Diploma Thesis

A novel score to predict mortality after transjugular intrahepatic portosystemic shunt (TIPS)

Submitted by

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Declaration

I hereby declare, that I have written the submitted thesis independently and without any inadmissible help from third parties. I confirm, that I have used no other than the declared sources. All utilized sources have been indicated as such and acknowledged by means of complete references in the text.

Graz, May 23, 2020 *Luisa Fürschuß eh*

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Content

Abbreviations and Acronyms

PH	portal hypertension
HVPG	hepatic venous pressure gradient
BCS	Budd-Chiari syndrome
TIPS	transjugular intrahepatic portosystemic shunt
HSC	hepatic stellate cells
MELD	Model for end-stage liver disease
INR	International Normalized Ratio
SBP	spontaneous bacterial peritonitis
HRS	hepatorenal syndrome
HPS	hepatopulmonary syndrome
PPHT	portopulmonary hypertension
CCM	cirrhotic cardiomyopathy
HCC	hepatocellular carcinoma
HBC	hepatitis B virus
ALT	alanine-aminotransferase
NAFLD	non-alcoholic fatty liver disease
ΔP	change of pressure
R	resistance
Q	flow
SEC	sinusoidal endothelial cells
NO	nitric oxide
VEGF	vascular endothelial growth factor (VEGF)
RAAS	renin-angiotensin-aldosterone-system
CRP	C-reactive protein
ACLF	acute on chronic liver failure
PAMPs	pathogen-associated molecular patterns
DAMPs	danger-associated molecular patterns
FHVP	free hepatic venous pressure
WHVP	wedge hepatic venous pressure
CSPH	clinically significant portal hypertension
kPa	kilopascal

mm	millimeter
TE	transient elastography
NSBB	non-selective beta blockers
SAAG	serum ascites albumin gradient
LVP	large volume paracentesis
RA	refractory ascites
EASL	European Association for the Study of the Liver
HH	hepatic hydrothorax
VH	variceal hemorrhage
EBL	endoscopic band ligation
AKI	acute kidney injury
CKD	chronic kidney disease
CT	computer tomography
MRI	magnetic resonance imaging
PTFE	polytetrafluoroethylene
PTLF	post-TIPS Liver Failure
AST	aspartate aminotransferase
HE	hepatic encephalopathy
LOLA	L-ornithine-L-aspartate
RCT	randomized controlled trial
FMT	fecal microbial transplant
GOV2	type 2 gastroesophageal varices
IGV1	type 1 isolated gastric varices
eGFR	estimated glomerular filtration rate
IQR	interquartile range
SD	standard deviation
MOTS	modified TIPS-score
AUROC	Area Under Receiver Operating Characteristic
LogMOTS	Logarithmic MOTS
ALD	alcohol-related liver disease
WBC	white blood cell count
GGT	gamma-glutamyltransferase
HR	hazard ratio
LN	natural logarithm

Tables

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Abstract

Background: Transjugular intrahepatic portosystemic shunt (TIPS) has been shown as an effective treatment of portal hypertension-related complications with beneficial effects on morbidity and mortality in selected patients. However, severe complications, such as post-TIPS HE and acute on chronic hepatic failure demand for optimal selection of candidates. Of the various risk-stratification tools that have been published, the Model of End-Stage Liver Disease (MELD) is the so far best validated model to predict post-TIPS mortality. **Methods:** Utilizing data from 158 cases of TIPS placement between 01/2004 and 12/2017 at the University Hospital Graz, we aimed to develop a mortality-predicting tool with beneficial features compared to MELD. **Results:** 144 patients were included in the analysis. Univariate and multivariate analyses of factors predicting mortality within 90 days were performed and a score integrating urea, INR and bilirubin was developed. Modified TIPS-Score (MOTS) ranges from 0-3 points: INR >1.6, urea >71 mg/dl and bilirubin >2.2 mg/dl imply plus one point each. 90-day mortality rates were 4%, 13%, 50% and 75% in patients with MOTS 0 points (n=50), 1 point (n=40), 2 points (n=12) and 3 points (n=8), respectively (p<0.001). Within the total cohort, the predictive performance of MOTS and MELD was similar (AUROC statistics; MOTS: 0.85 [95% CI: 0.74-0.96]; MELD 0.84; [0.74-0.96]. However, in patients with renal insufficiency (eGFR <60, n=31), MOTS predicted mortality with higher accuracy than MELD (MOTS: 0.85; [0.68-1.00]; MELD: 0.77 [0.57-0.97]). The results were validated in an external cohort from the University Hospital Innsbruck. **Conclusion:** With the simple MOTS, we developed a valuable tool to predict post-TIPS mortality, with higher accuracy than MELD in patients with eGFR <60. To optimize future patient selection, prospective validation of MOTS is crucial.

Kurzfassung

Einleitung: Der transjuguläre intrahepatische portosystemische Shunt (TIPS) ist eine wirkungsvolle Maßnahme zur Behandlung der portalen Hypertension und damit einhergehender Komplikationen. Bei optimaler PatientInnenselektion konnten positive Effekte auf Morbidität und Mortalität gezeigt werden. Schwerwiegende TIPS-assoziierte Komplikationen wie hepatische Enzephalopathie oder akut auf chronisches Leberversagen machen eine adäquate Risikoeinschätzung nach objektiven Kriterien unverzichtbar. Das derzeit am besten validierte Instrument mit dem höchsten prädiktiven Wert zur Einschätzung der Mortalität nach TIPS ist der Model of End-Stage Liver Disease (MELD) Score. **Methoden:** Anhand der Daten von 158 PatientInnen, die zwischen 01/2004 und 12/2017 an der Universitätsklinik Graz einen TIPS erhalten haben, sollte ein neues Tool zur verbesserten Risikoeinschätzung und mit prädiktiven Vorteilen gegenüber dem MELD Score entwickelt werden. **Ergebnisse:** 144 PatientInnen wurden in die statistische Auswertung inkludiert. Uni- und multivariate Modelle konnten mehrere prädiktive Faktoren für Mortalität innerhalb von 90 Tagen identifizieren. Wir entwickelten einen einfachen Punkte-Score bestehend aus drei Laborwerten. Der modifizierte TIPS-Score (MOTS) umfasst 0-3 Punkte: INR >1,6, Harnstoff >71 mg/dl und Bilirubin >2,2 mg/dl implizieren jeweils einen Punkt. Die 90-Tages Mortalitätsrate betrug 4% innerhalb der Gruppe mit einem MOTS von 0 Punkten (n=50), 13% für MOTS 1 (n=40), 50% für MOTS 2 (n=12) und 75% für MOTS 3 (n=8) (p<0,001). In der Gesamtkohorte war die Aussagekraft von MOTS und MELD ähnlich (AUROC-Statistik; MOTS: 0,85 [95% CI: 0,74-0,96]; MELD 0,84; [0,74-0,96], während MOTS die 90-Tages Mortalität bei niereninsuffizienten PatientInnen (n=31) mit höherer Genauigkeit vorhersagen konnte (MOTS: 0,85; [0,68-1,00]; MELD: 0,77 [0,57-0,97]). Die prädiktiven Vorteile des MOTS konnten in einer externen Kohorte der Universitätsklinik Innsbruck validiert werden. **Schlussfolgerung:** Mit dem MOTS konnten wir ein einfaches Instrument zur Einschätzung der Mortalität nach TIPS entwickeln, das insbesondere bei PatientInnen mit einer GFR <60 eine höhere Vorhersagekraft als der MELD Score aufweist. Um die PatientInnenselektion in Zukunft zu optimieren ist eine prospektive Validierung notwendig.

1 Introduction

1.1 Portal hypertension

Portal hypertension (PH); the state of increased portal venous pressure, is a clinical syndrome with relevant morbidity and mortality. The definition of PH is based on the measurement of the hepatic venous pressure gradient (HVPG) which quantifies the pressure-difference between the portal vein and the intraabdominal part of the inferior vena cava (1). As physiological HVPG amounts 1-5 mmHg, PH is defined as a HVPG of more than 5 mmHg. When exceeding 10 mmHg, complications of portal hypertension become very likely. Thus, this state is generally termed “clinically significant portal hypertension” (2).

1.2 Etiology of Portal Hypertension

Etiologies of PH are diverse and differ significantly among geographical regions. However, with approximately 90% of cases, liver cirrhosis of any etiology represents the clearly most frequent cause of portal hypertension (3). As the formerly widespread classification in “cirrhotic” and “non-cirrhotic” portal hypertension is very imprecise, it is now common to classify portal hypertension according to the location of the pathology leading to an increased portal venous pressure. Thus, we distinguish between prehepatic (A), intrahepatic (B, C, D) and posthepatic (E) portal hypertension (3,4). The different etiologies of PH are listed in Table 1 according to the corresponding anatomical regions illustrated in Figure 1.

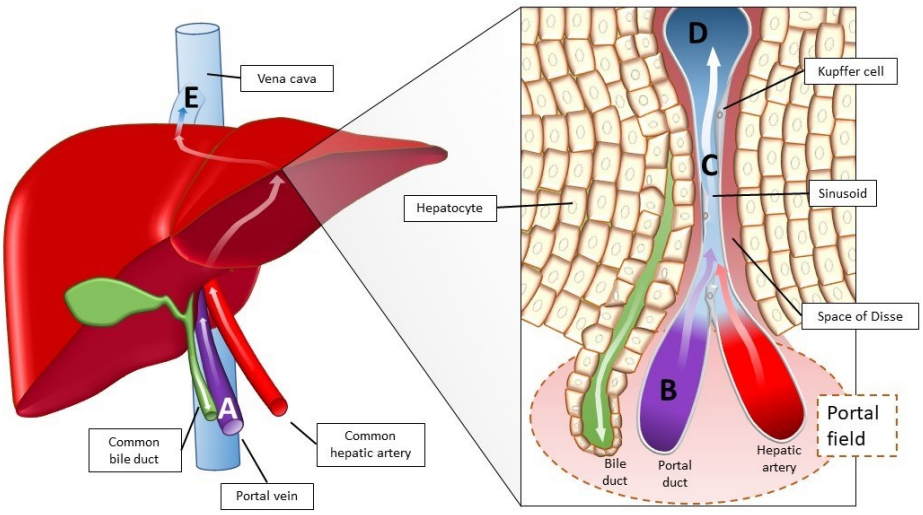


Figure 1, Anatomical regions of different pathologies causing PH, adapted from Nakhleh et al. (4). Levels of obstruction corresponding to table 1: A, extrahepatic portal vein; B, portal vein at the level of portal field; C, sinusoidal; D, juncture of sinusoids and central vein; E, extrahepatic part of hepatic vein.

	Location of obstruction	Etiologies	Pathophysiology	Hemodynamic findings	Imaging
A	Prehepatic	Portal vein thrombosis, tumors, pancreatitis	Extrahepatic portal vein occlusion	Normal measured HVPG but elevated portal pressure	Occlusion of splenic/mesenteric and/or portal vein, splenomegaly, collaterals, normal liver parenchyma
B	Intrahepatic presinusoidal	Schistosomiasis, tuberculosis, sarcoidosis, primary biliary cholangitis at early stages	Compression within the portal tract due to Schistosoma eggs or granuloma formation	Normal measured HVPG but elevated portal pressure	Continuous portal venous system, splenomegaly, collaterals, potentially nodular liver surface, periportal enhancement on ultrasonography
C	Intrahepatic sinusoidal	Cirrhosis, steatohepatitis, amyloidosis, nodular regenerative hyperplasia, congenital hepatic fibrosis	Impairment of sinusoidal blood flow due to altered sinusoidal microanatomy	Elevated HVPG	Continuous portal venous system, splenomegaly, collaterals, abnormal liver ultrasound pattern (nodular surface, heterogeneous), ascites may be present
D	Intrahepatic postsinusoidal	Sinusoidal obstructive syndrome (= Veno-occlusive disease)	Injury of zone 3 sinusoidal lining cells at the area where sinusoids communicate with the central vein which leads to a collapse of central vein walls	Elevated HVPG	Ultrasound: increased phasicity of portal venous flow with eventual development of portal flow reversal
E	Posthepatic	Budd-Chiari syndrome (BCS), cardiac failure with right heart involvement,	**BCS:** thrombosis of hepatic veins, (right) heart failure of any cause	Elevated portal pressure but normal HVPG	**BCS:** occluded hepatic veins, intrahepatic collaterals, atrophy of right lobe, hypertrophy of caudate lobe, marked ascites

	constrictive pericarditis	sinusoidal dilatation and congestion due to systemic venous backlog	**cardiac failure/constrictive pericarditis:** echocardiographic features plus dilated hepatic veins

Table 1, Etiologies of PH according to the corresponding anatomical regions illustrated in fig.1 (3,4)

In the following, cirrhosis and Budd-Chiari syndrome are described in detail since they represent two distinctive etiologies of PH eligible for transjugular intrahepatic portosystemic shunt (TIPS).

1.2.1 Cirrhosis

Cirrhosis of the liver and its consequence, intrahepatic sinusoidal obstruction, is the overall most common cause of portal hypertension (5). The main mechanism of cirrhosis development is progressive fibrosis, the replacement of injured organ parenchyma with scar tissue. Histologically, cirrhosis is characterized by diffuse nodular regeneration, fibrotic septa and disturbed vascular architecture (6).

1.2.1.1 Epidemiology and Etiology of Cirrhosis

Cirrhosis causes 1.03 million deaths per year worldwide. With 170.000 deaths per year, liver cirrhosis accounts for 1.8% of all deaths in Europe (7). In contrast to highly developed areas such as central Europe where leading causes are harmful alcohol consumption, viral hepatitis B and C and metabolic syndrome (7), in sub-Saharan Africa and Asia, hepatitis B infection is the most common cause (8).

1.2.1.2 Pathophysiology of Cirrhosis

Cirrhosis is the end-stage of chronic liver disease. As for most degenerative disorders, inflammation plays a key role in the progression of chronic liver disease. A pivotal cell type in disease progression are hepatic stellate cells (HSC). In the injured liver, these cells change into an activated state and produce extracellular matrix and collagen tissue. Other important factors of disease progression are increased angiogenesis and tissue destruction through vascular occlusion (8). The inflammatory processes lead to endothelial dysfunction and impaired release of vasoactive substances, e.g. nitric oxide. Increased hepatic resistance due to fibrosis,

angiogenesis and endothelial dysfunction as well as splanchnic vasodilation cause a raise in portal pressure (9).

1.2.1.3 Diagnosis of Cirrhosis

The presence of irregular nodular liver parenchyma in imaging (ultrasound, computer tomography, magnetic resonance imaging) and simultaneous impairment of liver synthesis is sufficient for the diagnosis of liver cirrhosis (8). Transient elastography, as a non-invasive modality to quantify hepatic fibrosis is more and more replacing liver biopsy, which still represents the gold standard of (etiologic) differential diagnosis (10). The cutoff for cirrhosis diagnosis in transient elastography is a confirmed liver stiffness of >15 kPa (11). Additionally, ascites, splenomegaly or other signs of portal hypertension (e.g. varices in gastroscopy, caput medusae, splenomegaly) as well as cutaneous signs of liver disease (e.g. spider angiomas, palmar erythema, jaundice) may be present. (see chapter 1.5 Diagnosis of Portal Hypertension)

1.2.1.4 Classification and Prognosis of Cirrhosis

A common clinical classification of cirrhosis is the division in a compensated and a decompensated stage. During the mainly asymptomatic compensated stage, portal pressure may be normal or below 10 mmHg. In the course of disease progression, portal pressure increases and when it exceeds the mark of clinically significant PH (10 mmHg), the probability of decompensating events significantly rises (12). Decompensating events, which include the development of ascites, jaundice, hepatic encephalopathy and variceal bleeding, occur at a rate of 5-7% per year and entail significant morbidity and mortality. This is underlined by a median survival time of >12 years in the compensated stage vs. ≈ 2 years in decompensated cirrhosis (12). A well validated prognostic tool is the Model for end-stage liver disease (MELD). Based on three laboratory variables; creatinine, bilirubin and International Normalized Ratio (INR), MELD estimates the severity of cirrhosis and predicts mortality (13). Child-Pugh score, an older but still widely used tool includes bilirubin and albumin levels as well as INR and additionally assigns scoring points for the presence and severity of ascites and hepatic encephalopathy. It ranges from 5 to 15 points and divides Child-Pugh class A (5-6 points), B (7-9 points) and C (10-15 points) (14).

1.2.1.5 Complications of Cirrhosis

Ascites, jaundice, variceal bleeding and hepatic encephalopathy are frequent complications of cirrhosis (see chapter 1.5 Management of Specific Portal Hypertensive Complications). The occurrence of these events mark the transition from a compensated to a decompensated stage (12). Other common complications of cirrhosis are bacterial infections such as spontaneous bacterial peritonitis (SBP), hepatorenal syndrome (HRS), hepatopulmonary syndrome (HPS), portopulmonary hypertension (PPHT) and cirrhotic cardiomyopathy (CCM) (15). Cirrhosis is also a major risk factor for the development of hepatocellular carcinoma (HCC). HCC can occur at any stage of cirrhosis of any cause whereas patients with chronic viral hepatitis carry the highest risk (15). Approximately one-third of patients with liver cirrhosis will develop HCC during their lifetime (14). (see chapter 1.7, Management of specific Portal Hypertensive Complications)

1.2.1.6 Treatment of Cirrhosis

The focus of therapeutic strategies depends on the stage and cause of chronic liver disease. In general, the first approach should be the removal of etiologic factors of cirrhosis development (15). In patients with alcohol-related liver disease, alcohol abstinence as sole treatment can lead to re-compensation of cirrhosis (17). Over the last 10 years, direct acting antiviral therapy could improve cure rates of chronic hepatitis C from 50% to over 90%. In chronic hepatitis B virus (HBV) infection, the treatment with potent nucleoside- and nucleotide analogues can reach long-term suppression of HBV DNA levels and normalization of alanine-aminotransferase (ALT) levels and significantly improve long-term outcome (15). For the treatment of overweight/obese non-alcoholic fatty liver disease (NAFLD), lifestyle changes with 7-10% weight loss are associated with improved histology as well as liver enzymes (18). Autoimmune hepatitis, as an example of relatively rare chronic liver disease, can be effectively treated with steroids and other immunosuppressive agents resulting in improved prognosis (19). In compensated cirrhosis, the main target is the prevention of the first decompensating event. The management of decompensated cirrhosis should be based on preventing further decompensation as well as on acute and chronic symptom control. The management of portal hypertensive complications will be discussed in chapter 1.7. At the moment, the only curative therapy of cirrhosis is liver transplantation, a valuable treatment option of

decompensated cirrhosis as well as hepatocellular carcinoma in cirrhotic patients (8).

1.2.2 Budd-Chiari Syndrome

Budd-Chiari Syndrome (BCS) is characterized by an obstruction of the hepatic outflow tract at any level from the small hepatic veins to the inferior vena cava. In primary BCS, the obstruction is caused by intravascular processes such as thrombotic occlusion (more prevalent in the West) or membranous obstruction (more prevalent in Asia) (20,21). Secondary BCS caused by external obstruction, such as tumor, will not be discussed in further detail. In a European multicenter study, at least one prothrombotic risk factor was present in 84% of 163 patients with BCS (22). These include myeloproliferative disorders, e.g. polycythemia vera and essential thrombocytosis. Clinical presentation of BCS ranges from an asymptomatic status (which is often correlated with sufficient collaterals) to ascites, jaundice, gastroesophageal bleeding and fulminant hepatic failure (23). For the therapy of BCS, a stepwise model adapted to the etiological factors is recommended. Effective treatment strategies include anticoagulant therapy, intravascular interventions such as angioplasty or stenting, transjugular intrahepatic portosystemic shunt (TIPS) and liver transplantation as an ultima ratio (23).

1.3 Pathophysiology of Portal Hypertension

As liver cirrhosis is the most common cause of PH, this chapter will be mainly focused on cirrhotic PH. Generally, a change of pressure (ΔP) across a vascular system is dependent on its resistance (R) and the flow through the system (Q). This phenomenon can be described with the formula $\Delta P = Q \times R$, which is the hemodynamic counterpart of Ohm's law. Thus, a rise of portal pressure can be either caused by an increased resistance of the vascular network of the liver, an elevated blood flow or both (5). However, on a microscopic level, the pathophysiology of portal hypertension is a complex interaction of vascular, cellular and extracellular factors.

1.3.1 Changes of Resistance (R)

Structural, Molecular and Functional Changes in Sinusoidal and Perisinusoidal Cells

Sinusoidal endothelial cells

Physiologically, sinusoidal endothelial cells are organized to fenestrated capillaries. However, in the injured liver, these fenestrae disappear and the endothelium becomes continuous. Besides these structural changes, sinusoidal endothelial cells (SEC) actively contribute to portal hypertension development. The dysfunctional sinusoidal endothelium cell produces only a fractional amount of nitric oxide (NO), a highly potent vasodilator, compared to the normal SEC (5). This effect is even reinforced by an increased release of vasoconstrictive substances, such as endothelin protein. On the other side, SEC participate in angiocrine signaling (e.g. via vascular endothelial growth factor (VEGF)) and angiogenesis in the hepatic sinusoids. Sinusoidal angiogenesis may contribute to the activation of other cells including HSC and appears to be responsible for early fibrosis (5). In addition to its angiocrine functions, VEGF provokes monocyte infiltration and the recruitment of fibrosis-associated macrophages (25).

Hepatic stellate cells

Being cells of the innate immune system, HSC particularly participate in inflammatory processes in chronic liver disease. Located in the perisinusoidal space (= space of Disse), they express immune receptors like toll-like receptor 4 and become activated after ligand binding, e.g. via lipopolysaccharide. This theory is supported by the correlation of liver injury and fibrosis with lipopolysaccharides derived from the gut (26). Responding to liver injury, HSC become activated resulting in increased contractility, migration and extracellular matrix production and deposition. All these changes lead to pathological sinusoidal remodeling and ultimately to an increase in vascular resistance due to fibrosis and tonicity changes (24). One example of a matrix protein released by activated HSC is fibronectin. Fibronectin itself activates HSC and SEC, thus completing the circle (27). As a consequence of all these characteristics, HSC form a crucial link between inflammation and the accumulation of extracellular matrix causing fibrosis.

Thrombotic processes

Cirrhosis is associated with severe alterations of the coagulation system resulting not only in elevated hemorrhagic risk but also in a high risk for thrombotic events (28). The correlation between sinusoidal thrombotic processes and fibrosis is not yet known in detail. However, chronic hepatic congestion due to partial vena cava ligation in mice was shown to provoke sinusoidal thrombosis and to aggravate hepatic fibrosis and disease progression (29).

1.3.2 Changes of Blood Flow (Q)

Hyperdynamic Circulation

Whilst in intrahepatic circulation, the imbalance of vasoactive substances leads to vasoconstriction, the opposite happens in splanchnic and systemic circulation. An oversupply of vasodilators including NO, prostacyclin I_2, carbon monoxide and endocannabinoids as well as the downregulation of the RhoA/Rho-kinase pathway lead to a loss of peripheral vascular resistance (30). Additionally, VEGF-driven splanchnic angiogenesis seems to promote the increase of perfusion of the splanchnic system (31). Splanchnic hyperperfusion in turn leads to a decrease of mean arterial pressure which causes the activation of compensatory systems. The activated renin-angiotensin-aldosterone-system (RAAS) expands plasma volume and cardiac index (CI; left ventricular output in one minute related to body surface area) rises above normal levels. In sum, this circulatory state is designated as “hyperdynamic syndrome” and represents an important promotor of portal hypertension (9).

Systemic Inflammation and Bacterial Translocation

Systemic inflammation is a hallmark of cirrhosis progression and moved into focus of scientific research within the last years. The fact that white blood cell count, activated neutrophil count, monocytes and C-reactive protein (CRP) are increased in cirrhosis gave a crucial clue. Macrophage activation, for example was shown to be associated with variceal bleeding and mortality in cirrhotic patients (32). The grade of systemic inflammation is correlated not only to the severity of liver disease but also to circulatory and renal dysfunction, hepatic encephalopathy and acute on chronic liver failure (ACLF) (33–36). Systemic inflammation and oxidative stress also effect the binding properties of albumin in cirrhotic patients with significant

consequences, e.g. altered drug transport and endotoxin binding (37). However, the main trigger of systemic inflammation in cirrhosis seems to be the translocation of viable bacteria and bacterial components (pathogen-associated molecular patterns, PAMPs) from the intestinal lumen. Once released to the circulation, PAMPs are recognized by pattern recognition receptors leading to an inflammatory response. So-called danger-associated molecular patterns (DAMPs) released by injured hepatocytes have parallel effects (33).

1.4 Consequences of Portal Hypertension (∆P)

PH is mainly responsible for disease progression, decompensation, need for transplantation and mortality in cirrhosis (12). The most important complications of portal hypertension are those leading to decompensation of cirrhosis, including variceal hemorrhage, ascites and hepatic encephalopathy (38). As portal hypertension leads to a variety of systemic (circulatory) dysfunctions, all organ systems can be affected. Potential systemic complications include hepatorenal syndrome, hepatopulmonary syndrome and hepatic hydrothorax. (see chapter 1.5)

1.5 Diagnosis of Portal Hypertension

When quantifying portal hypertension, the term hepatovenous pressure gradient (HVPG) is indispensable. For direct measurement of portal pressure, a measuring instrument inserted in the portal vein would be necessary. As this invasive procedure is difficult, resource demanding and dangerous, a technique was developed to indirectly measure portal pressure. With a balloon catheter inserted into one of the hepatic veins via jugular or femoral venous entrance, hepatic venous pressure is measured twice; free hepatic venous pressure (FHVP) first, and secondly, after inflating the balloon the wedge hepatic venous pressure (WHVP) is measured. HVPG can be determined by subtracting FHVP from WHVP (2). Physiologically, HVPG is below 5 mmHg. 6-9 mmHg are termed subclinical portal hypertension and HVPG ≥10 mmHg is defined as clinically significant portal hypertension (CSPH). Clinical signs of CSPH are gastroesophageal varices, ascites, episodes of variceal hemorrhage and portosystemic collaterals in imaging (11).

1.6 Treatment of Portal Hypertension

Even though the improving understanding of PH opens the horizon for new therapy targets, at the moment there are only few therapeutic options available, mainly targeting the reduction of portal blood flow (39).

1.6.1 Drugs Targeting Structural Alterations Leading to Increased Hepatic Resistance

Drugs with the property to reverse hepatic fibrosis are heavily researched on. At the moment, there is no antifibrotic medication approved in clinical practice. Currently, the most promising target for antifibrotic drugs are hepatic stellate cells (39). As thrombotic processes play an important role for the increase of vascular intrahepatic resistance, anticoagulants might be effective. Exemplarily, enoxaparin, a low molecular weight heparin has shown to decrease portal pressure by reducing intrahepatic vascular resistance in rats (40).

1.6.2 Drugs Targeting Functional Abnormalities Leading to Increased Hepatic Resistance

Due to endothelial dysfunction in cirrhosis, nitric oxide (NO) levels are decreased in chronic liver disease. Statins have been shown to lower intrahepatic resistance and portal pressure by activating NO pathways (41). Another factor involved in endothelial dysfunction is oxidative stress. Thus, antioxidant substances, e.g. ascorbic acid might improve intrahepatic endothelial dysfunction and portal hypertension (42). Further potentially effective substances targeting NO pathways are phosphodiesterase-5 inhibitors and obeticholic acid (39).

1.6.3 Drugs Targeting Changes in Systemic and Splanchnic Hemodynamics

Currently, non-selective beta blockers (NSBB) are a commonly used drug class to decrease splanchnic blood flow by vasoconstriction. Terlipressin, an analogue of vasopressin also acts via splanchnic vasoconstriction and is used in acute VH and HRS. Novel approaches include the interruption of angiogenesis as it participates in the formation of collaterals as well as to intrahepatic resistance rise. Thus, sorafenib, a multikinase inhibitor also targeting VEGF receptor 2 is a potential future medication for this indication (43). Transjugular intrahepatic portosystemic shunt

(TIPS) should be mentioned here as an invasive mechanical treatment option leading to fast discharge of the splanchnic blood flow.

1.6.4 Drugs Targeting Bacterial Translocation and Endotoxemia

As bacterial translocation and systemic inflammatory response play a crucial role in cirrhosis and PH, antibiotics as well as probiotics are being investigated in this context (39). Rifaximin, and non-absorbable antibiotic was shown to significantly decrease HVPG in patients with alcohol-related decompensated cirrhosis (44). Data regarding probiotics in PH therapy is still controversial (45).

Among all the above-mentioned drugs, only NSBB and Terlipressin have a solid foundation of evidence and are frequently used to treat portal hypertensive complications in clinical practice (11).

1.7 Management of Specific Portal Hypertensive Complications

1.7.1 Ascites

Ascites, the accumulation of fluid in the peritoneal cavity, is the most common cause of decompensation and occurs in 5-10% of compensated cirrhotic patients per year (46). The presence of ascites in cirrhotic patients is associated with a significantly higher mortality and amounts 15-20% within one year and 44% within five years (47).

Pathophysiology

A positive fluid balance emerges from renal sodium retention via the activated RAAS system and leads to extracellular fluid expansion (48). Additionally, hypoalbuminemia, resulting from the injured liver's inability to produce physiological amounts of proteins, causes excessive volume leaks from the splanchnic capillaries and hepatic sinusoids (15).

Diagnosis

The best approved tool for fast and reliable diagnosis of ascites is abdominal ultrasound. Ascites can be categorized into three grades: *Grade 1.* Mild ascites, only detectable by ultrasound examination, *Grade 2.* Moderate ascites with moderate symmetrical distension of the abdomen, *Grade 3*. Large ascites with marked

abdominal distension (49). Determination of the serum ascites albumin gradient (SAAG) is a reliable method to confirm the portal hypertensive etiology. For the calculation of SAAG, albumin concentration in the ascitic fluid is subtracted from serum albumin concentration. A SAAG ≥11g/L is associated with portal hypertension with a probability of 97% (50). Ascites can be further classified in uncomplicated (absence of infection, HRS and refractory ascites) and complicated ascites. The International Ascites Club defined refractory ascites as “ascites that cannot be mobilized or the early recurrence of which (i.e., after large volume paracentesis) cannot be satisfactorily prevented by medical therapy)”(51).

Management

Uncomplicated ascites

Uncomplicated ascites should be initially treated with sodium restriction of less than 5.2g NaCl/day and diuretic drug therapy. Starting with a dosage of 100mg of spironolactone and 40mg of furosemide, diuretic medication can be increased up to 400 mg (spironolactone) and 160 mg (furosemide), respectively (11). In patients with grade 3 ascites, large volume paracentesis (LVP) should be the first measure and should be followed by diuretic medical therapy. Albumin at a dose of 8g per liter of ascites removed by LVP should be administered intravenously (11). As the development of grade 2 or 3 ascites is associated with increased mortality, these patients should be evaluated for liver transplantation (15).

Refractory ascites (RA)

As refractory ascites (RA) does not respond to diuretic therapy, diuretics should be discontinued. The only reason to continue diuretic therapy is a urinary sodium excretion exceeding 30mmol/day (49). As RA is associated with poor prognosis, liver transplantation should be aimed in the first place (11). **TIPS implantation** is an effective treatment option for RA as it decreases the incidence of ascites recurrence from 87% in patients treated with LVP to 51% after TIPS (52). Since TIPS has been associated with improved survival in patients with refractory ascites (52–55), it is recommended with a high level of evidence in both, the Austrian Billroth III Consensus Guidelines, as well as the guidelines of the European Association for the Study of the Liver (EASL). If contraindications for TIPS and liver transplantation are present, repetitive LVP with albumin substitution and sodium restriction are the treatment of choice (11). A novel method is the implantation of low-flow pumps that

are able to transfer fluid from the peritoneal cavity to the urinary bladder (56,57). However, because of a high incidence of adverse events, this intervention is not yet implicitly recommended (11,15).

Spontaneous Bacterial Peritonitis

Spontaneous Bacterial Peritonitis (SBP) most commonly occurs in cirrhotic patients with ascites and is defined as the spontaneous bacterial infection of ascitic fluid, occurring without any intra-abdominal interventions (58). As SBP has a high risk of mortality, early and adequate antibiotic treatment is crucial (15).

Hepatic Hydrothorax (HH)

In up to 12% of patients with cirrhosis, pleural effusion occurs in the absence of cardiac or pulmonary disease (59). The effusion is typically more pronounced on the right side and in about 97% of patients with HH ascites can be detected (60). Common clinical symptoms of HH include cough and shortness of breath frequently together with symptoms of severe ascites (59). Diagnostic pleuracentesis and paracentesis should be performed to confirm the diagnosis. The primary management of HH should include diuretic therapy and sodium restriction (11). If drug-refractory HH occurs, TIPS should be considered in selected cases (11,15). A recent study shows no significant difference of clinical outcome and survival between patients receiving TIPS for HH and those receiving TIPS for RA (61).

1.7.2 Varices and Variceal Hemorrhage

As fluids choose the direction of the least resistance, the formation of portal-systemic collaterals in cirrhosis is a logical consequence. Esophageal and gastric varices are the most relevant collaterals and are present in 42% of Child A patients and 72% of Child B/C patients (62). The pathophysiology of variceal formation is not yet fully understood. However, there are probably two main mechanisms of collateral formation; Firstly, portal hypertension triggers the dilation of pre-existent vessels at sites of embryologic portosystemic shunts (5). Secondly, active angiogenesis plays an important role in portal-systemic collateral formation, mainly via VEGF (63,64). Tension of collateral vein walls increases proportionately with portal hypertension. Rupture of varices is further dependent on the radius of the varix and the thickness of the wall (5). The risk of variceal hemorrhage (VH) amounts 5-15% per year and each episode has an overall mortality of 15-20% at six weeks.

Two main factors associated with a high risk of variceal hemorrhage are severity of liver disease (Child B/C) and the presence of red wale marks on varices (15). In general, screening for gastroesophageal varices is recommended in all patients with advanced liver disease and a liver stiffness of more than 15 kPa in transient elastography (TE) or a platelet count below 150 G/L. If no varices are present in screening endoscopy, it is recommended to repeat endoscopy after one year in decompensated cirrhosis or after two years in compensated cirrhosis. Patients with gastroesophageal varices require further measures. Figure 2, (11) (See chapter 1.7.2.1)

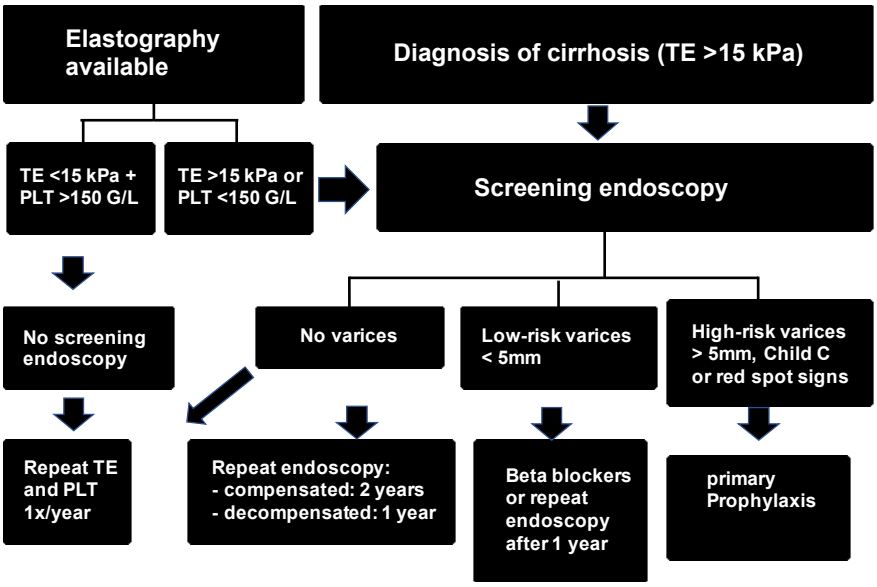


Figure 2, Algorithm: screening for varices in patients with cirrhosis, adapted from Austrian Billroth III Consensus Guidelines (11).

Management

Primary prophylaxis of VH

Primary prophylaxis is recommended in patients with high-risk varices, i.e. small varices with red wale marks, medium or large varices (11,15). For primary prophylaxis, two modalities are approved equally: NSBB and endoscopic band ligation (EBL). However, NSBB treatment with propranolol or carvedilol should be preferred in patients with medium to large varices, considering the additional effect of portal pressure decrease. In patients with contraindications for NSBB, EBL should be performed (11).

Management of acute VH

Acute VH is a major complication of portal hypertension and a medical emergency with a 6-week mortality rate of about 15% (65). Thus, the adequate management is indispensable. To reach acute decrease of portal pressure, vasoactive drug therapy with somatostatin or terlipressin is necessary. As antibiotic prophylaxis is associated with reduced re-bleeding and mortality, ceftriaxone or norfloxacine should be administered (15,66). Within the first 12 hours after bleeding onset, gastroscopy should be performed to confirm the location and provide endoscopic therapy. The current algorithm for the management of acute variceal hemorrhage is outlined in figure 3 (15).

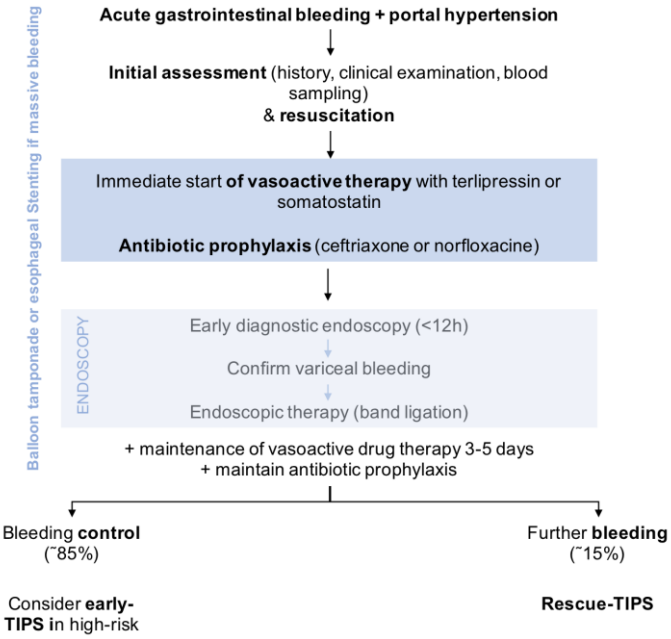


Fig 3, Algorithm for the management of acute gastrointestinal bleeding in patients with portal hypertension, adapted from EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis (15)

Early TIPS

Early TIPS, which means TIPS intervention within 72h after bleeding onset, improves survival in selected patients with advanced cirrhosis and acute VH (67). It is recommended in patients with Child-Pugh class B and active bleeding in endoscopy as well as in all patients with Child-Pugh class C until 13 points or HVPG >20 mmHg (11).

Rescue TIPS

In up to 20% of patients with acute VH persistent bleeding or early re-bleeding occurs despite adequate medical and endoscopic therapy (68). In these patients, TIPS is recommended as a rescue measure to gain bleeding control (11,15).

Secondary prophylaxis of VH

After the first event of VH, secondary prophylaxis should be started with a combination of NSBB and EVL. TIPS should be considered in patients with simultaneous severe or refractory ascites and patients with contraindications or non-response to NSBB treatment (11).

1.7.3 Hepatic Encephalopathy

Hepatic encephalopathy (HE) is a neuropsychiatric syndrome that occurs mainly in patients with cirrhosis, acute hepatic insufficiency or portosystemic shunting (69). As it represents one of the most dreaded complications of TIPS intervention, the pathophysiology and management of HE will be discussed in chapter 2.4.3.

1.7.4 Hepatorenal Syndrome

Hepatorenal syndrome (HRS) is a severe complication of chronic liver disease and portal hypertension. It is defined as a functional renal syndrome that results from systemic circulatory alterations in portal hypertension (70). Leading mechanisms of HRS development are splanchnic vasodilation as well as the activation of the sympathetic nervous system and RAAS system resulting in renal vasoconstriction (71). Recent studies indicate that systemic inflammation, a hallmark of chronic liver disease, plays a key role in HRS development (72,73). HRS can be classified into two main types: HRS type 1, going ahead with acute kidney injury (AKI) and HRS type 2, a slowly progressive loss of renal function. In newer literature, HRS-type 1 is replaced by the term HRS-AKI, whilst HRS-type 2 can either fulfill the criteria of chronic kidney disease (HRS-CKD) or HRS without AKI (non-AKI-HRS) (15).

Management of HRS-AKI

The basis of HRS-AKI management is the identification and correction of aggravating factors. Therefore, all medications have to be reviewed, diuretic therapy should be reduced and the continue of NSBB treatment should be carefully assessed. Additionally, patients have to be screened for infection (e.g. SBP) and hypovolemia. The medical therapy of HRS aims to improve renal perfusion. Thus,

vasoactive drugs (terlipressin or norepinephrine) are administered to achieve splanchnic vasoconstriction. In addition to vasoactive medication, albumin administration at a dose of 40g per day is recommended (11). The beneficial effect of albumin in HRS might be based on two mechanisms; Firstly, the improvement of renal perfusion via blood volume expansion and secondly, non-oncotic properties of albumin, such as endotoxin binding and antioxidant scavenging activities possibly improving chronic inflammation, a hallmark of HRS (74).

1.8 Transjugular Intrahepatic Portosystemic Shunt (TIPS)

1.8.1 History and Technical Evolution

In 1982, Colapinto et al. were the first to perform balloon dilatation of liver parenchyma via percutaneous catheterization to create a portosystemic shunt in a patient with cirrhosis and acute variceal hemorrhage. This first (rescue-) TIPS achieved a decrease of portal pressure from 45mmHg to 23 mmHg. However, only 36 hours later the patient died from sepsis and hepatic failure (75). Colapinto and Gordon thereafter applied the technique in a series of 20 patients with moderate success – early re-bleeding occurred in most patients and 9 of them died within one month (76). The first TIPS intervention with an expandable metallic stent (Palmaz-stent) was implemented in Freiburg in 1988. That was the starting gun for the Freiburg TIPS project, a series of about 10 patients treated in 1988 and over 500 patients until 1995. Due to a new technique using sonographic targeting of the portal vein, the duration of TIPS intervention could be diminished from an average of 8 hours in 1988 to 1 to 2 hours in 1993. In the last 25 years, knowledge was acquired and technical standards, indications and contraindications were further established (76).

1.8.2 TIPS Intervention – State of the Art

1.8.2.1 Pre-Interventional Examination and Measures

Prior to TIPS placement, the indication has to be confirmed and contraindications should be excluded. Imaging of the portal vein and hepatic veins should be performed using Doppler-ultrasound, computer tomography (CT) or magnetic resonance imaging (MRI). Additionally, patients should undergo echocardiography to exclude cardiac failure, especially of the right heart, as this represents a

contraindication for TIPS (11). Current Child-Pugh score and MELD should be assessed to exclude severe hepatic insufficiency. Before TIPS intervention, ascites grade 2 or 3 should be removed by LVP to improve preconditions for anesthesia and portal vein detection. In patients with hepatic hydrothorax, thoracentesis should be performed to improve respiratory functions during the intervention (11,76).

1.8.2.2 TIPS Intervention

Elective TIPS intervention can be performed in sedation as well as in general anesthesia with endotracheal intubation, which is the more frequently applied method (77). Although portal vein access can be obtained from all hepatic veins as well as directly from the inferior vena cava, most practitioners prefer the right hepatic vein approach. After hemodynamic measurement (chapter 1.5), an appropriate branch of the intrahepatic portal vein is punctured either with a modified Colapinto-Ross needle or a closed coaxial needle (76). There are numerous possibilities of imaging guidance to ease portal vein puncture, e.g. high-quality fluoroscopy, carbon dioxide wedged hepatic venography and percutaneous intravascular ultrasound guidance (78). At this point of the intervention, collaterals can be embolized if indicated. However, the effect of additional variceal embolization is not jet validated (11). The next steps are the introduction of a guidewire followed by portal venography and pressure measurement. Using an angioplasty balloon, the parenchymal tract is dilated and a stent is placed and dilated to the desired diameter. (Figure 4) Final hemodynamic measurement is performed in the portal vein and the right atrium to confirm the post-procedural portosystemic pressure gradient which should amount <12 mmHg or at least a 50% reduction in patients with an initial portosystemic pressure gradient >30mmHg (11). Polytetraflouroethylene (PTFE) – covered self- expandable stent grafts are the current standard and superior to bare metal stents since they are associated with beneficial effects on overall survival, shunt patency and hepatic encephalopathy (79). As smaller stent diameters (up to 8-millimeters nominal diameter) are associated with increased survival and lower risk of hepatic encephalopathy compared to larger diameters (e.g. 10mm), stent grafts with 8 mm nominal diameter should be preferred (80). It is controversially discussed if antibiotic prophylaxis is necessary to avoid systemic post-interventional infections and “endotipsitis”, a local infection with an estimated relative frequency of

1.3% (81). Thus, antibiotic prophylaxis e.g. with cephalosporins should be considered (11).

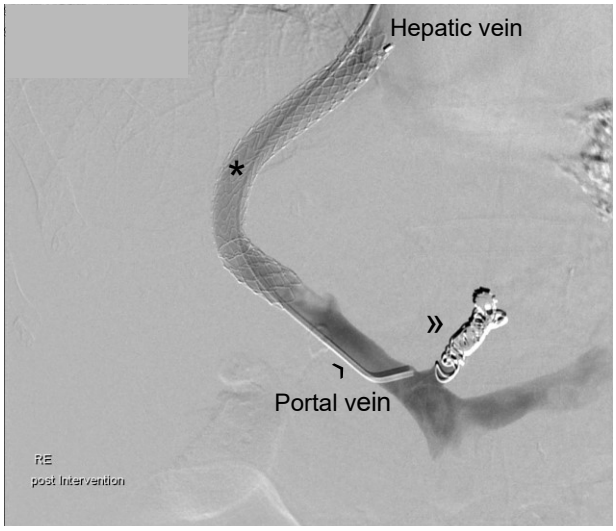


*Figure 4, * PFTE-covered TIPS-stent in optimal position, › angiography catheter in the portal vein, » gastric varix after coil embolization. Picture used with kind permission of Ao. Univ.-Prof. Dr. Rupert Horst Portugaller, Division of Neuroradiology, Vascular and Interventional Radiology, Medical University Hospital of Graz.*

1.8.3 Pathophysiological Effects of TIPS

By creating an artificial portosystemic shunt and surpassing portal venous blood directly to the systemic circulation, TIPS is an effective and fast option to reach an average portal pressure reduction of about 50% (78). Blood flow from the splanchnic circulation is directed into the systemic venous circulation resulting in an increased cardiac preload. In addition, portosystemic shunting leads to an accumulation of splanchnic vasodilators in the systemic circulation. These effects cause an initial aggravation of the hyperdynamic state in advanced liver disease. However, these alterations seem to normalize within months until one year and after this first phase of aggravation, the increased central blood volume improves effective arterial volume and consequentially deactivates RAAS (82,83). The deactivation of RAAS, in turn, seems to be a main mechanism of ascites control and renal functional improvement after TIPS placement (84).

1.8.4 Complications

Technical complications

A possible complication of TIPS intervention is the perforation of the liver capsule leading to intrahepatic hemorrhage. This potentially severe adverse event occurs in 1-2% of interventions. Injury of bile ducts with clinical hemobilia is a rare adverse

event, occurring in <1%. (77) Since the era of PTFE-covered stents, hemolysis, stent migration and stent misplacement have become unusual (76).

Post-TIPS Liver Failure (PTLF)

Acute hepatic failure marked by a rapid increase of ALT, aspartate aminotransferase (AST), bilirubin and INR is a major adverse event and occurs in up to 4% of patients (85). PTLF is associated with high mortality, prolonged hospitalization, increased rates of TIPS re-intervention (TIPS reduction) and liver transplantation (86).

Hepatic Encephalopathy (HE)

Hepatic encephalopathy is probably the most dreaded adverse event of TIPS placement and occurs with an incidence of 20-31% (78). It is defined as a complex neuropsychiatric syndrome resulting from biochemical alterations of brain function in patients with cirrhosis, acute hepatic failure and/or portal systemic shunting. HE manifests as a wide spectrum of confusion, impaired attention and consciousness as well as neuromuscular dysfunctions (87). Although the pathophysiology is not yet fully understood, it is presumed that increased portosystemic shunting of ammonia is a main mechanism of post TIPS-HE (88,89). HE can be classified according to the etiology; *Type A:* acute liver failure, *Type B:* portosystemic shunting, *Type C*: cirrhosis, according to severity (West Haven Grade 1-4, Table 1) and time-course (episodic/ recurrent/ persistent) (69). The risk of further HE episodes as well as 1-year mortality increases with each episode of overt HE (90).

West Haven Criteria		
Minimal	covert	no overt clinical symptoms but abnormal psychometric and neuropsychological tests
Grade 1	overt	trivial lack of awareness, euphoria or anxiety, decreased attention span, altered sleep rhythm, orientated to time and space
Grade 2		obvious personality change, inappropriate behavior, asterixis, dyspraxia, disorientation, lethargy, disorientation to time
Grade 3		somnolence, bizarre behavior, confusion, disorientation to time and space
Grade 4		coma

Table 2,Grades of hepatic encephalopathy according to West Haven criteria (69,87)

Prediction and risk factors of post-TIPS HE

The prediction of hepatic encephalopathy is an important target to reach optimal patient selection but remains difficult since it depends on various factors. Age, high bilirubin levels, low serum sodium and albumin concentrations and previous episodes of hepatic encephalopathy are independent risk factors of post-TIPS HE development (76). A recent study shows an association between proton pump inhibitor use and increased rates of HE after TIPS intervention (91).

Treatment

For the management of (overt) hepatic encephalopathy, only a handful of therapeutic options are available. Most of these drugs aim to lower the systemic ammonia level. This can be achieved either via reduction of ammonia production in the gut (non-absorbable disaccharides, antibiotics and probiotics) or by stimulation of ammonia conversion to urea (L-ornithine-L-aspartate, ornithine phenylacetate). (92) The fact that we do not completely understand the pathophysiology of HE complicates the development of effective new medication. L-ornithine-L-aspartate (LOLA) is a stable salt of the amino acids ornithine and aspartate, two key-components of the urea cycle. By oversupplying these amino acids, the conversion of toxic ammonia to urea becomes stimulated (93). A recent meta-analysis showed beneficial effects of intravenous LOLA administration for the prevention of overt HE in patients with cirrhosis as well as for post-TIPS HE prevention (92). However, stable data and well-designed RCTs on LOLA use, especially for prophylaxis are still missing (94). Non-absorbable disaccharides e.g. lactulose and lactitol are cost-effective and commonly used osmotic laxatives and are postulated to reduce ammonia production due to prebiotic and gut-acidifying properties (95). For the treatment of HE, non-absorbable antibiotics are a commonly used drug class, often combined with lactulose. Rifaximin, the most frequent used agent of this group, leads to decreased ammonia production mainly by changing intestinal urease producing microbiota (95). A randomized controlled trial on the maintenance of HE remission in cirrhotic patients over a period of six months showed superiority of rifaximin to placebo (96). Probiotics, a relatively new therapeutic option for HE, have been shown to improve minimal HE and to be effective for secondary prophylaxis of HE in patients with cirrhosis (97,98). A phase 1 study on fecal microbial transplant

(FMT) in cirrhotic patients with recurrent HE showed a tend towards improved cognition after FMT (99).

Management of Post-TIPS-HE

The management of TIPS-related hepatic encephalopathy remains challenging, as many standard medical treatment options for HE fail in the management of post-TIPS HE (100,101). The first approach is the identification and correction of aggravating factors, i.e. dehydration, electrolyte disturbances, medications or infections. TIPS re-intervention with stent reduction remains a valuable option for the management of severe post-TIPS HE. As an ultima-ratio, TIPS occlusion can be performed, however with potentially severe complications of abrupt portal pressure increase (101).

Prevention of Post-TIPS-HE

Previous randomized controlled trials could not show any beneficial effect of albumin, lactitol or rifaximin administration to prevent post-TIPS HE (102,103). Currently, the only evidence-based measure to prevent post-TIPS HE is the use of eight millimeter PTFE-covered stents (104).

1.8.5 TIPS Indications

Table 3 provides an overview of indications according to the current Billroth III Consensus and EASL guidelines (see chapter 1.5).

	Indication	Patient selection
Variceal hemorrhage	Early TIPS <72h after bleeding onset	I. Patients with Child-Pugh C10-C13 II. Patients with Child-Pugh B + active bleeding III. Patients with HVPG ≥ 20mmHg
	Rescue TIPS	I. Patients with uncontrollable bleeding/ re-bleeding under vasoactive therapy II. Patients with re-bleeding after esophageal stent placement (bleeding stent e.g. SX-ELLA Stent Danis)
	Elective TIPS	I. Secondary prophylaxis after failure of NSBB+EVL treatment II. Secondary prophylaxis in patients intolerant to NSBBs/ with contraindications for NSBBs III. Patients with cardiofundal varices (GOV2/IGV 1)
Ascites	Refractory ascites	Recurrent ascites despite maximum dosage of spironolactone and furosemide during sodium restriction
	Drug- intolerant ascites	Recurrent ascites and intolerance/ side effects of maximum dose of spironolactone and furosemide
Other indications	Hepatic hydrothorax (HH)	In selected patients with recurrent symptomatic HH
	Hepatorenal syndrome (HRS)	In selected patients with HRS Type II
	Budd-Chiari syndrome	Patients with ascites who do not improve under anticoagulation therapy
	Portal vein thrombosis (PVT)	Acute symptomatic non-malignant PVT
	Severe non-cirrhotic portal hypertension	I. Idiopathic non-cirrhotic PH II. Sinusoidal obstructive syndrome (Veno-occlusive disease)

Table 3, Overview of indications according to Billroth III Consensus and EASL guidelines (11,15,23); NSBB, non-selective beta blockers; EVL, endoscopic variceal ligation; GOV2, type 2 gastroesophageal varices; IGV1; type 1 isolated gastric varices.

1.8.6 TIPS Contraindications

In the latest European Association for the Study of the Liver (EASL) Clinical Practice Guidelines for the Management of Patients with Decompensated Cirrhosis, a careful patient selection for elective TIPS is suggested (15). TIPS placement is not recommended in patients with:

a. bilirubin > 3 mg/dl
b. platelet count < 75 x 10^9/L
c. current hepatic encephalopathy West-Haven Grade ≥ II
d. chronic hepatic encephalopathy
e. concomitant active infection
f. progressive renal failure
g. severe systolic or diastolic dysfunction
h. pulmonary hypertension

The Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III) define the contraindications for TIPS insertion as following:

a. severe liver failure defined as Child-Pugh class > C13 or MELD > 20
b. history of recurrent spontaneous episodes of HE West Haven grades III/ IV
c. right heart failure
d. pulmonary hypertension
e. anatomical/technical contraindications
f. unrelieved biliary obstruction
g. extensive hepatic malignancy

HE at the time of acute variceal bleeding should not be a contraindication for Early-TIPS (11).

1.8.7 Prediction of Post-Interventional Outcome and Risk Assessment

TIPS has been shown to be an effective treatment of portal hypertension-related complications with beneficial effects on morbidity and mortality in selected patients (67,105–107). However, severe complications, such as post-TIPS HE and acute hepatic insufficiency demand for optimal selection of candidates.

For this purpose, various models have been invented to predict post-TIPS outcome (108–112). In 2000, Malinchoc et al. described a model to predict three-month survival after TIPS integrating serum creatinine, serum bilirubin, INR and the etiology of cirrhosis (113). The model was simplified, and re-published without the etiology of cirrhosis, designated as Model of End-Stage Liver Disease (MELD) (114). MELD score is calculated with the formula:

$$MELD = 9.6 \times \log_e(\text{creatinine, mg/dL}) + 3.8 \times \log_e(\text{bilirubin, mg/dL}) + 11.2 \times \log_e(\text{INR}) + 6.4$$

Today, MELD is one of the best validated prognostic tools to estimate the severity of liver disease and its use for urgency-based organ-allocation in many countries has led to a reduction of deaths on the waiting list and median waiting time (13). It has also remained the best prognostic tool to predict post-TIPS mortality compared to other models, exemplarily Child-Pugh score, MELD-Na, Emory score, Platelet-Albumin-Bilirubin, CLIF-C and ACLF scores (108,109,115). One of its strengths is the objectivity due to the utilization of metric continuous variables. Creatinine is often considered as the component of MELD to be handled with care , as it may underestimate the severity of disease in patients with sarcopenia (13). For the prediction of post-TIPS outcome, creatinine bears the risk of overestimating mortality in patients with renal impairment (116,117). Glomerular filtration rate (GFR) might replace creatinine in the future, as a scoring model combining bilirubin, INR and measured (true) GFR was shown to be slightly better predictive for early mortality in patients with cirrhosis than MELD (118). Higher MELD is associated with poor outcome after TIPS (77,109,119). In a study investigating outcome of 101 patients with acute variceal hemorrhage receiving TIPS, three-months mortality rates were 9%; 13%; 36% and 83% in patients with MELD ≤10; 11-18; 19-25 and ≥ 26, respectively (119). Thus, the Austrian Billroth III Consensus guidelines defined MELD ≥ 20 as contraindication for TIPS (11). More accurate prediction of severe complications and mortality after TIPS and novel tools for individual risk assessment are crucial to improve patient selection and post-interventional early mortality rate.

2 Patients and Methods

All cases of TIPS placement at the Medical University Hospital of Graz performed between 01/2004 and 12/2017 were retrospectively analyzed. The study protocol was first approved by the Ethics Committee of the Medical University of Graz (30-169 ex 17/18). Data was collected between 03/2018 and 11/2018 via the medical information system “openMEDOCS”. The reason for choosing 01/2004 as starting point was due to the fact that “openMEDOCS” was implemented at that time. TIPS-revisions were not counted as independent cases but were recorded and assigned to the corresponding case. We excluded patients with I. a complete lack of pre-TIPS medical history and laboratory data or II. nonexistent follow-up data. The following data was assessed:

1. **Demographic patient data** including sex, age, etiology of portal hypertension, hospital admission reason, days of hospital admission and diagnosis of diabetes were assessed.
2. **TIPS technical data:** hepatovenous pressure gradient (HVPG) before and after TIPS, as well as stent type and diameter were captured.
3. **Pre-TIPS medical history:** Episodes of portal hypertensive bleeding, ascites with the need for large volume paracentesis, spontaneous bacterial peritonitis, hospital admission for hepatic encephalopathy, diagnosis of hepatocellular carcinoma as well as the presence of portal venous thrombosis were recorded.
4. **Laboratory parameters:** Before TIPS (no longer than 48h prior to the intervention), and at follow up, approximately six months after TIPS serum electrolytes, creatinine, eGFR, urea, bilirubin, albumin, INR, prothrombin time, ammonia, liver enzymes, c-reactive protein, fibrinogen and blood count were recorded. Child-Pugh and model for end-stage liver disease (MELD) scores were calculated at both times.
5. **Medication intake:** Information about the intake and dose of diuretic drugs, nonselective beta-blockers (NSBBs), proton pump inhibitors (PPIs), medication for the treatment of hepatic encephalopathy (L-ornithine-L-aspartate (LOLA), rifaximin and lactulose), statins, metformin as well as anticoagulant and antiplatelet drugs was collected at the time of TIPS and at 6-months follow-up.

6. **Post-TIPS medical history:** It was recorded whether patients developed hepatic encephalopathy, had episodes of portal hypertensive bleeding, were diagnosed with hepatocellular carcinoma or needed regular paracentesis or thoracentesis after TIPS. Death, liver transplantation and date of last follow-up were registered.

Six-Month Follow-up

Approximately six months after TIPS (minimum three, maximum nine months), laboratory values and current medication were reassessed. Follow-up data was not utilized when patients received liver transplant in the meantime as well as when they had symptoms of severe infections (e.g. spontaneous bacterial peritonitis, pneumonia), acute hepatic decompensation or a bleeding event at the time of follow-up assessment.

2.1 Statistical Analysis

Statistical analysis was performed using SPSS version 23 and MedCalc Statistical Software. Continuous variables were expressed as median (interquartile range, IQR) or mean value (± standard deviation, SD), as appropriate. Categorical variables were expressed as absolute number (percentage). For the comparison of categorical data, Pearson's chi-squared test or Fisher's exact test were utilized, whereas for the comparison of continuous variables, t test or non-parametrical tests were used. Changes of laboratory parameters between baseline and 6-months follow up were determined using paired t-test for normally distributed values and Wilcoxon signed-rank test for not normally distributed parameters. For all statistical tests, p values less than 0.05 were considered significant.

2.1.1 Survival Statistics

Patient survival was assessed by Kaplan-Meier estimates and compared using log-rank test and chi-square. Cox-Regression analysis was performed to identify predictive factors of mortality. Laboratory parameters significantly predictive in univariate analysis were included in multivariate Cox-Regression with stepwise backwards selection. Clinical parameters were excluded from multivariate analysis due to the retrospective character of the study since data quality varied. In case of loss of follow-up, patients were censored at the day of last follow-up. Additionally, patients who underwent liver transplantation were censored at the day of

transplantation. Predictive factors for the development of overt hepatic encephalopathy of any grade within 90-days were assessed in the same way.

2.1.2 Score Development - MOTS

We aimed to develop a modified TIPS-score (MOTS) based on the well-validated MELD, easy to calculate with routine parameters and of beneficial prognostic value compared to preexisting scores. The high prevalence of malnutrition and sarcopenia in cirrhotic patients as well as the fact that renal function improves after TIPS question the validity of creatinine as post-TIPS prognostic marker. Therefore, we tried to find a valid and reliable alternative parameter for our modified TIPS score (MOTS). Laboratory parameters that significantly predicted 90-day mortality in the multivariate stepwise backwards survival analysis were included into the scoring model. Youden's J statistic was utilized to define cut-off values of the score parameters. A large proportion of patients receiving TIPS for bleeding indications had active bleedings or recently received blood products which might affect laboratory parameters such as INR or renal functional parameters and cause statistical outliers (120–122). Given this instability, we decided to utilize only the data of patients receiving TIPS for ascites indications for cut-off definition in order to avoid statistical bias. First, ROC-curves of the parameters predicting 90-day mortality in multivariate analysis were charted and ROC coordinates were collected. Youden Index was determined for all coordinates. For each parameter, the best three cut-off values with the highest Youden Indices were selected and three scores were developed: Score 1 used the cut-offs with the highest Youden Index for each parameter, score 2 integrated the cut-offs with the second highest index and score 3 utilized the cut-offs with the third highest index. In order to further simplify the model, one point was allocated for each parameter with a value exceeding the cut-off threshold. The predictive performance of all three models was compared utilizing Area Under Receiver Operating Characteristic (AUROC) statistics and the score with the highest AUROC value was selected as final scoring model.

2.1.3 LogMOTS Development

To see whether a model using the same variables but with a continuous scale outperformed the simple MOTS, we developed LogMOTS. Therefore, we used the method Malinchoc et al. described in the original publication of the Model for End-

Stage Liver Disease (MELD) (113). Logistic regression of MOTS components predicting 90-day mortality was performed. For each parameter, the odds ratio (=1-regression coefficient) was utilized as the constant the natural logarithm of the absolute value is multiplied with. Multiplication of the whole term with the factor ten served to obtain a larger scale.

2.1.4 Comparison of Scoring Models

Prognostic capability of the scoring models was assessed using AUROC statistics and was expressed by AUROC values (= C-value) and corresponding 95% confidence intervals. Pairwise comparison of AUROCs was performed using both established methods; the method by Hanley & McNeil et al. (123) as well as DeLong et al (124).

3 Results

3.1 Demographic data

During the study period, 158 initial TIPS placements were performed. We included 144 patients in our final analysis since 14 patients were excluded due to a complete lack of pre-TIPS medical history and laboratory data or nonexistent follow-up data. (Figure 5)

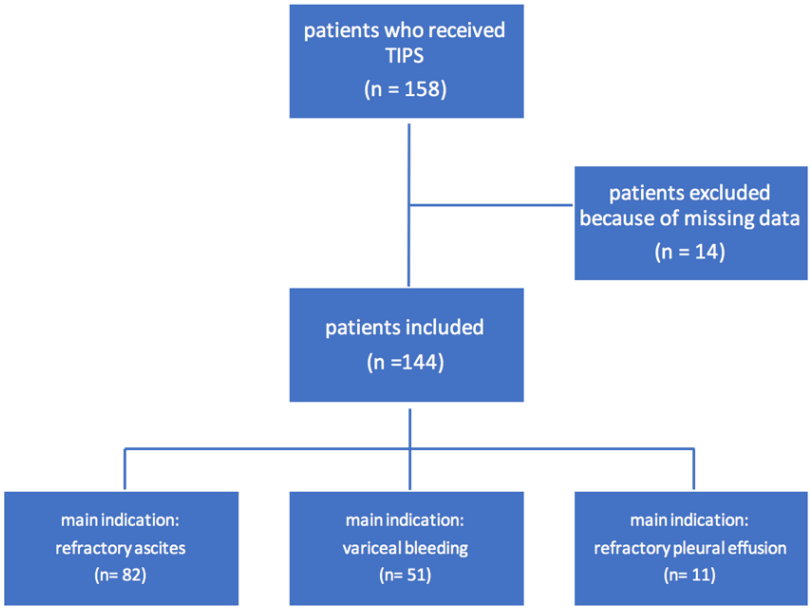


Figure 5, Flowchart of patients in the study

Most patients were male (78%) and age ranged from 23 to 90 with a median of 56 (IQR 16) years. Main indications for TIPS placement were drug-refractory or recurrent ascites (57%), portal hypertensive bleeding (35%) and refractory pleural effusion (8%). Among the 51 patients receiving TIPS for bleeding indications, 26 received Early TIPS, defined as TIPS placement within 72 hours after a bleeding event. The most abundant main etiology of portal hypertension was alcohol-related liver disease (ALD) in 74% of patients, followed by chronic viral hepatitis (9%), Budd-Chiari syndrome (BCS) (4%) and non-alcoholic fatty liver disease (NAFLD) (3%), figure 6. In 7 patients (5%) the etiology of portal hypertension was unknown. The entirety of etiologic categories is shown in Table 1. As 95% of patients were cirrhotic, the remaining 5% of non-cirrhotic portal hypertension were represented by Budd-Chiari syndrome (n=5), idiopathic portal hypertension (n=1) and chronic graft-versus-host disease (n=1) as underlying diseases. Table 4

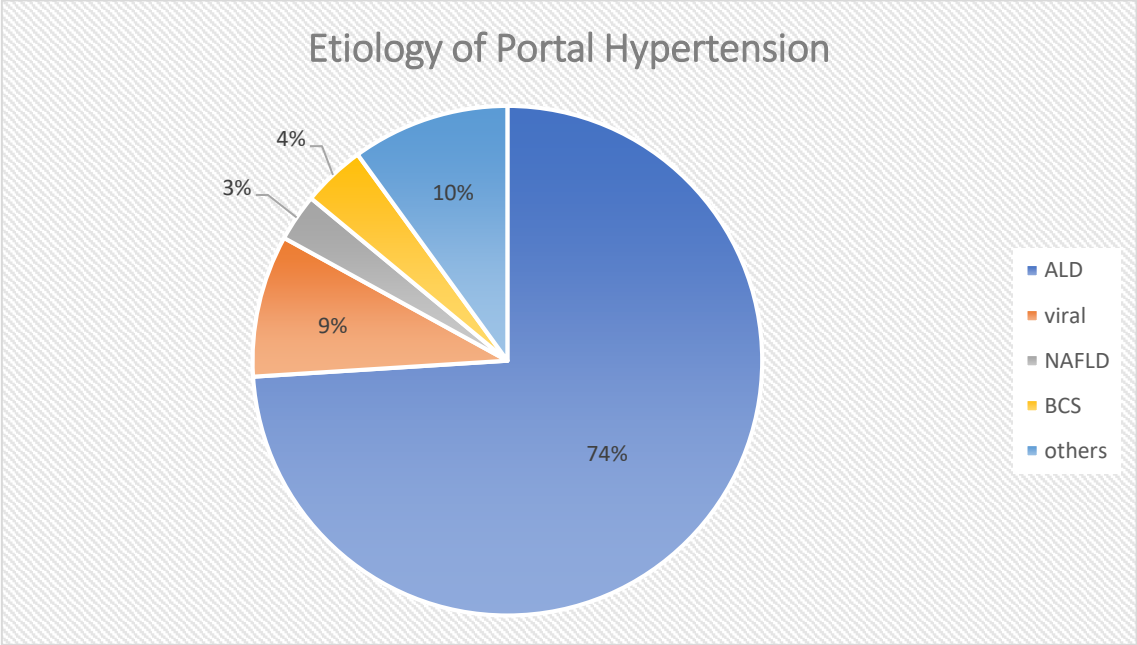


Figure 6, Etiologies of PH

Demographic data	**n = 144 (100%)**
Age (years), median (IQR)	56 (16)
Female sex, n (%)	31 (22)
Etiology of PH	
Alcohol-related liver disease, n (%)	107 (74)
Chronic viral hepatitis, n (%)	13 (9)
Budd-Chiari syndrome, n (%)	5 (4)
Non-alcoholic fatty liver disease, n (%)	4 (3)
Other causes, n (%)	15 (10)
Cirrhosis, unknown etiology, n (%)	7 (5)
HFE haemochromatosis, n (%)	2 (1)
Primary biliary cholangitis, n (%)	1 (1)
Autoimmune hepatitis, n (%)	1 (1)
Drug-induced liver injury, n (%)	1 (1)
Idiopathic non-cirrhotic PH, n (%)	1 (1)
Congestive hepatopathy, n (%)	1 (1)
Chronic graft-versus-host disease, n (%)	1 (1)
TIPS main indication	
Refractory/recurrent ascites, n (%)	82 (57)
Portal hypertensive bleeding, n (%)	51 (35)
Thereof Early-TIPS <72h after bleeding event, n (%)	26 (51)
Refractory pleural effusion, n (%)	11 (8)

Table 4, Demographic data

3.1.1 Hospital Admission

Only 35% of patients were initially hospitalized for elective TIPS whereas in the majority of patients, hospital admission was due to another reason and TIPS was planned and performed within the hospital stay. 26% were hospitalized for acute gastroesophageal bleeding, 23% for clinically symptomatic ascites and 10% for the evaluation of liver transplantation. Notably, in 4% the initial reason for hospital admission was overt hepatic encephalopathy. At the day of hospital admission, 15 patients (10%) had symptoms of mild to moderate hepatic encephalopathy (HE) (West-Haven grade I-II) and 1 patient presented with severe HE (grade III-IV). 45% had moderate to large ascites, 29% presented with mild ascites, only detectable with abdominal sonography (grade 1) and 24% had no detectable ascites at hospital admission. The median time of hospitalization was 12 days (IQR 19), counting only patients who were discharged alive from hospital (n=86%). Table 5

Admission data	**n = 144 (100%)**
Admission reason	
Elective for TIPS	51 (35)
Gastrointestinal bleeding	37 (26)
Symptomatic ascites	33 (23)
Evaluation for liver transplantation	14 (10)
Overt hepatic encephalopathy	5 (4)
Other reasons	4 (3)
Symptoms of HE upon admission	
None	124 (86)
Mild-moderate (West-Haven Grade I-II)	15 (10)
Severe (West-Haven Grade III-IV)	1 (1)
Unknown	4 (3)
Ascites upon admission	
None	35 (24)
Mild (only detectable by sonography)	42 (29)
Large ascites (grade II-III)	65 (45)
Unknown	2 (1)
Days of hospitalization, median (IQR)	12 (19)
In-hospital mortality	20 (14)

Table 5, Admission data

3.1.2 Pre-TIPS Medical History

The majority of patients (71%, n=102) had at least one therapeutic paracentesis in their pre-TIPS medical history and 44% had had one or more bleeding events. In 15%, at least one hospital admission for hepatic encephalopathy (HE) was reported. History of spontaneous bacterial peritonitis (SBP) was reported in 11% of patients. Four patients (3%) had previously diagnosed hepatocellular carcinoma (HCC). Notably, 25% had a previous diagnosis of diabetes mellitus (DM). Portal vein thrombosis (PVT) was reported in 14 patients (10%). Partial PVT (n=12) or total PVT (n=2) was diagnosed using Doppler ultrasound shortly before TIPS intervention or in portal venography during TIPS procedure. Table 6

Pre-TIPS medical history	**n = 144 (100%)**
Large volume paracentesis (⩾1 time)	102 (71)
Gastrointestinal bleeding (⩾1 episode)	63 (44)
Spontaneous bacterial peritonitis (⩾1 episode)	16 (11)
Hepatic encephalopathy (⩾1 episode)	21 (15)
Hepatocellular carcinoma	4 (3)
Diabetes	36 (25)
Portal vein thrombosis, partial	12 (8)
Portal vein thrombosis, total	2 (1)

Table 6, Pre-TIPS medical history

3.1.3 Baseline Medication Intake

Complete information about baseline medication intake was available in 127 patients (88%). Thereof, 70% were taking proton pump inhibiting drugs (PPIs) at the time of TIPS intervention. 71% received diuretic therapy with furosemide whereas anti-aldosteronic drugs (spironolactone, eplerenone) were taken by 67% of patients. Altogether, 58% of patients received NSBBs, either propranolol (27%) or carvedilol (31%). Furthermore, patients received lactulose (41%), LOLA (33%) and/or rifaximin (11%) mainly for the management or prevention of hepatic encephalopathy. Detailed information about baseline medication intake and dosage is shown in Table 7.

Medication at TIPS	**n = 128 (100%)**			
LOLA	42 (33)			
Lactulose	53 (41)			
Rifaximin	14 (11)			
Anti-PLT	7 (6)			
Statin	1 (1)			
Metformin	1 (1)			
LMWH	7 (6)			
Coumarin	4 (3)			
DOAC	1 (1)			
Furosemide (mg)	**91**		**71%**	
	Min	Max	Median	IQR
	20	250	40	20
Anti-aldosteronic diuretics (mg)	**86**		**67%**	
	Min	Max	Median	IQR
	25	600	100	100
Propranolol (mg)	**35**		**27%**	
	Min	Max	Median	IQR
	10	80	20	20
Carvedilol (mg)	**39**		**31%**	
	Min	Max	Median	IQR
	6.3	50.0	12.5	12.5
PPI (mg)	**90**		**70%**	
	Min	Max	Median	IQR
	20	120	40	25

Table 7, Medication at time of TIPS-placement

3.1.4 Baseline laboratory parameters

Pre-TIPS laboratory data was assessed within a period of 0-48 hours before the intervention. Baseline laboratory data is shown in Table 8.

Baseline laboratory data					
Normally distributed parameters	**Values existing**	**Min**	**Max**	**Mean**	**SD**
Na (mmol/l)	142	120	147	135.2	5.4
K (mmol/l)	141	1.9	6.0	4.1	0.7
GFR (ml/min/KOF)	124	6.7	311.0	79.9	40.1

PZ (%)	141	24	110	61.2	17.7
NH3 (µmol/L)	42	23,0	185.0	56.3	29.3
D-Dimer (mg/l)	4	2,9	12.0	6.5	4.1
HbA1c (mmol/mol)	2	42	154	98.0	79.2

Non-normally distributed parameters	**Values existing**	**Min**	**Max**	**Median**	**IQR**
Creatinine (mg/dl)	139	0.3	8.7	0.98	0.5
Urea (mg/dl)	136	4.0	289.0	40.5	51.0
Bilirubin (mg/dl)	120	0.2	32.0	1.5	1.7
Albumin (g/L)	98	1.20	4.70	3.3	0.7
INR	135	0.89	2.7	1.4	0.3
AST (U/L)	132	16	2703	39.5	25
ALT (U/L)	133	4	2017	22	18
GGT (U/L)	128	14	1660	93.5	117
CRP (mg/L)	131	0.6	194.9	11.1	18.3
Hemoglobin (g/dL)	142	5.9	16.7	10.1	2.7
Platelets (G/L)	142	20	466	110	96
White blood cell count (G/L)	142	1.2	32.2	6.6	4.3
Fibrinogen (mg/dL)	77	80	665	225	159

Table 8, Baseline laboratory data

3.1.5 Differences in Baseline Laboratory Data: Bleeding vs. Ascites

Patients receiving TIPS for ascites indications had significantly lower sodium levels, higher creatinine and lower glomerular filtration rate (GFR) at baseline than patients with bleeding indications. Conversely, patients with bleeding indications had significantly higher international normalized ratio (INR), lower prothrombin time, platelet count, albumin, hemoglobin and fibrinogen. Table 9

Differences in Baseline Laboratory Data (0-48h before TIPS)			
Normally distributed parameters (t-test for independent samples)	**Ascites (mean± SD)**	**Bleeding (mean± SD)**	**p**
Na (mmol/l)	134±5.1	138±4.7	<0.001
K (mmol/l)	4.2±0.7	4.0±0.8	0.14
GFR (ml/min/KOF)	70±29	96±51	0.001
PT (%)	65±20	56±14	0.008

NH3 (µmol/L)	51±21	68±42	0.08

Non-normally distributed parameters (Mann-Whitney U Test)	**Ascites, median (IQR)**	**Bleeding, median (IQR)**	**p**
Creatinine (mg/dl)	1.03 (0.59)	0.84 (0.56)	0.008
Urea (mg/dl)	43 (53)	40 (43)	0.3
Bilirubin (mg/dl)	1.3 (1.6)	1.8 (2.0)	0.1
Albumin (g/L)	3.4 (0.6)	3.1 (0.7)	<0.001
INR	1.3 (0.4)	1.4 (0.2)	0.02
AST (U/L)	41 (19)	49 (42)	0.5
ALT (U/L)	22 (12)	24 (30)	0.1
GGT (U/L)	85 (120)	109 (101)	0.3
CRP (mg/L)	12 (16)	9 (21)	0.1
Hemoglobin (g/dL)	10.7 (3.2)	9.5 (1.8)	<0.001
Platelets (G/L)	135 (100)	83 (69)	<0.001
White blood cell count (G/L)	6.7 (4.0)	5.8 (5.6)	0.4
Fibrinogen (mg/dL)	318 (249)	194 (86)	0.01

Table 9, Differences of baseline laboratory parameters in patients with ascites vs. bleeding

3.1.6 TIPS Technical Data

All patients received PTFE-covered stents with a nominal (=maximum) diameter of either 8 millimeter (mm) or 10 mm. For statistical analysis, we used the dilated stent diameters, as the majority of stent grafts were not dilated to their maximum diameter. This was also based on a study showing that underdilated stents do not expand to their nominal diameter over time (125). Dilated diameters ranged from 6 to 10 mm. Most patients received stents with a nominal diameter of 10mm or 8mm, balloon-dilated to 8 mm (n=140; 97%). Two patients received stents dilated to their nominal diameter of 10 mm whereas underdilation to 7 and 6 mm was performed in one case respectively. Before stent placement, the median HVPG was 17 mmHg (IQR 7) and decreased to 7 mmHg (IQR 5) after stent insertion. The difference of pre- and post-TIPS HVPG ranged from 0 to 30 mmHg with a median of 8 (IQR 8). (Table 10)

TIPS Technical Data	
TIPS dilated diameter	**n = 144 (100%)**
10 mm	2 (1.4)
8 mm	140 (97.2)
7 mm	1 (0.7)
6 mm	1 (0.7)

HVPG (mmHg)	Min	Max	Median	IQR
HVPG pre-TIPS	2	32	17	7
HVPG post-TIPS	1	32	7	5
HPVG difference	0	30	8	8

Table 10, TIPS technical data

3.2 Post-TIPS Follow-up

Median time of follow-up was 17.6 (IQR 45.2) months. During that period, overall mortality rate was 49% and the rate of liver transplantation was 22%. Overall, 27 patients (19%) were lost to follow up, which was defined as the last record in our medical information system being older than one year. 10 patients (7%) were newly diagnosed with hepatocellular carcinoma during post-TIPS follow-up. Sonographically confirmed TIPS-stent occlusion was observed in 11 patients (8%) and TIPS revision was necessary in 13 patients (9%). The re-interventions performed were angioplasty (n=3), new shunt creation (n=4), stent-reduction (n=3) and unsuccessful try of TIPS-angioplasty/new shunt creation (n=3).

3.2.1 Clinical efficacy of TIPS

Among patients receiving TIPS for ascites (n=82), clinical non-response defined as the need for two or more therapeutic paracenteses after TIPS was observed in 26 patients (32%). Within patients with bleeding indications (n=51), 16 patients (31%) had further bleeding events after TIPS. Among 11 patients receiving TIPS for hepatic hydrothorax, therapeutic failure, specified as requiring two or more therapeutic thoracenteses after TIPS occurred in four patients (36%).

3.2.2 Changes in Laboratory Parameters: Baseline (0-48 Hours Pre-TIPS) vs. Six-Month Follow-Up

Valid follow-up laboratory data was available in 64 patients. Median time between TIPS and follow-up blood sampling was 6.2 (IQR 1.8) months.

3.2.2.1 Hemoglobin

Among all TIPS recipients, hemoglobin was significantly higher at six-month follow-up than before the intervention (n=64; median hemoglobin 10.3 (IQR 3.3) g/dl vs. 11.6 (3.0); p<0.001). However, after distinguishing between the indication groups, this increase was only observed in patients with bleeding indications (n=25; median hemoglobin 9.0 (IQR 1.8) vs. 11.9 (2.6); p<0.001) but was not significant in patients who received TIPS for ascites (n=35; median hemoglobin 11.3 (IQR 3.6) vs. 11.5 (2.7); p=0.66). (Figure 7)

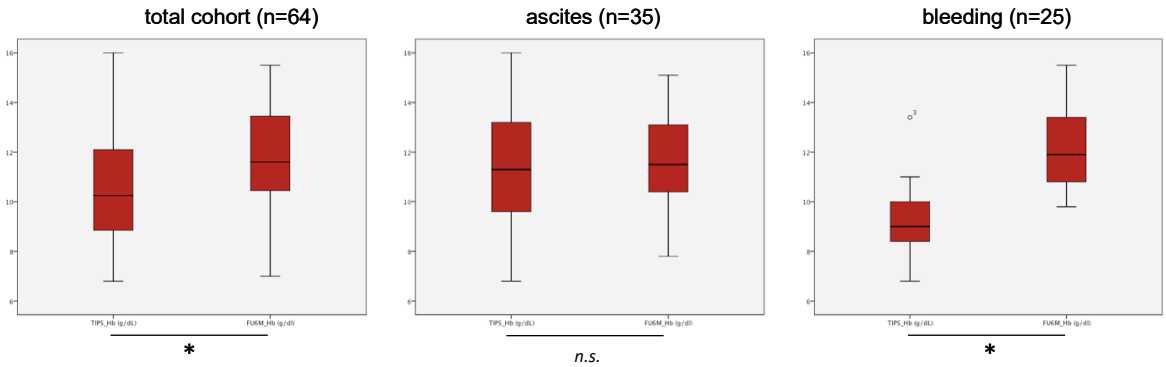


Figure 7, Hemoglobin changes

3.2.2.2 Platelet count

A significant decline of platelet count within six months was observed in the total cohort (median platelet count (G/L) 131 (IQR 116) vs. 109 (70); p=0.01). When analyzed separately, the decline was significant in patients with ascites indications (n=35; median platelet count 151 (IQR 117) vs. 131 (119); p=0.009) but was not statistically significant in patients who received TIPS for bleeding indications (n=25; 93 (IQR 73) vs. 85 (49); p=0.706). (Figure 8)

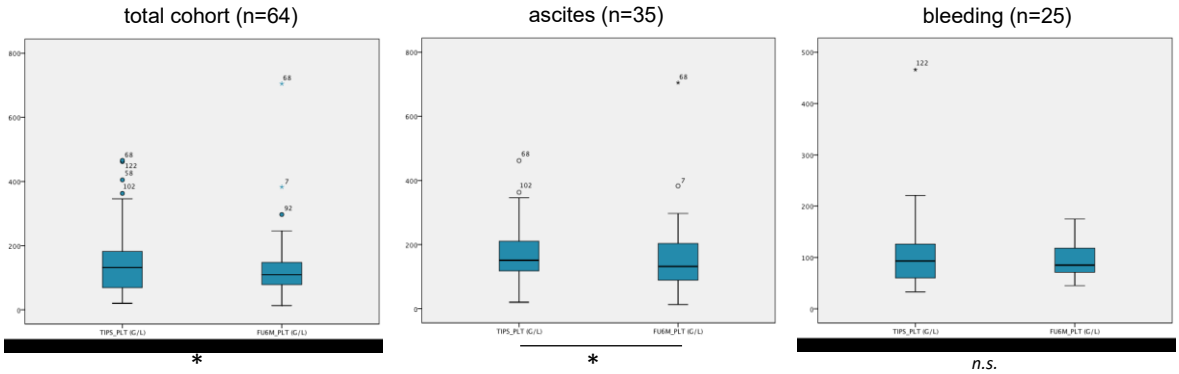


Figure 8, Changes of platelet count

3.2.2.3 White blood cell count (WBC)

WBC decreased significantly within the total cohort (n=64; median WBC (G/L) 6.0 (IQR 4.4) vs. 5.3 (2.9); p=0.012). This decline was significant in patients with variceal bleeding (n=25; median 5.9 (6.3) vs. 4.9 (2.7); p=0.004) but was not observed in patients with ascites indications (n=35; median WBC 5.8 (3.7) vs. 5.7 (3.0); p=0.56). (Figure 9)

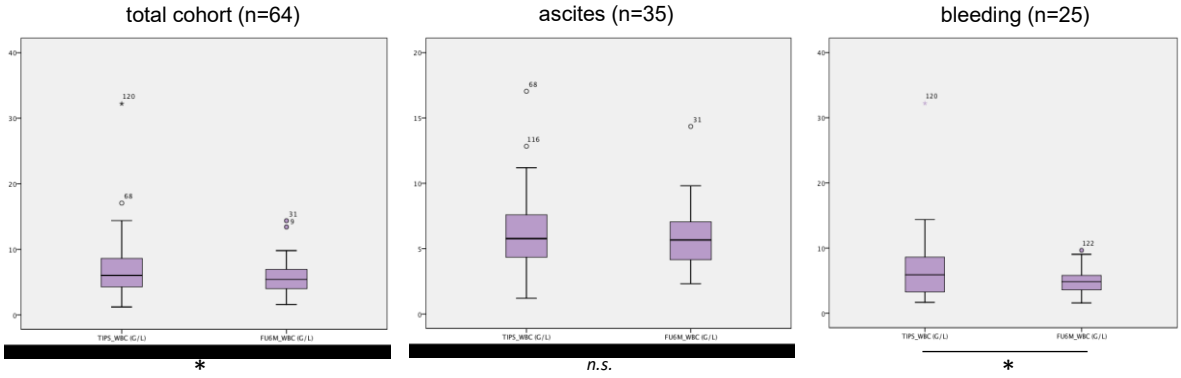


Figure 9, Changes in WBC

3.2.2.4 Estimated glomerular filtration rate (eGFR) and creatinine

Baseline and follow-up data were available for creatinine and eGFR in 62 and 54 patients, respectively. Within the total cohort, no significant change of eGFR levels was observed between baseline and six months after TIPS (n=54; mean eGFR (ml/min/m2) 81±33 vs. 84±28; p=0.5). Consistently, no significant change of serum creatinine level occurred (n=62; median serum creatinine (mg/dl) 0.99 (IQR 0.49) vs. 0.91 (0.42); p=0.7). However, on closer examination, in patients with baseline eGFR lower than 60, a 50% increase of eGFR (n=14; mean eGFR 40±17 vs. 60±25,

respectively; p=0.01) as well as a 35% decline of serum creatinine levels (n=14; median 1.61 (IQR 1.06) vs. 1.05 (0.66); p=0.03) was observed. No significant changes of eGFR (n=40; mean eGFR 96±24 vs. 92±24; p=0.25) and creatinine levels (n=41; 0.82 (0.44) vs. 0.85 (0.42); p=0.24) were observed in patients with an initial eGFR of 60 or higher. (Figure 10, 11)

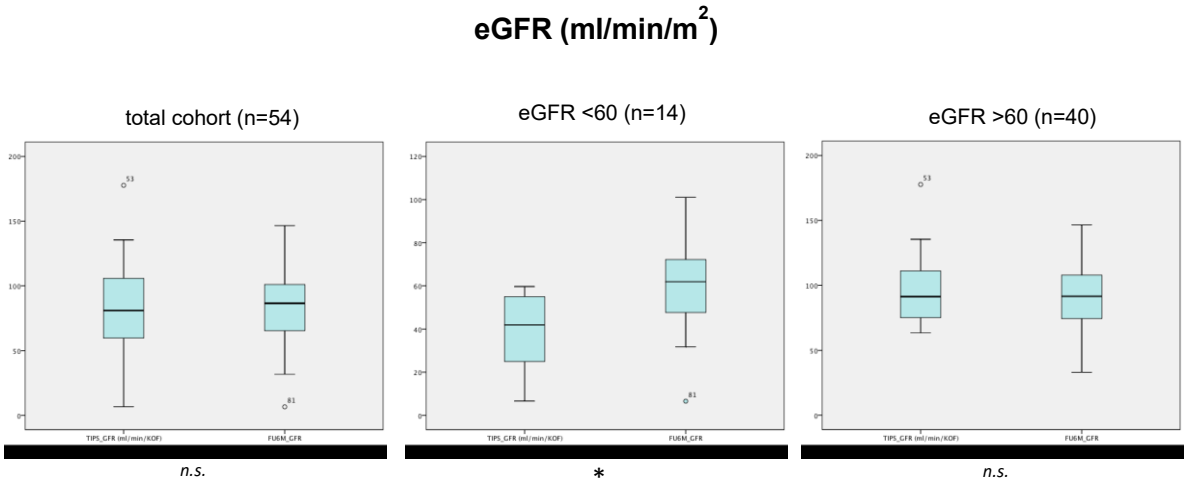


Figure 10, Changes of eGFR

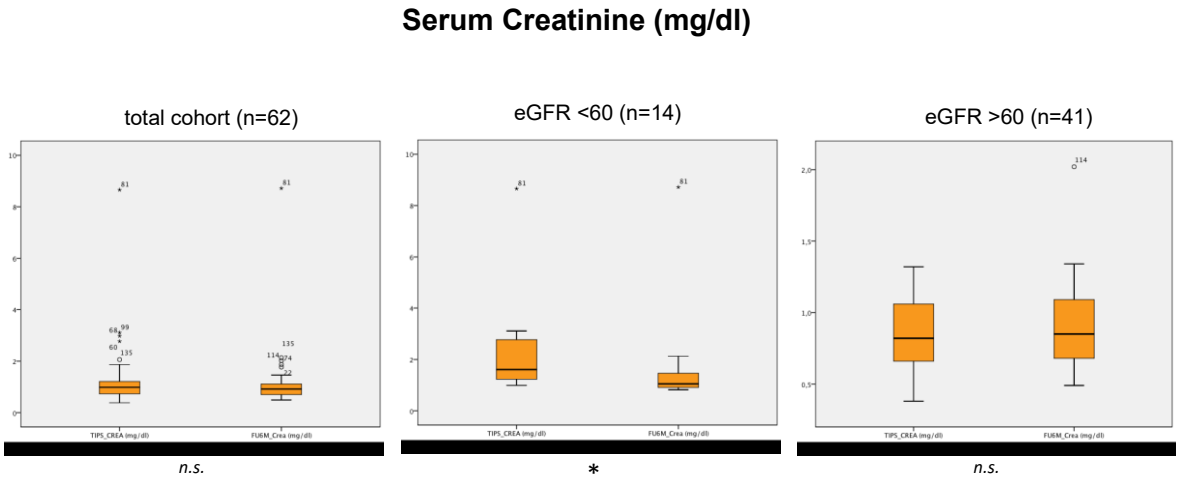


Figure 11, Changes in serum creatinine

3.2.2.5 Urea

Within the total cohort, serum urea levels decreased significantly between baseline and six-month follow-up (n=46; median serum urea (mg/dl) 42 (IQR 36) vs. 32 (31); p=0.01). The decline was more distinct in patients with initially lower eGFR (patients with eGFR<60 n=12; median urea 96 (74) vs. 41 (47); p=0.03; patients with eGFR ≥60: n= 27; median 40 (20) vs. 32 (25); p=0.04). (Figure 12)

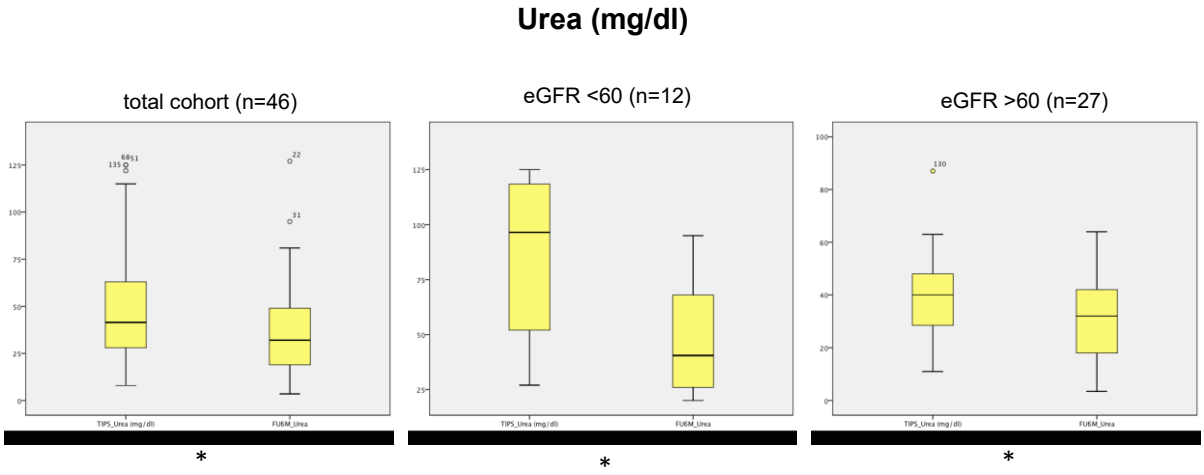


Figure 12, Changes of urea

3.2.2.6 CRP

A significant decline of C-reactive protein (CRP) was visible within the total cohort (n=57, median CRP (mg/L) 9.9 (IQR 17.6) vs. 4.2 (7.6); p=0.001) and was most distinct in patients with bleeding indications (median 13.4 (21.4) vs. 3.8 (4.2); p=0.006). In patients with refractory ascites a numeric but non-significant decline was observed (median 9.4 (13.0) vs. 4.9 (8.6); p=0.09). (Figure 13)

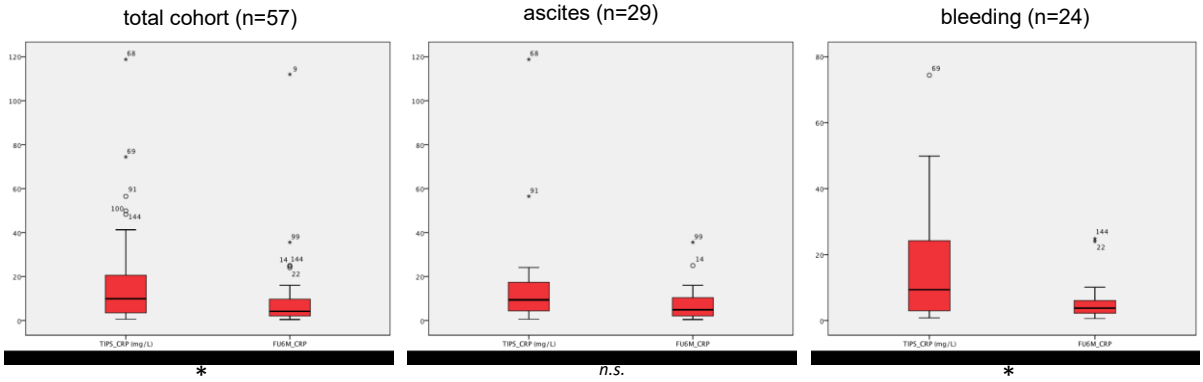


Figure 13, Changes of CRP levels

3.2.2.7 Liver function tests

No significant changes were observed in aspartate-aminotransferase (AST), alanine-aminotransferase (ALT) as well as gamma-glutamyltransferase (GGT), bilirubin, albumin, prothrombin time, fibrinogen as well as ammonia levels.

3.2.2.8 Electrolytes

Sodium as well as potassium levels did not significantly change between baseline and follow-up.

3.2.3 Post-TIPS Hepatic Encephalopathy

34 patients (23%) developed clinical symptoms of HE of any grade (according to West-Haven criteria, grades I-IV) during post-TIPS follow-up. The maximum grade of hepatic encephalopathy was I in 16%, II in 39%, III in 28% and IV in 17%. Univariate analysis determined previous history of HE (HR 4.1, p<0.001), high INR, AST and albumin levels as well as low hemoglobin, platelet count and fibrinogen as significant predictors of HE development within 90 days. (Table 11) In the multivariate model, previous history of HE, low fibrinogen and high AST remained significant independent predictors of post-TIPS HE within 90 days (Table 12).

Univariate Analysis: Post-TIPS Hepatic Encephalopathy **Total Cohort (N=144)**				
	N	HR	95% CI	P
Male sex	113	0.94	0.43-2.09	0.88
Etiology				
Alcohol	107	1.00		
Viral	13	0.72	0.17-3.03	0.65
BCS	5	0.79	0.11-5.84	0.82
Others	19	1.44	0.55-3.78	0.45
Indication				
Ascites	82	1.00		
Bleeding	51	0.79	0.37-1.71	0.56
Hepatic Hydrothorax	11	1.71	0.58-5.0	0.33
Diabetes	36	1.57	0.77-3.20	0.21
Pre-TIPS Bleeding	63	0.96	0.49-1.90	0.91
Pre-TIPS SBP	16	1.08	0.38-3.07	0.89
Pre-TIPS HE	21	4.10	2.03-8.30	**<0.001**
Pre-TIPS Ascites	102	1.34	0.62-2.87	0.45
TIPS PVT				
None	130	1.0		
Partial	12	1.07	0.33-3.51	0.91
Total	2	1.75	0.24-12.86	0.58
Pre-TIPS HCC	4	1.55	0.21-11.33	0.67

Age	1.03	0.99-1.06	0.09
Pre-TIPS HVPG	1.01	0.95-1.08	0.64
Post-TIPS HVPG	0.95	0.87-1.05	0.34
HVPG difference	1.05	0.99-1.12	0.12
Laboratory parameters			
Sodium (mmol/L)	0.98	0.92-1.04	0.45
Potassium (mmol/L)	0.82	0.49-1.37	0.45
Creatinine (mg/dl)	1.20	0.96-1.50	0.12
eGFR (ml/min/BS)	0.99	0.98-1.0	0.16
Urea (mg/dl)	1.01	1.00-1.01	0.07
Bilirubin (mg/dl)	1.04	0.98-1.1	0.23
Albumin (g/L)	2.21	1.03-4.74	**0.04**
INR	4.23	1.75-10.19	**0.001**
NH_3 (μmol/L)	1.01	0.99-1.02	0.50
AST (U/L)	1.001	1.0-1.002	**0.006**
ALT (U/L)	1.00	1.00-1.002	0.5
GGT (U/L)	1.00	0.99-1.0	0.07
CRP (mg/L)	1.00	0.98-1.02	0.94
Hemoglobin (g/dl)	0.81	0.67-0.97	**0.02**
Platelets (G/L)	0.99	0.98-1.00	**0.001**
White blood cell count (G/L)	1.00	0.91-1.09	0.94
Fibrinogen (mg/dl)	0.99	0.98-1.00	**0.01**

Table 11, Univariate analysis of factors predicting post-TIPS hepatic encephalopathy

Multivariate Analysis: Post-TIPS Hepatic Encephalopathy **Total Cohort (N=144)**			
	HR	**95% CI**	**P**
Pre-TIPS HE	14.54	2.24-94.39	**0.005**
Fibrinogen (mg/dl)	0.99	0.97-0.99	**0.03**
AST (U/L)	1.002	1.001-1.004	**0.007**

Table 12, Multivariate analysis of factors predicting post-TIPS hepatic encephalopathy

3.3 90-Day Mortality

Of all 144 patients, 136 (94%) had a confirmed vital status 90 days after TIPS. 90-day mortality rate was 19% (27 patients). 16 patients (11%) were censored due to transplantation (n=8) or loss of follow-up (n=8). Hence, the transplantation-free 90-day survival rate was 70% (n=101). There was a non-significant tendency towards a higher mortality risk in patients with bleeding indications compared to patients receiving TIPS for the treatment of ascites (HR 1.24, (95%CI: 0.54-2.83), whereas

hepatic hydrothorax was the indication group with the highest mortality compared to ascites (HR 2.81 (95% CI: 0.86-8.08). (Table 14) Acute on chronic hepatic failure was the most common cause of death by 90 days (n=5, 19% of deaths within 90-days). Notably, the second leading cause of early mortality (n=4, 15%) was the primary bleeding event that could not be solved by early- or rescue-TIPS. Three patients died in the course of a severe episode of hepatic encephalopathy due to aspiration pneumonia. The entirety of causes for early-mortality is listed in Table 13.

Causes of death within 90-days after TIPS	**% (N)**
Acute on chronic hepatic failure	19% (5)
Primary GI-bleeding, not resolvable by rescue-TIPS	15% (4)
GI-Bleeding, secondary	7% (2)
Non-gastrointestinal hemorrhage	11% (3)
Aspiration pneumonia during episode of hepatic encephalopathy West-Haven grade III-IV	11% (3)
Hepatocellular carcinoma	11% (3)
Sepsis	11% (3)
Right heart failure	4% (1)
Other, non-liver related causes	11% (3)
Total deaths	100% (27)

Table 13, Causes of death within 90-days after TIPS

3.3.1 Factors Predicting 90-Day Mortality Following TIPS

Baseline variables significantly predicting 90-day mortality in univariate analysis within the total cohort were:

- Pre-TIPS history of hepatic encephalopathy (HR 2.48, 95%CI: 1.09-5.67)
- Pre-TIPS diagnosis of hepatocellular carcinoma (HCC) (HR 4.81, 95%CI: 1.14-20.38)
- Etiology of portal hypertension classified as “other etiologies” (HR 3.10, 95%CI: 1.28-7-56)
- High urea, bilirubin, creatinine, INR, AST, ALT and white blood count
- Low hemoglobin, platelet count, GGT and fibrinogen
- High MELD and Child-Pugh score

Table 14, hazard ratios and 95% confidence intervals are to be interpreted per unit, respectively. Parameters that significantly predicted 90-day mortality in the univariate analysis were entered in a multivariate stepwise backward Cox-

Regression model. In this multivariate analysis, high urea and INR remained significant predictors of early mortality. (Table 15)

Univariate Analysis Total Cohort (N=144)	**N**	**HR**	**95% CI**	**p**
Male sex	113	0.94	0.38-2.32	0.89
Etiology				
Alcohol	107	1.00		
Viral	13	1.70	0.49-5.85	0.40
BCS	5	1.29	0.17-9.74	0.81
Others	19	3.10	1.28-7.56	**0.01**
Indication				
Ascites	82	1.00		
Bleeding	51	1.20	0.53-2.73	0.67
Hepatic Hydrothorax	11	2.71	0.88-8.32	0.08
Diabetes	36	0.82	0.50-1.34	0.43
Pre-TIPS Bleeding	63	0.81	0.37-1.74	0.58
Pre-TIPS SBP	16	1.33	0.46-3.84	0.60
Pre-TIPS HE	21	2.48	1.09-5.67	**0.03**
Pre-TIPS Ascites	102	1.35	0.57-3.20	0.49
Pre-TIPS portal venous thrombosis				
None	130	1.0		
Partial	12	1.40	0.42-4.65	0.59
Total	2	2.26	0.31-16.72	0.43
Pre-TIPS HCC	4	4.81	1.14-20.38	**0.03**
Age		1.02	0.99-1.06	0.20
Pre-TIPS HVPG		0.97	0.90-1.04	0.35
Post-TIPS HVPG		0.88	0.76-1.0	0.06
HVPG difference		1.01	0.94-1.08	0.83
Laboratory parameters				
Sodium (mmol/L)		0.97	0.91-1.05	0.45
Potassium (mmol/L)		1.56	0.94-2.61	0.09
Creatinine (mg/dl)		1.27	1.02-1.58	**0.03**
eGFR (ml/min/BS)		1.00	0.99-1.01	0.61
Urea (mg/dl)		1.02	1.01-1.03	**<0.001**
Bilirubin (mg/dl)		1.09	1.05-1.13	**<0.001**
Albumin (g/L)		0.70	0.35-1.40	0.31
INR		6.68	3.03-14.73	**<0.001**
NH_3 (μmol/L)		0.99	0.96-1.02	0.43
AST (U/L)		1.001	1.0-1.002	**0.002**
ALT (U/L)		1.001	1.0-1.002	**0.03**
GGT (U/L)		0.99	0.99-1.0	**0.03**
CRP (mg/L)		1.01	0.99-1.02	0.08
Hemoglobin (g/dl)		0.76	0.61-0.94	**0.02**
Platelets (G/L)		0.99	0.98-1.00	**0.009**
White blood cell count (G/L)		1.07	1.01-1.14	**0.02**
Fibrinogen (mg/dl)		0.99	0.99-1.00	**0.03**
MELD		1.18	1.12-1.26	**<0.001**

Child-Pugh score	1.50	1.15-1.92	**0.002**

Table 14, Univariate Cox regression analysis, 90-day mortality, total cohort

Multivariate Analysis Total Cohort (N=144)	**HR**	**95% CI**	**p**
Urea (mg/dl)	1.01	1.0-1.02	**0.003**
INR	6.67	2.05-21.76	**0.002**

Table 15, Multivariate Cox regression analysis, 90-day mortality, total cohort

3.3.1.1 Subgroup Analysis: Ascites

When looking exclusively at patients receiving TIPS for ascites indications (n=82), those with an etiology of portal hypertension classified as “other etiology” had a significantly higher 90-day mortality as well as patients with previous history of hepatic encephalopathy. High MELD and Child-Pugh score also significantly predicted mortality. Among laboratory parameters, high creatinine, urea, bilirubin, INR, AST and CRP as well as low hemoglobin and platelet count were significant predictors of 90-day mortality in the univariate analysis. (Table 16) In multivariate analysis of laboratory parameters, high creatinine and CRP were significant independent predictors of mortality. (Table 17)

Univariate Analysis Ascites (N=82)	**N**	**HR**	**95% CI**	**p**
Male sex	64	1.56	0.35-7.02	0.56
Etiology				
Alcohol	60	1.00		
Viral	4	3.98	0.48-33.10	0.20
BCS	5	1.99	0.24-16.50	0.53
Others	13	5.09	1.55-16.72	**0.007**
Diabetes	18	0.94	0.43-2.03	0.87
Pre-TIPS Bleeding	11	0.50	0.06-3.76	0.49
Pre-TIPS SBP	14	1.32	0.36-4.78	0.68
Pre-TIPS HE	13	3.56	1.16-10.91	**0.03**
Pre-TIPS portal venous thrombosis				
None	71	1.0		
Partial	9	2.80	0.76-10.35	0.12
Total	2	3.17	0.40-24.99	0.27
Pre-TIPS HCC	1	-	-	-
Age		1.03	0.97-1.10	0.28
Pre-TIPS HVPG		0.97	0.90-1.07	0.43
Post-TIPS HVPG		0.90	0.74-1.01	0.30
HVPG difference		1.01	0.91-1.11	0.87
Laboratory parameters				
Sodium (mmol/L)		1.01	0.90-1.13	0.93
Potassium (mmol/L)		1.63	0.73-3.63	0.24

Creatinine (mg/dl)	3.00	1.65-5.45	**<0.001**
eGFR (ml/min/BS)	0.98	0.96-1.01	0.13
Urea (mg/dl)	1.02	1.01-1.03	**0.002**
Bilirubin (mg/dl)	1.09	1.04-1.15	**0.001**
Albumin (g/L)	1.01	0.31-3.27	0.99
INR	7.59	2.51-22.94	**<0.001**
NH_3 (µmol/L)	0.98	0.93-1.04	0.50
AST (U/L)	1.001	1.0-1.002	**0.003**
ALT (U/L)	1.002	1.0-1.004	0.08
GGT (U/L)	0.99	0.99-1.00	0.46
CRP (mg/L)	1.02	1.00-1.04	**0.02**
Hemoglobin (g/dl)	0.70	0.51-0.96	**0.03**
Platelets (G/L)	0.99	0.98-0.99	**0.007**
White blood cell count (G/L)	1.10	0.97-1.24	0.13
Fibrinogen (mg/dl)	0.99	0.99-1.00	0.06
MELD	1.30	1.15-1.50	**<0.001**
Child-Pugh score	2.21	1.40-3.48	**0.001**

Table 16, Univariate Cox regression analysis of 90-day mortality in patients with ascites

Multivariate Analysis Ascites (N=82)	**HR**	**95% CI**	**p**
Creatinine (mg/dl)	11.7	1.23-111.06	**0.03**
CRP (mg/L)	1.28	1.01-1.62	**0.04**

Table 17, Multivariate Cox regression analysis of 90-day mortality in patients with ascites

3.3.1.2 Subgroup Analysis: Bleeding

Of the 51 patients receiving TIPS for bleeding indications, univariate analysis identified high urea, bilirubin, INR, white blood cell count and MELD as well as low GGT as significant predictors of 90-day mortality. (Table 18) In multivariate analysis, urea solely remained an independent significant predictor. (Table 19)

Univariate Analysis Bleeding (N=51)	**N**	**HR**	**95% CI**	**p**
Male sex	41	0.55	0.14-2.12	0.38
Etiology				
Alcohol	38	1.00		
Viral	8	0.60	0.07-4.85	0.63
Others	5	2.13	0.44-10.28	0.35
Diabetes	16	0.64	0.30-1.40	0.26
Pre-TIPS Ascites	13	2.57	0.72-9.12	0.14
Pre-TIPS SBP	1	-	-	-
Pre-TIPS HE	6	0.73	0.09-5.75	0.76
Pre-TIPS portal venous thrombosis				
None	48	1.0		
Partial	3	0.05	0.00-1913.6	0.57
Total	0			

Pre-TIPS HCC	2	-	-	-
Age		1.01	0.96-1.05	0.76
Pre-TIPS HVPG		0.95	0.85-1.06	0.36
Post-TIPS HVPG		0.88	0.71-1.09	0.23
HVPG difference		0.97	0.86-1.0	0.67
Laboratory parameters				
Sodium (mmol/L)		0.92	0.82-103	0.12
Potassium (mmol/L)		1.82	0.90-3.68	0.09
Creatinine (mg/dl)		1.11	0.78-1.56	0.56
eGFR (ml/min/BS)		1.00	0.99-1.01	0.88
Urea (mg/dl)		1.03	1.01-1.04	**<0.001**
Bilirubin (mg/dl)		1.11	1.03-1.20	**0.006**
Albumin (g/L)		0.46	0.16-1.37	0.16
INR		8.43	2.30-30.89	**0.001**
NH_3 (μmol/L)		0.98	0.92-1.04	0.44
AST (U/L)		1.001	1.0-1.003	0.20
ALT (U/L)		1.001	1.0-1.002	0.12
GGT (U/L)		0.98	0.96-0.99	**0.02**
CRP (mg/L)		1.00	0.99-1.02	0.76
Hemoglobin (g/dl)		0.79	0.51-1.23	0.29
Platelets (G/L)		0.99	0.98-1.01	0.29
White blood cell count (G/L)		1.07	1.00-1.15	**0.05**
Fibrinogen (mg/dl)		0.99	0.98-1.00	0.07
MELD		1.15	1.05-1.25	**0.002**
Child-Pugh score		1.33	0.89-1.97	0.16

Table 18, Univariate Cox regression analysis of 90-day mortality in patients with bleeding

Multivariate Analysis Bleeding (N=51)	**HR**	**95% CI**	**p**
Urea (mg/dl)	1.02	1.01-1.04	**0.002**

Table 19, Multivariate Cox regression analysis of 90-day mortality in patients with bleeding

3.3.1.3 Subgroup Analysis: Patients with Renal Insufficiency (eGFR <60)

Among patients with eGFR below 60, high urea, bilirubin and white blood cell count predicted early mortality in univariate analysis. Bilirubin and white blood cell count remained significant predictors in a multivariate model. (Table 20Table 21)

Univariate Analysis eGFR <60 (N=37)	**N**	**HR**	**95% CI**	**p**
Male sex	27	0.70	0.18-2.72	0.61
Etiology				
Alcohol	21	1.00		
Viral	5	0.00	0.00-	0.98
BCS	2	1.91	0.22-16.48	0.56
Others	9	2.76	0.74-10.32	0.13
Indication				
Ascites	25	1.00		
Bleeding	10	1.47	0.41-5.20	0.56

Hepatic Hydrothorax	2	-	-	-
Diabetes	12	0.91	0.40-2.07	0.83
Pre-TIPS Bleeding	12	1.28	0.36-4.54	0.70
Pre-TIPS SBP	8	1.31	0.34-5.06	0.70
Pre-TIPS HE	4	0.61	0.08-4.85	0.64
Pre-TIPS Ascites	29	1.40	0.30-6.60	0.67
Pre-TIPS portal venous thrombosis				
None	32	1.0		
Partial	5	1.43	0.30-6.74	0.65
Total	1	-	-	-
Pre-TIPS HCC	1	-	-	**-**
Age		0.97	0.92-1.02	0.28
Pre-TIPS HVPG		1.01	0.90-1.13	0.88
Post-TIPS HVPG		0.93	0.74-1.17	0.52
HVPG difference		1.04	0.92-1.18	0.51
Laboratory parameters				
Sodium (mmol/L)		1.01	0.92-1.12	0.84
Potassium (mmol/L)		1.50	0.69-3.27	0.30
Creatinine (mg/dl)		1.12	0.82-1.52	0.48
eGFR (ml/min/BS)		0.97	0.93-1.01	0.13
Urea (mg/dl)		1.02	1.01-1.04	**0.001**
Bilirubin (mg/dl)		1.10	1.02-1.18	**0.02**
Albumin (g/L)		0.41	0.14-1.19	0.10
INR		2.58	0.85-7.85	0.09
NH_3 (μmol/L)		0.98	0.93-1.03	0.32
AST (U/L)		1.001	1.0-1.002	0.06
ALT (U/L)		1.001	1.0-1.002	0.20
GGT (U/L)		1.00	0.99-1.01	0.91
CRP (mg/L)		1.01	0.99-1.03	0.14
Hemoglobin (g/dl)		0.76	0.51-1.14	0.19
Platelets (G/L)		0.99	0.98-1.00	0.14
White blood cell count (G/L)		1.11	1.02-1.22	**0.02**
Fibrinogen (mg/dl)		1.00	0.99-1.00	0.60
MELD		1.14	1.04-1.25	**0.007**
Child-Pugh score		1.44	1.01-2.07	**0.05**

Table 20, Univariate Cox regression analysis of 90-day mortality in patients with renal insufficiency

Multivariate Analysis eGFR <60 (N=37)	**HR**	**95% CI**	**p**
Bilirubin (mg/dl)	1.10	1.02-1.19	**0.02**
WBC (G/L)	1.16	1.03-1.31	**0.01**

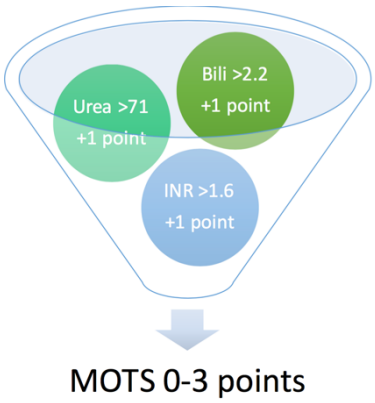
Table 21, Multivariate Cox regression analysis of 90-day mortality in patients with renal insufficiency

3.4 Score Development

3.4.1 Modified TIPS Score (MOTS)

In multivariate analysis, urea and INR were significant independent predictors for 90-day mortality within the total cohort. Given our intention to create a predictive

model based on MELD, we decided to integrate bilirubin as a third variable being a significant mortality predictor in univariate analysis of the total cohort as well as in all subgroups and in multivariate analysis including patients with renal insufficiency. Thus, a score integrating urea, INR and bilirubin was developed utilizing the method described in chapter 2.1.2.



MOTS ranged from 0-3 points: INR >1.6, urea >71 mg/dl and bilirubin >2.2 mg/dl implied plus one point each.

Figure 14, MOTS

3.4.2 Logarithmic Modified TIPS Score (LogMOTS)

To see whether a model using the same variables but with a continuous scale outperformed the simple MOTS, we developed LogMOTS. LogMOTS has a continuous scale and integrates the absolute values of urea, INR and bilirubin. For every parameter, the odds ratio (=1- regression coefficient) was utilized as the constant the natural logarithm of the absolute value is multiplied with. The factor ten served to obtain a larger scale.

LogMOTS = 10*(0.983*LN (Urea mg/dl) +0.763*LN (Bili mg/dl) +0.136*LN (INR))

3.5 Score Validation

For the validation of our newly created scoring models, we collaborated with the Department of Internal Medicine III, Medical University of Vienna as well as with the Department of Internal Medicine I at the University Hospital of Innsbruck. We first compared 338 patients from Vienna to the patients of our cohort (training cohort). The parameters to calculate MOTS and LogMOTS were available in only 33% of patients. Among baseline characteristics, patients from Vienna had significantly lower median MELD and LogMOTS. None of the patients from Vienna received TIPS for hepatic hydrothorax, whereas 8% received TIPS for an indication other than the three main indications in our cohort. Additionally, post-TIPS liver

transplantation rate was significantly lower in the Vienna cohort. A major difference was that within patients from the Vienna cohort, MELD was not predictive for 90-day mortality (AUROC 0.5880; 95%CI 0.49-0.68), (TTable 24). Among the 202 patients form the Innsbruck cohort, parameters to calculate MOTS and LogMOTS were available in 93%. There were significantly more patients who received TIPS for ascites and less with bleeding indications than in the training cohort. No significant differences were shown between baseline MELD, MOTS and LogMOTS compared to our patients. However, in the validation cohort from Innsbruck, 90-day mortality rate was significantly lower with a higher percentage of patients lost to follow up (Table 23). MELD significantly predicted 90-day mortality within the patients from this cohort (Table 24). Due to the low percentage of available MOTS and LogMOTS score parameters and to the fact that MELD was not predictive for mortality, we decided not to use the Vienna cohort for score validation. Thus, the Innsbruck cohort (n=202) was utilized to validate MOTS and LogMOTS.

Comparison of baseline and follow-up data	**Trainings cohort (Graz) n=144**	**External validation cohort I (Vienna) n=338**	**p-value**
Female sex	31 (22%)	99 (29%)	0.08
Age, median (IQR)	56 (16)	56 (14)	0.78
TIPS Indication			**<0.001**
Ascites	82 (57%)	184 (54%)	
Bleeding	51 (35%)	127 (38%)	
Hepatic Hydrothorax	11 (8%)	0	
others	0	27 (8%)	
MELD available	113 (79%)	284 (84%)	
MELD, median (IQR)	13 (7.5)	12 (5)	**0.004**
MOTS available	110 (76%)	112 (33%)	
MOTS			0.14
0	50 (46%)	57 (51%)	
1	40 (36%)	46 (41%)	
2	12 (11%)	8 (7%)	
3	8 (7%)	1 (1%)	
LogMOTS available	110 (76%)	112 (33%)	
LogMOTS, median (IQR)	39 (13.5)	30 (11)	**<0.001**
90-day mortality	27 (19%)	45 (13%)	0.13
90-day loss to follow-up	8 (6%)	11 (3%)	0.24
90-day LTX	8 (6%)	2 (1%)	**<0.001**

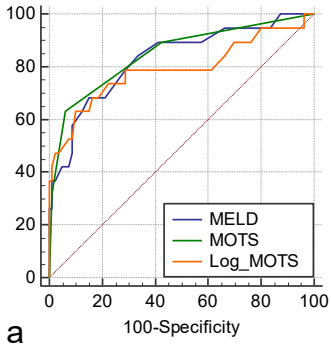
Table 22, Comparison of baseline and follow-up data between training cohort (Graz) and external validation cohort I (Vienna)

Comparison of baseline and follow-up data	Trainings cohort (Graz) n=144	External validation cohort II (Innsbruck) n=202	p-value
Female sex	31 (22%)	61 (30%)	0.07
Age, median (IQR)	56 (16)	58 (13)	0.33
TIPS Indication			**0.002**
Ascites	82 (57%)	151 (75%)	
Bleeding	51 (35%)	42 (21%)	
Hepatic Hydrothorax	11 (8%)	9 (5%)	
Others	0	0	
MELD available	113 (79%)	187 (93%)	
MELD, median (IQR)	13 (7.5)	13 (6.0)	0.44
MOTS available	110 (76%)	188 (93%)	
MOTS			0.36
0	50 (46%)	92 (49%)	
1	40 (36%)	70 (37%)	
2	12 (11%)	22 (12%)	
3	8 (7%)	4 (2%)	
LogMOTS available	110 (76%)	188 (93%)	
LogMOTS, median (IQR)	39 (13.5)	41 (12)	0.31
90-day mortality	27 (19%)	11 (5%)	**<0.001**
90-day loss to follow-up	8 (6%)	26 (13%)	**0.02**
90-day LTX	8 (6%)	9 (5%)	0.64

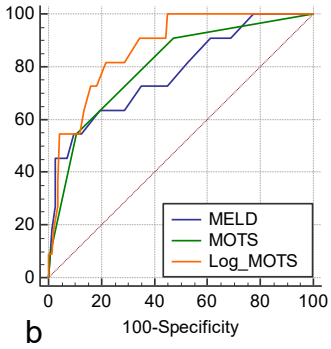
Table 23, Comparison of baseline and follow-up data between training cohort (Graz) and external validation cohort II (Innsbruck)

3.6 AUROCS Analysis: Prognostic Capability of MELD vs. MOTS and LogMOTS predicting 90-Day Mortality

When assessing the prognostic capability of MELD, MOTS and LogMOTS in terms of 90-day mortality, all three scores were significant predictors of mortality in the original cohort (Graz) as well as the validation cohort (Innsbruck). In the original cohort, MOTS had the highest AUROC of 0.85 (95% CI: 0.74-0.96) compared to MELD (AUROC 0.84; 95% CI: 0.74-0.96) and LogMOTS (AUROC 0.79; 95% CI: 0.65-0.93). In the validation cohort, LogMOTS, MOTS and MELD had AUROC values of 0.87 (95%CI 0.79-0.96), 0.80 (95%CI 0.67-0.94) and 0.77 (95%CI 0.62-0.93), respectively. (Table 24; a, b) In the Vienna cohort, LogMOTS was the only significant mortality-predicting model with an AUROC value of 0.74 (95%CI 0.59-0.89). (Table 24; c) In pairwise comparison of AUROCs, only the superiority of LogMOTS over MELD in the Vienna cohort was statistically significant. (Table 26; c)



a



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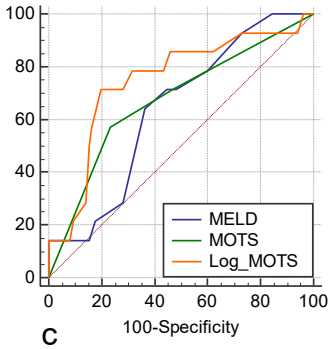


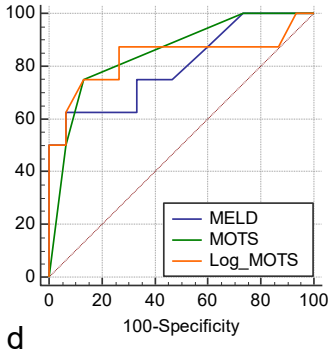
c

AUROC, 90-day mortality	Graz **(a)** N=110	Innsbruck **(b)** N=187	Vienna **(c)** N=112
MELD	0.835[1] (95%CI 0.73-0.94)	0.777[2] (95%CI 0.62-0.93)	0.588[0] (95%CI 0.49-0.68)
MOTS	**0.847**[1] (95%CI 0.74-0.96)	0.803[3] (95%CI 0.67-0.94)	0.627[0] (95%CI 0.47-0.78)
LogMOTS	0.790[1] (95%CI 0.65-0.93)	**0.874**[1] (95%CI 0.79-0.96)	**0.740**[4] (95%CI 0.59-0.89)

*Table 24, 90-day mortality in **all TIPS patients** of all cohorts, AUROC= area under receiver operating characteristics, * 90-day AUROC statistical significance: [1]p<0.001, [2]p=0.002, [3]p=0.001,[4]p=0.04,[0] =not significant*

3.6.1 Subgroup Analysis: Patients with GFR <60 ml/min/m^2

Within patients who had initial GFR lower than 60, all three scores significantly predicted 90-day mortality in the training cohort (Graz). MOTS had the highest AUROC of 0.85 (95%CI 0.68-1.00) followed by LogMOTS 0.83 (95%CI 0.62-1.00) and MELD 0.77 (95%CI 0.57-0.97). In the validation cohort (Innsbruck), MOTS was the only significant prognostic model with an AUROC of 0.81 (95%CI 0.64-0.98). (Table 25; d, e) None of the scores predicted 90-day mortality in the Vienna cohort (Table 25; f). The differences were not significant in pairwise AUROC comparison (Table 26).



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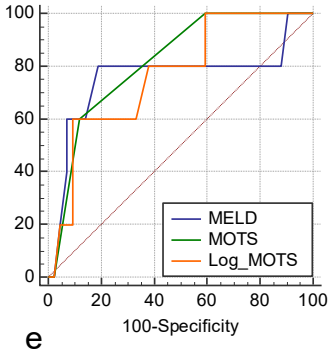

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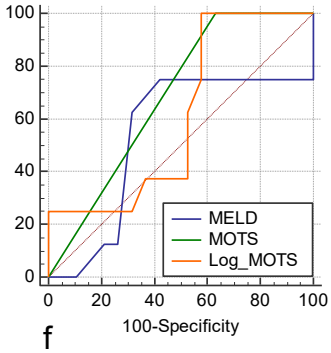


f

AUROC, 90-day mortality	Graz (d) N=31	Innsbruck (e) N=61	Vienna (f) N=30
MELD	0.770[1] (95%CI 0.57-0.97)	0.755[0] (95%CI 0.46-1.00)	0.453[0] (95%CI 0.30-0.61)
MOTS	**0.850**[2] (95%CI 0.68-1.00)	**0.814**[4] (95%CI 0.64-0.98)	0.554[0] (95%CI 0.33-0.77)
LogMOTS	0.833[3] (95%CI 0.62-1.00)	0.764[0] (95%CI 0.56-0.97)	0.577[0] (95%CI 0.35-0.81)

*Table 25, 90-day mortality in TIPS patients with baseline **GFR <60 ml/min/m²** of all cohorts, AUROC= area under receiver operating characteristics, * 90-day AUROC statistical significance: [1]p=0.03, [2]p=0.007, [3]p=0.01, [4]p=0.02, [0] =not significant*

Pairwise comparison of ROC curves

Hanley & McNeil[1]	a	b	c	d	e	f
MELD MOTS	p=0.72	p=0.69	p=0.56	p=0.62	p=0.69	p=0.24
MELD LogMOTS	p=0.46	p=0.11	p=0.06	p=0.75	p=0.94	p=0.56
MOTS LogMOTS	p=0.34	p=0.16	p=0.21	p=0.85	p=0.54	p=0.50
DeLong et al.[2]	a	b	c	d	e	f
MELD MOTS	p=0.54	p=0.69	p=0.53	p=0.46	p=0.67	p=0.48
MELD LogMOTS	p=0.34	p=0.07	p=0.02*	p=0.71	p=0.93	p=0.77
MOTS LogMOTS	p=0.17	p=0.17	p=0.13	p=0.83	p=0.62	p=0.44

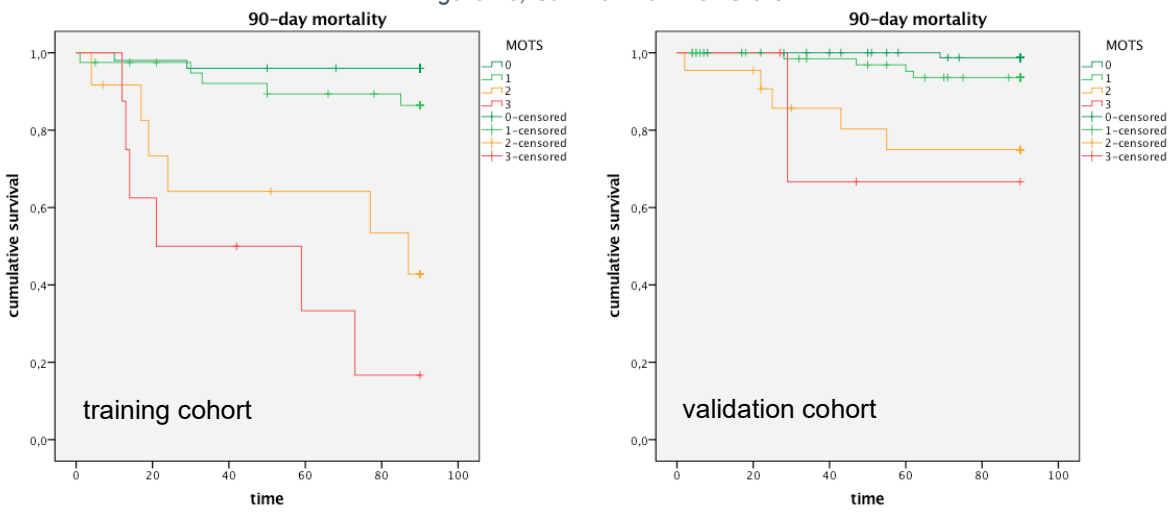
Table 26, a= Graz, all TIPS patients, b=Innsbruck, all TIPS patients, c= Vienna, all TIPS patients, d= Graz, GFR <60 ml/min/m2, e= Innsbruck, GFR <60 ml/min/m2, f= Vienna, GFR <60 ml/min/m2, [1] Hanley & McNeil et al. 1982, [2] DeLong et al. 1988

3.7 Kaplan-Meier Survival Statistics

3.7.1 Survival of Patients with MOTS 0-3

Overall, 27 patients (19%) of the training cohort (Graz) died within 90 days. Mortality rates were 4%, 13%, 50% and 75% in patients with MOTS 0 points (n=50), 1 point (n=40), 2 points (n=12) and 3 points (n=8), respectively (p<0.001, log rank-test; Chi-square: 49.9). In the validation cohort (Innsbruck), overall 90-day mortality rate was 5% (n=11). 1%, 6%, 23% and 25% of patients with a MOTS score of 0 points (n=92), 1 point (n=70), 2 points (n=22) and 3 points (n=4) died, respectively (p<0.001, log rank-test; Chi-square: 22.5). (Figure 15)

Figure 15, Survival with MOTS 0-3



3.7.2 TIPS or Not? MELD vs. MOTS to Identify Patients with Poor Outcome

For MELD, as suggested in previous guidelines (11,126), a threshold of 20 points was defined. For MOTS, the threshold of 2 points was determined graphically, as the Kaplan-Meier plot of MOTS 0-3 (Fig 16) showed distinct deviation of survival between MOTS 0-1 and 2-3.

90-Day Mortality

In our *training cohort*, 12% of patients with **MELD** ≤19 (n=93) died within 90 days, compared to 50% of patients with MELD ≥20 (n=20) (p<0.001, log rank-test; Chi-square: 21.1). For **MOTS**, the mortality rates were 8% vs. 60% for MOTS 0-1 (n=90) and 2-3 (n=20), respectively (p<0.001, log rank-test; Chi-square: 43.1). Among patients of the *validation cohort,* 90-day mortality rate was 4% in patients with **MELD** ≤19 (n=167) vs. 25% of patients with MELD ≥20 (n=20) (p<0.001, log rank-test; Chi-square: 21.1). For **MOTS**, the mortality rates were 3% vs. 23% in MOTS 0-1 (n=162) and 2-3 (n=26) (p<0.001, log rank-test; Chi-square: 20.5). (Figure 16)

One-Year Mortality

Within patients of the *training cohort*, one-year mortality rate was 19% in patients with **MELD** ≤19 (n=93) and 65% in patients with MELD ≥20 (n=20) (p<0.001, log rank-test; Chi-square: 24.5). For **MOTS**, the mortality rates were 17% vs. 70% in MOTS 0-1 (n=90) and 2-3 (n=20), respectively (p<0.001, log rank-test; Chi-square: 37.7). One-year mortality rate in the *validation cohort* amounted 7% in patients with **MELD** ≤19 (n=167) and 25% in patients with MELD ≥20 (n=20) (p=0.001, log rank-test; Chi-square: 12.1). **MOTS** of 0-1 points (n=162) was associated with a mortality rate of 6% vs. 27% in MOTS 2-3 points (n=26) (p<0.001, log rank-test; Chi-square: 17.8). (Figure 16)

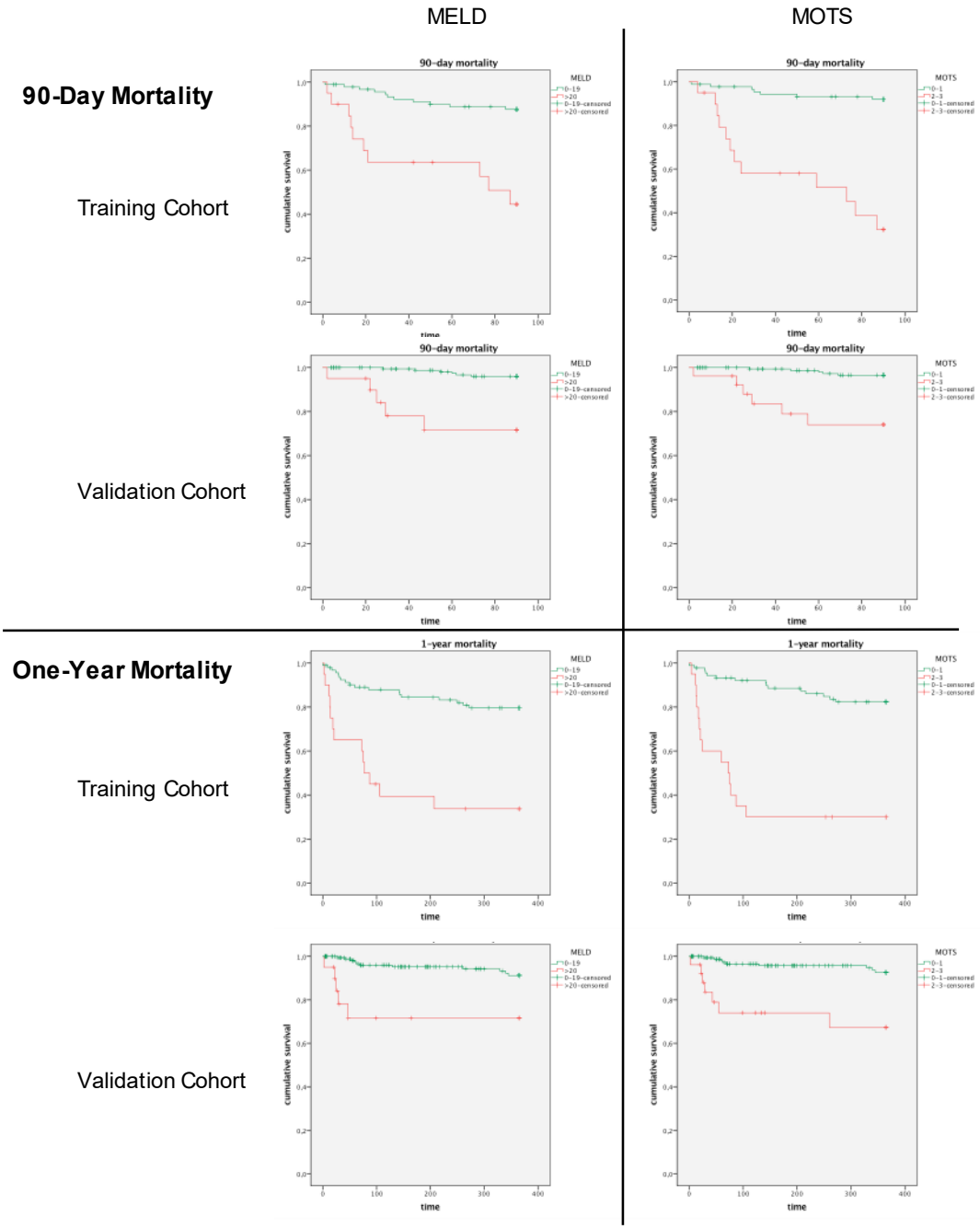


Figure 16, 90-day and one-year survival, MELD: green line: Patients with MELD ≤19, red line; ≥20); MOTS: green line: 0-1, red line: 2-3

3.7.2.1 Subgroup Analysis: Patients with Renal Insufficiency (eGFR <60)

<u>90-Day Mortality</u>

Within patients with eGFR below 60 in the *training cohort* (n=31), MELD of ≤19 (n=18) was associated with a 90-day mortality rate of 17% compared to 46% in patients with MELD ≥20 (n=13) (not significant (p=0.12), log rank-test; Chi-square: 2.4). Mortality rates of patients with **MOTS** 0-1 (n=19) and 2-3 (n=10), were 11% vs. 60%, respectively (p=0.004, log rank-test; Chi-square: 8.1). In the *validation cohort*

(eGFR<60, n=61), 4% of patients with **MELD** ≤19 (n=49) died within 90 days, compared to 25% of patients with MELD ≥20 (n=12) (p=0.01, log rank-test; Chi-square: 6.6) whereas mortality rates were 4% vs. 27% in MOTS 0-1 (n=50) and 2-3 (n=11), respectively (p=0.006, log rank-test; Chi-square: 7.6). (Figure 17)

One-Year Mortality

In the *training cohort,* 28% of patients with **MELD** ≤19 (n=18) died within one year, compared to 69% with MELD ≥20 (n=23) (p=0.02, log rank-test; Chi-square: 5.4). **MOTS** of 0-1 points (n=19) was associated with a mortality rate of 26% vs. 80% in MOTS 2-3 points (n=10) (p=0.001, log rank-test; Chi-square: 10.4). Within the *validation cohort*, 6% of patients with **MELD** ≤19 (n=49) died within one year, compared to 25% of patients with MELD ≥20 (n=12) (p=0.03, log rank-test; Chi-square: 5.0). **MOTS** of 0-1 points (n=50) was associated with a mortality rate of 4% vs. 36% in MOTS 2-3 points (n=11) (p<0.001, log rank-test; Chi-square: 12.5). (Figure 17)

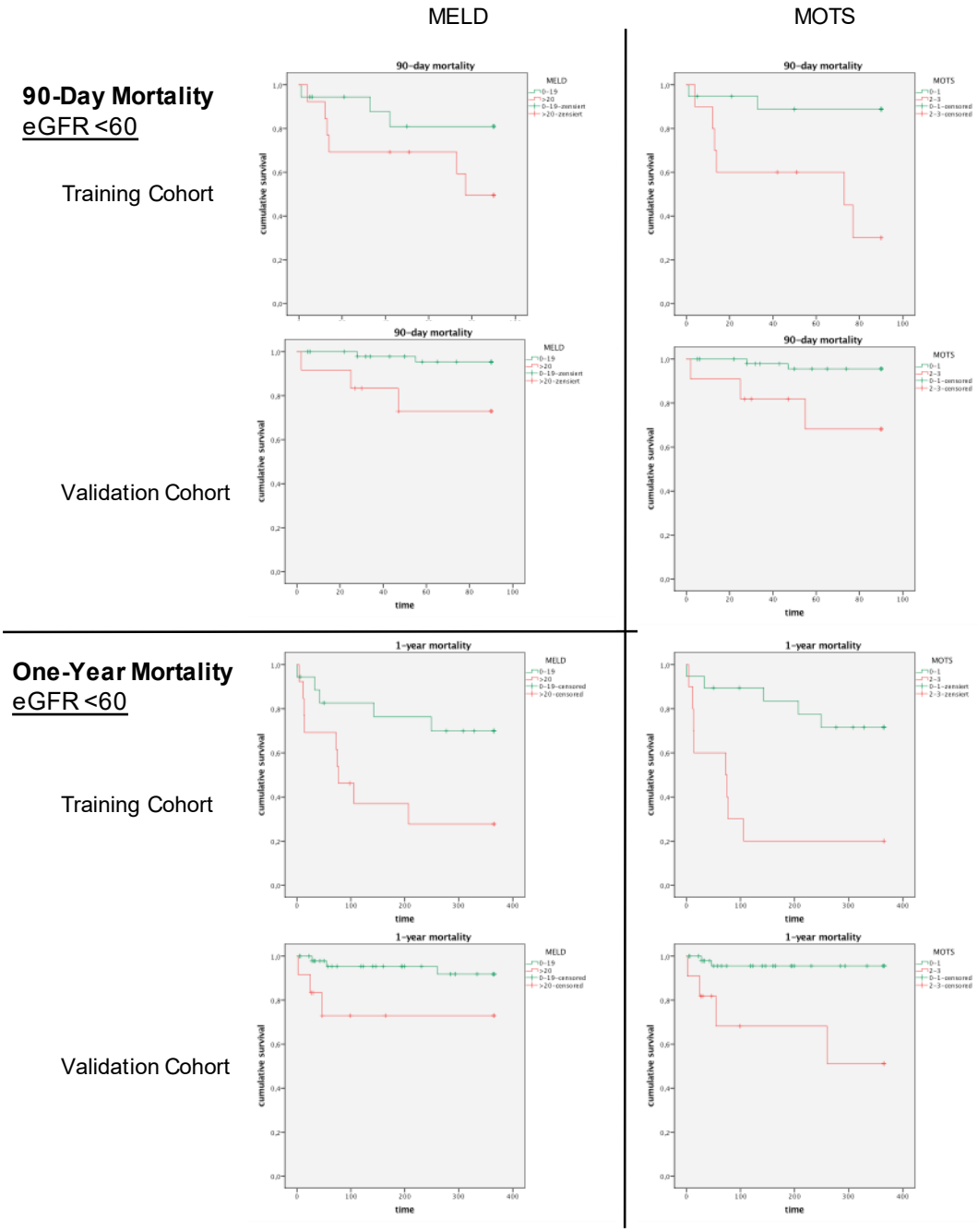


Figure 17, 90-day and one-year survival in patients with eGFR <60; MELD: green line: Patients with MELD ≤19, red line; ≥20); MOTS: green line: 0-1, red line: 2-3

3.7.3 TIPS or Not? LogMOTS to Identify Patients with Poor Outcome

LogMOTS did not outperform MOTS in the total training cohort and had lower AUROC values than MOTS in patients with renal insufficiency of both cohorts. Therefore, the performance of LogMOTS identifying patients with poor survival was not separately compared to MELD. The mortality rates of LogMOTS groups are presented below.

90-Day Mortality

For LogMOTS, the prognostic threshold of 50 points was identified using the value with the highest Youden-Index of ROC-coordinates predicting 90-day mortality. Within the total **training cohort**, in patients with a LogMOTS below 50 points, mortality was 8% (n=7) whereas among patients with a LogMOTS ≥50, the rate was significantly higher with 50% (n=12; p<0.001, log rank-test; Chi-square: 19.4). In the **validation cohort**, 3% (n=4) of patients with LogMOTS <50 and 23% (n=7) of patients with LogMOTS ≥50 died within 90-days (p<0.001, log rank-test; Chi-square: 20.6).

One-Year Mortality

In the **training cohort,** 17% (n=15) of patients with LogMOTS <50 died within one year compared to 58% (n=14) with a LogMOTS ≥50 (p<0.001, log rank-test; Chi-square: 22.5). Among patients in the **validation cohort** who had LogMOTS <50, 5% (n=8) died compared to 26% (n=8) of patients with LogMOTS ≥50 (p<0.001, log rank-test; Chi-square: 16.9).

3.7.3.1 Subgroup Analysis: LogMOTS in Patients with eGFR <60

90-Day Mortality

Training cohort: In patients with renal insufficiency and LogMOTS <50, 90-day mortality was 7% (n=1) compared to 50% (n=7) in patients with a LogMOTS ≥50 (p=0.01, log rank-test; Chi-square: 6.4). **Validation cohort:** 4% (n=2) of patients with LogMOTS <50 and 19% (n=3) with LogMOTS ≥50 died, respectively (p=0.08, log rank-test; Chi-square: 3.1).

One-Year Mortality

Training cohort: One-year mortality was 27% (n=4) in patients with eGFR<60 and LogMOTS <50 and 64% (n=9) in patients of the same cohort with LogMOTS ≥50 (p=0.02, log rank-test; Chi-square: 5.5). **Validation cohort:** 4% (n=2) and 25% (n=4) in the groups with LogMOTS <50 and ≥50 died, respectively (p=0.02, log rank-test; Chi-square: 5.5).

4 Discussion

In the current study, we retrospectively investigated all cases of TIPS placement within 13 years of clinical practice at the University Hospital of Graz in order to improve mortality prediction and patient selection. Of the total number of 158 cases, we excluded 14 patients due to insufficient data. During a median follow-up time of 17.6 months (IQR 45.2), 49% of patients died and 22% received liver transplantation. We aimed to utilize our data for the development of a new risk stratifying tool with beneficial predictive value compared to existing models. Inspired by the development of MELD (113), the so far best validated post-TIPS mortality predicting model, we decided to define 90-day mortality as the main outcome for survival statistics. Another major reason for this decision was the assumption that deaths related to severe TIPS complications, for instance acute liver failure or severe hepatic encephalopathy usually occur early after the intervention (127–129). Exactly these cases are of special interest, as it seems reasonable to suggest that improved patient selection might reduce the rate of early mortality as well as the proportion of patients who do not benefit from TIPS. With the simple MOTS, we developed a valuable tool to predict early post-TIPS mortality with higher AUROC-values than MELD, also in patients with eGFR < 60. The score was validated in an external cohort from the University Hospital of Innsbruck.

4.1 Baseline and Demographic Data

A noticeable finding of our baseline data analysis is the high percentage of alcohol-related liver disease, being the main cause of portal hypertension (PH) in 74% of patients. Due to the retrospective design of our study, a precise distinction of mixed etiologies was not feasible. Therefore, we recorded the main etiology only. However, this high percentage of alcohol-related liver disease is similar to published data from other central and southern European countries, such as France (112,130,131). In order to gain results comparable to real-life clinical practice, we did not include elective TIPS placements exclusively but analyzed all cases instead. Interestingly, only 35% of patients were initially hospitalized for elective TIPS, whereas in the majority of patients, the decision was made during hospitalization for instance for acute gastroesophageal bleeding (26%), clinically symptomatic ascites (23%), or evaluation for liver transplantation (10%).

4.2 Follow-Up Data

4.2.1 Clinical Efficacy of TIPS

Among patients receiving TIPS for refractory/recurrent ascites, clinical non-response defined as the need for two or more therapeutic paracenteses after TIPS was seen in 32%. Within patients with bleeding indications, 31% had further bleeding events. In the small group of 11 patients with hepatic hydrothorax, therapeutic failure, specified as requiring therapeutic thoracentesis at least twice after TIPS occurred in 36% of patients. Hence, clinical response was given in approximately two thirds of patients with a slightly higher rate of insufficiency in patients with hepatic hydrothorax. Clinical efficacy was consistent with previous research (59,61,132–134).

4.2.2 Laboratory Changes after TIPS

4.2.2.1 Parameters of Renal Function

Several studies have shown significant changes in renal functional parameters after TIPS creation. In our cohort, among patients with initial renal insufficiency (eGFR below 60 ml/min/m^2), we observed a 50% increase of mean eGFR and a consistent decline of creatinine by 35% whereas no significant changes could be observed in patients with initial eGFR above 60. These findings are similar to what has been reported from previous studies (84,135–137). However, in our study, the interval of 6.2 (IQR 1.8) months between pre-TIPS and follow-up blood sampling was relatively long compared to previous research (84,115). To the best of our knowledge, only one trial performing TIPS in five patients with type 1 HRS after treatment with midodrine, octreotide, and albumin (137) has observed that distinct effects on renal function over a period of approximately six months. Urea levels declined significantly in the total cohort but the decline was more distinct in patients with initially lower eGFR. This decline may be explained by the fact that the improved glomerular filtration leads to an improved renal urea excretion. Additionally, an increased direct shunting of ammonia to the systemic circulation may lead to a lower hepatic conversion of ammonia to urea.

4.2.2.2 *Parameters of Systemic Inflammation*

Interestingly, besides the expected rise of mean hemoglobin, a significant decline of leucocyte count and c-reactive protein (CRP) was observed in patients receiving TIPS for bleeding indications. A possible explanation for this finding might be that systemic inflammation caused by occult or overt bacterial infection favors portal hypertensive complications, such as variceal bleeding (138,139). In addition, gastrointestinal wound surfaces, such as ligated varices or portal hypertensive gastropathy may trigger a systemic inflammatory response. Importantly, six-months follow-up laboratory values were not utilized when patients simultaneously showed symptoms of severe infections, for instance pneumonia or were admitted due to bleeding episodes. This circumstance may have added to the low CRP and leucocyte levels at follow-up.

4.2.2.3 *Platelet Count*

Furthermore, in contrast to reported findings (140–142), we observed a significant drop of platelet count at follow-up. In the subgroup analysis, this decline was only significant in patients receiving TIPS for ascites, who had higher baseline platelet levels than bleeding patients. The pathophysiology of progressive thrombocytopenia in patients with portal hypertension is not fully understood. It is presumed that multiple factors probably including splenic sequestration, immunity reactions and lack of humoral factors contribute to a platelet decline (140). The observed 13% decline of median platelet count in patients receiving TIPS for ascites indications might have occurred independently from TIPS-placement as a consequence of cirrhosis progression.

4.2.3 Post TIPS HE

Similar to what has been reported in previous studies (76,104,143), in our cohort the rate of hepatic encephalopathy (HE) of any grade after TIPS was 23% during a median follow-up of 17.6 months. Incomplete understanding of the pathophysiologic mechanisms and lacking evidence for preventive measures are probably major reasons for the continuously high rates of post-TIPS HE. In order to keep the incidence of this severe complication leading to an increased mortality and morbidity (129) low, predictive tools are crucial. In a prospective trial, 54 patients have been examined prior to TIPS and a critical flicker frequency below 39 Hz as well as

previous episodes of HE were found to predict post-TIPS HE (144). In our study, multivariate analysis identified previous episodes of HE, low fibrinogen and high levels of aspartate aminotransferase (AST) as independent predictors of post-TIPS HE. However, it should be considered that clinical diagnosis and grading of hepatic encephalopathy is complex and therefore has limited validity in a retrospective study. Thus, further prospective trials on post-TIPS HE prediction, prevention and management are crucial.

4.2.4 Mortality after TIPS

We observed a 90-day mortality rate of 19% (n=27), increasing to 26% (n=37) one year after TIPS. Due to a 6% proportion of patients lost to follow-up, the actual rate might be higher. However, compared to previous studies with similar design and patient selection criteria which reported 90-day mortality rates between 25-30% the mortality rate in our cohort tended to be lower (109,115,135). In multivariate analysis, high serum urea and INR were significant independent predictors of early mortality. To our knowledge, so far, only one previous study has found a significant association between urea levels and post-TIPS mortality (145). Patients receiving TIPS for ascites tended to have a lower risk for early mortality than those receiving TIPS for bleeding or hepatic hydrothorax, however, this difference was not significant. Previous studies have shown similar survival rates in patients with bleeding and ascites indications (109,115,146). The high 90-day mortality rate in bleeding patients of our cohort might be related to the relatively high number of patients who received either rescue TIPS for active bleeding or early-TIPS within 72 hours after an acute bleeding event which accounted for 51% (n=26) of all patients with bleeding indications. Notably, 15% of deaths within 90 days were due to the primary bleeding event that could not be resolved by rescue-TIPS. The most common cause of mortality within 90 days, however, was acute on chronic hepatic failure (5 cases, 19% of early deaths). Ischemia due to sudden portal venous flow- and pressure reduction as well as a compression of arterial hepatic vessels are presumed to trigger hepatic failure after TIPS, a dreaded and severe complication. The high rate of hepatic-failure related early deaths in our cohort underlines the importance of careful patient selection for TIPS intervention. We utilized our data to develop an early-mortality stratifying tool, integrating urea, INR and bilirubin, which is discussed below.

4.3 Score Development

With MOTS, we developed a simple point-based bed-side tool to estimate mortality risk after TIPS. The score contains urea and INR as both were significant predictors in multivariate analysis. Additionally, bilirubin was integrated as it significantly predicted mortality in univariate analysis of the total cohort as well as in all subgroups and in multivariate analysis within patients with renal insufficiency. Cut-off values of the three parameters integrated in the model were determined utilizing Youden Index. Within the bleeding cohort, 51% of patients received early TIPS. Among these patients, many had received blood products or had an active bleeding at the time of pre-TIPS blood sampling. These factors might have an impact on laboratory parameters such as blood count, INR, urea and creatinine and cause statistical outliers (120–122). Given this circumstance, we decided to utilize the data of patients receiving TIPS for ascites for cut-off definition with the assumption that laboratory parameters are most stable in this group of patients. We aimed to develop a point-based score, even though these models have been subject to criticism. Statisticians frequently underline the higher accuracy of hazard models to directly estimate the incidence of the outcome for any risk factor (147). However, in clinical practice, simple point-based risk scores such as Child-Pugh score, qSOFA-score, Wells score or CHA_2DS_2-VASc often seem to prevail, whereas more complex models frequently fall into oblivion. To achieve simplicity, statistical compromises are inevitable. In case of MOTS, we decided to allocate one point for each of the three parameters when exceeding the cut-off. As the hazard ratio for INR (>1.6: HR 8.5) was approximately twice as high as for the other two parameters (bilirubin >2.2: HR 4.7, urea >71: HR 5.1), a scoring model allocating points according to the hazard ratio would imply 2 points for INR >1.6 and one point for urea >71 mg/dl and bilirubin >2.2 mg/dl, each. However, as the performance of this scoring model was not superior, we chose the simple approach.

4.4 Score Validation

In order to externally validate the mortality predicting models MOTS and LogMOTS, we compared our cohort to 338 patients from the Department of Internal Medicine III, Medical University of Vienna. However, due to missing data (MOTS and LogMOTS available in only 33% of patients) and to the fact that MELD was not predictive for mortality which is in contrast to results from previous studies as well

as to our data, we decided not to use this cohort for score validation. Notably, MOTS and LogMOTS had higher AUROC values than MELD and LogMOTS was the only model significantly predicting 90-day mortality in the total Vienna cohort. The next attempt of validation with 202 patients from the Innsbruck University Hospital of Internal Medicine was more promising as the predictive value of MELD was similar to that in our cohort. When comparing the baseline characteristics of the cohorts, it was noticeable that in the validation cohort more patients received TIPS for ascites indications whereas bleeding indications were less frequent. Furthermore, mortality rates were significantly lower in the validation cohort, however, account being taken on the higher proportion of patients lost to follow-up.

4.4.1 MOTS Score

In clinical practice, decision-making for invasive procedures in patients with severe chronic liver disease is challenging, inter alia due to impaired coagulation and immune function. Additionally, in TIPS procedure, severe intervention-related complications such as hepatic encephalopathy and acute liver failure aggravate the complexity of decision-making. Previous studies emphasized the importance of individual risk assessment and careful patient selection (148,149), however, few well-validated risk stratifying tools exist. In order to identify patients with a high post procedural risk, Child-Pugh score is still broadly used, even though several studies have shown predictive inferiority to MELD, the currently best validated mortality predicting tool for patients undergoing TIPS (109,115,150). Still, MELD may have limited validity in patients with renal insufficiency (116,118,151). With MOTS, we developed a simple and reliable tool to predict post-TIPS mortality with higher accuracy than MELD in patients with eGFR <60. The predictive features of MOTS were reproducible in an external validation cohort.

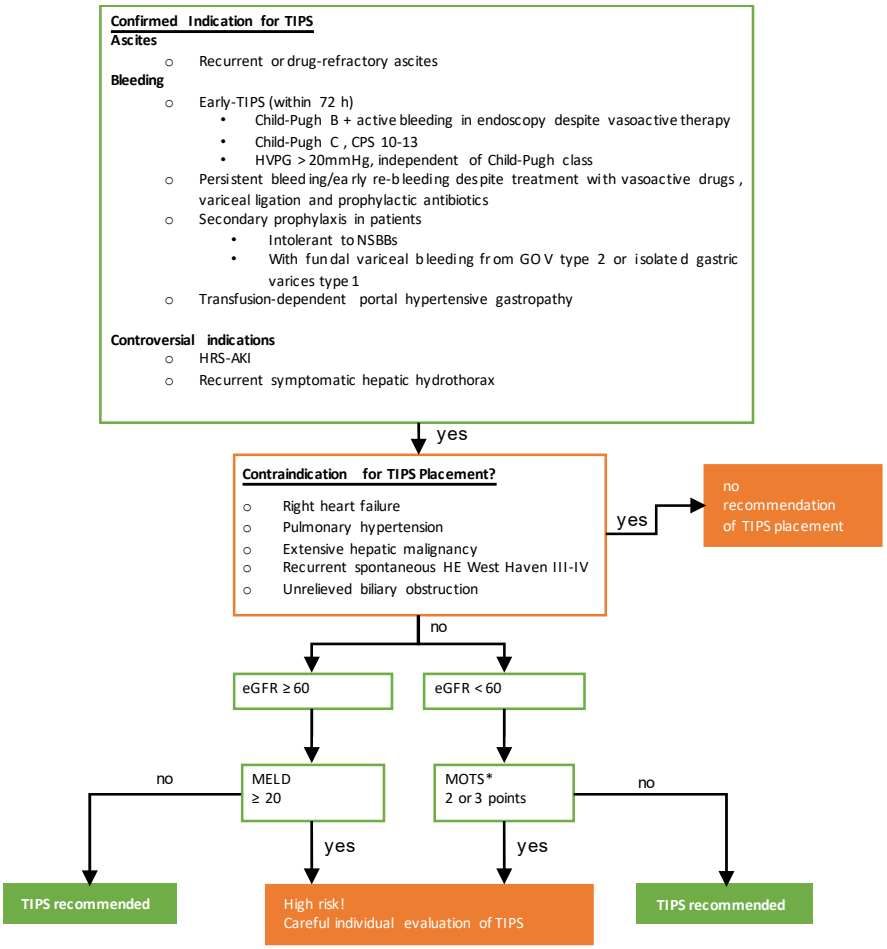
4.4.1.1 Why MOTS predicts mortality

The high prevalence of malnutrition and sarcopenia in cirrhotic patients as well as the fact that renal function improves after TIPS lead to the assumption that creatinine is not an ideal prognostic indicator. Sharing the two components bilirubin and INR with MELD, MOTS integrates serum urea instead of creatinine. Urea was selected, as in our cohort, it showed out as a strong predictive marker, clearly outperforming creatinine in univariate and multivariate analysis within the total

cohort. Naturally, our retrospective clinical study is not appropriate to make any causal pathophysiologic conclusions, thus we can only hypothesize. Unlike in many other centers, urea is included as a basic component of renal function tests in our standard admission laboratory protocol. Prior to our study, urea was already shown to be a prognostic marker in liver disease (145,152,153). Moreover, several studies have shown an association between urea levels and the severity of upper gastrointestinal bleedings (154–157). On the one hand, gastrointestinal breakdown of blood components leads to reabsorption of amino acids which in turn cause a rise of urea, the end product of amino acid metabolism (157). On the other hand, high urea is a marker for renal hypoperfusion and consequentially an indicator for hypovolemia (158). Given that urea was an independent predictor of early mortality in patients receiving TIPS for bleeding indications as well as in patients with ascites indications, the sole reabsorption of blood components cannot be the full explanation. Another possible link between high urea levels and mortality might be hepatic encephalopathy (HE). HE represents a major complication of TIPS procedure, affecting about 20-31% of patients (78). Secondary complications of HE, such as falls and aspiration lead to an increased mortality. In our cohort, 23% of patients developed symptoms of HE of any grade after TIPS intervention. Ammonia (NH_3), a toxic waste product of amino acid depletion is claimed to be a key molecule in the pathophysiology of hepatic encephalopathy (HE). In ammonia metabolism, the liver plays a major role as ammonia detoxification is mainly carried out via hepatic urea cycle. Urea, the end product of the urea-cycle that mainly takes place in periportal hepatocytes, is a non-toxic molecule containing two NH_2 groups and is mainly excreted by the kidneys (159). The presumed pathophysiologic mechanisms of post-TIPS HE include an increased direct shunting of ammonia from the portal drained viscera, the main source of ammonia, (160) via the portosystemic short circuit. In addition, portosystemic shunting has been shown to stimulate the activity of intestinal glutaminase in rat models, which directly leads to an increase of intestinal ammonia production (glutamine + H2O $\rightarrow$ $^{\text{glutaminase}}\rightarrow$ glutamate + NH_3 (161)). Due to in vitro deamination after sample taking, ammonia itself is known as an unstable biomarker that has to be interpreted with caution. In our cohort, ammonia neither predicted HE, nor mortality. Thus, it is possible that urea can be interpreted as a more stable indirect maker of in vivo ammonia levels, even though the injured liver has restricted capacity to convert ammonia into urea.

4.4.1.2 Applications of MOTS

In the total cohorts as well as in patients with renal insufficiency defined as eGFR lower than 60 ml/min/m^2, MOTS predicted 90-day mortality with higher accuracy than MELD. Among patients with eGFR below 60 in the training cohort, 90-day mortality rate was 11% in patients with MOTS 0-1 vs. 60% in patients with MOTS 2-3. In the same group, MELD distinguished the risk groups more imprecise; patients with MELD ≤19 had a 90-day mortality rate of 17% compared to 46% in MELD ≥20. In the validation group, a similar picture emerges, although with larger predictive superiority of MOTS for 1-year mortality than for 90-day mortality. Thus, for this patient group, we are confident, that MOTS will show superiority over other predictive models in future prospective cohorts and thereafter might be implemented as primary predictive tool for clinical decision-making. A possible outline of a future decision-making tool, considering current guidelines (11,18) as well as the results of our study is illustrated in the following decision tree (Figure 18). Starting at the green box that contains evidence-based indications, contraindications for TIPS are surveyed in the orange-bordered box. In the next step, the decision tree distinguishes between patients with eGFR ≥60 and eGFR below 60. For the former, MELD is utilized to define patients with high mortality risk due to severe liver failure with a threshold of 20 points as suggested in previous literature (11,126) whereas in the latter, MOTS carries out this task. The threshold of 2 points was determined graphically from Kaplan-Meier plots which showed distinct deviation of survival between MOTS 0-1 and 2-3. A meta-analysis on four RCTs as well as a recently published retrospective study comparing TIPS with serial large volume paracentesis in patients with ascites specifically analyzed patients with MELD >18/19. Notably, even though post-TIPS mortality was high, the mortality risk was similar or even higher in the paracentesis group (126,162,163). Thus, we suggest not to interpret the thresholds of MELD and MOTS as absolute contraindication for TIPS but as an indicator of high mortality risk in this group of severely ill patients that should lead to careful consideration of risks and benefits. To conclude, this simple decision tree might contribute to improve objective patient selection for TIPS intervention in clinical practice. However, prospective validation with a higher number of patients is crucial.



***MOTS score**

INR>1.6	→ +1
Urea > 71 mg/dl	→ +1
Bili >2.2 mg/dl	→ +1

= 0-3 points

Abbreviations

VH: variceal hemorrhage
CPS: Child-Pugh score
NSBBs: non-selective beta blocker
GOV: gastroesophageal varices
HRS-AKI: hepatorenal syndrome type acute kidney injury

References

- EASL Clinical Practice Guidelines for the management of patients with decompensated cirrhosis, 2018
- Austrian consensus guidelines on the management and treatment of portal hypertension (Billroth III), 2017

Figure 18, TIPS decision tree, considering current guidelines (11,18) as well as the results of our study

4.4.2 LogMOTS

A logarithmic scoring model, LogMOTS, was developed applying the same method the authors used for the development of MELD. LogMOTS integrates the same parameters as MOTS but uses the absolute values multiplied with the regression coefficients instead of allocating points for a defined range of values. The purpose of LogMOTS was to see, whether it outlined the simple MOTS. In our total training cohort, LogMOTS significantly predicted 90-day mortality but had a lower AUROC value than MOTS and MELD. In the training cohort, LogMOTS had the highest predictive value of all three models. In the validation cohort I from Vienna, LogMOTS

was slightly better predictive than MOTS and both outperformed MELD, that was not significantly predictive for 90-day mortality. However, when only including patients with renal insufficiency, MOTS had the highest predictive value in the training cohort as well as the validation cohort, whereas none of the three models was predictive in the Vienna cohort. Thus, we concluded that LogMOTS may have beneficial prognostic value in patients with normal renal function but does not outperform the simple MOTS.

4.5 Limitations

The limitations of our study are primarily rooted in the retrospective design. Adequate assessment of clinically diagnosed syndromes, such as hepatic encephalopathy, can only be performed in prospective trials with defined time points and diagnostic criteria. Thus, we were not able to accurately investigate the ability of MOTS/LogMOTS to predict post-TIPS HE. In addition, it is difficult to obtain valid information about clinical efficacy of TIPS in a retrospective study, as for example re-bleeding events or need for ascites paracentesis during follow up might not be recorded in our medical information system when treated in another province. Therefore, these outcomes should be further studied in prospective studies. Another limitation of our study is the relatively low number of patients. In the training cohort, 144 patients were included, however, score parameters for MELD, MOTS and LogMOTS were only available in 110 patients. The total number of patients in the validation cohort was 202, whereas all scores were available in 187 patients. Especially when taking a closer look at the group of patients with renal insufficiency, score statistics had to be carried out in a very small group of 31 patients in the training cohort and 61 patients in the validation cohort. A prospective TIPS trial in which the predictive features of MOTS should be further investigated is already being planned.

5 Conclusion

To conclude, utilizing the data of 144 TIPS placements at our center, we developed a simple tool that predicts early post-TIPS mortality with higher accuracy than MELD. These beneficial predictive features were most distinct in patients with renal insufficiency. Our results were reproducible in an external validation cohort. The modified TIPS score (MOTS) ranges from 0-3 points: INR >1.6, urea >71 mg/dl and

bilirubin >2.2 mg/dl imply plus one point each. We observed a distinct deviation of survival between MOTS 0-1 and 2-3, reflected by a 90-day mortality rate of 8% in the former group vs. 60% in the latter. In order to implement MOTS in clinical practice, we outlined a decision tree considering current guidelines as well as the results of our study. We are confident that this tool might simplify decision making and contribute to the reduction of early post-TIPS mortality. Its clinical applicability should be further investigated and steadily improved.

6 References

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