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REVIEW

# Outcomes of liver transplantation in patients with hepatorenal syndrome

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Author contributions: Modi RM and Mumtaz K decided upon the aims of the article, wrote the manuscript, and made necessary revisions; Patel N and Metwally SN helped in writing and reviewing the manuscript.

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## Abstract

Hepatorenal syndrome (HRS) plays an important role in patients with liver cirrhosis on the wait list for liver transplantation (LT). The 1 and 5-year probability of developing HRS in cirrhotic with ascites is 20% and 40%, respectively. In this article, we reviewed current concepts in HRS pathophysiology, guidelines for HRS diagnosis, effective treatment options presently available, and controversies surrounding liver alone *vs* simultaneous liver kidney transplant (SLKT) in transplant candidates. Many treatment options including albumin, vasoconstrictors, renal replacement therapy, and eventual LT have remained a mainstay in the treatment of HRS. Unfortunately, even after aggressive measures such as terlipressin use, the rate of recovery is less than 50% of patients. Moreover, current SLKT guidelines include: (1) estimation of glomerular filtration rate of 30 mL/min or less for 4-8 wk; (2) proteinuria > 2 g/d; or (3) biopsy proven interstitial fibrosis or glomerulosclerosis. Even with these updated criteria there is a lack of consistency regarding long-term benefits for SLKT *vs* LT alone. Finally, in regards to kidney dysfunction in the post-transplant setting, an estimation of glomerular filtration rate < 60 mL/min per 1.73 $m^2$ may be associated with an increased risk of patients having long-term end stage renal disease. HRS is common in patients with cirrhosis and those on liver transplant waitlist. Prompt identification and therapy initiation in transplant candidates with HRS may improve post-transplantation outcomes. Future studies identifying optimal vasoconstrictor regimens, alternative therapies, and factors predictive of response to therapy are needed. The appropriate use of SLKT in patients with HRS remains controversial and requires further evidence by the transplant community.

**Key words:** Liver transplantation; Simultaneous liver kidney transplantation; Vasopressors; Dialysis; Post-transplant outcomes; Hepatorenal syndrome

**Core tip:** We aim to review the literature on hepatorenal syndrome (HRS) in the setting of liver transplantation (LT) and address critical issues that are barriers to improved outcomes. Many consistencies have remained as treatment options including albumin, vasoconstrictors, renal replacement therapy, and eventual LT. Moreover, the utility of simultaneous liver kidney transplantation in HRS patients still requires further evidence by the transplant community.

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## INTRODUCTION

Prior to diagnosing a patient with hepatorenal syndrome (HRS) in the setting of liver transplantation (LT), it is important to rule out other etiologies of renal dysfunction. A broad differential should include reversible causes such as acute kidney injury (AKI) or acute tubular necrosis (ATN) and irreversible cause like chronic kidney disease (CKD) or parenchymal kidney disease.

Traditionally there are three types of AKI (pre-renal azotemia, intrinsic kidney disease, and post-obstructive causes) that are still common in patients with liver disease in addition to HRS[1]. Common causes of pre-renal injury independent of HRS include infection, intravascular fluid depletion, GI fluid losses, surgery or bleeding, and renal artery occlusion[2], all of which should appropriately respond to volume expansion with albumin within 48 h. If there is any recent contrast media or nephrotoxic agent with granular casts and proteinuria > 500 mg, it is important to consider ATN as a likely diagnosis[3]. A recent study evaluating patients with AKI [pre-renal azotemia ($n$ = 35), HRS ($n$ = 35), ATN ($n$ = 36)] revealed that pre-renal azotemia has a lower mortality when compared to both HRS ($P$ = 0.05) and ATN ($P$ = 0.04)[4].

Intrinsic kidney disease is more common than previously believed in the cirrhotic population, and is thought to be related to the underlying etiology of cirrhosis[2]. Kidney biopsy is most useful in intrinsic kidney disease with hematuria (50 red blood cells per high power field), proteinuria (> 500 mg/d), renal insufficiency of unknown origin, or HRS for a prolonged period of time. Histologically, IgA nephropathy, membrano-proliferative glomerulonephritis, focal global glomerulosclerosis, and diabetic nephropathy[5] are the most common biopsy findings. The importance of diagnosing parenchymal disease is especially important if a patient is being considered for combined liver-kidney transplantation[6]. Additionally, obstructive causes of renal dysfunction including nephrolithiasis, bladder outlet obstruction and other intra-abdominal etiologies should be assessed.

If the aforementioned workup returns negative, HRS should be considered as a potential cause of renal dysfunction. The 1-year and 5-year probability of developing HRS in patients with ascites is 20% and 40%, respectively[7]. The most recent diagnostic criteria for HRS from the International Ascites Club (IAC) in 2007 include creatinine (Cr) > 1.5 mg/dL, no improvement of Cr after volume expansion with albumin after 48 h, no current or recent exposure to nephrotoxic drugs, absence of parenchymal disease (proteinuria > 500 mg/d), microscopic hematuria (50 red blood cells per high power field), and abnormal renal ultrasonography[8].

In this review, we will focus on various aspects of HRS and its impact on various phases of LT. Literature was searched for this review from various search engines including PubMed, Cochrane, and Scopus. Each of the citations for the papers originally pulled was then reviewed for additional articles for inclusion.

## ROLE OF CR AND OTHER MARKERS OF RENAL IMPAIRMENT IN CIRRHOTICS

There is concern that serum Cr may not reflect accurate kidney function in the setting of HRS with significant liver dysfunction[8,9]. Cr is an indirect measure of renal function as it is derived from non-enzymatic conversion of creatine, which is stored in muscle and being produced within the liver. As patients develop cirrhosis there is increased muscle wasting, decreased protein intake, and diminished creatine synthesis resulting in overestimation of renal function[9,10]. Moreover, two individuals with similar glomerular filtration rates may have varying Cr levels due to variation associated with age, sex, race, body mass index, and bilirubin concentrations[11]. For example, women generally have lower serum Cr levels compared to men resulting in lower median MELD scores (14 *vs* 15, $P$ < 0.001) and a higher likelihood to die on the transplant list when compared to the pre-MELD era[12].

Multiple mathematical formulas have been developed to utilize serum Cr to calculate an estimation of glomerular filtration rate (eGFR). These include Cockcroft-Gault (C-G) and Modification of Diet in Renal Disease (MDRD) which incorporate different variables. C-G requires age, gender, weight, and serum Cr, while MDRD-4 utilizes age, gender, ethnicity, and serum Cr and MDRD-6 also involves albumin and urea[13,14]. In our cirrhotic population, MDRD-6 is used more widely when compared to C-G given inclusion of albumin and urea. Moreover, exogenous markers such as inulin have been previously documented to improve accuracy when determining renal function. Unfortunately the "gold standard" inulin infusion technique is time consuming, expensive, and potentially invasive making it a less viable option[15].

Multiple AKI biomarkers including NGAL, Cystatin C, IL-18, NAG, and KIM-1 have been well characterized

and may delineate patients who have the risk of progression of disease and will require renal replacement therapy (RRT)[2,16,17]. For example, Aberg *et al*[18] looked specifically at the urinary marker neutrophil gelatinase-associated lipocalin (NGAL) in 203 LT patients and demonstrated that raised urinary levels of NGAL independently predicted pre-LT kidney dysfunction in the setting of HRS and could have the potential to help decide the need to performed combined liver-kidney transplantation. Additionally, urinary NGAL levels to be a strong predictor for short-term mortality, with HRS patients having intermediate levels between prerenal azotemia and intrinsic AKI[19]. Furthermore, certain studies have also shown cystatin C level may be an important marker for predicting mortality in HRS[20,21]. However, it is important to note that at this time current IAC or Acute Dialysis Quality Initiative do not recommend evaluating for these biomarkers.

## BRIEF PATHOPHYSIOLOGY AND TYPES OF HRS

The pathophysiology of HRS has been well documented previously with portal hypertension leading to splanchnic artery dilatation[22,23]. This phenomenon results in a number of downstream effects including arterial underfilling, increased cardiac output, and vasoconstriction of renal arteries[8]. Ultimately the kidneys respond with increased activity of renin-angiotensin-aldosterone system as well as non-osmotic release of vasopressin, both of which result in worsening GFR, ascites, and hemodynamic instability[24,25].

HRS is typically divided into two subtypes, type 1 and type 2, based on the rate of progression of renal disease and prognosis. Diagnostic criteria for type 1 HRS (in addition to criteria for HRS according to IAC mentioned above) include serum Cr > 2.5 mg/dL, doubling of serum Cr in less than 2 wk, no history of diuretic resistant ascites, and generally a precipitating event. On the other hand, type 2 HRS is a gradually progressive renal impairment without any precipitating events and usually associated with diuretic resistant ascites. Additionally, patient outcomes in terms of survival were reported to be better with type 2 HRS *vs* type 1[26].

## CLASSIFICATIONS OF RENAL DYSFUNCTION IN PATIENTS WITH CIRRHOSIS

Various criteria are used for classification of renal dysfunction in patients with liver cirrhosis. Two of the most commonly used criteria include the Risk, Injury, Failure, Loss, and End-Stage Kidney Disease (RIFLE) and AKI network (AKIN). The RIFLE criteria utilize both serum Cr level and urine output to assess what stage of renal injury has occurred. For example, acute renal injury is Cr doubled from baseline and urine output < 0.5 mL/kg per hour over 12 h while acute renal failure is Cr tripled from baseline and urine output < 0.3 mL/kg per hour over 24 h. A major limitation of the RIFLE classification is that per these criteria a large number of cirrhotic patients would already present with some degree of AKI. In 2007 the AKIN has proposed a new definition of AKI that condenses RIFLE into 3 stages to increase sensitivity and specificity of diagnosing AKI. Moreover, the Kidney Disease Improving Global Outcomes recently defined AKI as diminished kidney function resulting in 0.3 mg/dL increase in serum Cr in 48 h, or a 50% increase in baseline Cr (within 7 d), or a urine volume of < 0.5 mL/kg per hour for 6 h[8,27]. It has been well documented that approximately 20% of patients hospitalized for decompensated cirrhosis present with a concomitant AKI[28]. This phenomenon is related to the progressive vasodilatory state of cirrhosis causing a decrease in arterial volume and resultant vasoconstriction of renal vessels. Interestingly, two prospective studies assessing AKI criteria in patients with cirrhosis found that AKI with serum Cr values < 1.5 mg/dL is a relatively benign and potentially reversible condition, while significant increase in Cr (> 1.5 mg/dL) is associated with a worse prognosis[29,30].

A retrospective study utilized the RIFLE classification to look at 283 patients who underwent LT and stratified them into three cohorts: Risk, injury, and failure. Moreover, the failure group was further subdivided by etiology (HRS *vs* ATN) and the clinical course was followed for 5 years. Comparing these groups, the ATN group had significantly worse 1- and 5-year survival and renal outcomes, with an increased incidence of stage 4 and 5 CKD[31]. While only a single-center retrospective study, it is instrumental in demonstrating that the etiology of AKI may be more important than initially thought in predicting renal recovery[32].

Prerenal injury, ATN, and HRS encompass close to 80% of AKI etiology in the in the pre-transplantation setting[33]. A United Network for Organ Sharing (UNOS) based study in 2002 found that 40% of LT candidates have kidney dysfunction, best defined as a GFR < 60 $cm^3$/min per square meter[34]. More recently, a prospective study following 463 patients classified renal failure into four main categories: Infections ($n$ = 213, 46%), hypovolemia associated renal failure ($n$ = 149, 32%), HRS ($n$ = 60, 13%), parenchymal nephropathy ($n$ = 41, 9%)[35]. While this is a simple classification, it is useful to assess prognosis and decisions regarding LT.

## PREVALENCE AND PRECIPITANTS OF HRS IN WAIT-LIST AND TRANSPLANT PATIENTS

The prevalence of HRS has been reported to increase with severity and duration of cirrhosis. Ginès *et al*[36] studied 229 patients with cirrhosis and found an 18% incidence of HRS at one year, with an increase to 39% within five years. Additionally, Wong *et al*[37] reported

HRS in 48% of patients on the LT waiting list, indicating an increased prevalence with disease progression. Various precipitants of HRS include spontaneous bacterial peritonitis, large volume paracentesis with inadequate albumin replacement, use of nephrotoxic drugs and hypovolemia due to bleeding and or dehydration. With the help of early diagnosis and aggressive management with vasopressors the incidence of HRS may decrease with an improvement in overall outcomes[38].

## MANAGEMENT OF HRS

Medical management of HRS has been shown to improve short-term outcomes; however, long term outcomes are dismal without LT. Current medical treatment includes avoidance of HRS precipitants and pharmacological management prior to considering transjugular intrahepatic portosystemic shunt (TIPS) and RRT. Pharmacological treatment serves as a bridge to transplantation to improve the patient's prognosis. There is a consensus on general measures in treating HRS including suspension of diuretic therapy, avoidance of nephrotoxic drugs and adjustment in doses of drugs. Moreover, per AASLD guidelines the role of albumin after large volume paracentesis (8 g of albumin for each liter of ascites removed) has been the standard of care.

### *Role of terlipressin in HRS*

Given the significance of arterial vasodilatation in the pathophysiology of HRS, vasoconstrictors along with albumin have improved renal function in approximately 40%-60% of patients with type 1 HRS (Table 1)[39]. Terlipressin plus albumin has been shown to improve renal function in 35%-40% of patients with type 1 HRS, with initial IV boluses of 0.5-1 mg every 4 h that can be titrated to 3 mg every 4 h if there is limited response[40-42]. A study comparing terlipressin bolus *vs* continuous infusion found that while the rate of response was not statistically significant, the rate of adverse of events was lower in the infusion group with lower associated dosing[43].

While many studies demonstrate the use of terlipressin as a bridge to transplantation, it is important to note that fewer than 50% of patients who used terlipressin in the setting of HRS recover from a renal standpoint. One study assessed the efficacy of terlipressin plus albumin *vs* albumin alone for treatment of HRS-1 in the setting of LT. The 6-mo survival rate for those in the terlipressin group was 100% for transplanted patients and 34% for non-transplanted patients, while in the control group survival was 94% for transplanted patients and 17% for non-transplanted patients[44]. This study was able to show that terlipressin likely improved pre-transplant renal function while having no significant impact on post-transplant survival. On the other hand, Sagi *et al*[45] concluded improved transplant-free survival at 90 d (RR = 1.86, 95%CI: 1.0-3.4, $P = 0.05$) in those in the terlipressin arm when studying 223 patients in 4 separate trials. A prospective, randomized, double-blind, placebo-controlled clinical trial showed that terlipressin group showed Cr improvement from baseline to day 14 while on the treatment[46]. It appears that terlipressin treatment beyond one week and up to 20 d has the potential for further improvement[47]. Moreover, a recent meta-analysis of randomized trials (5 trials, $n = 243$ patients), showed the overall rate of patients on terlipressin with HRS who recovered renal function was 8.09 (95%CI: 3.52-18.59, $P < 0.001$[48]).

One study found a better response to terlipressin in the setting of higher serum sodium concentrations and lower serum bilirubin at the beginning of treatment[49], which would indicate that the early identification and treatment of HRS-1 may improve outcomes. A larger study was able to identify independent predictors of survival in the setting of terlipressin including age, duration of treatment, MELD score, and alcoholic cirrhosis[50], while an additional study was able to identify low urinary sodium prior to treatment being associated with poor survival[51].

Similar to the type 1 HRS patient population, terlipressin has been shown to improve renal function in type 2 HRS (Cr improvement in 8 out of 11 patients) when compared to organic renal disease[52]. Interestingly, a recent study examined 56 patients awaiting LT who were diagnosed with type 2 HRS. A subset of patients were being treated with terlipressin and albumin, but no differences were found in mortality in peri-operative setting or in post-transplantation outcomes (AKI, need for RRT, or development of CKD) when compared to the control group[53]. Moreover, another study also showed no benefit in using terlipressin in the setting of type 2 HRS[54]. Furthermore, while LT helps reverse type 2 HRS, there may be an association with longer intensive care stays and early-post-transplant CKD stage 3[55].

### *Role of other vasoconstrictors in HRS*

Terlipressin is not available in United States; therefore midodrine, octreotide, ornipressin and noradrenaline with albumin have been used in uncontrolled studies to treat HRS. It was found that HRS patients were more likely to improve while treated with AVP when compared to octreotide alone[56]. Another study assessed the effect of octreotide, midodrine, and albumin on survival compared to control populations and found improved renal function and short-term survival in the setting of both HRS-1 and HRS-2[57]. With use of a combo of octreotide, midodrine and albumin, reversal of HRS has been reported to be as high as 40%[58].

Ornipressin is another potent splanchnic vasoconstrictor, but has been shown to have a higher incidence of vascular complications when compared to terlipressin[59]. In regards to noradrenaline, an unblinded study in 2007 was able to show that noradrenaline is an effective alternative to terlipressin in the setting of HRS type 1[60]. A more recent meta-analysis looked at 4 smaller studies where 154 patients were included and found that there was no difference between noradrenaline and terlipressin in regards to mortality at 30 d (RR = 0.89, 95%CI: 0.68 to 1.17) and reversal of HRS (RR = 0.97, 95%CI: 0.76 to 1.23)[61].

**Table 1 The role of terlipressin and albumin in hepatorenal syndrome-1**

| Ref. | Terlipressin dose | Albumin | Length | Terlipressin group: Cr (mg/dL) or Cr Cl (mL/min) | Control group: Cr (mg/dL) or Cr Cl (mL/min) | 30 d survival (terlipressin *vs* control) | Transplant free outcome |
|---|---|---|---|---|---|---|---|
| Hadengue *et al*[113] | 1 mg twice daily | No | 2 d | Cr Cl: 27 ± 4 | Cr Cl: 15 ± 2 | N/A | N/A |
| Halimi *et al*[49] | 4 mg/d | Yes | 7 d (mean) | Decline in Cr from 31%-75% from day 0 to day 5 | N/A | 13/18 (72%) patient response | N/A |
| Danalioglu *et al*[42] | 2-4 mg/d | Yes | 6 d | N/A | N/A | 20% *vs* 0% | N/A |
| Testro *et al*[54] | 1 mg every 6 h (max of 8 mg/d) | Yes | 12 d | N/A | N/A | 17/49 HRS type 1, 4/20 HRS type 2 | All transplant free outcomes responded to terlipressin |
| Sanyal *et al*[46] | 1 mg every 6 h (doubled on 4 d if Cr did not < 30%) | No (control group received albumin) | 14 d | Cr < 1.5 mg/dL (19/59, 33.9%) | Cr < 1.5 mg/dL (7/56, 12.5%) | N/A | 42.9% (24/56) *vs* 37.5% (21/56) in terlipressin *vs* control group at 180 d |
| von Kalckreuth *et al*[47] | 3.9 mg ± 1.3 mg (responders) *vs* 3.4 mg ± 1.4 mg (nonresponders) | Yes | 6 ± 4.9 d (responder) *vs* 8 ± 6.3 d (non-responders) | N/A | N/A | Complete response by day 7 was 52%, while at day 17 it was 84% | 25/38 (66%) of treatment complete response was achieved |
| Boyer *et al*[44] | 1 mg every 6 h | Yes | 6.3 d (mean) | Cr: 2.8 mg/dL | Cr: 3.8 mg/dL | N/A | 34% non-transplanted survival 100% transplant survival at 180 d |
| Hinz *et al*[51] | 2-6 mg/d | Yes | N/A | N/A | N/A | 57% of patients (12/21) responded to terlipressin. Age was a negative predictor for treatment response | No difference seen in mortality between responders and non-responders at 60 d |
| Heidemann *et al*[50] | 26.43 ± 30.86 (total dose for responders) *vs* 32.11 ± 31.57 (total dose for non-responders) | Yes | 9 d (responders) *vs* 10.5 d (non-responders) | N/A | N/A | One month survival was longer in responders *vs* non-responders ($P$ = 0.048) | N/A |
| Sagi *et al*[45] (meta-analysis) | N/A | Yes | Minimum of 3 d of terlipressin | Cr must have been < 1.5 mg/dL at treatment end | N/A | Four trials ($n$ = 223) with RR for reversal in type 1 HRS with terlipressin was 3.66 (95%CI: 2.15-6.23) | N/A |
| Fabrizi *et al*[48] (meta-analysis) | N/A | N/A | N/A | N/A | N/A | Five trials ($n$ = 243 patients) with pooled OR of HRS reversal was 8.09 (95%CI: 3.52; 18.59) | Recovery of renal function occurs in less than 50% of patients with HRS even with terlipressin |

Cr: Creatinine; Cr Cl: Creatinine clearance; HRS: Hepatorenal syndrome; N/A: Not available.

A recently published randomized study directly compared terlipressin with albumin to midodrine plus octreotide with albumin[62]. Terlipressin group was found to be significantly more effective in improving kidney function in HRS patients (70% *vs* 28%)[62]. Additionally, a small study that looked at three patients who were initially on terlipressin and attempted to switch treatment to midodrine plus octreotide on multiple attempts were found to have serum Cr elevation as well as diminished urine output[63].

### *Other treatment options for HRS*

Among other options available for HRS management, TIPS has been increasingly utilized. While it is well documented that TIPS is effective treatment for refractory variceal bleeding and ascites, its role in patients with renal dysfunction is unclear. Few small studies on HRS indicate some clear benefit after TIPS[64,65]. A study examining non-

transplantable cirrhotic (14 type 1 HRS and 17 type 2 HRS) patients showed renal function improved within two weeks after TIPS with improved mortality over the course of 18 mo[66]. A recent study utilizing UNOS demonstrated that patients on the LT list status-post TIPS procedure had a lower mortality rate compared to patients without TIPS[67]. This study hypothesized that the TIPS plays a role in promoting survival by improving nutritional status and preventing variceal bleeding, refractory ascites, and HRS. It is important to remember that TIPS can increase the risk of hepatic encephalopathy as well as liver failure in rare occasions[68].

Molecular absorbent recycling system (MARS) has the ability to remove both small- and medium-sized lipophilic toxins and may have a role in improving complications of liver disease such as hepatic encephalopathy and HRS. Multiple studies have shown MARS having the ability to reduce cholestatic parameters, improve mentation, as well as renal function especially in patients with a Model for End-Stage Liver Disease (MELD) between 20-29[69,70]. In 2002 a study showed when MARS was used there was improvement in mentation and hepatic encephalopathy in 14 out of 19 centers[71]. Interestingly, when MARS was directly compared to hemodiafiltration there was a decrease in Cr and bilirubin as well as a decrease in mortality at day 7[72]. Furthermore, a study looking at MARS use in the post-transplantation setting with HRS, HE, or intractable pruritis showed improvement in symptoms and laboratory findings[73]. However, none of these studies showed long term benefit in HRS patients including transplant free survival.

## PREDICTORS OF MORTALITY IN PATIENTS WITH HRS

Yang *et al*[74] studied the predictors of mortality in type 1 HRS in a tertiary care center and formulated a time-dependent proportional hazards model. Contrary to other studies reporting on MELD score as predictor mortality, they found increased Cr by each point and total bilirubin levels during the admission increased mortality risk by 29% and 4%, respectively. Increasing albumin level during the admission showed its protective value[74].

Sanchez *et al*[75] looked at pre and peri-transplant predictors of renal dysfunction requiring either RRT or HD. This study looked at 724 LT patients where a clinical prediction model was constructed to assess the probability of requiring dialysis post-transplantation in a prospective manner. Pre-LT Cr > 1.9 mg/dL (OR = 3.57), pre-LT BUN > 27 mg/dL (OR = 2.68), ICU stay > 3 d (OR = 10.23), and MELD score > 21 (OR = 2.5) were significant[75]. Furthermore, changes in MELD scores (influenced by Cr and bilirubin) during the admission predict prognosis more so than the initial MELD[74]. A recent study was performed in attempts to assess renal impairment prior to overt HRS development by measuring renal arterial resistance indices (RI)[76]. Interestingly, RI was significantly higher in patients with ascites than those without ascites and may be an independent predictor of subsequent HRS development. Another study was able to show that "MAP responders" had improved response with better transplant-free survival in both the short-term and long-term settings[77]. However, these innovative modalities need further studies before being used in daily practice.

## LT ALONE *VS* SIMULTANEOUS LIVER KIDNEY TRANSPLANT FOR HRS

Since the introduction of the MELD scoring system there has been an increase in the number of simultaneous liver-kidney transplants (SLKT). From 2002 to 2013, the percentage of SLKT has increased from 4.2% to 8.1%, respectively. The most recent recommendations for SLKT include: (1) eGFR of 30 mL/min or less for 4-8 wk; (2) proteinuria > 2 g/d; and (3) biopsy proven interstitial fibrosis or glomerulosclerosis (Figure 1)[78]. An unintentional by product of SLKT has been a decrease number of kidney donors available for end stage renal disease (ESRD) patients. There are numerous studies indicating we should have stricter criteria for allocating two grafts to one patient as well as a debate on duration of renal dysfunction and duration of RRT in the setting of SLKT. A recent study proposed raising the dialysis requirement to greater than 12 wk (rather than current recommendations of 4-8 wk) to increase the number of kidney transplantations available for ESRD patients[79]. Table 2 outlines the outcomes of studies comparing liver transplantation alone (LTA) alone *vs* SLKT in the setting of HRS. One study retrospectively looked at 69 LT patients with a pre-transplantation Cr $\geqslant$ 1.5 and found that duration of pre-transplantation RRT rather than cause of renal dysfunction was a predictor of 6- and 12-mo kidney function post-LTA[80]. Interestingly, earlier studies have shown mixed data in regards to the utility of SLKT in the setting of HRS. A 1997 UNOS study looked at 414 SLKT *vs* 2442 LTA with a Cr > 2.0 and found a 5 year survival of 62.2% for SLKT patients and 50.4% for LTA recipients, suggesting SLKT may be beneficial for HRS patients[81]. Furthermore, another study including local center and UNOS database (2002-2008) compared LTA *vs* SLKT in the setting of renal impairment. Diagnosis of HRS was presumptive in UNOS database and confirmed on the local data. UNOS data showed a survival benefit of SLKT over LTA for those patients with poor renal function, specifically those with HRS, whereas results of local center suggest otherwise[82].

On the other hand, a small study showed that in patients with HRS, SLKT did not confer a survival advantage over LTA (1-year patient survival was 72% *vs* 66%, *P*-value = 0.88)[83]. A much larger 2006 UNOS study that compared 1032 SLKT to 19137 LTA patients showed no mortality difference for patients with HRS (1 year survival was 72% *vs* 66%) unless the patient was receiving HD for longer than 8 wk, with a dialysis duration of > 12 wk that was a significant predictor for long-term outcomes[84]. Furthermore, one meta-analysis looked at 3536 SLKT

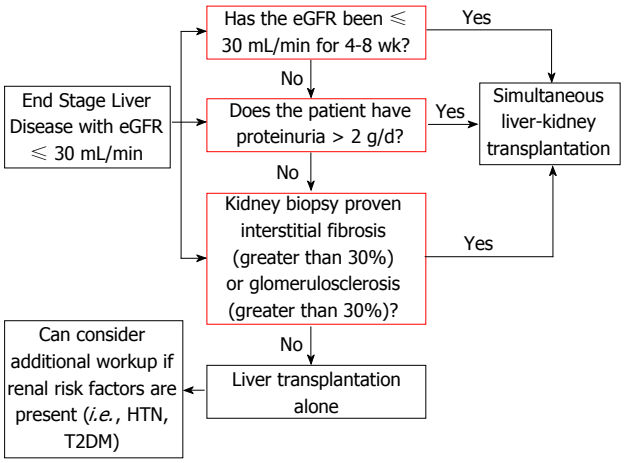


**Figure 1 Algorithm for evaluating for simultaneous liver-kidney transplantation in a liver transplant candidate with renal dysfunction.** Modified from Saxena *et al*[78]. eGFR: Estimation of glomerular filtration rate; T2DM: Type 2 diabetes mellitus; HTN: Hypertension.

(between 1984 to 2008) and found that the cumulative 1, 2, 3 and 5-year patient survival were 84.9%, 52.8%, 45.4% and 42.6%. It was concluded that there was no definitive evidence of better graft or patient survival in the SLKT population when compared to the LTA given the difficulty discerning irreversible kidney function in liver transplant candidates[85]. Additionally, one study found the rate of renal non-recovery within 6 mo of LTA for 2112 patients who underwent RRT within 90 d of their transplantation was only 8.9%, with risk factors for non-recovery including age, T2DM, and duration of RRT[86]. Because of this limitation as well as selection biases, the true survival benefit of SLKT in candidates without ESRD remains unproved[87].

It appears that UNOS database studies have heterogeneous groups, including patients with renal impairment due to multiple reasons and hence a selection bias for patients with HRS. Single center studies have issue of small sample size. Nevertheless, chances of misclassification bias in small studies are less. These studies do not report added benefit of SLKT over LTA in patients with HRS, not on HD and duration of renal dysfunction < 8 wk.

Interestingly some studies address benefit of SKLT over LTA alone with respect to immune safety liver graft on kidney graft function due to immunogenic effect of liver. These studies justified SLKT over LTA for two additional reasons: (1) it is well documented there is significant decrease in graft rejection when a patient has a SLKT over an LTA (15% decreased reduction in graft loss); and (2) there is superior recipient and graft survival when compared to Kidney After LT or Liver After Kidney Transplantation[88,89]. Priority for allocation of kidneys to kidney-liver candidates follows the allocation priority for the non-renal organ. However, due to shortage of organ and justification of an equitable distribution of organ it is not possible to perform SLKT for this indication.

## HRS AND POST-TRANSPLANT MANAGEMENT/OUTCOMES

### *Impact of HRS on outcomes of LT*

The impact of LT on overall renal function has been well documented. Lafayette *et al*[90] looked at renal function in the pre-transplantation setting and studied 115 liver transplant recipients by arbitrarily dividing them based on serum Cr into two groups (group 1 with Cr > 1.0, group 2 with < 1.0); they showed that group 1 patients had significantly longer ICU stays, higher hospital charges, and a greatly increased mortality rate[90]. Patients with HRS tend to require longer hospitalizations, increased intensive care duration, and further dialysis in the post-op setting[91]. Interestingly, when comparing HRS *vs* ATN post-transplant outcomes it was found that ATN was associated with higher mortality at 1 year post-LT along with increased incidence of CKD (stage 4 or 5) when compared to HRS[31].

One of the first studies to address HRS in the post-operative setting was in reported in 1991 where Gonwa *et al*[92] found close to 10% of HRS patients developed ESRD post-transplant when compared to 0.8% of non-HRS patients ($P$ < 0.005). However, a similar study revealed that while HRS patients were more likely to be dialyzed post-operatively, there was no difference between Cr levels at 24 wk between non-HRS *vs* HRS groups[93]. Park *et al*[94] also confirmed this concept in a study that yielded similar results in 1-year patient survival after LT in the HRS patients *vs* those without HRS ($P$ = 0.37).

In regards to AKI in the post-LT setting, a large study looking at 1352 LT recipients found that 162 (12%) patients developed acute renal failure (ARF) within the first week. Type 2 HRS with GFR < 50 mL/min was reported to be one of major risk factor[95]. However, López Lago *et al*[96] also looked at HRS *vs* non-HRS patients who developed ARF in the post-LT setting but found no differences in 1 year mortality, need for RRT, or rejection.

Many studies have aimed to identify the role of GFR following transplantation in stratifying risk of kidney impairment. Sato *et al*[97] showed that an eGFR < 60 mL/min per 1.73 $m^2$ during the first month post LT can be associated with increased rate of development of CKD, 2 years post-OLT. Interestingly, a recent study assessed 191 LT patients who underwent intense post LT GFR measurements (especially at 1 and 3 years). The study concluded that a low GFR (< 40 mL/min per 1.73 $m^2$) at 1 year was associated with higher risk for late renal dysfunction[98]. Moreover, Longenecker *et al*[99] looked at the progression of GFR over 15 years post transplantation and found that eGFR < 60 mL/min per 1.73 $m^2$ and type 2 diabetes at the time of transplantation were associated with increased rates of progression to ESRD. When discussing long-term requirement of RRT post-transplantation, one study assessed 208 LT recipients and found 5.8% of surviving

**Table 2 Comparing outcomes measures between liver transplantation alone *vs* simultaneous liver kidney transplantation including graft and patient survival as well as need for renal replacement therapy**

| Ref. | No. of LTA | No. of SLKT | Graft survival (LTA *vs* SLKT) | Patient survival (LTA *vs* SLKT) | Renal dysfunction post 1, 5 and 10 yr (LTA *vs* SLKT) | RRT post-transplantation (LTA *vs* SLKT) | Additional comments |
|---|---|---|---|---|---|---|---|
| Jeyarajah *et al*[81] | 2442 (Cr > 2.0, nationawide) | 29 (single center) + 414 (nationwide) | N/A | 5 yr survival nationwide (50.4% *vs* 62.2%) | N/A | N/A | Interestingly, single center study had increased better survival in LTA than SLKT group |
| Campbell *et al*[80] | 53 | 13 | N/A | N/A | 1 yr (1.4 mg/dL *vs* 1.5 mg/dL) | 2% *vs* 0% (at 12 mo) | Adjusting for baseline characteristics, SLKT patients had lower Cr than LTA at 12 mo ($P$ = 0.01) |
| Ruiz *et al*[83] | 80 (all with HRS) | 98 (22 with HRS and 76 with primary renal disease) | 1 yr SLKT survival (liver: 76% and kidney: 76%) | 1 yr survival (66% LTA *vs* 72% SLKT) | N/A | Post-op dialysis: (89% LTA pts for median of 9 d *vs* 55% SLKT pts for median 2.5 d) | 1 yr acute kidney rejection in CLKT was 14% *vs* 23% in 5 yr LT cohort |
| Locke *et al*[84] | 19137 | 1032 | N/A | 1 yr survival for pts with ⩾ 3 mo RRT: (70.8% LTA *vs* 84.5% SLKT) | N/A | N/A | Even after matched-control analysis, there was no benefit in SLKT cohort *vs* LTA cohort outside of aforementioned RRT |
| Mehrabi *et al*[85] (literature review) | N/A | 3536 | Cumulative 5 yr SLKT survival of both organs (60.9%) | Cumulative 5 yr survival 42.6% | N/A | N/A | It is concluded that there is no definitive evidence of better graft/patient survival in SKLT *vs* LTA |
| Chava *et al*[114] | N/A | 39 | 5 yr SLKT survival (liver: 73.7% and kidney: 70%) | 73.7% SLKT patient survival at 5 yr | N/A | N/A | 15 surviving patients (53.6%) had mild/moderate kidney dysfunction |
| Fong *et al*[82] | 2774 | 1501 | 5 yr survival (58.9% LTA *vs* 65.3%, SLKT, $P$ < 0.001) | 5 yr survival (62.9% LTA *vs* 67.4% SLKT, $P$ < 0.001) | 0% with severe renal dysfunction | N/A | Liver graft survival and patient survival was better in SLKT *vs* LTA group |
| Martin *et al*[88] 2012 | 66026 | 2327 | 15% decreased risk of graft loss with SLKT *vs* LTA ($P$ = 0.02) | N/A | N/A | N/A | SLKT had higher graft survival rates than both KALT and LAKT |
| Sharma *et al*[86] | 2112 (received RRT within 90 d before LT) | N/A | N/A | 78% LTA survival at 6 mo (not associated with RRT duration) | N/A | 8.90% | Risk for non-recovery increased by 3.6%/day of pre-LT RRT |
| Catalano *et al*[89] | 74 | 37 | 10 yr survival (77% LTA *vs* 80% SLKT, $P$ = 0.85) | 10 yr survival (79% LTA *vs* 86% SLKT, $P$ = 0.56) | N/A | N/A | Acute rejection episodes involving the liver were less in SLKT *vs* LTA |

LTA: Liver transplantation alone; SLKT: Simultaneous liver kidney transplantionl; RRT: Renal replacement therapy; HRS: Hepatorenal syndrome; KALT: Kidney after liver transplantation; LAKT: Liver after kidney transplantation; N/A: Not available.

patients required RRT at 3 mo. While there was no significant difference between underlying liver disease and immunosuppressive agents, patients who were on RRT at 3 mo were also on HD 2 years post-LT as well[100].

While the majority of studies seem to indicate HRS increases the risk for worse post-transplantation kidney function, there are certain exceptions found in the literature. One study looked at 419 LTA performed between 1995 to 2009 and found that MELD scoring system did not impact all-cause mortality in the post-transplantation setting; however, there was a 2-fold greater mortality risk if patients required the need for pre-transplant RRT and post-transplant kidney dysfunction[101].

### *Duration of pre-transplantation RRT and vasopressors for reversal of HRS*

In regards to post-LT outcomes in patients with HRS who required vasopressor treatment one study compared 27 cases (triple therapy of octreotide, midodrine, and albumin)

*vs* 16 controls (no vasopressor treatment) and found the GFR was similar at 1 mo ($P$ = 0.61) and 1 year ($P$ = 0.13)[58]. Moreover, 11 out of the 27 cases responded to triple therapy but there was no difference in GFR at 1 mo ($P$ = 0.96) and 1 year ($P$ = 0.48) between responders *vs* non-responders. A smaller study looked at 9 HRS patients on vasopressin *vs* 27 non-HRS patients and found there was no significant renal impairment between the two groups in regards to duration of hospitalizations, infections, or renal impairment post-transplantation[102]. These two studies are much different than the findings from Wong *et al*[103]; they found that patients without HRS reversal from triple therapy were found to have longer duration of pre-transplant dialysis and increase in post-transplant mortality[103].

One study assessed 253 living donor LT patients and compared survival between starting RRT in the pre-transplant setting *vs* post-transplant setting. It was found that the duration of RRT was significantly shorter in the RRT-pre group compared to the RRT-post group (5.3 ± 2.1 d *vs* 17.8 ± 14.1 d, $P$ = 0.02) as well as higher graft survival (100% *vs* 51.9%, $P$ < 0.01)[104].

### *How to manage immunosuppression in immediate post-LT period with HRS*

Acute or chronic rejection has become more of a rarity with the current immunosuppression therapies[105]. However, calcineurin inhibitors (CNI) have significant nephrotoxic effects by inducing interstitial fibrosis, chronic microangiopathy, and tubular atrophy *via* increased extracellular matrix production, vasoconstriction, and cyclosporine induced apoptosis[11,106]. The landmark study in 1994 comparing tacrolimus *vs* cyclosporine showed that both were comparable in patient and graft survival; however, tacrolimus had substantially more adverse events, including nephrotoxicity, requiring discontinuation of the drug[107].

It is standard practice in majority of transplant centers to use different types of T-cell specific antibody induction in patients with post LT renal dysfunction. Commonly used agents are interleukin-2 receptor antagonists (daclizumab, or basiliximab) and polyclonal antibodies (rabbit anti-thymocyte globulin) based on center preference. Also it is practiced to use mycophenolate mofetil (MMF) and wait for improvement in kidney function post LT and introduce CNI.

Unfortunately, currently there is still no treatment for nephrotoxicity outside of dose reduction of current immunosuppressive regimen[108]. Patients who are more than 10 years post-transplant have a higher incidence of ESRD and chronic renal failure, which is related to increase in serum Cr at various stages post-operatively[109]. MMF has been used in situations where CNIs are held to improve renal function[110] but there exists greater risk for rejection when using MMF[111]. Cincinnati *et al*[112] show that combined MMF and low dose CNI therapy may actually promote tolerance, as this combination seems to be nephroprotective.

## FURTHER RESEARCH AND CONCLUDING REMARKS

We aimed to review the literature on HRS in the setting of LT and focused on the critical issues that are barriers to improved outcomes. Many consistencies have remained as treatment options including albumin, vasoconstrictors, RRT, and eventual LT. One area that was not well addressed in our literature search was the utility of norepinephrine in the setting of type 1 HRS not responding to currently approved octreotide and terlipressin based pharmacotherapy.

While current guidelines for SLKT have been recently updated, there is still much debate regarding the utility of SLKT over LTA. Certain studies have shown improved graft and patient survival in the SLKT patient population, but the literature has not been consistent regarding long-term kidney benefit. This is a topic that we anticipate will need to be further explored given variable results seen at this time. Equity in organ allocation must be taken into consideration as SLKT unavoidably allocates multiple grafts to a single recipient and removes donor kidneys from the transplant pool otherwise meant for patients with primary renal disease.

Finally, in regards to post-transplantation kidney dysfunction an eGFR < 60 mL/min per 1.73 $m^2$ seems to be associated with an increased risk of patients having long-term ESRD. While patients continue to have increased patient and graft survival rates, future studies may benefit from continuing to delineate risk factors that may result in post-transplant RRT.

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MINIREVIEWS

# Rethinking the role of non-selective beta blockers in patients with cirrhosis and portal hypertension

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## Abstract

Non-selective beta blockers (NSBB) are commonly used to prevent portal hypertensive bleeding in cirrhotics. Nevertheless, in the last years, the use of NSBB in critically decompensated patients, especially in those with refractory ascites, has been questioned, mainly for an increased risk of mortality and worsening of systemic hemodynamics. Moreover, even if NSBB have been reported to correlate with a higher risk of renal failure and severe infection in patients with advanced liver disease and hypotension, their use has been associated with a reduction of risk of spontaneous bacterial peritonitis, modification of gut permeability and reduction of bacterial translocation. This manuscript systematically reviews the published evidences about harms and benefits of the use of NSBB in patients with decompensated cirrhosis.

**Key words:** Beta blockers; Ascites; Cirrhosis; Portal hypertension



**Core tip:** In this review, we've critically analyzed the recent evidence on the role played by non-selective beta blockers in patients with decompensated liver disease.

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## INTRODUCTION

Cirrhosis is among the leading causes of death worldwide and hepatocellular carcinoma and complications of portal hypertension (PH) represent the most frequent causes of death.

PH is characterized by a systemic hyperdynamic

circulation, with increase of cardiac output (CO) and heart rate (HR), and reduction of mean arterial pressure (MAP) and systemic vascular resistances[1]. The degree of PH correlates with the severity of hyperdynamic circulation, while the absence of hemodynamic imbalance (*i.e.*, preserved right heart preload) is associated with better prognosis[2].

Ascites, esophageal varices, encephalopathy and/or jaundice are the main features of decompensated cirrhosis. Ascites represents the first clinical sign of decompensation in 30%-50% of patients, being the incidence about 50% within 10 years[3]. Refractory ascites occurs in 5% to 10% of cases, leading to a significant shortening in survival[4]. Oesophageal varices occur in about 50% of cirrhotic patients[5] being the incidence of first variceal bleeding estimated to be about 12%-15% per year, and the mortality of 15%-20% for every episode[6]. Varices mainly develop due to increased PH, but Fernandez *et al*[7] reported that their formation was also modulated by active angiogenesis, and not by a simple mechanism of vasodilation.

Moreover, several external factors, such surgery, bacterial infections or bleeding, represent severe trigger factors for derangement of hemodynamic; for instance, infection seemed more frequent in those patients who developed an acute-on-chronic liver failure (32.6% *vs* 21.8%, $P < 0.01$)[8]. Phillip *et al*[9] showed that removal of > 5 L of ascites determined a significant reduction of MAP and SVR, which is usually associated with a counterbalancing increase of CO[10]. The hemodynamic imbalance after LVP led to an increased risk of renal dysfunction, and subsequently to an increased mortality, according to the well-defined Paracentesis Induced Circulatory Dysfunction (PICD)[11].

Heart dysfunction has been shown in decompensated cirrhosis[12], being caused both by organic (*i.e.*, alcoholic or septic cardiomyopathy) and/or functional [*i.e.*, cirrhotic cardiomyopathy (CM)] factors. CM is mainly due to chronic increase of pro-inflammatory cytokines, impairment of systemic and regional hemodynamic, and beta-adrenergic receptor desensitization, with reversible impairment of systolic contractility, diastolic function and electrophysiological activity[1,13]. The impaired CO may also contribute to a decrease in renal perfusion: For instance, Krag *et al*[14] demonstrated that a lower cardiac index was associated with an increased development of hepatorenal syndrome within 3 mo (43% *vs* 5%, $P = 0.04$). Although it's difficult to determine the prevalence of CM since it's usually masked at rest, it could be an important cause of multi-organ failure and death during stressing conditions, as infection or liver transplantation[15].

## ROLE OF NON-SELECTIVE BETA BLOCKERS IN THE TREATMENT OF PH

### *Non-selective beta blockers and variceal bleeding*

Non-selective beta blockers (NSBB) act reducing portal flow and PH by decreasing CO (through β1 receptors) and determining splanchnic vasoconstriction (through β2 receptors)[16]. In 1981 Lebrec *et al*[17] demonstrated for the first time the effectiveness of NSBB for variceal bleeding; the re-bleeding rate was 4% in the treated group, compared to 50% in the placebo group.

Several randomized studies confirmed that NSBB represent the preferred option in primary prophylaxis against no intervention[18] and in preventing re-bleeding in combination with endoscopic band ligation[19]. Furthermore, a Cochrane metanalysis[20] confirmed that NSBB were as effective as endoscopic band ligation for reducing bleeding related mortality [29/567 (5.1%) *vs* 37/585 (6.3%); RR = 0.85; 95%CI: 0.53 to 1.39].

However, identification of hemodynamic response to NSBB still remains challenging for the hepatologists. Heebøll *et al*[21] demonstrated that only 51/124 (40%) of patients with cirrhosis who underwent measurement of gradient between portal and hepatic veins (HVPG) presented a significant hemodynamic improvement (reduction greater than 20% or > 12 mmHg) after NSBB use. Moreover, authors did not demonstrate a significant association between improvement of HVPG and change of HR ($P = 0.8$), which is commonly used parameter to tailor propranolol therapy.

Importantly, all the trials often ruled out cirrhotics with decompensated liver disease (*i.e.*, those with refractory ascites) from the analysis.

## NSBBS IN DECOMPENSATED CIRRHOTICS

Serstè *et al*[22] showed for the first time in 2010 that the median survival was extremely reduced in 151 patients with cirrhosis and refractory ascites treated with propranolol (20.0 mo *vs* 5.0 mo; $P = 0.00001$); other factors associated with higher mortality were Child-Pugh class C, hyponatremia and renal failure. These data raised several concerns amongst hepatologists[23-25] about the use of NSBB in cirrhotics with more advanced liver disease.

First, the group receiving NSBB comprises obviously sicker patients, because of higher prevalence of oesophageal varices (77/77 *vs* 3/74; $P = 0.001$) and higher serum bilirubin (56 mg/dL *vs* 48 mg/dL, $P = 0.01$). Second, the propranolol dose of 160 mg/d was significantly higher (in about half of the patients) than the mean dose used in the previous RCTs. Third, mortality was extremely higher in the NSBB group (63/77, 85.1%, median survival time was 5 mo), and there was an increased prevalence of sepsis related mortality, which remain difficult to explain[25].

The French group hypothesized that NSBB use can worse hemodynamic after LVP; thus, reduced survival could be due to an increased incidence of PICD. A cross-over study published in 2011[26] including 10 patients with refractory ascites, investigated the incidence of PICD after LVP when patients were taking NSBB and after

drug discontinuation. The authors showed that PICD was extremely decreased after propranolol discontinuation (1/10 *vs* 8/10; *P* = 0.01). The hypothesis was that propranolol use determined a reduction of CO and consequently an increase of counter-regulatory vasoconstriction systems, as renin angiotensin aldosterone, whose permanent hyper-activation could be associated with poorer renal function and reduced paracentesis-free interval time.

The link between NSBB and hemodynamic impairment was explained with the reduced MAP, which is a known negative prognostic factor for hyperdynamic circulation and progression of liver disease[27]. For instance, in the French study by Serstè *et al*[22], the cohort receiving propranolol did have lower MAP (90 mmHg *vs* 83 mmHg). Nevertheless, NSBB have been shown not to reduce MAP after acute *i.v.* administration[28], and the detrimental effects which were seen by the authors could have been due to the dose related side effect made by propranolol. CO is not usually reduced by NSBB introduction[29].

The following clinical studies failed to find any association between the use of NSBB and increased risk of deaths in decompensated cirrhotics (Table 1). Leithead *et al*[30] analyzed a subgroup of 117 patients with refractory ascites listed for LT, receiving a median dose of propranolol of 80 mg/d. They demonstrated that NSBB were independently associated with reduced waitlist death (adjusted HR = 0.35, *P* = 0.022), without higher prevalence of sepsis related mortality. Moreover, an equal survival between patients with refractory ascites taking NSBB and patients without NSBB (12/38 *vs* 8/23; *P* = 0.79) was shown in another smaller single center retrospective analysis[31].

Bossen *et al*[32] not only confirmed similar mid-term mortality between 258 patients with refractory ascites receiving NSBB and a control group of 330 patients (30.8% *vs* 30.5%; adjusted HR = 1.02, 95%CI: 0.74-1.39) retrospectively evaluated, but also showed that discontinuation of NSBB was associated with an higher mortality (adjusted HR = 5.13, 95%CI: 2.28-11.55).

In addition, new data seemed to confirm the absence of correlation between mortality and NSBB. Pereira *et al*[33] included 163 patients with infection, of whom 104 were on NSBB. Use of NSBB was associated with lower frequency of sepsis (21% *vs* 42%, *P* = 0.03), being 3-mo survival not different between cohorts (59% *vs* 63%; *P* = ns). Mallawaarachchi *et al*[34] showed that 75 patients treated with NSBB (67 with carvedilol and 8 propranolol) presented equal mortality after a median follow-up time of 28.0 mo (60.0% *vs* 66.7%; *P* = 0.10); in those with moderate or severe ascites, survival was similar in both groups (*P* = 0.67), while it was better in NSBB patients in mild ascites (*P* = 0.02).

In a large multicentric cohort, Bhutta *et al*[35] confirmed that survival was significantly greater in patients on NSBB at admission with a median survival of 58 d compared to 32 d in patients not on NSBB (*P* = 0.033). No difference was found between those who did or did not discontinue NSBB (*P* = 0.91), being only systolic arterial pressure and acute renal failure independent predictors of death.

Onali *et al*[36] evaluating 316 patients (126 with refractory ascites), showed that those on NSBB (*n* = 128, 40.5%) had a higher frequency of previous variceal bleeding (50% *vs* 21%, *P* < 0.001) and spontaneous bacterial peritonitis (27% *vs* 17%, *P* = 0.025), but were at lower risk of death (16% *vs* 32%; *P* = 0.002). At multivariate analysis use of NSBB was associated with reduced mortality (HR = 0.511, 95%CI: 0.3-0.87, *P* = 0.014).

Finally, in a recent study provided on 349 acute-on chronic patients with cirrhosis, Mookerjee *et al*[37] demonstrated a significantly lower short term mortality in patients on NSBB compared to those without NSBB (24% *vs* 34%, *P* = 0.048). Interestingly, patients on NSBB had less severe progression to the stages of acute-on-chronic liver failure, and those who discontinued NSBB had a higher mortality (37% *vs* 13%), even if it might be due to an independently higher presence of circulatory dysfunction.

The association between increased mortality and NSBB could be explained with the worsening of an already impaired hemodynamics, especially in those who experience a greater decrease of cardiac function (*i.e*., of CO) and of MAP. However, in the study by Karagiannakis *et al*[15] in which the decrease of CO (and subsequently of cardiac index) has been correlated with a lower survival, the used cut-off (1.5 L/m per square meter) is not diffusely seen in cirrhotics, even when decompensated[38].

Simultaneous presence of several cofactors, as infection, could contribute to the change of clinical scenario, being patients at higher risk of hemodynamic derangement if NSBB are not withdrawn.

Mandorfer *et al*[39] showed that 245 patients with refractory ascites but without infection, taking NSBB, experienced a significant reduction in hospitalization rate (19.4 d *vs* 23.9 d per person-year); at multivariate analysis, NSBB treatment correlated with higher transplant-free survival (HR = 0.771; 95%CI: 0.598-0.993; *P* = 0.04). The Authors demonstrated a correlation between mortality and NSBB only in patients experiencing a previous episode of spontaneous bacterial peritonitis (SBP), with a significant difference in length of hospitalization (NSBB: 33.4 d per person-year; 95%CI: 31.9-34.9 *vs* no-NSBB: 28.8 d per person-year; 95%CI: 27.6-29.9), and impaired transplant-free survival (HR = 1.644; 95%CI: 1.145-2.361). These data may confirm that NSBB could negatively influence hemodynamic status in patients with infection, but not that NSBB represented a trigger for infection.

However, Galbois *et al*[40] showed that cirrhotics admitted to intensive care unit for sepsis or septic shock who were receiving NSBB were not at increased risk of early or mid-term mortality (15/26 *vs* 26/42, *P* = 0.8; and 21/26 *vs* 28/42; *P* = 0.27, respectively).

In summary, latest studies seem not to confirm correlation between NSBB and mortality. Another meta-

**Table 1 Available literature on the potential correlation between non-selective beta blockers and mortality in patients with cirrhosis**

| Ref. | Patients | Refractory ascites | Propranolol dose/day | Follow-up | Mortality | Sepsis |
|---|---|---|---|---|---|---|
| Serstè *et al*[22] | 74 | 100% | 40 mg (9); 80 mg (31); 120 mg (1); 160 mg (36) | 8 mo | 63/77 ($P < 0.0001$ *vs* No NSBB) | NA |
| Galbois *et al*[40] | 26 | 14 (53.8%) | NA | 6 mo | 21/26 (80.8%) | 100% |
| Robins *et al*[60] | 36 | 100% | 48.9 | 10 mo | 18/36 (50%) survival 18 mo | NA |
| Mandorfer *et al*[39] | 245 | 100% | 40 mg (20-120) | 660 persons/year | Higher transplant free survival (HR = 0.771, $P = 0.044$) | No correlation between NSBB and SBP (HR = 0.728, $P = 0.211$) |
| Kimer *et al*[31] | 23 | 100% | 80 mg (40-200) | Retrospective | 15/23 (65.2%) | NA |
| Leithead *et al*[30] | 159 (119 on propranolol) | NA | 80 mg (10-240) | Retrospective | 35/159 (22%) | NA |
| Bossen *et al*[32] | 559 | 46% | NA | 12 mo | 125/559 (22.5%) | NA |
| Mookerjee *et al*[37] | 164 (propranolol 111; nadolol 6; carvedilol 16; other 31) | NA | 40 (20-80; propranolol) | NA | 40/164 *vs* 63/184 (24.4% *vs* 34.1%, $P = 0.048$) Similar 6 and 12-mo mortality between groups ($P = 0.64$ and 0.35 respectively) | NA |
| Pereira *et al*[33] | 104 | NA | NA | NA | 67% *vs* 69% ($P$ = ns) | 21% *vs* 42% ($P$ = ns) |
| Mallawaarachchi *et al*[34] | 75 (8 propranolol) | NA | NA | 28 mo | 60% *vs* 66% ($P$ = ns) | NA |
| Bhutta *et al*[35] | 308 (nadolol 155; propranolol 64; carvedilol 72, other 62) | NA | NA | NA | Mean survival: 58 d in NSBB group (*vs* 32 d of control group; $P = 0.033$) | NA |
| Onali *et al*[36] | 126 | 100% | NA | 4 mo | 20 *vs* 60 (16% *vs* 32%; $P = 0.002$) | NA |

NA: Not available; NSBB: Non-selective beta blockers; SBP: Spontaneous bacterial peritonitis; ns: No significance.

analysis[41], which comprised 23 and 28 RCTs on primary and secondary prophylaxis for variceal bleeding, for a total of 4481 patients included (39.8% with ascites), extensively confirmed the absence of increased mortality for patients on NSBB. In primary prophylaxis, 215/955 patients died for bleeding-unrelated causes, in a proportion not different between those who were or were not on treatment with NSBB (OR = 0.91, 95%CI: 0.73-1.15). Similarly, in secondary prophylaxis RCTs, bleeding-unrelated deaths did not differ between groups (189/1143 *vs* 225/1208; OR = 0.90, 95%CI: 0.67-1.23). These data were confirmed in the subgroup taking 120 mg/d or more of propranolol (48/374 *vs* 57/309, OR = 1.01, 95%CI: 0.55-1.84), and in those with severe ascites (124/595 *vs* 151/627, OR = 0.93, CI: 0.61-1.43).

## SECOND GENERATION OF BETA BLOCKERS: CARVEDILOL

Carvedilol is a NSBB with mild anti-α1-adrenergic activity. It has been shown to be more effective than propranolol in reducing HVPG due to the α-1 blockage, which reduces intra-hepatic resistances. Its role was investigated for the first time more than 20 years ago[42], as a potential tool for reducing PH in patients with cirrhosis, with promising results. Since then, several studies demonstrated its effectiveness in terms of HVPG decrease, after acute administration and after chronic treatment[43].

In 2002, Bañares *et al*[44] demonstrated that 26 patients receiving carvedilol experienced a greater reduction of HVPG than 25 patients taking propranolol (-19% ± 2% *vs* -12% ± 2%; $P < 0.001$); the decrease of HVPG was higher in patients with more severe liver disease (Child-Pugh class B and C *vs* Child-Pugh class A: -25% ± 2% *vs* -14% ± 3% respectively).

Previous studies showed that, in patients with cirrhosis, acute administration of carvedilol could enhance hypotension and effective hypovolemia, reducing renal blood flow and consequently glomerular filtration rate. In the study by Bañares *et al*[44], renal function remained stable (glomerular filtration rate from 90 mL/min ± 4 mL/min to 84 mL/min ± 5 mL/min; $P$ = ns) in both groups, suggesting a potential chronic hemodynamic adjustment in response to arterial hypotension. Furthermore, the authors confirmed that reductions of HR and CO were lower with carvedilol than with propranolol. However, MAP was significantly reduced only in the carvedilol group (91.4 mmHg ± 2.5 mmHg *vs* 81.2 mmHg ± 2.9 mmHg; $P < 0.05$; propranolol: 88.6 mmHg ± 4.5 mmHg *vs* 83.8 mmHg ± 3.1 mmHg; $P$ = ns). Thus, despite promising data, the use of carvedilol as first choice drug remains controversial[19], especially in those patients with severely impairment of hemodynamic (*i.e.*, refractory ascites), because further reduction of MAP could be detrimental for organ perfusion. In fact in a recent metanalysis[45] on 5 studies which analyzed the role of carvedilol in a total of 90 patients, the number of patients achieving a reduction in HVPG to ⩾ 20% was markedly higher with carvedilol (57/94 *vs* 33/87), but hypotension occurred in one-third

more patients than with propranolol.

## NON-HEMODYNAMIC EFFECTS OF NSBBS IN PH

Several pleiotropic effects of NSBB have been recently demonstrated beyond their hemodynamic role[46].

In 2003 Abraldes *et al*[47] compared the incidence of complications due to PH in 28 patients responders to NSBB; after a follow-up of 8 years, they found that the risk of developing ascites ($P$ = 0.025), hepatorenal syndrome ($P$ = 0.026), and encephalopathy ($P$ = 0.024) were significantly lower than in the 45 patients non-responders. Another study of Hernández-Gea *et al*[48] demonstrated that an effective treatment (*i.e.*, significant reduction of HVPG) with NSBB for primary prophylaxis was associated with reduced risk of ascites development (19% *vs* 57% at 3 years, $P$ < 0.001).

Since bacterial translocation has been widely considered an important trigger factor for worsening of PH, also for the lack of response of immune system in cirrhosis[49], and since selective bacterial decontamination seems to partly reverse the hemodynamic derangement in cirrhosis[50], several studies tried to investigate whether NSBB could contribute to PH reduction through a modification of the protean interactions between the gut and the liver.

Propranolol seems to play a role in reduction of bacterial translocation, probably increasing bowel motility through a sympatholytic action[51]. After the confirmation that intestinal permeability was significantly impaired in cirrhotic than in controls (lactulose/mannitol ratio: 0.026 *vs* 0.014, $P$ = 0.001); we demonstrated that NSBB introduction determined a significant improvement of intestinal permeability, and reduction of hyper-vascularization at confocal microscopy[52]. Also Reiberger *et al*[53] showed a reduction of intestinal permeability after introduction of NSBB, and a contemporary reduction of bacterial translocation [LPS-binding protein: -16% ($P$ = 0.018); interleukin-6: -41% ($P$ < 0.0001)]; interestingly, the Authors showed equal effectiveness also in those whose HVPG did not significantly reduced after NSBB introduction.

Although a retrospective study on 134 patients with cirrhosis and ascites[54] did not show a reduction of SBP during therapy with NSBB (6/33 *vs* 33/101; OR = 0.46, $P$ = 0.17), a meta-analysis performed on 4 studies demonstrated a significant difference (12.1%, $P$ < 0.001) in favor of propranolol in preventing SBP[55].

Bacterial translocation is the main trigger factor for infection in cirrhosis, and infection is a known trigger for variceal bleeding[46]. Merli *et al*[56] demonstrated that in 140 patients with cirrhosis who experienced infection, those on NSBB showed a trend towards a lower incidence of sepsis (40% *vs* 57%), septic shock (8% *vs* 15%), hepatorenal syndrome (14% *vs* 17%) and mortality (15% *vs* 40%).

## CONCLUSION AND FUTURE PERSPECTIVES

To date, NSBB remain the treatment of choice for primary and secondary prophylaxis for portal hypertensive bleeding, even though new drugs, as statins[57], or new generation beta blockers, as carvedilol, may increase the rate of hemodynamic response. NSBB use has been associated with several pleiotropic characteristics, *i.e.*, reduction of bacterial translocation, prevention of spontaneous bacterial peritonitis - different from prevention of bleeding, suggesting a pleiotropic role in decompensated cirrhosis. Contrasting data on the use of NSBB in sickest patients with decompensated cirrhosis made their use controversial. A recent survey[58] about 629 physicians highlighted the high heterogeneity across centers. For instance, refractory ascites was considered a contraindication to NSBB use for 36% of responders, while for the 61% NSBB have to be withdrawn during HRS, highlighting a general lack of consensus across all the issues of the survey. A window hypothesis for therapy with NSBB in the natural history of cirrhosis was made by Krag *et al*[59]; according to this view, NSBB could play a detrimental role for cirrhotics at the earlier stage (*i.e.*, for pre-primary prophylaxis) and in the "extremely decompensated" phase, in those patients with MAP lower than 80 mmHg, decreased baseline CO of those with concomitant infections[19].

Since infected cirrhotics are those at greater risk of variceal bleeding and HVPG has been increased also after the resolution of infection[38], attention should be paid to a potential increase in the risk of portal hypertensive bleeding. In addition, the interplay between propranolol and sepsis has to be further investigated with future larger studies.

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ORIGINAL ARTICLE

Observational Study

# Hypolactasia is associated with insulin resistance in nonalcoholic steatohepatitis

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## Abstract

### *AIM*

To assess lactase gene (*LCT*)-13910C>T polymorphisms in Brazilian non-alcoholic fatty liver disease (NAFLD) and nonalcoholic steatohepatitis (NASH) patients in comparison with healthy controls.

### *METHODS*

This was a transverse observational clinical study with NAFLD patients who were followed at the Hepatology Outpatient Unit of the Hospital das Clínicas, São Paulo, Brazil. The polymorphism of lactase non-persistence/lactase persistence (*LCT*-13910C>T) was examined by PCR-restriction fragment length polymorphism technique in 102 liver biopsy-proven NAFLD patients (steatosis in 9 and NASH in 93) and compared to those of 501 unrelated healthy volunteers. Anthropometric, clinical, biochemical and liver histology data were analyzed. Continuous variables were compared using the *t* or Mann-Whitney tests, and categorical data were compared with the Fisher's exact test. Univariate logistic regression and

multivariate logistic regression adjusted for gender and age were performed.

***RESULTS***

No differences in the *LCT*-13910 genotype frequencies were noted between the NAFLD patients (66.67% of the patients with steatosis were CC, 33.33% were CT, and none were TT; 55.91% of the patients with NASH were CC, 39.78% were CT, and 4.3% were TT; $P = 0.941$) and the healthy controls (59.12% were CC, 35.67% were CT, and 5.21% were TT) or between the steatosis and NASH patients. That is, the distribution of the lactase non-persistence/lactase persistence polymorphism (*LCT*-13910C>T) in the patients with NAFLD was equal to that in the general population. In the NASH patients, the univariate analysis revealed that the lactase non-persistence (low lactase activity or hypolactasia) phenotype was associated with higher insulin levels (23.47 ± 15.94 μU/mL *vs* 15.8 ± 8.33 μU/mL, $P = 0.027$) and a higher frequency of insulin resistance (91.84% *vs* 72.22%, $P = 0.02$) compared with the lactase persistence phenotype. There were no associations between the *LCT* genotypes and diabetes ($P = 0.651$), dyslipidaemia ($P = 0.328$), hypertension ($P = 0.507$) or liver histology in these patients. Moreover, in the NASH patients, hypolactasia was an independent risk factor for insulin resistance even after adjusting for gender and age [OR = 5.0 (95%CI: 1.35-20; $P = 0.017$)].

***CONCLUSION***

The *LCT*-13910 genotype distribution in Brazilian NAFLD patients was the same as that of the general population, but hypolactasia increased the risk of insulin resistance in the NASH patients.

**Key words:** Lactose intolerance; Genetic polymorphism; Insulin resistance; Non-alcoholic fatty liver disease; Nonalcoholic steatohepatitis



**Core tip:** Non-alcoholic fatty liver disease (NAFLD) exhibits a close relationship with metabolic syndrome (MetS), but the associations of the lactase non-persistence/lactase persistence genotypes with MetS components are controversial. Therefore, we assessed hypolactasia (*LCT*-13910CC) and lactase persistence genotypes in 102 Brazilian NAFLD patients in comparison with 501 healthy controls, the associations of these polymorphisms were verified with the results of biochemical tests, MetS and severity of liver histology in nonalcoholic steatohepatitis (NASH) patients. No differences in the *LCT*-13910C>T polymorphisms were noted between the NAFLD and controls, but hypolactasia increased the risk of insulin resistance in the NASH patients.

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## INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of liver damage that ranges from steatosis to nonalcoholic steatohepatitis (NASH) and advanced fibrosis/cirrhosis in persons without significant alcohol consumption[1,2]. NAFLD is currently considered the most common liver disease and is associated to metabolic syndrome (MetS) components, such as obesity and diabetes[3-5]. Several studies have correlated the severity of liver injury with increased frequencies of such components, thus making these components important targets in the management of this condition[1,6-8]. However, while specific pharmacological therapy are still far from solving all of the issues related to fatty liver disease, the pursuit of high-risk individuals can be a strategy for concentrating efforts on its diagnosis and management.

Milk is the primary energy source for newborns and is rich in lactose. Lactase phlorizin hydrolase in the microvillus membrane of the small intestinal cells digests lactose. However, after 2-12 years of age, a physiological genetically programmed reduction in lactase activity occurs, hypolactasia or lactase non-persistence, which, when accompanied by symptoms, defines lactose intolerance[9]. In contrast some populations mainly from Northern Europe present lactase persistence during adulthood[10]. The most interesting report published in 2002[11] found that the polymorphisms in intron 13 [lactase gene (*LCT*)-13910C>T] and in intron 9 (*LCT*-22018G>A) of the *MCM6* gene conferred lactase persistence in several populations[9,12-14]. These genotypes render a person a lactose digester. The lactase-persistence phenotype has a prevalence of 43.4% in Caucasian Brazilians, and there is no difference between genders[12].

Recent studies have raised concerns regarding the possible associations of lactase persistence with the components of MetS. In Europeans those with hypolactasia genotype (*LCT*-13910CC) had lower body mass indices and waist circumferences than those with lactase persistence genotypes[15,16]. Likewise, in the Canary Islands, those with lactase persistence genotypes exhibit higher odds ratios for MetS than do subjects with the *LCT*-13910CC genotype[17].

However, other studies have demonstrated that dairy food consumption showed lower susceptibility to type 2 diabetes or worsening of glucose homeostasis indices[18-20]. Nicklas *et al*[21] applied a questionnaire to a sample of 3452 American adults and reported that diagnosis of diabetes and hypertension were higher in individuals that considered themselves lactose intolerant with lower ingestion of calcium from dairies. Additionally, Samara *et al*[22] assessed a French population and

reported that better metabolic profiles in men was associated with more dairies intake.

As noted, the role of milk in MetS is not clearly defined at this moment, and the literature is controversial[23]. Moreover, publications regarding the *LCT*-13910C>T polymorphism in patients with NAFLD are scarce. Therefore, the purpose was to assess expression profiles of the *LCT*-13910 genotypes in Brazilians with NAFLD compared to those of healthy individuals to investigate whether the *LCT*-13910C>T variant could be a predictor of NASH. An additional goal was to analyze the associations of the lactase-persistence genotype with biochemical tests, components of MetS and the severity of liver histology in NASH patients.

## MATERIALS AND METHODS

### Ethical considerations

The Ethics Committee of the Hospital das Clínicas (number 448520) approved this study that was conducted following the ethical guidelines of the 1975 Declaration of Helsinki.

### Patients and clinical design

This was a transverse study with NAFLD patients who were followed at the Hepatology Outpatient Unit of the Hospital das Clínicas, São Paulo, Brazil. *LCT*-13910C>T polymorphism was investigated in 102 liver biopsy-proven NAFLD patients and 501 unrelated healthy volunteers. All NAFLD patients were previously evaluated for other liver diseases, being excluded viral hepatitis, autoimmune hepatitis, hemochromatosis, Wilson disease and alpha 1-antitrypsin deficiency. MetS components identification followed the recommendations of the Adult Treatment Panel Ⅲ Report as follows: Triglycerides $\geqslant$ 150 mg/dL, high-density lipoproteins (HDL) < 40 mg/dL in men and < 50 mg/dL in women, fasting glucose $\geqslant$ 110 mg/dL, $\geqslant$ 130 mmHg systolic or $\geqslant$ 85 mmHg diastolic pressure, and abdominal obesity[24]. The study inclusion criteria were patients 18-75 years old with NAFLD diagnoses based on liver histology. Exclusion criteria were any other liver disease, significant alcohol intake (> 100 g/wk), previous exposure to drugs associated with liver steatosis or not accepting to participate in the study.

Liver histology were scored according to the macro- and micro-vacuolar steatosis, the inflammation and the hepatocyte ballooning. Fibrosis pattern and zonal distributions of the analysed variables were also recorded. The slides were classified according to the NASH Clinical Research Network[25]. The biochemical investigations included the following: Fasting glucose, plasma insulin, total cholesterol and fractions, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl transferase (GGT), which were collected after a 12-h overnight fast and evaluated at the time of the liver biopsy. Homeostatic Model of Assessment (HOMA-IR) was used to evaluate insulin resistance [22.5 × fasting insulin (mU/mL) × glucose (mmol/L)][26]. A HOMA-IR $\geqslant$ 2.5 was used as the cutoff point to define insulin resistance[27,28]. Retrospective information regarding co-morbidities was also collected.

### Genotyping

Leukocytes were used for genomic DNA extraction (Miller *et al*[29] 1988). The technique for *LCT*-13910 genotyping was described elsewhere[11,30-32].

### Statistical analysis

The continuous variables are presented as the means ± the standard deviations and were compared using the *t* test (the assumption of normality was verified using the Anderson-Darling test). When appropriate, the Mann-Whitney test was used. The categorical variables are expressed as the percentages (frequencies) of affected individuals and were compared using Fisher's exact test. Univariate logistic regression was performed to evaluate the odds ratios with the respective 95%CIs. Multivariate logistic regression adjusted for gender and age was performed. The best predictive cut-offs for the continuous variables were determined using conditional trees when the traditional cut-offs did not provide interesting information[33]. *P* values below 0.05 were considered statistically significant. The R Project for Statistical Computing ver. 3.1.1 (R Core Team, Vienna, Austria, 2014) software package was used for the statistical analyses[34]. A statistical review of the study was performed by a biomedical statistician (Márcio Augusto Diniz).

## RESULTS

The anthropometric, clinical, and biochemical characteristics of the patients are provided in Table 1. We evaluated 102 NAFLD patients, including 9 steatosis and 93 with NASH. All of the steatosis patients were women, whereas in the NASH group, 32 patients (34.41%) were men ($P$ = 0.04). The NASH patients had higher fasting glucose levels than did the patients with steatosis only (123.14 ± 48.28 *vs* 91.71 ± 9.2, respectively, $P$ = 0.033). There were no differences between the groups in terms of age, MetS components, BMI, insulin, HOMA-IR values $\geqslant$ 2.5, AST, ALT, GGT, total cholesterol, HDL, LDL or triglycerides (Table 1).

The distributions of alleles and genotypes are presented in Table 2. No differences in *LCT*-13910 genotype frequencies were noted between the NAFLD patients (66.67% patients with steatosis were CC, 33.33% were CT and none were TT; 55.91% of those with NASH were CC, 39.78% were CT and 4.3% were TT; $P$ = 0.941) and the healthy controls (59.12% were CC, 35.67% CT, 5.21% TT). Likewise, no differences in the *LCT*-13910C>T allele frequencies were noted between the groups (76.95% of the controls, 83.33% of those with steatosis and 75.81% of the NASH patients had the *LCT*-13910C allele; $P$ = 0.764). That is, the distribution of the *LCT*-13910C>T polymorphism in the patients with NAFLD was equal to that in the general population.

**Table 1 Demographic, clinical and biochemical characteristics of the non-alcoholic fatty liver disease patients**

| | Steatosis ($n$ = 9) | NASH ($n$ = 93) | $P$ value |
|---|---|---|---|
| Age | 55.11 ± 10.3 | 56.51 ± 10.13 | 0.692 |
| Men/women ($n$) | 0% (0)/100% (9) | 34.41% (32)/65.59% (61) | 0.04[a] |
| Type 2 diabetes ($n$) | 33.33% (2) | 60.67% (54) | 0.224 |
| Dyslipidaemia ($n$) | 83.33% (5) | 79.78% (71) | 1 |
| High-blood pressure ($n$) | 66.67% (4) | 64.04% (89) | 1 |
| BMI | 31.28 ± 5.79 | 31.25 ± 5.93 | 0.969 |
| Fasting glucose (mg/dL) | 91.71 ± 9.2 | 123.14 ± 48.28 | 0.033[a] |
| Insulin (μU/mL) | 12.44 ± 4.2 | 19.92 ± 13.29 | 0.102 |
| HOMA-IR value ⩾ 2.5 | 57.14% | 83.53% | 0.115 |
| AST (U/L) | 25.14 ± 6.89 | 38.8 ± 37.99 | 0.159 |
| ALT (U/L) | 40 ± 16.74 | 50.65 ± 54.99 | 0.934 |
| GGT (U/L) | 56.57 ± 59.9 | 87.36 ± 96.33 | 0.185 |
| Total cholesterol (mg/dL) | 203.29 ± 54.39 | 195.31 ± 45.71 | 0.863 |
| HDL (mg/dL) | 53 ± 6.58 | 46.15 ± 13.42 | 0.067 |
| LDL (mg/dL) | 124.14 ± 51.87 | 114.89 ± 39.74 | 0.72 |
| Triglycerides (mg/dL) | 130.43 ± 59.19 | 167.25 ± 82.02 | 0.258 |

[a]$P$ value < 0.05. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HDL: High-density lipoprotein; HOMA-IR: Homeostatic Model of Assessment; LDL: Low-density lipoprotein; GGT: Gamma glutamyl transferase; NASH: Nonalcoholic steatohepatitis.

Analysis *via* simple logistic regressions of the associations of the *LCT*-13910C>T polymorphisms with the results of the biochemical tests, components of MetS and severity of liver histology in the NAFLD patients (steatosis and NASH groups) did not reveal any associations (data not shown). Subsequently, we evaluated the patients with NASH (Table 3). In this group ($n$ = 93), univariate analysis revealed that the hypolactasia phenotype was associated with higher insulin levels ($P$ = 0.027) and greater insulin resistance ($P$ = 0.02). No associations were noted between the liver histology parameters (*i.e.*, steatosis, inflammation and fibrosis) and the *LCT*-13910 genotype or phenotype. Moreover, no associations were found between the components of MetS or MetS diagnosis ($P$ = 1.0) and the *LCT*-13910 genotype or phenotype.

Table 4 illustrates the logistic regression analysis that was adjusted for gender and age and assessed the independent associations of the *LCT*-13910C>T polymorphism with HOMA-IR, BMI ⩾ 30, insulin value and MetS in the NASH patients. Hypolactasia phenotype was associated with a 5-fold increase in insulin resistance (95%CI: 1.35-20; $P$ = 0.017). The *LCT*-13910CT genotype conferred a 6.25-fold decrease in insulin resistance (95%CI: 0.04-0.64; $P$ = 0.009). In this multivariate regression analysis, we no longer observed an association between hypolactasia and insulin level (even when using the cut-off of > 29.8 μU/mL, $P$ = 0.197) after adjusting for gender and age. Similarly, the MetS diagnosis and a BMI ⩾ 30 were not associated with the *LCT*-13910C>T polymorphism.

## DISCUSSION

### Key findings

In this transverse clinical study, we were unable to find any differences in the *LCT*-13910C>T polymorphism expression profile between Brazilian NAFLD patients and healthy controls ($P$ = 0.941). Moreover, the presence of the T allele was not able to differentiate steatosis from NASH in NAFLD patients ($P$ = 0.764). However, in NASH patients, the hypolactasia phenotype (*i.e.*, the *LCT*-13910CC genotype) was associated with insulin resistance, and conversely, the *LCT*-13910CT genotype conferred protection against its occurrence.

The *LCT*-13910C>T polymorphism prevalence varies among different populations across the globe. The lactase-persistence phenotype (*i.e.*, the *LCT*-13910-CT and *LCT*-13910-TT genotypes) can occur at rates as high as 72% and 73.7% in New Zealand and Sweden, respectively[13,35]. In Hungary, the prevalence is 35.9%, and in Caucasian Brazilians, the prevalence is 43.4%[12,36]. In contrast, in Chinese and Japanese Brazilians, the lactase-persistence phenotype was not found at all in some published studies[12,37]. The *LCT* genotype distribution was also the same in NAFLD patients regardless of the presence of NASH or steatosis only.

In a recent European meta-analysis with 31720 individuals, Kettunen *et al*[16] found that the *LCT*-13910CC genotype was associated with a decreased body mass index (BMI), when compared to *LCT*-13910CT/TT. In an analysis of 17374 Finns, it was observed that when the lactase persistent allele was present, BMI was 0.3 kg/m$^2$ higher, which corresponds to approximately 1 kg[16]. These findings were reproduced by Corella *et al*[15] in a Mediterranean population in which *LCT*-13910CC individuals exhibited a lower risk of obesity, lower body weights, lower BMIs and smaller waist circumferences than *LCT*-13910T-allele carriers. Although the association between the *LCT*-13910C>T genotypes and the diagnosis of full-blown MetS was not significant in the overall analysis in the study, a subgroup analysis revealed a significant association in the subjects with a lactose intake higher than 8 g/d[15]. In a cross-sectional

**Table 2 Allele and genotype frequencies of the lactase-13910C>T polymorphisms**

| | | Allele frequency % (*n*)[a] | | Total (%) | Genotype frequency % (*n*)[b] | | | Total (%) |
|---|---|---|---|---|---|---|---|---|
| | | C | T | | CC | CT | TT | |
| *LCT*-13910 | Control (*n* = 501) | 76.95 (768) | 23.05 (230) | 100 | 59.12 (295) | 35.67 (178) | 5.21 (26) | 100 |
| | Steatosis (*n* = 9) | 83.33 (15) | 16.67 (3) | 100 | 66.67 (6) | 33.33 (3) | 0 (0) | 100 |
| | NASH (*n* = 93) | 75.81 (141) | 24.19 (43) | 100 | 55.91 (52) | 39.78 (37) | 4.3 (3) | 100 |

[a]*P* = 0.764; [b]*P* = 0.941. NASH: Nonalcoholic steatohepatitis; *LCT*: Lactase gene.

**Table 3 Associations of the lactase-13910 phenotype in nonalcoholic steatohepatitis patients (*n* = 93)**

| | Hypolactasia | Lactase persistence | *P* value |
|---|---|---|---|
| Age | 55.96 ± 10.91 | 57.61 ± 9.33 | 0.443 |
| Gender: Female % (*n*) | 70.83 (34) | 60.98 (25) | 0.51 |
| Type 2 diabetes % (*n*) | 66.67 (30) | 57.5 (23) | 0.664 |
| Dyslipidaemia % (*n*) | 82.22 (37) | 77.5 (31) | 0.792 |
| High-blood pressure % (*n*) | 68.89 (31) | 57.5 (23) | 0.273 |
| BMI | 31.39 ± 6.55 | 31.28 ± 5.37 | 0.714 |
| BMI ⩾ 30 % (*n*) | 58.14 (25) | 65 (26) | 0.388 |
| Fasting glucose (mg/dL) | 122.61 ± 50.14 | 123.83 ± 46.43 | 0.892 |
| Insulin (μU/mL) | 23.47 ± 15.94 | 15.8 ± 8.33 | 0.027[a] |
| HOMA-IR value ⩾ 2.5 (n) | 91.84 (45) | 72.22 (26) | 0.02[a] |
| AST (U/L) | 38.94 ± 37.66 | 42.67 ± 40.15 | 0.121 |
| ALT (U/L) | 51.47 ± 69.44 | 52.12 ± 35.02 | 0.072 |
| GGT (U/L) | 97.49 ± 118.27 | 80.51 ± 65.6 | 0.427 |
| Total cholesterol (mg/dL) | 196.62 ± 47.13 | 195.55 ± 44.06 | 0.965 |
| HDL (mg/dL) | 46.38 ± 12.26 | 46.05 ± 15.06 | 0.698 |
| LDL (mg/dL) | 117.19 ± 39.47 | 114.25 ± 39.9 | 0.893 |
| Triglycerides (mg/dL) | 169.11 ± 82.97 | 162.3 ± 83.11 | 0.477 |
| Steatosis | | | |
| 1 | 21.28 (10) | 24.39 (10) | 0.453 |
| 2 | 51.06 (24) | 39.02 (16) | |
| 3 | 27.66 (13) | 36.59 (15) | |
| Inflammation | | | |
| 0 | 2.13 (1) | 7.32 (3) | 0.133 |
| 1 | 61.7 (29) | 46.34 (19) | |
| 2 | 23.4 (11) | 39.02 (16) | |
| 3 | 12.77 (6) | 7.32 (3) | |
| Fibrosis | | | |
| 0 | 18.75 (9) | 14.63 (6) | 0.804 |
| 1 | 39.58 (19) | 43.9 (18) | |
| 2 | 16.67 (8) | 17.07 (7) | |
| 3 | 20.83 (10) | 19.51 (8) | |
| 4 | 4.17 (2) | 4.88 (2) | |
| MetS | 51.92 (27) | 53.66 (19) | 1 |

[a]*P* value < 0.05. ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; BMI: Body mass index; HDL: High-density lipoprotein; HOMA-IR: Homeostatic Model of Assessment; LDL: Low-density lipoprotein; GGT: Gamma glutamyl transferase; MetS: Metabolic syndrome.

work conducted in the Canary Islands, Almon *et al*[17] demonstrated that subjects with the *LCT*-13910CT and *LCT*-13910TT genotypes exhibited higher odds ratio for MetS than subjects with the *LCT*-13910CC genotype. The authors concluded that the T allele might constitute a nutrigenetic factor that increases the susceptibility to MetS development, and this susceptibility was particularly noted in women[17].

Despite the aforementioned studies that have demonstrated correlations of the CC genotype with decreased BMI, a lower risk of obesity, a lower body weight, and smaller waist circumference compared with the CT and TT genotypes[15,16] and the even further increased higher odds ratio for MetS in individuals with the T allele[17], we could not corroborate these findings in our NAFLD population. Studying only the NASH patients in the univariate analysis, we did not find associations between the *LCT*-13910C>T polymorphism and BMI or MetS diagnoses even after adjusting for gender and age in the multivariate analysis. In fact, the patients with NASH and a genetic profile of persistent lactase activity exhibited less insulin resistance than the patients with hypolactasia. These divergences in our findings could be related to differences in the studied populations and possible positive effects of dairy ingestion on the metabolic profiles of these individuals.

**Table 4 Multivariate logistic regression analysis in nonalcoholic steatohepatitis patients**

| Factor | OR | 95%CI | *P* value |
|---|---|---|---|
| HOMA-IR value ⩾ 2.5 | | | |
| Hypolactasia phenotype | 5 | 1.35-20 | 0.017[a] |
| CT genotype | 0.16 | 0.04-0.64 | 0.009[a] |
| TT genotype | - | - | 0.994 |
| BMI ⩾ 30 | | | |
| Hypolactasia phenotype | 0.49 | 0.13-1.81 | 0.285 |
| CT genotype | 1.73 | 0.69-4.35 | 0.244 |
| TT genotype | 1.01 | 0.12-8.39 | 0.991 |
| Insulin > 29.8 | | | |
| Hypolactasia phenotype | 2.04 | 0.68-6.25 | 0.197 |
| CT genotype | 0.52 | 0.17-1.56 | 0.25 |
| TT genotype | - | - | 0.991 |
| MetS | | | |
| Hypolactasia phenotype | 0.94 | 0.47-2.42 | 0.89 |
| CT genotype | 1.07 | 0.46-2.49 | 0.866 |
| TT genotype | 0.91 | 0.11-7.3 | 0.929 |

[a]*P* value < 0.05. HOMA-IR: Homeostatic Model of Assessment; OR: Odds ratio; BMI: Body mass index; MetS: Metabolic syndrome.

Our studied population consisted only of NAFLD patients, among which the prevalences of MetS components are expected to be higher than those of the overall population. Therefore, firm direct comparisons are precluded. However, a recently published Brazilian study demonstrated that in the general population, the lactase non-persistence genotype subjects exhibit higher prevalences of hypertension ($P$ = 0.032) and MetS ($P$ = 0.01) than lactase-persistence genotype individuals based on univariate analysis[38]. Furthermore, multivariate analyses revealed that lactase persistence was associated with a lower risk for MetS after adjusting for gender, age, BMI and physical activity (OR = 0.462; $P$ = 0.009). These data are in line with our findings that demonstrated a favourable profile of MetS components and glucose homeostasis in the NASH patients with lactase persistence. Moreover, in a longitudinal French study encompassing 3575 subjects, Lamri *et al*[39] demonstrated that the C allele was associated with a higher frequency of impaired fasting glycaemia and type 2 diabetes. However, Enattah *et al*[40] were unable to demonstrate that lactase persistence polymorphisms were risk factors for type 1 or type 2 diabetes in the Finnish study. Similar to NASH, polycystic ovary syndrome is also frequently associated with metabolic disturbances, including dyslipidaemia, insulin resistance and central obesity, and NASH often coexists in these patients[41]. Lerchbaum *et al*[42] demonstrated a significantly higher prevalence of hypolactasia in polycystic ovary syndrome women, which also corroborates our findings.

Ultimately, we believe that dairy consumption appears to modulate the metabolic profiles of these different populations because of the strong association of the *LCT*-13910 genotype with dairies intake and lactose malabsorption[11,31,39,43]. Several studies have highlighted the benefits of dairy and dairy components on MetS components[18-22,44-46] and cardiovascular health[47]. The benefits of dairy products may be mediated through several mechanisms, including the following[23,48]: The insulinotropic role of whey and its beneficial effect on body weight and fat; the favorable effects of amino acids, medium chain fatty acids, calcium and other minerals found in milk and its derivatives; improvements in insulin sensitivity due to medium chain fatty acids; reductions in the absorption of cholesterol and other fats from fermented products; the probiotic bacteria present in these foods and the associated proteins and peptides; and improvements in weight control, blood pressure and plasma lipids due to lactose, citrate, proteins and peptides. Specifically addressing glucose homeostasis, a hypothetical explanation is that milk and dairy consumption may be associated with an enhanced insulinaemic response, decreased glycemic fluctuations, and increased secretion of glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide[49].

Experimental models also provide some mechanistic explanations that link dairy consumption with lower incidences of insulin resistance and diabetes[50]. Milk components such as rumenic acid, vaccenic acid, phytanic acid and its derivative pristanic acid have been demonstrated to improve insulin resistance though PPAR signalling activation in different rat models[51-54]. These findings suggest that dairy consumption could have a role in insulin resistance and NASH management.

However, in our study, there was no association between *LCT*-13910 genotype and the severity of liver histology in the NASH patients. The reason for this finding may be that the pathogenesis of NASH involves a complex multiple parallel hits process in which a number of different events may contribute to liver injury[55]. Lifestyle and genetic predisposition remain relevant disease determinants. The consumption of high-calorie diets rich in lipids results in weight gain, obesity and insulin resistance. Moreover, a diet high in carbohydrates (mainly fructose) and saturated fatty acids contributes to the production of excess free fatty acids, whose safe disposal is impaired, which results in oxidative stress and NASH[56]. Recent data have also demonstrated a potential role of the microbiota in the induction of insulin resistance and the development of NAFLD/NASH[57-59]. The major components of the gut microbiota at the phylum level are *Bacteroidetes* and *Firmicutes*[60]. It has been demonstrated that *Firmicutes* levels are elevated in obesity and related diseases, whereas *Bacteroidetes* levels are decreased, which leads to an increase in the *Firmicutes*/*Bacteroidetes* ratio[61,62]. Interestingly, it has been shown that lysozyme-rich milk consumption results in a decline in *Firmicutes* levels (mainly *Clostridia* spp.) and in an increase in *Bacteroidetes* levels over time[63,64]. Despite the absence of high levels of lysozyme in the milk of dairy animals, these studies highlighted the potential role of milk and its components in the composition of the microbiome in health and disease.

The main limitations of our study are the lack of alimentary reports from the NAFLD patients to quantify the dairy intakes and the absence of ethnic data because

the prevalence of *LCT*-13910C>T polymorphisms may vary widely, as has been previously demonstrated[12].

In conclusion, we demonstrate that hypolactasia (*i.e.*, the *LCT*-13910CC genotype) is associated with a higher insulin resistance frequency in NASH patients. However, further studies that include dairy ingestion reports are needed to elucidate the associations of the lactase-persistence phenotype with MetS and NAFLD/NASH in different populations.

## COMMENTS

### Background

Non-alcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of liver damage that ranges from steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis in persons without significant alcohol consumption and has a close relationship with metabolic syndrome (MetS). The lactase gene (*LCT*)-13910C>T polymorphism located upstream of the *LCT* is tightly associated with lactase persistence. The *LCT*-13910CT and *LCT*-13910TT genotypes are associated with the lactase-persistence phenotype, *i.e.*, they render a person a lactose digester, whereas the *LCT*-13910CC genotype is associated with lactose malabsorption.

### Research frontiers

The role of milk in MetS is not currently clearly defined, and the literature is controversial. Moreover, to our knowledge, there are no published data regarding the *LCT*-13910C>T polymorphism in patients with NAFLD. Therefore, the authors assessed the expression profile of *LCT*-13910 genotypes in Brazilian patients with NAFLD in comparison with those of healthy controls to investigate whether the *LCT*-13910C>T variant could be a predictor of NASH. Furthermore, in NASH patients, the authors analyzed the associations of the lactase-persistence genotype with the results of biochemical tests, components of MetS and the severity of liver histology.

### Innovations and breakthroughs

The authors were unable to find any differences in the *LCT*-13910C>T polymorphism expression profiles between Brazilian NAFLD patients and healthy controls. Moreover, the presence of the T allele was not able to discriminate steatosis from NASH in NAFLD patients. However, in NASH patients, the hypolactasia phenotype (*i.e.*, the *LCT*-13910CC genotype) was associated with insulin resistance, and conversely, the *LCT*-13910CT genotype conferred protection against its occurrence.

### Applications

Specific pharmacological therapy for NASH is still lacking, so the pursuit of high-risk individuals can be a strategy for concentrating efforts on its diagnosis and management. Dairy consumption appears to modulate the metabolic profile because hypolactasia was found to be an independent risk factor for insulin resistance in NASH patients. Further studies that include dairy ingestion reports are needed to elucidate the associations of the lactase-persistence phenotype with MetS and NAFLD/NASH in different populations.

### Terminology

NAFLD: Non-alcoholic fatty liver disease, which encompasses a wide spectrum of liver damage that ranges from steatosis to NASH and cirrhosis in persons without significant alcohol consumption. The MetS components include the following: Fasting glucose $\geqslant$ 110 mg/dL, triglyceride $\geqslant$ 150 mg/dL, high-density lipoprotein < 40 mg/dL in men or < 50 mg/dL in women, $\geqslant$ 130 mmHg systolic or $\geqslant$ 85 mmHg diastolic pressure and abdominal obesity. The *LCT*-13910CT and *LCT*-13910TT genotypes are associated with the lactase-persistence phenotype, *i.e.*, these genotypes render a person a lactose digester, whereas the *LCT*-13910CC genotype is associated with hypolactasia, *i.e.*, lactose malabsorption.

### Peer-review

The paper indicated that among nonalcoholic steatohepatitis patients, hypolactasia is associated with insulin resistance in Brazil. It is a very interesting and well-written paper.

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ORIGINAL ARTICLE

Observational Study

# Diagnostic non-invasive model of large risky esophageal varices in cirrhotic hepatitis C virus patients

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## Abstract

### *AIM*

To build a diagnostic non-invasive model for screening of large varices in cirrhotic hepatitis C virus (HCV) patients.

### *METHODS*

This study was conducted on 124 post-HCV cirrhotic patients presenting to the clinics of the Endemic Medicine Department at Mansoura University Hospital for evaluation before HCV antiviral therapy: 78 were Child A and 46 were Child B (score $\leqslant$ 8). Inclusion criteria for patients enrolled in this study was presence of cirrhotic HCV (diagnosed by either biopsy or fulfillment of clinical basis). Exclusion criteria consisted of patients with other etiologies of liver cirrhosis, *e.g.*, hepatitis B virus and patients with high MELD score on transplant list. All patients were subjected to full medical record, full basic investigations, endoscopy, and computed tomography

(CT), and then divided into groups with no varices, small varices, or large risky varices. In addition, values of Fibrosis-4 score (FIB-4), aminotransferase-to-platelet ratio index (APRI), and platelet count/splenic diameter ratio (PC/SD) were also calculated.

***RESULTS***

Detection of large varies is a multi-factorial process, affected by many variables. Choosing binary logistic regression, dependent factors were either large or small varices while independent factors included CT variables such coronary vein diameter, portal vein (PV) diameter, lieno-renal shunt and other laboratory non-invasive variables namely FIB-4, APRI, and platelet count/splenic diameter. Receiver operating characteristic (ROC) curve was plotted to determine the accuracy of non-invasive parameters for predicting the presence of large esophageal varices and the area under the ROC curve for each one of these parameters was obtained. A model was established and the best model for prediction of large risky esophageal varices used both PC/SD and PV diameter (75% accuracy), while the logistic model equation was shown to be (PV diameter × -0.256) plus (PC/SD × -0.006) plus (8.155). Values nearing 2 or more denote large varices.

***CONCLUSION***

This model equation has 86.9% sensitivity and 57.1% specificity, and would be of clinical applicability with 75% accuracy.

**Key words:** Diagnostic model; Large varices; Cirrhotic hepatitis C virus; Computed tomography; Noninvasive variceal diagnosis



**Core tip:** Hepatitis C virus infection is a major global health problem, with over 14% of the Egyptian population currently infected. End-stage liver disease with cirrhosis is commonly complicated by potentially life-threatening esophageal varices, which require regular screening by endoscopy. However, this invasive procedure is burdened by patient non-compliance and possible complications, thus prompting the search for alternative non-invasive yet accurate means of diagnosis. This study group aimed to assess the use of computed tomography to evaluate and grade variceal size, and to compare its diagnostic value with other non-invasive predictors of portal hypertension, such as platelet count to splenic diameter ratio, aminotransferase-to-platelet ratio index, and Fibrosis-4 score.

Elalfy H, Elsherbiny W, Abdel Rahman A, Elhammady D, Shaltout SW, Elsamanoudy AZ, El Deek B. Diagnostic non-invasive model of large risky esophageal varices in cirrhotic hepatitis C virus patients. *World J Hepatol* 2016; 8(24): 1028-1037 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i24/1028.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i24.1028

## INTRODUCTION

Hepatitis C virus (HCV) represents one of the major health problems affronting the medical community today, with chronic HCV infection affecting approximately 130-170 million people globally, or about 2%-3% of the world's population[1]. The largest HCV epidemic is currently found in Egypt, with an estimated national prevalence reported to be 14.7%[2]. As with any chronic liver disease, the end stage of chronic HCV infection is cirrhosis, ultimately complicated by portal hypertension, an established contributing factor in the evolution of a variety of complications of cirrhosis including ascites, hepatic encephalopathy, and esophageal varices[3].

Portal hypertension generates development of porto-systemic collaterals, giving rise to esophageal varices (OV), most notably gastroesophageal varices because of their enhanced tendency for bleeding[4]. Esophageal varices can be found in 60%-80% of cirrhotic patients[5], with variceal hemorrhage presenting as the most devastating complication of cirrhosis. Because of this dramatic course of events, it is imperative to prevent variceal bleeding either with non-selective beta-blockers or endoscopic variceal ligation[6]. However, in spite of recent progress, mortality rate due to bleeding from ruptured esophageal varices remains between 10%-20%[7].

Current guidelines advocate screening for esophageal varices in all cirrhotic patients at the time of diagnosis. Lack of detection of esophageal varices at the first endoscopic evaluation warrants repeat endoscopy annually in patients with decompensated liver cirrhosis and every 2-3 years in patients with compensated cirrhosis[8]. Although upper endoscopy is regularly performed and conveys a diminished risk of adverse effects[9], repeated endoscopies are associated with several side effects including aspiration, perforation, and bacteremia[10]. Furthermore, these recommendations impose a huge burden on medical resources and branch from expert assumption rather than being evidence-based. In addition to the invasive nature of the procedure and lack of patient compliance restricting its use, there is also a cost-ineffectiveness of this policy in lack of actual detection of varices in many of the patients[11]. These considerations have spurred several attempts to identify non-invasive clinical, radiological, and biochemical parameters, used either separately or in conjunction, to determine the presence of portal hypertension and esophageal varices.

Perhaps the best predictor of esophageal varices developed to date is the platelet count to splenic diameter ratio, which proposes linking thrombocytopenia to spleen size by considering that diminished platelet count is probably the result of hypersplenism due to splenomegaly caused by portal hypertension[12]. Other parameters have attempted to determine the state of liver tissue with good accuracy by evaluating the extent of fibrosis and cirrhosis as a predictive indicator of progression of portal hypertension, these including

aminotransferase-to-platelet ratio index (APRI), Fibro-index, and Fibrosis-4 score (FIB-4)[13].

Several radiological techniques have also been suggested for evaluation of esophageal varices. Doppler ultrasonography has been used for investigating portal and hepatic hemodynamics but its value in assessment of portal hypertension remains obscure. Although several indices for portal hypertension have been commonly used, inaccuracy remains due to fluctuating variations related to both observer and equipment[14].

Computed tomography (CT) has also been proposed as an evaluation tool for esophageal varices[15]. Examination of the correlation between CT findings and endoscopy from previous studies has shown better agreement between variceal size and radiological assessment than with endoscopic interpretation[16]. In addition, CT was found to be more desirable in initial screening of esophageal varices in comparison to endoscopy when considering patient preference and cost-effectiveness[17].

Therefore, considering these findings, we aimed to evaluate the use of CT in the diagnosis of esophageal varices, differentiating between small and large varices, and assessing its use in grading the size of varices. In addition, we aimed to compare the value of CT in diagnosis of esophageal varices with other non-invasive predictors of portal hypertension including laboratory indices such as platelet count to splenic diameter ratio, APRI, and FIB-4.

The objective of the study was to build a diagnostic non-invasive model for screening of large esophageal varices in cirrhotic HCV patients.

## MATERIALS AND METHODS

### Ethical approval

Informed consent was taken from each patient. The research protocol was approved by the Ethical Committee of Faculty of Medicine, Mansoura University.

### Study design

This comparative cross sectional study included subjects presenting to the Endemic Medicine Department clinic at Mansoura University Hospital for evaluation before HCV antiviral therapy during the period between December 2014 and June 2015. Inclusion criteria for patients enrolled in this study was presence of cirrhotic HCV as diagnosed either by biopsy (F4) or on the basis of clinical evaluation combined with laboratory findings and ultrasonography. Exclusion criteria consisted of patients with other etiologies of liver cirrhosis or those ineligible for the HCV therapy program, *e.g.*, HBV, Child C decompensated patients, and patients with high MELD score on transplant list. Patients with liver cirrhosis were then stratified according to endoscopic findings into groups with either no varices, small varices, or large varices.

The indication for CT imaging in the majority of cases was for evaluation of focal lesions for hepatocellular carcinoma while the entire laboratory assessment was done as a part of the HCV therapeutic evaluation program.

### Clinical and laboratory workup

All subjects were HCV infected and thus subjected to complete laboratory assessment before antiviral therapy, including complete blood picture, PCR for HCV, alpha fetal protein (AFP), alanine and aspartate transaminases, albumin, bilirubin, INR, creatinine, TSH, as well as abdominal ultrasound and biopsy in selected cases.

Those with findings of F4 on biopsy or showed clinical, laboratory, or ultrasonographic features of cirrhosis were selected for this study, to be then classified into case and control groups.

Cases were patients with post-HCV liver cirrhosis with esophageal varices on endoscopy, divided into two groups with either small or large varices, while the control group was patients with post-HCV liver cirrhosis without varices.

### Gastroscopy for varices evaluation and therapy

Using slight sedation with *IV* midazolam administered just before the session, patients were stratified by risk of first variceal hemorrhage into either high-risk patients, *i.e.,* those with medium/large varices, or low risk patients, *i.e.,* those with small varices occurring in a Child A or B patient. Trials have shown that patients with medium/large varices can be treated with either non-selective β-blockers (propranolol, nadolol) or esophageal band ligation.

### Calculation of non-invasive parameters (APRI, FIB4, platelet count/splenic diameter)

APRI = {[AST Level (IU/L)]/[AST (upper limit of normal) (IU/L)] × 100}/Platelet count ($10^9$/L)[18]

FIB4 = [age (years) × AST (IU/L)]/[PLT (× $10^9$/L)] × [√ALT (IU/L)][19,20].

Platelet count (PC) to spleen diameter (SD) ratio = PC (N/μL)/the maximum bipolar diameter of the spleen (mm)[21].

These parameters were selected based on the criteria of being simple routine laboratory tests that are also inexpensive.

### Multi-slice detector CT

For all patients, multi-slice detector CT (MDCT) scan of the abdomen and pelvis was performed on a 16-MDCT scanner (Brilliance, Philips) using a tube collimation of 16 mm × 1.5 mm with overlapping reconstruction at 2 mm slice thickness and 0.8 mm increment.

Examination was carried out using a multiphasic liver protocol starting with non-contrast examination. Arterial phase examination was carried out using bolus tracking technique and post-threshold delay of 12 s. Low osmolar iodinated intravenous contrast [Omnipaque™ (iohexol) 350, GE Healthcare] was injected using a power injector [MEDRAD Vistron CT® Injector, Medrad] administered in a dose of 1.5 mL/kg at a flow rate of 4-5 mL/s. Portal phase examination was carried out 40 s after threshold

and delayed phase examination after 5 min.

Images were reviewed on a dedicated workstation (Extended brilliance work space, Philips) in axial, coronal and sagittal planes. Images were evaluated for the following parameters: Maximum short axis diameter of the largest visible esophageal varix, diameter of coronary vein, diameter of the paraumbilical vein, maximum short axis diameter of the portal vein at the portahepatis, presence of ascites, and maximum height of the spleen. An esophageal varix was defined as an enhancing intramural nodular tubular structure (which may be bulging into the lumen of the esophagus or runs within the inner esophageal mucosa).

### Statistical analysis

Data were statistically analyzed using the Statistical Package for Social Science (SPSS) version 20. The quantitative data were presented in the form of mean and standard deviation. One-way Anova was used to compare between the three groups. $\chi^2$ test was used to compare the qualitative data. Receiver operating curve (ROC) was done to determine a cut-off point predicting large varices. Logistic regression was done to construct a model for predicting the occurrence of large varices. Significance was considered at *P* value of 0.05.

## RESULTS

### Patient characteristics

A total of 124 patients with hepatic cirrhosis were included in this study. The mean age of the included patients were 56.52 ± 5.759 (range 37-66) years with 26 patients (52%) being males. The etiology of cirrhosis in all included patients was HCV. Most patients (59.7%) had esophageal varices and 50 patients (40.3%) had no varices. According to gastroscopy, among those who had esophageal varices, 28 patients (22.6%) were classified as having small varices and 46 patients (37.1%) had large varices. According to Child-Turcotte-Pugh Classification, 78 patients (62.9%) were classified as class A, proven by liver biopsy and 46 (37.1%) as class B. There were 34 patients with diuretic responsive ascites (27.5%) and 90 patients (72.5%) without ascites. Ten patients (8.06%) had hepatocellular carcinoma less than 3 cm (Table 1).

### Comparison between non-invasive parameters in the studied groups

The values of Fib4 and APRI were significantly higher in cirrhotic patients with large esophageal varices than those in cirrhotic patients without varices or with small esophageal varices ($P$ = 0.001). Comparison of values of the PC/SD ratio between groups demonstrated a significant decrease in cirrhotic patients with large esophageal varices in comparison to cirrhotic patients without varices or with small esophageal varices ($P$ = 0.001).

Regarding the values of CT parameters, there was a demonstrable difference between groups, as the cirrhotic patients with esophageal varices had higher values of portal vein diameter (PVD) and splenic vein diameter (SVD) than cirrhotic patients without varices ($P$ = 0.012 *vs* 0.284, respectively). A coronary vein threshold ⩾ 7 mm as measured by CT was present in 16 of these cirrhotic patients (12.7%), of which 4 patients were without varices, 4 patients had small varices, and 8 patients had large varices ($P$ = 0.026). While the measurement of lieno-renal shunt by CT was ⩾ 12 mm, there were 8 cirrhotic patients (6.45%) without esophageal varices ($P$ = 0.006). In addition, CT significantly differentiated between presence and absence of OV. When CT reported that there were no variceal findings in 50 patients (40.3%), 46 of these were actually without varices and 4 patients had esophageal varices; CT indication of varices in 74 patients (59.7%) was confirmed in 70 of these patients who actually had OV ($P$ = 0.001) (Table 2).

### Non-invasive prediction of large risky esophageal varices

ROC curve was plotted to determine the accuracy of non-invasive parameters for predicting the presence of large esophageal varices rather than presence of varices and the area under the ROC curve for each one of these parameters was obtained. A FIB-4 ⩾ 3.13 had a sensitivity of 71.7% and a specificity of 50% with an area under the ROC curve of 0.585 (95%CI: 0.442-0.728). The area under the ROC curve for APRI was 0.558 (95%CI: 0.417-0.699). An APRI value of ⩾ 1.083 had a sensitivity of 63% and specificity of 46.4%. A PC/SD ratio of ⩽ 806.93 had 75% sensitivity and 47.8% specificity, with the area under the ROC curve being 0.558 (95%CI: 0.417-0.699). In addition, the PVD as measured by CT had a sensitivity of 71.1% and specificity of 37% at cutoff ⩾ 12.5 mm with an area under the ROC curve of 0.560 (95%CI: 0.425-0.630) (Table 3). ROC curves are demonstrated in Figure 1.

### Model for detecting large risky varices

The detection of large risky esophageal varices on the verge of rupture is a multi-factorial process affected by many variables. Statistically, the research team chose to use binary logistic regression. Dependent factors were either large or small varices while the independent factors measured by CT were coronary vein diameter, PVD and lieno-renal shunt in addition to various laboratory parameters including FIB-4, APRI, and PC/SD. The accuracy of this model was about 62.2%. After removal of insignificant predictors, *i.e.*, APRI, FIB-4, coronary vein diameter, and lieno-renal shunt, the accuracy of the model becomes 75%. If only PC/SD was used, the accuracy was 73%, while use of both PC/SD and PVD raised the accuracy to 75.7% (Tables 4-6).

## DISCUSSION

A major health problem facing the medical community

**Table 1 Patients characteristicsn *n* (%)**

| Variables | All patients (*n* = 124) | No varices (*n* = 50) | Small varices (*n* = 28) | Large varices (*n* = 46) | *P* value |
|---|---|---|---|---|---|
| Age, mean ± SD | 56.52 ± 5.759 | 57.28 ± 4.513 | 58.57 ± 3.072 | 54.43 ± 7.423 | 0.005 |
| Gender | | | | | |
| Female | 52 (41.9) | 24 (48.0) | 12 (42.9) | 16 (34.8) | 0.421 |
| Male | 72 (58.1) | 26 (52) | 16 (57.1) | 30 (65.2) | |
| Laboratory data (mean ± SD) | | | | | |
| Serumalbumin (g/dL) | 3.329 ± 0.43 | 3.452 ± 0.404 | 3.271 ± 0.352 | 3.229 ± 0.474 | 0.028 |
| Serum bilirubin (mg/dL) | 1.312 ± 0.572 | 1.093 ± 0.534 | 1.414 ± 0.591 | 1.489 ± 0.532 | 0.001 |
| INR | 1.326 ± 0.238 | 1.249 ± 0.225 | 1.431 ± 0.24 | 1.347 ± 0.226 | 0.003 |
| Serum creatinine (mg/dL) | 0.999 ± 0.179 | 0.956 ± 0.169 | 0.994 ± 0.178 | 1.047 ± 0.180 | 0.044 |
| AST (IU/L) | 68.00 ± 40.086 | 65.84 ± 44.072 | 63.71 ± 22.993 | 72.96 ± 43.797 | 0.561 |
| ALT (IU/L) | 55.18 ± 23.607 | 51.84 ± 19.844 | 57.43 ± 24.848 | 57.43 ± 26.519 | 0.436 |
| Platelet count (cells/mm$^3$) | 152.94 ± 22.012 | 145.96 ± 20.833 | 156.5 ± 27.941 | 1548.35 ± 17.071 | 0.001 |
| AFP (ng/mL) | 2.687 ± 2.687 | 3.646 ± 60.527 | 5.868 ± 1.854 | 3.274 ± 811.945 | 0.064 |
| Clinical data | | | | | |
| Spleen size (mm) | 152.94 ± 22.012 | 145.96 ± 20.833 | 156.5 ± 27.941 | 158.35 ± 17.071 | 0.013 |
| Presence of ascites | | | | | 0.017 |
| Mild (respo-nsive) | 34 (27.5) | 6 (12) | 8 (28.5) | 20 (43.4) | |
| No | 90 (72.6) | 44 (88) | 20 (71.4) | 26 (56.5) | |
| MELD score (mean ± SD) | 1.103 ± 2.828 | 9.852 ± 2.480 | 1.2 ± 2.55 | 1.171 ± 2.942 | 0.001 |
| History of encepha-lopathy | | | | | |
| No | 124 (100) | 50 (100) | 28 (100) | 46 (100) | |
| Yes | 0 (0) | 0 (0) | 0 (0) | 0 (0) | |
| Child Pugh Classification | | | | | |
| A | 78 (62.9) | 42 (84.3) | 18 (64.3) | 18 (39.1) | 0.001 |
| B | 46 (37.1) | 8 (16) | 10 (35.7) | 28 (60.9) | |

AST: Aspartate transaminase; ALT: Alanine aminotransferase; AFP: Alpha fetal protein.

**Table 2 Comparison of multiple variables between patients groups (mean ± SD) *n* (%)**

| Variables | All patients (*n* = 124) | No varices (*n* = 50) | Small varices (*n* = 28) | Large varices (*n* = 46) | *P* value |
|---|---|---|---|---|---|
| FIB-4 | 5.526 ± 3.239 | 4.432 ± 2.334 | 4.814 ± 2.457 | 7.149 ± 3.844 | 0.001 |
| APRI | 1.836 ± 1.256 | 1.408 ± 0.84 | 1.606 ± 1.02 | 2.442 ± 1.519 | 0.001 |
| PC/SD | 722.235 ± 316.5 | 891.133 ± 317.027 | 765.016 ± 326.324 | 512.611 ± 150.784 | 0.001 |
| PVD by CT | 14.116 ± 2.967 | 13.142 ± 2.959 | 14.929 ± 3.366 | 14.639 | 0.012 |
| SVD by CT | 10.903 ± 2.857 | 10.42 ± 2.989 | 11.071 ± 3.62 | 11.326 ± 2.063 | 0.284 |
| Coronary vein ⩾ 7 mm by CT | 16 (12.7) | 4 (8.0) | 4 (14.29) | 8 (17.39) | 0.026 |
| Lienorenal shunt ⩾ 12 mm by CT | 8 (6.45) | 8 (28.57) | 0 (0) | 0 (0) | 0.006 |
| Presence of varices in CT | | | | | 0.001 |
| Yes | 74 (59.7) | 4 (8.0) | 28 (100) | 42 (91.3) | |
| No | 50 (40.3) | 46 (92.0) | 0 (0) | 4 (8.7) | |

FIB-4: Fibrosis-4 score; APRI: Aminotransferase-to-platelet ratio index; PC/SD: Platelet count/splenic diameter ratio; PVD: Portal vein diameter; SVD: Splenic vein diameter; CT: Computed tomography.

**Table 3 Sensitivity and specificity of noninvasive parameters**

| Parameters | Sensitivity | Specificity | AUC | 95%CI | Cut-off | Significance |
|---|---|---|---|---|---|---|
| FIB-4 | 71.70% | 50% | 0.585 | 0.442-0.728 | 3.13 | 0.222 |
| APRI | 63% | 46.40% | 0.558 | 0.417-0.699 | 1.083 | 0.406 |
| PC/SD | 75% | 47.80% | 0.550 | 0.412-0.688 | 806.93 | 0.472 |
| PVD by CT | 71% | 37% | 0.560 | 0.425-0.695 | 12.5 | 0.396 |

FIB-4: Fibrosis-4 score; APRI: Aminotransferase-to-platelet ratio index; PC/SD: Platelet count/splenic diameter ratio; PVD: Portal vein diameter; CT: Computed tomography; AUC: Area under the curve.

today is chronic HCV infection, which affects about 2%-3% of the global population, or from 130-170 million people worldwide[1], with Egypt currently bearing the largest HCV epidemic which affects 14.7% of its national population[2]. Cirrhosis represents the end-stage of chronic liver disease, ultimately complicated by portal hypertension[3], the main inducing factor in the formation of esophageal varices[4], found in more than half (60%-80%) of cirrhotic patients[5]. These varices are ensuingly prone to consequent rupture and bleeding, with a devastatingly high

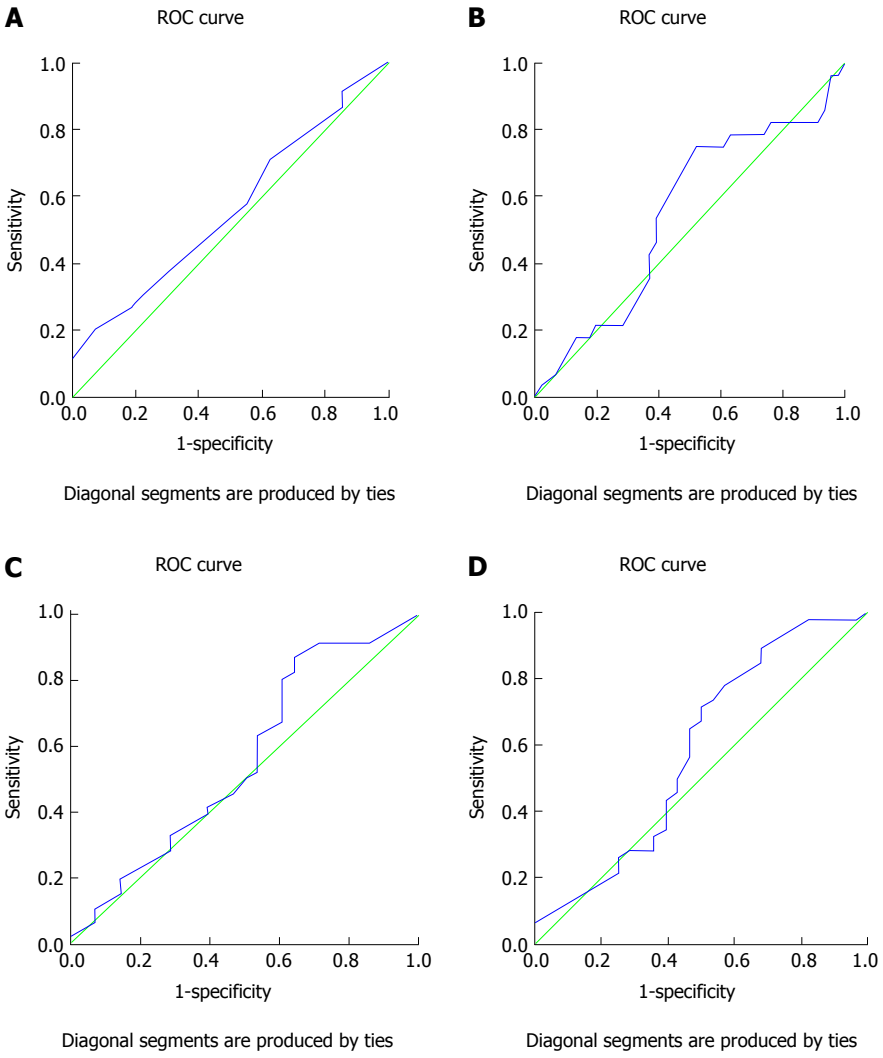


**Figure 1 Receiver operating characteristic curve of portal vein diameter (A), platelet countsplenic diameterratio (B), aminotransferase-to-platelet ratio index (C), and Fibrosis-4 score (D).** ROC: Receiver operating characteristic.

**Table 4 Diagnostic model of large varices**

| Variables in the Equation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B | SE | Wald | df | Sig. | Exp (B) | 95.0%CI for Exp (B) | |
| | | | | | | | | Lower | Upper |
| Step 1[1] | APRI | -0.444 | 0.813 | 0.298 | 1 | 0.585 | 0.641 | 0.130 | 3.155 |
| | FIB-4 | 0.236 | 0.340 | 0.484 | 1 | 0.487 | 1.267 | 0.651 | 2.465 |
| | PVD by CT | -0.257 | 0.123 | 4.398 | 1 | 0.036 | 0.773 | 0.608 | 0.983 |
| | PC/SD | -0.006 | 0.002 | 8.327 | 1 | 0.004 | 0.994 | 0.990 | 0.998 |
| | Coronary vein diameter by CT | -0.853 | 0.687 | 1.544 | 1 | 0.214 | 0.426 | 0.111 | 1.637 |
| | Lieno-renal vein diameter by CT | -0.747 | 0.805 | 0.860 | 1 | 0.354 | 0.474 | 0.098 | 2.297 |
| | Constant | 10.125 | 3.838 | 6.959 | 1 | 0.008 | 2.497E4 | | |

[1]Variable(s) entered: APRI, FIB-4, PVD by CT, PC/SD, coronary vein by CT, lieno-renal shunt diameter by CT. FIB-4: Fibrosis-4 score; APRI: Aminotransferase-to-platelet ratio index; PC/SD: Platelet count/splenic diameter ratio; PVD: Portal vein diameter; CT: Computed tomography; Exp: Exponential; SE: Standard error.

mortality rate of 10%-20%[7].

Current guidelines advocate screening for esophageal varices using endoscopy in all cirrhotic patients at the time of diagnosis[8]. However, the invasive nature and subsequent complications associated with this maneuver have prompted the search for further accurate and non-invasive techniques to evaluate the presence of esophageal varices resulting from portal hypertension in these cirrhotic patients.

Founded on the basis that liver fibrosis is the primary factor enhancing hepatic resistance resulting in portal hypertension, use of non-invasive serum markers of liver

**Table 5 Diagnostic model of large varices**

| Variables in the equation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | B | SE | Wald | df | Sig. | Exp (B) | 95%CI for Exp (B) | |
| | | | | | | | | Lower | Upper |
| PC/SD[1] | PC/SD | -0.005 | 0.001 | 10.721 | 1 | 0.001 | 0.995 | 0.992 | 0.998 |
| | Constant | 3.457 | 0.926 | 13.935 | 1 | 0.000 | 31.707 | | |
| PVD by CT and PC/SD[2] | PVD by CT | -0.256 | 0.116 | 4.879 | 1 | 0.027 | 0.774 | 0.617 | 0.972 |
| | PC/SD | -0.006 | 0.002 | 13.057 | 1 | 0.000 | 0.994 | 0.990 | 0.997 |
| | Constant | 8.155 | 2.465 | 10.942 | 1 | 0.001 | 3.480E3 | | |

[1]Variable entered: PC/SD; [2]Variable entered: PVD by CT and PC/SD. PC/SD: Platelet count/splenic diameter ratio; PVD: Portal vein diameter; CT: Computed tomography; Exp: Exponential; SE: Standard error.

**Table 6 Diagnostic model of large varices**

| Classification table[1] | | | | | |
|---|---|---|---|---|---|
| | Observed | | Predicted | | |
| | | | ROC size | | Percentage correct |
| | | | 1 | 2 | |
| PC/SD | ROC size | 1 | 12 | 16 | 42.9% |
| | | 2 | 4 | 42 | 91.3% |
| | Overall percentage | | | | 73% |
| PC/SD plus PVD by CT | ROC size | 1 | 16 | 12 | 57.1% |
| | | 2 | 6 | 40 | 87% |
| | Overall percentage | | | | 75.7% |

[1]The cut-off value is 0.500. PC/SD: Platelet count/splenic diameter ratio; PVD: Portal vein diameter; CT: Computed tomography; ROC: Receiver operating characteristic curve.

fibrosis has shown favorable outcomes when predicting presence of esophageal varices[21]. Expected findings from previous studies have demonstrated that scores of FIB-4 and APRI were significantly higher in cirrhotic patients with or without portal hypertension when compared to healthy volunteers or patients with chronic liver disease[3]. In our study, significantly higher values of FIB-4 and APRI were also found in cirrhotic patients with large esophageal varices in comparison to those without varices or with small esophageal varices ($P$ = 0.001).

Although several studies have previously demonstrated a strong relation between platelet count and splenic diameter with presence of esophageal varices[22,23], the decreased platelet count present in chronic liver disease may be the result of several factors other than portal hypertension, including diminished mean platelet life span, reduced production of thrombopoietin, or myelotoxic effects of hepatitis viruses[24]. An additional proposed underlying mechanism of "platelet exhaustion" states that hyperdynamic circulation causes platelet damage during intravascular activation with consequent hypofunction. However, the presence of splenomegaly in patients with cirrhosis is, in all likelihood, derived from vascular derangement mainly resulting from portal hypertension[25].

Consequently, Giannini *et al*[26] aimed to chart a new parameter bridging thrombocytopenia to splenomegaly so as to originate a variable that takes into account the diminished platelet count probably due to hypersplenism attributed to portal hypertension. A study performed by Giannini et al demonstrated that a PC/SD ratio cutoff < 909 had a positive predictive value of 96% and negative predictive value of 100%[26]. These data have been subsequently confirmed in a number of recent studies[27-30]; however, these studies focused mainly on presence of varices as a whole.

In the current study, our main target was detection of large risky varices subject to impending rupture. Comparison of values of PS/SD ratio between studied groups showed significant decrease in cirrhotic patients with large esophageal varices compared to those without varices or with small esophageal varices ($P$ = 0.001). These findings are in concordance with several previous studies demonstrating a similar significant correlation between platelet count/splenic size ratio with stages according to Child-Turcotte-Pugh classification, extent of ascites, and size of esophageal varices[31,32].

Findings indicative of portal hypertension can also be commonly detected with use of CT imaging, these including, in addition to splenomegaly and ascites, the presence esophageal varices, augmentation of portal vein, and existence of collateral vessel enlargement[33]. Several previous studies have investigated the interconnection between findings from both CT and endoscopy, and have demonstrated an agreement between variceal size and radiologic interpretations rather than between variceal size and endoscopic valuation[16,34]. However, CT scanning cannot adequately differentiate between small and large varices nor can it detect red signs on small varices that are also subject to a higher risk of bleeding[35].

Comparison of CT parameters between groups in this study demonstrated evident differences, as cirr-

hotic patients with esophageal varices had higher values for PVD as well as SVD when compared with cirrhotic patients without varices (0.0012 and 0.284 respectively). In addition, CT significantly differentiated between presence and absence of esophageal varices. Interpretation of CT imaging showing no varices in 50 patients (40.2%) proved accurate in 46 of these patients who truly had no varices while only 4 patients indeed had esophageal varices as detected by endoscopy. Furthermore, demonstration of varices by CT in 74 patients (59.7%) was correct in 70 of these patients who had endoscopic evidence of esophageal varices. These results indicate that CT is almost as effective in detection of esophageal varices as endoscopy, hence possibly providing an acceptable substitute to endoscopy in detection of esophageal varices in cirrhotic patients.

To evaluate the efficacy of these non-invasive parameters in detecting presence of large esophageal varices, our study group plotted a ROC curve and the area under the curve was obtained for each individual parameter. FIB-4 score of $\geqslant$ 3.13 was shown to have a sensitivity of 71.7% and a specificity of 50% with an area under the ROC curve of 0.585 (95%CI: 0.442-0.728), which are higher than those for APRI which at a value of $\geqslant$ 1.083 had a sensitivity of 63% and a specificity of 46.4%, with the area under the ROC curve being 0.550 (95%CI: 0.442-0.728). In addition, a PC/SD ratio of $\leqslant$ 806.93 had a sensitivity of 75% and specificity of 47.8%, while PVD measurement by CT had 71.1% sensitivity and 37% specificity at a cutoff of $\geqslant$ 12.5 mm, with area under the ROC curve of 0.560 (95%CI: 0.425-0.630). These results indicate that use of CT in detection of large esophageal varices offers results comparable to those provided by both FIB-4 and APRI values, as well by evaluation of PC/SD ratio.

Based on these data, we proposed a non-invasive model for the prediction of large esophageal varices in patients with cirrhosis. Being a multi-factorial process, the detection of large varies is affected by many variables. In order to construct a model for the prediction of large esophageal varices, the research team chose binary logistic regression as a statistical means of evaluation. Dependent factors were either large or small varices, while independent factors were coronary vein diameter, PVD, lieno-renal shunt, FIB-4, APRI, and PC/SD. The accuracy of this model was shown to be about 62.2%. However, after removal of insignificant factors such as APRI, FIB-4, coronary vein diameter, and lieno-renal shunt, accuracy of the model becomes 75%. With use of PC/SD alone, the model accuracy was shown to be 73%, but combined use of both PC/SD and PVD offered an accuracy of 75.7% for prediction of large risky esophageal varices.

In conclusion, endoscopy continues to be the mainstay in diagnosis of esophageal varices, in spite of its invasive nature, unacceptability by a large number of patients, and diverse side effects and complications; however, there remains a need for further non-invasive, effective tools for detection of large esophageal varices which may be subject to imminent rupture and hemorrhage in patients with cirrhosis. Thus, CT scanning may afford an adequate alternative to endoscopy in diagnosis of esophageal varices in patients afflicted with cirrhosis, as it appears to offer similar diagnostic value for large esophageal varices as other non-invasive parameters, with the added benefit of detection of other pathology of the liver, such as various hepatic lesions or masses, most notably hepatocellular carcinoma. In addition, parameters easily detectable by CT, such as PC/SD and PVD, form the basis for the model proposed by this study group, which provides accuracy of 75% for detection of large risky esophageal varices threatening to rupture in cirrhotic patients.

## COMMENTS

### Background

Chronic hepatitis C virus (HCV) infection currently affects approximately 130-170 million people globally, or about 2%-3% of the world's population, with the largest HCV epidemic currently found in Egypt, affecting about 14.7% of the Egyptian population. The end stage of chronic HCV infection is cirrhosis, often complicated by esophageal varices. While upper gastroscopy remains the gold standard for diagnosis of esophageal varices, several disadvantages of this invasive procedure have prompted the search for non-invasive parameters to determine the presence of esophageal varices.

### Research frontiers

Several parameters have emerged as predictors of esophageal varices including platelet count to splenic diameter ratio, aminotransferase-to-platelet ratio index (APRI), Fibroindex, and Fibrosis-4 score (FIB-4) as well as a number of radiological techniques including Doppler ultrasonography and computed tomography (CT). However, all of these elements are plagued by limitations. The research hotspot is to acknowledge these various parameters and their limitations to help other peers understand the background behind the search for an accurate.

### Innovations and breakthroughs

The search for a non-invasive method to accurately diagnose the presence of esophageal varices has been advancing in recent years. The present study involved a significant number of cirrhotic patients who underwent upper gastroscopy followed by CT imaging in addition toa series of simple inexpensive investigations to determine values for APRI, FIB-4, and platelet count/splenic diameter ratio (PC/SD). Patients undergoing the latter procedures were much more willing to comply when compared to those consenting for endoscopy, giving further support that endoscopy, in spite of its established benefits, remains a costly, uncomfortable procedure for many patients who prefer to avoid this invasive maneuver in any way possible, particularly when other accurate diagnostic tools are readily available.

### Applications

Data from this study suggest that CT scanning may afford an adequate alternative to endoscopy in diagnosis of esophageal varices in cirrhotic patients. In addition, parameters easily detectable by CT, such as PC/SD and portal vein diameter, form the basis for the model proposed by this study group.

### Terminology

Chronic HCV infection is a long-standing infection of the liver with HCV culminating into development of cirrhosis and its associated complications, including portal hypertension and esophageal varices. Esophageal varices are abnormally enlarged veins in the lower part of the esophagus, which may leak or even rupture, possibly causing life-threatening bleeding. Endoscopy continues to be the mainstay in diagnosis of esophageal varices.

### Peer-review

The work is really valuable occult blood in stool is always a diagnostic challenge.

Besides esophageal varices, acute mucosa lesions, venous bleeding caused by portal hypertension in any site of the gastrointestinal tract are equally causes.

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ORIGINAL ARTICLE

Prospective Study

# Liver resections can be performed safely without Pringle maneuver: A prospective study

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Author contributions: Maurer CA made the conception and design of the study; Maurer CA, Walensi M, Käser SA, Künzli BM and Lötscher R acquired the data; Maurer CA, Künzli BM and Zuse A analyzed the data; Maurer CA, Walensi M, Käser SA, Künzli BM, Lötscher R and Zuse A did the interpretation of the data; Maurer CA, Künzli BM and Zuse A drafted the manuscript; Maurer CA, Walensi M, Käser SA, Künzli BM, Lötscher R and Zuse A revised and approved the final version of the manuscript.

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## Abstract

### *AIM*

To evaluate liver resections without Pringle maneuver, *i.e.*, clamping of the portal triad.

### *METHODS*

Between 9/2002 and 7/2013, 175 consecutive liver resections ($n$ = 101 major anatomical and $n$ = 74 large atypical > 5 cm) without Pringle maneuver were performed in 127 patients (143 surgeries). Accompanying, 37 wedge resections (specimens < 5 cm) and 43 radiofrequency ablations were performed. Preoperative volumetric calculation of the liver remnant preceeded all anatomical resections. The liver parenchyma was dissected by water-jet. The median central venous pressure was 4 mmHg (range: 5-14). Data was collected prospectively.

### *RESULTS*

The median age of patients was 60 years (range: 16-85). Preoperative chemotherapy was used in 70 cases (49.0%). Liver cirrhosis was present in 6.3%, and liver steatosis of ⩾ 10% in 28.0%. Blood loss was median 400 mL (range 50-5000 mL). Perioperative blood transfusions were given in 22/143 procedures (15%). The median weight of anatomically resected liver specimens

was 525 g (range: 51-1850 g). One patient died postoperatively. Biliary leakages ($n$ = 5) were treated conservatively. Temporary liver failure occurred in two patients.

***CONCLUSION***

Major liver resections without Pringle maneuver are feasible and safe. The avoidance of liver inflow clamping might reduce liver damage and failure, and shorten the hospital stay.

**Key words:** Liver resection; Pringle maneuver; Blood loss



**Core tip:** This retrospective cohort study on 175 consecutive liver resections ($n$ = 101 major anatomical and $n$ = 74 large atypical > 5 cm) shows that major liver resections without Pringle maneuver are feasible and safe. The avoidance of liver inflow clamping might reduce liver damage and failure, and shorten the hospital stay.

Maurer CA, Walensi M, Käser SA, Künzli BM, Lötscher R, Zuse A. Liver resections can be performed safely without Pringle maneuver: A prospective study. *World J Hepatol* 2016; 8(24): 1038-1046 Available from: URL: http://www.wjgnet.com/1948-5182/full/v8/i24/1038.htm DOI: http://dx.doi.org/10.4254/wjh.v8.i24.1038

## INTRODUCTION

Massive haemorrhage is a key factor associated with poorer prognosis and outcome of patients undergoing liver resection[1,2]. The amount of blood loss correlates with postoperative morbidity and mortality[3]. Moreover, blood transfusion is linked to a decrease in cancer free survival[4]. Hence, it is a major goal to minimize the blood loss during liver resection. There are three main phases during liver resections when bleeding may occur: The liver mobilisation phase, the parenchymal dissection phase and the revascularization phase[1]. Portal triad clamping (PTC), also known as Pringle maneuver[5], is the most widely used technique to reduce bleeding during the parenchymal dissection phase. In addition, vascular clamping can also be applied to control venous backflow[6,7]. Thus, total hepatic vascular exclusion can be achieved when combining PTC with clamping of the liver veins or the inferior vena cava cranial and caudad of the liver[8]. Further techniques to minimize intraoperative blood loss such as hypoventilation[9] and reduction of the central venous pressure (CVP)[10] have been developed over the last decades.

Although partial or complete vascular clamping results in reduction of blood loss, there are concerns regarding ischemia/reperfusion (I/R) injury to the liver remnant mediated by cytokines and reactive oxygen species[11,12]. Therefore, various attempts have been made to decrease the I/R-injury associated with prolonged clamping of liver vessels: Use of drugs[13], *in situ* cooling[14], intermittent clamping[15,16], ischemic preconditioning[17] and ischemic postconditioning[18]. Ischemic preconditioning involves I/R for a short period of time before exposure to prolonged I/R. The molecule nitric oxide plays a critical role in the early[11,12] and late phases[11] of ischemic preconditioning. Furthermore, during I/R-injury neutrophil and kupffer cell-induced oxidative stress, hepatic circular disturbance as well as inflammatory processes occur. Circular dysfunction is based on sinusoidal endothelial damage[19] as well as unbalance of vasoconstrictive and vasodilating transmitters such as endothelin[20], tumor necrosis factor $\alpha$[21], and interleukins[22]. Other mediators and pathways, *e.g.,* CD39 and purinergic signalling, are believed to play a role in hepatic ischemia and reperfusion injury[23].

Thus, the molecular hepatic system is far better understood today and recent advances in surgical strategies and perioperative care have made liver resections much safer, allowing low mortality and morbidity in experienced hands. However, the question remains whether the risk of resective liver surgery can be further reduced by complete avoidance of any vascular clamping of the liver remnant and hence by minimizing the I/R injury.

The purpose of this retrospective single center data analysis was to assess the feasibility and safety of major liver resections without any Pringle maneuver or its variations. In the second step, we were interested in any differences in outcome between three subgroups: Anatomical resections, atypical resections and the combination of both, *i.e.,* the combination of anatomical and atypical resection.

## MATERIALS AND METHODS

### *Study population*

From September 2002 through July 2013, a prospective database was established including 175 liver resections [anatomical resections ($n$ = 101) and large atypical resections (specimens > 5 cm in at least one diameter, $n$ = 74)] which were performed at the occasion of 143 consecutive liver surgeries. Twenty-five patients had two stage procedures, 2 patients had 3 or more staged liver resections. The indications for these 143 liver surgeries were liver metastases ($n$ = 91, from the following primaries: 73 colorectal cancer, 2 ovarian, 5 breast, 1 gallbladder, 1 esophageal, 1 stomach, 1 leiomyosarcoma, 1 melanoma, 2 gastrointestinal stroma tumor, and 4 with unknown primary), hepatocellular carcinoma ($n$ = 11), follicular nodular hyperplasia ($n$ = 4), liver hemangioma ($n$ = 9), carcinoma of the gallbladder ($n$ = 4), cholangiolar carcinomas ($n$ = 8), liver adenomas ($n$ = 4), hepaticolithiasis ($n$ = 4), echinococcal cysts ($n$ = 5), benign liver cysts ($n$ = 2) and one sclerotic steatohepatitis. Patients' characteristics were summarized in Table 1. The extent of hepatectomy was depending on tumor size and localization, severity of liver steatosis and cirrhosis, age, nutritional status, preoperatively determined liver function and preopera-

**Table 1 Patients' characteristics shown as total and as subgroups according to the types of resection *n* (%)**

| Patient characteristics | Total | Anatomical resections | Atypical resections > 5 cm | Combination of ana-tomical and atypical resections > 5 cm | *P*-values[3] |
|---|---|---|---|---|---|
| No. of liver resections | 175 | 84 | 54 | 37 | n.d. |
| No. of liver surgeries | 143 | 77 | 50 | 16 | n.d. |
| No. of surgeries with ⩾ 2 similar resections | 14 (9.8) | 7 (9.1) | 4 (8.0) | 3 (18.8) | n.d. |
| No. of surgeries with ⩾ 1 additional wedge resection[5] | 29 (20.3) | 10 (13.0) | 14 (28) | 5 (31.3) | n.d. |
| No. of surgeries with ⩾ 1 additional radiofrequency ablation | 25 (17.5) | 7 (9.1) | 11 (22) | 7 (43.8) | n.d. |
| Demographics | | | | | |
| Gender (female/male)[1] | 74/69 | 41/36 | 24/26 | 9/7 | 0.4804[3] |
| BMI (kg/m$^2$)[2] | 25.5 (17.4-53.2) | 24.8 (17.4-53.2) | 27.1 (18.1-36.0) | 25.2 (18.8-29.6) | 0.3660[4] |
| Age (yr)[2] | 60.0 (16-85) | 59.0 (16-85) | 61.5 (28-84) | 63.5 (22-78) | 0.4952[4] |
| Preoperative ASA scores 1/2/3/4[1] | 8/77/58/0 | 3/42/32/0 | 2/28/20/0 | 3/7/6/0 | 0.4247[3] |
| | 5/54/41/0 | 4/54/42/0 | 4/56/40.0/0 | 19/44/37/0 | |
| Indications for liver surgery | | | | | < 0.0001[3] |
| Malignant primary liver tumors | 23 (16.1) | 15 (19.5) | 8 (16.0) | 0 | |
| Liver metastases | 91 (63.6) | 44 (57.1) | 34 (68.0) | 13 (81.2) | |
| Benign liver tumors | 19 (13.3) | 10 (13.0) | 6 (12.0) | 3 (18.8) | |
| Others | 10 (7.0) | 8 (10.4) | 2 (4.0) | 0 | |
| Preoperative chemotherapy[1] | 70 (49.0) | 33 (42.9) | 26 (52) | 11 (68.8) | 0.4281[3] |
| Steatosis grade of normal liver[2] | | | | | 0.9195[3] |
| Steatosis 0%-9% (grade 0) | 103 (72.0) | 56 (72.7) | 37 (74.0) | 10 (62.5) | |
| Steatosis 10%-29% (grade 1) | 26 (18.2) | 14 (18.2) | 8 (16.0) | 4 (25.0) | |
| Steatosis ⩾ 30% (grade 2) | 14 (9.8) | 7 (9.1) | 5 (10.0) | 2 (12.5) | |
| Cirrhosis (Child-Pugh A)[1] | 9 (6.3) | 5 (6.5) | 4 (8.0) | 0 | 0.8568[3] |

[1]Values are total number of patients (%); [2]Continuous variables are expressed as median (range); [3]*P*-values of categorical variables; [4]Calculated by $\chi^2$ test and continous ones by One-way Anova analysis of variance. No significance between the group of anatomical, atypical, and combinated resections for selected variables was found, except for indications for surgery; [5]Liver wedge resection is defined as obtaining a liver specimen with a maximum diameter of less than 5 cm. n.d.: Not determined; BMI: Body mass index.

**Table 2 Extent of anatomical resections based on segmental and sectorial anatomy of the liver according to Brisbane classification**

| Type of anatomical liver resection | *n* |
|---|---|
| Extended right hemihepatectomy | 6 |
| Extended left hemihepatectomy | 3 |
| Right hemihepatectomy | 31 |
| Left hemihepatectomy | 12 |
| Right posterior sectorectomy | 4 |
| Right anterior sectorectomy | 1 |
| Left lateral sectionectomy | 19 |
| Segmentectomy | 19 |
| Bisegmentectomy | 24 |
| Trisegmentectomy | 2 |
| Total of anatomical liver resections | 121 |

tive chemotherapy. The various extents of anatomical resections were classified according to Brisbane nomenclature[24] and were shown in Table 2.

### *Intraoperative anesthesia management*

Surgery was generally performed under low central venous pressure (LCVP). Therefore, the patient's internal jugular vein was cannulated using a dual-channel catheter and CVP was continuously measured. Values below 5 mmHg were targeted by limiting the volume of cristalloid infusion (lactated Ringer) and stimulating diuresis with furosemide (10-20 mg *i.v.*). At the same time, mean arterial blood pressure, determined within the radial artery, was maintained above 60 mmHg by intravenous infusion of norepinephrine (0-10 μg/min). During dissection of liver parenchyma intermittent positive pressure ventilation was reduced to an end-expiratory level of zero mmHg to further minimize the CVP.

### *Surgical procedures*

Following an intravenous antibiotic single shot prophylaxis, either a roof-top or midline abdominal incision without thoracotomy was used in all patients. After exclusion of extrahepatic intraabdominal tumor spread by exploration of the abdominal cavity and the hepatoduodenal ligament, careful visual and bimanual examination of the liver was performed. At least partial mobilization of the liver including dissection of round and falciforme ligament was done in almost all procedures. Inferior hepatic veins were dissected for hemihepatectomies and/or segment 1 resections, and as necessary in other types of resection. Intraoperative ultrasonography of the liver was systematically done to accurately determine the number and location of liver tumors and their relation to hepatic blood vessels and bile ducts. A Tru-Cut®-needle (CareFusion Temno needle 14G, 11 cm, distributed by Admedics, Zuchwil, Switzerland) biopsy of grossly normal liver was sent to frozen section to assess the grades of steatosis and cirrhosis.

Blood vessels of the liver were clamped and dissected from the later liver specimen, only. Temporary or intermittent clamping of vascular structures of the liver remnant or of the liver hilum has been strictly avoided in all patients. And, neither ischemic preconditioning nor

ischemic postconditioning has been used in any of the patients. Only twice, an anterior approach according to Launois[25] was necessary due to a large tumor mass of the right liver lobe.

In all surgeries, the liver parenchyma was cut by means of water-jet dissection. The hence visualized intrahepatic blood vessels and bile ducts were dissected between ligatures or metal clips, small ones were electrocoagulated. The resection surface was treated punctually by argon plasma coagulation and checked for small bile leaks using white gauzes. The resection surface was then covered by the fibrin-based hemostyptic Tachosil® or Beriplast® (Takeda/Nycomed, Basel, Switzerland). In all patients a silicone drain (EasyFlow®, Teleflex Medical GmbH, Kernen, Germany) without suction was inserted.

### *Perioperative assessment of liver function*

The liver function was assessed by measurement of indocyanine green (ICG) clearance[26]. The dye ICG is metabolized and eliminated by the liver, only. Therefore, their elimination velocity is directly corresponding with the functional capacity of the liver. Plasma disappearance rate (range of normal values from 18%-25%) of ICG and the residual ICG after 15 min (R15, normal range between 0%-10%) were examined pre-, intra- and postoperatively. At the beginning of the series, 6 patients had measurement of galactose elimination capacity (GEC) instead of ICG-clearance. No intra- or postoperative controls of GEC were performed at that time. Additionally, various serum parameters were measured repeatedly, most of them daily.

The volumina of total functional liver and the anticipated functional liver remnant (FLR) were calculated by computed tomography (CT), when a resection volume of more than 40% of the total functional liver volume was anticipated. Twenty percent to 25% of total functional liver volume was regarded as a sufficient FLR in an otherwise healthy and non-steatotic liver, and 30%-40% in a steatotic or chemotherapeutically pretreated liver, respectively. In advance of 8 anatomical liver resections, induction of an atrophy-hypertrophy complex by embolization or ligation of right or left portal vein was regarded necessary. One patient underwent preoperative chemoembolization. Patients with liver cirrhosis Child-Pugh stage B were not considered candidates for surgery, and stage A patients ($n$ = 9) had $\leqslant$ 2 liver segments resected.

### *Outcome measures and perioperative management*

Intraoperative blood loss was calculated by adding the blood volume in the suction device plus the blood kept in towels. The indications for blood transfusion were determined individually, according to patients' preoperative heart status and haemoglobin. Generally, patients with ASA-scores 1 or 2 did not receive blood transfusions before the haemoglobin decreased below a value of 80 g/L. For patients with coronary heart disease or hemodynamic instability, the administration of blood transfusion was less restrictive. Blood transfusions referred to the total time of hospital stay.

Postoperatively, patients were closely monitored at the intensive care unit (ICU). The Simplified Acute Physiology Score (SAPS) Ⅱ was used to assess the severity of illness in intensive care patients[27]. The SAPS Ⅱ predicts the risk of hospital mortality and provides an reliable estimation of the risk of death[27].

Bilirubin content was measured from the silicon drainage tube at days 2 and 4, or daily when the drained fluid was suspicious for bile leak. Bile leakage was defined as suggested by Koch *et al*[28] as bilirubin concentration in the drain fluid at least 3 times the serum bilirubin concentration on or after postoperative day 3; or further as the need for radiologic or operative intervention resulting from biliary collections or biliary peritonitis[28].

Resected specimens were weighed immediately after removal. Specimens of malignant neoplasias were sent to the department of pathology for marking the resection margins with ink before formaline fixation.

Liver cirrhosis was defined as F4 fibrosis according to the METAVIR score[29].

### *Statistical analysis*

Data in this study are presented as median and range or as mean ± standard error of mean. Statistical analysis of data was performed using the GraphPad PRISM6 software (GraphPad Software Inc., San Diego, CA, United States). Comparisons of continuous variables between groups were analyzed using one-way ANOVA analysis for multiple comparisons. Categorical variables were compared by chi-square test ($\chi^2$ test). Values of $P < 0.05$ are considered statistically significant.

## RESULTS

Data related to the operative procedure such as operation time, CVP, blood loss and substitution, length of ICU stay, SAPS, and specimen weight is summarized in Table 3. Data are presented as total of the $n$ = 143 liver surgeries and as subgroups according to the types of resection. From the 22 patients needing perioperative blood transfusions, 7 received them intraoperatively, 1 preoperatively and 14 postoperatively.

In patients with provided preoperative volumetry of the liver, *i.e.,* patients with anticipated minimum resected volume of $\geqslant$ 40% of total functional liver volume, the median effectively resected functional volume was 53% (20%-76%). A R0-resection at the liver site could be achieved in 98/114 (86.0%) procedures for malignant liver disease. No local R2-resection did occur.

### *Laboratory results*

Perioperative increases or decreases of relevant laboratory parameters are shown in Table 4, as total and as subgroups according to the types of resection. Table 5 summarizes the ICG-measurements preoperatively, intraoperatively immediately upon removal of the speci-

**Table 3 Perioperative parameters and characteristics of hepatic resections, shown as total and as subgroups according to the types of resection**

| Perioperative data | Total ($n$ = 143) | Anatomical resections ($n$ = 77) | Atypical resections > 5 cm ($n$ = 50) | Combination of anatomical and atypical resections ($n$ = 16) | $P$-values |
|---|---|---|---|---|---|
| Intraoperative parameters | | | | | |
| Median operation time (min) | 361 (78-726) | 386 (134-726) | 299 (78-692) | 362 (120-567) | 0.0061[3] |
| Median $CVP_{min}$ during liver resection (mmHg) | 4 (-5 to 14) | 3 (-5 to 12) | 5 (-3 to 14) | 4 (-4 to 12) | 0.0511 |
| Median total blood loss per procedure ($n$ = 143) (mL) | 500 (50-5000) | 500 (50-5000) | 400 (50-1500) | 700 (150-2400) | 0.0214[3] |
| No. of patients needing ECs (% of $n$ = 143 procedures)[1] | 22 (15%) | 14 (18%) | 6 (12%) | 2 (13%) | 0.9854 |
| Mean number of ECU during total hospital stay, per procedure ($n$ = 143)[2] | 0.4 ± 0.1 | 0.5 ± 0.1 | 0.3 ± 0.1 | 0.2 ± 0.1 | 0.4844 |
| Postoperative parameters | | | | | |
| Median length of ICU stay (d) | 3 (0-44) | 3 (0-15) | 3 (0-44) | 3 (2-5) | 0.2960 |
| Median length of hospital stay (d) | 13 (3-99) | 14 (3-95) | 12 (4-99) | 12 (7-32) | 0.0450[3] |
| Maximum SAPS, median (range) | 27 (7-40) | 26 (14-40) | 27 (7-40) | 27 (14-39) | 0.6001 |
| Median weight of resected liver tissue (g) per procedure ($n$ = 143) | 340 (8-1850) | 525 (51-1850) | 53 (8-490) | 352 (40-1018) | < 0.0001[3] |

[1]Since some patients had simultaneously more than 1 resection, the percentage of the perioperative need for ECs is calculated per number of procedures. $P$-values were calculated, comparing the variable of interest in between the different resection groups (Anova one-way analysis Kruskal-Wallis); [2]Continuous variables are expressed as median (range), except presented as mean ± SEM; [3]Denote statistical significance among resections in the group of anatomical, atypical, and combinated resections. CVP: Central venous pressure; EC: Erythrocyte concentrate; ECU: Erythrocyte concentrate unit; ICU: Intensive care unit; SAPS: Simplified acute physiology score.

mens and on postoperative day 2, again as total and as subgroups according to the type of resection. All 6 patients with preoperatively measured GEC showed values within the normal range. From further 22 patients, only the preoperative ICG-testing was available and resulted as normal (data not shown).

### *Morbidity and mortality*

There was one death in our series due to a preoperatively unknown high-grade stenosis at the origin of the superior mesenteric artery with consecutive extended mesenteric infarction in the postoperative course. Hence, in-hospital mortality was 1/143 procedures (0.7%).

The following major procedure-specific complications (9/143 procedures, 6.3%) occurred: 1 hemorrhage on postoperative day 9 after right hemihepatectomy in a patient needing therapeutic dosages of heparin, 5 biliary leakages treated conservatively and 2 temporary liver failures. From the later, one occurred in a patient after right hemihepatectomy who suffered from ischemic colon perforation, fecal peritonitis and multiorgan dysfunction. Another patient with extended left hemihepatectomy including segment 1 and includes hepatic artery and bile duct reconstruction for a Klatskin tumor developed intercurrent portal vein thrombosis with prolonged hepatic insufficiency. Relief was achieved by insertion of a portal stent. Finally, 1 patient with right hemihepatectomy developed postoperative peritonitis from an accidental small bowel leak, needing reintervention and laparostomy. No hepato-renal syndrome did occur.

Overall, the following advanced grades of complications according Dindo *et al*[30] were encountered: 2 patients with grade ⅢA, 4 with grade IVB and 1 with grade V complication.

## DISCUSSION

During hepatectomy, portal triad clamping developed by Pringle[5] is still commonly applied today as a routine procedure and gold standard to limit haemorrhage worldwide[18,31-35]. Clamping of the hepatoduodenal ligament and hence control of the hepatic vascular inflow is thought to reduce blood loss and to avoid blood transfusions[5], both associated with increased perioperative morbidity and mortality[4,36,37] as well as impaired long-term outcome[34].

Albeit the huge importance of this topic, only few studies investigated the value of Pringle maneuver in the past. No randomized study using a standard Pringle maneuver could be found in literature. And to our knowledge, only three randomized trials comparing liver resections with or without intermittent Pringle maneuver were performed so far[38-40]. The value of the intermittent Pringle maneuver is even more questionable, since these studies report conflicting results. Therefore, a very recent paper from Hoekstra *et al*[6] was entitled "vascular occlusion or not during liver resection: The continuing story".

### *Feasibility and safety of liver resections without Pringle maneuver*

In the present paper, a consecutive series of major liver resections is reported without any Pringle maneuver during the total operation time in all procedures. Accordingly, a conversion to Pringle maneuver as a salvage clamping was necessary in none of the patients. Furthermore, only a minor number of patients needed perioperative blood transfusions and in-hospital-mortality was minimal with 0.7%. Hence, the feasibility and safety

**Table 4 Perioperative alterations of laboratory parameters, shown as total and as subgroups according to the types of resection**

| Serum parameters | Total ($n$ = 143) | Anatomical resections ($n$ = 77) | Atypical resections > 5 cm ($n$ = 50) | Combination of ana-tomical and atypical resections > 5 cm ($n$ = 16) | $P$-values |
|---|---|---|---|---|---|
| | Median Δ-values[1] (ranges) | Median Δ-values[1] (ranges) | Median Δ-values[1] (ranges) | Median Δ-values[1] (ranges) | |
| ASAT (U/L, norm < 41) | 304 (-486 to 9885) | 346 (-486 to 9885) | 285 (-137 to 2361) | 463 (-5 to 1270) | 0.1747 |
| ALAT (U/L, norm < 41) | 299 (-356 to 3909) | 300 (-356 to 3909) | 245 (-250 to 2200) | 421 (-27 to 1093) | 0.2635 |
| Bilirubin (μmol/L, norm < 20) | 7 (-130 to 234) | 9 (-130 to 234) | 4 (-36 to 152) | 7 (-0.1 to 33.4) | 0.4605 |
| Ammonia (μmol/L, norm 12-48) | 39[3] (14 to 155) | 41[3] (14 to 155) | 39[3] (20 to 90) | 37[3] (25 to152) | 0.5026[4] |
| Albumin (g/L, norm 35-50) | -8 (-41 to 192) | -8 (-19 to 12) | -6 (-20 to 192) | -8 (-18 to 1) | 0.2262 |
| Hemoglobin (g/L, norm 130-180) | -37 (-83 to 0) | -35 (-83 to 0) | -37 (-71 to -4) | -39 (-68 to -22) | 0.4654 |
| Prothrobine time: Quick (%, norm > 70) | -27 (-108 to 62) | -32 (-81 to -9) | -22 (-53 to 13) | -35 (-63 to -7) | 0.0005[2] |

[1]Medians and ranges of Δ-values are presented. Δ-values are calculated by the difference between preoperative value and the maximum postoperative value or postoperative nadir. *P*-values were calculated, comparing the Δ-value of each serum marker among the different resection groups (One-way Anova analysis of variance); [2]Denote statistical significance among resections in the group of anatomical, atypical, and combinated resections; [3]Variable is presented as median value and range of postoperative maximum, since no preoperative values were available; [4]*P*-value was calculated, comparing postoperatively determined ammonia levels (maximum) among the different resection groups (One-way Anova analysis of variance). ASAT: Aspartate transaminase; ALAT: Alanine aminotransferase.

**Table 5 Pre-, intra- and postoperative values of Indocyangreen-clearance testing were available in 45 liver surgeries and were presented as total as well as subgroups according to the type of liver resection**

| ICG data[1] | Total ($n$ = 45) | Anatomical resections ($n$ = 27) | Atypical resections > 5 cm ($n$ = 13) | Combination of anatomical and atypical resections > 5 cm ($n$ = 5) | $P$-values |
|---|---|---|---|---|---|
| R15 (%, norm 0-10) | | | | | |
| Preoperative | 3.6 (0.1 to 28.4) | 3.6 (0.1 to 28.4) | 3.6 (0.2 to 16.3) | 2.7 (0.8 to 15) | 0.4573 |
| Intraop. after resection | 12.4 (0.5 to 69.8) | 17.3 (0.5 to 69.8) | 6.5 (0.9 to 15.3) | 22.4 (1.3 to 28.8) | 0.0302[3] |
| Postoperative day 2 | 5.8 (0.2 to 26.7) | 7.8 (0.2 to 26.7) | 3.2 (0.7 to 13.4) | 7.6 (0.9 to 12.1) | 0.0420[3] |
| R15 Δ[2] | 1.8 (-8.4 to 14.1) | 4.2 (-8.4 to 14.1) | -0.2 (-5.2 to 9.8) | 0.5 (-0.9 to 8.4) | 0.0693 |
| PDR (%, norm 18-25) | | | | | |
| Preoperative | 22.2 (8.4 to 48) | 21.4 (8.4 to 48) | 22.2 (12.1 to 40.1) | 24.1 (12.0 to 31.0) | 0.6772 |
| Intraop. after resection | 14.4 (2.4 to 35.3) | 11.7 (2.4 to 35.3) | 18.2 (12.5 to 31.2) | 9.5 (8.3 to 26.0) | 0.0047[3] |
| Postoperative day 2 | 19.0 (8.8 to 40.3) | 17.5 (8.8 to 40.3) | 22.5 (13.4 to 28.4) | 17.5 (14.1 to 31.3) | 0.5732 |
| PDR Δ[2] | -1.4 (-15 to 37.1) | -3.7 (-12.9 to 37.1) | 0.1 (-15 to 7.4) | -2.2 (-24.6 to 4.7) | 0.5534 |

[1]Median values and range of data are presented. As sensitive indicator for liver function the retention rate after 15 min (R15) and the plasma disappearance rate (PDR) were evaluated; [2]Δ values of R15 and PDR were determined by the difference of preoperative and postoperative day 2 values. *P* values were calculated, comparing the variable of interest in between the different resection group (one-way Anova analysis of variance); [3]Denote statistical significance among resections in the group of anatomical, atypical, and combinated resections. ICG: Indocyanine green clearance.

to principally avoid the Pringle maneuver seems to be demonstrated.

### *Comparison of blood loss and blood transfusions without Pringle maneuver in the present series vs the literature with Pringle maneuver*

In the present series, having used water jet dissection but no Pringle maneuver for all hepatic resections, the median blood loss of 500 mL was comparable with other reported series using a Pringle maneuver[38,40], varying between 370 and 610 mL. Additionally, the percentage of patients who needed perioperative blood transfusions was 15 in this data and again comparable with data from studies having used Pringle maneuver, ranging from 13% to 36%[35,39,40]. It is noteworthy that excessive intraoperative blood losses in this series, in one patient up to 5000 mL, were exceptional and resulted all from bleeding from the inferior vena cava or the liver veins that would not have been improved by the use of a Pringle maneuver.

### *Conditions facilitating the avoidance of Pringle maneuver*

The following points are regarded as crucial if avoidance of Pringle maneuver is intended: Good exposure of the liver, careful planning of the dissection plane(s) on behalf of the preoperative imaging procedures and the intraoperative ultrasound, knowledge of the liver anatomy and its variants, low CVP during parenchyma dissection phase[38,41,42] and a completed learning curve in major hepatic surgery[43]. Furthermore, various dissection tools such as water jet, harmonic knife, ultrasound, humid bipolar clamp and other devices are thought to facilitate a well controlled parenchyma dissection and avoidance of major blood loss[43,44].

### *How to obtain low CVP?*

The goal is a CVP below 5 mmHg at the time point of hepatic parenchyma dissection. There is a direct relation between the pressure of the hepatic sinusoidal system with CVP. Bleeding during resection phase is proportional

to the pressure gradient across vascular walls and diameter of injured vessels. Therefore, lowering of the CVP contributes to minimizing the blood loss during dissection phase[45]. Besides a close cooperation and communication between surgeon and anesthesiologist, the following measures may support lowering the CVP: Omittance of any positive endexspiratory pressure during ventilation, restrictive intravenous fluid administration, forced diuresis, and a liberal use of drugs sustaining arterial blood pressure.

### *Advantages of liver resections without Pringle maneuver*

The most important advantage of obstaining from Pringle maneuver is the fact that the I/R injury to the liver remnant is almost nihil. This is especially relevant in patients with pre-existing liver damage since the toxic effects of liver ischemia with consecutive liver dysfunction lead to morbidity and mortality[15].

Furthermore, PTC may lead to significant higher systemic vascular resistance combined with decrease in cardiac index as well as increase in mean arterial pressure and, thus, increasing risk of perioperative cardiovascular complications[16].

Although various modifications of Pringle maneuver such as intermittent PTC, ischemic preconditioning and more recently pharmacological preconditioning have been developed to limit these disadvantages[16,46-48], excessive bleeding during reperfusion period partially counterbalances the positive effects regarding minimizing damage of residual liver tissue.

### *Perioperative monitoring of I/R-injury and liver function*

Ischemia/reperfusion (I/R)-injury is usually monitored by measuring levels of aminotransaminases, bilirubin and prothrombin. The trauma during liver surgery caused by manipulation and parenchyma dissection usually result in a mild to moderate increase of transaminases in the serum (not more than 10-fold normal values), with a quick tendency to recover from postoperative day 1 or 2 on. Such mild increases in liver enzymes are usually not relevant for clinical outcome. However, strong elevation of transaminases (more than 20-fold normal level) with a continuous increase over at least 3 postoperative days may be the result of I/R-injury or decreased blood supply to the liver remnant. Levels of transaminases are well correlating with the ischemic damage[49]. I/R-injury may cause postoperative liver failure, mainly in preconditioned patients (*e.g.,* steatosis) with lower tolerance towards ischemia. In the present series without Pringle maneuver, no death occurred due to postoperative liver failure. Only 2 patients experienced temporary liver insufficiency, one due to a septic complication, and another due to postoperative thrombosis of portal vein. It is supposed that these favorable results with regard to postoperative liver failure may be attributed to the maintenance of optimum blood supply to the liver remnant at any time and hence the avoidance of I/R-injury. Accordingly, only moderate increases of transaminases (AST and ALT) in this series were noticed (Table 4).

Additional serum markers that are thought to have stronger validity and more sensitive indication for liver failure and prognosis are increased bilirubin and ammonia as well as decreased prothrombin levels[50]. No serious changes in these parameters were observed with the exception of the 2 mentioned patients with severe complications.

### *Comparison of anatomical vs atypical resection*

As expected, no significant difference in perioperative and laboratory parameters was observed between the group of anatomical resections *vs* the group of atypical resections, with two exceptions: Operation time was significantly shorter and prothrombin time was significantly less reduced in the atypically resected group when compared to the group with anatomical resections. Especially, blood loss, blood transfusions and the length of stay in the ICU were similar in both groups.

### *Limitations of the study*

Data of this study originates from a single center. However, it is a consecutive series with prospective data recording. Large atypical liver resections were also included in this study although they would not belong to major liver resections per definition. However, with view on the study aim, we considered the inclusion of atypical liver resections of at least 5 cm diameter as appropriate, since atypical resections may be accompanied by technical difficulties and inadvertent blood loss similar to segment oriented liver resections.

In conclusion, the data of this study suggests that major liver resections may be performed safely without Pringle maneuver. The low morbidity and mortality rate might be due to minimizing the postoperative liver failure rate by avoidance of the I/R injury to the liver. Anatomical and large atypical liver resections may attempted to be performed without portal triad clamping.

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## COMMENTS

### *Background*

The role of Pringle maneuver in liver resection is under debate.

### *Research frontiers*

Different techniques of Pringle maneuver have been compared.

### *Innovations and breakthroughs*

The present study shows that major liver resections may be performed safely without Pringle maneuver.

### *Applications*

Major liver resections can be done avoiding Pringle maneuver.

### *Peer-review*

This study suggests that major liver resections may be performed safely without Pringle maneuver.

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