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EDITORIAL

# From the liver to the heart: Cardiac dysfunction in obese children with non-alcoholic fatty liver disease

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## Abstract

In the last decades the prevalence of non-alcoholic fatty liver disease (NAFLD) has increased as a consequence of the childhood obesity world epidemic. The liver damage occurring in NAFLD ranges from simple steatosis to steatohepatitis, fibrosis and cirrhosis. Recent findings reported that fatty liver disease is related to early atherosclerosis and cardiac dysfunction even in the pediatric population. Moreover, some authors have shown an association between liver steatosis and cardiac abnormalities, including rise in left ventricular mass, systolic and diastolic dysfunction and epicardial adipose tissue thickness. In this editorial, we provide a brief overview of the current knowledge concerning the association between NAFLD and cardiac dysfunction.

**Key words:** Cardiac dysfunction; Non-alcoholic fatty liver disease atherosclerosis; Children; Cardiovascular risk



**Core tip:** Recently, growing scientific evidences suggest that obese children with non-alcoholic fatty liver disease are more predisposed to cardiovascular disease. Interestingly, this association seems to be independent from adiposity. In fact, based on recent findings, it has been proposed that liver steatosis plays an independent role in determining early atherosclerosis and cardiac dysfunction.

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## INTRODUCTION

Currently, non-alcoholic fatty liver disease (NAFLD) represents the major cause of chronic liver disease in childhood and is considered a multisystem disease that affects many extra-hepatic organs[1]. Experimental evidence suggests that children with NAFLD have a higher risk of developing end stage liver disease than the general population of United States of same age and gender[2]. Moreover, NAFLD has emerged as an independent risk factor for cardiovascular diseases (CVD)[3,4], including coronary artery disease and cardiac dysfunction[5-8].

The molecular mechanisms linking NAFLD to cardiovascular complications are still poorly understood[6,8]. Children with NAFLD display increased free fatty acids that may lead to myocardial lipid accumulation with consequent impairments in myocardial substrate metabolism and efficiency and, finally, cardiac dysfunction[7,8]. Moreover, the presence of a low-grade inflammatory state in these patients contributes to the release of several mediators that amplify this condition[6,8]. Therefore, it has been hypothesized that intra-hepatic fat might exert a key pathogenetic role in developing cardio-metabolic complications (Figure 1).

In the last 20 years, NAFLD has become the most common liver disease in pediatrics[1], as result of the increased prevalence of early onset obesity[2-4]. Although NAFLD develops in the context of insulin resistance related to obesity, it is possible that a parental effect exists. As suggested by experimental studies in rats, in fact, paternal and maternal obesity during preconception could lead to obesity, glucose metabolism abnormalities and liver steatosis in the offspring[5].

## ATHEROSCLEROSIS

NAFLD represents an independent risk factor for CVD as it is associated with dyslipidemia, insulin resistance and alterations of cardiac function independent of the degree of obesity[3,4].

Recent studies[2,3,6] have shown that atherosclerosis and alterations of cardiac function may occur already during childhood, as demonstrated by the presence of early onset subclinical atherosclerosis as measured by impaired flow-mediated vasodilation and increased carotid artery intimal medial thickness as well as by the presence of abnormalities in myocardial structure and function in obese children and adolescents[3,4] (Table 1).

Despite this evidence, the relationship between NAFLD and cardiovascular alterations is still poorly understood. Moreover, it is unclear whether there is a causal relationship between intra-hepatic fat accumulation and alterations of cardiac dynamics or whether the two phenomena are just independent complications of obesity.

It is possible that intra-hepatic fat accumulation may be a pathogenic determinant of CVD. In fact, NAFLD can lead to atherosclerosis by causing an abundant secretion from the liver of lipoproteins [large very low density lipoproteins (VLDL)][7], which, in obese individuals with NAFLD, are abundant in oxidized fatty acids[8,9]. The higher concentration of large VLDL results in a high concentration in plasma of very small LDL, which in turn are a major contributor to the atherosclerotic plaque[7], and their accumulation within the plaque would ultimately lead to ischemic events. NAFLD *per se*, in fact, is a hyperlipidemic state in which adipose tissue insulin resistance[10] and enhanced hepatic *de novo* lipogenesis[11] lead to an abnormal accumulation of fat in the liver, turning the hepatocytes in a fat producing factory.

It is important to remember that myocardial atherogenesis occurs very early in life. Seminal studies in the Bogalusa cohort showed that atherosclerosis often begins in pediatric age[12], as demonstrated by the fact that fatty streaks are detected already in the aorta and the coronary arteries of children[6,13]. Since NAFLD can begin during childhood in obese children, it is reasonable to think that it can be an important determinant of these early events observed already in the pediatric population.

## CARDIAC ABNORMALITIES

While, the association between NAFLD and atherosclerosis could be easily explained by the abundance of circulating lipids present in obese children with NAFLD, it is more difficult to explain the relationship between NAFLD and cardiac function and geometry[14,15]. It has been reported that adolescents with NAFLD show an impaired systolic and diastolic function and an increased left ventricular mass compared to both healthy controls and age and gender matched obese adolescents without NAFLD[14,15] (Table 1).

To explain this observation several pathogenic mechanisms have been hypothesized, including the role of the liver as a generator of circulating mediators that could be involved in the cardiac remodeling[3,11,16,17]. In fact, the presence of a low-grade inflammatory state in patients obese patients with NAFLD and insulin resistance contributes to release of several cytokines and adipokines (*e.g.,* IL-6, TNF-alpha, visfatin, FGF-21, adiponectin, resistin, leptin) that amplify this condition and worsen the metabolic phenotype[3,11,17]. Whether the trigger for this condition, usually refereed to as "sterile inflammation", is NAFLD or insulin resistance *per se* is unclear, but a large body of evidence suggests that inflammatory cytokines may be the link among fatty liver, insulin resistance and myocardial changes[3,17]. In fact, adiponectin, a strong insulin sensitizer, seems to be

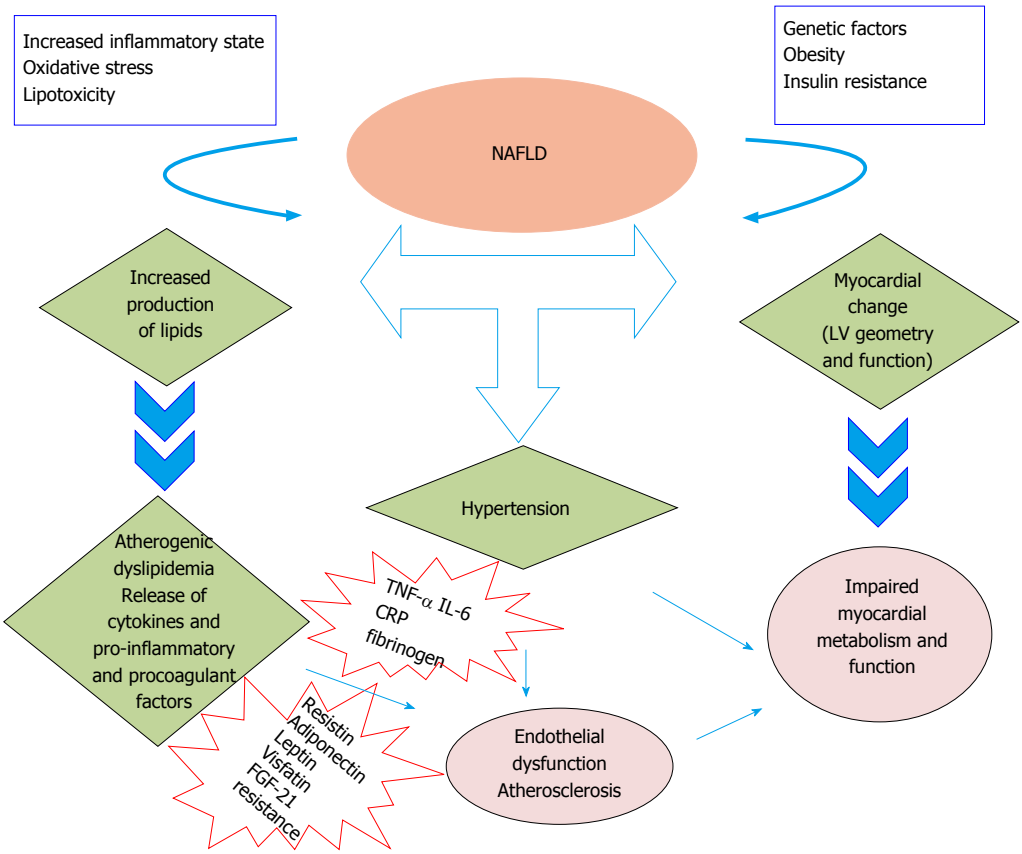


**Figure 1 The multifactorial mechanisms leading nonalcoholic fatty liver disease patients to unfavorable cardiac outcomes.** CRP: C-reactive protein; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α; FGF-21: Fibroblast growth factor-21; NAFLD: Nonalcoholic fatty liver disease; LV: Left ventricular.

decreased in patients with NAFLD and some studies have suggested that low adiponectin levels may affect cardiac function and atherogenic risk. In contrast, patients with NAFLD experience also an increased production of pro-inflammatory and pro-atherogenic cytokines (IL-6, IL-12, TNF-alpha), which in turn worsens insulin resistance, mostly through the down-regulation of insulin-receptor-substrate and by affecting gluconeogenesis[3,17], these compounds could also affect the cardiac morphology and dynamics. More importantly, some data suggest that fibroblast growth factor 21 (FGF-21), a protein synthetized and secreted by the liver in high amounts in obese subjects with fatty liver, might play a role in cardiac hypertrophy[16]. Some investigators have speculated that FGF-21 resistance occurring in NAFLD could led to cardiac damage in NAFLD patients[16].

On the other hand, given that NAFLD is associated with high systolic blood pressure[18] it could be also argued that changes in myocardial structure might be the consequence of high blood pressure[18]. Against the latter hypothesis, there is the evidence that changes in cardiac morphology observed in children with NAFLD do not resemble the cardiac adaptation consequence of high blood pressure[19]. In fact, hypertension increases left ventricular (LV) mass and changes heart morphology as a result of overload. Recent findings reported that obese children both with and without NAFLD showed no differences in LV mass and posterior wall thickness, while children with NAFLD were more likely to present low LV strain rate - a load - independent parameter that expresses LV elastance and deformation-than those without NAFLD. Therefore, the authors suggested that NAFLD affects myocardial fiber organization leading to systolic and diastolic dysfunction[19].

## CONCLUSION

Besides the large amount of literature suggesting an association between NAFLD and CVD, the pathophysiologic mechanisms underlying these associations are far from being clear, therefore, in the future more studies should be focused on this area of research to unravel those mechanisms and to develop novel therapeutic strategies.

Moreover, we need to establish also whether NAFLD could be considered a marker of subclinical atherosclerosis as well as a cardiovascular risk factor even at a very early age. In fact, because of its strong relationship with CVD, NAFLD diagnosis could represent a red flag for the presence of high cardiovascular risk. In this scenario the prevention and treatment of NAFLD may play a crucial role in avoiding not only end-stage liver disease but also CVD.

**Table 1 Principal features and findings of the studies regarding the association between non-alcoholic fatty liver diseas and cardiac dysfunction**

| Ref. | Study design and methods | Population (*n*) | Main findings |
|---|---|---|---|
| Bonci *et al*[4] | Systematic review and meta-analysis<br>Systematic literature search for papers from January 2000 to September 2014 | 12 observational studies:<br>9 studies based on adult population and 3 studies performed in pediatric population were selected | Children with NAFLD were not different from those without for LV mass<br>Both children with and without NAFLD presented an increased LV mass compared to controls<br>However children with NAFLD presented higher E/e' ratio rather those without NAFLD |
| D'Adamo *et al*[7] | Cross-sectional study<br>NAFLD diagnosis performed by MRI<br>Evaluation of VAT<br>Lipoprotein particle characterized by MRS | Mean age 14.6 yr<br>Obese African American (33)<br>Obese Hispanic (33) | In multiple regression analyses liver fat accumulation resulted independently and significantly related to large VLDL concentrations |
| Sert *et al*[14] | Cross-sectional study<br>NAFLD diagnosis performed by ultrasound and elevated serum alanine aminotransferase<br>Pulsed and tissue doppler Echocardiography | Mean age 13.3 yr<br>Healthy (68)<br>Obese with NAFLD and elevated ALT (97) | NAFLD children showed increased CIMT and abnormalities of both LV structure and function<br>LV CIMT and LV mass were positively related to HOMA-IR in obese children with NAFLD |
| Alp *et al*[15] | Cross-sectional study<br>NAFLD diagnosis performed by liver biopsy<br>Echocardiography<br>Tissue doppler Echocardiography | Obese without NAFLD and low ALT (83)<br>Mean age 12 yr<br>Healthy (150)<br>Obese with NAFLD at United States (93)<br>Obese without NAFLD at United States (307) | NAFLD group had increased epicardial fat thickness, end-systolic thickness of the interventricular septum, and larger LV mass, as well as LV systolic and diastolic dysfunction |
| Pacifico *et al*[18] | Cross-sectional study<br>NAFLD diagnosis performed by MRI | Mean age 12.5 yr<br>Healthy (18) | Children with NAFLD presented signs of left ventricular dysfunction compared to children without NAFLD<br>Subjects with a more severe NASH had a worse cardiac dysfunction |
| Singh *et al*[19] | Liver biopsy for NASH in 41 subjects<br>Echocardiography<br>Cross-sectional study<br>NAFLD diagnosis performed by MRS<br>Echocardiography | Obese with NAFLD at MRI (54)<br>Obese without NAFLD at MRI (54)<br>Mean age 15 yr<br>Lean (14)<br>Obese with Intrahepatic triglyceride content (15)<br>Obese with increased Intrahepatic triglyceride content (15) | Obese adolescents with NAFLD show a worse systolic and diastolic functions rather than lean and obese adolescents without NAFLD independent from anthropometric parameters and blood pressure |

MRI: Magnetic resonance imaging; NAFLD: Nonalcoholic fatty liver disease; MRS: Magnetic resonance spectrometry; VAT: Visceral adipose tissue; NASH: Non-alcoholic steatohepatitis; LV: Left ventricular; ALT: Alanine transaminase; CIMT: Carotis intima media thickness; VLDL: Very low density lipoproteins.

## REFERENCES


1 **Loomba R**, Sirlin CB, Schwimmer JB, Lavine JE. Advances in pediatric nonalcoholic fatty liver disease. *Hepatology* 2009; **50**: 1282-1293 [PMID: 19637286 DOI: 10.1002/hep.23119]

2 **Feldstein AE**, Charatcharoenwitthaya P, Treeprasertsuk S, Benson JT, Enders FB, Angulo P. The natural history of non-alcoholic fatty liver disease in children: a follow-up study for up to 20 years. *Gut* 2009; **58**: 1538-1544 [PMID: 19625277 DOI: 10.1136/gut.2008.171280]

3 **Pacifico L**, Chiesa C, Anania C, De Merulis A, Osborn JF, Romaggioli S, Gaudio E. Nonalcoholic fatty liver disease and the heart in children and adolescents. *World J Gastroenterol* 2014; **20**: 9055-9071 [PMID: 25083079 DOI: 10.3748/wjg.v20.i27.9055]

4 **Bonci E**, Chiesa C, Versacci P, Anania C, Silvestri L, Pacifico L. Association of Nonalcoholic Fatty Liver Disease with Subclinical Cardiovascular Changes: A Systematic Review and Meta-Analysis. *Biomed Res Int* 2015; **2015**: 213737 [PMID: 26273598 DOI: 10.1155/2015/213737]

5 **Ornellas F**, Souza-Mello V, Mandarim-de-Lacerda CA, Aguila MB. Programming of obesity and comorbidities in the progeny: lessons from a model of diet-induced obese parents. *PLoS One* 2015; **10**: e0124737 [PMID: 25880318 DOI: 10.1371/journal.pone.0124737]

6 **Pais R**, Giral P, Khan JF, Rosenbaum D, Housset C, Poynard T, Ratziu V. Fatty liver is an independent predictor of early carotid atherosclerosis. *J Hepatol* 2016; **65**: 95-102 [PMID: 27129836 DOI: 10.1016/j.jhep.2016.02.023]

7 **D'Adamo E**, Northrup V, Weiss R, Santoro N, Pierpont B, Savoye M, O'Malley G, Caprio S. Ethnic differences in lipoprotein subclasses in obese adolescents: importance of liver and intraabdominal fat accretion. *Am J Clin Nutr* 2010; **92**: 500-508 [PMID: 20573788 DOI: 10.3945/ajcn.2010.29270]

8 **Santoro N**, Caprio S, Giannini C, Kim G, Kursawe R, Pierpont B, Shaw MM, Feldstein AE. Oxidized fatty acids: A potential pathogenic link between fatty liver and type 2 diabetes in obese adolescents? *Antioxid Redox Signal* 2014; **20**: 383-389 [PMID: 23815500 DOI: 10.1089/ars.2013.5466]

9 **Santoro N**, Caprio S, Feldstein AE. Oxidized metabolites of linoleic acid as biomarkers of liver injury in nonalcoholic steatohepatitis. *Clin Lipidol* 2013; **8**: 411-418 [PMID: 26405460]

10 **D'Adamo E**, Cali AM, Weiss R, Santoro N, Pierpont B, Northrup V, Caprio S. Central role of fatty liver in the pathogenesis of insulin resistance in obese adolescents. *Diabetes Care* 2010; **33**: 1817-1822 [PMID: 20668154 DOI: 10.2337/dc10-0284]

11 **Santoro N**, Caprio S, Pierpont B, Van Name M, Savoye M, Parks EJ. Hepatic De Novo Lipogenesis in Obese Youth Is Modulated by a Common Variant in the GCKR Gene. *J Clin Endocrinol Metab* 2015; **100**: E1125-E1132 [PMID: 26043229 DOI: 10.1210/jc.2015-1587]

12 **Zhang H**, Zhang T, Li S, Li Y, Hussain A, Fernandez C, Harville E, Bazzano LA, He J, Chen W. Long-term Impact of Childhood Adiposity on Adult Metabolic Syndrome Is Modified by Insulin Resistance: The Bogalusa Heart Study. *Sci Rep* 2015; **5**: 17885 [PMID: 26640243 DOI: 10.1038/srep17885]
13 **Lamotte C**, Iliescu C, Libersa C, Gottrand F. Increased intima-media thickness of the carotid artery in childhood: a systematic review of observational studies. *Eur J Pediatr* 2011; **170**: 719-729 [PMID: 20978785 DOI: 10.1007/s00431-010-1328-y]
14 **Sert A**, Aypar E, Pirgon O, Yilmaz H, Odabas D, Tolu I. Left ventricular function by echocardiography, tissue Doppler imaging, and carotid intima-media thickness in obese adolescents with nonalcoholic fatty liver disease. *Am J Cardiol* 2013; **112**: 436-443 [PMID: 23642511 DOI: 10.1016/j.amjcard.2013.03.056]
15 **Alp H**, Karaarslan S, Selver Eklioğlu B, Atabek ME, Altın H, Baysal T. Association between nonalcoholic fatty liver disease and cardiovascular risk in obese children and adolescents. *Can J Cardiol* 2013; **29**: 1118-1125 [PMID: 23040432 DOI: 10.1016/j.cjca.2012.07.846]
16 **Santoro N**, Caprio S. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis in obese adolescents: a looming marker of cardiac dysfunction. *Hepatology* 2014; **59**: 372-374 [PMID: 23913480 DOI: 10.1002/hep.26663]
17 **Abenavoli L**, Peta V. Role of adipokines and cytokines in non-alcoholic fatty liver disease. *Rev Recent Clin Trials* 2014; **9**: 134-140 [PMID: 25514909 DOI: 10.2174/1574887109666141216102458]
18 **Pacifico L**, Di Martino M, De Merulis A, Bezzi M, Osborn JF, Catalano C, Chiesa C. Left ventricular dysfunction in obese children and adolescents with nonalcoholic fatty liver disease. *Hepatology* 2014; **59**: 461-470 [PMID: 23843206 DOI: 10.1002/hep.26610]
19 **Singh GK**, Vitola BE, Holland MR, Sekarski T, Patterson BW, Magkos F, Klein S. Alterations in ventricular structure and function in obese adolescents with nonalcoholic fatty liver disease. *J Pediatr* 2013; **162**: 1160-1168, 1168.e1 [PMID: 23260104 DOI: 10.1016/j.jpeds.2012.11.024]

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EDITORIAL

# Hepatic structural enhancement and insulin resistance amelioration due to AT1 receptor blockade

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## Abstract

Over the last decade, the role of renin-angiotensin system (RAS) on the development of obesity and its comorbidities has been extensively addressed. Both circulating and local RAS components are up-regulated in obesity and involved in non-alcoholic fatty liver disease onset. Pharmacological manipulations of RAS are viable strategies to tackle metabolic impairments caused by the excessive body fat mass. Renin inhibitors rescue insulin resistance, but do not have marked effects on hepatic steatosis. However, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ARB) yield beneficial hepatic remodeling. ARBs elicit body mass loss and normalize insulin levels, tackling insulin resistance. Also, this drug class increases adiponectin levels, besides countering interleukin-6, tumoral necrosis factor-alpha, and transforming growth factor-beta 1. The latter is essential to prevent from liver fibrosis. When conjugated with peroxisome proliferator-activated receptor (PPAR)-alpha activation, ARB fully rescues fatty liver. These effects might be orchestrated by an indirect up-regulation of MAS receptor due to angiotensin Ⅱ receptor type 1 (AT1R) blockade. These associations of ARB with PPAR activation and ACE2-angiotensin (ANG) (1-7)-MAS receptor axis deserve a better understanding. This editorial provides a brief overview of the current knowledge regarding AT1R blockade effects on sensitivity to insulin and hepatic structural alterations as well as the intersections of AT1R blockade with peroxisome proliferator-activated receptor activation and ACE2-ANG (1-7) - MAS receptor axis.

**Key words:** Non-alcoholic fatty liver disease; Insulin resistance; Angiotensin receptor blockers; MAS receptor; Renin-angiotensin system



**Core tip:** Intrahepatic renin-angiotensin system activation contributes to insulin resistance and non-alcoholic fatty liver disease onset. ANG Ⅱ interaction with angiotensin Ⅱ receptor type 1 (AT1R) mediates pro-inflammatory and pro-fibrogenic responses, besides enhancing the oxidative stress, which makes the liver more prone to

noxious liver diseases. AT1R blockers mitigate insulin resistance and fatty liver by enhancing beta-oxidation, reducing lipogenesis and controlling inflammation. The impact of the AT1R blockade on liver ACE2-angiotensin (1-7)-MAS receptor axis remains to be fully unraveled.

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## INTRODUCTION

Liver injuries can result from virus infection, alcohol and/or drugs abuse, and autoimmune diseases[1]. However, the increase in high-energy dense food availability combined with a sedentary lifestyle brought up unprecedented obesity rates, with the consequent increase in its comorbidities (hypertension, type 2 diabetes, and dyslipidemias) prevalences[2]. The metabolic disturbances caused by obesity also impair liver structure and physiology, with increasing prevalence of non-alcoholic fatty liver disease (NAFLD) and greater susceptibility to more harmful types of liver diseases such as non-alcoholic steatohepatitis (NASH) and liver fibrosis[3,4].

Insulin resistance (IR) plays a central role in NAFLD pathogenesis[5]. Also, the low-grade inflammation observed in obese subjects and the increased adipocyte lipolysis are key factors for a more pronounced lipid droplet deposition within the hepatocytes[6]. Briefly, IR has opposite effects on adipose tissue and liver. On one hand, resistance to insulin action elicits enhanced lipolysis rate in the white adipose tissue as an attempt to compensate for the lack of glucose to be used as fuel by the adipocytes. Hence, increased free fatty acids (FFAs) are delivered to the liver[3,7]. On the other hand, insulin resistance impairs beta-oxidation within hepatocytes by reducing the expression of carnitine palmitoyltransferase 1 in the hepatic mitochondrion, besides reducing very low-density lipoprotein (VLDL) secretion. These conditions lead to unbalanced hepatic lipid metabolism as FFAs inflow surpasses fatty acid oxidation and lipoprotein exportation[8,9]. Therefore, excessive fatty acids are converted into triglycerides through the up-regulated lipogenic pathways, which accumulate as lipid droplets within hepatic parenchyma, characterizing the NAFLD[10].

Considering that NAFLD is currently considered as the hepatic manifestation of the metabolic syndrome and that this condition, despite benign at first, can initiate a harmful spectrum of liver diseases, treatments should target hepatic alterations, but also alleviate others comorbidities such as hypertension, inflammation, and insulin resistance[11,12]. Recently, the activation of a local renin-angiotensin system (RAS) in the liver has been linked to NAFLD onset and progression towards liver fibrosis[13]. In this way, the RAS emerges as a potential target to tackle hepatic alterations stemmed from obesity and other metabolic constraints imposed by increased body fat mass[14].

## CIRCULATING RAS

From a classical view, the circulating RAS is implicated in the systemic hemodynamic regulation. Briefly, under a reduced renal perfusion, renin is secreted by the juxtaglomerular apparatus. This enzyme converts angiotensinogen (produced by the liver) in angiotensin 1 (ANG I), which is converted into angiotensin 2 (ANG Ⅱ) by the angiotensin-converting enzyme (ACE). ANG Ⅱ has countless physiological effects such as the stimulation of aldosterone release, which promptly reestablishes the hemodynamic control by enhancing water and sodium retention in the kidneys[15,16].

ANG Ⅱ exerts its main effects by interacting with two main receptors: Angiotensin Ⅱ receptor type 1 (AT1R) or angiotensin Ⅱ receptor type 2 (AT2R). AT1R has an important role in tissue repair and cell proliferation. However, when overexpressed, mediates pro-inflammatory and pro-atherogenic effects. Conversely, AT2R has anti-inflammatory effects, mainly by down-regulating tumoral necrosis factor-alpha (TNF-alpha) and nuclear factor-kappa B (NF-KB) pathways and by exerting anti-fibrogenic properties, besides reducing oxidative stress and cell proliferation[17,18]. Bearing this in mind, the angiotensin receptor blockers (ARBs) represents an evolution of the ACE inhibitors as they block exclusively the actions mediate by the interaction of ANG Ⅱ with the AT1R[19,20]. Thus, important physiological effects stemmed from ANG Ⅱ interaction with AT2R are maintained, leading to reduced atherogenesis, greater cardiac and endocrine pancreas functions, reduced glomerulosclerosis and fatty liver[21,22].

Recently, with the discovery of ACE2, another branch of RAS has been described. ACE2 converts ANG Ⅱ to ANG (1-7) and cleaves ANG I into ANG (1-9), which is also converted to ANG (1-7) by ACE. ANG (1-7) exerts its physiological effects through the MAS receptor. It can be argued that [ACE2-ANG (1-7)-MAS axis] counters the (ACE - ANG Ⅱ-AT1R axis) effects. So, ACE2/ACE balance is an important target to tackle metabolic diseases[23-25].

## LOCAL RAS: HEPATIC EFFECTS

Lately, apart from this circulating RAS, many local RAS have been described in organs such as heart, pancreas, adipose tissue, skeletal muscle, and liver[17,26,27]. Animal models of obesity show raised circulating renin, angiotensinogen, and ANG Ⅱ[28], besides higher expression of ACE and AT1R in the pancreas, which inhibit important steps of the insulin signaling cascade and contribute to IR and type 2 diabetes onset[29,30]. Intrahepatic activation of RAS favors NAFLD onset as it elicits greater triglycerides accumulation due to impaired beta-oxidation in conjunction with a significant fall in VLDL secretion.

These conditions comply with the increase of *de novo* lipogenesis (the formation of fatty acids from excessive dietary carbohydrate)[27,31]. Concomitantly, the increased production of reactive oxygen species by mitochondria and the raised expression of pro-inflammatory cytokines contribute to the progression to NASH[22]. These effects are mainly mediated by higher expression of ACE, ANG Ⅱ, and AT1R concomitant to reduced ACE2 tissue expression in the hepatocytes of obese mice[32].

Moreover, ANG Ⅱ activates hepatic stellate cells (HSCs). Enhanced transforming growth factor-beta 1 (TGF-beta1) underlies this event, which implies a higher susceptibility to hepatic fibrosis, once HSCs acquire a myofibroblast phenotype[33,34]. These harmful effects of ANG Ⅱ on liver structure and function are mediated predominantly by its interaction with the AT1R and results in collagen synthesis, pro-inflammatory cytokines release, stimulation of cell migration and proliferation[27,35]. These events altogether contribute to the second hit proposed by the two-hit theory, where inflammation and fibrogenesis play a decisive role in NAFLD progression to NASH[36].

Obese mice show higher hepatic steatosis rate coupled with insulin resistance, a pro-inflammatory adipokine profile, reduced hepatic beta-oxidation of fatty acids and enhanced lipogenesis[37]. Recently, it has been shown that a mouse model of NAFLD, even without obesity, presents with enhanced ACE/AT1R expression locally in the liver[38]. Rats with liver fibrosis present with favored ACE-ANG Ⅱ-AT1R axis over ACE2-ANG (1-7)-MAS receptor axis, confirming that AT1R is involved with NAFLD progression to NASH and fibrosis[24,25]. These observations suggest that the local expression of AT1R is related to NASH onset and AT1R blockade, with the consequent ACE2 induction, emerging as a potential approach to prevent liver fibrosis and chronic inflammation.

## BLOCKADE OF AT1 RECEPTOR EFFECTS ON INSULIN RESISTANCE AND FATTY LIVER

The impact of pharmacological manipulations of the RAS system on insulin resistance and liver structure is a new field of study. Evidence from animal studies shows that aliskiren (a direct renin inhibitor) rescued insulin resistance and hepatic steatosis, though its effects are not more advantageous than ARBs[39,40].

Angiotensin-converting enzyme inhibitors (ACEi) inhibit ANG Ⅰ to ANG Ⅱ conversion and, therefore, enhances the availability of bradykinin[41]. This peptide yields cardiovascular protection by stimulating the release of important vasodilatators such as nitric oxide and prostacyclin[42]. Bradikinin reduces the hepatic expression of glucose-6 - phosphatase and phosphoenolpyruvate carboxykinase, inhibiting hepatic gluconeogenesis. Furthermore, isolated myocytes and adipocytes treated with bradykinin exhibited improved glucose uptake due to greater glucose transporter 4 translocation to the cell membrane[43]. These events show that by enhancing bradykinin availability, ACEi are able to mitigate insulin resistance and counter NAFLD. Even though ACEi represent a potent approach as it combines benefits from bradykinin and ANG Ⅱ inhibition, ARBs preserve AT2R-mediated benefits and favor ACE2-ANG (1-7)-MAS receptor axis. These properties make ARBs an attractive option to treat metabolic impairments.

Olmesartan, a pure ARB, reduced body mass and hepatic triglyceride content, besides recovering the expression of hepatic antioxidant enzymes and sensitivity to insulin in rats[44,45]. The recovery of uncoupling protein 2 expression is put forward as the main mechanism that enhances hepatic lipid metabolization and antioxidant capacity after the blockade of AT1R[44]. Amelioration of IR after olmesartan treatment is also perceived in humans[46].

Irbesartan, another ARB, and an ACEi (perindopril) prevented obese Zucker rats from developing fatty liver in a recent study. Both treatments elicited a marked reduction in hepatic steatosis percentage, with no difference with the lean control group[47]. A remarkable reduction in hepatic expression of TNF-alpha, interleukine-6, and TGF-beta1 is produced by enhanced ACE2-ANG (1-7)-MAS receptor, leading to the alleviation of hepatic IR and, consequently, reducing fatty liver[25]. Furthermore, low TGF-beta1 expression complies with the marked reduction in liver fibrosis in obese animals treated with irbesartan[44]. In agreement to this, losartan, an ARB, led to anti-proliferative and anti-fibrogenic effects in ANG Ⅱ stimulated HSCs *in vitro*. Once again, a marked reduction in TGF-beta1 expression and AT1R down-regulation explain these findings[48].

It was recently proposed a synergistic action between hepatic cholesterol metabolism and intrahepatic RAS activation in the physiopathology of NAFLD. In this context, chronic local RAS activation in the liver augments the extracellular matrix synthesis and disrupts LDL metabolism by impairing LDL receptor functioning. These alterations seem to rely on AT1R activation by ANG Ⅱ. In agreement to this, telmisartan, an ARB that is also a partial peroxisome proliferator-activated receptor (PPAR)-gamma agonist, prevented from lipid deposition and overrode the translocation of SCAP/SREBP-2 complex from the endoplasmic reticulum to Golgi, blocking LDL receptor gene transcription in HepG2 cells[31].

Animal studies show that telmisartan rescues the sensitivity to insulin, markedly reduces hepatic steatosis and augments the numerical density of mitochondria per area of hepatic tissue in diet-induced obese mice[49]. These events rely on PPAR-alpha activation in the liver coupled with dual AT1R blockade/partial PPAR-gamma agonist properties, which determine enhanced adiponectin levels, favored beta-oxidation over lipogenesis and reduced HSCs activity[49,50].

Also, telmisartan limits hepatic fibrosis by enhancing mRNA levels of ACE2 and MAS receptor concomitant to reducing ACE, AT1R, collagen type Ⅱ and TGF-beta1, besides blocking HSCs activation in bile duct-ligated rats[51]. However, some effects are stemmed from the partial PPAR-gamma agonist property, such as IR alleviation,

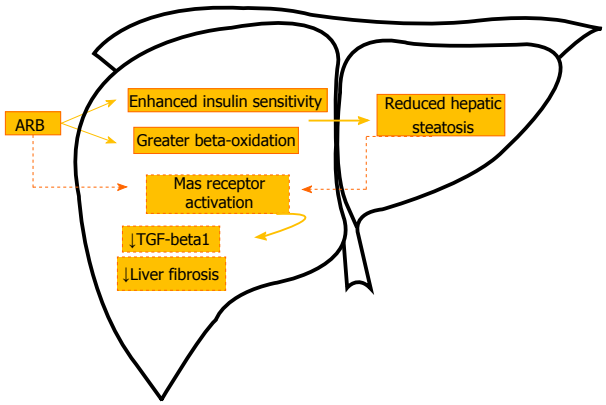


**Figure 1 Overview of angiotensin receptor blockers actions on the liver.** ARBs reduce hepatic steatosis through favored beta-oxidation and reduced insulin resistance. Concomitantly, it indirectly enhances Mas receptor activity, eliciting hepatoprotective effects by low TGF-beta1 expression, which limits hepatic stellate cells activation and prevents liver fibrosis. ARBs: Angiotensin receptor blockers; TGF-beta1: Transforming growth factor-beta 1.

reduced oxidative stress, and hepatic lipid deposition[52].

It is likely that the favored activity of the ACE2-ANG (1-7)-MAS receptor action under the AT1R blockade mediates the beneficial findings[25]. With regard to this, the infusion of ANG (1-7) in bile duct-ligated rats elicited fibrosis attenuation by the suppression of HSCs activity, while the use of MAS receptor antagonist confirmed these findings as the animals presented with a maximization of liver fibrosis, supported by higher expression of collagen and TGF-beta1[53]. Figure 1 illustrates the main pathways related to ARBs effects on the liver.

## CONCLUSION

Increasing rates of obesity and NAFLD have drawn the attention of the scientific community to strategies to treat these metabolic diseases. Local RAS is up-regulated in the liver from obese individuals and in lean individuals with fatty liver. Among the pharmacological manipulations of RAS, AT1R blockade is considered the best approach as it favors AT2R effects and seems to activate indirectly the ACE2-ANG (1-7)-MAS receptor axis, with additional beneficial effects. The combination of AT1R blockers with oral ANG (1,7) treatment seems to be a promising approach to treating NAFLD and NASH and prevent liver fibrosis.

## REFERENCES


1 **Lee MH**, Song HK, Ko GJ, Kang YS, Han SY, Han KH, Kim HK, Han JY, Cha DR. Angiotensin receptor blockers improve insulin resistance in type 2 diabetic rats by modulating adipose tissue. *Kidney Int* 2008; **74**: 890-900 [PMID: 18596725 DOI: 10.1038/ki.2008.313]

2 **Seidell JC**, Halberstadt J. The global burden of obesity and the challenges of prevention. *Ann Nutr Metab* 2015; **66** Suppl 2: 7-12 [PMID: 26045323 DOI: 10.1159/000375143]

3 **Angulo P**. Obesity and nonalcoholic fatty liver disease. *Nutr Rev* 2007; **65**: S57-S63 [PMID: 17605315 DOI: 10.1111/j.1753-4887.2007.tb00329.x]

4 **Ahmed M**. Non-alcoholic fatty liver disease in 2015. *World J Hepatol* 2015; **7**: 1450-1459 [PMID: 26085906 DOI: 10.4254/wjh.v7.i11.1450]

5 **Berlanga A**, Guiu-Jurado E, Porras JA, Auguet T. Molecular pathways in non-alcoholic fatty liver disease. *Clin Exp Gastroenterol* 2014; **7**: 221-239 [PMID: 25045276 DOI: 10.2147/CEG.S62831]

6 **Gustafson B**, Smith U. Regulation of white adipogenesis and its relation to ectopic fat accumulation and cardiovascular risk. *Atherosclerosis* 2015; **241**: 27-35 [PMID: 25957567 DOI: 10.1016/j.atherosclerosis.2015.04.812]

7 **Gustafson B**, Hedjazifar S, Gogg S, Hammarstedt A, Smith U. Insulin resistance and impaired adipogenesis. *Trends Endocrinol Metab* 2015; **26**: 193-200 [PMID: 25703677 DOI: 10.1016/j.tem.2015.01.006]

8 **Fabbrini E**, Mohammed BS, Magkos F, Korenblat KM, Patterson BW, Klein S. Alterations in adipose tissue and hepatic lipid kinetics in obese men and women with nonalcoholic fatty liver disease. *Gastroenterology* 2008; **134**: 424-431 [PMID: 18242210 DOI: 10.1053/j.gastro.2007.11.038]

9 **Magliano DC**, Bargut TC, de Carvalho SN, Aguila MB, Mandarim-de-Lacerda CA, Souza-Mello V. Peroxisome proliferator-activated receptors-alpha and gamma are targets to treat offspring from maternal diet-induced obesity in mice. *PLoS One* 2013; **8**: e64258 [PMID: 23700465 DOI: 10.1371/journal.pone.0064258]

10 **Abd El-Kader SM**, El-Den Ashmawy EM. Non-alcoholic fatty liver disease: The diagnosis and management. *World J Hepatol* 2015; **7**: 846-858 [PMID: 25937862 DOI: 10.4254/wjh.v7.i6.846]

11 **den Boer M**, Voshol PJ, Kuipers F, Havekes LM, Romijn JA. Hepatic steatosis: a mediator of the metabolic syndrome. Lessons from animal models. *Arterioscler Thromb Vasc Biol* 2004; **24**: 644-649 [PMID: 14715643 DOI: 10.1161/01.ATV.0000116217.57583.6e]

12 **Eckel RH**, Grundy SM, Zimmet PZ. The metabolic syndrome. *Lancet* 2005; **365**: 1415-1428 [PMID: 15836891 DOI: 10.1016/S0140-6736(05)66378-7]

13 **Zhang W**, Miao J, Li P, Wang Y, Zhang Y. Up-regulation of components of the renin-angiotensin system in liver fibrosis in the rat induced by $CCL_4$. *Res Vet Sci* 2013; **95**: 54-58 [PMID: 23433841 DOI: 10.1016/j.rvsc.2013.01.028]

14 **Day CP**. Clinical spectrum and therapy of non-alcoholic steatohepatitis. *Dig Dis* 2012; **30** Suppl 1: 69-73 [PMID: 23075871 DOI: 10.1159/000341128]

15 **Nguyen Dinh Cat A**, Touyz RM. A new look at the renin-angiotensin system--focusing on the vascular system. *Peptides* 2011; **32**: 2141-2150 [PMID: 21945916 DOI: 10.1016/j.peptides.2011.09.010]

16 **Dzau VJ**. Circulating versus local renin-angiotensin system in cardiovascular homeostasis. *Circulation* 1988; **77**: I4-13 [PMID: 3286045]

17 **Thatcher S**, Yiannikouris F, Gupte M, Cassis L. The adipose renin-angiotensin system: role in cardiovascular disease. *Mol Cell Endocrinol* 2009; **302**: 111-117 [PMID: 19418627 DOI: 10.1016/j.mce.2009.01.019]

18 **Pershadsingh HA**. Dual Peroxisome Proliferator-Activated Receptor-alpha/gamma Agonists : In the Treatment of Type 2 Diabetes Mellitus and the Metabolic Syndrome. *Treat Endocrinol* 2006; **5**: 89-99 [PMID: 16542049 DOI: 10.2165/00024677-200605020-00003]

19 **Ostergren J**. Renin-angiotensin-system blockade in the prevention of diabetes. *Diabetes Res Clin Pract* 2007; **76** Suppl 1: S13-S21 [PMID: 17320999 DOI: 10.1016/j.diabres.2007.01.018]

20 **Gawrieh S**, Chalasani N. Pharmacotherapy for Nonalcoholic Fatty Liver Disease. *Semin Liver Dis* 2015; **35**: 338-348 [PMID: 26378648 DOI: 10.1055/s-0035-1562951]

21 **Casillas-Ramirez A**, Amine-Zaouali M, Massip-Salcedo M, Padrissa-Altés S, Bintanel-Morcillo M, Ramalho F, Serafín A, Rimola A, Arroyo V, Rodés J, Roselló-Catafau J, Peralta C. Inhibition of angiotensin II action protects rat steatotic livers against ischemia-reperfusion injury. *Crit Care Med* 2008; **36**: 1256-1266 [PMID: 18379253 DOI: 10.1097/CCM.0b013e31816a023c]

22 **Moreira de Macêdo S**, Guimarães TA, Feltenberger JD, Sousa Santos SH. The role of renin-angiotensin system modulation on treatment and prevention of liver diseases. *Peptides* 2014; **62**: 189-196 [PMID: 25453980 DOI: 10.1016/j.peptides.2014.10.005]

23 **Bindom SM**, Lazartigues E. The sweeter side of ACE2: physiological evidence for a role in diabetes. *Mol Cell Endocrinol* 2009; **302**: 193-202 [PMID: 18948167 DOI: 10.1016/j.mce.2008.09.020]

24 **Cao X**, Yang F, Shi T, Yuan M, Xin Z, Xie R, Li S, Li H, Yang JK. Angiotensin-converting enzyme 2/angiotensin-(1-7)/Mas axis activates Akt signaling to ameliorate hepatic steatosis. *Sci Rep* 2016; **6**: 21592 [PMID: 26883384 DOI: 10.1038/srep21592]

25 **Cao X**, Yang FY, Xin Z, Xie RR, Yang JK. The ACE2/Ang-(1-7)/Mas axis can inhibit hepatic insulin resistance. *Mol Cell Endocrinol* 2014; **393**: 30-38 [PMID: 24911884 DOI: 10.1016/j.mce.2014.05.024]

26 **Skipworth JR**, Szabadkai G, Olde Damink SW, Leung PS, Humphries SE, Montgomery HE. Review article: pancreatic renin-angiotensin systems in health and disease. *Aliment Pharmacol Ther* 2011; **34**: 840-852 [PMID: 21851372 DOI: 10.1111/j.1365-2036.2011.04810.x]

27 **Lubel JS**, Herath CB, Burrell LM, Angus PW. Liver disease and the renin-angiotensin system: recent discoveries and clinical implications. *J Gastroenterol Hepatol* 2008; **23**: 1327-1338 [PMID: 18557800 DOI: 10.1111/j.1440-1746.2008.05461.x]

28 **Frigolet ME**, Torres N, Tovar AR. The renin-angiotensin system in adipose tissue and its metabolic consequences during obesity. *J Nutr Biochem* 2013; **24**: 2003-2015 [PMID: 24120291 DOI: 10.1016/j.jnutbio.2013.07.002]

29 **Zhang F**, Liu C, Wang L, Cao X, Wang YY, Yang JK. Antioxidant effect of angiotensin (1-7) in the protection of pancreatic β cell function. *Mol Med Rep* 2016; **14**: 1963-1969 [PMID: 27430410 DOI: 10.3892/mmr.2016.5514]

30 **Kalupahana NS**, Moustaid-Moussa N. The renin-angiotensin system: a link between obesity, inflammation and insulin resistance. *Obes Rev* 2012; **13**: 136-149 [PMID: 22034852 DOI: 10.1111/j.1467-789X.2011.00942.x]

31 **Wu Y**, Ma KL, Zhang Y, Wen Y, Wang GH, Hu ZB, Liu L, Lu J, Chen PP, Ruan XZ, Liu BC. Lipid disorder and intrahepatic renin-angiotensin system activation synergistically contribute to non-alcoholic fatty liver disease. *Liver Int* 2016; **36**: 1525-1534 [PMID: 27028410 DOI: 10.1111/liv.13131]

32 **Yokohama S**, Yoneda M, Haneda M, Okamoto S, Okada M, Aso K, Hasegawa T, Tokusashi Y, Miyokawa N, Nakamura K. Therapeutic efficacy of an angiotensin II receptor antagonist in patients with nonalcoholic steatohepatitis. *Hepatology* 2004; **40**: 1222-1225 [PMID: 15382153 DOI: 10.1002/hep.20420]

33 **Bataller R**, Sancho-Bru P, Ginès P, Brenner DA. Liver fibrogenesis: a new role for the renin-angiotensin system. *Antioxid Redox Signal* 2005; **7**: 1346-1355 [PMID: 16115040 DOI: 10.1089/ars.2005.7.1346]

34 **Moreno M**, Gonzalo T, Kok RJ, Sancho-Bru P, van Beuge M, Swart J, Prakash J, Temming K, Fondevila C, Beljaars L, Lacombe M, van der Hoeven P, Arroyo V, Poelstra K, Brenner DA, Ginès P, Bataller R. Reduction of advanced liver fibrosis by short-term targeted delivery of an angiotensin receptor blocker to hepatic stellate cells in rats. *Hepatology* 2010; **51**: 942-952 [PMID: 20044807 DOI: 10.1002/hep.23419]

35 **Moreno-Alvarez P**, Sosa-Garrocho M, Briones-Orta MA, González-Espinosa C, Medina-Tamayo J, Molina-Jijón E, Pedraza-Chaverri J, Macías-Silva M. Angiotensin II increases mRNA levels of all TGF-beta isoforms in quiescent and activated rat hepatic stellate cells. *Cell Biol Int* 2010; **34**: 969-978 [PMID: 20557291 DOI: 10.1042/CBI20090074]

36 **Day CP**, James OF. Steatohepatitis: a tale of two "hits"? *Gastroenterology* 1998; **114**: 842-845 [PMID: 9547102 DOI: 10.1016/S0016-5085(98)70599-2]

37 **Fraulob JC**, Ogg-Diamantino R, Fernandes-Santos C, Aguila MB, Mandarim-de-Lacerda CA. A Mouse Model of Metabolic Syndrome: Insulin Resistance, Fatty Liver and Non-Alcoholic Fatty Pancreas Disease (NAFPD) in C57BL/6 Mice Fed a High Fat Diet. *J Clin Biochem Nutr* 2010; **46**: 212-223 [PMID: 20490316 DOI: 10.3164/jcbn.09-83]

38 **Magliano DC**, Penna-de-Carvalho A, Vazquez-Carrera M, Mandarim-de-Lacerda CA, Aguila MB. Short-term administration of GW501516 improves inflammatory state in white adipose tissue and liver damage in high-fructose-fed mice through modulation of the renin-angiotensin system. *Endocrine* 2015; **50**: 355-367 [PMID: 25854303 DOI: 10.1007/s12020-015-0590-1]

39 **Lee KC**, Hsieh YC, Yang YY, Chan CC, Huang YH, Lin HC. Aliskiren Reduces Hepatic steatosis and Epididymal Fat Mass and Increases Skeletal Muscle Insulin Sensitivity in High-Fat Diet-Fed Mice. *Sci Rep* 2016; **6**: 18899 [PMID: 26732252 DOI: 10.1038/srep18899]

40 **Rabie EM**, Heeba GH, Abouzied MM, Khalifa MM. Comparative effects of Aliskiren and Telmisartan in high fructose diet-induced metabolic syndrome in rats. *Eur J Pharmacol* 2015; **760**: 145-153 [PMID: 25917321 DOI: 10.1016/j.ejphar.2015.04.019]

41 **Ceconi C**, Francolini G, Olivares A, Comini L, Bachetti T, Ferrari R. Angiotensin-converting enzyme (ACE) inhibitors have different selectivity for bradykinin binding sites of human somatic ACE. *Eur J Pharmacol* 2007; **577**: 1-6 [PMID: 17716647 DOI: 10.1016/j.ejphar.2007.07.061]

42 **Morishita T**, Tsutsui M, Shimokawa H, Tasaki H, Suda O, Kobayashi K, Horiuchi M, Okuda H, Tsuda Y, Yanagihara N, Nakashima Y. Long-term treatment with perindopril ameliorates dobutamine-induced myocardial ischemia in patients with coronary artery disease. *Jpn J Pharmacol* 2002; **88**: 100-107 [PMID: 11855668 DOI: 10.1254/jjp.88.100]

43 **Barros CC**, Haro A, Russo FJ, Schadock I, Almeida SS, Reis FC, Moraes MR, Haidar A, Hirata AE, Mori M, Bacurau RF, Würtele M, Bader M, Pesquero JB, Araujo RC. Bradykinin inhibits hepatic gluconeogenesis in obese mice. *Lab Invest* 2012; **92**: 1419-1427 [PMID: 22868909 DOI: 10.1038/labinvest.2012.105]

44 **Montez P**, Vázquez-Medina JP, Rodríguez R, Thorwald MA, Viscarra JA, Lam L, Peti-Peterdi J, Nakano D, Nishiyama A, Ortiz RM. Angiotensin receptor blockade recovers hepatic UCP2 expression and aconitase and SDH activities and ameliorates hepatic oxidative damage in insulin resistant rats. *Endocrinology* 2012; **153**: 5746-5759 [PMID: 23087176 DOI: 10.1210/en.2012-1390]

45 **Hirose A**, Ono M, Saibara T, Nozaki Y, Masuda K, Yoshioka A, Takahashi M, Akisawa N, Iwasaki S, Oben JA, Onishi S. Angiotensin II type 1 receptor blocker inhibits fibrosis in rat nonalcoholic steatohepatitis. *Hepatology* 2007; **45**: 1375-1381 [PMID: 17518368 DOI: 10.1002/hep.21638]

46 **Enjoji M**, Kotoh K, Kato M, Higuchi N, Kohjima M, Nakashima M, Nakamuta M. Therapeutic effect of ARBs on insulin resistance and liver injury in patients with NAFLD and chronic hepatitis C: a pilot study. *Int J Mol Med* 2008; **22**: 521-527 [PMID: 18813860]

47 **Toblli JE**, Muñoz MC, Cao G, Mella J, Pereyra L, Mastai R. ACE inhibition and AT1 receptor blockade prevent fatty liver and fibrosis in obese Zucker rats. *Obesity* (Silver Spring) 2008; **16**: 770-776 [PMID: 18239590 DOI: 10.1038/oby.2007.114]

48 **Wei YH**, Jun L, Qiang CJ. Effect of losartan, an angiotensin II antagonist, on hepatic fibrosis induced by CCl4 in rats. *Dig Dis Sci* 2004; **49**: 1589-1594 [PMID: 15573910 DOI: 10.1023/B:DDAS.0000043369.88701.5b]

49 **Souza-Mello V**, Gregório BM, Cardoso-de-Lemos FS, de Carvalho L, Aguila MB, Mandarim-de-Lacerda CA. Comparative effects of telmisartan, sitagliptin and metformin alone or in combination on obesity, insulin resistance, and liver and pancreas remodelling in C57BL/6 mice fed on a very high-fat diet. *Clin Sci* (Lond) 2010; **119**: 239-250 [PMID: 20415664 DOI: 10.1042/CS20100061]

50 **Kudo H**, Yata Y, Takahara T, Kawai K, Nakayama Y, Kanayama M, Oya T, Morita S, Sasahara M, Mann DA, Sugiyama T. Telmisartan attenuates progression of steatohepatitis in mice: role of hepatic macrophage infiltration and effects on adipose tissue. *Liver Int* 2009; **29**: 988-996 [PMID: 19386026 DOI: 10.1111/j.1478-3231.2009.02006.x]

51 **Yi ET**, Liu RX, Wen Y, Yin CH. Telmisartan attenuates hepatic fibrosis in bile duct-ligated rats. *Acta Pharmacol Sin* 2012; **33**: 1518-1524 [PMID: 23103625 DOI: 10.1038/aps.2012.115]

52 **Benson SC**, Pershadsingh HA, Ho CI, Chittiboyina A, Desai P, Pravenec M, Qi N, Wang J, Avery MA, Kurtz TW. Identification of telmisartan as a unique angiotensin II receptor antagonist with selective PPARgamma-modulating activity. *Hypertension* 2004; **43**: 993-1002 [PMID: 15007034 DOI: 10.1161/01.HYP.0000123072.34629.57]

53 **Zhang LL**, Huang S, Ma XX, Zhang WY, Wang D, Jin SY, Zhang YP, Li Y, Li X. Angiotensin(1-7) attenuated Angiotensin II-induced hepatocyte EMT by inhibiting NOX-derived H2O2-activated NLRP3 inflammasome/IL-1β/Smad circuit. *Free Radic Biol Med* 2016; **97**: 531-543 [PMID: 27445100 DOI: 10.1016/j.freeradbiomed.2016.07.014]

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REVIEW

# Systemic treatment for hepatocellular carcinoma: Still unmet expectations

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## Abstract

Many patients with hepatocellular carcinoma (HCC) are diagnosed in an advanced stage, so they cannot be offered the option of curative treatments. The results of systemic chemotherapy are unsatisfactory and this has led to molecular targeted approaches. HCC develops in chronically damaged tissue due to cirrhosis in most patients. Several different cell types and molecules constitute a unique microenvironment in the liver, which has significant implications in tumor development and invasion. This, together with genome instability, contributes to a significant heterogeneity which is further enhanced by the molecular differences of the underlying causes. New classifications based on genetic characteristics of the tissue microenvironment have been proposed and key carcinogenic signaling pathways have been described. Tumor and adjacent tissue profiling seem biologically promising, but have not yet been translated into clinical settings. The encouraging first results with molecular - genetic signatures should be validated and clinically applicable. A more personalized approach to modern management of HCC is urgently needed.

**Key words:** Systemic; Chemotherapy; Hepatocellular carcinoma; Prognosis



**Core tip:** The complete failure of chemotherapy in previous years gradually shifted hepatocellular carcinoma (HCC) treatment to the molecular targeted therapies. The initial-albeit limited - effectiveness of the currently approved systemic therapy, sorafenib, is due to the successful combination of targeting cancer cells and their microenvironment. Trials on drugs other than sorafenib, alone or in combination with drugs or transcatheter arterial chemoembolization were disappointing. Recently, genomic based analyses in HCC patients have proposed subclasses, based on molecular characteristics and a proliferative or non-proliferative genotypes. Combined targeted therapies, driven by specific molecular signatures for treatment selection and monitoring, potentially with immunotherapy, could be a future personalized approach.

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## INTRODUCTION

Hepatocellular carcinoma (HCC) represents globally the fifth most common cancer and is considered the third most frequent cause of cancer related death[1]. In recent years there has been a significant progress in clarifying pathogenesis, etiology, and risk factors for hepatocarcinogenesis. Understanding the importance of underlying cirrhosis in the majority of HCCs led to more integrated approach, as in the majority of cases we have to deal with two diseases, cirrhosis and cancer.

The adoption of the barcelona-clinic liver cancer (BCLC) classification[2,3] offered the opportunity to better categorize HCC patients and select the best treatment option according to tumor stage, degree of liver function impairment and patient characteristics. The outcomes for surgical resection have improved and specific factors, as tumor and liver function characteristics, are being taken into account before the patient is referred for an operation[4]. Moreover, the widespread application of the Milan criteria in the field of transplantation, has changed the transplant procedure from an experimental approach to a standard of care therapy for HCC, which can treat at the same time the tumor and the underlying pre-neoplastic process (namely cirrhosis)[5].

Despite screening patients at risk[6], adopting regular surveillance rules and the impressive improvements in imaging, still many patients with HCCs are diagnosed in an advanced stage, thus being ineligible for radical treatments [transplantation, resection or Radiofrequency ablation (RFA)] or even for ablative techniques [trans-catheter arterial chemoembolization (TACE)] that can also provide survival benefit[7].

Patients with advanced HCC, especially if complicated with advanced cirrhosis, have a dismal prognosis. Several therapeutic efforts on this group of patients gave disappointing results in the past. The complete failure of systemic chemotherapy in previous years gradually shifted HCC treatment to the molecular targeted therapies. The first successful trials of sorafenib[8,9] provided a meaningful survival benefit in patients with advanced HCC, leaving at the same time many unresolved issues. This review attempts to present the effort of the scientific research to address the problem of HCC in multiple levels and to critically evaluate the inadequacies of the current trials of systemic treatments.

## THE STORY OF NEAR-FAILED SYSTEMIC TREATMENTS

Initial approaches with systemic therapy were ineffective, as HCC is refractory to conventional chemotherapy and poorly tolerable in the context of liver cirrhosis due to altered drug metabolism and toxicity. Initial evidence for some efficacy of the anti-estrogen agent Tamoxifen in small trials were not confirmed in larger clinical trials and the drug has been abandoned[10].

More interesting data came in to light with clinical studies of Somatostatin and its long acting analogues for advanced HCC with very promising initial results[11,12], given the antiproliferative activity of the hormone and the positivity of HCC in somatostatin receptors in roughly 40% of the tumors[13]. Further publications have documented that somatostatin leads to apoptosis and has antineoplastic properties. Nevertheless, randomized trials - mainly from western countries - did not identify a clear survival benefit and this treatment is no longer recommended. There has been criticism for the methodology of these trials and the heterogeneity of selected patient population[14].

Sorafenib, the only currently approved systemic treatment, that demonstrated statistically significant improvement in overall survival and prolonged time to progression in two large randomized controlled trials (Sharp and Asian Pacific)[8,15]. The efficacy of Sorafenib has been attributed to blockade of multiple kinases, most of them involved in the VEGF, PDGF, c-Kit and B-Raf and p38 signaling pathways[16]. Despite the low response rates and the associated toxicity, the drug showed survival benefit in Child's A patients with a good performance status.

The safety and efficacy of this treatment was further investigated in the Gideon trial (global phase Ⅳ, ongoing), focusing on patients with Child's B that were under represented in the registration trials. The interim analysis showed better outcomes for patients on the full dose (800 mg) as compared to the reduced (400 mg) dose, without significant differences in safety profile[17,18]. However, the median life expectancy of patients under Sorafenib treatment is generally less than one year, and this clearly needs to be improved. For the time being there are no validated factors to predict effectiveness or the possibility of adverse effects[19].

More issues are still open, as what to do when the patient fails to respond or is intolerant to Sorafenib, or if Sorafenib could have a role as adjuvant treatment to other modalities like TACE. More data are expected and towards this direction is a recent study showed that tumor associated neutrophils (TAN) mediate the intratumoral infiltration of macrophages and Tregs by secreting the chemotactic C-C motif ligands CCL2 and CCL17. Thus neovascularization is being stimulated, and HCC growth and metastasis are promoted, all contributing to resistance to Sorafenib[20]. Thus, TAN infiltration is proposed as a potential biomarker.

Sunitinib, a potent multi-targeted receptor tyrosine kinase inhibitor of VEGFR, PDGFR, and c-KIT, reached to phase Ⅲ study as compared to Sorafenib. The trial was terminated prematurely due to higher incidence of side effects in the sunitinib arm, besides demonstrating no superiority over sorafenib[21].

Brivanib is a potent and selective inhibitor of VEGFR and FGFR and pre-clinical studies have shown *in vivo* antitumor activity[22]. Three phase Ⅲ studies have been conducted, yielding negative results. The BRISK-FL study tested the efficacy of Brivanib *vs* Sorafenib, in patients with advanced HCC without prior systemic treatment[23]. The BRISK-PS study tested Brivanib *vs* placebo in patients that failed or were intolerant to Sorafenib[24]. In both studies Brivanib failed to improve OS but it did improve time to tumor progression (TTP), indicating some anti-tumor activity. Due to these results, a phase Ⅲ trial in which Brivanib was used as an adjuvant to TACE was terminated prematurely[25].

Linifanib is a multi-targeted receptor tyrosine kinase inhibitor effective on VEGFR and PDGFR. A phase Ⅲ trial with 1035 patients comparing Sorafenib with Linifanib, showed similar overall survival in advanced HCC with a more favorable safety profile for Sorafenib; predefined superiority and non-inferiority overall survival boundaries were not met by Linifanib, which was more toxic than Sorafenib[26].

Erlotinib is an orally active inhibitor of epidermal growth factor receptor (EGFR) tyrosine kinase. A phase Ⅲ randomized trial (SEARCH) with 720 HCC patients (Child A cirrhosis) were assigned to Sorafenib/Erlotinib or Sorafenib/placebo[27]. The median OS and TTP were similar in both groups, thus adding Erlotinib to Sorafenib did not improve survival, but increased toxicity instead.

Dovotinib, a VEGFR, PDGFR, FGFR inhibitor was compared head to head with Sorafenib, in a randomized study in the Asian-Pacific in patients with advanced HCC. Although Dovotinib was well tolerated, it failed to show greater efficacy than sorafenib, and thus there will be no phase Ⅲ trial[28].

In patients who stopped Sorafenib due to disease progression or intolerance, a randomized phase Ⅲ trial assessed Ramucirumab, a recombinant monoclonal IgG1 and VEGFR-2 blocking antibody (REACH). Despite acceptable safety profile, the study drug did not reached statistically significant survival benefit *vs* placebo[29]. However, a sub-population with αFP > 400 ng/mL might have benefited from this 2$^{nd}$ line treatment and this is explored in an ongoing trial. Recently Codrituzumab, a humanized monoclonal antibody against Glypican-3 which is expressed in HCC, was studied *vs* placebo in a phase Ⅱ randomized trial without showing any clinical benefit[30].

Tivantinib is an oral selective small MET tyrosine kinase inhibitor with antitumor activity in MET-high patients. A phase Ⅱ randomized placebo-controlled study in patients with advanced HCC, Child's A score and intolerant or progressing under the first line treatment, showed some promising results on time to progression, but with notable neutropenia in some patients[31]. A phase Ⅲ study in patients with advanced HCC expressing high levels of c-MET after Sorafenib failure is underway.

Mammalian target of rapamycin (mTOR) regulates cell growth, metabolism and aging in response to nutrients, cellular energy state and growth factors[32]. It is frequently up-regulated in cancer, including HCC, and is associated with poor differentiation and bad prognosis. Blocking this pathway appears an attractive option for HCC treatment. It is well known from the research on transplantation - given its immunosuppressive properties - that mTOR inhibitors (Sirolimus) are associated with better clinical outcomes in patients transplanted for HCC[33,34].

Preliminary data in the non-transplant setting with Sirolimus and Everolimus treatment in HCC patients were encouraging. In the EVOLVE-1 phase Ⅲ study, patients with advanced HCC and failure/intolerance to Sorafenib, randomized to Everolimus or placebo[35]. Everolimus did not improve OS with no difference to TTP *vs* placebo. Moreover, Everolimus led to hepatitis B virus (HBV) re-activation in 37% of the cases despite preventive antiviral therapies. A recent phase Ⅱ randomized trial of the combination of Everolimus with Sorafenib *vs* Sorafenib alone, in patients with advanced HCC with Child's score ⩽ 7, showed that the combination was not more beneficial; in contrast it was more toxic[36].

TACE is the treatment of choice for intermediate stage HCC. However, following TACE the hypoxic micro-environment promotes up-regulation of proangiogenic factors as VEGF and PDGF. This is the theoretical basis for the combination of TACE with drugs that inhibit angiogenesis, as Sorafenib and Birivanib. A recent review and meta-analysis reported that this combined approach may bring benefit to unresectable HCC in terms of TTP but not OS[37]. Recent studies (START, SOCRATES) that investigated the efficacy and safety of Sorafenib as an adjuvant to TACE displayed good tolerability and interesting response rate[38,39]. Clearly a better defined population of advanced HCC -that might have the maximal benefit from this approach- should be tested in clinical trial. Unfortunately, the recently published SPACE trial[40] showed that despite the combination of DC beads TACE with Sorafenib was feasible, this combination did not actually improve time to tumor progression in intermediate HCC.

Beyond TACE, efficacy and safety of Sorafenib was studied in a randomized phase Ⅲ trial *vs* placebo, in patients with HCC after resection or local ablation (STORM trial)[41]. The recurrence free survival was identical in the two arms, whereas side effects were significantly more frequent in patients receiving Sorafenib in whom dose modification was necessary in 90% of the cases.

The combination of Sorafenib with other cytotoxic agents was tested to improve the disappointing results of conventional chemotherapy. In a phase Ⅱ trial[42] the combination of Sorafenib/Doxorubicin was compared to Doxorubicin alone in Child-A cirrhotic patients with advanced HCC. The trial showed that the combination was better than doxorubicin alone as regards time to progression and overall survival. Whether there is benefit of the combination or this is an effect of sorafenib itself, will be clarified in an on-going phase Ⅲ trial.

The efficacy and safety of GEMOX (Gemcitabin/Oxaliplatin) plus sorafenib, followed by sorafenib mono-

**Table 1 Randomized Phase Ⅲ trials in advanced hepatocellular carcinoma**

| Drug | *n* (patients) | OS (mo) SOR/Exp arm | HR |
|---|---|---|---|
| First line completed (Sorafenib standard) | | | |
| Brivanib | 1155 | 9.9/9.5 | 1.06 |
| Sunitinib | 1074 | 10.2/7.9 | 1.3 |
| Sorafenib/Erlotinib | 720 | 8.5/9.5 | 0.92 |
| Linifanib | 1035 | 9.8/9.1 | 1.04 |
| Second line completed (placebo standard) | | | |
| Brivanib | 395 | 8.2/9.4 | 0.89 |
| Everolimus | 546 | 7.3/7.6 | 1.05 |
| Ramucirumab | 565 | 7.6/9.2 | 0.86 |

OS: Overall survival; SOR: Sorafenib arm.

therapy was examined in a small trial with 49 patients diagnosed with advanced HCC[43]. This approach was found effective (overall survival 15.7 mo) with manageable toxicity, and these results should be validated in a larger controlled trial. The data of a subsequent phase Ⅱ randomized study on this combination, as well as the results of a single arm phase Ⅱ study combining sorafenib with oxaliplatin/capecitabin, showed modest synergistic effect[44]. Further combinations that were tested, such as sorafenib with EGFR inhibitors or with mTOR inhibitors, both failed to show any meaningful antitumor activity.

Finally, the combination of Sorafenib with Octreotide was tested in a phase Ⅱ study, recruiting 50 patients with advanced HCC and Child-Pugh score A or B[45]. The combination was well tolerated and displayed TTP 7 mo and median overall survival 12 mo. Nevertheless these results have not been confirmed in a larger phase Ⅲ study as yet. We believe that this combination could provide an option for patients with inadequate response or intolerance to sorafenib (Figure 1).

The apparent failure of phase Ⅲ trials beyond sorafenib, was disappointing but not discouraging for the scientific community (Table 1). Factors contributing to this failure and were related to drug toxicity (especially in cirrhotic patients), lack of significant antitumoural potency, lack of our understanding on diverse mechanisms of tumor progression and metastasis or biomarkers predictive of the efficacy of therapy[16]. Study design was another weak point for some trials. Trials in patients with advanced HCC should also pay attention to specific factors as portal vein invasion, the extrahepatic metastases, and the degree of liver impairment.

## EXPLORING THE ETIOPATHOGENESIS

### *Molecular and phenotypic diversity of HCC - Oncogenic pathways*

Beyond the success and wide adoption of the BCLC system on staging and prognosis of HCC[46], recently new molecular classifications based on genetic characteristics of the tissue microenvironment have been proposed. However, HCC is a heterogeneous disease and each tumor is a result of unique combination of several genomic defects that lead to a significant diversity in the pathways of carcinogenesis. It is documented that several differences exist not only amongst different patients, but also between different tumor nodules in the same liver, and even differences in the same nodule.

Cancer cells and stem cells have similar capacity as regards self-renewal, indefinite division, and generation of heterogeneous cell population. The concept of cancer stem cell, referring to a subset of cells bearing stem cell characteristics that is indispensable for tumour development and perpetuation, has been recently adopted[47]. Cancer stem cells are now considered an important target for the eradication of HCC. Furthermore, a 20%-40% of HCC subtypes show progenitor signature suggesting that these tumours derive from liver progenitor cell. These subtypes are highly aggressive and correlate with early recurrence after treatment and metastatic potential, thus correlated to worse prognosis. CD133 antigen (prominin-1) has been identified as a cancer stem cell marker in various cancers, including HCC. Patients with increased CD133 levels have shorter overall survival and higher recurrence rates compared to those with low expression. Recent data showed that IL-6/STAT3 signalling induced CD133 expression, through function co-operation with NF-κB and hypoxia-inducible factor 1 alpha (HIF-1α) during hepatocarcinogensis[48] (Figure 2A).

Recently genomic based analyses in HCC patients have identified subclasses, based on molecular characteristics and proliferative and non-proliferative genotypes have been proposed[49]. The proliferative subclass - which is associated with a poor outcome - has been linked to the activation of RAS, mTOR, and/or IGF signaling. This has been further categorized into two phenotypic groups: The Wnt/TGF-β group (activation of these pathways) and the progenitor cell group. In the former, the activation of the Wnt and the TGF-β was the predominant feature, while the latter was enriched in progenitor cell, epithelial cell adhesion molecule and cytoskeletal markers and was associated with increased α-fetoprotein at early stages[50]. On the other hand, the non-proliferative subclass was a heterogeneous one, with patients sharing only β-katenin in their molecular profiles[51]. The prognostic implications of these subclasses have been studied but there is no consensus on it and there is no translational clinical research has been done yet.

The paradigm from the management of other cancers such as colorectal cancer and non-small lung cell carcinoma, where mutations of K-Ras and EGFR drive the therapeutic choices, supports this new approach[52]. Unfortunately, HCC is still away from this path despite the success of sorafenib, a multi kinase inhibitor, which seems a proof towards the right direction. A key point may be that in HCC an average of 30-40 mutations were estimated per tumor, with 5-8 of them being the driver mutations[49] affecting cellular homeostasis and involved in the development of malignant phenotype.

A recent elegant study performing exome sequencing analysis of 243 surgically resected HCCs revealed mutational signatures associated with specific risk factors, as combined tobacco and alcohol use, or aflatoxin

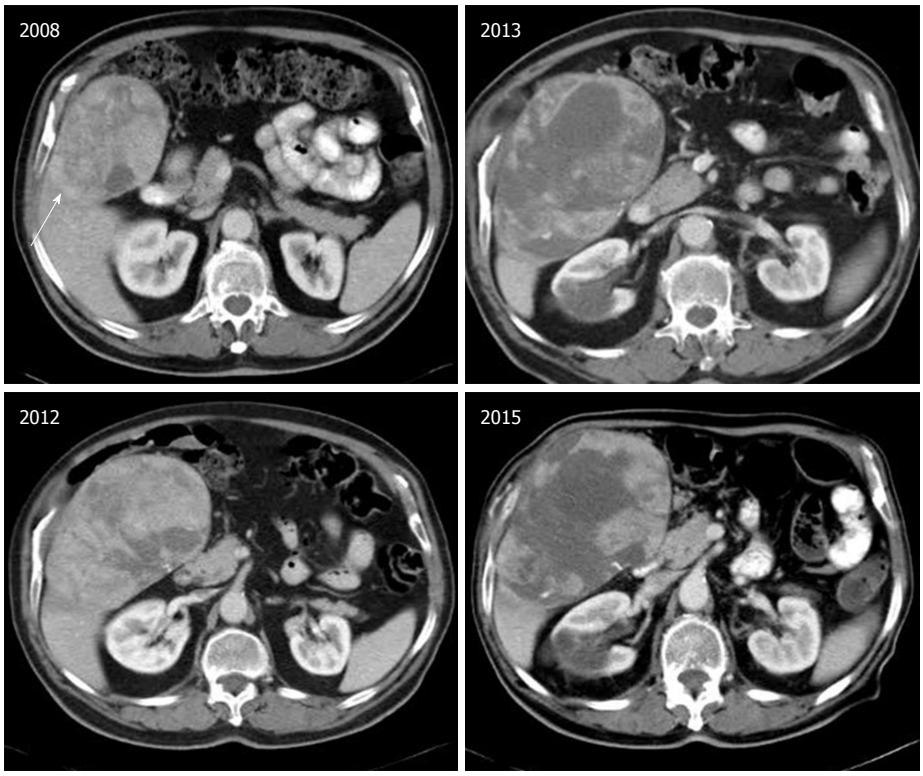


**Figure 1 Serial computed tomography scans of a hepatocellular carcinoma patient with multiple co-morbidities precluding radical treatment, surviving 7 years with sequential approach in systemic treatment (Octreotide long acting release, followed by sorafenib).** Despite an increase in tumor size, it is evident the central necrosis related to Sorafenib treatment (which was commenced when it became available).

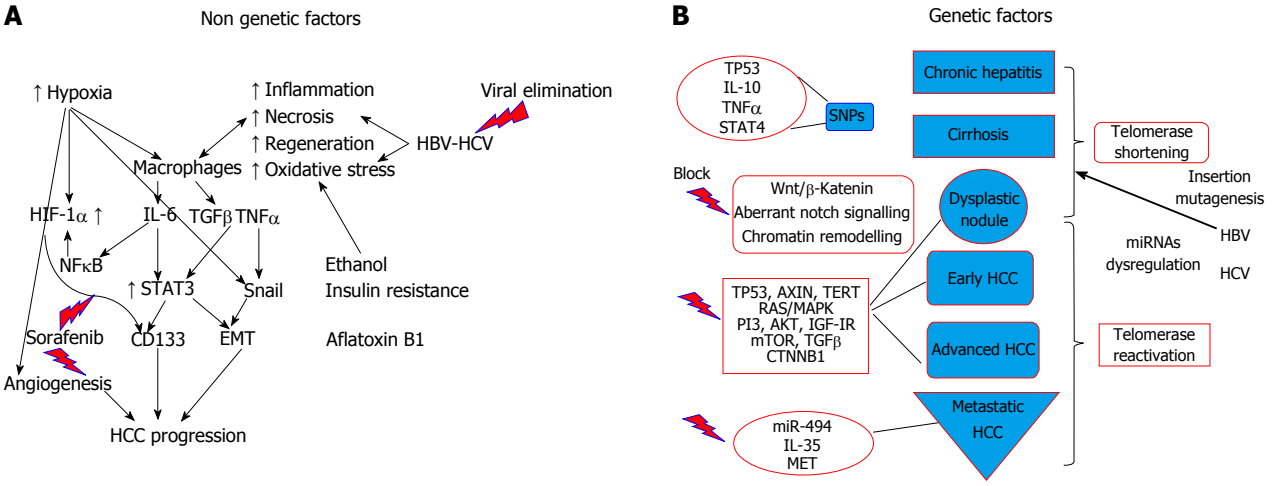


**Figure 2 Interplay between genetic and non-genetic factors in the pathogenesis of hepatocellular carcinoma.** Potential treatment targets. Hepatocellular carcinoma (HCC) is a complex entity with multifactorial pathogenesis. Control of non-genetic factors (A) (*e.g.*, viral elimination, inhibition of CD133 positive cancer cell overexpression) may lead to alteration of the progress from cirrhosis to HCC. On the other hand, the various genetic irregularities (B) may lead to different HCC profiles with respect to invasiveness (miR-494) or response to treatment. New targeted treatments are also directed against Wnt/β-katenin. HBV: Hepatitis B virus; HCV: Hepatitis C virus; HIF-1α: Hypoxia-inducible factor 1 alpha; TNF: Tumor necrosis factor; IL-6: Interleukin-6; NFκB: Nuclear factor-kappa B.

B1. The researchers identified 161 putative driver genes associated with 11 recurrent pathways[53]. Moreover, a molecular 5 gene score (based on combined expression level of HN1, RAN, RAMP3, KRT19, and TAF9) was studied in surgical resected samples of 314 HCC, and was found significantly associated with outcomes[54]. Also recent data show that it is possible to modulate gene expression profiles (interfering with histone acetylation) and thus increase the sensitivity to chemotherapeutic agents[55].

Activation of telomerase is the earliest and most frequent alteration in the process of HCC development (mutations in TERT promoter in 60% - most frequently mutated gene - associated with increased telomerase expression)[56]. Genes as *TP53* and *CTNNB1* are also frequently mutated in HCC, whereas inactivating muta-

tions in TP53 are commonly found (especially with HBV etiology). Recently identified alterations in genes encoding metabolic enzymes, chromatin remodelers and a high rate of mTOR pathway activations could offer potential therapeutic targets[57]. Members of the Wnt pathway (crucial for hepatocarcinogensesis) are involved in the process of cell differentiation, which is frequently altered in cancer cells, whereas failure to control oxidative stress can favor additional DNA mutations and cellular damage.

Key carcinogenic signaling pathways have been described for HCC: Wnt/β-katenin [that can be triggered *via* both catenin β1 (CTNNB1)-dependent and CTNNB1 independent pathways][58], a proliferation and hepatoblastoma-like pathway[59]. Nevertheless, their molecular signature is broad and for the time being this knowledge is unlikely to have clinical application. Notch signaling is important for normal liver development and aberrant Notch signaling is related to hepatocarcinogenesis (Figure 2B). Chromatin remodeling is important for the maintenance of DNA integrity, which is in turn crucial for cellular homeostasis. Aberrant chromatin remodeling has been implicated with HCC pathogenesis[57] as well as genes that are involved in oxidative stress (which induces mutations).

In respect to the receptor signaling pathways, RAS/MAPK pathway is activated in all patients with advanced HCC and in a large proportion of those with an early stage HCC[60]. PI3/AKT/mTOR and MAPK pathways related to proliferation, apoptosis and survival, as well as pro inflammatory cytokines (IL1, TNFα) and growth factors, such as TGFβ (tumor stroma, progression, metastasis), are potential future clinical targets in HCC therapeutics (Figure 2B).

Very recently, IL-35 expression was found to correlate with HCC aggressiveness, conferring the rational for another novel therapeutic target[61]. IFG-1R signalling is activated in a proportion of patients with HCC and its targeting had demonstrated antitumor activity in experimental models; however a phase Ⅱ trial with an anti-IFG-1R monoclonal antibody did not show clinical benefit in unselected patients[62]. Finally, dysregulation of MET receptor and its ligand HGF, are crucial for hepatocyte regeneration after liver injury and are common events in HCC patients[49]. Activation of MET is found in half of advanced HCCs, and this pathway is currently tested in clinical trials. A MET inhibitor, cabozantinib, was found to suppress tumour growth and metastasis in a phase Ⅱ study[63] and is further tested in a phase Ⅲ second line clinical trial (in patients with high MET expression, treated with tivantinib).

### *Tissue microenvironment and the role of cirrhosis*

**Scientific basis:** Chronic liver injury triggers a sequence of cell death, inflammation, compensatory regeneration and genetic damage, which drives the development of HCC. In the majority of cases, HCC develops in chronically damaged tissue due to cirrhosis-irrespective of etiology - whereas the other malignancies develop on an otherwise healthy tissue. This, together with genome instability, contributes to a significant heterogeneity which is further enhanced by the molecular differences of the underlying causes, *i.e.*, viral, alcohol, metabolic[52]. Moreover, epithelial plasticity is an important parameter in HCC, as strong inducers of epithelial to mesenchymal transition like TGFβ are able to co-ordinate both fibrogenesis and carcinogenesis, showing rising cytokine levels in cirrhosis as well as late stage HCC[64].

Several different cell types and molecules constitute a microenvironment in the liver, which has significant implications in tumor development and invasion. Myeloid cells, including macrophages and neutrophils are the most abundant cells in the tumor microenvironment[65]. Tumor-associated macrophages acquire protumorigenic properties in primary and metastatic sites and support cancer development and progression, by stimulating cell proliferation and survival, angiogenesis, invasive behavior and suppression of cytotoxic T lymphocytes responses[66]. Tumor-associated neutrophils exhibit both antitumoral and protumoral functions. Dendritic cells, the main type of antigen presenting cells, play an important role in T cell priming. The generation and protective antitumour immunity depends on dendritic cell maturation and antigen presentation[67].

It is generally accepted that dysregulated microenvironment affects tumorigenesis, based on the concept that chronic inflammation is associated with cancer[68]. Moreover, the stromal microenvironment has been recognized as a crucial element for cancer metastasis in general. A reasonable hypothesis is that an altered liver microenvironment, through reprogramming of the inflammatory milieu, may contribute to hepatocarcinogenesis, taking in account that HCC is an inflammation-associated cancer[69]. This microenvironment plays a major role in anti-tumor immunity.

**Therapeutic implications:** The effectiveness of the currently approved systemic therapy, sorafenib, is due to the successful combination of targeting cancer cells and their microenvironment, as a result of multiple kinases inhibition. Between sorafenib targets, an increasing amount of evidence has suggested that HSC are key regulators of hepatocarcinogenesis through a variety of mechanisms, including direct effects on malignant hepatocytes, and indirect *via* modulation of the peritumoral stroma and immune responses[70]. Moreover, activated stellate cells produce extracellular matrix.

Laminin-332 is produced and excreted by these cells in HCC but not in the surrounding non-neoplastic liver; this stimulates chemotaxis and migration of HCC cells in experimental models and promotes proliferation as well[52]. An association between Ln-332 and Keratin -19 has been documented, the latter being a marker of cholangiocytes[71].

VEGF not only regulates tumor angiogenesis but also has important immunomodulatory functions. It inhibits dendritic cell maturation *in vitro* and *in vivo*, through activation of NFκB. Additionally VEGF may regulate T-cell

differentiation and its cytotoxic function and can enhance expression of immune checkpoint molecules[72]. This provides the rational of combining anti-VEGF therapy with checkpoint inhibitors.

Another area of active research is on the effect of mTOR inhibitors on advanced HCC in the non-transplant setting. Recent data showed that mTOR inhibition improves FGFR targeting[73] and reduces the activity level of Golgi protein 73, which is a serum marker for HCC[74]. However, the first results of trials with mTOR inhibitors were less than encouraging. Despite potential applications, the role of the whole tissue microenvironment is difficult to be reduced to the effect of just one molecule or protein.

### *Immunity and implications*

**Scientific basis:** Inflammation affects every single step of tumourigenesis from initiation, to tumor promotion and metastatic progress. Cancer development and its response to treatment are significantly influenced by innate and adaptive immunity, which either promote or attenuate tumourigenesis[66]. Various types of immune and inflammatory cells are present within tumours; these affect malignant cells through production of cytokines, chemokines, growth factors, prostaglandins and reactive oxygen and nitrogen species[68].

The liver has been considered as an immunologically advantaged organ. A profound clinical paradigm is the development of tolerance in the context of transplantation. It is equipped with several myeloid and non-myeloid cell populations which affect both innate and adaptive responses in physiological conditions as well as in the context of defense against tumors[75].

Kupffer cells represent the largest macrophage population in the human body and together with sinusoidal endothelial and hepatic stellate cells, play a critical role in physiology and disease. Local immunosuppression by these cells is induced by pro-inflammatory cytokines[69] whereas different immune cell subtypes have been related to antitumor immunity in HCC. Kupffer cells in analogy to the two subtypes of macrophages are now characterized as M1 and M2 types. In the case of HCC M2 cells are detrimental and M1 demonstrate anti-tumoral activity, contrary to the opposite effects of those cell subpopulations have in inflammation.

Among immunosuppressive cell populations, myeloid derived suppressor cells and T regulatory cells have the key role in cancer immunosurveillance[76]. A prominent humoral cytokine profile occurs in metastatic liver milieu and a shift towards anti-inflammatory/immunosuppressive responses is significant for HCC metastases[77].

**Therapeutic implications:** The liver is a privileged organ with respect to immune function and possesses a unique form of immune regulation: Tolerance is induced to avoid chronic inflammation caused by antigens coming from the portal vein blood. This may hampers an effective immune response against cancer cells[78]. Moreover this is a challenge on the use of conventional immunotherapy is challenged. Immunotherapy trials have so far given suboptimal results. On the other hand, spontaneous immune responses as well as tumor regression have been reported in relation to systemic inflammatory responses[79]. This could as well be a result of M1 effect as previously mentioned.

Adaptive immune responses are well described in various conventional HCC treatments and are related to their effects. This has been extensively investigated in patients undergoing ablative therapies (TACE, RFA), and provide the theoretical basis for combined approaches. This applies to cytotoxic agents as well, and experience with sorafenib in experimental and clinical level is a paradigm.

While growing tumors acquire mutations, some of which create neoantigens that influence the response of patients to immune checkpoint inhibitors[80]. There are other studies supporting that cancers with high rate of somatic mutations respond best to immune check point blockade by triggering tumor rejection *via* activation of cytotoxic T-lymphocytes, a recent approach with acknowledged success in recent years in melanoma and non-small cell lung cancer[81].

Preclinical and clinical studies have shown potential benefit of modulating immunogenicity of HCC and relevant approaches are currently being tested[82]. The rational to target immune-checkpoints is based on data that HCCs may evade the immune system by expressing molecules as PD-1, CTLA-4, TIM-3, LAG-3 and many more. Despite the fact that the blockade of PD-1 and CTLA-4 is already providing encouraging results in initial trials, overall the therapeutic relevance of blocking these agents is unclear[72].

## CONCLUSION

HCC is one of the most lethal cancers and management still deems ineffective. Apart from the problems in prevention or early diagnosis, there are no persuasive answers for those (many) patients with advanced neoplasms. Systemic treatment was disappointing in the past, somehow improved with Sorafenib but with many weaknesses and grey zones, whereas the trials of new compounds beyond Sorafenib provided suboptimal results.

The complexity and heterogeneity of HCC pathogenesis is disregarded in treatment decisions. Is a personalized approach feasible with the limitations of current knowledge? Tumor and adjacent tissue profiling seems biologically significant, but not yet translated into the clinical setting. The role of liquid biopsy, *i.e.,* detection of circulating tumor cells, a hot topic in tumor biology is also inadequately explored in the case of HCC.

Nevertheless, encouraging first results with molecular - genetic signatures are promising towards -at least- prognosis. Additionally, miRNAs which are important regulators of gene expression, have been associated

with the occurrence of HCC. In addition, miRNAs are of potential value not only in diagnosis but also in the management of HCC.

Clinical scoring systems incorporating molecular profile characteristics, may better stratify patients at risk for HCC but further prospective validation is needed. The ideal future approach would be combined targeted therapies - driven by specific molecular signatures for the selection and the monitoring during treatment- potentially incorporating immunotherapeutic modalities, such as vaccination and/or check-point blockade.

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## REFERENCES

1 **Bosetti C**, Turati F, La Vecchia C. Hepatocellular carcinoma epidemiology. *Best Pract Res Clin Gastroenterol* 2014; **28**: 753-770 [PMID: 25260306 DOI: 10.1016/j.bpg.2014.08.007]

2 **Forner A**, Reig ME, de Lope CR, Bruix J. Current strategy for staging and treatment: the BCLC update and future prospects. *Semin Liver Dis* 2010; **30**: 61-74 [PMID: 20175034 DOI: 10.1055/s-0030-1247133]

3 **Bruix J**, Reig M, Sherman M. Evidence-Based Diagnosis, Staging, and Treatment of Patients With Hepatocellular Carcinoma. *Gastroenterology* 2016; **150**: 835-853 [PMID: 26795574 DOI: 10.1053/j.gastro.2015.12.041]

4 **Au JS**, Frenette CT. Management of Hepatocellular Carcinoma: Current Status and Future Directions. *Gut Liver* 2015; **9**: 437-448 [PMID: 26087860 DOI: 10.5009/gnl15022]

5 **Menon KV**, Hakeem AR, Heaton ND. Review article: liver transplantation for hepatocellular carcinoma - a critical appraisal of the current worldwide listing criteria. *Aliment Pharmacol Ther* 2014; **40**: 893-902 [PMID: 25155143 DOI: 10.1111/apt.12922]

6 **Zhu AX**, Abrams TA, Miksad R, Blaszkowsky LS, Meyerhardt JA, Zheng H, Muzikansky A, Clark JW, Kwak EL, Schrag D, Jors KR, Fuchs CS, Iafrate AJ, Borger DR, Ryan DP. Phase 1/2 study of everolimus in advanced hepatocellular carcinoma. *Cancer* 2011; **117**: 5094-5102 [PMID: 21538343 DOI: 10.1002/cncr.26165]

7 **Forner A**, Gilabert M, Bruix J, Raoul JL. Treatment of intermediate-stage hepatocellular carcinoma. *Nat Rev Clin Oncol* 2014; **11**: 525-535 [PMID: 25091611 DOI: 10.1038/nrclinonc.2014.122]

8 **Llovet JM**, Ricci S, Mazzaferro V, Hilgard P, Gane E, Blanc JF, de Oliveira AC, Santoro A, Raoul JL, Forner A, Schwartz M, Porta C, Zeuzem S, Bolondi L, Greten TF, Galle PR, Seitz JF, Borbath I, Häussinger D, Giannaris T, Shan M, Moscovici M, Voliotis D, Bruix J. Sorafenib in advanced hepatocellular carcinoma. *N Engl J Med* 2008; **359**: 378-390 [PMID: 18650514 DOI: 10.1056/NEJMoa0708857]

9 **Cheng AL**, Kang YK, Chen Z, Tsao CJ, Qin S, Kim JS, Luo R, Feng J, Ye S, Yang TS, Xu J, Sun Y, Liang H, Liu J, Wang J, Tak WY, Pan H, Burock K, Zou J, Voliotis D, Guan Z. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: a phase III randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2009; **10**: 25-34 [PMID: 19095497 DOI: 10.1016/S1470-2045(08)70285-7]

10 **Nowak AK**, Stockler MR, Chow PK, Findlay M. Use of tamoxifen in advanced-stage hepatocellular carcinoma. A systematic review. *Cancer* 2005; **103**: 1408-1414 [PMID: 15744746 DOI: 10.1002/cncr.20963]

11 **Kouroumalis E**, Skordilis P, Thermos K, Vasilaki A, Moschandrea J, Manousos ON. Treatment of hepatocellular carcinoma with octreotide: a randomised controlled study. *Gut* 1998; **42**: 442-447 [PMID: 9577356 DOI: 10.1136/gut.42.3.442]

12 **Samonakis DN**, Moschandreas J, Arnaoutis T, Skordilis P, Leontidis C, Vafiades I, Kouroumalis E. Treatment of hepatocellular carcinoma with long acting somatostatin analogues. *Oncol Rep* 2002; **9**: 903-907 [PMID: 12066229 DOI: 10.3892/or.9.4.903]

13 **Abdel-Rahman O**, Lamarca A, Valle JW, Hubner RA. Somatostatin receptor expression in hepatocellular carcinoma: prognostic and therapeutic considerations. *Endocr Relat Cancer* 2014; **21**: R485-R493 [PMID: 25336571 DOI: 10.1530/ERC-14-0389]

14 **Samonakis DN**, Notas G, Christodoulakis N, Kouroumalis EA. Mechanisms of action and resistance of somatostatin analogues for the treatment of hepatocellular carcinoma: a message not well taken. *Dig Dis Sci* 2008; **53**: 2359-2365 [PMID: 18273705 DOI: 10.1007/s10620-007-0175-9]

15 **Abou-Alfa GK**, Schwartz L, Ricci S, Amadori D, Santoro A, Figer A, De Greve J, Douillard JY, Lathia C, Schwartz B, Taylor I, Moscovici M, Saltz LB. Phase II study of sorafenib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2006; **24**: 4293-4300 [PMID: 16908937 DOI: 10.1200/JCO.2005.01.3441]

16 **Llovet JM**, Hernandez-Gea V. Hepatocellular carcinoma: reasons for phase III failure and novel perspectives on trial design. *Clin Cancer Res* 2014; **20**: 2072-2079 [PMID: 24589894 DOI: 10.1158/1078-0432.CCR-13-0547]

17 **Di Marco V**, De Vita F, Koskinas J, Semela D, Toniutto P, Verslype C. Sorafenib: from literature to clinical practice. *Ann Oncol* 2013; **24** Suppl 2: ii30-ii37 [PMID: 23715941 DOI: 10.1093/annonc/mdt055]

18 **Lencioni R**, Kudo M, Ye SL, Bronowicki JP, Chen XP, Dagher L, Furuse J, Geschwind JF, de Guevara LL, Papandreou C, Takayama T, Yoon SK, Nakajima K, Lehr R, Heldner S, Sanyal AJ. GIDEON (Global Investigation of therapeutic DEcisions in hepatocellular carcinoma and Of its treatment with sorafeNib): second interim analysis. *Int J Clin Pract* 2014; **68**: 609-617 [PMID: 24283303 DOI: 10.1111/ijcp.12352]

19 **Kudo M**. Biomarkers and Personalized Sorafenib Therapy. *Liver Cancer* 2014; **3**: 399-404 [PMID: 26280001 DOI: 10.1159/000343870]

20 **Zhou SL**, Zhou ZJ, Hu ZQ, Huang XW, Wang Z, Chen EB, Fan J, Cao Y, Dai Z, Zhou J. Tumor-Associated Neutrophils Recruit Macrophages and T-Regulatory Cells to Promote Progression of Hepatocellular Carcinoma and Resistance to Sorafenib. *Gastroenterology* 2016; **150**: 1646-1658.e17 [PMID: 26924089 DOI: 10.1053/j.gastro.2016.02.040]

21 **Cheng AL**, Kang YK, Lin DY, Park JW, Kudo M, Qin S, Chung HC, Song X, Xu J, Poggi G, Omata M, Pitman Lowenthal S, Lanzalone S, Yang L, Lechuga MJ, Raymond E. Sunitinib versus sorafenib in advanced hepatocellular cancer: results of a randomized phase III trial. *J Clin Oncol* 2013; **31**: 4067-4075 [PMID: 24081937 DOI: 10.1200/JCO.2012.45.8372]

22 **Chen J**, Gao J. Advances in the study of molecularly targeted agents to treat hepatocellular carcinoma. *Drug Discov Ther* 2014; **8**: 154-164 [PMID: 25262594 DOI: 10.5582/ddt.2014.01031]

23 **Johnson PJ**, Qin S, Park JW, Poon RT, Raoul JL, Philip PA, Hsu CH, Hu TH, Heo J, Xu J, Lu L, Chao Y, Boucher E, Han KH, Paik SW, Robles-Aviña J, Kudo M, Yan L, Sobhonslidsuk A, Komov D, Decaens T, Tak WY, Jeng LB, Liu D, Ezzeddine R, Walters I, Cheng AL. Brivanib versus sorafenib as first-line therapy in patients with unresectable, advanced hepatocellular carcinoma: results from the randomized phase III BRISK-FL study. *J Clin Oncol* 2013; **31**: 3517-3524 [PMID: 23980084 DOI: 10.1200/JCO.2012.48.4410]

24 **Llovet JM**, Decaens T, Raoul JL, Boucher E, Kudo M, Chang C, Kang YK, Assenat E, Lim HY, Boige V, Mathurin P, Fartoux L, Lin DY, Bruix J, Poon RT, Sherman M, Blanc JF, Finn RS, Tak WY, Chao Y, Ezzeddine R, Liu D, Walters I, Park JW. Brivanib in patients with advanced hepatocellular carcinoma who were intolerant to sorafenib or for whom sorafenib failed: results from the randomized phase III BRISK-PS study. *J Clin Oncol* 2013; **31**: 3509-3516 [PMID: 23980090 DOI: 10.1200/JCO.2012.47.3009]

25 **Kudo M**, Han G, Finn RS, Poon RT, Blanc JF, Yan L, Yang J, Lu L, Tak WY, Yu X, Lee JH, Lin SM, Wu C, Tanwandee T, Shao G, Walters IB, Dela Cruz C, Poulart V, Wang JH. Brivanib as adjuvant therapy to transarterial chemoembolization in patients with hepatocellular carcinoma: A randomized phase III trial. *Hepatology* 2014; **60**: 1697-1707 [PMID: 24996197 DOI: 10.1002/hep.27290]

26 **Cainap C**, Qin S, Huang WT, Chung IJ, Pan H, Cheng Y, Kudo M, Kang YK, Chen PJ, Toh HC, Gorbunova V, Eskens FA, Qian J, McKee MD, Ricker JL, Carlson DM, El-Nowiem S. Linifanib versus Sorafenib in patients with advanced hepatocellular carcinoma: results of a randomized phase III trial. *J Clin Oncol* 2015; **33**: 172-179 [PMID: 25488963 DOI: 10.1200/JCO.2013.54.3298]

27 **Zhu AX**, Rosmorduc O, Evans TR, Ross PJ, Santoro A, Carrilho FJ, Bruix J, Qin S, Thuluvath PJ, Llovet JM, Leberre MA, Jensen M, Meinhardt G, Kang YK. SEARCH: a phase III, randomized, double-blind, placebo-controlled trial of sorafenib plus erlotinib in patients with advanced hepatocellular carcinoma. *J Clin Oncol* 2015; **33**: 559-566 [PMID: 25547503 DOI: 10.1200/JCO.2013.53.7746]

28 **Cheng AL,** Thongprasert S, Lim HY, Sukeepaisarnjaroen W, Yang TS, Wu CC, Chao Y, Chan SL, Kudo M, Ikeda M, Kang YK, Pan H, Numata K, Han G, Balsara B, Zhang Y, Rodriguez AM, Zhang Y, Wang Y, Poon RT. Randomized, Open-Label Phase 2 Study Comparing Frontline Dovitinib vs Sorafenib in Patients With Advanced Hepatocellular Carcinoma. *Hepatology* 2016; **64**:774-784 [PMID: 27082062 DOI: 10.1002/hep.28600]

29 **Zhu AX**, Park JO, Ryoo BY, Yen CJ, Poon R, Pastorelli D, Blanc JF, Chung HC, Baron AD, Pfiffer TE, Okusaka T, Kubackova K, Trojan J, Sastre J, Chau I, Chang SC, Abada PB, Yang L, Schwartz JD, Kudo M. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib (REACH): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol* 2015; **16**: 859-870 [PMID: 26095784 DOI: 10.1016/S1470-2045(15)00050-9]

30 **Abou-Alfa GK**, Puig O, Daniele B, Kudo M, Merle P, Park JW, Ross P, Peron JM, Ebert O, Chan S, Poon TP, Colombo M, Okusaka T, Ryoo BY, Minguez B, Tanaka T, Ohtomo T, Ukrainskyj S, Boisserie F, Rutman O, Chen YC, Xu C, Shochat E, Jukofsky L, Reis B, Chen G, Di Laurenzio L, Lee R, Yen CJ. Randomized phase II placebo controlled study of codrituzumab in previously treated patients with advanced hepatocellular carcinoma. *J Hepatol* 2016; **65**: 289-295 [PMID: 27085251 DOI: 10.1016/j.jhep.2016.04.004]

31 **Santoro A**, Rimassa L, Borbath I, Daniele B, Salvagni S, Van Laethem JL, Van Vlierberghe H, Trojan J, Kolligs FT, Weiss A, Miles S, Gasbarrini A, Lencioni M, Cicalese L, Sherman M, Gridelli C, Buggisch P, Gerken G, Schmid RM, Boni C, Personeni N, Hassoun Z, Abbadessa G, Schwartz B, Von Roemeling R, Lamar ME, Chen Y, Porta C. Tivantinib for second-line treatment of advanced hepatocellular carcinoma: a randomised, placebo-controlled phase 2 study. *Lancet Oncol* 2013; **14**: 55-63 [PMID: 23182627 DOI: 10.1016/S1470-2045(12)70490-4]

32 **Matter MS**, Decaens T, Andersen JB, Thorgeirsson SS. Targeting the mTOR pathway in hepatocellular carcinoma: current state and future trends. *J Hepatol* 2014; **60**: 855-865 [PMID: 24308993 DOI: 10.1016/j.jhep.2013.11.031]

33 **Menon KV**, Hakeem AR, Heaton ND. Meta-analysis: recurrence and survival following the use of sirolimus in liver transplantation for hepatocellular carcinoma. *Aliment Pharmacol Ther* 2013; **37**: 411-419 [PMID: 23278125 DOI: 10.1111/apt.12185]

34 **Cholongitas E**, Mamou C, Rodríguez-Castro KI, Burra P. Mammalian target of rapamycin inhibitors are associated with lower rates of hepatocellular carcinoma recurrence after liver transplantation: a systematic review. *Transpl Int* 2014; **27**: 1039-1049 [PMID: 24943720 DOI: 10.1111/tri.12372]

35 **Zhu AX**, Kudo M, Assenat E, Cattan S, Kang YK, Lim HY, Poon RT, Blanc JF, Vogel A, Chen CL, Dorval E, Peck-Radosavljevic M, Santoro A, Daniele B, Furuse J, Jappe A, Perraud K, Anak O, Sellami DB, Chen LT. Effect of everolimus on survival in advanced hepatocellular carcinoma after failure of sorafenib: the EVOLVE-1 randomized clinical trial. *JAMA* 2014; **312**: 57-67 [PMID: 25058218 DOI: 10.1001/jama.2014.7189]

36 **Koeberle D**, Dufour JF, Demeter G, Li Q, Ribi K, Samaras P, Saletti P, Roth AD, Horber D, Buehlmann M, Wagner AD, Montemurro M, Lakatos G, Feilchenfeldt J, Peck-Radosavljevic M, Rauch D, Tschanz B, Bodoky G. Sorafenib with or without everolimus in patients with advanced hepatocellular carcinoma (HCC): a randomized multicenter, multinational phase II trial (SAKK 77/08 and SASL 29). *Ann Oncol* 2016; **27**: 856-861 [PMID: 26884590 DOI: 10.1093/annonc/mdw054]

37 **Liu L**, Chen H, Wang M, Zhao Y, Cai G, Qi X, Han G. Combination therapy of sorafenib and TACE for unresectable HCC: a systematic review and meta-analysis. *PLoS One* 2014; **9**: e91124 [PMID: 24651044 DOI: 10.1371/journal.pone.0091124]

38 **Chao Y**, Chung YH, Han G, Yoon JH, Yang J, Wang J, Shao GL, Kim BI, Lee TY. The combination of transcatheter arterial chemoembolization and sorafenib is well tolerated and effective in Asian patients with hepatocellular carcinoma: final results of the START trial. *Int J Cancer* 2015; **136**: 1458-1467 [PMID: 25099027 DOI: 10.1002/ijc.29126]

39 **Erhardt A**, Kolligs F, Dollinger M, Schott E, Wege H, Bitzer M, Gog C, Lammert F, Schuchmann M, Walter C, Blondin D, Ohmann C, Häussinger D. TACE plus sorafenib for the treatment of hepatocellular carcinoma: results of the multicenter, phase II SOCRATES trial. *Cancer Chemother Pharmacol* 2014; **74**: 947-954 [PMID: 25173458 DOI: 10.1007/s00280-014-2568-8]

40 **Lencioni R**, Llovet JM, Han G, Tak WY, Yang J, Guglielmi A, Paik SW, Reig M, Kim do Y, Chau GY, Luca A, del Arbol LR, Leberre MA, Niu W, Nicholson K, Meinhardt G, Bruix J. Sorafenib or placebo plus TACE with doxorubicin-eluting beads for intermediate stage HCC: The SPACE trial. *J Hepatol* 2016; **64**: 1090-1098 [PMID: 26809111 DOI: 10.1016/j.jhep.2016.01.012]

41 **Bruix J**, Takayama T, Mazzaferro V, Chau GY, Yang J, Kudo M, Cai J, Poon RT, Han KH, Tak WY, Lee HC, Song T, Roayaie S, Bolondi L, Lee KS, Makuuchi M, Souza F, Berre MA, Meinhardt G, Llovet JM. Adjuvant sorafenib for hepatocellular carcinoma after resection or ablation (STORM): a phase 3, randomised, double-blind, placebo-controlled trial. *Lancet Oncol* 2015; **16**: 1344-1354 [PMID: 26361969 DOI: 10.1016/S1470-2045(15)00198-9]

42 **Abou-Alfa GK**, Johnson P, Knox JJ, Capanu M, Davidenko I, Lacava J, Leung T, Gansukh B, Saltz LB. Doxorubicin plus sorafenib vs doxorubicin alone in patients with advanced hepatocellular carcinoma: a randomized trial. *JAMA* 2010; **304**: 2154-2160 [PMID: 21081728 DOI: 10.1001/jama.2010.1672]

43 **Liu Y**, Yue H, Xu S, Wang F, Ma N, Li K, Qiao L, Wang J. First-line gemcitabine and oxaliplatin (GEMOX) plus sorafenib, followed by sorafenib as maintenance therapy, for patients with advanced hepatocellular carcinoma: a preliminary study. *Int J Clin Oncol* 2015; **20**: 952-959 [PMID: 25712158 DOI: 10.1007/s10147-015-0796-5]

44 **Hollebecque A**, Malka D, Ferté C, Ducreux M, Boige V. Systemic treatment of advanced hepatocellular carcinoma: from disillusions to new horizons. *Eur J Cancer* 2015; **51**: 327-339 [PMID: 25559615 DOI: 10.1016/j.ejca.2014.12.005]

45 **Prete SD**, Montella L, Caraglia M, Maiorino L, Cennamo G, Montesarchio V, Piai G, Febbraro A, Tarantino L, Capasso E, Palmieri G, Guarrasi R, Bianco M, Mamone R, Savastano C, Pisano A, Vincenzi B, Sabia A, D'Agostino A, Faiola V, Addeo R. Sorafenib plus octreotide is an effective and safe treatment in advanced hepatocellular carcinoma: multicenter phase II So.LAR. study. *Cancer Chemother Pharmacol* 2010; **66**: 837-844 [PMID: 20041325 DOI: 10.1007/s00280-009-1226-z]

46 **Forner A**, Llovet JM, Bruix J. Hepatocellular carcinoma. *Lancet* 2012; **379**: 1245-1255 [PMID: 22353262 DOI: 10.1016/S0140-6736(11)61347-0]

47 **Oishi N**, Yamashita T, Kaneko S. Molecular biology of liver cancer stem cells. *Liver Cancer* 2014; **3**: 71-84 [PMID: 24944998 DOI: 10.1159/000343863]

48 **Reiberger T**, Chen Y, Ramjiawan RR, Hato T, Fan C, Samuel R, Roberge S, Huang P, Lauwers GY, Zhu AX, Bardeesy N, Jain RK, Duda DG. An orthotopic mouse model of hepatocellular carcinoma

with underlying liver cirrhosis. *Nat Protoc* 2015; **10**: 1264-1274 [PMID: 26203823 DOI: 10.1038/nprot.2015.080]
49 **Llovet JM**, Villanueva A, Lachenmayer A, Finn RS. Advances in targeted therapies for hepatocellular carcinoma in the genomic era. *Nat Rev Clin Oncol* 2015; **12**: 408-424 [PMID: 26054909 DOI: 10.1038/nrclinonc.2015.103]
50 **Lee JS**, Heo J, Libbrecht L, Chu IS, Kaposi-Novak P, Calvisi DF, Mikaelyan A, Roberts LR, Demetris AJ, Sun Z, Nevens F, Roskams T, Thorgeirsson SS. A novel prognostic subtype of human hepatocellular carcinoma derived from hepatic progenitor cells. *Nat Med* 2006; **12**: 410-416 [PMID: 16532004 DOI: 10.1038/nm1377]
51 **Lachenmayer A**, Alsinet C, Savic R, Cabellos L, Toffanin S, Hoshida Y, Villanueva A, Minguez B, Newell P, Tsai HW, Barretina J, Thung S, Ward SC, Bruix J, Mazzaferro V, Schwartz M, Friedman SL, Llovet JM. Wnt-pathway activation in two molecular classes of hepatocellular carcinoma and experimental modulation by sorafenib. *Clin Cancer Res* 2012; **18**: 4997-5007 [PMID: 22811581 DOI: 10.1158/1078-0432.CCR-11-2322]
52 **Giannelli G**, Rani B, Dituri F, Cao Y, Palasciano G. Moving towards personalised therapy in patients with hepatocellular carcinoma: the role of the microenvironment. *Gut* 2014; **63**: 1668-1676 [PMID: 25053718 DOI: 10.1136/gutjnl-2014-307323]
53 **Schulze K**, Imbeaud S, Letouzé E, Alexandrov LB, Calderaro J, Rebouissou S, Couchy G, Meiller C, Shinde J, Soysouvanh F, Calatayud AL, Pinyol R, Pelletier L, Balabaud C, Laurent A, Blanc JF, Mazzaferro V, Calvo F, Villanueva A, Nault JC, Bioulac-Sage P, Stratton MR, Llovet JM, Zucman-Rossi J. Exome sequencing of hepatocellular carcinomas identifies new mutational signatures and potential therapeutic targets. *Nat Genet* 2015; **47**: 505-511 [PMID: 25822088 DOI: 10.1038/ng.3252]
54 **Nault JC**, De Reyniès A, Villanueva A, Calderaro J, Rebouissou S, Couchy G, Decaens T, Franco D, Imbeaud S, Rousseau F, Azoulay D, Saric J, Blanc JF, Balabaud C, Bioulac-Sage P, Laurent A, Laurent-Puig P, Llovet JM, Zucman-Rossi J. A hepatocellular carcinoma 5-gene score associated with survival of patients after liver resection. *Gastroenterology* 2013; **145**: 176-187 [PMID: 23567350 DOI: 10.1053/j.gastro.2013.03.051]
55 **Gillet JP**, Andersen JB, Madigan JP, Varma S, Bagni RK, Powell K, Burgan WE, Wu CP, Calcagno AM, Ambudkar SV, Thorgeirsson SS, Gottesman MM. A Gene Expression Signature Associated with Overall Survival in Patients with Hepatocellular Carcinoma Suggests a New Treatment Strategy. *Mol Pharmacol* 2016; **89**: 263-272 [PMID: 26668215 DOI: 10.1124/mol.115.101360]
56 **Zucman-Rossi J**, Villanueva A, Nault JC, Llovet JM. Genetic Landscape and Biomarkers of Hepatocellular Carcinoma. *Gastroenterology* 2015; **149**: 1226-1239.e4 [PMID: 26099527]
57 **Totoki Y**, Tatsuno K, Covington KR, Ueda H, Creighton CJ, Kato M, Tsuji S, Donehower LA, Slagle BL, Nakamura H, Yamamoto S, Shinbrot E, Hama N, Lehmkuhl M, Hosoda F, Arai Y, Walker K, Dahdouli M, Gotoh K, Nagae G, Gingras MC, Muzny DM, Ojima H, Shimada K, Midorikawa Y, Goss JA, Cotton R, Hayashi A, Shibahara J, Ishikawa S, Guiteau J, Tanaka M, Urushidate T, Ohashi S, Okada N, Doddapaneni H, Wang M, Zhu Y, Dinh H, Okusaka T, Kokudo N, Kosuge T, Takayama T, Fukayama M, Gibbs RA, Wheeler DA, Aburatani H, Shibata T. Trans-ancestry mutational landscape of hepatocellular carcinoma genomes. *Nat Genet* 2014; **46**: 1267-1273 [PMID: 25362482 DOI: 10.1038/ng.3126]
58 **Liu LJ**, Xie SX, Chen YT, Xue JL, Zhang CJ, Zhu F. Aberrant regulation of Wnt signaling in hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**: 7486-7499 [PMID: 27672271 DOI: 10.3748/wjg.v22.i33.7486]
59 **Bruix J**, Gores GJ, Mazzaferro V. Hepatocellular carcinoma: clinical frontiers and perspectives. *Gut* 2014; **63**: 844-855 [PMID: 24531850 DOI: 10.1136/gutjnl-2013-306627]
60 **Newell P**, Toffanin S, Villanueva A, Chiang DY, Minguez B, Cabellos L, Savic R, Hoshida Y, Lim KH, Melgar-Lesmes P, Yea S, Peix J, Deniz K, Fiel MI, Thung S, Alsinet C, Tovar V, Mazzaferro V, Bruix J, Roayaie S, Schwartz M, Friedman SL, Llovet JM. Ras pathway activation in hepatocellular carcinoma and anti-tumoral effect of combined sorafenib and rapamycin in vivo. *J Hepatol* 2009; **51**: 725-733 [PMID: 19665249 DOI: 10.1016/j.jhep.2009.03.028]
61 **Fu YP**, Yi Y, Cai XY, Sun J, Ni XC, He HW, Wang JX, Lu ZF, Huang JL, Cao Y, Zhou J, Fan J, Qiu SJ. Overexpression of interleukin-35 associates with hepatocellular carcinoma aggressiveness and recurrence after curative resection. *Br J Cancer* 2016; **114**: 767-776 [PMID: 27002937 DOI: 10.1038/bjc.2016.47]
62 **Abou-Alfa GK**, Capanu M, O'Reilly EM, Ma J, Chou JF, Gansukh B, Shia J, Kalin M, Katz S, Abad L, Reidy-Lagunes DL, Kelsen DP, Chen HX, Saltz LB. A phase II study of cixutumumab (IMC-A12, NSC742460) in advanced hepatocellular carcinoma. *J Hepatol* 2014; **60**: 319-324 [PMID: 24045151 DOI: 10.1016/j.jhep.2013.09.008]
63 **Xiang Q**, Chen W, Ren M, Wang J, Zhang H, Deng DY, Zhang L, Shang C, Chen Y. Cabozantinib suppresses tumor growth and metastasis in hepatocellular carcinoma by a dual blockade of VEGFR2 and MET. *Clin Cancer Res* 2014; **20**: 2959-2970 [PMID: 24700742 DOI: 10.1158/1078-0432.CCR-13-2620]
64 **Giannelli G**, Koudelkova P, Dituri F, Mikulits W. Role of epithelial to mesenchymal transition in hepatocellular carcinoma. *J Hepatol* 2016; **65**: 798-808 [PMID: 27212245 DOI: 10.1016/j.jhep.2016.05.007]
65 **Ruffell B**, Coussens LM. Macrophages and therapeutic resistance in cancer. *Cancer Cell* 2015; **27**: 462-472 [PMID: 25858805 DOI: 10.1016/j.ccell.2015.02.015]
66 **Shalapour S**, Karin M. Immunity, inflammation, and cancer: an eternal fight between good and evil. *J Clin Invest* 2015; **125**: 3347-3355 [PMID: 26325032 DOI: 10.1172/JCI80007]
67 **Broz ML**, Binnewies M, Boldajipour B, Nelson AE, Pollack JL, Erle DJ, Barczak A, Rosenblum MD, Daud A, Barber DL, Amigorena S, Van't Veer LJ, Sperling AI, Wolf DM, Krummel MF. Dissecting the tumor myeloid compartment reveals rare activating antigen-presenting cells critical for T cell immunity. *Cancer Cell* 2014; **26**: 638-652 [PMID: 25446897 DOI: 10.1016/j.ccell.2014.09.007]
68 **Grivennikov SI**, Greten FR, Karin M. Immunity, inflammation, and cancer. *Cell* 2010; **140**: 883-899 [PMID: 20303878 DOI: 10.1016/j.cell.2010.01.025]
69 **Greten TF**, Wang XW, Korangy F. Current concepts of immune based treatments for patients with HCC: from basic science to novel treatment approaches. *Gut* 2015; **64**: 842-848 [PMID: 25666193 DOI: 10.1136/gutjnl-2014-307990]
70 **Thompson AI**, Conroy KP, Henderson NC. Hepatic stellate cells: central modulators of hepatic carcinogenesis. *BMC Gastroenterol* 2015; **15**: 63 [PMID: 26013123 DOI: 10.1186/s12876-015-0291-5]
71 **Govaere O**, Komuta M, Berkers J, Spee B, Janssen C, de Luca F, Katoonizadeh A, Wouters J, van Kempen LC, Durnez A, Verslype C, De Kock J, Rogiers V, van Grunsven LA, Topal B, Pirenne J, Vankelecom H, Nevens F, van den Oord J, Pinzani M, Roskams T. Keratin 19: a key role player in the invasion of human hepatocellular carcinomas. *Gut* 2014; **63**: 674-685 [PMID: 23958557 DOI: 10.1136/gutjnl-2012-304351]
72 **Chen Y**, Ramjiawan RR, Reiberger T, Ng MR, Hato T, Huang Y, Ochiai H, Kitahara S, Unan EC, Reddy TP, Fan C, Huang P, Bardeesy N, Zhu AX, Jain RK, Duda DG. CXCR4 inhibition in tumor microenvironment facilitates anti-programmed death receptor-1 immunotherapy in sorafenib-treated hepatocellular carcinoma in mice. *Hepatology* 2015; **61**: 1591-1602 [PMID: 25529917 DOI: 10.1002/hep.27665]
73 **Scheller T**, Hellerbrand C, Moser C, Schmidt K, Kroemer A, Brunner SM, Schlitt HJ, Geissler EK, Lang SA. mTOR inhibition improves fibroblast growth factor receptor targeting in hepatocellular carcinoma. *Br J Cancer* 2015; **112**: 841-850 [PMID: 25688743 DOI: 10.1038/bjc.2014.638]
74 **Chen X**, Wang Y, Tao J, Shi Y, Gai X, Huang F, Ma Q, Zhou Z, Chen H, Zhang H, Liu Z, Sun Q, Peng H, Chen R, Jing Y, Yang H, Mao Y, Zhang H. mTORC1 Up-Regulates GP73 to Promote Proliferation and Migration of Hepatocellular Carcinoma Cells and Growth of Xenograft Tumors in Mice. *Gastroenterology* 2015;

**149**: 741-752.e14 [PMID: 25980751]
75 **Wirth TC**. Spontaneous and therapeutic immune responses in hepatocellular carcinoma: implications for current and future immunotherapies. *Expert Rev Gastroenterol Hepatol* 2014; **8**: 101-110 [PMID: 24410473 DOI: 10.1586/17474124.2014.862497]
76 **Ilkovitch D**, Lopez DM. The liver is a site for tumor-induced myeloid-derived suppressor cell accumulation and immunosuppression. *Cancer Res* 2009; **69**: 5514-5521 [PMID: 19549903 DOI: 10.1158/0008-5472.CAN-08-4625]
77 **Budhu A**, Forgues M, Ye QH, Jia HL, He P, Zanetti KA, Kammula US, Chen Y, Qin LX, Tang ZY, Wang XW. Prediction of venous metastases, recurrence, and prognosis in hepatocellular carcinoma based on a unique immune response signature of the liver microenvironment. *Cancer Cell* 2006; **10**: 99-111 [PMID: 16904609 DOI: 10.1016/j.ccr.2006.06.016]
78 **Aerts M**, Benteyn D, Van Vlierberghe H, Thielemans K, Reynaert H. Current status and perspectives of immune-based therapies for hepatocellular carcinoma. *World J Gastroenterol* 2016; **22**: 253-261 [PMID: 26755874 DOI: 10.3748/wjg.v22.i1.253]
79 **Huz JI**, Melis M, Sarpel U. Spontaneous regression of hepatocellular carcinoma is most often associated with tumour hypoxia or a systemic inflammatory response. *HPB* (Oxford) 2012; **14**: 500-505 [PMID: 22762397 DOI: 10.1111/j.1477-2574.2012.00478.x]
80 **McGranahan N**, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, Jamal-Hanjani M, Wilson GA, Birkbak NJ, Hiley CT, Watkins TB, Shafi S, Murugaesu N, Mitter R, Akarca AU, Linares J, Marafioti T, Henry JY, Van Allen EM, Miao D, Schilling B, Schadendorf D, Garraway LA, Makarov V, Rizvi NA, Snyder A, Hellmann MD, Merghoub T, Wolchok JD, Shukla SA, Wu CJ, Peggs KS, Chan TA, Hadrup SR, Quezada SA, Swanton C. Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. *Science* 2016; **351**: 1463-1469 [PMID: 26940869 DOI: 10.1126/science.aaf1490]
81 **Pardoll DM**. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer* 2012; **12**: 252-264 [PMID: 22437870 DOI: 10.1038/nrc3239]
82 **Hato T**, Goyal L, Greten TF, Duda DG, Zhu AX. Immune checkpoint blockade in hepatocellular carcinoma: current progress and future directions. *Hepatology* 2014; **60**: 1776-1782 [PMID: 24912948 DOI: 10.1002/hep.27246]

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ORIGINAL ARTICLE

Case Control Study

# Predictors for advanced fibrosis in morbidly obese non-alcoholic fatty liver patients

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## Abstract

***AIM***

To investigate predictors for fibrosis specifically in a high risk population of morbidly obese patients, including detailed evaluation of lifestyle.

***METHODS***

We conducted a cross-sectional study among morbidly obese patients attending the bariatric clinic at the Tel-Aviv Medical Center between the years 2013-2014 with body mass index (BMI) above 40 or above 35 with co-morbidity. Patients with serum hepatitis B surface antigen or anti-hepatitis C virus antibodies, genetic liver diseases, autoimmune disease or high alcohol intake ($\geqslant$ 30 g/d in men or $\geqslant$ 20 g/d in women) were excluded from the study. Liver fibrosis was estimated by transient elastography (FibroScan®), using the "XL" probe. We collected data on age and gender, education, smoking status and amount, medical history, nutrition and lifestyle habits. All these data were collected using structured and validated questionnaires. Fasting blood test were available for a subsample.

***RESULTS***

Fibroscan was performed on a total of 91 patients, of which 77 had a valid examination according to the

accepted criteria. Of those, 21% had significant fibrosis (F2) and 39% had advanced or severe fibrosis (F3 or F4). In multivariate analysis, male gender and BMI had a positive association with advanced fibrosis; the OR for fibrosis F ⩾ 2 was 7.93 (95%CI: 2.36-26.64, $P$ = 0.001) for male gender and 1.33 (1.11-1.60 kg/m$^2$, $P$ = 0.002) for BMI. The OR for fibrosis F ⩾ 3 was 2.92 (1.08-7.91, $P$ = 0.035) for male gender and 1.17 (1.03-1.33, $P$ = 0.018) for BMI. Subjects were categorized to subgroups based on the combination of male gender and BMI of 40 and above. A significant dose response association with stiffness level was noted across these categories, with the highest stiffness among men with a higher BMI ($P$ = 0.001). In addition, a significant positive correlation between pack-years cigarette smoking and liver stiffness was demonstrated among men ($r$ = 0.54, $P$ = 0.012).

***CONCLUSION***

In the morbidly obese population, a higher BMI, male gender and degree of smoking in men bears a greater risk for advanced nonalcoholic fatty liver disease.

**Key words:** Non-alcoholic fatty liver disease; Morbid obesity; Fibrosis; Fibroscan; Diet



**Core tip:** The presented results indicate that male gender and a higher body mass index (BMI) are risk factors for advanced fibrosis in morbidly obese patients. There is also a positive correlation between cigarette smoking and liver stiffness in men. Our study highlights the fact that even in the upper BMI ranges, higher BMI bears greater risk for advanced disease. Therefore, in the morbidly obese population it may seem useful to emphasize the importance of weight reduction, even within the range of obesity.

Zelber-Sagi S, Shoham D, Zvibel I, Abu-Abeid S, Shibolet O, Fishman S. Predictors for advanced fibrosis in morbidly obese non-alcoholic fatty liver patients. *World J Hepatol* 2017; 9(2): 91-98 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i2/91.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i2.91

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is the most common liver disease in the developed[1] and developing countries[2,3] with estimated prevalence of 20%-40%, and is predicted to become the leading indication for liver transplantation in the United States[4]. NAFLD is tightly associated with the metabolic syndrome and its complications. Obesity is the most important risk factor for NAFLD, which affects as much as 74% of obese individuals[5]. Two large electronic databases have demonstrated a clear association between a higher body mass index (BMI), diabetes and male gender and the risk for NAFLD[6]. Furthermore, among morbidly obese patients, who are candidates for bariatric surgeries, the prevalence is even higher and reaches 96%[7-10].

NAFLD encompasses a wide spectrum of histological and clinical manifestations, ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis[11]. It is estimated that approximately 6%-13% of patients with simple steatosis progress to steatohepatitis, of which approximately 10%-29% reach liver cirrhosis within 10 years[12]. Moreover, non-alcoholic steatohepatitis cirrhosis is a known risk factor for hepatocellular carcinoma[4]. Given the relative high prevalence of severe fibrosis (12%) in morbidly obese patients[7-10], this population is especially prone to a detrimental course. Therefore, it is of upmost importance to identify those patients with high likelihood for advanced fibrosis who may later develop cirrhosis and hepatocellular carcinoma.

Several studies have aimed to find predictors and risk factors for advanced fibrosis, although most of them did not focus on morbidly obese population. In a study of 103 NAFLD patients who underwent serial liver biopsies to follow fibrosis progression rate[13], only type-2 diabetes mellitus (T2DM), BMI and initial stage of fibrosis were associated with a higher rate of disease progression. Of note, in this study only 68% of patients were obese. Sub-analysis of 3041 subjects from the Rotterdam study[14] revealed that liver stiffness above 8 kilopascals (kPa), as measured by FibroScan, was strongly associated with steatosis and T2DM. In this cohort the average BMI was 27, thus not representing a morbidly obese population. With respect to lifestyle and other co-morbidities, smoking and obstructive sleep-apnea were demonstrated to be positively associated with liver fibrosis[15,16]. Once again, most of the patients were not morbidly obese with an average BMI of 34 and 28 respectively.

Given the scarce data regarding risk factors for advanced fibrosis in morbidly obese population, the aim of the present study was to investigate predictors for fibrosis, specifically in this high risk population, including detailed evaluation of lifestyle. To none invasively assess liver fibrosis we used transient elastography (FibroScan®), which is a validated tool to determine liver stiffness[17], and was demonstrated to be one of the most accurate tests for the non-invasive evaluation of liver fibrosis in NAFLD with a clinical prognostic value[18].

## MATERIALS AND METHODS

We conducted a cross-sectional study among morbidly obese patients attending the bariatric clinic at the Tel-Aviv Medical Center between the years 2013-2014 with BMI above 40 or above 35 plus at least one co-morbidity (*i.e.*, hypertension, type 2 diabetes, cardiovascular disease, lung disease and respiratory disorders), according to the Israeli Health Ministry indications published on 2013 (http://www.health.gov.il/hozer/mr33_2013.pdf). Patients with serum HBsAg or anti-hepatitis C virus antibodies, genetic liver diseases, autoimmune disease or high alcohol intake (⩾ 30 g/d in men or ⩾

**Table 1 Clinical characteristics of the study population**

| Variable | *n*[1] | Mean ± SD |
|---|---|---|
| Age (yr) | 77 | 42.4 ± 12.98 |
| Gender (male) % | 77 | 46.8 |
| BMI (kg/m$^2$) | 77 | 41.71 ± 4.68 |
| Glucose (mg/dL) (< 100) | 48 | 116.81 ± 35.08 |
| Total cholesterol (mg/dL) (< 200) | 42 | 191.97 ± 34.46 |
| LDL (mg/dL) | 42 | 112.80 ± 33.05 |
| HDL (mg/dL) | 40 | 44.19 ± 11.87 |
| TG (mg/dL) (< 150) | 42 | 182.38 ± 56.36 |
| ALT (U/L) (5-39) | 47 | 44.28 ± 44.49 |
| AST (U/L) (7-40) | 47 | 28.91 ± 20.11 |
| Success rate % | 77 | 84.31 ± 13.55 |
| Stiffness | 77 | 10.24 ± 6.27 |
| Sedentary time[2] (min/d) | 77 | 263.84 ± 176.56 |
| Daily activity (score[3]) | 77 | 20.56 ± 3.47 |
| Alcohol servings/week | 77 | 0.66 ± 1.67 |
| Current or past smokers % | 77 | 48.1 |

[1]Indicates on the number of people with available measure; [2]Time spent by using a computer, watching television or reading; [3]Climbing stairs, short walking and house-keeping chores, *etc*. The higher the score the lower is the activity (1-every day, 5-never). BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate transaminase; TG: Triglycerides.

20 g/d in women)[19,20] were excluded from the study. All procedures performed in this study were approved by the institutional research committee of the Tel-Aviv Medical Center and in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all participants included in the study.

### *Liver stiffness measurement*

Liver stiffness measurement (LSM) was measured using the "XL" probe. LSM were considered representative only if they had at least 10 valid acquisitions with a success rate > 60%[21]. All measurements were taken by the same operator (experience, > 10000 measurements) which was blinded to other parameters of the patients. As previously described[22], the examination was performed with the patient lying down in the dorsal decubitus position with the right arm in maximal abduction. The tip of the probe transducer was placed on the skin, between the ribs at the level of the right lobe of the liver. The results were expressed in kPa and each LSM corresponds to the median of 10 validated measurements. The cut-off values for fibrosis stage were according to the suggested best cutoffs to distinguish between fibrosis levels among NAFLD patients[23,24]: < 7.1; F0-F1: 7.1-9.5 kPa; F2: 9.6-11.5; F3: > 11.5; and F4: Significant fibrosis was defined as F $\geqslant$ 2, and advanced fibrosis was defined as F $\geqslant$ 3[25-27].

### *Demographic, health and lifestyle data*

We collected data on age and gender, education, smoking status and amount, medical history including diabetes and medical treatment, nutrition, lifestyle habits and health status. All these data were collected using a structured and uniform questionnaire completed by all participants, tailored for the current study based on validated questionnaires used in national Israeli surveys[28]. Fasting blood test were available for a subsample of 40-48 patients.

### *Statistical analysis*

Statistical analyses were performed using SPSS version 22 (SPSS Inc., Chicago, IL, United States) software. Continuous variables are presented as means ± SD. To test differences in continuous variables between the two groups the independent samples *t*-test or the Mann-Whitney *U* test were performed. Associations between nominal variables were performed with the Pearson $\chi^2$ test. The Pearson correlation was used for the evaluation of the correlation between liver stiffness and other measurements. A multivariate logistic regression analysis was performed to test the adjusted association between significant liver stiffness and potential predictors. Using a receiver operating characteristic curve, the best BMI cutoff point to predict significant fibrosis was 40, which represents grade-3 obesity. To test the combined effect of male gender and BMI of 40 and above (high BMI), we created a new variable with three categories: Lower BMI plus female gender, either male gender or high BMI, both male gender and high BMI. One way ANOVA of variance was used to test the difference in the distribution of liver stiffness between the categories with a *P* for trend test. Pearson $\chi^2$ test was used to test the association between these categories and the categories of fibrosis severity with a *P* for trend test. $P < 0.05$ was considered statistically significant for all analyses.

## RESULTS

### *Description of the study population*

A total of 201 consecutive patients were recruited, of which 91 agreed to undergo Fibroscan exam, and 77 patients had a valid examination according to the accepted criteria[21]. As depicted in Table 1, the average BMI was 41.71 ± 4.68 kg/m$^2$, with a range between 32.25 to 56.36 kg/m$^2$, 48 had a BMI of 40 and above. Alcohol consumption was very low and no patient had to be excluded due to excessive consumption. The available blood tests indicated impaired fasting glucose and mildly elevated triglycerides and ALT levels. Most patients (60%) had some level of fibrosis (F2 and above) according to the Fibroscan examination. Of note, 39% of the patients had advanced or severe fibrosis (F3 or F4), 21% had significant fibrosis (F2) and only 40% of the patients had minimal or no fibrosis (F0-F1) (Figure 1).

### *Comparison between subjects with significant or advanced fibrosis and subjects with minimal or no fibrosis*

Male gender was significantly more prevalent in subjects with fibrosis level of F2 and above or F3 and above, as compared to subjects with minimal or no fibrosis (63% *vs* 22.6%, $P < 0.001$ and 63.3% *vs* 36.2%, $P = 0.020$, respectively) (Tables 2 and 3). In addition, BMI was

**Table 2 Comparison between subjects with fibrosis degree F < 2 and subjects with significant fibrosis degree F ⩾ 2 (mean ± SD, unless otherwise stated)**

| Variable | F < 2 (*n* = 31) | F ⩾ 2 (*n* = 46) | *P* |
|---|---|---|---|
| Gender (men) % | 22.6 | 63 | < 0.001 |
| Age (yr) | 42.32 ± 13.89 | 42.96 ± 12.29 | 0.838 |
| Education (yr) | 13.13 ± 2.05 | 13.78 ± 2.9 | 0.281 |
| BMI (kg/m$^2$) | 39.82 ± 3.16 | 42.99 ± 5.11 | < 0.001 |
| Type 2 diabetes drugs (%) | 19.4 | 17.4 | 0.827 |
| All sugared soft drinks (cups/d) | 1.76 ± 2.74 | 1.38 ± 2.24 | 0.502 |
| Carbonated sugared drinks intake (cups/d) | 0.99 ± 1.52 | 0.89 ± 1.98 | 0.816 |
| Diet carbonated drinks intake (cups/d) | 0.46 ± 0.98 | 0.88 ± 1.6 | 0.196 |
| Coffee intake (cups/d) | 2.22 ± 1.87 | 1.77 ± 1.74 | 0.287 |
| Alcohol servings/week | 0.97 ± 1.80 | 0.46 ± 1.56 | 0.189 |
| Current or past smokers (%) | 48.4 | 47.8 | 0.961 |
| Fruits intake (portions/d) | 1.71 ± 1.35 | 1.74 ± 1.31 | 0.924 |
| Vegetables intake (portions/d) | 2.77 ± 2.38 | 2.64 ± 1.93 | 0.788 |
| Fried food intake (portions/d) | 1.18 ± 1.25 | 1.08 ± 0.77 | 0.690 |
| Leisure time physical activity (min/wk) | 189 ± 83.06 | 237.69 ± 437.89 | 0.733 |
| Sedentary time[1] (min/d) | 264.19 ± 171.7 | 263.61 ± 181.65 | 0.989 |
| Daily activity (score[2]) | 20.19 ± 2.83 | 20.8 ± 3.85 | 0.452 |
| Glucose (mg/dL) | 113.72 ± 42.35 | 119.42 ± 28.13 | 0.580 |
| Total cholesterol (mg/dL) | 202.68 ± 37.79 | 182.24 ± 28.6 | 0.054 |
| LDL (mg/dL) | 121.52 ± 38.77 | 104.04 ± 23.97 | 0.088 |
| HDL (mg/dL) | 46.55 ± 11.42 | 41.83 ± 12.13 | 0.213 |
| Triglycerides (mg/dL) | 170.73 ± 60.25 | 192 ± 52.3 | 0.228 |
| ALT (U/L) | 34.89 ± 37.77 | 50.66 ± 48.13 | 0.237 |
| AST (U/L) | 26.4 ± 24.47 | 30.78 ± 16.43 | 0.467 |
| GGT (U/L) | 22.52 ± 12.01 | 43.06 ± 23.53 | 0.090 |

[1]Time spent by using a computer, watching television or reading; [2]Climbing stairs, short walking and house-keeping chores, *etc*. The higher the score the lower is the activity (1-every day, 5-never). BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate transaminase; GGT: Glutamyl transpeptidase.

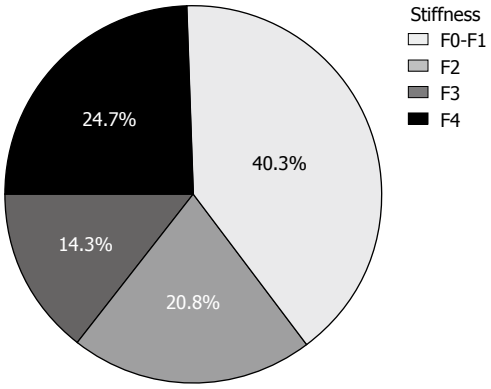


**Figure 1 Distribution of liver stiffness levels according to Fibroscan.**

significantly higher in subjects with fibrosis level of F2 and above or F3 and above as compared to subjects with minimal or no fibrosis (42.99 ± 5.11 kg/m$^2$ *vs* 39.82 ± 3.16 kg/m$^2$, $P < 0.001$ and 42.32 ± 5.3 kg/m$^2$ *vs* 40.68 ± 3.96 kg/m$^2$, $P = 0.023$, respectively) (Tables 2 and 3). No other significant differences were noted between groups in nutritional, physical activity and biochemical parameters (Tables 2 and 3). Of note, there was no correlation between ALT and fibrosis (correlation $r = 0.17$, $P = 0.253$).

### *Multivariate analysis for the prediction of significant or advanced fibrosis*

In multivariate analysis, including age, gender and BMI, the positive association between male gender (OR = 7.93, 95%CI: 2.36-26.64, $P = 0.001$) and BMI (OR = 1.33, 95%CI: 1.11-1.60, $P = 0.002$) and fibrosis F ⩾ 2 was maintained. Similarly, the positive association between male gender (OR = 2.92, 95%CI: 1.08-7.91, $P = 0.035$) and BMI (OR = 1.17, 95%CI: 1.03-1.33, $P = 0.018$) and fibrosis F ⩾ 3 was maintained (Table 4).

### *The dose response association of the combined categories of BMI of 40 and above (grade 3 obesity) and male gender with fibrosis level*

Subjects were categorized to subgroups based on the combination of gender and BMI of 40 and above: Subgroup (1) women and BMI below 40; subgroup (2) either men or BMI of 40 and above; subgroup (3) both men and BMI of 40 and above. A significant dose response association was noted across these categories for stiffness as a continuous variable ($P$ for trend = 0.001) (Figure 2A), for the rate of subjects with F ⩾ 2 ($P$ for trend < 0.001) (Figure 2B) and for the rate of subjects with F ⩾ 3 ($P$ for trend = 0.011) (Figure 2C). The highest stiffness or prevalence of significant/advanced fibrosis was among men with a higher BMI.

### *Cigarette smoking and fibrosis level*

Twenty one of the men and 16 of the women were current or past smokers. Among them, there was a significant positive correlation between cigarette smoking measured by pack-years (number of packs multiplied with the number of years of smoking) and liver stiffness ($r = 0.37$, $P = 0.025$). However, stratification by gender

**Table 3 Comparison between subjects with fibrosis degree F < 3 and subjects with advanced fibrosis degree F ⩾ 3 (mean ± SD, unless otherwise stated)**

| Variable | F < 3 (*n* = 47) | F ⩾ 3 (*n* = 30) | *P* |
|---|---|---|---|
| Gender (male) % | 36.2 | 63.3 | 0.020 |
| Age (yr) | 42.47 ± 14 | 43.07 ± 11.09 | 0.836 |
| Education (yr) | 13.19 ± 2.59 | 14.03 ± 2.55 | 0.166 |
| BMI (kg/m$^2$) | 40.68 ± 3.96 | 42.32 ± 5.3 | 0.023 |
| Type 2 diabetes drugs (%) | 17 | 20 | 0.741 |
| All sugared soft drinks (cups/d) | 1.64 ± 2.45 | 1.37 ± 2.46 | 0.635 |
| Carbonated sugared drinks intake (cups/d) | 0.9 ± 1.55 | 0.98 ± 2.16 | 0.850 |
| Diet carbonated drinks intake (cups/d) | 0.73 ± 1.44 | 0.68 ± 1.33 | 0.890 |
| Coffee intake (cups/d) | 1.96 ± 1.88 | 1.93 ± 1.69 | 0.951 |
| Alcohol (servings/wk) | 0.87 ± 1.76 | 0.33 ± 1.47 | 0.152 |
| Current or past smokers (%) | 48.9 | 46.7 | 0.846 |
| Fruits intake (portions/d) | 1.57 ± 1.25 | 1.97 ± 1.4 | 0.204 |
| Vegetables intake (portions/d) | 2.43 ± 2.11 | 3.12 ± 2.07 | 0.162 |
| Fried food intake (portions/d) | 1.12 ± 1.12 | 1.12 ± 0.75 | 0.999 |
| Leisure time physical activity (min/wk) | 155.62 ± 89.96 | 355.71 ± 585.97 | 0.403 |
| Sedentary time[1] (min/d) | 265.66 ± 178.79 | 261.00 ± 176.01 | 0.911 |
| Daily activity (score[2]) | 20.32 ± 3.49 | 20.93 ± 3.45 | 0.452 |
| Glucose (mg/dL) | 117 ± 39.93 | 116.53 ± 27.08 | 0.964 |
| Total cholesterol (mg/dL) | 197.75 ± 37.39 | 180.41 ± 25 | 0.083 |
| LDL (mg/dL) | 117.81 ± 35.94 | 101.61 ± 22.00 | 0.087 |
| HDL (mg/dL) | 44.85 ± 11.16 | 42.82 ± 13.6 | 0.619 |
| Triglycerides (mg/dL) | 176.28 ± 55.14 | 194.57 ± 58.84 | 0.328 |
| ALT (U/L) | 36.5 ± 33.26 | 55.76 ± 56.26 | 0.147 |
| AST (U/L) | 26.89 ± 21.99 | 31.89 ± 17.11 | 0.409 |
| GGT (U/L) | 29.89 ± 26.25 | 43.4 ± 16.96 | 0.241 |

[1]Time spent by using a computer, watching television or reading; [2]Climbing stairs, short walking and house-keeping chores, *etc*. The higher the score the lower is the activity (1-every day, 5-never). BMI: Body mass index; LDL: Low density lipoprotein; HDL: High density lipoprotein; ALT: Alanine aminotransferase; AST: Aspartate transaminase; GGT: Glutamyl transpeptidase.

**Table 4 Multivariate analysis for the prediction of significant or advanced fibrosis**

| Variable | Model 1: F ⩾ 2 | | Model 2: F ⩾ 3 | |
|---|---|---|---|---|
| | OR (95%CI) | *P* | OR (95%CI) | *P* |
| Age (yr) | 1.03 (0.99-1.08) | 0.153 | 1.03 (0.98-1.07) | 0.246 |
| Gender (male) | 7.93 (2.36-26.64) | 0.001 | 2.92 (1.08-7.91) | 0.035 |
| BMI (kg/m$^2$) | 1.33 (1.11-1.60) | 0.002 | 1.17 (1.03-1.33) | 0.018 |

The models are adjusted for all variables listed in the model. BMI: Body mass index.

reveled that this association existed among men ($r$ = 0.54, $P$ = 0.012) (Figure 3), but not among women ($r$ = -0.10, $P$ = 0.716).

## DISCUSSION

The presented results indicate that male gender and a higher BMI are risk factors for advanced fibrosis in morbidly obese patients. Notably, there is also a positive correlation between cigarette smoking measured by pack-years and liver stiffness in men. Our data corroborate previous publications[5,7-10], demonstrating high rate of NAFLD with significant percent of severe (F4) fibrosis in morbidly obese patients, which in our population reached approximately 25% of the patients. Given the magnitude of the disease in the morbidly obese patients, only few attempts have been performed to stratify the risk for advanced fibrosis in this unique population, mostly among patients undergoing bariatric surgery. Ong *et al*[29] have found in 212 consecutive morbidly obese patients in whom liver biopsy was taken during bariatric surgery, that waist to hip ratio and AST levels were independently associated with severe fibrosis. In our cohort, liver enzymes were not predictive of advanced fibrosis. In another study[7] which obtained liver biopsy from 181 patients undergoing bariatric surgery, only age was significantly associated with advanced disease (moderate and severe fibrosis), in contrast to our results which did not show such an association (Tables 2 and 3). In line with our results, Dixon *et al*[8] have found in 105 consecutive biopsied bariatric patients that advanced fibrosis was associated with male gender and not with the presence of T2DM. In contrast, Beymer *et al*[9] has found T2DM as the only predictor to advanced fibrosis. This discrepancy may be explained by systemic insulin resistance characterizing most of the patients in the aforementioned cohorts who have not developed overt diabetes yet. This assumption is supported by the higher C-peptide level found in patients with advance fibrosis in Dixon's cohort[8]. Interestingly, a recent cohort analyzing 134 South Indian patients have found arterial hypertension as a sole independent risk factor for fibrosis[30].

In our study we have extended the search for advanced liver fibrosis predictors toward diet elements, eating behavior and lifestyle variables, all of which have shown an association with obesity in general[31] and some of them with NAFLD in particular[32]. Whereas the

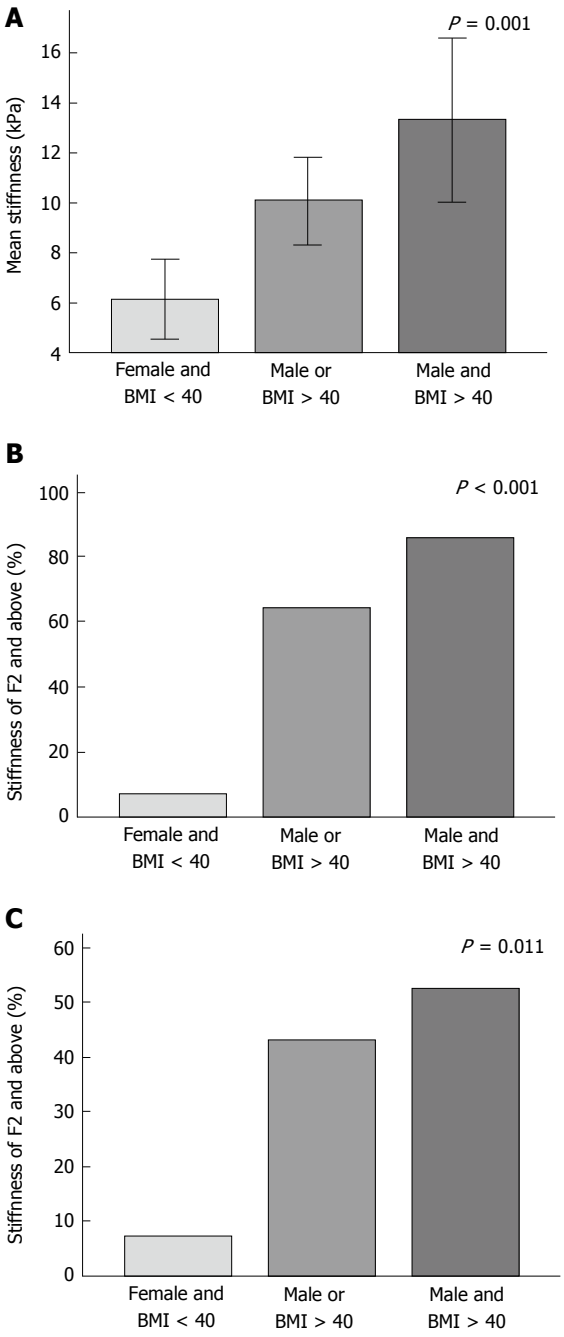


**Figure 2 Dose response relationship of the combined categories of body mass index of 40 and above (grade 3 obesity) and male gender with fibrosis level.** Women + BMI < 40; *n* = 14, men or BMI ⩾ 40; *n* = 42, men + BMI ⩾ 40; *n* = 21). BMI: Body mass index.

association between active and passive smoking and NAFLD has been already demonstrated[33], we succeeded to show a significant positive correlation between cigarette smoking measured by pack-years and liver stiffness in men (Figure 2). Our findings are corroborated by the data of the Multicenter Nonalcoholic Steatohepatitis Clinical Research Network generated from 1081 patients[16], in which multivariate analysis has demonstrated 1.6 fold increased odds for advanced fibrosis among those with a smoking history of ⩾ 10 pack-years. Among non-diabetics, a history of ⩾ 10 pack-years was associated with even a higher chance of 2.5 fold for advanced fibrosis. Multiple mechanisms may be involved in smoking injury,

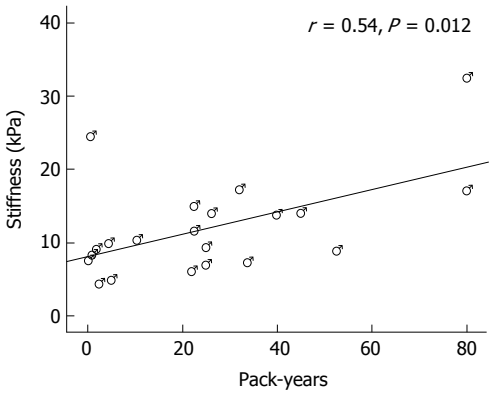


**Figure 3 Correlation between pack-years and liver stiffness among ever smoking men (*n* = 21).**

such as insulin resistance, oxidative stress and hypoxia[16]. Further studies are needed to confirm this finding among morbid obese patients and to elucidate this phenomenon.

We failed to find an association between liver stiffness and dietary parameters or eating patterns in this study. This lack of association may stem from potential sources of bias that need to be considered. First, recall and reporting bias may exist, especially on lifestyle habits and partially because of social desirability among obese population[34]. The bias was minimized by the use of structured and validated questionnaires. Also, no information about the purpose and the hypotheses of the study was provided to the participants in order to minimize the report bias. In addition, the interview was performed before receiving the results of the Fibroscan and thus the information bias is expected to be non-differential. Second, a measurement of liver stiffness is not the gold standard for the assessment of liver fibrosis. However, the Fibroscan test with the XL transducer is adjusted for patients with obesity and morbid obesity and compared with the standard transducer leads to lower rates of test failure (1.1% *vs* 16%) and an established validity[17,21]. However, among obese subjects, unreliable results may still be observed with the XL probe[35]. Nevertheless, despite this disadvantage, Fibroscan was demonstrated to be one of the most accurate tests for the non-invasive diagnosis of liver fibrosis in NAFLD[18].

In conclusion, our study highlights the fact in even in the upper BMI ranges, higher BMI bears greater risk for advanced disease. In addition, male gender may a risk factor for advanced disease in the morbidly obese population. The suggested association with the degree of smoking in men will have to be confirmed in further studies with a larger sample size.

## ACKNOWLEDGMENTS

We would like to thank Ms. Stella Levit for performing the Fibroscan examinations.

## COMMENTS

### *Background*

Given the high prevalence of severe fibrosis (12%) in morbidly obese patients,

this population is especially prone to a detrimental course of nonalcoholic fatty liver disease (NAFLD). Therefore, it is of upmost importance to identify those patients with high likelihood for advanced fibrosis who may later develop cirrhosis and hepatocellular carcinoma.

### Research frontiers

The presented results indicate that male gender and a higher body mass index (BMI) are risk factors for advanced fibrosis in morbidly obese patients. There is also a positive correlation between cigarette smoking and liver stiffness in men.

### Innovations and breakthroughs

Their study highlights the fact in even in the upper BMI ranges, higher BMI bears greater risk for advanced disease. In addition, male gender may be a risk factor for advanced disease in the morbidly obese population.

### Applications

This study may indicate that weight reduction, even a modest one within the morbid obesity range, may be helpful in prevention of advanced fibrosis in morbid obese patients. Men may need more closer monitoring of fibrosis, and if supported by larger studies, may be advised to undergo smoking cessation.

### Terminology

NAFLD encompasses a wide spectrum of histological and clinical manifestations, ranging from simple steatosis to steatohepatitis, fibrosis and cirrhosis.

### Peer-review

This is an interesting and well-organized study. The results are clearly presented.

## REFERENCES


1 **Farrell GC**. Non-alcoholic steatohepatitis: what is it, and why is it important in the Asia-Pacific region? *J Gastroenterol Hepatol* 2003; **18**: 124-138 [PMID: 12542595 DOI: 10.1046/j.1440-1746.2003.02989.x]

2 **Masarone M**, Federico A, Abenavoli L, Loguercio C, Persico M. Non alcoholic fatty liver: epidemiology and natural history. *Rev Recent Clin Trials* 2014; **9**: 126-133 [PMID: 25514916 DOI: 10.2174/1574887109666141216111143]

3 **Loomba R**, Sanyal AJ. The global NAFLD epidemic. *Nat Rev Gastroenterol Hepatol* 2013; **10**: 686-690 [PMID: 24042449 DOI: 10.1038/nrgastro.2013.171]

4 **Cohen JC**, Horton JD, Hobbs HH. Human fatty liver disease: old questions and new insights. *Science* 2011; **332**: 1519-1523 [PMID: 21700865 DOI: 10.1126/science.1204265]

5 **Angulo P**, Lindor KD. Non-alcoholic fatty liver disease. *J Gastroenterol Hepatol* 2002; **17** Suppl: S186-S190 [PMID: 12000605 DOI: 10.1046/j.1440-1746.17.s1.10.x]

6 **Loomis AK**, Kabadi S, Preiss D, Hyde C, Bonato V, St Louis M, Desai J, Gill JM, Welsh P, Waterworth D, Sattar N. Body Mass Index and Risk of Nonalcoholic Fatty Liver Disease: Two Electronic Health Record Prospective Studies. *J Clin Endocrinol Metab* 2016; **101**: 945-952 [PMID: 26672639 DOI: 10.1210/jc.2015-3444]

7 **Crespo J**, Fernández-Gil P, Hernández-Guerra M, Cayón A, Mayorga M, Domínguez-Diez A, Fernández-Escalante JC, Pons-Romero F. Are there predictive factors of severe liver fibrosis in morbidly obese patients with non-alcoholic steatohepatitis? *Obes Surg* 2001; **11**: 254-257 [PMID: 11433896 DOI: 10.1381/096089201321336548]

8 **Dixon JB**, Bhathal PS, O'Brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. *Gastroenterology* 2001; **121**: 91-100 [PMID: 11438497 DOI: 10.1053/gast.2001.25540]

9 **Beymer C**, Kowdley KV, Larson A, Edmonson P, Dellinger EP, Flum DR. Prevalence and predictors of asymptomatic liver disease in patients undergoing gastric bypass surgery. *Arch Surg* 2003; **138**: 1240-1244 [PMID: 14609874 DOI: 10.1001/archsurg.138.11.1240]

10 **Gholam PM**, Kotler DP, Flancbaum LJ. Liver pathology in morbidly obese patients undergoing Roux-en-Y gastric bypass surgery. *Obes Surg* 2002; **12**: 49-51 [PMID: 11868297 DOI: 10.1381/096089202321144577]

11 **McPherson S**, Hardy T, Henderson E, Burt AD, Day CP, Anstee QM. Evidence of NAFLD progression from steatosis to fibrosing-steatohepatitis using paired biopsies: implications for prognosis and clinical management. *J Hepatol* 2015; **62**: 1148-1155 [PMID: 25477264 DOI: 10.1016/j.jhep.2014.11.034]

12 **Hsu CS**, Kao JH. Non-alcoholic fatty liver disease: an emerging liver disease in Taiwan. *J Formos Med Assoc* 2012; **111**: 527-535 [PMID: 23089687 DOI: 10.1016/j.jfma.2012.07.002]

13 **Adams LA**, Sanderson S, Lindor KD, Angulo P. The histological course of nonalcoholic fatty liver disease: a longitudinal study of 103 patients with sequential liver biopsies. *J Hepatol* 2005; **42**: 132-138 [PMID: 15629518 DOI: 10.1016/j.jhep.2004.09.012]

14 **Koehler EM**, Plompen EP, Schouten JN, Hansen BE, Darwish Murad S, Taimr P, Leebeek FW, Hofman A, Stricker BH, Castera L, Janssen HL. Presence of diabetes mellitus and steatosis is associated with liver stiffness in a general population: The Rotterdam study. *Hepatology* 2016; **63**: 138-147 [PMID: 26171685 DOI: 10.1002/hep.27981]

15 **Agrawal S**, Duseja A, Aggarwal A, Das A, Mehta M, Dhiman RK, Chawla Y. Obstructive sleep apnea is an important predictor of hepatic fibrosis in patients with nonalcoholic fatty liver disease in a tertiary care center. *Hepatol Int* 2015; **9**: 283-291 [PMID: 25788200 DOI: 10.1007/s12072-015-9615-3]

16 **Zein CO**, Unalp A, Colvin R, Liu YC, McCullough AJ. Smoking and severity of hepatic fibrosis in nonalcoholic fatty liver disease. *J Hepatol* 2011; **54**: 753-759 [PMID: 21126792 DOI: 10.1016/j.jhep.2010.07.040]

17 **Naveau S**, Lamouri K, Pourcher G, Njiké-Nakseu M, Ferretti S, Courie R, Tranchart H, Ghinoiu M, Balian A, Prévot S, Perlemuter G, Dagher I. The diagnostic accuracy of transient elastography for the diagnosis of liver fibrosis in bariatric surgery candidates with suspected NAFLD. *Obes Surg* 2014; **24**: 1693-1701 [PMID: 24841950 DOI: 10.1007/s11695-014-1235-9]

18 **Boursier J**, Vergniol J, Guillet A, Hiriart JB, Lannes A, Le Bail B, Michalak S, Chermak F, Bertrais S, Foucher J, Oberti F, Charbonnier M, Fouchard-Hubert I, Rousselet MC, Calès P, de Lédinghen V. Diagnostic accuracy and prognostic significance of blood fibrosis tests and liver stiffness measurement by FibroScan in non-alcoholic fatty liver disease. *J Hepatol* 2016; **65**: 570-578 [PMID: 27151181 DOI: 10.1016/j.jhep.2016.04.023]

19 **Chalasani N**, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ. The diagnosis and management of non-alcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Hepatology* 2012; **55**: 2005-2023 [PMID: 22488764 DOI: 10.1002/hep.25762]

20 **Ratziu V**, Bellentani S, Cortez-Pinto H, Day C, Marchesini G. A position statement on NAFLD/NASH based on the EASL 2009 special conference. *J Hepatol* 2010; **53**: 372-384 [PMID: 20494470 DOI: 10.1016/j.jhep.2010.04.008]

21 **Myers RP**, Pomier-Layrargues G, Kirsch R, Pollett A, Duarte-Rojo A, Wong D, Beaton M, Levstik M, Crotty P, Elkashab M. Feasibility and diagnostic performance of the FibroScan XL probe for liver stiffness measurement in overweight and obese patients. *Hepatology* 2012; **55**: 199-208 [PMID: 21898479 DOI: 10.1002/hep.24624]

22 **Zelber-Sagi S**, Yeshua H, Shlomai A, Blendis L, Leshno M, Levit S, Halpern Z, Oren R. Sampling variability of transient elastography according to probe location. *Eur J Gastroenterol Hepatol* 2011; **23**: 507-514 [PMID: 21537125 DOI: 10.1097/MEG.0b013e328346c0f7]

23 **Wong VW**, Vergniol J, Wong GL, Foucher J, Chan HL, Le Bail B, Choi PC, Kowo M, Chan AW, Merrouche W, Sung JJ, de Lédinghen V. Diagnosis of fibrosis and cirrhosis using liver stiffness measurement in nonalcoholic fatty liver disease. *Hepatology* 2010; **51**: 454-462 [PMID: 20101745 DOI: 10.1002/hep.23312]

24 **Dowman JK**, Tomlinson JW, Newsome PN. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Aliment Pharmacol Ther* 2011; **33**: 525-540 [PMID: 21198708 DOI: 10.1111/j.1365-2036.2010.04556.x]

25 **Schwabl P**, Bota S, Salzl P, Mandorfer M, Payer BA, Ferlitsch A, Stift J, Wrba F, Trauner M, Peck-Radosavljevic M, Reiberger T. New reliability criteria for transient elastography increase the number of accurate measurements for screening of cirrhosis and portal hypertension. *Liver Int* 2015; **35**: 381-390 [PMID: 24953516 DOI: 10.1111/liv.12623]

26 **Foucher J**, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, Bertet J, Couzigou P, de Lédinghen V. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut* 2006; **55**: 403-408 [PMID: 16020491 DOI: 10.1136/gut.2005.069153]

27 **de Lédinghen V**, Wong VW, Vergniol J, Wong GL, Foucher J, Chu SH, Le Bail B, Choi PC, Chermak F, Yiu KK, Merrouche W, Chan HL. Diagnosis of liver fibrosis and cirrhosis using liver stiffness measurement: comparison between M and XL probe of FibroScan®. *J Hepatol* 2012; **56**: 833-839 [PMID: 22173167 DOI: 10.1016/j.jhep.2011.10.017]

28 **Nitzan Kaluski D**, Goldsmith R, Chinitz A, Ben Arie-Magled O, Mayer C, Green M. First National Health and Nutrition Survey. Israel Center for Disease Control, 2004

29 **Ong JP**, Elariny H, Collantes R, Younoszai A, Chandhoke V, Reines HD, Goodman Z, Younossi ZM. Predictors of nonalcoholic steatohepatitis and advanced fibrosis in morbidly obese patients. *Obes Surg* 2005; **15**: 310-315 [PMID: 15826462 DOI: 10.1381/096089205376820]

30 **Praveenraj P**, Gomes RM, Kumar S, Karthikeyan P, Shankar A, Parthasarathi R, Senthilnathan P, Rajapandian S, Palanivelu C. Prevalence and Predictors of Non-Alcoholic Fatty Liver Disease in Morbidly Obese South Indian Patients Undergoing Bariatric Surgery. *Obes Surg* 2015; **25**: 2078-2087 [PMID: 25835982 DOI: 10.1007/s11695-015-1655-1]

31 **Jensen MD**, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, Hu FB, Hubbard VS, Jakicic JM, Kushner RF, Loria CM, Millen BE, Nonas CA, Pi-Sunyer FX, Stevens J, Stevens VJ, Wadden TA, Wolfe BM, Yanovski SZ, Jordan HS, Kendall KA, Lux LJ, Mentor-Marcel R, Morgan LC, Trisolini MG, Wnek J, Anderson JL, Halperin JL, Albert NM, Bozkurt B, Brindis RG, Curtis LH, DeMets D, Hochman JS, Kovacs RJ, Ohman EM, Pressler SJ, Sellke FW, Shen WK, Smith SC, Tomaselli GF. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. *Circulation* 2014; **129**: S102-S138 [PMID: 24222017 DOI: 10.1161/01.cir.0000437739.71477.ee]

32 **Zelber-Sagi S**, Ratziu V, Oren R. Nutrition and physical activity in NAFLD: an overview of the epidemiological evidence. *World J Gastroenterol* 2011; **17**: 3377-3389 [PMID: 21876630 DOI: 10.3748/wjg.v17.i29.3377]

33 **Liu Y**, Dai M, Bi Y, Xu M, Xu Y, Li M, Wang T, Huang F, Xu B, Zhang J, Li X, Wang W, Ning G. Active smoking, passive smoking, and risk of nonalcoholic fatty liver disease (NAFLD): a population-based study in China. *J Epidemiol* 2013; **23**: 115-121 [PMID: 23399520]

34 **Lissner L**. Measuring food intake in studies of obesity. *Public Health Nutr* 2002; **5**: 889-892 [PMID: 12638596 DOI: 10.1079/PHN2002388]

35 **European Association for Study of Liver; Asociacion Latinoamericana para el Estudio del Higado**. EASL-ALEH Clinical Practice Guidelines: Non-invasive tests for evaluation of liver disease severity and prognosis. *J Hepatol* 2015; **63**: 237-264 [PMID: 25911335 DOI: 10.1016/j.jhep.2015.04.006]


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ORIGINAL ARTICLE

Retrospective Cohort Study

# Impact of transjugular intrahepatic porto-systemic shunt on post liver transplantation outcomes: Study based on the United Network for Organ Sharing database

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## Abstract

### *AIM*

To determine the impact of transjugular intrahepatic porto-systemic shunt (TIPS) on post liver transplantation (LT) outcomes.

### *METHODS*

Utilizing the United Network for Organ Sharing (UNOS) database, we compared patients who underwent LT from 2002 to 2013 who had underwent TIPS to those without TIPS for the management of ascites while on the LT waitlist. The impact of TIPS on 30-d mortality, length of stay (LOS), and need for re-LT were studied. For evaluation of mean differences between baseline

characteristics for patients with and without TIPS, we used unpaired *t*-tests for continuous measures and $\chi^2$ tests for categorical measures. We estimated the impact of TIPS on each of the outcome measures. Multivariate analyses were conducted on the study population to explore the effect of TIPS on 30-d mortality post-LT, need for re-LT and LOS. All covariates were included in logistic regression analysis.

***RESULTS***

We included adult patients (age ⩾ 18 years) who underwent LT from May 2002 to September 2013. Only those undergoing TIPS after listing and before liver transplant were included in the TIPS group. We excluded patients with variceal bleeding within two weeks of listing for LT and those listed for acute liver failure or hepatocellular carcinoma. Of 114770 LT in the UNOS database, 32783 (28.5%) met inclusion criteria. Of these 1366 (4.2%) had TIPS between the time of listing and LT. We found that TIPS increased the days on waitlist (408 ± 553 d) as compared to those without TIPS (183 ± 330 d), $P < 0.001$. Multivariate analysis showed that TIPS had no effect on 30-d post LT mortality (OR = 1.26; 95%CI: 0.91-1.76) and re-LT (OR = 0.61; 95%CI: 0.36-1.05). Pre-transplant hepatic encephalopathy added 3.46 d (95%CI: 2.37-4.55, $P < 0.001$), followed by 2.16 d (95%CI: 0.92-3.38, $P = 0.001$) by TIPS to LOS.

***CONCLUSION***

TIPS did increase time on waitlist for LT. More importantly, TIPS was not associated with 30-d mortality and re-LT, but it did lengthen hospital LOS after transplantation.

**Key words:** Transjugular intrahepatic porto-systemic shunt; Shunt; Liver; Transplantation; Ascites; Model for end-stage liver disease; Mortality; Transjugular



**Core tip:** The study was completed to determine the impact of transjugular intrahepatic porto-systemic shunt (TIPS) on post liver transplantation (LT) outcomes. Utilizing the United Network for Organ Sharing database, we compared patients who underwent LT from 2002 to 2013 who had undergone TIPS to those without TIPS for the management of ascites while on the LT waitlist. The impact of TIPS on 30-d mortality, length of stay (LOS), and need for re-LT were studied. TIPS was not commonly used in patients with ascites on the waitlist but did increase time on waitlist for LT. More importantly, TIPS was not associated with 30-d mortality and re-LT, but it did increase hospital LOS after transplantation.

Mumtaz K, Metwally S, Modi RM, Patel N, Tumin D, Michaels AJ, Hanje J, El-Hinnawi A, Hayes Jr D, Black SM. Impact of transjugular intrahepatic porto-systemic shunt on post liver transplantation outcomes: Study based on the United Network for Organ Sharing database. *World J Hepatol* 2017; 9(2): 99-105 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i2/99.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i2.99

## INTRODUCTION

Transjugular intrahepatic portosystemic shunts (TIPS) play an important role in the treatment of recurrent esophageal varices, bleeding gastric varices and refractory ascites. Multiple randomized trials and meta-analyses have reported the superiority of TIPS over large volume paracentesis in controlling refractory ascites with no effect on long-term survival[1-8]. One study compared 149 patients with refractory ascites allocated to TIPS and 156 to paracentesis with significant improvement in the TIPS population regarding transplant-free survival of cirrhotic patients with refractory ascites[6].

A few single-center studies have reported the impact of TIPS on liver transplant metrics[9-11]. When comparing TIPS *vs* non-TIPS patients, studies revealed comparable transfusion requirements and operative time between the two cohorts and also demonstrated operative mortality and early graft function not to be influenced by TIPS placement[9,10]. In fact, TIPS may offer an advantage in reducing ascites at the time of transplantation, which in turn may expedite the transplant time[11].

Other single center studies explored the impact of TIPS on post-transplant survival and found no significant difference[12-14]. Guerrini *et al*[15], however, found that patients who underwent TIPS pre-liver transplantation (pre-LT) had a lower risk of mortality at 1 year after LT. These potential advantages associated with the use of TIPS, however, are balanced by technical complications associated with it at time of LT[16].

Previously, most single center studies and meta-analyses evaluating the utility of TIPS in the context of LT have explored the survival at 1 year or longer[12-14]. It appears that TIPS may improve portal hypertension related issues in immediate post-transplant setting by reducing the flow of blood in the collateral circulation, thus improving portal supply to the graft[15]. Keeping in mind the mechanism by which TIPS may be helpful or disadvantageous, it's prudent to study short-term outcomes such as 30-d mortality and re-LT.

We utilized the United Network for Organ Sharing (UNOS) database to determine if TIPS had an influence on short-term outcomes of LT. We hypothesized that TIPS is not associated with an increase in 30-d post LT mortality and rate of re-LT.

## MATERIALS AND METHODS

### Data collection

A retrospective cohort study was performed on adult LT candidates who were registered in the Organ Procurement and Transplant Network (OPTN) Standard Transplant Analysis and Research Database (Reference:

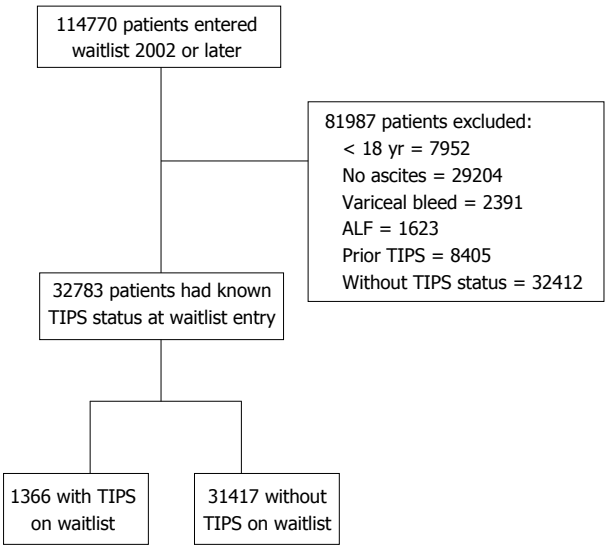


**Figure 1 Flow diagram of inclusion criteria.** TIPS: Transjugular intrahepatic porto-systemic shunt; ALF: Acute liver failure.

UNOS/Organ Procurement and Transplantation Network Standard Transplant Analysis and Research Database. Available from: https://optn.transplant.hrsa.gov/data/about-data/, Accessed September 6, 2013). The study was approved by the Nationwide Children's Hospital Institutional Review Board with a waiver of individual consent (IRB14-00716). The UNOS/OPTN liver database was queried for all patients with cirrhosis listed from May 2002 to September 2013. Each first-time LT candidate listed was tracked until death. All patients with TIPS for ascites who ultimately underwent LT were included in this sample.

The data available from the UNOS Registry included status of TIPS in patients with ascites. Other variables included in analysis were gender, age, diabetes mellitus, body mass index (BMI) at listing, cold ischemia time (CIT), waitlist hepatic encephalopathy, etiology of liver disease (alcoholic *vs* other), model for end-stage liver disease (MELD) score at listing, MELD score at LT; biochemical tests including serum creatinine, bilirubin, albumin, and international normalized ratio (INR). We studied various outcomes including mortality at 30-d, need for re-LT and hospital length of stay (LOS) during admission for LT.

### Study sample

We included adult patients (age ⩾ 18 years) who underwent LT from May 2002 to September 2013 [*i.e.*, after the inception of the MELD score and use of expanded-polytetrafluoroethylene (ePTFE) covered TIPS]. Only those undergoing TIPS after listing and before liver transplant were included in the TIPS group. We excluded patients with variceal bleeding within two weeks of listing (in order to exclude TIPS for variceal bleed) for LT and those listed for acute liver failure or hepatocellular carcinoma. After application of exclusion criteria (Figure 1) the analytic sample consisted of 32783/114770 (28.5%) patients with ascites who underwent LT and had a known TIPS status. Among these 32783 patients with ascites, 1366 patients underwent TIPS while 31417 patients did not undergo TIPS.

### Statistical analysis

All values were expressed as means ± SD for continuous measures, and counts and percentages for categorical variables. For all analyses, a *P*-value < 0.05 was considered statistically significant. For evaluation of mean differences between baseline characteristics for patients with and without TIPS, we used unpaired *t*-tests for continuous measures and $\chi^2$ tests for categorical measures. We estimated the impact of TIPS on each of the outcome measures. Multivariate analyses were conducted on the study population to explore the effect of TIPS on 30-d mortality post-LT, need for re-LT and LOS. All covariates were included in logistic regression analysis. All analyses were performed using Stata/MP, version 13.1 (College Station, TX: StataCorp LP). The statistical review of this study was performed by a biomedical statistician.

## RESULTS

### Study population

After applying the inclusion/exclusion criteria a total of 32783 patients with ascites from database were selected. A total of 1366 (4.2%) underwent TIPS for management of refractory ascites while awaiting LT (Figure 1). Those without TIPS (*n* = 31417) were selected as a control group for comparison.

Demographics such as gender, age and BMI were comparable in the two groups; albumin and CIT were also equally distributed (Table 1). Patients with TIPS on waitlist had a lower mean MELD score at time of listing (16.6 ± 6.7) as compared to those without TIPS (19.7 ± 8.9), (*P* < 0.001). Plausibly, TIPS group had a lower creatinine, bilirubin and INR. Interestingly, the MELD score at transplantation was higher in the TIPS group (23.2 ± 9.2) as compared to without TIPS group (22.6 ± 9.8) (*P* = 0.03). Plausibly, there were less patients with severe hepatic encephalopathy (HE) in the TIPS group (*n* = 68; 4.9%) as compared to without TIPS (*n* = 2218; 7%) (*P* = 0.01).

On univariate analysis (Table 2), we found that TIPS increases the days on LT waitlist (408 ± 553 d) as compared to those without TIPS (183 ± 330 d), (*P* < 0.001). TIPS group had comparable 30-d post LT mortality as compared to non-TIPS group (46; 3.51% *vs* 915; 3.05%; *P* = 0.34). There was also a comparable re-LT rate at 30 d (15; 1.1% *vs* 560; 1.78%; *P* = 0.06) and hospital LOS (17.58 *vs* 16.62; *P* = 0.12) between the two groups.

### Thirty-days post LT mortality predictors

On logistic regression, TIPS had no effect on 30-d post LT mortality (OR = 1.26; 95%CI: 0.91-1.75). However, the significant predictors of mortality at 30-d were advanced age (OR = 1.02; 95%CI: 1.01-1.03, *P* < 0.001),

**Table 1 Demographics and clinical variables categorized by transjugular intrahepatic porto-systemic shunt status**

| Variables | TIPS on waitlist ($n$ = 1366; % or mean ± SD) | Non TIPS on waitlist ($n$ = 31417; % or mean ± SD) | *P*-values |
|---|---|---|---|
| Male candidate | 943 (69) | 21374 (68) | 0.43 |
| Candidate race | | | < 0.001 |
| White | 1072 (78.4) | 23063 (73.4) | |
| Black | 75 (5.4) | 2865 (9.1) | |
| Other | 219 (16) | 5489 (17.4) | |
| Diabetes mellitus | 380 (28) | 7769 (24.8) | 0.009 |
| ALD | 311 (22.7) | 6615 (21) | 0.13 |
| Hepatic encephalopathy | | | 0.01 |
| None | 373 (27.3) | 8409 (26.7) | |
| Grade 1-2 | 925 (67.7) | 20790 (66.1) | |
| Grade 3-4 | 68 (4.9) | 2218 (7) | |
| Arterial hypertension | 68 (14.8) | 2254 (19.7) | 0.01 |
| Age | 53.5 ± 8.5 | 53.6 ± 9.3 | 0.65 |
| MELD score at listing | 16.6 ± 6.6 | 19.66 ± 8.8 | < 0.001 |
| Creatinine | 1.2 ± 0.8 | 1.4 ± 1.2 | < 0.001 |
| Bilirubin | 4.1 ± 6.3 | 6.61 ± 9.0 | < 0.001 |
| INR | 1.5 ± 0.4 | 1.7 ± 0.8 | < 0.001 |
| Albumin | 2.9 ± 0.6 | 2.9 ± 0.6 | 0.66 |
| BMI at list entry | | | |
| Continuous (kg/m$^2$) | 28.8 ± 5.6 | 28.8 ± 5.7 | 0.89 |
| Dichotomous (≥ 26 kg/m$^2$) | 905 (66.4) | 20747 (66.2) | 0.85 |
| Cold ischemia time | | | |
| Continuous (h) | 7.1 ± 3.7 | 6.9 ± 3.5 | 0.03 |
| Dichotomous (> 12 h) | 66 (5.0) | 1360 (4.5) | 0.38 |
| MELD score at transplantation | 23.1 ± 9.1 | 22.6 ± 9.7 | 0.03 |

TIPS: Transjugular intrahepatic porto-systemic shunt; ALD: Alcoholic liver disease; MELD: Model for end-stage liver disease; INR: International normalized ratio; BMI: Body mass index.

**Table 2 Comparison of various outcomes on univariate analysis on waitlist and post liver transplant**

| | TIPS on waitlist ($n$ = 1366) % or mean ± SD | No TIPS on waitlist ($n$ = 31417) % or mean ± SD | *P*-values |
|---|---|---|---|
| Days on LT waitlist | 408 ± 552.6 | 183 ± 330.5 | < 0.001 |
| Mortality within 30 d | 46 (3.5) | 915 (3.0) | 0.344 |
| Length of hospital stay | 17.58 ± 22.4 | 16.62 ± 22.1 | 0.118 |
| Re-LT at 30 d | 15 (1.1) | 560 (1.8) | 0.06 |

TIPS: Transjugular intrahepatic porto-systemic shunt; LT: Liver transplantation.

low serum albumin (OR = 0.88; 95%CI: 0.79-0.98, $P$ = 0.029), and increasing CIT (OR = 1.04; 95%CI: 1.02-1.05, $P$ < 0.001). Another predictor of 30-d mortality was bilirubin (OR = 1.014; 95%CI: 1.004-1.024; $P$ = 0.008 (Table 3).

### *TIPS and re-LT at 30 d*

On logistic regression, TIPS was not associated with re-LT at 30 d (OR = 0.61; 95%CI: 0.36-1.05). Predictors of re-LT at 30 d included advanced age (OR = 0.97; 95%CI: 0.96-0.98; $P$ < 0.001), creatinine (OR = 0.87; 95%CI: 0.77-0.99; $P$ = 0.032) and CIT (OR = 1.05; 95%CI: 1.03-1.07; $P$ < 0.001) (Table 4).

**Table 3 Multivariable logistic regression analysis to assess the impact of transjugular intrahepatic porto-systemic shunt on 30-d mortality after liver transplant**

| Variable | OR (95%CI) | *P*-values |
|---|---|---|
| TIPS | 1.26 (0.90-1.75) | 0.17 |
| Male candidate | 0.83 (0.71-0.95) | 0.01 |
| Candidate race | | |
| White | Ref. | |
| Black | 1.08 (0.85-1.37) | 0.54 |
| Other | 1.08 (0.90-1.29) | 0.40 |
| Diabetes mellitus | 1.12 (0.95-1.31) | 0.17 |
| ALD | 0.89 (0.74-1.07) | 0.22 |
| Hepatic encephalopathy | | |
| None | Ref. | |
| Grade 1-2 | 0.86 (0.73-1.01) | 0.06 |
| Grade 3-4 | 1.12 (0.85-1.47) | 0.41 |
| Age | 1.02 (1.01-1.03) | < 0.001 |
| MELD score | 1.02 (1.00-1.04) | 0.05 |
| Creatinine | 1.03 (0.97-1.10) | 0.33 |
| Bilirubin | 1.01 (1.00-1.02) | 0.008 |
| INR | 0.97 (0.86-1.09) | 0.59 |
| Albumin | 0.88 (0.79-0.98) | 0.03 |
| BMI | 1.00 (0.99-1.02) | 0.86 |
| Cold ischemia time | 1.04 (1.02-1.05) | < 0.001 |

TIPS: Transjugular intrahepatic porto-systemic shunt; ALD: Alcoholic liver disease; MELD: Model for end-stage liver disease; INR: International normalized ratio; BMI: Body mass index.

### *TIPS and LOS*

Advanced HE (grade 3-4) on waitlist contributed most days to LOS (β = 3.46; 95%CI: 2.37-4.55, $P$ < 0.001), followed by TIPS (β = 2.16; 95%CI: 0.92-3.38, $P$ = 0.001). Other factors that contributed to LOS were black race (β = -1.58; 95%CI: -2.46 to -0.69, $P$ < 0.001) and advanced age (β = 0.09; 95%CI: 0.06-0.11, $P$ < 0.001). High MELD score, INR, albumin, BMI and CIT also significantly contributed to LOS after LT (Table 5).

## DISCUSSION

The most important finding of the current study is that TIPS for the treatment of ascites in the MELD era for LT is not associated with heightened 30-d mortality or the need for re-transplantation. However, hospital LOS was increased in patients with TIPS which may point to post-operative morbidity. TIPS was found to increase time on waitlist in patients with ascites.

Our findings of safety of TIPS in terms of short term mortality and need for re-LT is in line with multiple other studies, as these also did not find any difference in operative time, transfusion and LOS[9,12,14,17]. One of the largest retrospective studies of 207 patients explored the impact of TIPS on post-transplant survival and graft loss and found no significant difference[12]. In fact, a recent study went even further to find lower risk of mortality in TIPS group at 1 year after LT[15].

Our study holds many advantages to prior studies including the use of a national database and large sample size. Furthermore, our study had increased homogeneity as it was limited to those undergoing TIPS for refractory

**Table 4 Multivariable logistic regression analysis to assess the impact of transjugular intrahepatic porto-systemic shunt on retransplantation**

| Variable | OR (95%CI) | *P*-values |
|---|---|---|
| TIPS | 0.61 (0.36-1.05) | 0.07 |
| Male candidate | 1.02 (0.85-1.24) | 0.81 |
| Candidate race | | |
| White | Ref. | |
| Black | 1.22 (0.91-1.64) | 0.18 |
| Other | 1.05 (0.83-1.32) | 0.69 |
| Diabetes mellitus | 0.98 (0.78-1.21) | 0.83 |
| ALD | 0.98 (0.78-1.24) | 0.90 |
| Hepatic encephalopathy | | |
| None | Ref. | |
| Grade 1-2 | 0.92 (0.76-1.13) | 0.44 |
| Grade 3-4 | 1.02 (0.69-1.51) | 0.91 |
| Age | 0.97 (0.96-0.98) | < 0.001 |
| MELD score | 0.99 (0.97-1.02) | 0.51 |
| Creatinine | 0.87 (0.77-0.99) | 0.03 |
| Bilirubin | 0.99 (0.98-1.02) | 0.54 |
| INR | 1.01 (0.86-1.18) | 0.9 |
| Albumin | 1.03 (0.89-1.19) | 0.65 |
| BMI | 1.005 (0.98-1.02) | 0.54 |
| Cold ischemia time | 1.05 (1.03-1.07) | < 0.001 |

TIPS: Transjugular intrahepatic porto-systemic shunt; ALD: Alcoholic liver disease; MELD: Model for end-stage liver disease; INR: International normalized ratio; BMI: Body mass index.

**Table 5 Ordinary least squares regression to assess the impact of transjugular intrahepatic porto-systemic shunt on length of hospital stay after liver transplant**

| Variable | β (95%CI) | *P*-values |
|---|---|---|
| TIPS | 2.16 (0.92-3.38) | 0.001 |
| Male candidate | -1.99 (-2.52-1.46) | < 0.001 |
| Candidate race | | |
| White | Ref. | |
| Black | -1.58 (-2.46-0.69) | < 0.001 |
| Other | 0.11 (-0.53-0.77) | 0.72 |
| Diabetes mellitus | 0.52 (-0.05-1.10) | 0.07 |
| ALD | 0.17 (-0.44-0.79) | 0.57 |
| Hepatic encephalopathy | | |
| None | Ref. | |
| Grade 1-2 | -0.10 (-0.66-0.46) | 0.73 |
| Grade 3-4 | 3.46 (2.37-4.55) | < 0.001 |
| Age | 0.09 (0.06-0.11) | < 0.001 |
| MELD score | 0.37 (0.31-0.44) | < 0.001 |
| Creatinine | 0.05 (-0.21-0.31) | 0.71 |
| Bilirubin | 0.03 (-0.008-0.08) | 0.1 |
| INR | -1.06 (-1.50-0.61) | < 0.001 |
| Albumin | -0.63 (-1.01-0.24) | 0.001 |
| BMI | -0.05 (-0.100-0.01) | 0.01 |
| Cold ischemia time | 0.36 (0.29-0.43) | < 0.001 |
| Constant | 7.83 (5.38-10.27) | < 0.001 |

TIPS: Transjugular intrahepatic porto-systemic shunt; ALD: Alcoholic liver disease; MELD: Model for end-stage liver disease; INR: International normalized ratio; BMI: Body mass index.

ascites and was limited to a study period in the post-MELD era and with more homogeneity in shunt type (*i.e.*, ePTFE covered).

Existing literature on LOS is variable with certain studies describing intra-operative complications in patients who have undergone TIPS[16]. On the other hand, additional studies have not found TIPS to affect the LOS in post LT setting[14,18]. It has been shown in our study that advanced HE (grade 3-4) on waitlist cirrhotics contributes the most to LOS adding 3.5 d followed by TIPS insertion which prolonged stay by an average of 2.16 d. This finding is remarkable given encephalopathy is a known complication of TIPS[7,8]. We can hypothesize that TIPS insertion may contribute to ongoing encephalopathy and therefore increase length of hospital stay.

Among other predictors of increased LOS were advanced age, high MELD score and CIT. All these factors are recognized predictors of increased LOS and reported in literature[19,20]. Of note, the TIPS group in our study began with a lower MELD score at the time of listing but had higher MELD scores at the time of LT. This finding suggests patients undergoing TIPS were able to survive longer on the wait list with continued progression of liver disease at the time of LT. More advanced disease among TIPS patients would explain increased LOS post-LT.

We found that increased time on the waitlist in the TIPS group was consistent with findings from single center studies[18]. Several randomized controlled trials and a meta-analysis of individual patient data also found TIPS superior to repeated paracentesis in increasing time on waitlist and therefore transplant free survival[2,5,6]. The increased time on LT wait list may be explained by decreased portal hypertension produced by the TIPS and mortality associated with complications of portal hypertension. One study found that TIPS lowered mortality rate while on waitlist and decreased need for transplantation[21]. Hence, it is possible TIPS can be utilized as a bridge to transplant and even to improve waitlist survival of listed patients.

Our findings demonstrate the challenge of using TIPS in patients who need to undergo LT. Following TIPS placement, this patient population has an increased wait time for LT, yet suffers comparable immediate post procedural mortality as their non-TIPS counterparts. This longer time on the waitlist may allow for other decompensated non-TIPS patients with higher MELD scores to undergo LT first. Thus, it appears that a disparity is created where the patient population requiring more advanced treatment of ascites (*i.e.*, TIPS) have increased time on waitlist through improvement of the MELD score and therefore experience a delay in transplantation. Based on our findings, we propose an idea to potentially provide special circumstances to patients requiring TIPS on the waitlist for LT as their outcomes after transplantation are not influenced by placement of the shunt. An example of special circumstances could be exceptional MELD points to avoid further delay in LT.

Limitations of our study are mainly related to availability of variables in the UNOS database. This database only lists TIPS status at the time of LT recipient registration and does not provide information on control and recurrence of tense ascites, post TIPS encephalopathy, intra- and post-LT information such as operative time and blood

product transfusion requirements. Waitlist mortality, intensive care unit stay, and complications of TIPS placement such as TIPS migration and endovascular stenting were also not available to us. Due to these database limitations we cannot directly measure the number of patients on waitlist undergoing TIPS or the waitlist mortality. As a result, days on waitlist had to be used as a surrogate measure for waitlist mortality and transplant free survival.

In conclusion, we found that TIPS had no effect on the 30-d mortality after LT and the need for re-LT. TIPS increased time on LT waitlist while also increasing length of hospital stay post-LT. It was found that TIPS is not a commonly used intervention for the management of ascites in patients on the waitlist for LT. With TIPS not influencing 30-d mortality and need for re-LT, it appears that more patients may benefit from its use. However, one of the downsides of using TIPS could be a potential delay in LT due to improvement in MELD score. These important factors must be considered and discussed with patients before pursuing TIPS procedure.

## COMMENTS

### Background

Prior studies exploring the role of transjugular intrahepatic porto-systemic shunt (TIPS) with regards to cirrhotic patients being evaluated for liver transplant were limited by small sample sizes, single center studies, and heterogeneous study groups that resulted in poor generalizability. Further, these studies were completed prior to advent of expanded-polytetrafluoroethylene covered stents and introduction of model for end-stage liver disease allocation system. Here the authors would like to utilize the United Network for Organ Sharing (UNOS) database to address the effect of TIPS on waitlist times, liver transplantation (LT) morbidity and mortality, and hospital length of stay.

### Research frontiers

Since its inception, TIPS has been touted as a potential bridge to LT by possibly improving transplant free survival. Studies such as that performed by Berry *et al* have recently used the UNOS data base to confirm TIPS' role in improving transplant free survival and support the notion that TIPS is a bridge to LT.

### Innovations and breakthroughs

To our knowledge no study has utilized the UNOS database in exploring post-LT outcomes in the TIPS population. The study confirmed findings of prior single center studies that TIPS does not significantly affect post-LT outcomes. Of note, their large study group size adds power and improves generalizability of these findings. Short term outcomes were their primary focus given the concern for potential for intra-operative LT complications in patients who have undergone TIPS.

### Applications

The authors' findings support prior single center and more recent meta-analyses and database reviews in confirming increased transplant free survival while not affecting post-LT outcomes. The study supports the notion that TIPS can be utilized as a bridge to transplantation. Prospective studies will be necessary to further elucidate the influence of TIPS on LT outcomes and the potential detriments resulting from prolonged waitlist times.

### Terminology

CIT: Cold ischemia time; ePTFE: Expanded-polytetrafluoroethylene; HE: Hepatic encephalopathy; LOS: Length of hospital stay; LT: Liver transplantation; LVP: Large volume paracentesis; MELD: Model for end-stage liver disease; TIPS: Transjugular intrahepatic porto-systemic shunt; UNOS: United Network for Organ Sharing.

### Peer-review

The paper is well written and the design is good.

## REFERENCES


1 **Lebrec D**, Giuily N, Hadengue A, Vilgrain V, Moreau R, Poynard T, Gadano A, Lassen C, Benhamou JP, Erlinger S. Transjugular intrahepatic portosystemic shunts: comparison with paracentesis in patients with cirrhosis and refractory ascites: a randomized trial. French Group of Clinicians and a Group of Biologists. *J Hepatol* 1996; **25**: 135-144 [PMID: 8878773]

2 **Rössle M**, Ochs A, Gülberg V, Siegerstetter V, Holl J, Deibert P, Olschewski M, Reiser M, Gerbes AL. A comparison of paracentesis and transjugular intrahepatic portosystemic shunting in patients with ascites. *N Engl J Med* 2000; **342**: 1701-1707 [PMID: 10841872 DOI: 10.1056/nejm200006083422303]

3 **Ginès P**, Uriz J, Calahorra B, Garcia-Tsao G, Kamath PS, Del Arbol LR, Planas R, Bosch J, Arroyo V, Rodés J. Transjugular intrahepatic portosystemic shunting versus paracentesis plus albumin for refractory ascites in cirrhosis. *Gastroenterology* 2002; **123**: 1839-1847 [PMID: 12454841 DOI: 10.1053/gast.2002.37073]

4 **Sanyal AJ**, Genning C, Reddy KR, Wong F, Kowdley KV, Benner K, McCashland T. The North American Study for the Treatment of Refractory Ascites. *Gastroenterology* 2003; **124**: 634-641 [PMID: 12612902 DOI: 10.1053/gast.2003.50088]

5 **Salerno F**, Merli M, Riggio O, Cazzaniga M, Valeriano V, Pozzi M, Nicolini A, Salvatori F. Randomized controlled study of TIPS versus paracentesis plus albumin in cirrhosis with severe ascites. *Hepatology* 2004; **40**: 629-635 [PMID: 15349901 DOI: 10.1002/hep.20364]

6 **Salerno F**, Cammà C, Enea M, Rössle M, Wong F. Transjugular intrahepatic portosystemic shunt for refractory ascites: a meta-analysis of individual patient data. *Gastroenterology* 2007; **133**: 825-834 [PMID: 17678653 DOI: 10.1053/j.gastro.2007.06.020]

7 **Rosado B**, Kamath PS. Transjugular intrahepatic portosystemic shunts: an update. *Liver Transpl* 2003; **9**: 207-217 [PMID: 12619016 DOI: 10.1053/jlts.2003.50045]

8 **Patidar KR**, Sydnor M, Sanyal AJ. Transjugular intrahepatic portosystemic shunt. *Clin Liver Dis* 2014; **18**: 853-876 [PMID: 25438287 DOI: 10.1016/j.cld.2014.07.006]

9 **Barbier L**, Hardwigsen J, Borentain P, Biance N, Daghfous A, Louis G, Botta-Fridlund D, Le Treut YP. Impact of transjugular intrahepatic portosystemic shunting on liver transplantation: 12-year single-center experience. *Clin Res Hepatol Gastroenterol* 2014; **38**: 155-163 [PMID: 24183545 DOI: 10.1016/j.clinre.2013.09.003]

10 **Gimson AE**. Transjugular intrahepatic portosystemic stent-shunt and liver transplantation--how safe is the bridge? *Eur J Gastroenterol Hepatol* 2002; **14**: 821-822 [PMID: 12172399]

11 **Somberg KA**, Lombardero MS, Lawlor SM, Ascher NL, Lake JR, Wiesner RH, Zetterman RK. A controlled analysis of the transjugular intrahepatic portosystemic shunt in liver transplant recipients. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Liver Transplantation Database. *Transplantation* 1997; **63**: 1074-1079 [PMID: 9133467]

12 **Levi Sandri GB**, Lai Q, Lucatelli P, Melandro F, Guglielmo N, Mennini G, Berloco PB, Fanelli F, Salvatori FM, Rossi M. Transjugular intrahepatic portosystemic shunt for a wait list patient is not a contraindication for orthotopic liver transplant outcomes. *Exp Clin Transplant* 2013; **11**: 426-428 [PMID: 23745783 DOI: 10.6002/ect.2013.0013]

13 **Moreno A**, Meneu JC, Moreno E, Fraile M, García I, Loinaz C, Abradelo M, Jiménez C, Gomez R, García-Sesma A, Manrique A, Gimeno A. Liver transplantation and transjugular intrahepatic portosystemic shunt. *Transplant Proc* 2003; **35**: 1869-1870 [PMID: 12962829]

14 **Menegaux F**, Baker E, Keeffe EB, Monge H, Egawa H, Esquivel CO. Impact of transjugular intrahepatic portosystemic shunt on orthotopic liver transplantation. *World J Surg* 1994; **18**: 866-870;

discussion 870-871 [PMID: 7846910]
15 **Guerrini GP**, Pleguezuelo M, Maimone S, Calvaruso V, Xirouchakis E, Patch D, Rolando N, Davidson B, Rolles K, Burroughs A. Impact of tips preliver transplantation for the outcome posttransplantation. *Am J Transplant* 2009; **9**: 192-200 [PMID: 19067664 DOI: 10.1111/j.1600-6143.2008.02472.x]
16 **Millis JM**, Martin P, Gomes A, Shaked A, Colquhoun SD, Jurim O, Goldstein L, Busuttil RW. Transjugular intrahepatic portosystemic shunts: impact on liver transplantation. *Liver Transpl Surg* 1995; **1**: 229-233 [PMID: 9346571]
17 **Irausquin H**. The value of clinical chemistry data in animal screening studies for safety evaluation. *Toxicol Pathol* 1992; **20**: 515-517; discussion 515-517 [PMID: 1296282]
18 **Freeman RB**, FitzMaurice SE, Greenfield AE, Halin N, Haug CE, Rohrer RJ. Is the transjugular intrahepatic portocaval shunt procedure beneficial for liver transplant recipients? *Transplantation* 1994; **58**: 297-300 [PMID: 8053050]
19 **Foxton MR**, Al-Freah MA, Portal AJ, Sizer E, Bernal W, Auzinger G, Rela M, Wendon JA, Heaton ND, O'Grady JG, Heneghan MA. Increased model for end-stage liver disease score at the time of liver transplant results in prolonged hospitalization and overall intensive care unit costs. *Liver Transpl* 2010; **16**: 668-677 [PMID: 20440776 DOI: 10.1002/lt.22027]
20 **Buchanan P**, Dzebisashvili N, Lentine KL, Axelrod DA, Schnitzler MA, Salvalaggio PR. Liver transplantation cost in the model for end-stage liver disease era: looking beyond the transplant admission. *Liver Transpl* 2009; **15**: 1270-1277 [PMID: 19790155 DOI: 10.1002/lt.21802]
21 **Berry K**, Lerrigo R, Liou IW, Ioannou GN. Association Between Transjugular Intrahepatic Portosystemic Shunt and Survival in Patients With Cirrhosis. *Clin Gastroenterol Hepatol* 2016; **14**: 118-123 [PMID: 26192147 DOI: 10.1016/j.cgh.2015.06.042]

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ORIGINAL ARTICLE

Retrospective Study

# Vasopressin use in critically ill cirrhosis patients with catecholamine-resistant septic shock: The CVICU cohort

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Author contributions: Myc LA and Stine JG should be considered co-first authors of this manuscript as both made equally important contributions to the final manuscript; Myc LA and Argo CK generated the research concept and hypothesis; Myc LA, Stine JG and Argo CK designed research; Myc LA and Chakrapani R extracted data; Stine JG and Myc LA analyzed data; Myc LA, Stine JG, Chakrapani R, Kadl A and Argo CK composed the manuscript.

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## Abstract

***AIM***

To examine patient-centered outcomes with vasopressin (AVP) use in patients with cirrhosis with catecholamine-refractory septic shock.

***METHODS***

We conducted a single center, retrospective cohort study enrolling adult patients with cirrhosis treated for catecholamine-resistant septic shock in the intensive care unit (ICU) from March 2011 through December 2013. Other etiologies of shock were excluded. Multivariable regression models were constructed for seven and 28-d mortality comparing AVP as a second-line therapy to a group of all other vasoactive agents.

***RESULTS***

Forty-five consecutive patients with cirrhosis were treated for catecholamine-resistant septic shock; 21 received AVP while the remaining 24 received another agent [phenylephrine (10), dopamine (6), norepinephrine (4), dobutamine (2), milrinone (2)]. In general,

no significant differences in baseline demographics, etiology of cirrhosis, laboratory values, vital signs or ICU mortality/severity of illness scores were observed with the exception of higher MELD scores in the AVP group (32.4, 95%CI: 28.6-36.2 *vs* 27.1, 95%CI: 23.6-30.6, $P = 0.041$). No statistically significant difference was observed in unadjusted 7-d (52.4% AVP *vs* 58.3% and $P = 0.408$) or 28-d mortality (81.0% AVP *vs* 87.5% non-AVP, $P = 0.371$). Corticosteroid administration was associated with lower 28-d mortality (HR = 0.37, 95%CI: 0.16-0.86, $P = 0.021$) independent of AVP use.

***CONCLUSION***

AVP is similar in terms of patient centered outcomes of seven and 28-d mortality, in comparison to all other vasopressors when used as a second line vasoactive agent in catecholamine resistant septic shock. Large-scale prospective study would help to refine current consensus standards and provide further support to our findings.

**Key words:** Portal hypertension; Vasopressor; Liver; Intensive care unit; Hepatology



**Core tip:** Although the management of septic shock has evolved dramatically in recent decades, data regarding optimal vasopressor therapy in critically-ill patients with cirrhosis is less robust and is based largely on consensus expert opinion. We found no difference in 7-d or 28-d mortality with vasopressin use when compared to all other vasoactive agents as a second line agent in catecholamine-resistant septic shock. Further large-scale studies are needed to refine current consensus standards and provide further support to our findings.

Myc LA, Stine JG, Chakrapani R, Kadl A, Argo CK. Vasopressin use in critically ill cirrhosis patients with catecholamine-resistant septic shock: The CVICU cohort. *World J Hepatol* 2017; 9(2): 106-113 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i2/106.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i2.106

## INTRODUCTION

The management of septic shock has evolved since the inception of the Surviving Sepsis Campaign and the adoption of early goal-directed therapy, with short-term mortality rates improving markedly over the past decade[1]. Improved outcomes appear to have extended to special populations as well, including patients with cirrhosis of the liver, a population in which sepsis has traditionally been characterized by extremely high mortality rates of nearly 100% in some studies, well above those of the general population which approximate 40% at 28-d[2-4]. Concurrent with the development of bundled care protocols, the incorporation of arginine vasopressin (AVP) into the management of septic shock has generated significant clinical and research interest. Based on reports of inappropriately low levels of circulating AVP coupled with apparent AVP-hypersensitivity in patients with cirrhosis and septic shock, exogenous AVP was seen as potentially restorative of both vascular tone and catecholamine-sensitivity in septic states[5-7].

Current recommendations for AVP use in managing septic shock largely derive from the published results of the Vasopressin and Septic Shock Trial (VASST) which reported no significant difference in 28-d mortality in patients with septic shock treated with vasopressin *vs* norepinephrine[4]. Nevertheless, the authors did report improved 28-d mortality in a pre-specified sub-group of patients with less severe septic shock as well as decreased norepinephrine requirements in patients receiving AVP, leading to the adoption of exogenous AVP use as an ungraded recommendation into the Surviving Sepsis Guidelines.

Appreciating these general recommendations, it remains unclear what role exogenous AVP may serve in patients with cirrhosis given the unique characteristics of septic shock in this population. Although low levels of AVP coinciding with AVP-vasosensitivity have been reported in patients with cirrhosis, the distinctive features of septic shock in this population including hyperdynamic circulation, relative adrenal insufficiency, blood volume sequestration in the splanchnic venous plexus, and hypothermia together with underlying thrombocytopenia and varying degrees of hepatic dysfunction introduce ambiguity as to whether the generic Surviving Sepsis guidelines ought to be applied to patients with cirrhosis[2,3,8-10]. Data regarding AVP and AVP analogue use in patients with cirrhosis and septic shock are sparse.

Recently published guidelines addressing management of critically ill patients with cirrhosis do incorporate AVP use for treatment of persistent hypotension, however this recommendation relies largely on studies of terlipressin in non-cirrhotic populations[11]. In this respect, it should be noted that only 11.3% of the patients enrolled in the VASST study had any liver disease at all. While AVP may have salient effects in this population relating to improved hemodynamics, mobilization of large splanchnic blood volume, norepinephrine sparing, and improved catecholamine resistance, potential adverse effects specific to the cirrhotic state cannot be excluded and may include acute-on-chronic liver failure, worsening thrombocytopenia and hyponatremia, and decreased cardiac output[4,12-17]. Decreased cardiac output may be particularly significant in this population, which may be more dependent on oxygen delivery for oxygen consumption[18]. Together, such hepatic, renal and hematologic effects of AVP may be disproportionately detrimental in a vulnerable cirrhotic population often characterized by baseline hyponatremia and thrombocytopenia complicating underlying hepatic dysfunction.

In this single center retrospective cohort study,

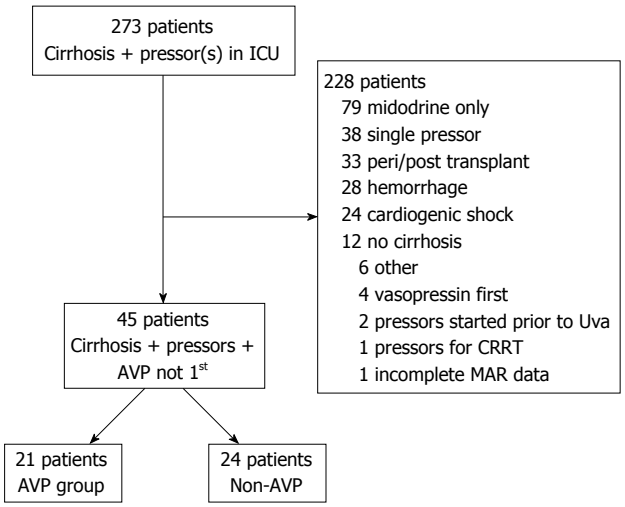


**Figure 1 Study enrollment.** CRRT: Crrtcontinuous renal replacement therapycrrt; ICU: Intensive care unit; AVP: Arginine vasopressin.

we aimed to characterize 7-d and 28-d mortality outcomes of AVP use in patients with cirrhosis and catecholamine-refractory septic shock (CRSS). Secondarily, we aimed to investigate the effect of AVP on 24-h changes in important laboratory parameters including aminotransferases, total bilirubin and platelet concentrations as well as heart rate. We hypothesized that use of AVP as a second vasopressor in cirrhosis patients with catecholamine-resistant septic shock would be associated with increased mortality when compared with cirrhosis patients receiving an alternate adjunct vasoactive agent (*e.g.,* norepinephrine, phenylephrine, dopamine).

## MATERIALS AND METHODS

### *Cohort selection*

All adult patients with cirrhosis treated for CRSS shock requiring medical intensive care unit (ICU) care between March 4, 2011 and December 31, 2013 were identified through the University of Virginia Clinical Data Repository using billing and administrative codes in conjunction with data derived from medication administration reports. Cirrhosis of the liver was confirmed by direct histological examination of liver biopsy or by biochemical and imaging findings suggesting advanced liver disease with portal hypertension. Catecholamine-resistant septic shock was defined as a clinical requirement for $\geqslant$ 2 vasopressors (the first of which had to be a catecholaminergic agent) for hypotension attributable to an infectious origin on the basis of either culture data or clear clinical suspicion. Patients with cirrhosis meeting this definition of CRSS were included in our analysis. Patients with other etiologies of shock (*e.g.,* hemorrhagic, obstructive, *etc.*) were excluded, as were patients who received AVP as the first vasopressor agent, patients who received vasopressors in the peri-transplant setting or for purposes of tolerating renal replacement therapy, or patients who were initiated on vasopressor therapy at an undetermined time prior to interhospital transfer to our facility (Figure 1).

Baseline patient characteristics were reviewed, including demographics, medical comorbidities (coronary artery disease, congestive heart failure, chronic obstructive pulmonary disease, chronic kidney disease, diabetes, hypertension), smoking and alcohol use, etiology of liver disease with portal hypertensive complications (ascites, and hepatic encephalopathy), vital signs (heart rate, minimum mean arterial pressure, temperature, maximum respiratory rate) and laboratory values. MELD score was calculated using the standard formula: 11.2 × ln(INR) + 9.57 × ln[creatinine (mg/dL)] + 3.78 × ln[bilirubin (mg/dL)] + 6.43 with a lower limit of 1.0 for all variables[19]. ICU severity of illness variables were also collected including fraction of inspired oxygen, partial pressure of arterial carbon dioxide, partial pressure of arterial oxygen, pH, mean number of vasopressors, days on vasopressors, need for continuous renal replacement therapy, intubation, urine output over the first 24 h, new hemorrhage and new diagnosis of venous thrombosis. Illness severity scores were calculated [acute physiology and chronic health evaluation Ⅱ (APACHE Ⅱ), simplified acute physiology score (SAPS Ⅱ), sequential organ failure assessment (SOFA)]. ICU medications were reviewed (volume of intravenous fluid, octreotide, antibiotic administration, albumin administration, proton pump inhibitor, corticosteroids and first vasopressor use). Captured outcomes included mean survival, hospital and ICU length of stay, ventilator free days, mortality (7-d, 28-d and 90-d), in-hospital mortality, in-ICU mortality and withdrawal of care. The 24-h changes in laboratory parameters (platelets, liver associated enzymes, heart rate, total bilirubin) were also extracted on the basis of the first available value of the parameter of interest available 24-48 h following vasopressor initiation.

### *Statistical analysis*

Subjects were sorted into two groups, those patients who received AVP as the second-line agent and those patients where another vasopressor was utilized as the second-line agent. The AVP group was compared to the non-AVP group in multiple factors including baseline patient demographics, medical comorbidities, smoking and alcohol use, etiology of liver disease, portal hypertensive complications, vital signs, laboratory values, severity of illness variables, ICU medications administered and patient-centered outcomes of mortality and withdrawal of care. Multivariable models were constructed to assess statistical associations and risk factors for 7-d and 28-d mortality. Individual factors were included in the multivariable model if they were statistically significant to $P < 0.10$ in the univariate analysis, were clinically important, or have been shown in the literature to be of clinical significance. Univariate comparisons were performed using the Student-*t* test, Wilcoxon sign rank test, $\chi^2$ test, or Fisher exact test as appropriate. Multivariable models were constructed using Cox proportional hazards models and analysis of maximum likelihood estimates. Modeling both with composite MELD score and

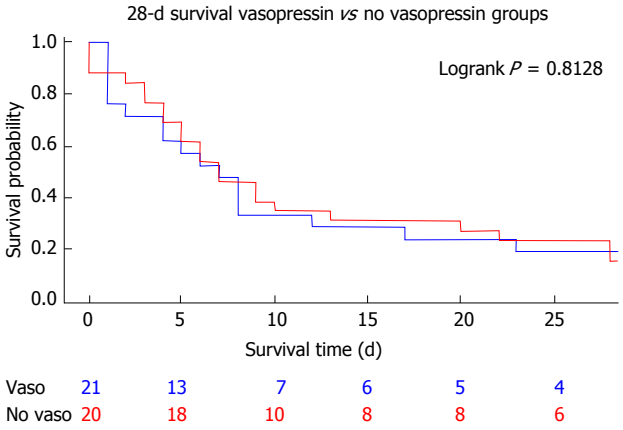


**Figure 2 Twenty-eight-day survival comparing second line vasopressors in catecholamine-resistant septic shock.**

examining each variable in the MELD score independently were performed to ensure no one variable was dominant. Unadjusted, stratified Kaplan-Meier survival curves were constructed for 7-d and 28-d survival utilizing the log-rank test to determine statistical significance ($P \leqslant 0.05$). All statistical tests for significance were two-sided and a significance level p less than or equal to 0.05 was considered statistically significant. All data set manipulation and statistical analyses were performed using SAS (version 9.4, Cary, NC). Institutional review board approval was obtained for this study.

## RESULTS

Forty-five consecutive patients with cirrhosis were treated for catecholamine-resistant septic shock; 21 received AVP as the second-line vasopressor while the remaining 24 received some other agent [phenylephrine (10), dopamine (6), norepinephrine (4), dobutamine (2), milrinone (2)]. Mean age was 57.2 ± 14.0 years. The cohort was 53.3% male and nearly ¾ had either alcoholic liver disease or chronic hepatitis C as the underlying etiology of cirrhosis (alcoholic alone 35.6%, chronic hepatitis C alone 26.7%, concomitant alcohol and hepatitis C 8.9%). All patients had either Child-Turcotte-Pugh Class B ($n$ = 8, 14.5%) or Class C ($n$ = 37, 85.5%) liver disease. Mean MELD score was 29.0 ± 9.0. Overall 7-d and 28-d mortality were 55.6% and 84.4% respectively, with two patients eventually undergoing liver transplantation at 34 and 67 d out from diagnosis of CRSS, respectively.

In general, no significant differences in baseline demographics, etiology of cirrhosis, laboratory values, vital signs or ICU mortality/severity of illness scores were observed when comparing those subjects who received AVP to those who received any other vasoactive agent, with the exception of higher MELD scores in the AVP group (32.4, 95%CI: 28.6-36.2 *vs* 27.1, 95%CI: 23.6-30.6, $P$ = 0.041) (Table 1). Glomerular filtration rates were also different between the two groups (23.9 mL/min, 95%CI: 18.6-29.2 in the AVP group *vs* 40.0 mL/min, 95%CI: 29.1-51.0 in the non-AVP group, $P$ = 0.013). Mean APACHE Ⅱ scores were statistically similar (33.5, 95%CI: 30.6-36.5 in the AVP group *vs* 31.8, 95%CI: 29.4-34.2) as were SAPS Ⅱ (72.6, 95%CI: 63.5-81.7 in the AVP group *vs* 70.3, 95%CI: 64.5-76.1 in the non-AVP group) and SOFA (17.6, 95%CI: 15.9-19.3 AVP *vs* 16.9, 95%CI: 15.9-18.0 non-AVP). Corticosteroid administration was also statistically similar (76.2% AVP *vs* 79.2% non-AVP) as was time to first vasopressor initiation (6.8, 95%CI: 4.9-8.7 h AVP *vs* 7.4, 95%CI: 5.7-9.3 h non-AVP). No statistically significant difference was observed in unadjusted 7-d mortality (52.4% AVP *vs* 58.3% and $P$ = 0.408) or 28-d mortality (81.0% AVP *vs* 87.5% non-AVP, $P$ = 0.813) (Figure 2). There was also no significant change in any recorded laboratory value of interest as measured 24-48 h after vasopressor initiation (Table 2).

On adjusted multivariable analysis, AVP use was not associated with increased 28-d mortality (HR = 0.77, 95%CI: 0.39-1.52, $P$ = 0.771). Age in years (HR = 1.05, 95%CI: 1.01-1.08, $P$ = 0.004) was associated with increased 28-d mortality (Table 3). In other words, for each addition year of age from the baseline cohort average, the mortality rate was increased 5%. Corticosteroid administration was a significant predictor of improved 28-d mortality (HR = 0.37, 95%CI: 0.16-0.86, $P$ = 0.021). The initiation of renal replacement therapy was associated with lower mortality (HR = 0.40, 95%CI: 0.19-0.85, $P$ = 0.017). No significant difference was found for MELD score.

## DISCUSSION

After adjusting for multiple confounding factors, we report that AVP is not associated with disparate outcomes when compared to all other vasoactive agents in terms of 7-d and 28-d mortality when used as a second line vasopressor in catecholamine-resistant septic shock. These results are particularly notable considering the extent to which our AVP group was comprised of patients with a higher severity of illness as reflected by statistically higher baseline MELD scores as well as severity of illness scores which, while not individually differing statistically between the two groups, nevertheless all tended to be higher in the AVP group. Estimated glomerular filtration rates were also significantly lower in the AVP group, however these data need to be interpreted with caution as several of these patients were already receiving some form of renal replacement therapy at the time of vasopressor initiation. Additionally, we report no statistically significant difference in the total number of vasoactive agents used among the groups with both groups receiving approximately three such agents during the study period, a surrogate outcome which may indicate that AVP did not impair attainment of target mean-arterial pressures when compared with other agents. We do acknowledge that, due to the high rate of transition to comfort care measures, these data should also be interpreted cautiously, nevertheless rates of changes in goals of care were essentially equivalent

**Table 1 Baseline patient characteristics**

| | Vasopressin ($n$ = 21) | No Vasopressin ($n$ = 24) | $P$ value |
|---|---|---|---|
| Patient demographics | | | |
| Age, yr (95%CI) | 56.2 (50.2-62.3) | 57.0 (50.7-63.3) | 0.681 |
| Male gender | 10 (47.6) | 14 (53.9) | 0.672 |
| Body mass index, kg/m$^2$, (95%CI) | 34.2 (30.5-37.9) | 31.2 (28.0-34.3) | 0.150 |
| Comorbidities, $n$ (%) | | | |
| CAD | 3 (14.2) | 4 (16.7) | 0.985 |
| CHF | 1 (5.3) | 6 (23.1) | 0.103 |
| COPD | 3 (16.7) | 4 (16.7) | 1.00 |
| CKD | 6 (28.6) | 7 (29.2) | 0.956 |
| DM | 7 (35.0) | 8 (30.8) | 0.762 |
| HTN | 13 (61.3) | 16 (66.7) | 0.916 |
| Smoking, $n$ (%) | 5 (23.8) | 5 (23.8) | 0.756 |
| Alcohol use (active), $n$ (%) | 9 (42.9) | 8 (33.3) | 0.392 |
| Liver disease etiology, $n$ (%) | | | |
| Alcohol | 6 (28.6) | 10 (41.7) | 0.477 |
| NASH/crypto | 5 (23.4) | 7 (29.2) | 0.240 |
| HBV | 0 (0.0) | 0 (0.0) | 1.00 |
| HCV | 3 (14.2) | 3 (12.5) | 0.566 |
| Cardiac | 1 (4.8) | 1 (4.2) | 0.947 |
| Cholestatic | 2 (9.5) | 1 (4.2) | 0.445 |
| AIH | 0 (0.0) | 1 (4.2) | 0.497 |
| HCV/alcohol | 3 (14.3) | 1 (4.2) | 0.329 |
| PSE | 14 (66.7) | 15 (62.5) | 0.927 |
| Laboratory values and vital signs | | | |
| MELD, (95%CI) | 32.4 (28.6-36.2) | 27.1 (23.6-30.6) | 0.041 |
| CTP, $n$ (%) | | | |
| A | 0 (0.0) | 0 (0.0) | 1.00 |
| B | 2 (9.5) | 6 (25.0) | 0.074 |
| C | 19 (90.5) | 18 (75.0) | 0.162 |
| AST, U/L, (95%CI) | 429 (283-1141) | 289 (90-667) | 0.763 |
| ALT, U/L, (95%CI) | 180 (79-438) | 133 (24-290) | 0.795 |
| Alk phos, U/L, (95%CI) | 155 (109-200) | 138 (90-185) | 0.740 |
| Bilirubin, mg/dL, (95%CI) | 15.4 (9.0-21.9) | 10.0 (5.3-14.6) | 0.109 |
| BUN, mg/dL, (95%CI) | 58.0 (45.0-70.9) | 48.7 (36.5-60.9) | 0.222 |
| Platelets, k/uL, (95%CI) | 84.5 (66.2-102.8) | 88.8 (68.9-108.8) | 0.402 |
| Creatinine, mg/dL, (95%CI) | 3.02 (2.16-3.88) | 2.50 (1.59-3.41) | 0.37 |
| GFR, mL/min per 1.73 m$^2$, (95%CI) | 23.9 (18.6-29.2) | 40.0 (29.1-51.0) | 0.013 |
| Sodium, mmol/L, (95%CI) | 135.8 (131.8-139.8) | 134.1 (130.8-137.5) | 0.553 |
| INR, (95%CI) | 2.63 (1.79-3.48) | 2.15 (1.82-2.47) | 0.176 |
| Hematocrit, %, (95%CI) | 25.7 (22.9-28.6) | 28.0 (26.1-30.0) | 0.200 |
| Lactate, mmol/L, (95%CI) | 3.90 (2.58-5.21) | 3.60 (2.52-4.68) | 0.669 |
| WBC (max), k/uL, (95%CI) | 16.1 (12.8-19.5) | 16.7 (12.7-20.6) | 0.607 |
| Heart rate, (95%CI) | 106 (96-115) | 110 (102-118) | 0.591 |
| MAP (min), (95%CI) | 45.1 (34.2-56.1) | 50.5 (46.9-54.0) | 0.197 |
| Temperature, C, (95%CI) | 36.3 (35.5-37.1) | 36.7 (35.9-37.4) | 0.125 |
| RR (max), breaths/min, (95%CI) | 35.7 (30.5-40.8) | 31.8 (25.4-38.3) | 0.145 |
| ICU level of illness, (95%CI) | | | |
| $FiO_2$ | 0.48 (0.36-0.59) | 0.44 (0.34-0.54) | 0.953 |
| $PaCO_2$ | 35.6 (32.7-38.5) | 35.7 (32.1-39.3) | 0.856 |
| $PaO_2$ | 100.2 (49.1-151.4) | 70.4 (60.2-80.6) | 0.235 |
| pH | 7.30 (7.24-7.35) | 7.34 (7.30-7.37) | 0.149 |
| APACHE Ⅱ | 33.5 (30.6-36.5) | 31.8 (29.4-34.2) | 0.306 |
| GCS | 7.1 (5.0-9.3) | 6.9 (5.2-8.6) | 0.547 |
| SAPSⅡ | 72.6 (63.5-81.7) | 70.3 (64.5-76.1) | 0.975 |
| SOFA | 17.6 (15.9-19.3) | 16.9 (15.9-18.0) | 0.173 |
| Average number of vasopressors | 2.9 (2.4-3.3) | 3.3 (2.9-3.6) | 0.357 |
| Days on vasopressors | 6.3 (3.7-8.9) | 6.3 (3.6-9.0) | 0.756 |
| CRRT/HD, $n$ (%) | 13 (65.0) | 17 (70.8) | 0.762 |
| Intubated, $n$ (%) | 18 (85.7) | 22 (91.7) | 0.466 |
| UOP first 24 h, mL, (95%CI) | 459.9 (225.8-694.0) | 698.1 (383.9-1012.3) | 0.067 |
| GI bleed, $n$ (%) | 1 (20.0) | 5 (20.8) | 0.948 |
| New VTE, $n$ (%) | 4 (20.0) | 3 (12.5) | 0.635 |
| ICU medications | | | |
| Volume of IVF (L), (95%CI) | 4.02 (2.52-5.53) | 4.44 (2.62-6.26) | 0.891 |
| Octreotide, $n$ (%) | 14 (66.7) | 12 (52.2) | 0.329 |
| Antibiotics, $n$ (%) | 21 (100.0) | 24 (100.0) | 0.790 |
| Choice of first vasopressor, $n$ (%) | | | |

| | | | |
|---|---|---|---|
| Norepinephrine | 18 (85.7) | 17 (70.8) | 0.412 |
| Dopamine | 1 (4.8) | 3 (12.5) | 0.398 |
| Phenylephrine | 2 (9.5) | 4 (16.7) | 0.207 |
| Albumin given, *n* (%) | 18 (85.7) | 21 (95.5) | 0.954 |
| PPI, *n* (%) | 18 (90.0) | 19 (79.2) | 0.388 |
| Corticosteroids, *n* (%) | 16 (76.2) | 19 (79.2) | 0.701 |
| Outcomes, (95%CI) | | | |
| Days to death | 8.9 (5.2-11.4) | 7.8 (4.4-11.1) | 0.672 |
| ICU LOS, d | 13.5 (8.1-18.8) | 12.3 (4.4-20.3) | 0.114 |
| Vent free days | 22.6 (20.1-25.1) | 15.8 (4.1-27.6) | 0.633 |
| Mortality, *n* (%) | | | |
| 7 d | 11 (52.4) | 14 (58.3) | 0.408 |
| 28 d | 17 (81.0) | 21 (87.5) | 0.371 |
| 90 d | 18 (85.7) | 21 (87.5) | 0.303 |
| In hospital | 18 (85.7) | 20 (83.3) | 0.654 |
| ICU | 17 (81.0) | 18 (75.0) | 0.360 |
| Transition to comfort care | 16 (76.2) | 18 (75.0) | 0.808 |

CAD: Coronary heart disease; CHF: Congestive heart failure; COPD: Chronic obstructive pulmonary diseases; CKD: Chronic kidney diseases; DM: Diabetes mellitus; HTN: Hypertension; NASH: Non-alcoholic steatohepatitis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AIH: Autoimmune hepatitis; PSE: Portosystemic encephalopathy; CTP: Child-Turcotte-Pugh score; AST: Aspartate aminotransferase; ALT: Alanine transaminase; BUN: Blood urea nitrogen; WBC: White blood cell; ICU: Intensive care unit; APACHE Ⅱ: Acute physiology and chronic health evaluation Ⅱ; SAPSⅡ: Simplified acute physiology score; SOFA: Sequential organ failure assessment; CRRT: Continuous renal replacement therapy; HD: Hemodialysis; GI: Gastrointestinal; PPI: Proton pump inhibitors.

**Table 2 Change in laboratory parameters with vasopressor support as measured 24 h after vasopressor initiation**

| | Vasopressin (*n* = 21) | No Vasopressin (*n* = 24) | *P* value |
|---|---|---|---|
| Platelets, k/uL, (95%CI) | -18.7 (-42.3, 4.9) | -13.6 (-31.6, 4.4) | NS |
| ALT, U/L, (95%CI) | 47.2 (-12.1, 106.6) | 206.3 (-113.3, 525.9) | NS |
| AST, U/L (95%CI) | 236.7 (74.0, 399.4) | 292.4 (-247.0, 831.8) | NS |
| Alkaline phosphatase, U/L, (95%CI) | -10.5 (-48.7, 27.8) | -19.6 (-39.5, 0.3) | NS |
| Heart rate, (95%CI) | -6.7 (-12.3, -1.0) | 0.6 (-11.8, 13.0) | NS |
| Bilirubin, mg/dL, (95%CI) | 0.45 (-0.99, 1.89) | 0.87 (-0.64, 2.38) | NS |

AST: Aspartate aminotransferase; ALT: Alanine transaminase; NS: No statistical significance.

**Table 3 Adjusted multivariable analysis for predictors of 28-d all-cause mortality**

| | Hazard ratio | 95%CI | *P* value |
|---|---|---|---|
| Vasopressin[1] | 0.77 | 0.39-1.52 | NS |
| Age (yr) | 1.05 | 1.01-1.08 | 0.004 |
| CRRT | 0.40 | 0.19-0.85 | 0.017 |
| Corticosteroids | 0.37 | 0.16-0.86 | 0.021 |
| Sodium (mmol/L) | 1.00 | 0.96-1.04 | NS |
| Platelets (k/uL) | 0.99 | 0.98-1.00 | NS |
| MELD | 1.04 | 0.98-1.09 | NS |

[1]Compared to reference of non-vasopressin group ($P$ = 0.553). CRRT: Continuous renal replacement therapy; NS: No statistical significance.

in the 2 groups. Well-designed, prospective, randomized studies are needed to clarify whether AVP should be preferred as the second-line vasopressor in this patient population.

Potential adverse effects of AVP administration were not different when compared to all other vasoactive agents. While others have published reports suggesting acute-on-chronic liver failure, worsening thrombocytopenia and a decline in cardiac output with AVP use[4,12-17] our results do not lend support to these concerns during early treatment, as we did not find any significant laboratory changes in these parameter between the two groups as measured 24-48 h after vasopressor initiation. Consonant with these findings, we report similar rates of *de novo* venous thromboembolic disease among the two groups. While direct measurement of cardiac output or cardiac index was not obtainable in our retrospective analysis, heart rate did not decline significantly after one-day of vasopressor therapy in the AVP group when compared with the non-AVP group, lessening concerns regarding clinically significant negative chronotropy affecting cardiac output in this population. Although some reports suggest mortality benefit with attenuation of tachycardia in patients with septic shock, a decline in cardiac output mediated by decreased heart rate may have a disparate and adverse effect in cirrhosis patients when compared to the general population given the possible underlying dependence of oxygen consumption on oxygen delivery in this population[18,20].

From a safety and efficacy standpoint, our findings confirm a salient role for AVP use in cirrhosis patients with CRSS and strengthen the current level of evidence provided in support of recent consensus guidelines for critical care in patients with cirrhosis which are based largely on data extrapolated from studies of terlipressin administration[11].

On adjusted multivariable analysis, corticosteroid use emerged as a marked predictor of improved 28-d mortality with a 63% reduction in death with corticosteroid administration. Current Surviving Sepsis guidelines do recommend low-dose hydrocortisone for patients with septic shock unresponsive to fluid resuscitation and 60 min of vasopressors support. However, while the prevalence of adrenal insufficiency among patients with cirrhosis and sepsis has been generally reported as higher than expected, upwards of some 76% of this population, a recent randomized-controlled trial did not evidence a mortality benefit when stress-dosed steroids were employed in the ICU management of these patients[10]. In a randomized, placebo-controlled trial of 75 cirrhosis patients admitted to an intensive care unit with septic shock that was stopped early due to futility, Arabi *et al*[10] reported a 28-d mortality of 85% in the group of patients randomized to receive low-dose corticosteroids compared with 72% in the placebo-allocated group. While our mortality rates approximate those in the steroid-receiving group reported by Russell *et al*[21] it is clear that our patients suffering CRSS represented a more critically ill population as evidenced not only by a pre-specified requirement for 2 or more vasopressors, but also by the higher APACHE Ⅱ and SOFA scores which characterized our patients. While the discrepancy regarding steroid-benefit may be real and attributable to the differing populations under study, another intriguing hypothesis which emerged from a post-hoc substudy of VASST relates to a possible beneficial synergy between AVP and corticosteroid, with the authors of this substudy reporting a decrease in 28-d mortality from 44.7% to 35.9% in patients receiving corticosteroids plus AVP when compared with patients receiving corticosteroids in addition to norepinephrine.

Finally, rates of gastrointestinal hemorrhage, including that from gastroesophageal varices, were also similar between the AVP and non-AVP groups.

Our study has several limitations. First, it is retrospective in nature and suffers from missing data, a deficiency common to most retrospective analyses. Second, ours is a single center study with a relatively small sample size constraining analysis of additional variables. Third, we acknowledge the heterogeneity of the comparative group regarding the variety of second-line agents used. However, on the other hand, a salient feature of this study is that the 2$^{nd}$ vasoactive agent used in the comparator group was almost exclusively a catecholaminergic agent, which in effect resulted in a study comparing second-line vasopressin use *vs* second-line catecholaminergic augmentation.

Fourthly, an additional limitation relates to "cross-over" analysis, as we did not analyze our cohort of patients on the basis of whether or not they received AVP at any time during their course. Furthermore, we did not investigate the possible interaction between AVP and corticosteroids as discussed earlier. Our study is also relatively underpowered given the high 28-d mortality rates observed and the low-even rate of patient survival. Other limitations include a lack of direct measurement of cardiac output or index with right heart catheterization in order to better characterize changes in hemodynamics following AVP administration.

Nevertheless, we provide more methodologically robust evidence for AVP use as a second-line vasopressor in catecholamine resistant septic shock and for attention to vasopressor selection in patients with cirrhosis. While further, large-scale multicenter prospective studies would be of benefit to refine current consensus standards, all potential lifesaving interventions, as long as the potential for iatrogenic harm is minimal, should be considered in this extremely sick patient population with 28-d mortality rates approaching 85%. Ultimately, the goal of correcting catecholamine-resistant septic shock in these patients involves both recovery from their immediate, life-threatening illness as well as providing for relative convalescence which may enable the individual patient to recover and receive a liver transplantation.

## COMMENTS

### Background

Cirrhosis patients with septic-shock requiring intensive care unit medical care have an exceedingly high mortality rate and are excluded from many existing clinical trials. Recent consensus guidelines suggest a role for vasopressin use in this patient population; however, this is based largely on expert opinion.

### Research frontiers

With the increasing prevalence of cirrhosis globally and improved access to tertiary medical care, the care of the critically ill patient with cirrhosis of the liver cannot be ignored. Current research and clinical care focuses largely on keeping the critically ill patient with cirrhosis alive in order to eventually receive a life-saving liver transplantation. The role of vasopressin in this population remains unknown.

### Innovations and breakthroughs

In the present study, the authors found that vasopressin is similar to all other vasopressors in terms of 7-d and 28-d mortality and in the absence of significantly more deleterious effects suggest a role for vasopressin use in patients with cirrhosis admitted to the intensive care unit with septic shock.

### Applications

The present report provides further evidence on the safety and efficacy of vasopressin use in patients with cirrhosis, and may suggest revisiting the currently available critical care guidelines.

### Peer-review

This retrospective cohort adds useful information for both clinical practice and further academic research with the goal of impacting common patient centered outcomes for critically ill patients with extremely high mortality rates.

## REFERENCES

1 **Pavon A**, Binquet C, Kara F, Martinet O, Ganster F, Navellou JC, Castelain V, Barraud D, Cousson J, Louis G, Perez P, Kuteifan K, Noirot A, Badie J, Mezher C, Lessire H, Quantin C, Abrahamowicz M, Quenot JP. Profile of the risk of death after septic shock in the present era: an epidemiologic study. *Crit Care Med* 2013; **41**: 2600-2609 [PMID: 23963127 DOI: 10.1097/CCM.0b013e31829a6e89]

2 **Galbois A**, Aegerter P, Martel-Samb P, Housset C, Thabut D, Offenstadt G, Ait-Oufella H, Maury E, Guidet B. Improved

prognosis of septic shock in patients with cirrhosis: a multicenter study. *Crit Care Med* 2014; **42**: 1666-1675 [PMID: 24732239 DOI: 10.1097/CCM.0000000000000321]
3 **Moreau R**, Hadengue A, Soupison T, Kirstetter P, Mamzer MF, Vanjak D, Vauquelin P, Assous M, Sicot C. Septic shock in patients with cirrhosis: hemodynamic and metabolic characteristics and intensive care unit outcome. *Crit Care Med* 1992; **20**: 746-750 [PMID: 1597026]
4 **Russell JA**, Walley KR, Singer J, Gordon AC, Hébert PC, Cooper DJ, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ, Ayers D. Vasopressin versus norepinephrine infusion in patients with septic shock. *N Engl J Med* 2008; **358**: 877-887 [PMID: 18305265 DOI: 10.1056/NEJMoa067373]
5 **Landry DW**, Levin HR, Gallant EM, Ashton RC, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin deficiency contributes to the vasodilation of septic shock. *Circulation* 1997; **95**: 1122-1125 [PMID: 9054839]
6 **Landry DW**, Levin HR, Gallant EM, Seo S, D'Alessandro D, Oz MC, Oliver JA. Vasopressin pressor hypersensitivity in vasodilatory septic shock. *Crit Care Med* 1997; **25**: 1279-1282 [PMID: 9267938]
7 **Sharshar T**, Blanchard A, Paillard M, Raphael JC, Gajdos P, Annane D. Circulating vasopressin levels in septic shock. *Crit Care Med* 2003; **31**: 1752-1758 [PMID: 12794416 DOI: 10.1097/01.CCM.0000063046.82359.4A]
8 **Wagener G**, Kovalevskaya G, Minhaz M, Mattis F, Emond JC, Landry DW. Vasopressin deficiency and vasodilatory state in end-stage liver disease. *J Cardiothorac Vasc Anesth* 2011; **25**: 665-670 [PMID: 21126886 DOI: 10.1053/j.jvca.2010.09.018]
9 **Fernández J**, Escorsell A, Zabalza M, Felipe V, Navasa M, Mas A, Lacy AM, Ginès P, Arroyo V. Adrenal insufficiency in patients with cirrhosis and septic shock: Effect of treatment with hydrocortisone on survival. *Hepatology* 2006; **44**: 1288-1295 [PMID: 17058239 DOI: 10.1002/hep.21352]
10 **Arabi YM**, Aljumah A, Dabbagh O, Tamim HM, Rishu AH, Al-Abdulkareem A, Knawy BA, Hajeer AH, Tamimi W, Cherfan A. Low-dose hydrocortisone in patients with cirrhosis and septic shock: a randomized controlled trial. *CMAJ* 2010; **182**: 1971-1977 [PMID: 21059778 DOI: 10.1503/cmaj.090707]
11 **Nadim MK**, Durand F, Kellum JA, Levitsky J, O'Leary JG, Karvellas CJ, Bajaj JS, Davenport A, Jalan R, Angeli P, Caldwell SH, Fernández J, Francoz C, Garcia-Tsao G, Ginès P, Ison MG, Kramer DJ, Mehta RL, Moreau R, Mulligan D, Olson JC, Pomfret EA, Senzolo M, Steadman RH, Subramanian RM, Vincent JL, Genyk YS. Management of the critically ill patient with cirrhosis: A multidisciplinary perspective. *J Hepatol* 2016; **64**: 717-735 [PMID: 26519602 DOI: 10.1016/j.jhep.2015.10.019]
12 **Leone M**, Albanèse J, Delmas A, Chaabane W, Garnier F, Martin C. Terlipressin in catecholamine-resistant septic shock patients. *Shock* 2004; **22**: 314-319 [PMID: 15377885 DOI: 10.1097/01.shk.0000136097.42048.bd]
13 **Morelli A**, Ertmer C, Lange M, Westphal M. Continuous terlipressin infusion in patients with septic shock: less may be best, and the earlier the better? *Intensive Care Med* 2007; **33**: 1669-1670 [PMID: 17530219 DOI: 10.1007/s00134-007-0676-1]
14 **Albanese J**, Leone M, Delmas A, Martin C. Terlipressin or norepinephrine in hyperdynamic septic shock: A prospective, randomized study. *Crit Care Med* 2005; **33**: 1897-1902 [PMID: 16148457 DOI: 10.1097/01.CCM.0000178182.37639.D6]
15 **O'Brien A**, Clapp L, Singer M. Terlipressin for norepinephrine-resistant septic shock. *Lancet* 2002; **359**: 1209-1210 [PMID: 11955542 DOI: 10.1016/S0140-6736(02)08225-9]
16 **Luckner G**, Dünser MW, Jochberger S, Mayr VD, Wenzel V, Ulmer H, Schmid S, Knotzer H, Pajk W, Hasibeder W, Mayr AJ, Friesenecker B. Arginine vasopressin in 316 patients with advanced vasodilatory shock. *Crit Care Med* 2005; **33**: 2659-2666 [PMID: 16276194 DOI: 10.1097/01.CCM.0000186749.34028.40]
17 **Umgelter A**, Reindl W, Schmid RM, Huber W. Continuous terlipressin infusion in patients with persistent septic shock and cirrhosis of the liver. *Intensive Care Med* 2008; **34**: 390-391 [PMID: 17917713 DOI: 10.1007/s00134-007-0877-7]
18 **Moreau R**, Lee SS, Hadengue A, Ozier Y, Sicot C, Lebrec D. Relationship between oxygen transport and oxygen uptake in patients with cirrhosis: effects of vasoactive drugs. *Hepatology* 1989; **9**: 427-432 [PMID: 2493414 DOI: 10.1002/hep.1840090314]
19 **Kamath PS**, Wiesner RH, Malinchoc M, Kremers W, Therneau TM, Kosberg CL, D'Amico G, Dickson ER, Kim WR. A model to predict survival in patients with end-stage liver disease. *Hepatology* 2001; **33**: 464-470 [PMID: 11172350 DOI: 10.1053/jhep.2001.22172]
20 **Morelli A**, Ertmer C, Westphal M, Rehberg S, Kampmeier T, Ligges S, Orecchioni A, D'Egidio A, D'Ippoliti F, Raffone C, Venditti M, Guarracino F, Girardis M, Tritapepe L, Pietropaoli P, Mebazaa A, Singer M. Effect of heart rate control with esmolol on hemodynamic and clinical outcomes in patients with septic shock: a randomized clinical trial. *JAMA* 2013; **310**: 1683-1691 [PMID: 24108526 DOI: 10.1001/jama.2013.278477]
21 **Russell JA**, Walley KR, Gordon AC, Cooper DJ, Hébert PC, Singer J, Holmes CL, Mehta S, Granton JT, Storms MM, Cook DJ, Presneill JJ. Interaction of vasopressin infusion, corticosteroid treatment, and mortality of septic shock. *Crit Care Med* 2009; **37**: 811-818 [PMID: 19237882 DOI: 10.1097/CCM.0b013e3181961ace]

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ORIGINAL ARTICLE

Observational Study

# Percutaneous drainage as a first therapeutic step prior to surgery in liver hydatid cyst abscess: Is it worth it?

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## Abstract

***AIM***

To delay surgery until the patient is in a better condition, and thus to decrease postoperative morbidity.

***METHODS***

Using this algorithm we treated three patients aged 55, 75 and 80 years. In all three patients the clinical presentation was fever without a clear source of infection; all had nonspecific symptoms such as general malaise, dyspnea, and abdominal discomfort in the previous 15 d. They came to the emergency room at our hospital due to deterioration of their general condition. Analytical tests showed leukocytosis, neutrophilia and increased polymerase chain reaction. In all cases an abdominal computed tomography (CT) was performed and liver hydatid abscess (LHA) was detected. The mean size of the LHA was 12 cm.

***RESULTS***

All patients underwent CT-guided percutaneous drainage. The purulent material obtained was cultured, and Klebsiella pneumoniae, Streptococcus viridans and Streptococcus salivarius were identified. Antibiotic treatment was given adapted to antibiotic sensitivity testing. Surgery was performed two weeks after admission, once the patient's condition had improved. All three patients underwent an almost total cystectomy, cholecystectomy and omentoplasty in the residual cavity. Complications were: Clavien Ⅰ (atelectasis and pleural effusion) and Clavien Ⅱ (transfusion). The average length of stay (pre and postoperative) was 23 d. At the follow-up, no

relapses were recorded.

***CONCLUSION***

LHA management is not standardized. Emergency surgery offers suboptimal results. Percutaneous drainage plus antibiotics allows improving patient's general condition. This enables treating patients in greater safety and also reduces complications.

**Key words:** Hydatidosis; Review; Surgery; Abscess; Liver



**Core tip:** Liver hydatid abscess (LHA) management is not standardized. The traditional treatment is emergency surgery but the results are usually suboptimal because the patients are in poor medical condition. The initial treatment of LHA in septic patients with percutaneous drainage in combination with antibiotic therapy and supportive measures allows control of the infection and improves the patient's general condition. This enables the physician to treat the patient in greater safety and also reduces complications.

Lopez-Marcano AJ, Ramia JM, Arteaga V, De la Plaza R, Gonzales JD, Medina A. Percutaneous drainage as a first therapeutic step prior to surgery in liver hydatid cyst abscess: Is it worth it? *World J Hepatol* 2017; 9(2): 114-118 Available from: URL: http://www.wjgnet.com/1948-5182/full/v9/i2/114.htm DOI: http://dx.doi.org/10.4254/wjh.v9.i2.114

## INTRODUCTION

Cystic echinococcosis is a zoonotic disease that is found worldwide. It is caused by larvae of the genus *Echinococcus*, and is endemic in certain areas of the planet[1]. The liver is the most common location for cyst development[2]. Infection of the liver hydatid cyst (LHC) and pyogenic abscess formation is a rare but highly severe complication. The clinical course is insidious and it is usually diagnosed when the infection has progressed, affecting the patient's overall condition and possibly even causing septic shock[3]. The treatment of liver hydatid abscess (LHA) is not yet standardized. Several options are available with the dual purpose of draining the LHA and treating the LHC, including simple surgical drainage, or surgical drainage associated with total or subtotal pericystectomy and percutaneous drainage[3]. We propose percutaneous drainage of the LHA as a first therapeutic step, and later, when the patient's general condition improves, surgical treatment of the LHC.

## MATERIALS AND METHODS

From May 1, 2007 to March 1, 2016 we treated 135 patients with LHC, of whom 72 underwent surgery. Three of these patients debuted with a severe septic condition caused by LHA. These patients were initially treated with computed tomography (CT)-guided percutaneous drainage of the abscess, and then underwent scheduled surgery when their condition had improved. Their data are included in Table 1.

We also conducted an unlimited literature search in PubMed, updated on 1 January 2016, with the following strategy: [(echinococcosis hepatic complications) and (liver abscess)], which yielded 136 papers. Review of the abstracts found three papers related to the topic of the current paper, and their references were analyzed. The aim of this review was to assess the literature on the value of percutaneous drainage in LHA for delaying surgery until the patient is in a better overall condition, in order to reduce postoperative morbidity and to perform definitive treatment of LHC.

## RESULTS

### *Patients 1*

Male, 80 years old, came to the Emergency Department due to fever, dyspnea and general malaise of 15 d's duration with hypotension, tachypnea and tachycardia. Past medical history: Mild Alzheimer's disease. His analysis showed: 18610 leukocytes, 90.8% neutrophils, hemoglobin 8.4 g/dL, INR 1.13, Cr 0.75 mg/dL, GGT 433 U/L, AST 35 U/L. Abdominal ultrasound showed a right liver lesion with calcified wall and echoes inside, probably detritus, compatible with LHA. Abdominal CT revealed a 13 cm liver mass with hypodense fluid level suggestive of LHA (Figure 1). CT-guided percutaneous drainage was performed and obtained purulent material. In the microbiology cultures, *Klebsiella pneumoniae* was identified. The patient received antibiotic therapy adjusted to antibiogram (piperacillin-tazobactam 4 g-0.5 g/8 h). Sixteen days later, with the patient in a satisfactory clinical and analytical condition, a subtotal cystectomy was performed after extensive cleaning of the cyst, cholecystectomy, bile duct exploration, closure of small cystobiliary communications and omentoplasty. Histopathology study showed the typical pericystic wall of LHC. After surgery, the patient suffered atelectasis and pleural effusion, and fungaemia (*Candida Albicans*) treated by fluconazole and requiring transfusion. He was discharged on postoperative day 34 (total stay: 50 d). He died 14 mo later of other medical causes, with no evidence of LHC recurrence at the CT performed one year after surgery.

### *Patients 2*

Female, 75 years old. Past medical history: Hypertension and diabetes mellitus. She came to the Emergency Department due to fever and malaise of several days, severe, with hypotension, tachypnea and tachycardia. Analysis: 24610 leukocytes (95% neutrophils), Hb 10.9 g/dL, INR 1.24, Cr 1.56 mg/dL, polymerase chain

**Table 1 Clinical debut, analysis, diagnostic methods, surgery, morbidity and follow-up of our cases**

| | Case 1 | Case 2 | Case 3 |
|---|---|---|---|
| Sex | Male | Female | Female |
| Age (yr) | 80 | 75 | 55 |
| Age | 80 | 75 | 55 |
| Clinic | Fever, dyspnoea and malaise last 15 d duration<br>Poor general condition | Fever and malaise for several days<br>Poor general condition | High fever (> 39 ℃) accompanied by discomfort in right hypochondrium<br>Poor general condition |
| Analytics | 18610 leukocytes, 90.8% neutrophils, Hgb 8.4 g/dL INR 1.13, Cr 0.75 mg/dL, GGT 433 U/L, AST 35 U/L | 24610 leukocytes (95% neutrophils), Hgb 10.9 g/dL, INR 1.24, Cr 1.56 mg/dL, PCR 315 mg/L, GGT 70 U/L and AST 47 U/L | 18666 leukocytes, 84.8% neutrophils, Hgb 10.6 g/dL, INR 1.14, PCR 19.4 mg/dL, GGT 270 U/L, AST 379 U/L |
| Radiography/ultrasound | A right liver lesion with calcified wall and echoes inside, probably detritus, compatible with LHA | - | An abdominal mass with fluid level in right hypocondrium was seen |
| Abdominal CT | An abdominal mass with fluid level in right hypochondrium | A 12 cm abscess in the liver compatible with LHA | An 11.5 cm liver mass located in segments Ⅵ and Ⅶ with fluid level, communicating with bile duct and causing inferior vena cava compression |
| Size | 13 cm | 12 cm | 11.5 cm |
| Culture | *Klebsiella pneumoniae* | *Streptococcus viridans* | *Streptococcus salivarius* |
| Time from pair to surgery | 16 d | 12 d | 15 d |
| Surgery | Subtotal cystectomy cholecystectomy, bile duct exploration, closure of small cystobiliary communications and omentoplasty | Subtotal cystectomy, cholecystectomy and bile duct clearance | Subtotal cystectomy and bile duct clearance |
| Morbidity | Atelectasis and pleural effusion, fungaemia (*Candida Albicans*) and transfusion | No | Red blood cell transfusion |
| Postsurgical stay | 34 d | 5 d | 4 d |
| Total stay | 50 d | 17 d | 19 d |
| Follow-up | No recurrence<br>14 mo | No recurrence<br>6 yr | No recurrence<br>2.5 yr |

CT: Computed tomography; LHA: Liver hydatid abscess; PCR: Polymerase chain reaction.

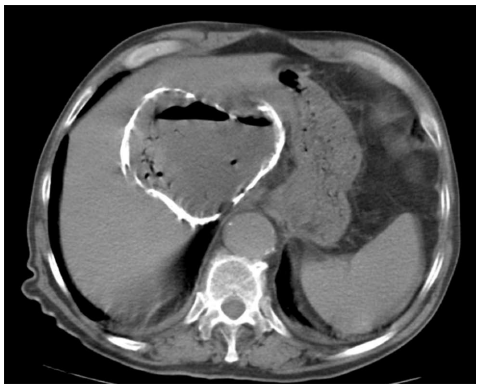

**Figure 1 Abdominal computed tomography: Liver hydatid abscess.**

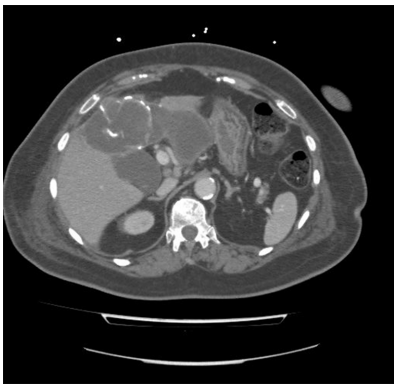

**Figure 2 Abdominal computed tomography: Percutaneous drainage inside liver hydatid abscess.**

reaction (PCR) 315 mg/L, GGT 70 U/L and AST 47 U/L. Abdominal CT revealed a 12 cm abscess in the left liver compatible with LHA. CT percutaneous drainage was performed, obtaining purulent material (Figure 2). In microbiological cultures *Streptococcus viridans* was identified She received empiric antibiotic treatment adjusted later to amoxicillin/clavulanic acid (1 g/8 h) as a result of the antibiogram. She was admitted to the intensive care unit due to severe SIRS and finally underwent surgery after 12 d when her clinical condition had improved. A right subcostal laparotomy was performed, revealing a LHA located in segments Ⅲ, Ⅳb, Ⅴ and Ⅵ. Subtotal cystectomy, cholecystectomy and bile duct clearance were performed. Postoperative course was uneventful and the patient was discharged after 5 d (total stay: 17 d). Histopathology showed chronic cholecystitis and hydatid cyst wall. No recurrence was seen at follow-up sessions over a 6-year period.

### *Patients 3*

Female, 55 years old. Past medical history: Human immunodeficiency virus infection and pulmonary fibrosis. She came to the Emergency Department for high

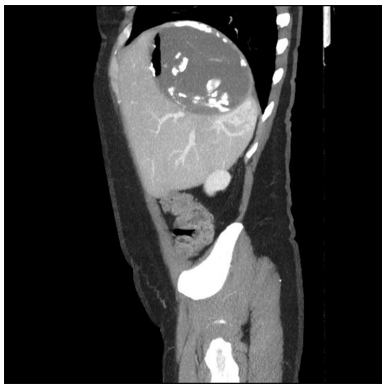

**Figure 3 Abdominal computed tomography: Liver hydatid abscess.**

fever (>39 ℃) accompanied by discomfort in right hypochondrium, with hypotension, tachypnea and tachycardia. Analytical results: 18666 leukocytes, 84.8% neutrophils, Hgb 10.6 g/dL, INR 1.14, PCR 19.4 mg/dL, GGT 270 U/L, AST 379 U/L. Abdominal radiography revealed an abdominal mass with fluid level in right hypochondrium. Abdominal CT showed a 11.5 cm liver mass located in segments Ⅵ and Ⅶ with fluid level (Figure 3), communicating with the bile duct and causing inferior vena cava compression. Empirical broad spectrum antibiotic therapy (piperacillin-tazobactam) was given. CT-guided percutaneous drainage was performed obtaining purulent material. *Streptococcus salivarus* was identified in microbiological cultures. Antibiotic therapy was changed to amoxicillin/clavulanic acid (1 g/8 h) as a result of the antibiogram. ERCP plus sphincterotomy was performed because of a frank intrabiliary rupture identified on CT. She was scheduled for surgery 15 d after coming to our center. After right subcostal incision, an 11-cm LHC was found in segments Ⅶ and Ⅷ attached to the diaphragm, right hepatic vein and inferior cava vein. A subtotal cystectomy was performed. Postoperatively, the patient required red blood cell transfusion and was discharged on the fourth day (total stay: 19 d). Histopathology showed a pericystic wall with fibrosis, inflammation and calcification. No recurrence was seen at the last follow-up visit 2.5 years later.

## DISCUSSION

The most severe complications of LHC are rupture, biliary fistula and infection of the cyst, evolving into a liver hydatid abscess[4]. LHA has a prevalence of about 25%. In Manterola's series it was the most frequent complication (24.6%), but in ours it accounted for only 4.1%[3]. We attribute this huge difference to the lack of a generally accepted worldwide definition of LHA. Some authors define LHA as any hydatid cyst which presents purulent content if opened during surgery, but others require bacterial growth in microbiological cultures in both cases with or without infectious symptoms. Our idea is that LHA should be defined not only in the presence of pus or positive cultures but always with severe infectious symptoms such as high fever, malaise, or even septic shock. The infection that provokes LHA may be primary, due to the invasion of bacteria from small bile ducts communicating into the cyst or rarely through the hematogenous route, or secondary, due to a communication through a fistula with the peritoneal cavity, bronchi, digestive tract, or skin, and after conservative surgery or incomplete PAIR[4].

LHA patients are generally asymptomatic or have nonspecific clinical manifestations. Diagnosis is often made due to the clinical manifestations of other complications such as acute cholangitis, peritonitis, pericarditis or bronchobiliary fistula[5]. In the days prior to diagnosis all our patients reported nonspecific and insidious symptoms such as fever, malaise, dyspnea, abdominal discomfort and a progressive and significant deterioration in their general condition. The scarcity of symptoms of LHA (compared with pyogenic liver or intra-abdominal abscess) is probably due to the action of the pericystic wall offering theoretical protection against infectious dissemination[6].

Usually, the first tool for diagnosing LHA is ultrasound. The ultrasound image of the LHA may not be characteristic, and differential diagnosis should include uncomplicated cyst type Ⅰ Gharbi, liver abscess from another origin, or infected simple cyst[7]. In one of the cases reported here abdominal radiography provided important clues for diagnosis. CT was the best diagnostic method in our short series, but no evidence-based medicine information can be drawn from only three cases.

The management of LHA is not standardized. Simple surgical drainage of the cyst has been described, but this technique may need subsequent additional surgical procedures; if cyst surgery is not performed, relapse and chronic complications due to the persistence of residual cyst cavity are frequent[6]. The most widely accepted approach is non-scheduled conservative surgery, usually subtotal pericystectomy including opening of the cavity, exhaustive cleaning of the cyst, eradication of the parasite and closing of the cystobiliary fistulas. But this type of surgery could be suboptimal because the patient is often in a poor clinical condition, and in fact LHA is a risk factor for postoperative complications (especially infections) in patients undergoing surgery for LHC[8]. To our knowledge, percutaneous drainage of the cyst, supportive measures and intravenous antibiotics as a therapeutic bridge to more radical and safer surgery have not been described previously. Here we present three patients treated with this approach in whom we were able to control the infection and improve the patients' clinical condition prior to scheduled surgery two weeks later. What is more, we were able to perform an ERCP in one of our patients with a frank intrabiliary rupture. The improved medical condition allowed us the possibility of resecting a greater quantity of cyst, thus reducing the risk of possible relapse.

To conclude, percutaneous drainage of LHA as a bridge to surgery may be a valid procedure especially

in patients at high surgical risk due to septic conditions. With this approach we were able to control the infection with antibiotics and perform surgery once the patient's overall condition had improved.

## COMMENTS

### Background

Cystic echinococcosis is a zoonotic disease that is found worldwide. It is caused by larvae of the genus *Echinococcus*, and is endemic in certain areas of the planet. The liver is the most common location for cyst developmen. Infection of the liver hydatid cyst (LHC) and pyogenic abscess formation is a rare but highly severe complication.

### Research frontiers

The clinical course is insidious and it is usually diagnosed when the infection has progressed. The treatment of liver hydatid abscess (LHA) is not yet standardized. Several options are available with the dual purpose of draining the LHA and treating the LHC, including simple surgical drainage, or surgical drainage associated with total or subtotal pericystectomy and percutaneous drainage.

### Innovations and breakthroughs

The authors propose percutaneous drainage of the LHA as a first therapeutic step, and later, when the patient's general condition improves, surgical treatment of the LHC.

### Applications

The authors present a new therapeutical option that could let surgeons to obtain better results.

### Peer-review

Interesting case series of three cases. Detailed description and very helpful Table 1.

## REFERENCES


1 **Ramia JM**, Serrablo A, De la Plaza R, Esarte J, Gijón L, Sarria L, Figueras J, García-Parreño J. Is radical surgery feasible in liver hydatid cysts in contact with the inferior vena cava? *World J Surg* 2014; **38**: 2940-2945 [PMID: 24889413 DOI: 10.1007/s00268-014-2658-0]

2 **Ramia JM**, Poves I, Castellón C, Diez-Valladares L, Loinaz C, Serrablo A, Suarez MA. Radical laparoscopic treatment for liver hydatidosis. *World J Surg* 2013; **37**: 2387-2392 [PMID: 23838933 DOI: 10.1007/s00268-013-2150-2]

3 **Manterola C**, Moraga J, Urrutia S, MINCIR GROUP. Aspectos clínico-quirúrgicos de la hidatidosis hepática, una zoonosis de creciente preocupación. *Rev Chil Cir* 2011; **63**: 641-649 [DOI: 10.4067/S0718-40262011000600017]

4 **Prousalidis J**, Kosmidis C, Anthimidis G, Fachantidis E, Harlaftis N, Aletras H. Forty-four years' experience (1963-2006) in the management of primarily infected hydatid cyst of the liver. *HPB* (Oxford) 2008; **10**: 18-24 [PMID: 18695754 DOI: 10.1080/13651820701854669]

5 **Manterola C**, Barroso M, Vial M, Bustos L, Muñoz S, Losada H, Bello N, Hernández F, Carrasco R. Liver abscess of hydatid origin: clinical features and results of aggressive treatment. *ANZ J Surg* 2003; **73**: 220-224 [PMID: 12662231 DOI: 10.1046/j.1445-2197.2003.02354.x]

6 **Manterola C**, Urrutia S. Infected Hepatic Echinococcosis: Results of Surgical Treatment of a Consecutive Series of Patients. *Surg Infect* (Larchmt) 2015; **16**: 553-557 [PMID: 26125624 DOI: 10.1089/sur.2014.054]

7 **Manterola C**, Acencio L, Garrido L, Molina E, Barroso M. Absceso hepático de origen hidatídico: resultados de la cirugía de urgencias. *Rev Chil Cir* 1997; **49**: 510-514

8 **Manterola C**, Sanhueza A, Vial M, Moraga J, MINCIR. ¿Es el absceso hepático de origen hidatídico un factor de riesgo para el desarrollo de complicaciones postoperatorias en pacientes intervenidos por hidatidosis hepática? *Rev Chil Cir* 2009; **61**: 333-338 [DOI: 10.4067/S0718-40262009000400005]


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