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MINIREVIEWS

# Addictive behaviors in liver transplant recipients: The real problem?

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## Abstract

Liver transplantation (LT) is the gold standard treatment for end-stage liver disease. Whatever the primary indication of LT, substance abuse after surgery may decrease survival rates and quality of life. Prevalence of severe alcohol relapse is between 11 and 26%, and reduces life expectancy regardless of the primary indication of LT. Many patients on waiting lists for LT are smokers and this is a major risk factor for both malignant tumors and cardiovascular events post-surgery. The aim of this review is to describe psychoactive substance consumption after LT, and to assess the impact on liver transplant recipients. This review describes data about alcohol and illicit drug use by transplant recipients and suggests guidelines for behavior management after surgery. The presence of an addiction specialist in a LT team seems to be very important.

**Key words:** Liver transplantation; Tobacco use; Illicit drugs; Behavior management; Severe alcohol relapse



**Core tip:** Liver transplantation is the best treatment for end-stage liver disease. However, some transplant recipients use or abuse alcohol, tobacco and illicit drugs during the post-transplant period. Given the scarcity of organs, this type of consumption, which can affect life expectancy and quality, must be addressed with kindness and without moralizing. Although specific behavior treatment does not exist in this indication, specialists in addiction should be part of the transplant team.

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## INTRODUCTION

Liver transplantation (LT) is the gold standard curative treatment for end-stage liver disease, acute liver failure and hepatocellular carcinoma. The aim of LT is to improve life expectancy and quality. Hepatitis C is the most common indication for LT, and the major risk factor for hepatitis C virus (HCV) infection is intravenous drug abuse. Alcoholic liver disease (ALD) is the second most common indication for LT in the United States and Europe[1]. Except for alcohol consumption, addictive behavior is poorly studied in transplant patients[2], and there are many obstacles to obtaining pre- and post-transplant data for psychoactive substance consumption. Currently, the question of how to select transplant candidates is often posed; selection is intended to guarantee a survival probability of at least 50% at 5 years with good quality-of-life. How psychoactive substance consumption affects survival rates and post-surgery outcome are major questions that must be answered.

Firstly, the aim of this review is to describe psychoactive substance consumption of patients after LT; and secondly the various treatments available for patients presenting with substance abuse will be described.

## PSYCHOACTIVE SUBSTANCE CONSUMPTION AFTER LT

### *Alcohol consumption in LT patients*

Currently, ALD is the second most common indication of LT worldwide, with 30% to 50% of all LT in Europe and 17% in the United States[3]. The survival rates in Europe are 75% at 5 years and 68% at 10 years[1].

The rates of alcohol relapse vary from 7% to 95% because of the heterogeneity of its definition[4-7]. The notion of relapse goes from "slips" to severe relapse[8,9]. The moment and the intensity of alcohol relapse are both important. DiMartini *et al*[9] identified four distinct types of alcohol consumption in liver transplant recipients. Patients who drank low amounts infrequently, patients with early moderate use that decreased over time, patients with later moderate use that increased over time and patients with early and increasing use. Patients who died of recurrent alcoholic liver diseases were in groups with early alcohol relapse after LT[9,10].

Severe relapse consists in the consumption of more than 14 units of alcohol per week for women and more than 21 per week for men[8-12]. The frequency of severe relapse is estimated at 11% to 26%[13] and 5 years after LT this type of relapse decreases life expectancy regardless of the primary indication of surgery[14-17].

Previous studies have attempted to identify the risk factors of alcohol relapse such as the duration of pre-transplantation abstinence, the severity of alcohol dependence, neurocognitive data, male sex, polyaddiction, and social isolation[18-20]. These risk factors are not clearly adapted to the prediction of severe relapse. Some LT teams have suggested calculating a risk of relapse score[21], but their multi-center findings are not yet available[17]. The effect of addiction treatment before LT has been little studied as yet[22,23]; these studies used classical behavioral therapies and were limited with regard to medication, which is not indicated for patients with end-stage liver disease. More recently, baclofen, which is not metabolized by the liver, has demonstrated some effectiveness in maintaining abstinence in cirrhosis patients[24]. This pre-graft period is very special because the question of "life or death" is posed, and there is a serious deterioration in the quality-of-life. Patients on the waiting list are extremely anxious and some present symptoms of depression, stress or insomnia and are in denial of their disease[25]. Apart from a standard addictological follow-up, implementation of any new addictological procedures at this difficult time is neither suitable nor effective. Masson *et al*[26] tried to define an "alcohol contract" before LT in which patients awaiting transplant confirmed their abstinence. This contract did not have any effect on severe relapse rates after LT. In the general population there is a wide variety of alcohol use disorders (AUD), and most people with AUD go into remission after three years without any specific addiction treatment[27]. As Dom says very well[18] some patients with an AUD are more at risk of relapse than others and the course of LT tends to have selected those patients with a low risk of alcohol relapse.

For a minority of transplanted patients, severe relapse exists. The diagnosis of severe alcohol relapse after LT is very difficult for the transplant team. It can be made using several tools such as clinical, blood or urinary analysis, an interview with an addiction specialist or histological data[28,29]. Diagnosis and treatment of severe relapse requires the presence of an addiction unit within the LT center[30,31]. In Table 1, previous significant reports on alcohol relapse are given.

### *Tobacco consumption in LT patients*

Tobacco use is the first preventable cause of mortality in the general population of the United States with a prevalence of 20.9%[2]. During the pre-transplant period, 57% of patients have a lifetime prevalence of smoking, and 27% of all patients are active smokers[32]. Tobacco use is associated with graft loss and higher mortality in kidney, pancreas, lung and heart transplant patients[33]. In LT patients, tobacco use is associated with an increase in the incidence of vascular complications, but this was not found in

**Table 1 Previous significant reports on alcohol relapse after liver transplantation**

| Theme | Ref. | Year | Journal |
|---|---|---|---|
| Risk factors of alcohol relapse | De Gottardi *et al*[21] | 2007 | *Arch Intern Med* |
| | Dew *et al*[4] | 2008 | *Liver Transpl* |
| Types of relapse | Tome *et al*[8] | 2003 | *J Hepatol* |
| | DiMartini *et al*[9] | 2010 | *Am J Transplant* |
| | Faure *et al*[15] | 2012 | *Journal of Hepatology* |
| | Dumortier *et al*[10] | 2015 | *Am J Gastroenterol* |
| Treatment of alcohol relapses | Dimartini *et al*[28] | 2001 | *Psychosomatics* |
| | Weinrieb *et al*[23] | 2007 | *Liver Transpl* |
| | Addolorato *et al*[31] | 2013 | *Alcohol Clin Exp Res* |
| | Dom *et al*[17] | 2015 | *World J Hepatol* |
| | Donnadieu-Rigole *et al*[30] | 2017 | *Alcohol Clin Exp Res* |

all the series[32,34,35]. *De novo* cancers are the second cause of late mortality after LT; during recent years, series of LT patients have shown an increase in upper aerodigestive tract, colon and kidney tumors[36-38]. Tobacco use before transplantation seems to be a risk factor for malignancies in LT patients presenting with alcoholic liver disease[39]. Other risk factors for malignancies are advanced age, alcohol consumption pre-and post-transplantation, viral infections, sun exposure, obesity, premalignant lesions and tacrolimus exposure levels[36,37]. Cardiac events in LT patients also limited long-term survival[40] and tobacco is a well-known risk factor for cardiovascular diseases[39].

Some authors believe that tobacco use should be a contraindication to organ allocation demanding smoking cessation before transplantation; other authors just recommended abstinence[41]. For kidney transplant recipients, a program for treating tobacco use was designed by Ehlers *et al*[42]. This program could be adapted to LT patients with systematic addiction consultations before and after LT.

Iruzubieta *et al*[43] proposed pre- and post-transplant follow-up during which tobacco use after LT should be taken care of.

### *Polysubstance abuse in LT patients*

There are very few exact descriptions of the prevalence of polysubstance use in LT patients during pre- or post-transplant periods.

When a patient is dependent on a psychoactive substance they are at higher risk of being dependent on another one; this is true for tobacco and cannabis, so any detection of cannabis use must be systematically investigated in pre- and post-LT patients. Cannabis use is often associated with other psychoactive substance consumption in a context of polysubstance abuse[44]. In this series of polysubstance abuse in LT patients, the mean number of substances consumed was 3 before LT. The etiology of the end-stage liver disease was HCV infection and substance abuse had no impact on survival rates after LT. In the event of HCV infection as the primary indication, lifelong abuse of alcohol or other substances is often missed by the referent physician[45,46].

Patients on methadone maintenance therapy (MMT) for opiate dependence have not been well studied after LT; Weinrieb *et al*[47] and Tome *et al*[48] described more severe recurrent HCV infection and 20% of alcohol or illicit drug use after LT in these patients, but larger studies are necessary.

## TREATMENT OF ADDICTIVE BEHAVIORS IN LT PATIENTS

### *Treatment of alcohol relapses*

Although LT is the treatment of choice in the event of liver failure, some patients need specific follow-up post-surgery. No specific follow-up treatment is recommended for transplant recipients with addiction disorders, but motivational therapies have proved their effectiveness in this indication[49,50]. In the general population, they reduce mortality of liver diseases[51]. Psychotherapies include Twelve-step Facilitation Therapy, which is recommended by Alcoholics Anonymous; Cognitive-Behavioral Therapy and Motivational Enhancement Therapy can promote abstinence or help to reduce the amount of alcohol drunk[52-55].

Medication exists to treat alcohol dependence. Acamprosate is a medication that has proved its effectiveness in maintaining abstinence[55]. Naltrexone, an opioid receptor inhibitor, is effective on alcohol craving[56]. These two medicinal products are poorly studied in liver disease, so they are not currently approved in LT recipients and further studies are necessary[57]. Disulfiram (an acetaldehyde dehydrogenase) is a treatment which causes unpleasant sensations that prevent alcohol consumption. This treatment is potentially hepatotoxic and must be used with caution in LT patients[52]. Baclofen is the only treatment of alcohol dependence that has been studied in patients with alcoholic cirrhosis[24]. Pharmacotherapy should be associated with psychosocial support[58].

### *Treatment of opioid dependence*

MMT for opiate-dependent patients at any dosage is not a contraindication for transplantation[59,60] but MMT patients continue to be discriminated against and it is very important to repeat that patients

should not be weaned from methadone before liver transplantation[59]. This treatment may be associated with anti-rejection drugs without specific supervision.

### *Treatment of tobacco cessation*

For tobacco, patients transplanted for alcoholic liver disease often resume smoking very soon after surgery and the number of cigarettes smoked increases rapidly with patients smoking more than during the pre-transplantation period[61]. Nicotine replacement therapies can be used after LT. Bupropion should be used with caution in patients with liver disease and there are no contraindications for varenicline except allergy[62] but these medicinal products have not been studied in LT recipients.

In our LT center a systematic addiction consultation was made before LT and follow-up was proposed to patients with a high level of risk factors, but this did not result in the reduction of severe alcohol relapse.

A structured addiction consultation such as BRENDA[63] (B for biopsychosocial evaluation, R for restitution, E for Empathy, N for Needs identification, D for Direct counseling, A for Assess) in order to prevent and diagnose any alcohol relapse as soon as possible is now proposed systematically one month after LT.

Furthermore, these addiction consultations will promote tobacco cessation and/or prevention and treatment of psychoactive substance consumption.

## CONCLUSION

There are many barriers to obtaining and documenting data about alcohol and illicit drug use by transplant recipients. One such barrier is the fear of patients and their referent physicians of judgment and medical sanction. But the objectives of addiction specialists are to improve life expectancy and quality without automatically obtaining total abstinence in patients. For all patients the period of LT surgery is a real "psychological earthquake" and causes behavioral changes that should be systematically evaluated after a few weeks of convalescence. Whatever the primary indication of LT, all transplanted patients should be seen at least once during the post-transplantation period to document present or past use of tobacco, alcohol, opiates, marijuana, cocaine and other drugs. There are no specific guidelines for behavioral management in LT patients, but non-judgmental care and a fostering attitude by the transplant team is recommended[64,65]. As well as transplant surgeons and anesthetists, addiction specialists must actively participate in the patient's clinical journey before, and especially after, LT.

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ORIGINAL ARTICLE

Retrospective Study

# Low serum albumin predicts early mortality in patients with severe hypoxic hepatitis

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## Abstract

### *AIM*

To evaluate the incidence, etiology, and predictors of mortality of severe hypoxic hepatitis.

### *METHODS*

We used computerized patient records to identify consecutive cases of severe hypoxic hepatitis admitted to a tertiary hospital in Singapore over a one-year period. We defined severe hypoxic hepatitis as elevation of serum transaminases more than 100 times upper limit of normal in the clinical setting of cardiac, circulatory or respiratory failure after exclusion of other causes of hepatitis. We used multivariable regression analysis to determine predictors for mortality.

### *RESULTS*

We identified 75 cases of severe hypoxic hepatitis out of 71380 hospital admissions over one year, providing an incidence of 1.05 cases per 1000 admissions. Median age was 65 years (range 19-88); 57.3% males. The most common etiologies of severe hypoxic hepatitis were acute myocardial infarction and sepsis. Fifty-three patients (71%) died during the hospitalization. The sole independent predictive factor for mortality was serum albumin measured at the onset of severe hypoxic hepatitis. Patients with low serum albumin of less than 28 g/L have more than five-fold increase risk of death

(OR = 5.39, 95%CI: 1.85-15.71).

***CONCLUSION***
Severe hypoxic hepatitis is uncommon but has a high mortality rate. Patients with low serum albumin are at highest risk of death.

**Key words:** Severe; Mortality; Albumin; Incidence; Hypoxic hepatitis; Predictors; Etiology; Prognosis



**Core tip:** Hypoxic hepatitis is an important cause of liver injury that is associated with a high mortality rate. We sought to evaluate the incidence, etiology and predictors of mortality of severe hypoxic hepatitis in a large tertiary-level hospital in Singapore. Our findings confirm that the prevalence and mortality rate of severe hypoxic hepatitis in Asians is consistent with previous studies. Importantly, the unique finding from our study is that low serum albumin level is an independent predictive factor for mortality in severe hypoxic hepatitis, with a five-fold increase in risk of death in patients with serum albumin less than 28 g/L.

Chang PE, Goh BBG, Ekstrom V, Ong ML, Tan CK. Low serum albumin predicts early mortality in patients with severe hypoxic hepatitis. *World J Hepatol* 2017; 9(22): 959-966 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i22/959.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i22.959

## INTRODUCTION

Hypoxic hepatitis - inflammation and necrosis of the liver due to hypoxia - can be a devastating disease. It is characterized by a substantial but transient increase in serum transaminase levels in the setting of cardiac, circulatory or respiratory failure, after exclusion of viral hepatitis and drug-induced liver injury[1]. Although initially referred to as "ischemic hepatitis", the term hypoxic hepatitis is now preferred as it is recognized that ischemia is not the sole contributing factor[2-4]. The typical presentation of hypoxic hepatitis is a sudden massive increase in serum transaminases, typically above ten times the upper limit of normal, due to massive hepatocyte necrosis. Characteristically there is predominant elevation of aspartate transaminase (AST) over alanine transaminase (ALT) followed by their rapid decline.

Severe hypoxic hepatitis can occur when there is massive elevation of serum transaminases, more than 100 times the upper limit of normal. The incidence, causes and predictive factors of mortality in patients with severe hypoxic hepatitis have not been well described. In a previous study examining the clinical outcomes of patients with extreme elevations of serum transaminases (ALT and/or AST more than 3000 U/L), we observed a high rate of mortality in patients with low serum albumin and advanced age[5]. In this present study, we sought to determine the incidence and predictors of mortality in patients with severe hypoxic hepatitis.

## MATERIALS AND METHODS

### *Identification of patients with severe hypoxic hepatitis*

Consecutive cases of severe hypoxic hepatitis were identified from the computerized database of patient admissions to a large tertiary care hospital in Singapore over a one-year period. Cases of severe hypoxic hepatitis were defined by the presence of the following three factors: Massive elevation of serum transaminases (either ALT and/or AST values greater than 3000 U/L), with rapid decline over 5 d, a typical clinical setting of cardiac, circulatory or respiratory failure, and the exclusion of all other causes of liver necrosis, particularly viral or drug-related hepatitis[1].

The ethics committee of the hospital approved waiver of informed consent for this retrospective study, which was conducted in accordance with the Declaration of Helsinki. Case records of patients fulfilling the above criteria were retrieved and two independent reviewers (Chang PE and Goh BBG) systematically extracted the relevant patient demographic data, clinical details and hemodynamic data. Relevant laboratory data was analyzed, including liver function, renal function and cardiac function tests. Specifically, the date of elevation of serum transaminases to > 3000 U/L and the trend of resolution were analyzed. Baseline laboratory data was defined as the laboratory values performed on the day of onset of elevation of serum transaminases to > 3000 U/L.

### *Analysis of precipitating factors for severe hypoxic hepatitis*

Patient records were analyzed in detail to identify precipitating factors for hypoxic hepatitis. In particular, episodes of hypotension, arrhythmia, bradycardia, hypoxia and acidosis in the 48 h prior to the development of severe hypoxic hepatitis were analyzed. A hypotensive episode was defined as documented systolic blood pressure < 90 mmHg on at least two separate readings. Arrhythmia was defined as an abnormally rapid heart rate > 120 beats per minute, accompanied by electrocardiogram evidence of an abnormal heart rhythm. Bradycardia was defined as documented heart rate less than 60 beats per minute or a lowering of the heart rate by more than 25% of the baseline heart rate. Hypoxic episodes were defined as arterial oxygen saturation < 90% on pulse oximetry and/or partial pressure of oxygen < 60 mmHg on arterial blood gas. Metabolic acidosis was defined as a pH < 7.4 on arterial blood gas associated with serum bicarbonate of < 20 mmol/L. The inpatient medication records and clinical drug history were carefully analyzed to identify any potential hepatotoxic medications taken prior to the onset of severe hypoxic hepatitis.

**Table 1 Clinical characteristics of patients with severe hypoxic hepatitis *n* (%)**

| | *n* = 75 |
|---|---|
| Demographics | |
| Age | 61.9 ± 16.6 |
| Male gender | 43 (57.3) |
| Race (Chinese/Malay/Indian) | 51/20/4 (68/26.7/5.3) |
| Pre-existing co-morbidities | |
| Pre-existing ischemic heart disease | 41 (54.7) |
| Pre-existing cardiac failure | 27 (36.0) |
| Pre-existing renal failure | 27 (36.0) |
| Pre-existing chronic viral hepatitis | 5 (6.7) |
| Precipitating conditions | |
| Documented hypotension | 55 (73.3) |
| Documented bradycardia | 11 (14.7) |
| Documented metabolic acidosis | 43 (57.3) |
| Baseline laboratory parameters[1] | |
| Albumin (g/L) | 25.3 ± 6.9 |
| Bilirubin (μmol/L) | 76.1 ± 82.6 |
| GGT (U/L) | 126 ± 90 |
| Creatinine (mmol/L) | 321 ± 211 |
| Prothrombin time (seconds) | 27.8 ± 12.2 |
| ALT (U/L) | 2295 ± 1656 |
| AST (U/L) | 4896 ± 2986 |
| ALT/AST ratio_D1[2] | 0.70 ± 1.36 |
| Peak ALT (U/L) | 2834 ± 1938 |
| Peak AST (U/L) | 5894 ± 3148 |
| Clinical outcome | |
| Admitted to ICU | 50 (66.7) |
| Died within same admission | 53 (70.7) |

[1]Measured at onset of severe hypoxic hepatitis; [2]Ratio of the ALT to AST at the first documentation of either ALT or AST > 3000U/L. AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase; ICU: Intensive care unit.

### *Clinical course of severe hypoxic hepatitis*

The clinical evolution of consecutive patients with severe hypoxic hepatitis was recorded for each subject. This included admissions to the intensive care unit (ICU), length of stay in ICU and survival to discharge from hospital. For patients who died, the cause of death was based on the diagnosis stated on the death certificate. In cases where post-mortem examination was performed, the cause of death was based on the final coroner's report. The etiology of hypoxic hepatitis was based on thorough review of clinical data, laboratory results, clinical evolution and autopsy details.

### *Study outcome*

The data was analyzed to identify potential predictive factors for mortality, defined as death within the same admission as the episode of severe hypoxic hepatitis. Patients who survived to discharge were followed up for a further six months to determine the incidence of delayed mortality.

### *Statistical analysis*

Clinical variables were compared between patients who died and those who survived to discharge. $\chi^2$ analysis was performed for comparisons of discrete variables and Students *t*-test was used for comparison of continuous variables. Multivariable regression analysis was performed to identify independent predictors of early mortality. Survival comparisons were performed using Kaplan Meier analysis and compared using log rank statistics. All statistical analyses were performed using SPPS version 21 (Chicago, IL, United States). A $P$ value of $< 0.05$ was considered statistically significant. Values in the text are described as mean ± SD or number (percentage of total) unless specified otherwise.

## RESULTS

### *Incidence of severe hypoxic hepatitis*

Of a total of 71380 admissions to the Singapore General Hospital over the course of one year, 75 patients fulfilled the predefined criteria for severe hypoxic hepatitis, providing an incidence of 1.05 cases of severe hypoxic hepatitis per 1000 admissions.

### *Clinical characteristics of severe hypoxic hepatitis*

The clinical characteristics of the 75 patients are summarized in Table 1. Median age was 65 years, of which 57% of were male. All patients were Asians, with a predominance of Chinese followed by Indians and Malays respectively, in keeping with the multi-ethnic nature of the Singapore population. A pre-existing history of ischemic heart disease and cardiac failure was present in 55% and 36% respectively. A precipitating hypotensive event in the 48 h preceding the rise in liver enzymes was documented in 73% of cases. Precipitating episodes of bradycardia and metabolic acidosis were identified in 14.7% and 57.3% respectively. As expected, AST levels were higher than ALT levels at the onset of hypoxic liver injury with mean ALT and AST levels of 2295 ± 1656 U/L and 4896 ± 2986 U/L respectively. The mean ratio of ALT to AST at onset (ALT/AST ratio_D1) was 0.70 ± 1.36. Peak ALT and AST levels reached 2834 ± 1938 U/L and 5894 ± 3149 U/L respectively, typically within the first 3 d. Normalization of serum transaminases occurred in 82% of the 22 patients who survived. Mean number of days to normalization of ALT was 43 ± 46 d and 29 ± 23 d for AST.

Fifty patients (66.7%) with severe hypoxic hepatitis required admission to the ICU. All patients required vasopressor support. Of these, 37 (74.0%) died. Mean duration of stay in ICU was significantly longer in those who died compared to those who survived (9.4 ± 12.1 d *vs* 3.2 ± 2.0 d, $P = 0.02$). All 13 patients who were discharged from ICU recovered and were safely discharged from hospital.

### *Etiology of severe hypoxic hepatitis*

The underlying etiology of severe hypoxic hepatitis was due to acute myocardial infarction (AMI) in 36% and septicemic shock in 32% (Figure 1). Congestive cardiac

**Table 2 Comparison between patients with severe hypoxic hepatitis who died and survived *n* (%)**

| | Died (*n* = 53) | Survived (*n* = 22) | *P* value |
|---|---|---|---|
| Demographics | | | |
| Age | 64.3 ± 17.6 | 56.3 ± 12.8 | 0.059 |
| Male gender | 35 (66.0) | 8 (36.4) | 0.018 |
| Race (Chinese/Malay/Indian) | 36/13/4 | 15/7/0 | 0.373 |
| Pre-existing co-morbidities | | | |
| Pre-existing ischemic heart disease | 27 (50.9) | 12 (54.5) | 0.793 |
| Pre-existing cardiac failure | 16 (30.2) | 11 (50.0) | 0.104 |
| Pre-existing renal failure | 19 (35.8) | 8 (36.4) | 0.966 |
| Precipitating conditions | | | |
| Documented hypotension | 45 (84.9) | 14 (63.6) | 0.041 |
| Documented bradycardia | 9 (17.0) | 2 (9.1) | 0.379 |
| Documented metabolic acidosis | 33 (62.3) | 10 (45.5) | 0.180 |
| Baseline laboratory parameters[1] | | | |
| Albumin (g/L) | 23.7 ± 6.8 | 29.1 ± 5.8 | 0.001 |
| Bilirubin (μmol/L) | 79.2 ± 84.4 | 68.8 ± 79.7 | 0.625 |
| ALT (U/L) | 2051 ± 1601 | 2880 ± 1674 | 0.048 |
| AST (U/L) | 5093 ± 2943 | 4440 ± 3103 | 0.395 |
| ALT/AST ratio_D1[2] | 0.50 ± 0.80 | 1.18 ± 2.15 | 0.051 |
| GGT (U/L) | 111 ± 67 | 158 ± 123 | 0.161 |
| Creatine kinase | 2949 ± 6180 | 395 ± 419 | 0.006 |
| Creatine kinase MB | 37.1 ± 56.6 | 13.5 ± 20.7 | 0.015 |
| Troponin T (Trop T) | 2.02 ± 4.21 | 0.49 ± 1.42 | 0.031 |
| Lactate dehydrogenase | 2503 ± 2552 | 4035 ± 3671 | 0.229 |
| Creatinine (mmol/L) | 297.3 ± 172.9 | 376.6 ± 276.3 | 0.143 |
| Prothombin time (seconds) | 27.8 ± 12.5 | 27.7 ± 11.9 | 0.980 |
| Peak ALT (U/L) | 2572 ± 2026 | 3464 ± 1575 | 0.069 |
| Peak AST (U/L) | 6223 ± 3138 | 5131 ± 3110 | 0.176 |

[1]Measured at onset of severe hypoxic hepatitis; [2]Ratio of the ALT to AST at the first documentation of either ALT or AST > 3000 U/L. AST: Aspartate transaminase; ALT: Alanine transaminase; GGT: Gamma glutamyl transferase.

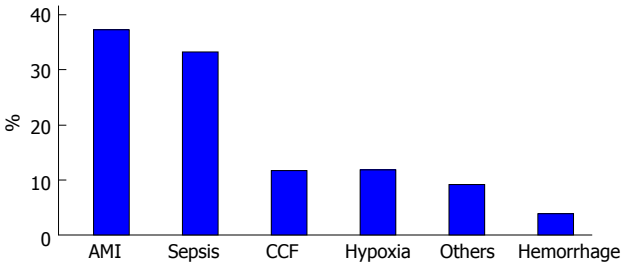


**Figure 1 Etiology of severe hypoxic hepatitis.** AMI: Acute myocardial infarction; CCF: Congestive cardiac failure.

failure, chronic respiratory failure and gastrointestinal hemorrhage accounted for the remaining cases of severe hypoxic hepatitis.

### *Mortality in severe hypoxic hepatitis*

Severe hypoxic hepatitis was associated with a high mortality rate, accounting for 53 (71%) deaths within the same admission. The main causes of death were AMI in 39.6%, sepsis in 30.2%, metastatic cancer in 13.2% and gastrointestinal hemorrhage in 5.7%. Amongst the survivors who were discharged, there were no cases of delayed mortality in the 6-mo follow-up period. The ability to recover from the acute hypoxic injury was thus associated with an excellent prognosis. The clinical characteristics of patients who survived and died within the same admission are compared in Table 2.

On univariate analysis, four variables were found to be significantly different between cases of severe hypoxic hepatitis who survived and those who died within the same admission (Table 3). Mortality was more common in males and in those with a precipitating hypotensive event. Interestingly, baseline serum albumin level and ALT (but not AST) levels measured at onset of severe hypoxic hepatitis were significantly lower in patients who died. However, the peak ALT and AST levels did not have any discerning effect on mortality. Markers of cardiac infarction (CK, CKMB and troponin T) were significantly elevated in those who died whereas bilirubin and prothrombin time were not different in the two groups, suggesting that the underlying cause of death in severe hypoxic hepatitis is related to underlying cardiac ischemia and not to liver failure.

On multivariable analysis (Table 3), the sole independent predictor of early inpatient mortality in severe hypoxic hepatitis was baseline serum albumin. Using area under receiving operator curve (AUROC) statistics (Figure 2), serum albumin was determined to be an accurate predictor of mortality in severe hypoxic hepatitis with an AUROC of 0.740 ($P$ = 0.001, 95%CI: 0.617-0.862). Baseline serum albumin < 28 g/L was an accurate predictor of mortality with a sensitivity of 75%, specificity of 64% and positive predictive value of 83%. Using logistic regression analysis, a baseline serum albumin lower than 28 g/L was associated with

**Table 3 Univariate and multivariable analysis of predictive factors for mortality in severe hypoxic hepatitis**

| Variable | Univariate analysis | | Multivariable analysis | |
|---|---|---|---|---|
| | HR (95%CI) | *P* value | HR (95%CI) | *P* value |
| Age | 1.03 (0.99-1.06) | 0.069 | 1.07 (0.99-1.14) | 0.056 |
| Male gender | 0.29 (0.10-0.83) | 0.021 | 0.17 (0.03-1.19) | 0.074 |
| Precipitating hypotensive episode | 3.21 (1.02-10.14) | 0.046 | 4.40 (0.47-40.9) | 0.192 |
| Albumin | 0.88 (0.80-0.96) | 0.004 | 0.83 (0.71-0.96) | 0.015 |
| ALT | 1.00 (0.99-1.00) | 0.054 | 1.00 (1.00-1.00) | 0.609 |
| Creatine kinase | 1.00 (1.00-1.00) | 0.032 | 1.00 (1.00-1.00) | 0.068 |
| Creatine kinase MB | 1.02 (0.99-1.05) | 0.122 | 0.98 (0.94-1.02) | 0.330 |
| Troponin T | 1.39 (0.88-2.16) | 0.178 | 1.29 (0.74-2.27) | 0.374 |
| ALT/AST ratio_D1[1] | 0.65 (0.35-1.19) | 0.160 | 0.22 (0.04-13.1) | 0.465 |

[1]Ratio of the ALT to AST at the first documentation of either ALT or AST > 3000 U/L. ALT: Alanine transaminase; AST: Aspartate transaminase.

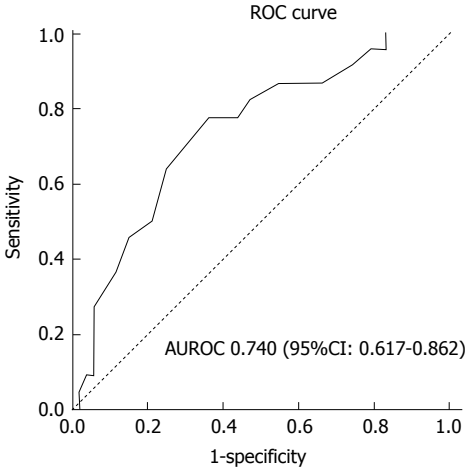


**Figure 2 Receiver operating curve of baseline serum albumin to predict mortality in severe hypoxic hepatitis.** AUROC: Area under receiving operator curve; ROC: Receiver operating curve.

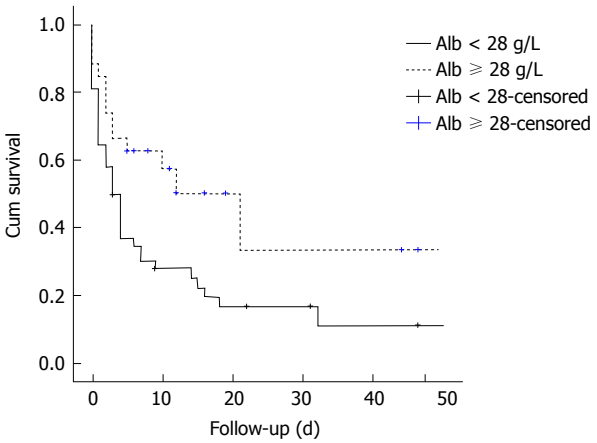


**Figure 3 Kaplan-Meier comparison of survival between severe hypoxic hepatitis patients with baseline serum album < 28 g/L and ⩾ 28 g/L.** Alb: Albumin.

a five-fold increased risk of early mortality (OR = 5.39, 95%CI: 1.85-15.71). Median survival was 85% lower in severe hypoxic hepatitis patients with baseline serum albumin less than 28 g/L compared to those with baseline albumin greater than 28 g/L (3.0 d *vs* 21.0 d, *P* = 0.015 by log-rank comparison, Figure 3).

## DISCUSSION

To our knowledge, this is the first study to describe the clinical course and outcome of Asian patients with severe hypoxic hepatitis. Several key findings are noted - firstly, severe hypoxic hepatitis occurs with an incidence of 1.05 in every 1000 admissions to a tertiary level general hospital in Singapore. The clinical presentation of severe hypoxic hepatitis in Asian patients is not different from that reported in Western studies[6-8]. Secondly, the clinical outcome of severe hypoxic hepatitis is poor with a high mortality rate of 71%. Thirdly, most deaths associated with severe hypoxic hepatitis are due to acute myocardial infarction and sepsis and not due to liver failure. Finally and most importantly, the unique finding in our study is that low serum albumin at baseline is an independent predictor of early mortality in patients with severe hypoxic hepatitis.

There is a wide variation in the reported incidence of hypoxic hepatitis ranging from 1 per 1000 admissions to 4 per 100 admissions[6,7]. The reason for this wide variation is the denominator, *i.e.*, the population of patients studied. The incidence of hypoxic hepatitis is expectedly lower in studies including all general admissions compared to those focusing on admissions to intensive care units[8-10]. The denominator in our study was all admissions to a tertiary care hospital over a one-year period. The incidence of 1.05 cases of severe hypoxic hepatitis per 1000 admissions in our Asian center is consistent with the literature from studies performed in Western populations[11-14].

Our study demonstrates that the clinical profile of Asian patients with severe hypoxic hepatitis is similar to that reported in Western studies. A history of ischemic heart disease and cardiac failure are common and was present in 55% and 36% of our study cohort respectively. Pre-existing passive hepatic congestion has been proposed as a pre-requisite condition for the development of hypoxic hepatitis[15,16]. Patients with chronically elevated right heart pressures are

prone to developing congestive hepatopathy resulting in decreased hepatic perfusion to hepatocytes. In such patients, a slight decrease in the hepatic arterial perfusion pressure may be sufficient to cause hypoxic hepatitis. Indeed, Seeto *et al*[17] have demonstrated that as little as 15 min of transient systemic hypotension is sufficient to produce massive hepatocyte necrosis in patients with pre-existing congestive hepatopathy. However, as demonstrated in our study, a precipitating episode of hypotension is not necessarily seen in all patients with hypoxic hepatitis[16].

Severe hypoxic hepatitis is associated with a high mortality rate[18]. More than two-thirds of patients in our study cohort died, which is at the higher end of the range of 30%-77% reported in similar studies[6,9,10,18]. The underlying etiology of severe hypoxic hepatitis is strongly associated with risk of early mortality. Ninety-three percent of patients with severe hypoxic hepatitis due to AMI died compared to only 58% of non-AMI-related etiologies. However, neither the severity of elevation of liver transaminases nor the rate of resolution of elevated transaminases was associated with mortality. The cause of death has not been reported in meta-analysis of studies on hypoxic hepatitis[7]. In our study, the main cause of death was due to cardiovascular failure in 40%, followed by septic shock with multi-organ failure in 30%. In both conditions, the underlying pathophysiological process is inadequate perfusion pressure to the essential organs. Importantly, liver failure is not the cause of death in patients with severe hypoxic hepatitis. This reinforces the point that the primary strategy in the management of patients with severe hypoxic hepatitis is to focus on maintaining systemic perfusion pressure and to correct the underlying cause of hypoperfusion be it due to primary cardiac pump failure, massive peripheral vasodilatation due to sepsis or hypovolemia from hemorrhage[6].

The novel aspect of this study is the finding that baseline serum albumin is an independent predictor of early mortality in patients with severe hypoxic hepatitis. Duration of hypoxic hepatitis, INR, presence of septic shock, SOFA score, jaundice, need for renal replacement and vasopressor therapy have previously been suggested to be factors that predict mortality in hypoxic hepatitis[9,18-21]. However, serum albumin has never been previously reported to be an independent predictor for mortality in hypoxic hepatitis.

Hypoalbuminemia is a well-known predictor of mortality in patients with acute illness[22,23]. Serum albumin on admission has been shown to be a strong predictor of inpatient mortality in internal medicine wards[24,25]. Furthermore, a progressive decrement of serum albumin concentration is associated with a 24%-56% increase in odds of death[26]. Decline in albumin levels occurs in acute illnesses due to increased catabolism, reduced hepatic synthesis and renal loss. Albumin is often viewed as a non-specific negative acute phase protein that reflects the severity of the underlying illness. It is thus conceivable that low serum albumin may be associated with increased mortality in patients with hypoxic hepatitis, as in any other systemic illness. However, our study provides evidence that albumin is an independent predictor for mortality in severe hypoxic hepatitis, with a strong odds ratio. This suggests that low serum albumin levels may play a direct role in causing cardiovascular-related mortality in patients with severe hypoxic hepatitis.

Low serum albumin levels are associated with increased risk of mortality in coronary disease[27] and cardiac failure[28,29]. This is attributed to slower coronary flow in patients with low albumin levels[30]. In a study investigating the relationship between serum albumin and coronary flow rate following primary percutaneous coronary intervention[31], baseline serum albumin levels were significantly lower in the group with no coronary reflow compared to normal coronary reflow and serum albumin was identified as an independent predictor of no-reflow. Low levels of serum albumin cause an increase in coronary blood viscosity and disruption of endothelial function due to increased concentrations of free lysophosphatidylcholine[32]. In addition, albumin is an important inhibitor of platelet aggregation through increases in production of antiaggregatory prostaglandin PGD2 from cyclic endoperoxidases[33]. Low levels of serum albumin thus increase risk of platelet aggregation in the coronary vasculature, hence increasing risk of AMI. The novel association observed between low serum albumin levels and increased mortality risk in severe hypoxic hepatitis can thus be potentially explained by the effects of low albumin on slowing coronary flow and increased platelet aggregation, thus increasing risk of acute myocardial infarction and early death. However, this postulation remains speculative and needs to be evaluated in future prospective studies.

Low serum albumin levels are also associated with increased mortality in patients with severe sepsis[34]. Serum albumin plays an important role in modulating innate immune responses to systemic inflammation and sepsis[35]. The ability of serum albumin to modulate inflammation and oxidative stress as well as inhibit neutrophil adhesion could provide some protection from endothelial dysfunction mediated by these factors[36,37]. Although several studies have demonstrated efficacy of albumin infusions in improving outcome in septic patients[38], others have not demonstrated any meaningful benefit[39,40]. It thus remains unclear whether low serum albumin is a direct cause of mortality or a surrogate for severity of illness in patients with sepsis.

Our findings are clinically important because it provides the clinician with a simple way to identify patients with severe hypoxic hepatitis who are at highest risk of death. Patients with severe hypoxic hepatitis with a baseline serum albumin level less than 28 g/L can be fast-tracked for ICU care and early vasopressor therapy to maintain adequate central perfusion. Of interest is whether timely intervention

with intravenous albumin will result in a reduction of mortality in patients with severe hypoxic hepatitis.

There are several limitations to this study, including the retrospective study design. The study was limited to a single center, which may limit the generalizability of the findings. This study focused on patients with severe elevation of serum transaminases beyond 100 times the upper limit of normal. The findings of our study are thus limited to patients with severe hypoxic hepatitis and may not be applicable to milder degrees of hypoxic hepatitis.

In conclusion, severe hypoxic hepatitis is associated with high mortality. Most deaths are related to underlying cardiovascular failure and septic shock with multi-organ failure. Low serum albumin levels at the onset of severe hypoxic hepatitis is an independent predictor of mortality and is a useful clinical marker for early prognostication of patients at high risk of death.

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## COMMENTS

### Background

Hypoxic hepatitis is an important cause of acute liver injury that is associated with a high mortality rate.

### Research frontiers

The novel aspect of this study is the finding that baseline serum albumin is an independent predictor of early mortality in patients with severe hypoxic hepatitis.

### Innovations and breakthroughs

This is the first study to describe the clinical course and outcome of Asian patients with severe hypoxic hepatitis. The unique finding in this study is that low serum albumin at baseline is an independent predictor of early mortality in patients with severe hypoxic hepatitis.

### Applications

These findings are important because it provides the clinician with a simple way to identify patients with severe hypoxic hepatitis who are at the highest risk of death.

### Peer-review

It was a nice retrospective study and very interesting to read. What I especially liked that you did not forget to state that mortality actually depends on the underlying disease and not the condition of the liver itself.

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EVIDENCE-BASED MEDICINE

# Serum cholinesterase: A predictive biomarker of hepatic reserves in chronic hepatitis D

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## Abstract

***AIM***

To determine the predictive performance of cholinesterase compared to existing prognostic models in evaluating liver function in patients with chronic hepatitis D.

***METHODS***

In an observational, cross-sectional and retrospective study, consecutive patients with hepatitis D cirrhosis were evaluated. Demographic, clinical and laboratory parameters were recorded. Serum cholinesterase levels were correlated with existing scoring models for chronic liver disease and Liver function tests. Receiver operating characteristic (ROC) curves were constructed to find an optimal cholinesterase level predicting ascites, Child Turcotte Pugh (CTP) score $\geqslant$ 10, model for end stage liver disease (MELD) score $\geqslant$ 15, baseline-event-anticipation (BEA) score for hepatitis D $\geqslant$ 5 and the aspartate transaminase to Platelet Ratio Index (APRI) $\geqslant$ 1.5.

***RESULTS***

This study investigated 233 patients with chronic liver disease due to hepatitis D; 192 were male, median age 42 (16-69 years). Fifty patients had ascites and 15 had encephalopathy. One hundred and sixty-seven (71.7%) were in Child class A, 52 (22.3%) in Child class B and 14 (5.0%) in class C. A MELD score of 15 or more was seen in 24 patients. Cholinesterase levels correlated well with the INR, albumin, CTP score, MELD, MELD sodium, BEA and APRI scores ($P$ < 0.001 each). Area under the ROC curve for ascites, CTP $\geqslant$ 10, MELD $\geqslant$ 15, BEA $\geqslant$ 5, APRI $\geqslant$ 1.5 was 0.836, 0.966, 0.913, 0.871 and 0.825 respectively ($P$ < 0.001 each). Cut off values of cholinesterase (IU/L) for predicting ascites, CTP $\geqslant$ 10, MELD $\geqslant$ 15, BEA $\geqslant$ 5 and APRI $\geqslant$ 1.5

were < 3812, < 2853, < 2829, < 4719 and < 3954 with a sensitivity of 80%, 100%, 91.67%, 82.50%, 58.0% and specificity of 81.97%, 84.79%, 87.56%, 77.06% and 55.64% respectively.

***CONCLUSION***

Serum cholinesterase demonstrates promising correlations with serum albumin, INR and CTP, MELD, BEA and APRI scores and is predictive of liver reserves in hepatitis D cirrhosis.

**Key words:** Cholinesterase; Liver function; cirrhosis; Model for Endstage Liver Disease score; Aspartate transaminase-to-platelet ratio index; Hepatitis D; Child Turcotte Pugh score; Baseline-event-anticipation score



**Core tip:** Prognostic models to assess liver function in patients with chronic liver disease are used extensively in clinical settings. These systems employ multiple clinical and laboratory parameters to evaluate liver reserves and predict outcome. In our study we assessed cholinesterase as an independent predictor of hepatic reserves. We found that its values correlated strongly with Liver function tests and with the existing scoring models. Thereafter, we defined optimal cholinesterase levels corresponding to the different stages and classes of the scoring systems and hence the severity of chronic liver disease. The study's subjects were patients suffering from cirrhosis due to hepatitis D.

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## INTRODUCTION

Prognostic models to evaluate liver function include the Child Turcotte Pugh (CTP) score, the Model for Endstage Liver Disease (MELD) score and the aspartate transaminase to Platelet Ratio Index (APRI). The CTP score is often used to assess the risk of surgery in patients with cirrhosis and it correlates with survival[1]. The MELD score is used by the United Network of Organ Sharing (UNOS) to prioritize patients awaiting cadaveric liver transplant[2]. An increase in the MELD score is associated with an increasing severity of hepatic dysfunction and an increased three-month mortality risk. The APRI is considered as an alternative to liver biopsy for predicting liver fibrosis[3]. However, its role in some etiologies is controversial. Increasing levels > 1.5 may show decreasing hepatocyte mass and increasing fibrosis. Recently, a baseline-event-anticipation (BEA) score has been developed for hepatitis D to define clinical parameters associated with worse outcomes[4].

Commonly used liver synthetic function tests include serum albumin and prothrombin time and international normalized ratio. Serum butyrylcholinesterase, commonly known as serum cholinesterase, is an enzyme synthesized by hepatocytes and has the half-life of eleven days[5]. Its serum level is decreased in chronic liver damage, infections, and malnutrition[6].

Chronic hepatitis D is a severe disease with rapid progression of fibrosis leading to cirrhosis, decompensation and hepatocellular carcinoma[7]. The role of cholinesterase to assess the liver reserves in hepatitis D patients has not been well defined. The objective of this study is to determine the performance of cholinesterase in predicting liver function compared to existing synthetic liver function tests and scoring models in patients with hepatitis D and cirrhosis.

## MATERIALS AND METHODS

This observational, cross-sectional study examined the efficacy of cholinesterase as a liver function test to assess the synthetic reserve in a retrospective fashion. Two hundred and thirty-three consecutive patients presenting to the liver clinic with cirrhosis due to chronic hepatitis D were evaluated. Available baseline demographic and clinical parameters were recorded. Serum cholinesterase levels were checked as a routine test to evaluate liver function.

Data were expressed as the number of subjects with percentages for nominal variables. These variables were compared by $\chi^2$ or Fisher exact test. Continuous variables were presented as means with standard deviation, and compared using Student *t* test, Mann-Whitney *U* test and ANOVA. Correlations were tested using tests Pearson's correlation test. Receiver operating characteristic (ROC) curves were constructed to determine optimal cholinesterase levels predicting multiple state variables such as MELD score $\geqslant$ 15. Areas under receiver operating characteristic curves, sensitivity and specificity were used to examine the accuracy of the cholinesterase for various predictions. The state variables examined included Ascites, MELD score $\geqslant$ 15, MELD score > 10, APRI $\geqslant$ 1.5, BEA $\geqslant$ 5, CTP $\geqslant$ Class B and CTP $\geqslant$ Class C. Cutoff cause were determined by Youden's J statistic (verified by a unit weighted ROC cutoff based on minimizing the distance from the point representing perfect classification to the ROC curve). Statistical analyses were performed using SPSS 23.0 software (IBM SPSS Statistics, New York, NY, United States). All tests were 2-tailed and a *P* value < 0.05 was required for statistical significance.

## RESULTS

Out of 233 patients with chronic liver disease due to hepatitis D, 192 (82.4%) were male, the median age was 42 (range 16-69 years). Fifty (21.5%) patients had

**Table 1 Baseline characteristics of the study patients**

| No. of patients | 233 |
|---|---|
| Male:female | 192:41 |
| Age (yr) | 42 (16-69) |
| BMI (kg/m$^2$) | 23.4 (14.3-40) |
| Ascites | 50 (21.5) |
| Encephalopathy | 15 (6.4) |
| Bilirubin (mg/dL) | 0.90 (0.2-6.9) |
| Albumin (g/dL) | 3.8 (1.8-5.0) |
| INR | 1.13 (0.6-2.6) |
| Creatinine (mg/dL) | 0.8 (0.4-1.96) |
| Sodium (mmol/L) | 139 (120-150) |
| AST (IU/L) | 53 (10-638) |
| Platelets (× 10$^9$/L) | 120 (22-388) |
| Cholinesterase (IU/L) | 5508 (861-12891) |
| Child class | |
| A | 167 (71.7) |
| B | 52 (22.3) |
| C | 14 (5.0) |
| CTP score | 5 (5-13) |
| MELD score | 8 (6-24) |
| MELD sodium | 9 (6-26) |
| MELD score 15 or more | 24 (10.3) |
| APRI | 1.26 (0.19-10.8) |
| APRI 1.5 or more | 100 (42.9) |
| BEA class | |
| A | 6 (2.6) |
| B | 164 (70.4) |
| C | 63 (27) |
| BEA score | 4 (1-7) |

Values are median (range) or *n* (%). BMI: Body mass index; INR: International normalization ratio; AST: Aspartate aminotransferase; CTP: Child Turgotte Pugh; MELD: Model for End Stage Liver Disease; APRI: AST to platelet ratio index; BEA: Baseline-event-anticipation.

**Table 2 Mean cholinesterase levels**

| Parameter | Values (U/L) | *P* value |
|---|---|---|
| Child class | | |
| A (CTP up to 6) | 7058 ± 208 | |
| B (CTP 7-9) | 3773 ± 372 | < 0.001 (A *vs* B) |
| C (CTP ⩾ 10) | 1605 ± 129 | < 0.001 (B *vs* C) |
| MELD score | | |
| ⩾ 15 | 2285 ± 373 | |
| < 15 | 6423 ± 206 | < 0.001 |
| APRI | | |
| ⩾ 1.5 | 4002 ± 219 | |
| < 1.5 | 7498 ± 251 | < 0.001 |
| BEA score | | |
| A | 8036 ± 967 | |
| B | 6993 ± 222 | 0.337 (A *vs* B) |
| C | 3211 ± 258 | < 0.001 (B *vs* C) |

Values are mean ± SE. CTP: Child Turcotte Pugh; MELD: Model for End Stage Liver Disease; APRI: AST to platelet ratio index; BEA: Baseline-event-anticipation.

**Table 3 Receiver operating characteristic analysis**

| State variable | AUC | Std. error | Asymptotic sig. (*P* value) | 95%CI |
|---|---|---|---|---|
| Ascites | 0.836 | 0.038 | < 0.001 | 0.762-0.910 |
| CTP ⩾ 7 | 0.889 | 0.029 | < 0.001 | 0.832-0.946 |
| CTP ⩾ 10 | 0.966 | 0.013 | < 0.001 | 0.940-0.992 |
| MELD ⩾ 10 | 0.798 | 0.034 | < 0.001 | 0.731-0.864 |
| MELD ⩾ 15 | 0.913 | 0.038 | < 0.001 | 0.838-0.987 |
| APRI ⩾ 1.5 | 0.825 | 0.026 | < 0.001 | 0.773-0.877 |
| BEA ⩾ 5 | 0.871 | 0.028 | < 0.001 | 0.816-0.926 |

CTP: Child Turcotte Pugh; MELD: Model for End Stage Liver Disease; APRI: AST to platelet ratio index; BEA: Baseline-event-anticipation.

ascites and 15 (6.4%) encephalopathy. One hundred and sixty-seven (71.7%) were classified into Child class A, 52 (22.3%) into Child class B and 14 (5.0%) into class C. A MELD score of 15 or more was seen in 24 (10.3%). Cholinesterase levels (mean ± SEM) in males were 6177 ± 228 and in females were 5151 ± 452 ($P$ = 0.06). A statistically significant difference was not found between gender and BMI at any stage of the disease. The baseline characteristics of the study patients are recorded in Table 1. Cholinesterase levels correlated with the albumin, INR, CTP score, MELD, MELD sodium, APRI and BEA scores with the Pearson correlation coefficient, $r$ values of 0.724, -0.520, -0.624, -0.561, -0.533, -0.531, and -0.591 respectively ($P$ < 0.001 each) (Figure 1). The mean cholinesterase levels for each class are shown in Table 2.

Area under the ROC curve for ascites, CTP ⩾ 10, MELD ⩾ 15, BEA ⩾ 5, APRI ⩾ 1.5 was 0.836, 0.966, 0.913, 0.871 and 0.825 respectively ($P$ < 0.001 each) (Table 3 and Figure 2). Cut off values of cholinesterase (IU/L) for predicting ascites, CTP ⩾ 10, MELD ⩾ 15, BEA ⩾ 5 and APRI ⩾ 1.5 were < 3812, < 2853, < 2829, < 4719 and < 3954 with a sensitivity of 80%, 100%, 91.67%, 82.50%, 58.0% and specificity of 81.97%, 84.79%, 87.56%, 77.06 and 55.64% respectively (Table 4). Mean serum cholinesterase decreased with reduced hepatic reserves. For example patients in Child Class A had a mean cholinesterase of 7058 compared to those in Class B with 3773 and Class C with 1605. This is also reflected in the optimal cutoff values of < 3812 at Child Class B (CTP score 7-9) and < 2853 at Child Class C (CTP ⩾ 10) and similarly a value of < 4719 at MELD ⩾ 10 and < 2829 at MELD ⩾ 15.

## DISCUSSION

Traditional liver function tests and scoring systems used to stage severity of the liver disease face several inherent limitations. For example, the LFTs investigated in this study maybe abnormal in illnesses not associated with liver dysfunction. Aminotransferase levels may increase in non-hepatic disease such as myocardial infarction[8] while bilirubin maybe altered by hemolysis. Moreover, the CTP score includes subjective parameters such as the degree of ascites and encephalopathy[9] and these findings may be altered substantially by medical interventions. Furthermore, its role is limited due to a ceiling and floor effect: An inability to discriminate values for bilirubin > 3.0 mg /dL, INR greater > 2.3 and albumin less < 2.8 g/dL. Finally, the CTP score does not include creatinine for the

**Table 4 Optimal cholinesterase cutoffs**

| State variable | Cholinesterase cut off value (IU/L) | Sensitivity, % (95%CI) | Specificity, % (95%CI) | Likelihood ratio |
|---|---|---|---|---|
| Ascites | < 3812 | 80.00 (66.28- 89.97) | 81.97 (75.62-87.25) | 4.436 |
| CTP ⩾ 7 | < 3812 | 79.10 (67.43-88.08) | 67.47 (59.78-74.53) | 2.432 |
| CTP ⩾ 10 | < 2853 | 100.00 (79.41-100.00) | 84.79 (79.31-89.29) | 6.576 |
| MELD ⩾ 10 | < 4719 | 72.09 (61.38-81.23) | 80.27 (72.91-86.37) | 3.654 |
| MELD ⩾ 15 | < 2829 | 91.67 (73.00-98.97) | 87.56 (82.31-91.71) | 7.369 |
| BEA ⩾ 5 | < 4719 | 82.54 (70.90-90.95) | 77.06 (70.00-83.15) | 3.598 |
| APRI ⩾ 1.5 | < 3954 | 58.00 (47.71-67.80) | 55.64 (46.78-64.25) | 1.307 |

CTP: Child Turcotte Pugh; MELD: Model for End Stage Liver Disease; APRI: AST to platelet ratio index; BEA: Baseline-event-anticipation.

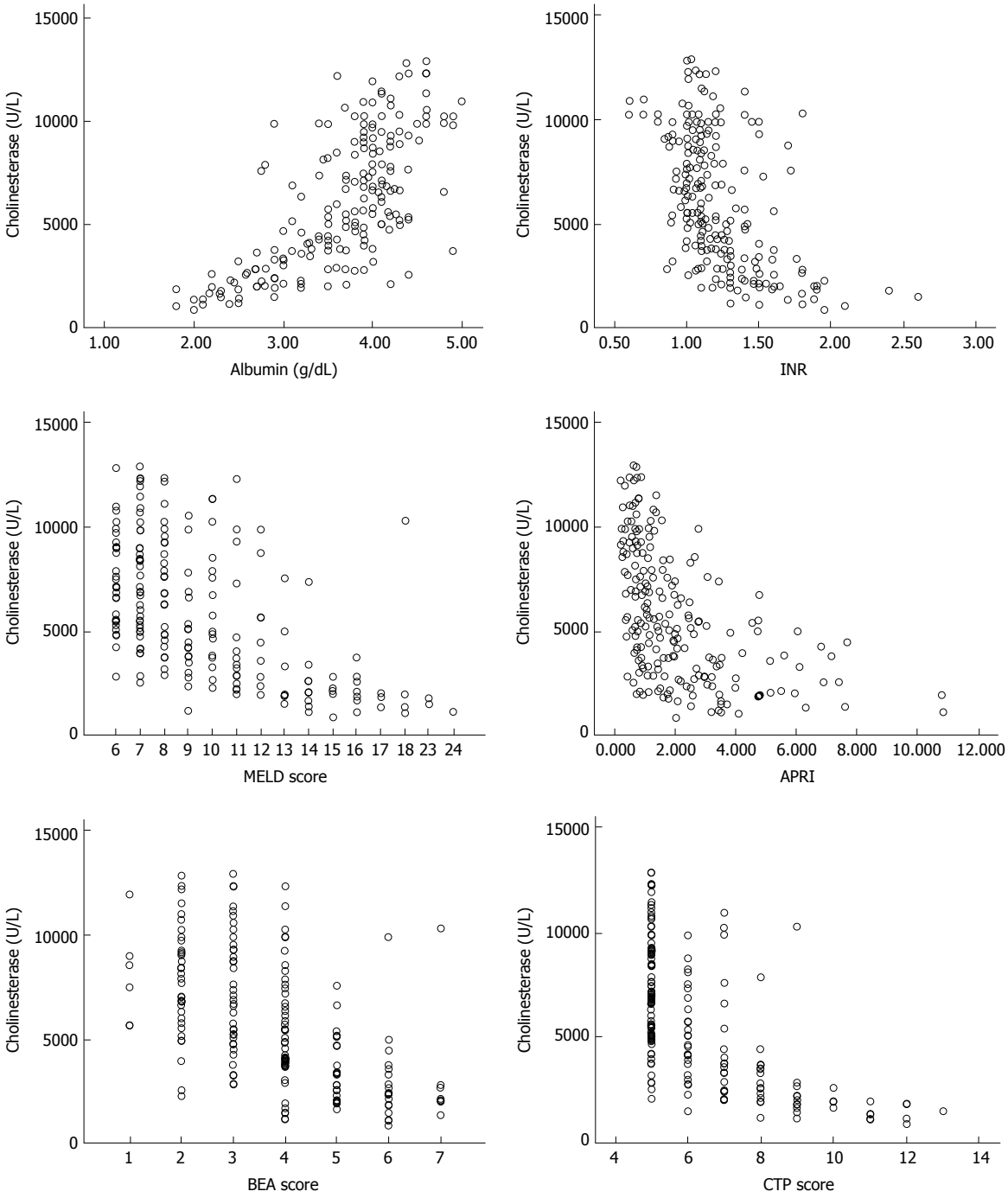


**Figure 1 Correlations of cholinesterase levels with the synthetic liver function tests and liver function prognostic models.** INR: international normalization ratio; MELD: Model for end stage liver disease; APRI: AST to platelet ratio index; BEA: baseline-event-anticipation; CTP: Child Turgotte Pugh.

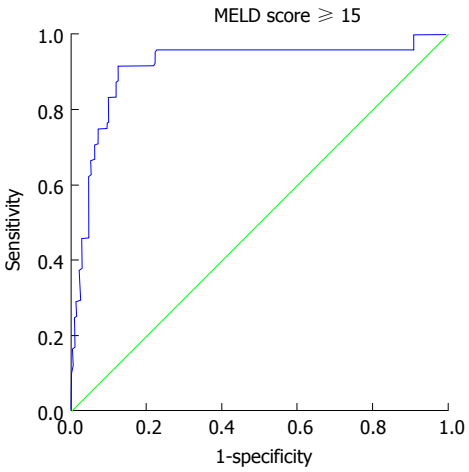


**Figure 2 Receiver operating characteristic curve.** Cholinesterase levels for model for end stage liver disease score 15 or more (A smaller test result indicates a more positive test). MELD: Model for Endstage Liver Disease.

assessment of renal function, another major marker of the severity of the disease.

The MELD score has been criticized for several different reasons[10-13]. It is vulnerable to variations in laboratory measurements and does not include portal hypertensive complications (*e.g.,* ascites, encephalopathy, variceal bleeding, and spontaneous bacterial peritonitis). Again, it suffers from a floor and ceiling effect: Patients with the combination of an INR of $\leqslant$ 1, creatinine $\leqslant$ 1 mg/dL, and bilirubin $\leqslant$ 1 mg/dL receive the minimum score of 6 MELD points, while UNOS set an upper limit for the MELD score at 40 points. Modifications of the MELD scoring system have been implemented by introducing the MELD sodium, by reweighting MELD components (lower weights ascribed to serum creatinine and international normalized ratio (INR) and a higher weight to serum bilirubin), by refitting MELD [by implementing new upper and lower bounds for creatinine (0.8 and 3.0 mg/dL, respectively) and for INR (1.0 and 3.0, respectively)], and by dynamic changes in MELD scoring (Delta MELD).

The scoring systems use multiple clinical and laboratory parameters to evaluate liver reserves and predict outcomes. In our study we assessed cholinesterase as an independent test for liver function and hepatic reserves.

Cholinesterase levels have been assessed to predict survival in patients with Parenchymal cirrhosis[14], predict outcome in graft-*vs*-host disease[15], distinguish between liver disease and non-liver disease aberration in liver function tests[16] and differentiate cirrhosis from non-cirrhosis[17]. Serum cholinesterase levels have also been found to correlate with CTP Class[18,19]. In addition, cholinesterase levels have been shown to recover with improvements in hepatic function[20] at a rate exceeding recovery from organophosphate poisoning.

Our study showed that cholinesterase levels could be used in conjunction with existing scoring systems as a prognostic marker of hepatic reserves. However, serum cholinesterase levels may be affected by gender, nutritional status and carcinomas[6]. We did not find any differences related to gender and body mass index. None of our patients had malignancy while all of the patients included in this study were suffering from cirrhosis related to hepatitis D. So differences in the etiology of the liver disease could not affect the results of this study. The prevalence of inherited atypical cholinesterase has been reported to be low in multiple studies[21]. So any genetic variations are less likely to influence the results of this study.

In conclusion, serum cholinesterase is an excellent biomarker of the synthetic function of liver in CLD with hepatitis D. Cholinesterase levels should be routinely checked to assess liver function and may be incorporated in MELD scoring. It can be effectively used to follow the staging of liver disease in hepatitis D. Our results should be validated in other cohorts and etiologies of CLD.

## COMMENTS

### Background

Chronic hepatitis D is a severe disease with rapid progression of fibrosis leading to cirrhosis, decompensation and hepatocellular carcinoma. Commonly used liver synthetic function tests include serum albumin and prothrombin time and international normalized ratio. The objective of this study was to determine the performance of cholinesterase levels in predicting liver function compared to the existing scoring models in patients with hepatitis D and cirrhosis.

### Research frontiers

The authors defined optimal cholinesterase levels corresponding to the different stages and classes of the scoring systems assessing the severity of chronic liver disease.

### Innovations and breakthroughs

Serum cholinesterase demonstrated promising correlations with serum albumin, international normalized ratio and Child Turcotte Pugh, Model for Endstage Liver Disease, baseline-event-anticipation and aspartate transaminase to Platelet Ratio Index scores.

### Applications

Serum cholinesterase levels can be effectively used to monitor the staging of liver disease in hepatitis D. These results may be validated in other cohorts and etiologies of chronic liver disease to predict the liver reserves.

### Terminology

Serum butyrylcholinesterase, commonly known as serum cholinesterase, is an enzyme synthesized by hepatocytes and has the half-life of eleven days

### Peer-review

The authors investigated the role of cholinesterase levels as predictor of hepatic reserves in chronic hepatitis D patients. This paper is generally well conducted and straightforward. The authors concluded that cholinesterase levels can be considered a biomarker of liver function in these patients.

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CASE REPORT

# Extrahepatic metastasis of hepatocellular carcinoma to the paravertebral muscle: A case report

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Author contributions: Takahashi K and Kim DY designed the report; Takahashi K, Putchakayala KG and Safwan M collected the data; Takahashi K and Kim DY wrote the paper; Putchakayala KG and Safwan M performed critical revisions of the paper.

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## Abstract

Identification of extrahepatic metastases (EHM) of hepatocellular carcinoma (HCC) has been paradoxically increasing due to an increase in the survival of HCC patients. However, metastasis of HCC to the skeletal muscle tissue is extremely rare. We describe a unique case of HCC metastasizing to the paravertebral muscle. A 55-year-old man with a history of hepatitis B cirrhosis underwent partial liver resection with complete removal of HCC. Three months later, a computed tomography (CT) scan showed intrahepatic recurrence. The tumors were treated with yttrium-90 microspheres, trans-catheter arterial chemoembolization, and sorafenib. Six months later, a CT scan showed an enhancing lesion of the left paravertebral muscle that on biopsy were consistent with metastatic HCC. The tumor was treated with stereotactic hypo-fractionated image-guided radiation therapy (SHFRT). A follow-up scan 3 mo post-radiotherapy revealed a stable appearance of the paravertebral muscle metastasis. Because of the progression in the intrahepatic tumors, the patient was treated with capecitabine, which was changed to dasatinib 6 mo later. The patient passed away three years after the primary surgical resection. Management of EHM poses an extreme challenge. This is the first case of HCC with EHM to the paravertebral muscle in which stability of disease was achieved using SHFRT. This case highlights the importance of early detection of hepatitis B viral infection and initiation of anti-viral therapy to decrease recurrence of HCC and prevent EHM.

**Key words:** Hepatocellular carcinoma; Skeletal muscle; Paravertebral muscle; Extrahepatic metastasis; Stereotactic hypo-fractionated image guided radiation therapy;

Hepatitis B virus



**Core tip:** Extrahepatic metastases (EHM) of hepatocellular carcinoma (HCC) to skeletal muscle are extremely rare. We describe the first case of HCC with EHM to the paravertebral muscle, in which stability of disease was achieved using stereotactic hypo-fractionated image-guided radiation therapy. A literature review revealed the strong relationship between hepatitis B viral infection and EHM. This case highlights the importance of early detection of viral infection and initiation of anti-viral therapy to decrease recurrence of HCC and prevent EHM.

Takahashi K, Putchakayala KG, Safwan M, Kim DY. Extrahepatic metastasis of hepatocellular carcinoma to the paravertebral muscle: A case report. *World J Hepatol* 2017; 9(22): 973-978 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i22/973.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i22.973

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth most common malignancy and the third most common cause of cancer-related death in the world[1-3]. Worldwide incidence is between 250000 and 1000000 new cases per year, and it has been rapidly increasing due to the prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections[1-3]. In the United States, HCC related to HCV infection has become the fastest rising cause of cancer-related death, and the incidence has tripled during the past two decades. Survival time in patients with HCC has recently increased as a consequence of advanced diagnostic modalities and treatment methods; however, the 5-year survival rate still remains low at approximately 16%[1,3,4]. Current available treatment methods include surgical resection, radio-frequency ablation, trans-catheter arterial chemoembolization (TACE), yttrium-90 microspheres, liver transplantation, chemotherapy, and radiotherapy[5].

Because of the improvement in survival, extrahepatic metastases (EHM) are becoming more commonly recognized in patients with HCC, with a reported incidence of 15%-17%[6,7]. The most common sites of EHM are lungs, lymph nodes, bones, and adrenal glands; however, HCC can metastasize to the skeletal muscles and subcutaneous tissues, albeit rarely[7]. In this report, we describe a unique case of HCC metastasizing to the paravertebral muscle, which was treated with stereotactic hypo-fractionated image guided radiation therapy (SHFRT) and achieved disease stability. We report this case along with a review of the recent literature.

## CASE REPORT

A 55-year-old male with a history of HBV-associated liver cirrhosis had an incidental right lobe liver mass 6.0 cm in size identified during a routine computed tomography (CT) scan. His serum alpha-fetoprotein (AFP) level was within the normal range. A magnetic resonance imaging (MRI) scan showed a hyper-intense irregular T2 focus, which distorted the contours of the liver. This focus demonstrated moderate enhancement on the initial phase post-Gadolinium images, with a central hypo-intense area. These imaging characteristics were most compatible with focal nodular hyperplasia, and follow-up at the outpatient clinic was advised. However, the patient was non-compliant and did not visit the clinic until three years later. MRI scan at that time showed that the tumor had increased in size to 9.4 cm, and the patient had a mild elevation in AFP level (15.1 ng/mL). His HBV DNA level was 12.7 × $10^6$ copies/mL and he had not received any anti-viral therapies. The patient then underwent partial liver resection with complete removal of the tumor. Histopathological examination revealed the tumor to be a moderate-to-poorly differentiated HCC with vascular invasion. According to the Union for International Cancer Control guidelines, the final stage of the tumor was stage Ⅱ (pT2N0M0). Due to the elevated viral titer, entecavir 1 mg daily was instituted postoperatively.

Three months later, CT scan showed recurrence of the tumor as three foci: 4 mm in size along the resected plane, 7 mm at S4, and 6 mm at S7. The patient's HBV DNA level was less than 300 copies/mL. The tumors were treated with yttrium-90 microspheres (TheraSphere®, BTG IM, London, United Kingdom). A total dose of 90 Gy was delivered. One year later, he developed multiple enhancing lesions in the liver. He received three sets of TACE with adriamycin, and finally sorafenib (Nexavar®, Bayer HealthCare AG, Leverkusen, Germany) 200 mg twice daily. Six months later, he complained of back pain, and CT scan showed an enhancing lesion 3.7 cm in size in the left paravertebral muscle (Figure 1). A biopsy of the mass showed moderate-to-poorly differentiated HCC, consistent with metastatic HCC (Figure 2). The tumor was treated with four rounds of SHFRT at 10 Gy per fraction with a total dose of 40 Gy. A follow-up scan at 3 mo post-radiotherapy revealed a stable appearance of the paravertebral muscle metastasis. Because of progression of the intrahepatic tumors, the patient was switched to capecitabine (Xeloda®, Roche, Basel, Switzerland) 1500 mg twice daily once a week for 2 wk. He was later enrolled in a clinical trial and started on dasatinib. The patient passed away more than three years after the primary liver resection.

## DISCUSSION

Despite significant advances in the treatment of HCC, the prognosis remains poor. Median survival times for

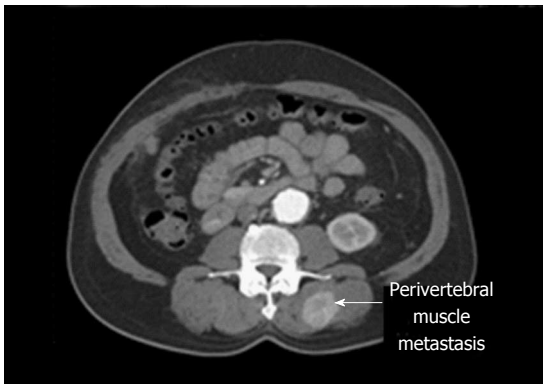


**Figure 1 Computed tomography of the recurrent tumor.** Computed tomography scan showing an enhancing lesion 3.7 cm in size in the left paravertebral musculature.

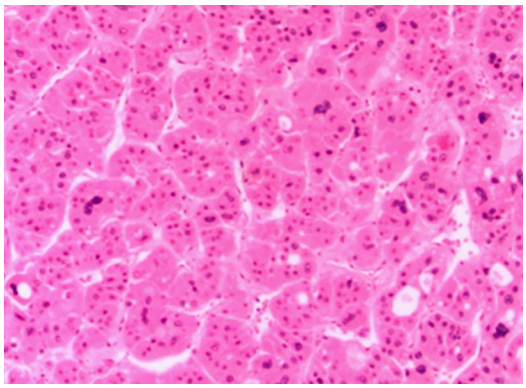

**Figure 2 Histology of the paravertebral muscle tumor.** A biopsy of the mass showed moderate-to-poorly differentiated hepatocellular carcinoma (HCC), consistent with metastatic HCC (hematoxylin and eosin, × 200).

patients with HCC who have EHM are 4.9-7.0 mo. One, three, and five year survival rates are 21.7%-31.0%, 7.0%-7.1%, and 4.0%, respectively[8]. Currently, there is no standardized treatment for HCC patients with EHM. Sorafenib is the first systemic agent that has demonstrated a significant improvement in survival time in patients with advanced HCC; however, the modest improvement of 3 mo is far from satisfactory[9]. Systemic cytotoxic chemotherapy agents, such as adriamycin, fluorouracil, cisplatin, etc. are considered palliative treatment options for advanced HCC but have low response rates of less than 10%. Recently, there have been some reports on the efficacy of capecitabine as a second-line treatment following sorafenib[10,11]. However, these studies are retrospective in nature with low levels of evidence. Other target agents such as regorafenib, c-Met inhibitor, and check point inhibitors are promising, but still under investigation. Dasatinib, an Src family kinase inhibitor, is reported to have effects on human HCC cell lines[12,13], however, the results of a recent clinical study showed insufficient response rates[14]. Due to lack of highly effective systemic chemotherapy for HCC, enrolling in a clinical trial with a new chemotherapeutic agent is the only option for patients with advanced HCC[15,16].

Several authors have reported long-term survivors after aggressive surgery for EHM[17,18]. From the viewpoint of reducing tumor burden, loco-regional therapy may be a reasonable strategy when the target lesions account for a major portion of the total tumor volume. These reports suggest a potential benefit to loco-regional treatment for intra and/or extrahepatic tumor in HCC patients with EHM. Patients with T1/2 primary tumor or less than two EHM were described as good candidates for aggressive local therapy[19,20]. A retrospective analysis reported that surgical resection of peritoneal or thoraco-abdominal wall implants from HCC in selected patients (limited number of implanted lesions; intrahepatic lesions absent or predicted locally controllable; and the absence of ascites with sufficient hepatic functional reserve) improved long-term survival, with 1, 3 and 5 year overall survival rate of 71%, 44% and 39%, respectively[21]. On the other hand, the cause of death in HCC patients with extrahepatic metastasis were mostly related to problems as a consequence of intrahepatic tumors, such as liver failure[8,18]. In our case, SHFRT was selected for local treatment of EHM, in addition to sorafenib as a systemic treatment, since the tumor invaded deeply into the paravertebral muscle and multiple intrahepatic recurrent HCC foci were identified, suggesting a poor prognosis even after the resection. Although the primary purpose for this radiation was for pain control, it was also effective in the control of disease progression. Our case is the first report of EHM treated by a non-surgical method which led to extrahepatic disease stability.

Vascular invasion of HCC has proven to be a strong determinant of EHM. Hematogenous spread to the lungs, lymph nodes, bones, and adrenals are reported to be the most common sites for EHM. Metastasis of HCC to muscle tissue is an infrequent phenomenon. Skeletal muscle and cardiac muscle are classified as striated muscles, which contain sarcomeres that are arranged into highly organized bundles. The infrequency of muscle metastasis seen in HCC may be attributed to the contractility of muscle, the local pH environment, and the presence of tumor suppressors in the muscle tissue[22]. Over 40 cases of cardiac muscle metastasis of HCC have been reported, whereas only found 17 cases of skeletal muscle metastasis of HCC have been reported (Table 1)[17,23-37]. All these cases were reported after 2005, two years before sorafenib was approved by the Food and Drug Administration for the treatment of HCC. Skeletal muscle recurrence occurred in various locations throughout the body, the trunk, and the peripheral musculature, with one case of extraocular muscle metastasis[28]. The majority of patients were male (16/18 cases) and had a history of HBV infection (10/13 cases, excluding 5 cases with unknown etiology). HBV viral load and anti-viral treatment were not recorded except in our case. Most cases underwent surgical resection as a local treatment (9/17 cases, excluding one case with unknown treatment), and some received radiation therapy as palliative therapy

**Table 1 Skeletal muscle metastasis of hepatocellular carcinoma**

| Ref. | Year | Age/gender | Background | Treatment (primary lesion) | Muscle recurrence site | Recurrence time (mo)[1] | Treatment (metastasis) | Other lesions[2] | Simultaneous systemic treatment |
|---|---|---|---|---|---|---|---|---|---|
| This case | 2017 | 55/M | HBV | Resection | Paravertebral muscle | 21 | SHFRT | Multiple intrahepatic HCC | Sorafenib |
| [23] | 2014 | 36/M | Unknown | Chemo-radiotherapy | Chest wall | 0 | Chemo-radiotherapy | Liver, peripancreatic region, brain, cervical lymph node | Chemo-radiotherapy |
| [23] | 2014 | 31/M | HBV HIV | Cisplatin/ adriamycin | Chest wall, pectoral muscles | 0 | Cisplatin/ adriamycin | Intrahepatic HCC | Cisplatin/ adriamycin |
| [24] | 2014 | 47/M | Unknown | Resection | Rectus muscle | 13 | Resection | None | None |
| [17] | 2013 | 55/M | HBV HCV | Resection | Pectoralis major Deltoid, left teres minor | 54 | Radiotherapy | Brain metastasis | Sorafenib |
| [25] | 2013 | 61/M | Alcohol | None | Iliac muscle | 0 | Chemotherapy | Diffuse intrahepatic HCC | Chemotherapy |
| [26] | 2012 | 65/M | HBV | RFA TACE | Intercostal muscle | 24 | Resection | None | None |
| [27] | 2012 | 72/M | Alcohol | None | Medial pterygoid muscle | 0 | Radiotherapy | Multiple intrahepatic HCC | Sorafenib |
| [28] | 2012 | 44/M | Unknown | Resection | Extraocular muscle | 17 | Radiotherapy | None | None |
| [29] | 2011 | 70/M | HBV | Resection | Humorous muscle | 108 | Resection | None | Unknown |
| [30] | 2009 | 82/M | Unknown | Resection | Diaphragm | 30 | Resection | None | None |
| [31] | 2009 | 62/unknown | HBV | TACE resection | Pectineal muscle | 96 | Unknown | Multiple intrahepatic HCC | Unknown |
| [32] | 2008 | 54/M | HBV | Resection | Rectus femoris muscle | 60 | Sorafenib | Multiple pulmonary metastasis | Sorafenib |
| [33] | 2008 | 52/M | HBV | Liver transplant | Chest wall | 60 | Resection | None | None |
| [34] | 2007 | 63/M | Unknown | Resection | Gastrocnemius muscle | 18 | Resection | None | None |
| [35] | 2007 | 53/M | HCV | None | Gluteus maximus muscle | 0 | Resection | None | None |
| [36] | 2006 | 50/M | HBV | Resection | Psoas muscle | 12 | Resection | None | None |
| [37] | 2005 | 39/F | HBV | Resection | Chest wall | 11 | Resection | None | None |

[1]Months after the primary treatment; [2]At the time of muscle recurrence. M: Male; F: Female; HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; TACE: Transcutaneous chemoembolization; SHFRT: Stereotactic hypofractionated image-guided radiation therapy; HCC: Hepatocellular carcinoma.

(three cases). In cases with simultaneous recurrence similar to ours, sorafenib or another chemotherapeutic agent was used as systemic therapy[17,23,25,27,32]. However, even with these treatments, prognosis was extremely poor, ranging from a few weeks to 6 mo.

Previous studies have described the importance of controlling viral status to prevent HCC recurrence and improve survival after curative treatment for HBV-related HCC[38,39]. Huang *et al*[38] reported that preoperative antiviral treatment decreased viral reactivation rate, and pre- plus postoperative antiviral treatment achieved a better 5-year overall survival rate than postoperative antiviral treatment alone by decreasing HBV-related HCC recurrence. On the other hand, only one study described a correlation between HBV status and EHM. Sasaki *et al*[40] reported that HBV infection was an independent predictor for the occurrence of EHM in patients with large HCC tumors. In addition, the authors posit that HBV infection might promote the establishment of EHM through modulation of the adhesion-de-adhesion balance of HCC cells[40]. In our case, although the patient's HBV status was well-controlled by entecavir after hepatectomy, the patient did not receive any anti-viral treatment preoperatively despite a high viral load. No previous case reports of muscle recurrence included patient HBV status or antiviral treatments. Although the relationship between HBV infection and skeletal muscle recurrence has not been clarified, we consider controlling HBV viral load through antiviral treatment prior to surgical intervention important due to the high incidence of HBV infection among patients with HCC with EHM recurrence.

We report the first case of HCC with EHM to the paravertebral muscle. Though this is a single case, it raises interest in detecting EHM at an earlier stage and initiating therapy if the patient's overall health permits.

A study of surgical and non-surgical treatment with systemic *vs* loco-regional therapy may shed further light on this topic.

## ACKNOWLEDGMENTS

We acknowledgements Transplant and Hepatobiliary Surgery Henry Ford Hospital, 2790 West Grand Boulevard, Detroit, MI 48202, United States.

## COMMENTS

### *Case characteristics*

A 55-year-old male with a history of hepatitis B virus (HBV) induced liver cirrhosis complained of back pain two years after removal of hepatocellular carcinoma (HCC).

### *Clinical diagnosis*

Computed tomography (CT) scan showed a mass at the left paravertebral muscle, biopsy of which was consistent with moderate to poorly differentiated HCC.

### *Differential diagnosis*

Rhabdomyosarcoma, fibromatoses, hemangioma, or metastatic tumor of HCC.

### *Laboratory diagnosis*

A mild elevation of the alpha-fetoprotein level (15.1 ng/mL). HBV DNA counts of $12.7 \times 10^6$ copies/mL.

### *Imaging*

CT scan showed an enhancing lesion 3.7 cm in size at the left paravertebral muscle.

### *Pathological diagnosis*

A biopsy of the mass showed moderate to poorly differentiated HCC, consistent with metastatic HCC.

### *Treatment*

The tumor was treated with four sessions of stereotactic hypo-fractionated image guided radiation therapy at 10 Gy per fraction with a total dose of 40 Gy.

### *Related reports*

There were only 17 cases of the skeletal muscle metastasis of HCC. These were at various locations from the skeletal muscles of body trunk to peripheral muscles.

### *Term explanation*

Extrahepatic metastases (EHM) of HCC to the skeletal muscle tissue are extremely rare. Median survival times for patients with HCC who have EHM are 4.9-7.0 mo. Currently, there is no standardized treatment for HCC patients with EHM.

### *Experiences and lessons*

This case invites interest in detecting EHM at an earlier phase and the initiation of therapy if the patient's health and overall assessment permits. A study of surgical and non-surgical treatment with systemic *vs* loco-regional therapy may shed further light on this situation.

### *Peer-review*

The paper is well-written.

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