ISSN 1948-5182 (online)

World Journal of *Hepatology*

World J Hepatol 2019 September 27; 11(9): 663-700

Published by Baishideng Publishing Group Inc

World Journal of Hepatology

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World Journal of Hepatology

Volume 11 Number 9 September 27, 2019

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The *WJH* is now abstracted and indexed in PubMed, PubMed Central, Emerging Sources Citation Index (Web of Science), Scopus, China National Knowledge Infrastructure (CNKI), China Science and Technology Journal Database (CSTJ), and Superstar Journals Database.

RESPONSIBLE EDITORS FOR THIS ISSUE

Responsible Electronic Editor: *Lu-Lu Qi*

Proofing Production Department Director: *Xiang Li*

NAME OF JOURNAL
World Journal of Hepatology

ISSN
ISSN 1948-5182 (online)

LAUNCH DATE
October 31, 2009

FREQUENCY
Monthly

EDITORS-IN-CHIEF
Ke-Qin Hu, Koo Jeong Kang, Nikolaos T Pyrsopoulos

EDITORIAL BOARD MEMBERS
https://www.wjgnet.com/1948-5182/editorialboard.htm

EDITORIAL OFFICE
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PUBLICATION DATE
September 27, 2019

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World J Hepatol 2019 September 27; 11(9): 663-677

DOI: 10.4254/wjh.v11.i9.663

ISSN 1948-5182 (online)

REVIEW

Cirrhotic patients and older people

Paul Carrier, Marilyne Debette-Gratien, Jérémie Jacques, Véronique Loustaud-Ratti

ORCID number: Paul Carrier (0000-0001-9750-2506); Marilyne Debette-Gratien (0000-0001-6039-1355); Jérémie Jacques (0000-0003-4105-6804); Véronique Loustaud-Ratti (0000-0002-6951-0784).

Author contributions: Carrier P wrote the manuscript and oversaw editorial consistency; Debette-Gratien M and Jacques J reread the manuscript and assisted in the constitution of the bibliography; Loustaud-Ratti V reread the manuscript and oversaw editorial consistency.

Conflict-of-interest statement: The author declares no potential conflicts of interest in relation to this publication.

Manuscript source: Invited manuscript

Received: April 17, 2019
Peer-review started: April 17, 2019
First decision: June 3, 2019
Revised: June 18, 2019
Accepted: July 16, 2019
Article in press: July 17, 2019

Paul Carrier, Marilyne Debette-Gratien, Véronique Loustaud-Ratti, Fédération d'Hépatologie, Centre Hospitalier Universitaire Dupuytren de Limoges, Limoges 87042, France

Paul Carrier, Marilyne Debette-Gratien, Véronique Loustaud-Ratti, Faculté de Médecine et de Pharmacie de Limoges, Rue Docteur Marcland, Limoges 87042, France

Jérémie Jacques, Service de Gastroentérologie, Centre Hospitalier Universitaire Dupuytren de Limoges, Limoges 87042, France

Corresponding author: Véronique Loustaud-Ratti, MD, Professor, Fédération d'Hépatologie, Centre Hospitalier Universitaire Dupuytren de Limoges, 2 Avenue Martin Luther King, Limoges 87042, France. veronique.loustaud-ratti@unilim.fr
Telephone: +33-5-5556684

Abstract

The global population is aging, and so the number of older cirrhotic patients is increasing. Older patients are characterised by a risk of frailty and comorbidities, and age is a risk factor for mortality in cirrhotic patients. The incidence of non-alcoholic fatty liver disease as an aetiology of cirrhosis is increasing, while that of chronic viral hepatitis is decreasing. Also, cirrhosis is frequently idiopathic. The management of portal hypertension in older cirrhotic patients is similar to that in younger patients, despite the greater risk of treatment-related adverse events of the former. The prevalence of hepatocellular carcinoma increases with age, but its treatment is unaffected. Liver transplantation is generally recommended for patients < 70 years of age. Despite the increasing prevalence of cirrhosis in older people, little data are available and few recommendations have been proposed. This review suggests that comorbidities have a considerable impact on older cirrhotic patients.

Key words: Liver cirrhosis; Portal hypertension; Liver cancer; Liver transplantation; Old age; Older; Elderly

Core tip: Few large studies have addressed the needs of older cirrhotic patients. The concept of healthy ageing is increasingly important. Cirrhosis is underdiagnosed in older patients, and comorbidities, comedications, and frailty impact the prognosis. The frequency of non-alcoholic fatty liver disease as an aetiology of cirrhosis is increasing, while that of viral hepatitis is decreasing, and the role of alcohol consumption is underestimated. The management of complications in older cirrhotic patients is similar to that in younger patients despite the higher risk of treatment-related adverse events. Therapeutic indications for a transjugular intrahepatic portosystemic shunt or admission

Published online: September 27, 2019

P-Reviewer: Kim IH, Manenti A, Yoshioka K
S-Editor: Cui LJ
L-Editor: Filipodia
E-Editor: Qi LL

to an intensive care unit should be carefully considered. Finally, older patients require tailored exercise and nutrition programs, and treatment of osteoporosis is crucial.

Citation: Carrier P, Debette-Gratien M, Jacques J, Loustaud-Ratti V. Cirrhotic patients and older people. *World J Hepatol* 2019; 11(9): 663-677
URL: https://www.wjgnet.com/1948-5182/full/v11/i9/663.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i9.663

INTRODUCTION

The definition of older people varies from ≥ 60 years to ≥ 80 years of age. However, according to the World Health Organisation, the cut-off is 60 years of age, despite the increasing focus on the concept of healthy ageing[1,2]. Patients > 80 years of age are typically defined as being extremely old. Life expectancy has increased recently due to health, social, and economic development. According to the World Health Organisation, the number of people ≥ 65 years of age will increase from an estimated 524 million in 2010 to almost 1500 million in 2050, representing 22% of the global population[3]. Thus, the healthcare of older people is an emerging issue, particularly in Western countries.

The incidence of liver diseases increases with age[4]. Liver cirrhosis is an important health problem globally, and the prevalence of its numerous aetiologies varies geographically. General recommendations for the management of cirrhotic patients have been published, but these are not specific to older people[5].

This review focuses on problems specific to older cirrhotic patients.

PATHOPHYSIOLOGY OF THE AGEING LIVER

The liver undergoes physiological evolution with age, and this process involves several mechanisms. First, liver volume and blood flow decrease[6]. The liver decreases to one-third of its original size, more markedly in women[7], and a one-third decrease in hepatic blood flow has been reported, particularly in subjects over 75-years-old[8,9]. However, these results are controversial, and more data are needed[10]. Scintigraphy has shown that compared to the whole body, the size and functionality of the liver decrease with age[11]. Moreover, endothelial cell fenestration tends to decrease with age[8], the sinusoid vascular system is damaged, and secretion of bile acids is reduced. Regarding metabolic parameters, glucogenesis decreases with age but physiological lipids accumulate, enhancing steatosis[12]. Also, liver fat composition changes with age[13]; the level of high-density cholesterol and neutral fat is increased by neoglucogenesis. Moreover, older people tend to have higher levels of cholestatic enzymes and bilirubin[14].

Second, the number of hepatocytes and Kupffer cells and sinusoid capillaries decreases[8], and hepatocytes decrease in size with aging. The frequency of hepatocyte polyploidy increases with age and is associated with dysfunction or a decreased number of mitochondria[15]. Autophagy is modulated by accumulation of lipofuscin, a non-degradable aggregate of proteins impacted by reactive oxidative species[16]. Kupffer cells are also involved in ageing[17]. Cellular senescence is linked to chromosome alterations; telomere shortening occurs more frequently in Kupffer cells than in hepatocytes[18]. Apoptosis occurs more frequently in older patients, and senescent cells are resistant to apoptosis[19]. Nevertheless, targeting apoptosis of senescent cells could assist the restoration of liver homeostasis[20].

Third, the risk of fibrosis and steatosis increases with age[21]; for instance, in chronic hepatitis C virus (HCV) infection[22,23]. Fibrosis is a consequence of altered liver regeneration in response to injury. Responses to oxidative stress, cell senescence, and disrupted mitochondrial homeostasis may explain the greater risk of both fibrosis and steatosis in older patients[24]. In mouse models, mitochondria are damaged and the risk of DNA damage is increased by oxidative stress[12,25]. Altered liver regeneration may involve a multiprotein complex comprising CCAAT/enhancer binding protein α. Accumulation of this complex inhibits E2F-dependent promoters[26]. The somatotropic axis is also involved in liver regeneration[27]; however, a full mechanistic understanding remains elusive.

The immune system changes with age: Regulatory T cells, peripheral B cells,

monocytes/macrophages, and natural killer cells have reduced functionality, and dendritic cells have defective Ag presentation and T-cell activation[28,29]. The levels of markers of oxidation are not different between younger and older mice with CCl4 injury. However, the number of proinflammatory CD4+ cells, the expression level of T-helper type-2 cytokines by macrophages, and fibrogenesis are greater in older mice[30,31]. Furthermore, suppression of autophagy favours inflammation[32], and a high-fat diet increases the risk of liver fibrosis in older mice[33]. These factors also increase the risk of infection.

The role of ageing in carcinogenesis is debated—both protective and inductive mechanisms are reported[29,34,35]. The duration of exposure to carcinogens and a history of cirrhosis may promote hepatocellular carcinoma (HCC). Therefore, the aged liver is more sensitive to acute and chronic injury and is at greater risk of severe fibrosis or cirrhosis.

EPIDEMIOLOGY

Cirrhosis may be underdiagnosed in older persons, which is likely to be due to the presence of fewer clinical signs at presentation and less-frequent use of invasive diagnostic modalities[36,37].

Older patients with cirrhosis have a reduced life expectancy. Among 135 patients ≥ 80 years of age, Hoshida *et al*[38] showed that HCC, thrombocytopenia, and advanced fibrosis were associated with a low survival rate and that the alpha-fetoprotein and bilirubin levels were associated with hepatic carcinogenesis.

Older people also manifest deterioration in their general health[39], and cirrhosis may contribute to their frailty. Sarcopenia is frequent in older and in cirrhotic patients and contributes to the frailty of the former[33]. Specific policies to combat this are needed.

Finally, older patients have a higher incidence of complications, to which changes in the liver may contribute. Nevertheless, liver status does not impact the mortality rate of older patients. Effective screening methods and preventive measures are however essential.

AETIOLOGIES

The risk of transmission of hepatitis B virus increases with age, and the prevalence varies geographically. Epidemiological studies in the United States reported a higher prevalence among patients > 50 years of age compared to those 20-49 and 6-19 years of age (1.5-2 fold and 15-20-fold, respectively), irrespective of ethnicity[40]. Although vaccination policies have decreased the global prevalence of hepatitis B virus infection, there is no specific prevention strategy for older patients, in whom vaccination shows reduced efficacy[41].

In Western countries, the so-called baby-boomer generation is aging. The prevalence of HCV infection is high in this population: In the United States, > 75% of patients with HCV belong to this generation, and specific screening policies have been proposed[42]. HCV-related cirrhosis develops on average > 20 years after contact, which explains its incidence in this generation[43]. Nevertheless, the efficacy and tolerability of new direct anti-viral agents (DAA) is likely to decrease the prevalence of HCV infection in these geographical areas. However, many viraemic patients are unaware of their status, *e.g*., > 100,000 patients in France have not been diagnosed or treated[44-47]. In a large retrospective study conducted in 2006, *i.e*. prior to the DAA era, Thabut *et al*[23] showed that patients > 65 years of age had a high prevalence of chronic hepatitis C and 14% had liver cirrhosis; interestingly, patients > 80 years of age had a lower alanine transaminase level than those < 65 years of age. Interferon-based treatments are typically not tolerated by older patients, but new available treatments have fewer side effects in polymedicated older patients, provided that the necessary precautions are taken, particularly in patients with a cardiac history and renal insufficiency, and that drug interactions are evaluated before starting treatment[48-50]. Older patients have been included in therapeutic studies[51]. The available treatments are effective in older patients, and no specific recommendations concern this population, including those with cirrhosis[50]. Decisions regarding the treatment of extremely old patients must take into account the benefit-risk ratio and the public-health perspective.

Metabolic syndrome is emerging globally, especially in Western countries, which have a higher prevalence of metabolic risk factors[52]. However, developing countries, including those in Asia and the Middle East, are also affected[53]. Metabolic syndrome

is common in older people[54], who are at risk of evolution towards cirrhosis[55] and have an increasing prevalence of cirrhosis[56]. Furthermore, > 60-year-old patients with non-alcoholic fatty liver disease are more susceptible to HCC[52]. Treatment is non-specific and based on weight loss[57,58], although vitamin E reportedly impacts life expectancy[59]. However, use of vitamin E in older males is associated with an increased risk of prostate cancer[60].

The prevalence of cryptogenic cirrhosis is high in some countries. For instance, in India[61], patients tend to have or have had metabolic risk factors for cirrhosis, in agreement with Japanese data[62]. Also, older studies indicated an important role for hepatitis C[63].

Alcohol consumption is frequent and more deleterious in older persons[64,65]; indeed, its prevalence in the United States increased between 2001-2002 and 2012-2013[66]. The social problems faced by older persons, such as isolation, widowhood, and chronic illness, can promote alcohol consumption. Alcohol accumulation in the liver impacts survival in patients with liver disease, such as hepatitis C[67]. The prognosis is poor; half of cirrhotic patients die within 1 year of diagnosis[68,69]. Older patients are also impacted by a variety of other alcohol-related complications[70]. From a public-health perspective, alcohol consumption should be assessed using the Alcohol Use Disorder Identification Test-C questionnaire and hepatic risk by performing non-invasive tests for fibrosis[70]. Alcohol withdrawal should be managed by a healthcare professional specialised in addiction with an elder-specific focus[71,72]. Short- and intermediate-acting benzodiazepines are recommended for older patients with alcohol-withdrawal syndrome, particularly those with cirrhosis[73].

Autoimmune hepatitis is also frequent in older patients, especially post-menopausal females[74]. These individuals are more likely to have asymptomatic liver cirrhosis and HLA DR4. Treatment is based on corticosteroids and azathioprine, as in younger patients; however, the risk of relapse after steroid withdrawal is lower[74]. Nevertheless, in older patients with initial mild fibrosis, the benefit-risk ratio of steroid treatment must be discussed due to their lower risk of fibrosis progression and higher risk of side effects, notably osteoporosis, psychiatric conditions, and diabetes, compared to younger patients[75]. That is why budesonide or a minimal corticosteroid regimen is preferred[76]. Furthermore, older patients with autoimmune hepatitis should undergo regular evaluations of bone density.

Primary biliary cholangitis is frequent in older patients, particularly females[77]. Interestingly, ursodeoxycholic acid is more effective in older patients[78]. However, older patients were not specifically analysed in two recent phase-III studies of obeticholic acid and bezafibrate[79,80].

Primary sclerosing cholangitis (PSC) is generally diagnosed in the third to fourth decades of life, but a second peak around 70 years of age was noted in a Japanese population, with no mention of the fibrosis stage[81]. Eaton *et al*[82] indicated that older patients with PSC have a 10% risk of cirrhosis, similar to that in younger patients, but have a lower prevalence of small-duct PSC. Finally, hepatobiliary malignancy is more frequent in older patients. There are no specific recommendations concerning the treatment and management of complications, including the role of therapeutic endoscopy[83]. McGee *et al*[84] suggested a link between autoimmune liver disease and liver cancer, *i.e*. intrahepatic cholangiocarcinoma, extrahepatic cholangiocarcinoma, gallbladder cancer, and ampulla of Vater cancer, in older patients, particularly those with primary biliary cholangitis.

Other causes, such as alpha-1-anti-trypsin, Wilson disease, and haemochromatosis, particularly haemochromatosis of weak phenotypic penetrance, may be diagnosed late[69], especially in post-menopausal women. This means that complications, such as cirrhosis and HCC, are frequently present at the time of diagnosis[85,86]. Alpha-1-anti-trypsin deficiency is typically diagnosed at a late stage unless pulmonary symptoms are evident and early screening for liver disease is performed[87]. Wilson disease is frequently diagnosed early, although a few advanced cases have been reported[88,89].

COMPLICATIONS OF CIRRHOSIS

HCC

HCC is the fifth most prevalent cancer worldwide and the third most important cause of cancer-related mortality[90]. The incidence of HCC increases with age, and the prognosis is poor. However, aggressive treatment of HCC in older (including extremely old) patients with good liver function and a good performance status might improve the survival rate[91]. In an Italian cohort, older patients with HCC had at the time of diagnosis a higher prevalence of comorbidities that negatively impacted the prognosis but a lower HCC stage, and better liver function than younger patients[92].

In another study, survival of elderly HCC patients was associated with liver damage and stage, but not age, with the exception of patients ≥ 80 years of age with a poor performance status[93].

Although HCC is more frequent in males, the proportion of females is higher among extremely old patients. The clinical presentation is typically weakness, nausea, and abdominal pain[69]. Ascites and hepatomegaly were frequent complications in a retrospective study[94]. Liver cirrhosis is a risk factor for HCC in younger and older patients, for whom the HCC screening recommendations are identical[95].

The therapeutic panel is the same in young and old patients, although decision-making is hampered by comorbidities, performance status, and life expectancy[92,96,97]. Specific age-linked scales have been developed[98]. The majority of the relevant studies were conducted in Asia. In large retrospective studies, surgery showed a trend towards an increase in the mortality rate with age[99-103]. Tumour size may not be a contraindication[104], and perioperative management and careful selection are needed[105]. Radiofrequency ablation can be effective against small tumours, *i.e*. radiofrequency ablation was more effective than hepatic resection in older patients with ≤ 3 cm HCC[106]. In another study, the global survival rate, but not the incidence of procedure-related adverse events, was comparable in older and younger patients[107]. Percutaneous injection of ethanol is effective against < 2 cm tumours[108].

The results of palliative transarterial chemoembolisation for older patients with advanced tumours are heterogeneous[96,109]. In a large retrospective trial, the overall survival rate of older patients was increased, but they were treated at an early stage[110]. Conversely, age over 60 years was independently associated with a poor prognosis. Interestingly, older patients were at greater risk of peptic ulcer (2.5% *vs* 0.5%)[111]. Although no data are available, radioembolisation is an interesting option for older patients with HCC[112] and is well tolerated by those with unresectable metastatic colon cancer[113].

Sorafenib is the most frequently prescribed chemotherapeutic. A French retrospective study showed that patients > 80 years of age had low tolerance of a fixed dose, and two thirds of them experienced grade IV adverse events[114]. Several Japanese studies have reported more hopeful results[115,116]. In one, a half dose of sorafenib was useful in the presence of adverse events and was better tolerated[116]. Age does not seem to influence the safety and efficacy of levantinib[117]. Phase III studies of Regorafenib and Ramucirumab have not specifically addressed older patients[118,119], but second-line cabozantinib increased the overall survival rate of patients > 65 years of age[120]. Unfortunately, data on immunotherapies, especially Nivolumab, are sparse.

Portal hypertension

Older people have a lower portal velocity and are not at increased risk of portal hypertension[121,122]. The treatment strategy is the same globally[5]. Betablockers are permitted despite various contraindications, and complications, such as cardiovascular and pulmonary events and an increased frequency of hospital admission[123]. Hyponatremia, hypotension, and renal insufficiency are contraindications for use of beta-blockers in older patients, as in younger patients[124].

According to the REPOSI Italian register, liver cirrhosis is the major cause of variceal and non-variceal upper gastrointestinal bleeding in older patients[125].

Proton pump inhibitors are associated with an increased risk of infection and encephalopathy in cirrhotic patients, irrespective of age[126-128]. In older patients, the therapeutic recommendations must be respected to prevent inappropriate prescriptions.

There is no specific recommendation concerning ascites in older patients. Diuretics should be prescribed with caution because of an increased risk of complications, particularly hyponatremia[129]. Older patients are at greater risk of acute renal insufficiency, independently of the aetiology[130]. Age does not affect survival in patients with refractory ascites, although terlipressin may be associated with vascular complications[131]. Transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation are interesting therapeutic options but have limitations in older patients, as discussed below.

Encephalopathy

Encephalopathy is a life-threatening complication of cirrhosis to which older people are particularly susceptible[39], and it may be linked to an altered brain-gut axis[132]. Infection, myocardial infarction, and central nervous system injury can favour this complication[133]. Minimal hepatic encephalopathy is associated with falls[134]. Older patients, especially the most fragile, require supervision and care. Their treatment is not different from that of younger patients[135]. Preventative therapy is essential in cases of cirrhotic decompensation and constipation must be controlled.

ACUTE ALCOHOLIC HEPATITIS

Acute alcoholic hepatitis is linked to a history of alcohol consumption and typically occurs in patients around 50 years of age[136]; however, older patients predominate in nosocomial studies[136]. Age is predictive of survival and of the presence of liver cirrhosis and is included in the Age, Serum bilirubin, International Normalised Ratio, and Serum creatinine score and the Lille model[137,138]. Although older patients were not included in the largest therapeutic studies, it is a prognostic factor for post-treatment survival [139]. Prednisolone is the only validated medical treatment, but data on its efficacy in older patients are lacking. Furthermore, recent studies of liver transplantation did not include patients > 61 years of age[140].

PULMONARY AND CARDIAC COMPLICATIONS

The definition of hepatopulmonary syndrome differs according to age: An alveolar-arterial gradient of 15 and 20 mmHg in patients < 65 and ≥ 65 years of age, respectively[5,141]. Long-term oxygen therapy is recommended[5]. Liver transplantation is curative, and age does not influence the outcome of patients with hepatopulmonary syndrome[142].

Among other causes of pulmonary hypertension, cirrhosis is one of the most important in older people[143,144]. The presentation can differ with age; older patients are more likely to have oedema and a more severe presentation[145]. Their management does not differ from that of patients in other age groups, and the prognosis is similar[5,109].

Hydrothorax is also observed in older cirrhotic patients, and its management, despite the lack of data, is identical to that for younger patients. TIPS is a therapeutic solution, but, as in ascites, careful selection of patients is mandatory[146].

Old age is associated with an increased risk of cardiac dysfunction and cirrhotic cardiomyopathy[147]. Because of its frequency and prognostic impact, systematic screening for these conditions among older patients is justified[5].

PATIENTS IN CRITICAL CONDITION

The survival rate of cirrhotic patients in the intensive care unit is 34% to 69%[148]. Age > 75 years impacts the global, but not the intensive care unit, survival rate[149]. Although the severity of cirrhosis is more predictive of survival than age, age is an indication for admission to the intensive care unit[5]. Indeed, age is a parameter of the prognostic Chronic Liver Failure Consortium acute decompensation score and the Chronic Liver Failure Consortium acute on chronic liver failure score[150,151]. Hepatorenal syndrome and spontaneous bacterial peritonitis are associated with a poor prognosis[152].

INFECTIONS

Older cirrhotic patients are at increased risk of infection due to their impaired immunity defences[153]. Spontaneous bacterial peritonitis has a higher mortality rate in older than in younger people[154], and, although the data are sparse, older people are more susceptible to renal failure[155]. In cirrhotic patients, bacterial resistance to antibiotics is promoted by the high frequency of antibiotic use[156]. Age impacts the occurrence and mortality rate of infection with multiresistant bacteria, but not the risk of inappropriate treatment[157].

As mentioned above, the use of proton-pump inhibitors by older patients increases the risk of infection, and their use should be restricted. Of note, vitamin D deficiency, which is more frequent in older cirrhotic patients, is also a risk factor for infection[158]. Thus, screening for and correction of this deficiency is essential in older cirrhotic patients[159].

SPECIFIC MANAGEMENT

Nutrition

Although there are no specific recommendations for older cirrhotic patients, both age and cirrhosis are associated with frailty and malnutrition[160,161]. Sarcopenia is present in 1% to 29% of community-dwelling patients and in 14% to 33% of those in long-term

care[160]. In older cirrhotic patients, assessment and correction of sarcopenia are crucial—computed tomography, measurement of the muscle area at L3, dual-energy X-ray absorptiometry, subjective global assessment, and Royal Free Hospital-Global assessment are useful in this regard[161]. Nutritional support can be helpful, particularly for critically ill patients. Exercise and physical activity tailored to the patient's age and general condition are also required[58]. Furthermore, systematic screening for osteoporosis is advisable in cirrhotic patients and is vital in older cirrhotic patients.

TIPS

Age is a limiting factor for TIPS, independently of the model for end-stage liver disease (MELD) score[162,163]. This is why cardiac function (diastolic function, pulmonary arterial hypertension) and risk of encephalopathy of older patients must be evaluated. Altered cardiac pressure in the right atrium and in pulmonary vessels is associated with mortality[163]. Correction of the natriuresis balance in older patients is delayed after TIPS insertion[164]. Although they were not included in the largest study[5], recent retrospective data show that the procedure is beneficial in selected older patients[146].

LIVER TRANSPLANTATION

Durand *et al*[29] reviewed liver transplantation in older patients. In practice, liver transplantation is rarely possible in patients > 70 years of age. However, the proportion of patients > 65 years of age who are candidates for liver transplantation is increasing in the United States and in Europe[29,165]. Also, the epidemiology is changing: In the United States, the frequency of nonalcoholic steatohepatitis and HCC as indications for liver transplantation is increasing, whereas that of HCV patients is decreasing[165]. The mortality rate among patients on the waiting list is higher in older people[165], as is the risk of dropping out; the mortality rate is higher in patients with a lower MELD score than in those < 64 years of age[165].

The 5-year post-transplantation mortality rate increases linearly with age in older recipients[166]. The MELD score is associated with mortality early post-liver transplantation[166], and older patients have a higher incidence of cardiac, pulmonary, and renal complications as well as of malignancies. Also, post-transplantation renal function is a key prognostic factor in patients transplanted for cirrhosis. Age impacts the occurrence of renal insufficiency (relative risk per 10-year increment, 1.36; $P < 0.001$)[167] as does pre-transplantation acute renal insufficiency, especially when associated with hepatorenal syndrome. However, older patients are at greater risk of chronic renal insufficiency before liver transplantation[168]. So, selection of patients is crucial to prevent post-transplantation complications-such as cancer, metabolic disease, or renal insufficiency-and to improve overall survival. The recently developed Liver Frailty Index may be predictive of survival post-transplantation[169].

Notably, donor age impacts survival post liver transplantation. The impact of donor age begins at 40 years and increases with age, particularly at > 60 years of age[170]. Moreover, improvements in liver-graft selection have resulted in a 5-year post-transplantation survival rate of > 70%[171]. The Donor Risk Index includes the donor's age, which is one of the three important risk factors for graft failure, in addition to donation after cardiac death and split/partial grafts[170]. Grafts with an increased Donor Risk Index are preferentially transplanted into older candidates > 50 years of age with moderate disease severity.

Finally, age matching, although complex, is warranted by a number of policies. A summed recipient and donor age of > 120 years may be prognostic, independently of other factors[172]. Other scores, such as the Survival Outcomes Following Liver Transplantation and Balance of Risk scores, include both donor and recipient factors[173,174].

In conclusion, few large studies have focused on older cirrhotic patients. The relevance of recent global recommendations on cirrhosis and transplantation is thus limited. In older patients, evaluation of comorbidities, comedications, and frailty is essential.

Relevant scores, such as the Frailty Liver Index, should be considered, and customised exercise and nutrition programs and osteoporosis therapy should be proposed to older cirrhotic patients. Moreover, attention should be paid to the choice of HCC treatment, the indications for TIPS insertion in patients with portal hypertension, and the indications for admission to the intensive care unit. Prevention policies are needed, because the causes of cirrhosis generally begin in the first decades of life. Finally, studies involving older cirrhotic patients, as well as specific

recommendations, are needed.

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World Journal of Hepatology

Submit a Manuscript: https://www.f6publishing.com

World J Hepatol 2019 September 27; 11(9): 678-688

DOI: 10.4254/wjh.v11.i9.678

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Basic Study

Hepatocellular carcinoma staging systems: Hong Kong liver cancer *vs* Barcelona clinic liver cancer in a Western population

Laura Bainy Rodrigues de Freitas, Larisse Longo, Deivid Santos, Ivana Grivicich, Mário Reis Álvares-da-Silva

ORCID number: Laura Bainy Rodrigues de Freitas (0000-0002-7571-2980); Larisse Longo (0000-0002-4453-7227); Deivid Santos (0000-0001-7300-422X); Ivana Grivicich (0000-0001-9820-5730); Mário Reis Álvares-da-Silva (0000-0002-5001-246X).

Author contributions: de Freitas LBR and Longo L performed the majority of experiments and analyzed the data; Santos D performed clinical data collection; Grivicich I analysis and interpretation of data; Álvares-da-Silva MR designed and coordinated the research; de Freitas LBR, Longo L and Álvares-da-Silva MR wrote the manuscript; All the authors participated in the critical review and in the final approval of the manuscript.

Institutional review board statement: This study was approved by the Hospital de Clínicas de Porto Alegre Ethics Committee (CAAE 57899016.8.0000.5327) and followed recommended guidelines for studies of human subjects.

Laura Bainy Rodrigues de Freitas, Larisse Longo, Mário Reis Álvares-da-Silva, Graduate Program in Gastroenterology and Hepatology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS 90035-003, Brazil

Laura Bainy Rodrigues de Freitas, Larisse Longo, Mário Reis Álvares-da-Silva, Experimental Hepatology and Gastroenterology Laboratory, Center for Experimental Research, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS 90035-003, Brazil

Deivid Santos, Mário Reis Álvares-da-Silva, School of Medicine, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS 90035-003, Brazil

Ivana Grivicich, Graduate Program in Health-Applied Cellular and Molecular Biology, ULBRA. Canoas, RS 92425-900, Brazil

Mário Reis Álvares-da-Silva, Department of Gastroenterology, Hospital de Clínicas de Porto Alegre, Porto Alegre, RS 90035-003, Brazil

Corresponding author: Laura Bainy Rodrigues de Freitas, MD, Medical Assistant, Graduate Program in Gastroenterology and Hepatology, Universidade Federal do Rio Grande do Sul, Porto Alegre, RS 90035-003, Brazil. laurabrfreitas@gmail.com
Telephone: +55-51-981105083
Fax: +55-51-33598760

Abstract

BACKGROUND

Despite being the world's most widely used system for staging and therapeutic guidance in hepatocellular carcinoma (HCC) treatment, the Barcelona clinic liver cancer (BCLC) system has limitations, especially regarding intermediate-grade (BCLC-B) tumors. The recently proposed Hong Kong liver cancer (HKLC) staging system appears useful but requires validation in Western populations.

AIM

To evaluate the agreement between BCLC and HKLC staging on the management of HCC in a Western population, estimating the overall patient survival.

METHODS

This was a retrospective study of HCC patients treated at a university hospital in southern Brazil between 2011 and 2016. Demographic, clinical, and laboratory data were collected. HCC staging was carried out according to the HKLC and BCLC systems to assess treatment agreement. Overall survival was estimated

Manuscript source: Unsolicited manuscript

Received: May 28, 2019
Peer-review started: May 29, 2019
First decision: June 13, 2019
Revised: July 8, 2019
Accepted: August 20, 2019
Article in press: August 20, 2019
Published online: September 27, 2019

P-Reviewer: Gatselis NK, Nah YW, Streba LAM, Tchilikidi KY
S-Editor: Ma YJ
L-Editor: A
E-Editor: Qi LL

based on the treatment proposed in each system.

RESULTS

A total of 519 HCC patients were assessed. Of these, 178 (34.3%) were HKLC-I; 95 (18.3%) HKLC-IIA; 47 (9.1%) HKLC-IIB; 29 (5.6%) HKLC-IIIA; 30 (5.8%) HKLC-IIIB; 75 (14.4%) HKLC-IV; and 65 (12.5%) HKLC-V. According to the BCLC, 25 (4.9%) were BCLC-0; 246 (47.4%) BCLC-A; 107 (20.6%) BCLC-B; 76 (14.6%) BCLC-C; and 65 (12.5%) BCLC-D. The general agreement between the two systems was 80.0% - BCLC-0 and HKLC-I (100%); BCLC-A and HKLC-I/HKLC-II (96.7%); BCLC-B and HKLC-III (46.7%); BCLC-C and HKLC-IV (98.7%); BCLC-D and HKLC-V (41.5%). When sub-classifying BCLC-A, HKLC-IIB, HKLC-IIIA and HKLC-IIIB stages according to the up-to-7 in/out criterion, 13.4, 66.0, 100 and 36.7%, respectively, of the cases were classified as up-to-7 out.

CONCLUSION

In a Western population, the general agreement between the two systems was 80.0%, although in BCLC-B cases the agreement was low, suggesting that some individuals could be candidates for the curative treatment recommended by the HKLC. The authors suggest that the BCLC system should be routinely employed, although for BCLC-B cases it should be associated with the HKLC system.

Key words: Barcelona clinic liver cancer staging system; Hepatocellular carcinoma; Hong Kong liver cancer staging system

Core tip: Despite being the world's most widely used system for staging and therapeutic guidance in hepatocellular carcinoma (HCC) treatment, the Barcelona clinic liver cancer (BCLC) system has limitation. Proposed Hong Kong liver cancer (HKLC) staging appears useful but requires validation in Western populations. This study showed that there is adequate agreement between the HKLC and BCLC systems regarding therapeutic management of HCC in Western populations, except in cases of intermediate HCC. Although staging systems should be further refined to cover the full diversity of HCC cases, these findings suggest that the BCLC system, which is more simple and intuitive, should be applied in all HCC cases, and that in BCLC-A and, especially, BCLC-B cases, the HKLC can contribute important information regarding patient management.

Citation: Freitas LBR, Longo L, Santos D, Grivicich I, Álvares-da-Silva MR. Hepatocellular carcinoma staging systems: Hong Kong liver cancer *vs* Barcelona clinic liver cancer in a Western population. *World J Hepatol* 2019; 11(9): 678-688
URL: https://www.wjgnet.com/1948-5182/full/v11/i9/678.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i9.678

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 90% of primary malignant neoplasms, being the sixth most prevalent type of cancer and the second most common cause of cancer-related mortality worldwide[1-3]. Although most cases occur in developing countries, their incidence in developed countries has increased in recent years due to the high prevalence of chronic hepatitis C, immigration from areas where hepatitis B and hepatitis C are common, and the increased prevalence of non-alcoholic fatty liver disease (NAFLD)[2-4]. Heterogeneous data on HCC incidence have been reported in Latin America[2,5-7]. In Brazil, the HCC incidence varies from 3.3%-6.0% per 100000 per year, and the mortality rates are similar due to high intrahepatic recurrence, distant metastasis and lack of effective treatment for cases diagnosed at an advanced stage[8,9]. The prognosis is generally somber and essentially depends on the tumor stage at diagnosis. In cirrhosis patients, the American Association for the Study of the Liver Diseases (AASLD) recommends screening for HCC by ultrasound, with or without an alpha-fetoprotein test, every six months[10,11]. Although HCC is commonly associated with cirrhosis, approximately one in five cases are unrelated to

it. In such cases, the tumor is often detected in advanced stages, since non-cirrhotic patients are usually not screened. Chronic hepatitis B or NAFLD patients may also develop a tumor without associated cirrhosis[12,13]. In recent years, five-year HCC survival rates have improved considerably due to early detection and curative therapies[14]. However, despite efforts to detect the disease in early stages among patients with risk factors, a substantial number of cases are diagnosed at intermediate and late stages, when the survival rate is lower[4,15]. In Brazil, recent DATASUS figures indicate that upon diagnosis, palliative care is the only possible treatment in 62.2% of the cases[16].

Treating patients with HCC is not simple, since two serious diseases usually coincide: Cirrhosis and a malignant tumor. A number of staging systems have proposed treatment guidelines for HCC according to evolutionary stage[17-21]. The Barcelona Clinic Liver Cancer (BCLC) staging system, which considers tumor characteristics, liver function and performance status, is the most widely used and endorsed system in Western HCC management guidelines[4,11,17,22]. Published in 2014, the Hong Kong liver cancer (HKLC) staging system identifies subsets of patients with intermediate and advanced HCC and proposes more aggressive treatment to improve survival rates[18]. However, the HKLC system still requires validation in Western populations, since it was developed at a single Asian center that principally treats patients infected with the hepatitis B virus (HBV)[18,23]. Both systems suggest curative, supportive or palliative care according to the patient's stage. The objective of this study was to assess the agreement of BCLC and HKLC therapeutic approaches according to HCC evolutionary stage in a Western population.

MATERIALS AND METHODS

This retrospective cross-sectional study analyzed data from the medical records of individuals over 18 years of age diagnosed with HCC and treated at a referral service in a university hospital in southern Brazil between 2011 and 2016. Upon diagnosis, demographic and clinical data and laboratory results were collected, as well as performance status and Child-Pugh (CP) scores. Diagnosis was based on AASLD criteria[17]. Tumor characteristics (size, number of nodules, intra- and/or extrahepatic dissemination) were assessed with dynamic imaging (computed tomography or magnetic resonance imaging) prior to treatment and near the time of diagnosis. Tumors were considered multifocal when they involved more than three nodules, regardless of size. The management of each complication presented in decompensated patients was made accordingly the hospital Liver Unit protocol.

The patients were staged according to BCLC criteria[24,25]. For the purposes of this study, since the BCLC does not set a tumor size limit for BCLC-A cases, patients thus staged were classified according to the up-to-7 criterion as either in or out, *i.e.*, when the sum of the nodules plus the diameter of the largest nodule is ≤ 7, these patients are most likely candidates for curative treatment, whereas when it is > 7, palliative treatment is usually recommended. The patients were also staged according to the HKLC system[18]. According to tumor size in relation to the proposed treatment, HKLC-IIB, -IIIA and -IIIB patients were subclassified as up-to-7 in/out. The approach of decompensated patients with BCLC, CP-B patients were managed with curative or palliative therapies depending on HCC characteristics and the presence of metastasis and/or vascular invasion, while CP-C ones were candidates for best supportive care. When applying HKLC scheme, CP-B patients were managed with curative or palliative therapies depending on HCC characteristics and the presence of metastasis and/or vascular invasion, while CP-C ones were either candidates for liver transplantation or best supportive care.

After the patients were staged according to both systems, the systems' agreement regarding therapeutic approach for different stages was analyzed (Table 1). Overall patient survival was estimated from HCC diagnosis until the outcome, *i.e.*, death, loss of follow-up, or the date of the last appointment at the referral hospital.

This study was approved by the Hospital de Clínicas de Porto Alegre Ethics Committee (CAAE 57899016.8.0000.5327) and followed recommended guidelines for studies of human subjects.

Statistical analysis

Quantitative variables were expressed as mean ± SD or median and interquartile range (25th-75th). Categorical variables were described as frequencies and percentages. The Kaplan-Meier curve was applied to estimate survival time, and the log-rank test was used to calculate survival probability. A $P \leq 0.05$ was considered statistically significant. Data were stored and processed using the Statistical Package

Table 1 Concordance in the treatment of hepatocellular carcinoma proposed by the Hong Kong liver cancer system and Barcelona clinic liver cancer classification

	BCLC-0 (ablation, LR or LT)	BCLC-A (ablation, LR or LT)	BCLC-B (TACE)	BCLC-C (SOR)	BCLC-D (ST)
HKLC-I (ablation, LR or LT)	√	√			
HKLC-IIA (ablation, LR or LT)	√	√			
HKLC-IIB (LR)	√	√			
HKLC-IIIA (TACE)			√		
HKLC-IIIB (TACE)			√		
HKLC-IVA (SOR)				√	
HKLC-IVB (SOR or ST)				√	
HKLC-VA (LT)					
HKLC-VB (ST)					√

The tick in the table means that there was agreement in the treatment of HCC proposed by the HKLC system and BCLC classification. BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma; HKLC: Hong Kong liver cancer; LR: Liver resection; LT: Liver transplantation; ST: Symptomatic treatment; SOR: Sorafenib; TACE: Transarterial chemoembolization.

for the Social Sciences 18.0 (SPSS Inc., Chicago, IL, United States).

RESULTS

General characteristics of patients

A total of 568 patients were diagnosed with HCC according to AASLD criteria between 2011 and 2016. Of these, 49 (8.6%) were excluded because their medical records included no CP score report and/or no assessment of performance status. Thus, the final sample totaled 519 patients.

The patients' demographic, laboratory and clinical data are described in Table 2. The median age at diagnosis was 60.9 (56.2-67.7) years; the sample was predominantly male (64.7%). The most common underlying etiology was hepatitis C virus infection (HCV – 78.4%), followed by alcohol abuse (37.4%). Most patients were staged as CP-A (52.6%), followed by CP-B (34.9%). Multifocal tumors were observed in 50.3% of the cases, and in 86.5% of the cases the size of the largest nodule was less than 10 cm.

HCC staging systems: BCLC vs HKLC

In the BCLC system, curative treatment is recommended for HCC stages BCLC-0 and A, palliative treatment with transarterial chemoembolization (TACE) is recommended for stage BCLC-B, systemic treatment is recommended for stage BCLC-C, and supportive treatment is the only alternative for BCLC-D. The cases, stratified according to the BCLC and HKLC systems, are shown in Figure 1.

According to the HKLC system, 178 (34.3%) of the 519 patients were HKLC-I and 95 (18.3%) were HKLC-IIA, stages in which curative therapy is recommended, including resection, liver transplantation or ablation. Another 47 cases (9.1%) were classified as HKLC-IIB, of which 16 (34.0%) were up-to-7 in and 31 (66.0%) were up-to-7 out. The HKLC system recommends resection in these cases. A total of 29 (5.6%) patients were classified as HKLC-IIIA, all of them up-to-7 out, and 30 (5.8%) were classified as HKLC-IIIB, for which the HKLC system indicates palliative care, with TACE as an optional procedure. However, of the 30 HKLC-IIIB cases, only 11 were up-to-7 out. In addition, 75 cases (14.4%) were classified as HKLC-IV, of which 32 (42.7%) were HKLC-IVA, for which systemic therapy is recommended. The 65 (12.5%) remaining cases were classified as HKLC-V, with 38 (58.5%) as HKLC-VA, *i.e.*, candidates for liver transplant.

According to BCLC staging, 25 (4.9%) of the 519 patients were BCLC-0, 246 (47.4%) were BCLC-A, 213 (86.6%) of which were up-to-7 in and 33 (13.4%) up-to-7 out, 107 (20.6%) were BCLC-B (intermediate HCC), 76 (14.6%) were BCLC-C (advanced HCC), and 65 (12.5%) were BCLC-D (terminal HCC).

The treatment agreement between the BCLC and HKLC staging systems is shown in Table 3. The overall agreement for the two curative and palliative classifications was 80.0%. The treatment for all BCLC-0 cases was in agreement with that of HKLC-I. The agreement between BCLC-A cases and HKLC-I, HKLC-IIA and HKLC-IIB stages was 96.7%. However, the agreement between treatments for BCLC-B and parallel

Table 2 General data of patients with hepatocellular carcinoma

Variables[1]	HCC (*n* = 519)
Race	
White	462 (89.0)
Black	35 (6.8)
Others	22 (4.2)
Etiology	
HCV	407 (78.4)
Alcohol abuse	194 (37.4)
HBV	31 (6.0)
NAFLD	23 (4.4)
Cryptogenic cirrhosis	9 (1.7)
Alpha-fetoprotein (ng/mL)	
< 400	361 (69.6)
≥ 400	109 (21.0)
Data not available	49 (9.4)
Child-Pugh score	
A	273 (52.6)
B	181 (34.9)
C	65 (12.5)
Multifocal Tumor	
Yes	261 (50.3)
No	258 (49.7)
Tumor size, cm	
< 10 cm	449 (86.5)
≥ 10 cm	30 (5.8)
Data not available	40 (7.7)

[1]Variables described by frequency (%). HCC: Hepatocellular carcinoma; NAFLD: Non-alcoholic fatty liver disease; HBV: Hepatitis B virus; HCV: Hepatitis C virus.

HKLC stages was only 46.7%. Agreement between BCLC-C and HKLC was 98.7%, including stages HKLC-IVA and HKLC-IVB. The agreement between BCLC-D and HKLC-V was also low (41.5%).

Overall survival analysis

The median overall survival was 32.7 mo (95%CI: 25.1-40.3). A total of 265 patients (51.1%) had died by the time of data collection. The overall survival probability one year after diagnosis was 67.6%, which decreased to 35.9% after five years (Figure 2A).

The median overall survival was 75.7 mo (95%CI: 41.2–110.1) for BCLC-0 cases, 60.0 mo (95%CI: 38.0–81.9) for BCLC-A, 19.6 mo (95%CI: 11.5–27.6) for BCLC-B, 3.5 mo (95%CI: 2.6–4.3) for BCLC-C, and 5.2 mo (95%CI: 2.2–8.3) for BCLC-D ($P < 0.001$). The median overall survival rate was 79.2 mo (95%CI: 56.9–101.6) for HKLC-I; 44.7 mo (95%CI: 18.8–70.7) for HKLC-IIA; 35.5 mo (95%CI: 12.6–58.4) for HKLC-IIB; 13.2 months (95%CI: 8.6–17.7) for HKLC-IIIA, 4.7 mo (95%CI: 1.6–7.9) for HKLC-IIIB, 11.2 mo (95%CI: 2.5–6.2) for HKLC-IVA, 2.3 mo (95%CI: 1.7–3.0) for HKLC-IVB, 21.5 mo (95%CI: 1.9–41.0) for HKLC-VA, and 1.5 months (95%CI: 0.4–2.5) for HKLC-VB ($P < 0.001$).

Median overall survival of BCLC-0 and BCLC-A patients was significantly higher than BCLC-B ($P = 0.001$ and $P < 0.001$, respectively), BCLC-C ($P < 0.001$ and $P < 0.001$, respectively), and BCLC-D patients ($P < 0.001$ and $P < 0.001$, respectively). Median overall survival was significantly higher for BCLC-B patients than BCLC-C ($P < 0.001$) and BCLC-D ($P = 0.011$) patients. The overall survival probability of BCLC-0 and BCLC-A patients 7 years after diagnosis was similar: 46.0% and 44.0%, respectively. The survival probability of BCLC-B cases two years after diagnosis was 45.6%, which was significantly higher than BCLC-C (19.4%) and BCLC-D (30.5%) (Figure 2B).

The median overall survival for HKLC-I was significantly higher than HKLC-IIB ($P = 0.015$), HKLC-IIIA ($P < 0.001$), HKLC-IIIB ($P < 0.001$), HKLC-IVA ($P < 0.001$), HKLC-IVB ($P < 0.001$), HKLC-VA ($P < 0.001$), and HKLC-VB ($P < 0.001$). This significant

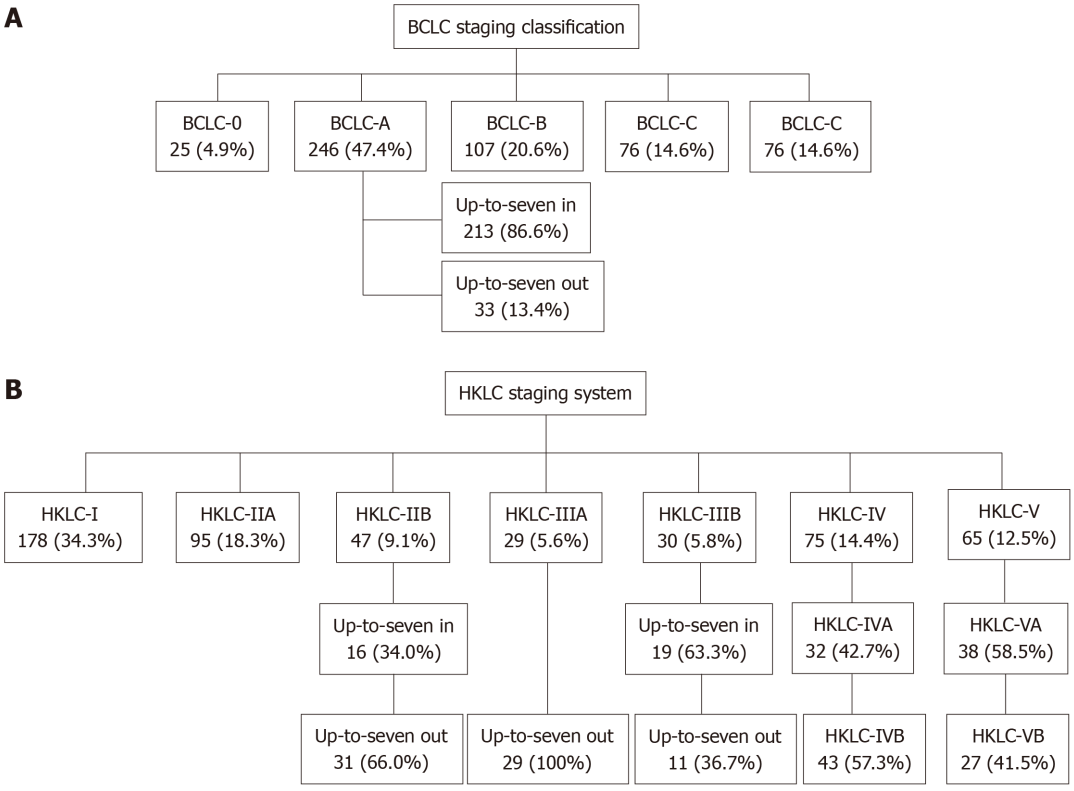

Figure 1 Distribution algorithm of hepatocellular carcinoma patients according to Barcelona clinic liver cancer (A) and Hong Kong liver cancer (B) staging in the present study. BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma; HKLC: Hong Kong liver cancer.

increase in overall survival was also observed for HKLC-IIA and HKLC-IIB cases compared to HKLC-IIIA ($P < 0.001$), HKLC-IIIB ($P < 0.001$), HKLC-IVA ($P < 0.001$), HKLC-IVB ($P < 0.001$ and $P = 0.002$, respectively) and HKLC-VB ($P < 0.001$). Median overall survival for HKLC-IIIA, HKLC-IIIB and HKLC-IVA was significantly higher than HKLC-IVB ($P < 0.001$, $P = 0.003$ and $P < 0.001$, respectively) or HKLC-VB ($P = 0.004$, $P = 0.023$ and $P < 0.001$, respectively). Median overall survival for HKLC-VA was higher than HKLC-VB (P <0.001). The overall survival probability of HKLC-I patients 7 years after diagnosis was 48.7%. The overall survival probability for HKLC-IIA and HKLC-IIB cases 2 years after diagnosis was 67.3% and 64.5% respectively. This probability was lower for HKLC-IIIA (22.3%), HKLC-IIIB (30.7%) and HKLC-IVA (34.2%) patients. The overall survival probability of HKLC-VA patients 1 year after diagnosis was 57.3%, which was higher than that of HKLC-IVB (7.0%) or HKLC-VB (7.7%) patients (Figure 2C).

DISCUSSION

Over the last 30 years, a number of staging systems have been developed to address the interrelationship of prognostic factors in HCC patients and to propose an adequate course of therapy according to disease stage. However, due to the clinical, biological and etiological heterogeneity of different populations, there is no flawless staging system. Despite the fact that the BCLC is the most predominant system worldwide and is mandatory in HCC management, it involves controversial points, such as the maximum tumor diameter in BCLC-A and recommending TACE for all patients with intermediate tumors (BCLC-B). Moreover, especially in the latter case, the BCLC does not consider moving from palliative to curative therapy in TACE responders or escalating to systemic therapy for TACE non-responders or those who have multifocal tumors without metastases.

The objective of this study was to evaluate the agreement between BCLC and HKLC staging systems regarding therapeutic management of HCC in Western populations, and the results showed high general agreement between the two systems. However, agreement was low in intermediate HCC cases, indicating, as the HKLC suggests, that TACE is not mandatory for all BCLC-B cases. It was not surprising that agreement was also low for BCLC-D cases, since the BCLC suggests

Table 3 Concordance in the treatment of hepatocellular carcinoma proposed by the Hong Kong liver cancer system and Barcelona clinic liver cancer classification in a South American population

Variables[1]	BCLC-0 (ablation, LR or LT)	BCLC-A (ablation, LR or LT)	BCLC-B (TACE)	BCLC-C (SOR)	BCLC-D (ST)
HKLC-I (ablation, LR or LT)	25 (100%)	129 (52.4%)	24 (22.4%)		
HKLC-IIA (ablation, LR or LT)		84 (34.1%)	11 (10.3%)		
HKLC-IIB (LR)		25 (10.2%)	22 (20.6%)		
HKLC-IIIA (TACE)		8 (3.3%)	20 (18.7%)	1 (1.3%)	
HKLC-IIIB (TACE)			30 (28.0%)		
HKLC-IVA (SOR)				32 (42.1%)	
HKLC-IVB (SOR or ST)				43 (56.6%)	
HKLC-VA (LT)					38 (58.5%)
HKLC-VB (ST)					27 (41.5%)

[1]Variables described by frequency (%). The highlighted square in the table means that there was agreement in the treatment of HCC proposed by the HKLC system and BCLC classification. BCLC: Barcelona clinic liver cancer; HCC: Hepatocellular carcinoma; HKLC: Hong Kong liver cancer; LR: Liver resection; LT: Liver transplantation; ST: Symptomatic treatment; SOR: Sorafenib; TACE: Transarterial chemoembolization.

supportive treatment for CP-C patients, while according to HKLC this population could, depending on tumor mass, benefit from liver transplant. Because this discrepancy can be easily dealt with, BCLC-D patients will not be further discussed.

Tumor etiology is among the most significant variables in determining therapy type, and it involves important regional differences[2,3,26]. HCV infection and NAFLD, the main causes of HCC in Western populations, are usually associated with cirrhosis[10,26], while HBV infection is the leading cause of HCC in Asian and African populations. Many of these patients are not cirrhotic and have preserved liver function, which facilitates the success of curative treatments[26]. Thus, Asians with HCC could particularly benefit from HKLC, since it indicates more aggressive curative treatments than the BCLC. However, like many previous studies, the present study involved a Western sample[8,23,27,28]. Only 6% of the cases were HBV related, and most patients had chronic HCV infection. Cirrhosis was present in all cases, especially CP-A patients, characterizing a population with controlled liver disease, which facilitates more aggressive HCC treatments.

Although treatment selection is crucial for patient survival, determining the most appropriate therapy has been controversial[29,30]. A previous study showed that the HKLC system has greater discriminatory and prognostic power than the BCLC[18]. However, no external validation has been performed. Similar studies to this one have been conducted in different countries, but with disparate results[23,30-32]. A Korean study found that the overall survival of intermediate-stage HCC patients (BCLC-B) was higher for liver resection (which is proposed by HKLC) than TACE[33]. On the other hand, a multicenter study in France found that the HKLC system is not associated with better prognostic or therapeutic power than the BCLC [31]. This divergence is probably due to etiological and pathophysiological differences between Asian and European populations. The present study, conducted with Latin American patients, found high agreement between the staging systems, except for certain niches, especially patients with intermediate HCC. Most of the patients were candidates for curative treatments, which agrees with other published studies[23,26,31,34]. The fact that these patients were diagnosed with early-stage HCC can probably be attributed to screening, since these cirrhosis cases were diagnosed and followed up at a university institution, which contributed to greater overall survival. In addition, studies show that tumor diagnosis tends to occur at earlier stages in populations in which HCV and alcohol are the most frequent etiologies[23,31].

The median overall survival in this study was 32.7 mo, which was higher than the 12.7 mo observed by Yau *et al*[18]. Overall survival was significantly higher in BCLC-0 and BCLC-A than the other stages, as expected. In the HKLC system, the highest survival rates were in the HKLC-I, HKLC-IIA and HKLC-IIB stages.

Although the BCLC staging system is currently the main tool for determining the prognosis and treatment of HCC[17], it has been criticized for being too conservative, especially in therapeutic management of the BCLC-B stage[35-37]. This point was highlighted in the results of the present study since, according to the HKLC, more than 50% of these patients could have been candidates for curative treatment rather than the palliative treatment recommended by BCLC. These findings agree with prior publications in Asia and Europe[26,30,31,34].

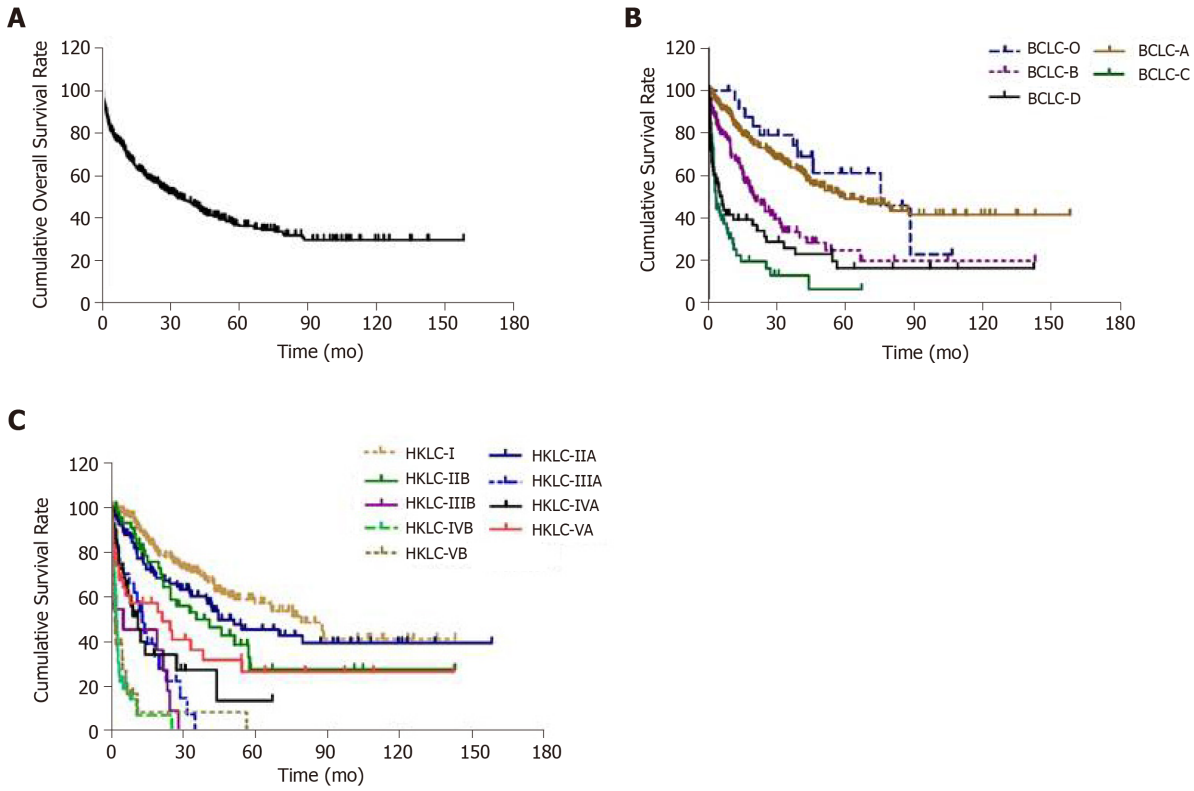

Figure 2 Kaplan-Meier curve for the overall survival probability of patients with hepatocellular carcinoma, according to the Hong Kong liver cancer and Barcelona clinic liver cancer staging systems. A: Overall survival; B: Overall survival according to BCLC; C: Overall survival according to Hong Kong liver cancer. BCLC: Barcelona clinic liver cancer.

Although the HKLC and BCLC staging systems are comprehensive, some patients do not fit neatly into the pre-specified categories. This could lead to different therapeutic recommendations for the same patient[37],which reinforces the need to further explore the issue. In this study, the highest agreement was found between stages HKLC-I and BCLC-0 (100%) and HKLC-IV and BCLC-C (98.7%). These results can be explained by the tumor characteristics and liver function common to both systems. Cases staged as BCLC-A, as well as HKLC-IIB, HKLC-IIIA and HKLC-IIIB, were subdivided according to the up-to-7 in/out criterion, which demonstrates the limitations of both systems, since they cannot clearly discriminate between patients who need curative or palliative care. Although the up-to-7 criterion is an anatomopathological, rather than radiological, classification, it has been used in a similar fashion in clinical practice. However, rather than indicating a limitation in these systems, it shows that therapy should be individualized[38]. We found BCLC-A and HKLC-IIB, HKLC-IIIA and HKLC-IIIB up-to-7 out patients who would not qualify as liver transplant candidates due to their tumor volume[39,40], as well as HKLC-IIIA and HKLC-IIIB patients who would not qualify as TACE candidates because they have nodules larger than 10 cm or have decompensated cirrhosis (CP-B and CP-C)[41].

This study presents some limitations that should be addressed. First, the differences in overall survival are not exactly real because they were estimated according to the different therapeutic options suggested by the systems. Some other should be considered, such as the fact that it is a single center, observational and retrospective analysis.

In conclusion, this study showed that there is adequate agreement between the HKLC and BCLC staging systems regarding therapeutic management of HCC in Western populations, except in cases of intermediate HCC (BCLC-B). However, it is clear that both systems have limitations, as demonstrated by the need to apply the up-to-7 criterion in BCLC-A, HKLC-IIB, HKLC-IIIA and HKLC-IIIB to determine when curative treatment should be recommended. Although staging systems should be further refined to cover the full diversity of HCC cases, these findings suggest that the BCLC system, which is more simple and intuitive, should be applied in all HCC cases, and that in BCLC-A and, especially, BCLC-B cases, the HKLC can contribute important information regarding patient management.

ARTICLE HIGHLIGHTS

Research background

Treating patients with hepatocellular carcinoma (HCC) is not simple, since two serious diseases usually coincide: Cirrhosis and a malignant tumor. The Barcelona clinic liver cancer (BCLC) staging system, is the most widely used and endorsed system in Western HCC management guidelines. The Hong Kong liver cancer (HKLC) staging system identifies subsets of patients with intermediate and advanced HCC and proposes more aggressive treatment; however, this system still requires validation in Western populations. This study to assess the agreement of BCLC and HKLC therapeutic approaches according to HCC evolutionary stage in this population.

Research motivation

Evaluating the agreement of the treatments proposed by the BCLC and HKLC system according to HCC evolutionary stage in a Western population, can optimize the therapeutic approaches, promoting an increase in patient survival time.

Research objectives

This study aimed first to evaluate the agreement between BCLC and HKLC staging on the management of HCC in a Western population. Secondary aim was estimating the overall patient survival with HCC.

Research methods

Retrospective cross-sectional study analyzed data from the medical records of individuals over 18 years of age diagnosed with HCC and treated at a referral service in a university hospital in southern Brazil between 2011 and 2016. Upon diagnosis, demographic and clinical data and laboratory results were collected, as well as performance status and Child-Pugh (CP) scores. Diagnosis was based on the American Association for the Study of the Liver Diseases criteria. The patients were staged according to BCLC criteria and HKLC system. After, the agreement of the treatment proposed by both systems was performed. Overall patient survival was estimated from HCC diagnosis until the outcome, *i.e.*, death, loss of follow-up, or the date of the last appointment at the referral hospital.

Research results

A total of 519 HCC patients were assessed. Of these, 178 (34.3%) were HKLC-I; 95 (18.3%) HKLC-IIA; 47 (9.1%) HKLC-IIB; 29 (5.6%) HKLC-IIIA; 30 (5.8%) HKLC-IIIB; 75 (14.4%) HKLC-IV; and 65 (12.5%) HKLC-V. According to the BCLC, 25 (4.9%) were BCLC-0; 246 (47.4%) BCLC-A; 107 (20.6%) BCLC-B; 76 (14.6%) BCLC-C; and 65 (12.5%) BCLC-D. The general agreement between the two systems was 80.0% - BCLC-0 and HKLC-I (100%); BCLC-A and HKLC-I/HKLC-II (96.7%); BCLC-B and HKLC-III (46.7%); BCLC-C and HKLC-IV (98.7%); BCLC-D and HKLC-V (41.5%). When sub-classifying BCLC-A, HKLC-IIB, HKLC-IIIA and HKLC-IIIB stages according to the up-to-7 in/out criterion, 13.4, 66.0, 100 and 36.7%, respectively, of the cases were classified as up-to-7 out.

Research conclusions

This study showed that there is adequate agreement between the BCLC and HKLC staging systems (80.0%) regarding therapeutic management of HCC in Western populations, although in BCLC-B cases the agreement was low, suggesting that some individuals could be candidates for the curative treatment recommended by the HKLC. However, it is clear that both systems have limitations to determine when curative treatment should be recommended. Although staging systems should be further refined to cover the full diversity of HCC cases, these findings suggest that the BCLC system should be routinely employed in Western populations; although for BCLC-B cases it should be associated with the HKLC system.

Research perspectives

Demonstrated adequate agreement between the BCLC and HKLC systems in relation to the therapeutic management of HCC in Western population evaluated. However, new multicenter and prospective studies are needed to assess this issue in the Western population.

ACKNOWLEDGEMENTS

The authors would like to thank the Research Incentive Fund of the Hospital de Clínicas de Porto Alegre, CNPq (National Counsel of Technological and Scientific Development) and CAPES (Coordination for the Improvement of Higher Education Personnel) for financial support.

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World Journal of Hepatology

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World J Hepatol 2019 September 27; 11(9): 689-700

DOI: 10.4254/wjh.v11.i9.689

ISSN 1948-5182 (online)

ORIGINAL ARTICLE

Retrospective Cohort Study

Hepatic flow is an intraoperative predictor of early allograft dysfunction in whole-graft deceased donor liver transplantation: An observational cohort study

Pablo Lozano Lominchar, Maitane Igone Orue-Echebarria, Lorena Martín, Cristina Julia Lisbona, María Magdalena Salcedo, Luis Olmedilla, Hemant Sharma, Jose Manuel Asencio, José Ángel López-Baena

ORCID number: Pablo Lozano Lominchar (0000-0002-5413-8449); Maitane Igone Orue-Echebarria (0000-0002-4559-3968); Lorena Martín (000-0003-0423-910X); Cristina Julia Lisbona (0000-0002-9585-437X); María Magdalena Salcedo (0000-0002-1239-5746); Luis Olmedilla (0000-000205628-723X); Hemant Sharma (0000-0002-3717-7200); Jose Manuel Asencio (0000-0002-7533-5513); José Ángel López-Baena (0000-0001-8450-0798).

Author contributions: Lozano P and Baena JAL participated in research design; Lozano P and Orue-Echebarria LM participated in data analysis; Lozano P, Baena JAL, Olmedilla L, Asencio JM, Salcedo MM and Lisbona CJ carried out the research; Lozano P, Sharma H and Martin L wrote the paper.

Institutional review board statement: This clinical research study was approved by the Hospital General Universitario Gregorio Maranon Local Ethical Committee.

Informed consent statement: A consent form was signed by or on behalf of each patient enrolled in the study.

Conflict-of-interest statement: None of the authors have any conflicts of interest to disclose.

STROBE statement: The STROBE

Pablo Lozano Lominchar, Maitane Igone Orue-Echebarria, Lorena Martín, Jose Manuel Asencio, José Ángel López-Baena, General Surgery Department, Liver Transplant Unit, Hospital General Universitario Gregorio Maranon, Madrid 28007, Spain

Cristina Julia Lisbona, Luis Olmedilla, Anesthesiology Department, Liver Transplant Unit, Hospital General Universitario Gregorio Maranon, Madrid 28007, Spain

María Magdalena Salcedo, Hepatology Department, Liver Transplant Unit, Hospital General Universitario Gregorio Maranon, Madrid 28007, Spain

Hemant Sharma, Department of Transplant Surgery, Oschner Medical Center, New Orleans, LA 70816, United States

Corresponding author: Pablo Lozano, MD, PhD, General Surgery Department, Liver Transplant Unit, Hospital Universitario Gregorio Maranon, C/ Doctor Esquerdo 44, Madrid 28007, Spain. lozanon57@hotmail.com
Telephone: +34-639-011522

Abstract

BACKGROUND

Early allograft dysfunction (EAD) after liver transplantation (LT) is an important cause of morbidity and mortality. To ensure adequate graft function, a critical hepatocellular mass is required in addition to an appropriate blood supply. We hypothesized that intraoperative measurement of portal venous and hepatic arterial flow may serve as a predictor in the diagnosis of EAD.

AIM

To study whether hepatic flow is an independent predictor of EAD following LT.

METHODS

This is an observational cohort study in a single institution. Hepatic arterial blood flow and portal venous blood flow were measured intraoperatively by transit flow. EAD was defined using the Olthoff criteria. Univariate and multivariate analyses were used to determine the intraoperative predictors of EAD. Survival analysis and prognostic factor analysis were performed using the Kaplan-Meier and Cox regression models.

RESULTS

Manuscript source: Unsolicited manuscript

Received: April 13, 2019
Peer-review started: April 15, 2019
First decision: June 5, 2019
Revised: June 25, 2019
Accepted: September 5, 2019
Article in press: September 5, 2019
Published online: September 27, 2019

P-Reviewer: Bhatti ABH, Junge N, Tzamaloukas AHH
S-Editor: Ma YJ
L-Editor: A
E-Editor: Qi LL

A total of 195 liver transplant procedures were performed between January 2008 and December 2014 in 188 patients. A total of 54 (27.7%) patients developed EAD. The median follow-up was 39 mo. Portal venous flow, hepatic arterial flow (HAF) and total hepatic arterial flow were associated with EAD in both the univariate and multivariate analyses. HAF is an independent prognostic factor for 30-d patient mortality.

CONCLUSION
Intraoperative measurement of blood flow after reperfusion appears to be a predictor of EAD; Moreover, HAF should be considered a predictor of 30-d patient mortality.

Key words: Hepatic flow; Early allograft dysfunction; Liver transplant

Core tip: Early allograft dysfunction (EAD) is a problem that can soon occur after liver implantation. Currently, there are a large number of predictive models for graft failure. In general, the models try to predict the development of liver dysfunction and aid clinicians in the decision-making process of selecting the liver graft. These variables do not need to be modified, so we propose that measurable arterial and venous flow intraoperatively after implantation may be useful in predicting the development of EAD. A study of the intraoperative factors that may influence the development of EAD should be performed to address additional, related problems in the field.

Citation: Lominchar PL, Orue-Echebarria MI, Martín L, Lisbona CJ, Salcedo MM, Olmedilla L, Sharma H, Asencio JM, López-Baena JÁ. Hepatic flow is an intraoperative predictor of early allograft dysfunction in whole-graft deceased donor liver transplantation: An observational cohort study. *World J Hepatol* 2019; 11(9): 689-700
URL: https://www.wjgnet.com/1948-5182/full/v11/i9/689.htm
DOI: https://dx.doi.org/10.4254/wjh.v11.i9.689

INTRODUCTION

Early allograft liver dysfunction (EAD) is a condition that prematurely identifies grafts that are at risk of having marginal function after liver transplantation (LT). The development of graft dysfunction is multifactorial. The degree of impairment can range from a very mild and temporary form to a more severe and potentially deadly form unless the patient receives an early retransplantation. The regenerative capacity of the hepatic parenchyma conditions most dysfunctions to be transient[1,2].

Currently, there are a large number of predictive models for graft failure, all of which are heterogeneous because they use different criteria to select the independent variables. In general, the models have the same goal, which is to predict the development of liver dysfunction and provide an evidence-based tool that is useful during the liver graft selection process[3-5]. To ensure proper function of a liver graft, the hepatocellular critical mass is needed to maintain synthetic function and adequate blood supply through the vascular tree. Hepatic flow is a determining factor in early graft function. The hepatic circulation system is highly complex due to its dual irrigation. The hepatic artery contributes 25% of the hepatic blood flow (30 mL/min per 100 g of liver mass) and provides 30-50% of the oxygen requirement of the liver. Moreover, the portal vein provides 75% of the hepatic blood flow (90 mL/min per 100 g of liver mass) and provides 50%-70% of the oxygen requirements of the liver with partially deoxygenated blood arriving from splanchnic circulation. These two systems are closely related and conform to what is known as the "hepatic arterial response buffer"[6]. This mechanism explains the changes in arterial blood flow as compensatory to the changes in the portal flow so that the arterial system is able to compensate for changes of up to 25%-60% in portal flow. However, the portal system is unable to compensate for the changes in arterial blood flow[7]. This buffer system remains active after LT, as shown by authors such as Cantré *et al*[8]. The intraoperative reading of arterial and venous blood flow after LT may be useful in predicting the development of early graft dysfunction because blood flow values offer an indirect measurement of

the oxygen and nutrient levels being supplied to the liver parenchyma at a given point in time.

MATERIALS AND METHODS

This is an observational study based on a single cohort of 195 consecutive patients who underwent LT with a prospective collection of data and a retrospective analysis. This study was carried out in the Liver Transplant Unit of Hospital General Universitario Gregorio Marañón, Madrid, Spain, a tertiary referral centre, during the study period between January 2008 and December 2014. The study was performed according to the International Guidelines for Ethical Review of Epidemiological Studies [Council for the International Organizations of Medical Sciences (CIOMS), Geneva, 2008] and to the Declaration of Helsinki (Seoul, October, 2008). The study was reviewed and approved by the Clinical Research Ethics Committee. All patients gave their written informed consent prior to study enrolment. All recruited candidates were adult patients who received an orthotopic full cadaveric donor liver transplant, including an urgent transplant, early retransplantation due to primary graft dysfunction and late retransplantation. The cases in which the intraoperative vascular blood flow measurements could not be obtained due to technical problems or those in which liver graft dysfunction was secondary to acute vascular complications were excluded.

Surgical technique

All patients underwent deceased donor LT using standard techniques without the use of venovenous bypass in favour of the piggyback technique. Anastomosis techniques related to the portal vein and hepatic artery were not modified.

Study variables were collected prospectively and recorded on an electronic case report.

Donor data

Donor data included age, cause of death, serum sodium level, ALT, AST, GGT, sex, blood group, weight, height, body mass index (BMI), body surface area (BSA) and donor risk index (DRI). Donor status was also evaluated by the need for epinephrine, evidence of shock, or the need for cardiopulmonary resuscitation or intensive care unit (ICU) stay.

Graft preservation data

Graft preservation data included cold ischaemia time and the graft preservation solution: The University of Wisconsin (UW) solution, the histidine-tryptophan ketoglutarate (HTK) solution or Celsior.

Recipient data

Recipient data included age, sex, weight, height, BSA, BMI, indications for LT, the model for end-stage liver disease (MELD) and Na, creatinine, ALT, AST and preoperative bilirubin levels. The intraoperative variables registered were surgical time, the need for red blood, platelet or plasma transfusion, and the need for cryoprecipitate.

Intraoperative measurements were performed with a flowmeter (Medistin, Norway) based on the measurement of transit time (MFTT) and Doppler technology. The Doppler effect uses the transmission of a continuous wave, and MFTT employs the transmission of pulses. By applying the Doppler concept to the components of the blood, we can measure the vessel blood flow velocity. If the sound is directed in the direction of flow, the received signal will be different depending on whether the blood components are near or far from the transducer. The sensor used by the MFTT contains two transducers and a reflector. The two transducers are located on one side of the vessel and the reflector on the opposite side; this arrangement causes a double ultrasound passage through the vessel. After performing vascular and biliary anastomoses, at the end of the procedure, the hepatic artery and portal vein flow just distal to the suture on the graft's side were sequentially measured. The absence of intraoperative blood flow or obtaining a very poor flow measurement were considered to be an indication for reviewing the arterial anastomosis after verifying the absence of the compensatory effect of the portal flow.

The duration of ICU stay, the need for mechanical ventilation and the length of hospital stay were also registered.

The modified version of the criteria for EAD into the MELD era by Olthoff *et al*[9] was used. EAD was defined as the presence of one or more of the following previously defined postoperative laboratory findings reflective of liver injury and

dysfunction: Bilirubin level greater than or equal to 10 mg/dL on day 7, international normalized ratio greater than or equal to 1.6 on day 7, and AST or ALT level of 2000 IU/L within the first 7 d.

Follow-up

The follow-up started on the day of LT and was routinely performed at outpatient clinics. Patient follow-up was continued until August 1, 2015.

Study endpoints

The primary endpoint was EAD. The secondary endpoint was postoperative 30-d mortality.

Statistical analysis

Unless otherwise stated, the data are expressed as the mean ± SD or *n* (%). When data were normally distributed (based on the Kolmogorov-Smirnov test), comparisons were performed using Student's *t*-test. The qualitative variables and risk measurements were analysed using the χ^2 test. Univariate and multivariate analyses of graft dysfunction were performed using a logistic regression test. Predictive analysis was conducted using receiver operating characteristic (ROC) curves. To assess the impact of the risk score on survival, Kaplan-Meier survival curve analysis was performed, and the results were compared with the log-rank test. The collected data were entered into a database created in SPSS version 20 for Mac (SPSS, Inc., Chicago, Illinois, United States).

RESULTS

During the study period from January 2008 to December 2014, 195 cadaveric liver transplant surgeries were performed in 188 patients (Figure 1). According to the Olthoff criteria for EAD, 54 patients with EAD (27.70%) were identified, 5 of whom underwent an urgent retransplant surgery (9.30%). Of the 54 patients who developed EAD, 68.50% (37) of patients were alive at the end of the study period, while 31.50% (17) of patients died during the follow-up period. The overall mortality rates for patients with EAD were 5.60%, 11.10% and 25.90% at 7 d, 30 d and 6 mo, respectively. The median observation period was 39 mo.

Baseline characteristics

Demographic data and liver disease aetiologies are shown in Table 1. The characteristics of patients who reached and did not reach the endpoint (EAD) are shown in Table 2.

Cold ischaemia time was significantly higher in the group with EAD (525.74 ± 153.03 min) when compared to the no-EAD group (464.94 ± 142.52 min), $P = 0.01$. However, no significant differences were found in the estimated graft volume and the estimated volume of the liver receptor. There were also no significant differences in the ratio of the estimated graft volume to the estimated recipient volume or in relation to other anthropometric parameters registered, such as weight, height, BMI, or BSA. Other characteristics of the donor and recipient showed no statistically significant differences between the groups.

The variables used to study the characteristics of the hospital stay were length of ICU stay, length of hospital stay and the need for mechanical ventilation. Significant differences in the time of ICU stay were found between patients who developed EAD (6.42 ± 6.50 d) and those who did not develop EAD (4.36 ± 5.04 d), $P < 0.01$. Likewise, the need for mechanical ventilation in patients with EAD was 7940 ± 14185 h compared to 4151 ± 11323 h in patients who showed no EAD ($P = 0,02$). Furthermore, the length of hospital stay in patients who developed EAD was 3567 ± 2808 d, compared to no-EAD 2618 ± 1824 d ($P < 0.01$).

Effect of liver blood flow on early allograft dysfunction

Table 2 shows the relationship between haemodynamic hepatic blood flow and EAD. Significant differences between arterial, portal and total liver blood flow were observed.

Hepatic artery flow: HAF was significantly lower in the group with EAD (227.74 ± 134.13 mL/min) than in the no-EAD group (279.67 ± 152.87 mL/min, $P = 0.01$). However, no significant differences were found between the groups regarding the percentage of total blood liver supply carried by HAF. The HAF variable was later categorized into two groups to label individuals in a clinically relevant manner. The cutoff value was 180 mL/min such that individuals with an HAF blood flow > 180

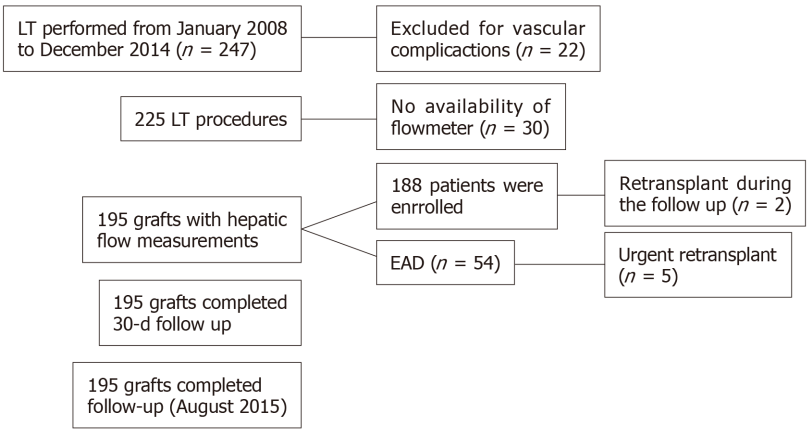

Figure 1 Study flowchart. EAD: Early allograft dysfunction; LT: Liver transplantation.

mL/min were considered to be normal and those with HAF blood flow < 180 mL/min were considered to have insufficient blood flow. The association of HAF with the endpoint was then analysed (OR = 2.25, 95%CI: 1.16–4.35, P = 0.02, Figure 2).

Portal venous flow: PVF was significantly lower in the group with EAD (1363.84 ± 602.06 mL/min) than in the no-EAD group (1606.73 ± 491.51 mL/min, P = 0.01). There was no difference between the EAD and no-EAD groups regarding the percentage of total blood liver supply by the portal venous flow. The PVF variable was categorized into two groups using the cutoff value of PVF < 1200 to interpret its clinical relevance with respect to the end point, and its significant relationship with the endpoint was analysed (OR = 3.36, 95%CI: 1.83–6.16, P < 0.01, Figure 3).

Total hepatic blood flow: THF was significantly lower in the group with EAD (1591.81 ± 631.07 mL/min) than in the group with no-EAD (1883.28 ± 513.15 mL/min). THF was categorized into two clinically relevant groups using the cutoff value of 1500 ml/min so that individuals with THF < 1500 mL/min were considered to have an inadequate THF. Its association with the endpoint was then analysed (OR = 3.05; 95%CI: 1.59–5.88; P < 0.01). The multivariate analysis showed that cold ischaemia time and HAF< 180 mL/min and PVF < 1200 mL/min were predictors of EAD (Table 2).

Effects of liver blood flow on 30-d patient mortality: We also evaluated the effects of our categorized blood flow variables on patient mortality at 30 d. In the univariate Cox regression analysis, only 5 variables were significantly associated with 30-d survival (HAF, PVF, THF, AST at day 1 and INR at day 1; Table 3). In the multivariate analysis, HAF < 180 mL/min and AST > 2000 UI/dL were independent prognostic factors for 30-d patient mortality. In addition to these results, the AUROC of the risk score developed showed a better diagnostic performance [area under the ROC curve (AUROC): 0.814; 95%CI: 0.674-0.954; P < 0.01].

DISCUSSION

EAD following cadaveric donor LT affects both graft and patient survival[9]. In an attempt to prevent EAD, many predictive models using donor and receptor variables, graft characteristics, intraoperative events, and functional tests have been developed[10-12]. Most of these variables, which influence the risk of developing EAD, are not treatable. Therefore, the aims of new studies are to identify different treatable or preventable intraoperative variables that may aid in the decision-making process during both the surgical act and the immediate postoperative period. In this sense, the measurement of intraoperative (arterial and venous) hepatic blood flow after reperfusion as an indirect measurement of the hepatic parenchyma oxygen and nutrient input could be used as intraoperative parameters to predict EAD[13,14]. These differences differ from the non-treatable variables in that hepatic inflow has the potential to be intraoperatively modified in cases in which the measured blood flow predisposes a patient to EAD and therefore worse overall outcomes of LT.

The exact definition for EAD has not yet been established because there is still plenty of variability found in the published literature. In this study, we used the

Table 1 Demographic baseline characteristics

Baseline characteristics	
Age (yr)	51.45 (9.92)
Gender (male/female)	152/43
Weight (kg)	76.39 (13.71)
Height (cm)	168.74 (7.77)
MELD score (points)[1]	15.3 (6.82)
Aetiology of liver diseases [number (%)]	
Viral cirrhosis	65 (33.3)
Hepatocellular carcinoma	95 (41.7)
Alcoholic cirrhosis	51 (26.2)
Fulminant hepatic failure	3 (1.3)
Primary biliary cirrhosis	5 (2.2)
Acute retransplantation	5 (2.2)
Chronic rejection	1 (0.4)
Sclerosing cholangitis	6 (2.6)
Cryptogenic cirrhosis	11 (4.8)
Hemochromatosis	1 (0.4)

[1]The MELD score does not take into account extra exception points. MELD: Model of end liver disease.

Olthoff criteria to define EAD[9]. Olthoff defined EAD as the presence of at least one postoperative variable previously associated with liver injury and function, such as serum levels of transaminases, bilirubin and INR. According to Olthoff *et al*[9], EAD increases the risk of death by ten times at 6 mo after an LT. In this study, the incidence of EAD was 27.7%, out of which 18.8% died, while only 1.8% of patients in the no-EAD group died. Graft loss occurred in 26.1% of patients with EAD. Our EAD incidence was similar to that found in previous studies, with an incidence ranging between 2%-32%. In our view, efforts should be oriented to employ intraoperative measurements of graft function, either through the measurement of blood supply or by directly measuring liver function (*e.g.*, blood supply, LIMAX, or clearance of indocyanine green)[15-17], to allow an early diagnosis of EAD which, in turn, would aid the decision-making process.

When we analysed the differences between patients with and without EAD, CIT was significantly higher in the group with EAD and was also a significant predictive factor of EAD in the multivariate analysis. The association between CIT and ischaemia-reperfusion injury has already been described. In particular, a CIT greater than 12 h is an independent variable of poor prognosis and is, therefore, associated with worse graft function[18,19]. However, CIT could be considered a confusion factor due to the established relationship between prolonged CIT and ischaemia-reperfusion injury that leads to an early endothelial injury and consequently increases vascular resistance to hepatic artery flow.

The measurement of intraoperative blood flow was performed with a flow metre VeriQ, based on measuring the transit time (MFTT) and Doppler technology. This system has been validated in previous studies and generates reproducible measurements[20-22].

In our group, the mean HAF was 265.15 ± 149.45 mL/min. Vascular patency was assessed postoperatively with Doppler ultrasound. When we looked at the differences between the groups according to the presence of EAD or nor, statistically significant differences were observed. We set the cutoff in HAF < 180 mL/min because it was the best discriminatory measure between the two EAD groups (Figure 2). We note that the EAD development risk was doubled, and it became a prognostic factor for 30-d patient survival in the multivariate analysis. In the intraoperative setting, decreased HAF may guide the surgical team to undertake intraoperative tests of graft inflow modulation. First, we evaluated the patency of the anastomosis, as indicated by the absence of blood flow. Once thrombosis was ruled out, the portal drainage was occluded with the aim to observe the arterial buffer system response. If there were modifications in HAF during this response, manoeuvres such as splenectomy or ligation of the splenic artery if PVF was greater than 1300 mL/min could be performed in response to these tests[23]. At other times when flow modulation is not a problem, hypotheses arise as to whether the decreased HAF is a consequence of an

Table 2 Univariate and multivariate analysis for the development of early allograft dysfunction

Variables	Univariate analysis			Multivariate logistic regression		
	EAD (*n* = 54)	Non-EAD (*n* = 141)	*P* value	β	Relative risk (95%CI)	*P* value
Donor						
Age	62.30 ± 15.67	58.17 ± 18.10	0.21			
Donor AST (IU/L)	50.77 ± 56.65	43.44 ± 43.88	0.71			
Donor ALT (IU/L)	48.64 ± 53.36	38.97 ± 51.51	0.04			
Donor GGT (IU/L)	70.67 ± 111.53	60.63 ± 116.96	0.59			
Epinephrine dose (mg/kg/min)	0.27 ± 0.32	0.30 ± 0.36	0.78			
Na levels in donor blood	147.13 ± 8.52	146.94 ± 8.47	0.99			
DRI	1.61 ± 0.29	1.57 ± 0.32	0.46			
ICU time (d)	4.13 ± 4.83	3.17 ± 3.75	0.64			
Recipient						
Age	52.11 ± 9.21	51.89 ± 10.21	0.88			
MELD	15.11 ± 6.86	15.37 ± 6.83	0.73			
MELD-Na	17.49 ± 7.57	17.71 ± 7.66	0.99			
Creatinine (mg/dL)	0.91 ± 0.48	1.08 ± 1.09	0.26			
GOT basal (IU/L)	426.88 ± 1168.84	164.58 ± 435.5	0.52			
Bilirubin basal (mg/dL)	7.21 ± 8.74	6.23 ± 8.14	0.74			
INR basal	1.61 ± 0.69	1.58 ± 1.06	0.53			
Preservation						
Cold ischaemia time (min)	525.74 ± 153.03	464.94 ± 142.52	0.01			
Hot ischaemia time (min)	57.26 ± 21.08	54.57 ± 22.4	0.20			
Total ischaemia time (min)	584.17 ± 154.18	520.53 ± 139.1	0.01			
Intraoperative						
Intraoperative red blood cells (units)	3.00 ± 2.54	3.08 ± 3.18	0.73			
Intraoperative platelets (units)	2.00 ± 2.69	2.56 ± 3.76	0.83			
Intraoperative plasma (units)	0.91 ± 1.72	0.75 ± 1.74	0.53			
Intraoperative cryoprecipitate (g)	1.59 ± 1.57	1.44 ± 1.86	0.22			
Hepatic arterial flow (mL/min)	227.74 ± 134.13	279.67 ± 152,8	0.01			
Portal venous flow (mL/min)	1363.84 ± 602.06	1606.7 ± 491.5	0.01			
Hepatic total flow (mL/min)	1591.81 ± 631.07	1883.2 ± 513.1	0.01			
HAF < 180 mL/min				2.41	(1.18-4.89)	0.02
PVF < 1200 mL/min				2.89	(1.45-5.73)	0.01
TIT > 610 min				2.31	(1.15-4.65)	0.02

DRI: Donor risk index; HAF: Hepatic artery flow; ICU: Intensive care unit; INR: International normalized ratio; MELD: Model of end liver disease; PVF: Portal vein flow; THF: Total hepatic flow.

increase in intrahepatic resistance. Marginal graft use is known to have poor tolerance to I/R injury. Therefore, in recent years, the use of new devices for machine liver perfusion can be useful in evaluating the increase in intrahepatic resistance that leads to worse intraoperative liver flow. As previously stated, there currently exists no agreement on a minimum value of HAF that serves as a predictor of worse outcomes[24].

With respect to PVF, Lisik *et al*[25] suggested a link between PVF and EAD; however, their study only included 15 patients, hence its limited clinical relevance. The minimum acceptable PVF value for adequate graft function is approximately 1000 mL/min. Gastaca *et al*[26] showed that PVF is related to anthropometric parameters and to the patient's clinical conditions and suggests that a PVF of less than 1000 mL/min is more common in women and in patients with less advanced liver disease. Cirrhosis is associated with portal hypertension, with hyperdynamic syndrome being one of its late consequences. In our study, we found no differences in these characteristics between the groups with portal flows < 1200 mL/min and > 1200 mL/min, but there was a significant difference in terms of cardiac output. The authors note that primary non-function (PNF) is greater in the group with portal flow less than 1 L/min, but it is not associated with the development of EAD. In their study,

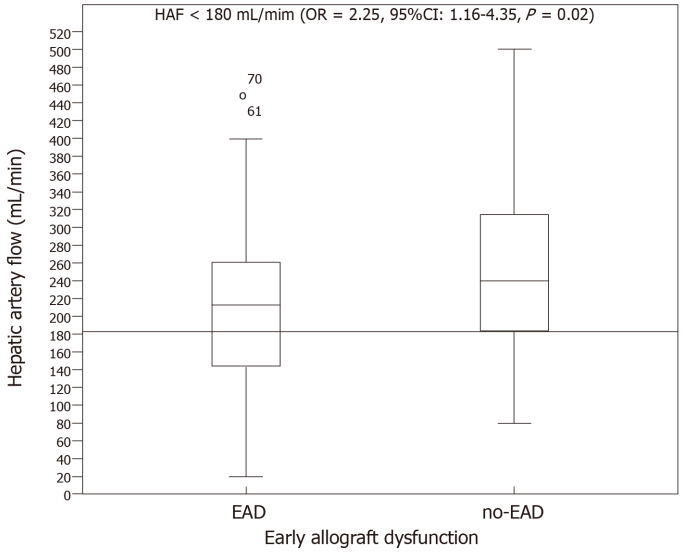

Figure 2 Hepatic artery flow and development of early allograft dysfunction. EAD: Early allograft dysfunction.

after adjusting portal flow by graft weight (measured, not estimated), a portal flow of < 80 mL/min × 100 g was correlated with an elevated risk of PNF development and graft loss in the first year after transplantation. Our analysis showed that PVF was associated with developing EAD, with statistically significant differences when comparing both groups. A PVF less than 1200 mL/min conferred three times the risk of developing EAD and was also a prognostic factor for 30-d survival in the univariate analysis but not in the multivariate analysis.

The study is, however, limited because the degree of steatosis in the grafts was not measured nor taken into count, which has been shown to behave as a risk factor for developing EAD. In this study, the information about blood flow within the graft is limited to macrovascular measurements, without taking into consideration the potential changes that occur in the microcirculation or the interaction between both factors. Microcirculatory changes occur during ischaemic phenomena of reperfusion injury. Puhl *et al*[14] demonstrated a significant correlation between the initial microcirculation and early graft function postoperatively. Studies have correlated measurement and microcirculation through a laser Doppler flowmeter on the liver surface with the macrovascular total hepatic flow[28].

In conclusion, we have shown that intraoperative measurements of hepatic blood flow can predict the development of EAD and that hepatic artery flow has an impact on survival at 30 d. Consequently, future efforts may focus on study strategies directed at identifying those grafts that are more susceptible to developing alterations in blood flow and how we can mend these alterations in hepatic blood flow in the intraoperative setting.

Table 3 Univariate and multivariate Cox regression models of mortality at 30 d

Variables	Univariate Cox regression			Multivariate Cox regression		
	β	Relative risk (95%CI)	*P* value	β	Relative risk (95%CI)	*P* value
Donor						
Age	1.03	(0.97-1.08)	0.28			
Donor AST (IU/L)	1	(0.99-1.02)	0.84			
Donor ALT (IU/L)	0.99	(0.97–1.02)	0.63			
Donor GGT (IU/L)	1	(0.99–1.01)	0.93			
Epinephrine dose (mg/kg/min)	0.03	(0.00–5.69)	0.93			
Na levels in donor blood	0.93	(0.84–1.03)	0.19			
DRI	4.49	(0.26–76.92)	0.3			
ICU time (d)	1.04	(0.89–1.22)	0.62			
Recipient						
Age	1.04	(0.94-1,14)	0.43			
MELD	0.88	(0.72–1.08)	0.22			
MELD-Na	0.98	(0.87–1.11)	0.76			
Creatinine (mg/dL)	1.08	(0.52–2.26)	0.83			
AST basal (IU/L)	1	(1-1)	0.03			
Bilirubin basal (mg/dL)	0.98	(0.88–1.09)	0.75			
INR basal	1.03	(0.44–2.39)	0.95			
Preservation						
Cold ischaemia time (min)	1	(0.99–1.00)	0.31			
Hot ischaemia time (min)	1	(0.98–1.04)	0.56			
Total ischaemia time (min)	1	(0.99-1)	0.33			
Intraoperative						
Need red blood cells (units)	1.17	(0.91–1.50)	0.37			
Need intraoperative platelets (units)	0.92	(0.70–1.20)	0.54			
Need intraoperative plasma (units)	0.93	(0.60–1.43)	0.74			
Need intraoperative cryoprecipitate (g)	1.1	(0.71–1.70)	0.68			
Hepatic arterial flow (mL/min)	0.99	(0.97-1)	0.01			
Portal venous flow (mL/min)	0.99	(0.99–1.00)	0.01			
Total hepatic flow (mL/min)	0.99	(0.98–1.00)	0.04			
HAF < 180 mL/min	5.9	(1.13–30.99)	0.04	5.33	(1.01–28.22)	0.04
PVF < 1200 mL/min	5.31	(1.02–27.70)	0.04			
INR day 1 > 2,2	6.07	(1.11–33.22)	0.04			
AST day 1 > 2000 UI/dL	10.82	(1.26–92.97)	0.03	9.856	(1.15–84.78)	0.04

DRI: Donor risk index; HAF: Hepatic artery flow; ICU: Intensive care unit; INR: International normalized ratio; MELD: Model of end liver disease; PVF: Portal vein flow; THF: Total hepatic flow.

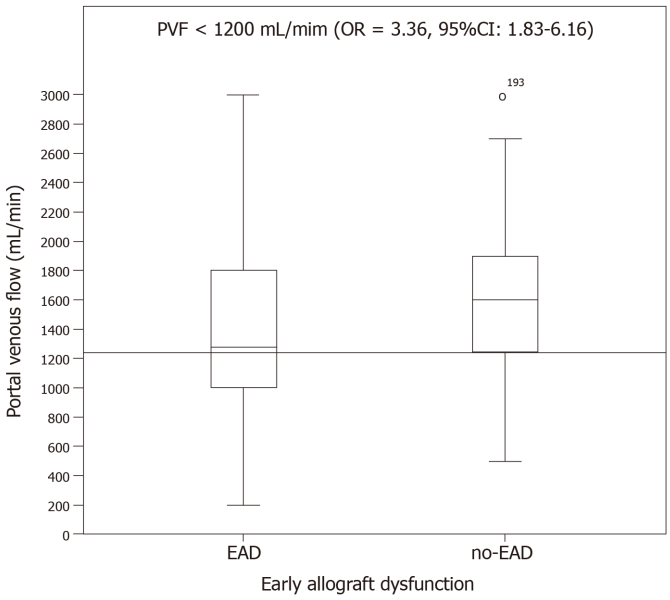

Figure 3 Portal vein flow and development of early allograft dysfunction. EAD: Early allograft dysfunction.

ARTICLE HIGHLIGHTS

Research background

Early allograft dysfunction (EAD) after liver transplantation (LT) is an important cause of morbidity and mortality. To ensure adequate graft function, a critical hepatocellular mass is required in addition to an appropriate blood supply. We hypothesized that intraoperative measurement of portal venous and hepatic arterial flow may serve as a predictor in the diagnosis of EAD.

Research motivation

EAD is a condition that can occur after implantation. The development of graft dysfunction is multifactorial. The degree of impairment can range from a very mild and temporary form to a more severe and potentially deadly form unless the patient receives an early retransplantation, which is determined by initial poor function. The regenerative capacity of the hepatic parenchyma conditions most dysfunctions to be transient. Currently, there are a large number of predictive models for graft failure, all of which are heterogeneous because they use different criteria to select the independent variables. In general, the models try to predict the development of liver dysfunction and aid clinicians in the liver graft selection process. To ensure proper function of a liver graft, the hepatocellular critical mass is needed to maintain synthetic function and adequate blood supply through the vascular tree. Hepatic flow is a determining factor in early graft function. Intraoperatively, measurable arterial and venous flow after implantation may be useful in predicting the development of EAD because blood flow values provide an indirect measurement of the oxygen and nutrient levels. A study of the intraoperative factors that may influence the development of EAD should be performed to address additional, related problems in the field.

Research objectives

To study whether hepatic flow is an independent predictor of EAD following LT.

Research methods

This is an observational cohort study performed in a single institution. Hepatic arterial and portal venous blood flows were measured intraoperatively by transit flow. The measurement of the intraoperative flows was performed with a VeriQ™ flowmeter (Medistin, Norway). VeriQ™ offers both proven transit time flow measurement and Doppler velocity measurements that are specifically designed for intraoperative blood flow and graft patency verification. The Doppler effect uses the transmission of a continuous wave, and MFTT employs the transmission of pulses. By applying the Doppler concept to the blood components, we can measure the vessel blood flow velocity. If the sound is directed in the direction of flow, the received signal will be different depending on whether the blood components are near or far from the transducer. The sensor used by the MFTT contains two transducers and a reflector. The two transducers are located on one side of the vessel and the reflector on the opposite side; this arrangement causes a double ultrasound passage through the vessel. The crystal located in the direction of flow generates a pulse of ultrasound that is captured by the glass oriented in the opposite direction. The difference in transit time depends on the volume of blood flow. Measurement probes of 5-7 mm calibre are used for the hepatic artery and 8-12 mm for the portal vein. Once the vascular

anastomoses have been performed, a brief period of approximately 5 min is allowed for the intrahepatic flow to stabilize, and then the arterial and portal flows are measured sequentially at one centimetre distal to the suture on the side of the graft. In cases where the arterial intraoperative flow measured is absent or very poor, revision of the arterial anastomosis is indicated, once the absence of the portal flow compensatory effect ("hepatic arterial buffer effect") has been proven. EAD was defined using the Olthoff criteria. Univariate and multivariate analyses were used to determine intraoperative predictors of EAD. Survival analysis and prognostic factor analysis were performed using the Kaplan-Meier and Cox regression models.

Research results

A total of 195 liver transplants were performed between January 2008 and December 2014 in 188 patients. A total of 54 (27.7%) patients developed EAD. The median follow-up was 39 mo. Portal venous flow, hepatic arterial flow (HAF) and total hepatic arterial flow were associated with EAD in both univariate and multivariate analyses. HAF is an independent prognostic factor for 30-d patient mortality. This is the first study that relies on current EAD criteria and 30-d patient survival data based on hepatic flow measured intraoperatively.

Research conclusions

In conclusion, we have shown that intraoperative measurements of hepatic blood flow can predict the development of EAD and that hepatic artery flow has an impact on survival at 30 d.

Research perspectives

Future efforts may focus on study strategies directed at identifying those grafts that are more susceptible to developing alterations in blood flow and how we can mend these alterations in hepatic blood flow in the intraoperative setting.

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