ( $P$  value  $< 0.000$  and  $< 0.004$ ). The 6-wk and 5-d rebleeding rate in cirrhosis were also high at 53% and 25% compared to 32% and 3% respectively in patients with schistosomal PPF ( $P$  value  $< 0.015$  and  $< 0.002$ ). In conclusion the 6-wk and 5-d mortality and rebleeding were significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

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### INTRODUCTION

Variceal bleeding is a devastating complication of portal hypertension. The 6-wk mortality in patients with liver cirrhosis is between 17%-28%<sup>[1-3]</sup> and the risk of

rebleeding after acute variceal haemorrhage (AVH) is highest within the first 6 wk with a peak in the first 5 d<sup>[2]</sup>. In Sudan, a country endemic with schistosomiasis, AVH in the majority of cases is caused by portal hypertension due to schistosomal periportal fibrosis (PPF), while cirrhosis is less common<sup>[4]</sup>. Published data from Sudan showed that the crude mortality rate of schistosomiasis in a village in the Gezira state; an area endemic for schistosomiasis was 51/100000 per year with a case fatality per year of 1/1000 in those secreting eggs and 11/100 in those with bleeding varices<sup>[5]</sup>. Significant risk factors for variceal bleeding in patients with schistosomal portal hypertension, after at least one episode of bleeding compared to patients with schistosomal PPF without bleeding were splenic longitudinal dimension of more than 11 cm and PPF of  $\geq$  grade III<sup>[6]</sup>. The 6-wk and 5-d mortality and rebleeding rate following AVH in schistosomal portal hypertension have not been well studied.

The objectives of this study were to investigate mortality and rebleeding rate and identify associated risk factors for 6 wk and 5 d following acute variceal haemorrhage in patients with portal hypertension secondary to liver cirrhosis and schistosomal PPF.

### MATERIALS AND METHODS

This is a prospective study conducted at Mohamed Salih Idris bleeding centre in Khartoum state, Sudan from March to December 2014. Patients presenting with acute upper gastrointestinal (GI) bleeding, whether it was their first bleeding episode or otherwise, were included if they were  $> 16$  years old, had portal hypertensive variceal bleeding (diagnosed on upper gastrointestinal endoscopy) secondary to liver cirrhosis (group A) or PPF (group B) presenting within 24 h of the onset of the bleeding. Patients were excluded if they were  $\leq 16$  years, had hepatocellular carcinoma or had non variceal upper gastrointestinal bleeding. Data were collected in a specially designed sheet which included patients' demographics and clinical presentation, baseline laboratory tests done upon initial presentation (CBC, RFT, LFT's and INR), patients' hemodynamic status upon presentation, the number of blood units transfused, the amount of the vasopressor agent Terlipressin acetate (Glypressin<sup>®</sup>, Ferring, Germany) used, endoscopic findings and endoscopic management done. All patients received Terlipressin 2 mg intravenously bolus dose followed by 1 mg 6 hourly whenever the drug was available. All patients underwent upper gastrointestinal endoscopy within 12 h of admission to identify the source of bleeding. Oesophageal varices were graded according to Paquet<sup>[7]</sup> and gastric varices were graded according to Sarin *et al*<sup>[8]</sup>. Oesophageal varices and junctional varices (GOV1) were treated with injection sclerotherapy or band ligation, whichever was available, 5% ethanolamine oleate was the agent used for injection sclerotherapy and the volume used for each patient was documented, junctional varices (GOV2) and isolated gastric varices

**Table 1** Demographic criteria and clinical presentation in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)

Variable	PPF ( <i>n</i> = 62)	Cirrhosis ( <i>n</i> = 32)	<i>P</i> value
Males	56 (90.3)	27 (84.4)	0.395
Females	6 (9.7)	5 (15.6)	
Mean age (yr)	49.3 ± 13.4	48.7 ± 15.1	0.840
HBV	4 (6.5)	8 (25)	0.004 <sup>1</sup>
HCV	2 (3.2)	1 (3)	
HBV and HCV	0 (0)	3 (9.4)	
SBP > 100, PR < 100	50 (80.6)	18 (56.2)	0.012 <sup>1</sup>
SBP < 100, PR > 100	12 (19.4)	14 (43.8)	
Hb < 5 g/dL	10 (16.1)	4 (12.5)	0.236
Hb 5-10 g/dL	36 (58.1)	24 (75)	
Hb > 10 g/dL	16 (25.8)	4 (12.5)	

<sup>1</sup>Significant risk factor. HBV: Hepatitis B virus; HCV: Hepatitis C virus; SBP: Systolic blood pressure; PR: Pulse rate; Hb: Haemoglobin.

were treated with the injection of cyanoacrylate (Histoacryl®, B Braun, Spain) and Sengstaken Blakemore tube was used to control bleeding if initial endoscopy was not successful. Cirrhotic patients were covered with prophylactic antibiotics. An appointment for secondary prophylactic endoscopic treatment was given within 2 wk and B-blockers were prescribed if not contraindicated. The diagnosis of cirrhosis was established by clinical, radiological and laboratory findings and the cause of cirrhosis was looked for and documented. Child-Turcotte-Pugh (CTP) classification and the model for end stage liver disease (MELD) score were calculated for each patient. In the case of schistosomal PPF, the severity of liver fibrosis was graded as described by Homeida *et al.*<sup>[9]</sup> from I - III as follows: Grade I : Mild echogenic thickening of one or two portal vein radicles with little change in the walls of the portal vein; Grade II : Moderate to severe periportal irregular thickening of most of the portal vein radicles, with marked narrowing of the central lucency, marked thickening at the bifurcation of the portal vein, and mild thickening of the main portal vein; and Grade III: Marked thickening of the walls of the portal vein radicles with obliteration of the central lucency in the peripheral branches forming thick irregular echogenic 10-20 mm bands reaching the periphery of the liver with thickening down to main portal vein walls.

Patients were followed every 24 h for the first 5 d and then at 6 wk for mortality and rebleeding. Rebleeding was defined according to the Baveno V consensus as a single episode of clinically significant rebleeding from portal hypertensive sources (recurrent melena, hematemesis resulting in hospital admission, blood transfusion, 3 g drop in haemoglobin or death). Rebleeding during the first 120 h (5 d) was regarded as treatment failure, whereas rebleeding up to 6 wk was regarded as failure of secondary prophylaxis<sup>[10]</sup>.

The primary endpoint of this study was the rate of variceal rebleeding and mortality at 5 d and at 6 wk following AVH in portal hypertension secondary to cirrhosis or PPF. The secondary endpoints were to determine risk factors associated with variceal rebleeding and

mortality at 5 d and 6 wk among the study population.

The study was reviewed and approved by the Research and Ethics Review Committee at Mohamed Salih Idris Centre. All study participants or their legal guardian provided their informed consent before being enrolled in the study.

### Statistical analysis

Analysis of data was done by Microsoft Excel and comparison between groups was done by Statistical Package of Social Sciences version 20 to calculate means and find the levels of statistical differences and define the mortality rates, the *P* value of < 0.05 was considered to be significant.

## RESULTS

A total of 94 patients were enrolled in the study with a mean age of 49 ± 1.0 years, and males constituted 88% with M:F ratio of 7:1.

### Group A (liver cirrhosis)

There were 32 patients (34%) in group A. Demographic criteria and clinical presentation are shown in Table 1, clinical findings and medical management in Table 2 and endoscopic findings/management are shown in Table 3. After discharge from the bleeding centre, patients were advised to attend for further endoscopic management in order to eradicate the varices with the earliest session to be done at 2 wk. A total of 19% underwent upper endoscopy at less than 2 wk because of rebleeding, 31% performed the session at the advised 2 wk, 13% at 3 wk, 3% at 4 wk and 3% beyond 4 wk, whereas 31% did not attend for the second endoscopy session.

### Group B (schistosomal PPF)

There were 62 patients (66%) in group B. The clinical and demographic data are shown in Table 1, ultrasound findings and medical management in Table 2 and endoscopic findings/management are presented in Table 3.

After discharge from the bleeding centre patients were advised to continue endoscopic management in order to eradicate the varices with the earliest session to be done at 2 wk. A total of 5% of the patients underwent upper endoscopy at less than 2 wk because of rebleeding, 48% performed the session at the advised 2 wk, 23% at 3 wk, 8% at 4 wk and 11% beyond 4 wk while 5% did not attend for the second endoscopy session.

### Overall mortality

The 6-wk and 5-d mortality were 53% and 16% respectively in group A compared to 10% and 0% in group B (*P* value < 0.000 and < 0.004 respectively) (Table 4).

### Factors related to mortality

In group A, the CTP class C and rebleeding within 5 d were significant risk factors for 5 d mortality (*P* value < 0.029 and < 0.049 respectively). CTP class C was also

**Table 2 Clinical findings and medical management provided in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)**

Variable	PPF ( <i>n</i> = 62)	Cirrhosis ( <i>n</i> = 32)	<i>P</i> value
Jaundice	0 (0)	16 (50)	0.000 <sup>1</sup>
Ascites	5 (8.1)	16 (50)	0.000 <sup>1</sup>
Encephalopathy	3 (4.8)	9 (28.1)	0.001 <sup>1</sup>
Child class A	-	9 (28)	-
Child class B	-	13 (41)	-
Child class C	-	10 (31)	-
MELD score < 18		19 (59.4)	-
MELD score > 18		13 (40.6)	-
PPF grade II	29	-	-
PPF grade III	71	-	-
Mean portal vein diameter	17.4 ± 3.3 mm	16.4 ± 3.1 mm	0.155
Terlipressin stat dose 2 mg IV	48 (77.4)	27 (84.4)	0.426
Terlipressin 6 hourly over 24 h	15 (24.2)	14 (43.8)	0.052
Requirement for blood transfusion (mean number of units)	2 ± 1 units	2 ± 1 units	-

<sup>1</sup>Significant risk factor. PPF: Periportal fibrosis; MELD: Model for end stage liver disease.

**Table 3 Endoscopy findings and endoscopic management in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)**

Variable	PPF ( <i>n</i> = 62)	Cirrhosis ( <i>n</i> = 32)	<i>P</i> value
Grade II OV	5 (8.1)	2 (6.3)	0.961
Grade III OV	17 (27.4)	10 (31.3)	
Grade IV OV	23 (37.1)	14 (43.8)	
Gastric varices	17 (27.4)	6 (18.8)	
Band ligation	8 (12.9)	1 (3.1)	0.318
Sclerotherapy	45 (72.6)	28 (87.5)	
Histoacryl injection	4 (6.5)	2 (6.3)	
Both histoacryl/sclerotherapy/band	5 (8.1)	1 (3.1)	

OV: Oesophageal varices; PPF: Periportal fibrosis.

a significant risk factor for 6-wk mortality (*P* value < 0.018) (Table 5).

In group B, rebleeding within the 6-wk follow-up period and blood transfusion on admission were significant risk factors for mortality (*P* value < 0.005 and < 0.049 respectively) (Table 6).

### Rebleeding rate

The 6-wk and 5-d rebleeding rate in group A were 56% and 25% respectively compared to 32% and 3% in group B (*P* value < 0.015 and < 0.002) (Table 4).

### Factors related to variceal rebleeding within 6 wk

In group A, no significant factors were related to rebleeding within 6 wk.

In group B, grade III PPF and blood transfusion on admission were significant risk factors associated with rebleeding in this group with a *P* value < 0.004 and < 0.02 respectively (Tables 5 and 6).

### Factors related to variceal rebleeding within 5 d

In group A, clinical presentation with encephalopathy was a significant risk factor for rebleeding within 5 d (*P* value < 0.005). In group B there were no significant factors

**Table 4 Study outcomes in 94 patients with liver cirrhosis and periportal fibrosis presenting with acute variceal haemorrhage *n* (%)**

	PPF ( <i>n</i> = 62)	Cirrhosis ( <i>n</i> = 32)	<i>P</i> value
Mortality at 6 wk	10	53	0.000 <sup>1</sup>
Mortality at 5 d	0	16	0.004 <sup>1</sup>
Rebleeding at 6 wk	32	56	0.015 <sup>1</sup>
Rebleeding at 5 d	3	25	0.002 <sup>1</sup>

<sup>1</sup>Significant risk factor. PPF: Periportal fibrosis.

contributing to rebleeding within 5 d (Tables 5 and 6).

## DISCUSSION

In this study, we evaluated early mortality and rebleeding following AVH. In this part of Africa minimal data is available with regards to mortality following AVH due to scarcity of endoscopy services. This study is unique because we evaluated the patients in two groups according to the etiology of the underlying liver disease, either liver cirrhosis or schistosomal periportal fibrosis. Previous studies on early mortality following AVH were done exclusively on patients with liver cirrhosis<sup>[3,11-13]</sup>.

In this study, in the cirrhosis group, the 6-wk and 5-d mortality were both high at 53% and 16% respectively, whereas the 6-wk mortality following AVH in patients with schistosomal PPF was 10% with no deaths reported during the first 5 day (*P* value < 0.000 and < 0.004). This high rate of mortality in cirrhosis following variceal bleeding is well described by D'Amico; where four clinical stages of cirrhosis were agreed upon in the Baveno IV consensus conference. Each stage with different features and a different prognosis as follows: Stage 1 no varices or ascites, mortality rate is 1%, stage 2 varices without ascites and without bleeding, mortality rate is 3.4% per year, stage 3 is characterised by ascites with or without varices but never bled, mortality rate is 20% per year, stage 4 is characterised by GI bleeding with or without ascites, in this stage the one year mortality is 57% and

**Table 5** Factors associated with mortality and rebleeding in 32 patients with liver cirrhosis

Study outcome	Factors	P value
Mortality at 6 wk	CTP score C	0.018 <sup>1</sup>
Mortality at 5 d	CTP score C	0.029 <sup>1</sup>
	Rebleeding within 5 d	0.049 <sup>1</sup>
Rebleeding at 6 wk	Non	Non
Rebleeding at 5 d	Encephalopathy	0.005 <sup>1</sup>

<sup>1</sup>Significant risk factor. CTP: Child-Turcotte-Pugh.

nearly half of these deaths occur within 6 wk from the initial episode of bleeding<sup>[14]</sup>.

This difference in mortality rate between the two groups is most likely due to preserved liver cell function in most patients with PPF compared to patients with liver cirrhosis<sup>[15]</sup>. In this study we observed that only a minority of patients with schistosomal PPF presented with clinical evidence of liver cell failure; mainly ascites in 2% and encephalopathy in 3%, it has been reported that a few patients with schistosomiasis do evolve to an end stage of the disease with hepatocellular failure, this is known as decompensated schistosomiasis<sup>[15]</sup>.

Le Moine *et al*<sup>[3]</sup> reported predictive factors for mortality at 6 wk in cirrhotic patients being prolonged prothrombin time, encephalopathy and number of blood units transfused. Krige *et al*<sup>[12]</sup> found in a study done exclusively in alcoholic cirrhosis, that CTP class C, encephalopathy, ascites, bilirubin > 51 mmol/L, INR > 2.3, albumin < 25 g/L and patients who require balloon tamponade were factors related to 6-wk mortality. In this study we also found that the CTP class C was significantly related to 6-wk mortality (*P* value < 0.02) this was similar to findings in other studies<sup>[3,12,13]</sup>. Furthermore factors related to mortality within the first 5 d following AVH in cirrhosis were again the CTP class C and the rebleeding within these 5 d. Bambha *et al*<sup>[11]</sup> suggested that the MELD score rather than CTP class was more powerful in predicting 6-wk mortality. In this study, the MELD score was not a significant risk factor for mortality. We found that mortality following AVH in schistosomal PPF (10%) is much less when compared to cirrhotic patients (56%). There is scanty data on the early outcomes of patients with schistosomal PPF presenting with AVH, however, a study from Tanzania found that mortality following AVH in patients with schistosomal PPF after 8 wk of follow-up was quite similar to this study at 10%<sup>[16]</sup>. In this study, no deaths occurred within the first 5 d in the PPF group.

Factors significantly contributing to the 6-wk mortality in PPF included blood transfusion within the first 24 h and rebleeding within the 6-wk follow-up period (*P* values < 0.049, < 0.005 respectively). The 6-wk rebleeding rate in the PPF group was (32%), less than cirrhosis group at 56% (*P* value < 0.004). Significant factors contributing to the 6-wk rebleeding rate in PPF group were grade III PPF on abdominal ultrasound and blood transfusion on admission (*P* value < 0.004 and < 0.02 respectively). A previous study from Sudan demonstrated that rebleeding

**Table 6** Factors associated with mortality and rebleeding in 62 patients with periportal fibrosis

Study outcome	Factors	P value
Mortality at 6 wk	Blood transfusion	0.049 <sup>1</sup>
	Rebleeding within 6 wk	0.005 <sup>1</sup>
Mortality at 5 d	Non	Non
Rebleeding at 6 wk	Blood transfusion	0.021 <sup>1</sup>
	Grade III PPF	0.004 <sup>1</sup>
Rebleeding at 5 d	Non	Non

<sup>1</sup>Significant risk factor. PPF: Periportal fibrosis.

was more in grade III PPF<sup>[17]</sup>. A study from Brazil also found that the sonographic grade of periportal fibrosis was an important tool in predicting variceal complications in patients with schistosomal PPF<sup>[18]</sup>, whereas the longitudinal spleen dimension of more than 11 cm, was an important tool in predicting variceal bleeding in another study<sup>[6]</sup>. It is well known that a conservative blood transfusion strategy is associated with better survival outcomes in patients with upper gastrointestinal bleeding<sup>[19]</sup>. In this study blood transfusion was provided to 58% of patients with PPF with a mean of 2 ± 1 units of blood. Requirement of blood transfusion was a significant factor for both mortality and rebleeding in PPF group (*P* value < 0.049 and < 0.02 respectively).

Rebleeding within 5 d in PPF occurred in two patients (3%), which is much less than in cirrhosis group at 25% (*P* value < 0.002). Both patients had grade III PPF, were hemodynamically stable and did not require blood transfusion, however, none of the factors evaluated contributed to rebleeding within 5 d. Further studies are needed to reveal other causes contributing to rebleeding such as the portal vein pressure and intra variceal pressure.

In this study, the rebleeding rate among cirrhosis group was high at 56% and 25% of these patients developed rebleeding within the first 5 d. The 6-wk rebleeding rate reported in literature was 16.2%, 30% and 24.2%<sup>[2,12,13]</sup>.

It has been reported that the severity of liver disease in terms of presence of ascites and encephalopathy contributes to the rebleeding rate<sup>[3,12]</sup>. In this study, the presence of hepatic encephalopathy in patients with cirrhosis was a significant factor for rebleeding within 5 d of AVH (*P* value < 0.005). Non of the other factors evaluated were found significant for 6-wk rebleeding in cirrhosis, perhaps larger studies with bigger sample sizes are needed to reveal the factors contributing to rebleeding in patients with cirrhosis in our region.

It is known that the use of vasopressor agents improve outcomes following AVH<sup>[20]</sup>. In this study, Terlipressin was provided to patients whenever available, however there was no significant difference on survival or rebleeding rate between patients with liver cirrhosis and patients PPF with use of Terlipressin.

In patients with PPF and cirrhosis the mean portal vein diameter was 17.4 ± 3.3 mm and 16.4 ± 3.1 mm

respectively, reflecting high portal pressure and hence high variceal pressure. Therefore, effective lowering of portal pressure should be paramount in order to prevent the dreadful complication of variceal bleeding.

HBsAg seroprevalence among PPF patients was 6%, similar to seroprevalence of HBsAg among the general population in central Sudan<sup>[21]</sup>, hence HBV screening and vaccination in patients with PPF should be encouraged.

In conclusion, this study has demonstrated that the 6-wk and 5-d mortality and rebleeding are significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis. Effective secondary prophylaxis after AVH needs to be adhered to and when resuscitating patients with AVH, blood transfusion should be given carefully and HBV vaccination should be actively encouraged.

## COMMENTS

### Background

Variceal bleeding is a devastating complication of portal hypertension. In patients with liver cirrhosis the risk of rebleeding after acute variceal haemorrhage is highest within the first 6 wk with a peak in the first 5 day.

### Research frontiers

In Sudan, a country endemic with schistosomiasis, acute variceal haemorrhage (AVH) in the majority of cases is caused by portal hypertension due to schistosomal periportal fibrosis, while cirrhosis is less common. The 6-wk and 5-d mortality and rebleeding following AVH in schistosomal portal hypertension have not been well studied.

### Innovations and breakthroughs

In this study, the authors evaluated early mortality and rebleeding following AVH. In this part of Africa minimal data is available with regards to mortality following AVH due to scarcity of endoscopy services. This study is unique because the authors evaluated the patients in two groups according to the etiology of the underlying liver disease, either liver cirrhosis or schistosomal periportal fibrosis. Previous studies on early mortality following AVH were done exclusively on patients with liver cirrhosis.

### Applications

This study has demonstrated that the 6-wk and 5-d mortality and rebleeding are significantly higher in patients with liver cirrhosis compared to patients with schistosomal periportal fibrosis.

### Terminology

Schistosomiasis is endemic in Sudan; the mortality of schistosoma mansoni infection is mostly due to development of periportal fibrosis with subsequent development of portal hypertension and oesophageal varices causing significant morbidity and mortality.

### Peer-review

This is a well conducted prospective study about variceal bleeding complications in African Setting.

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