



# What constitutes liver failure after transjugular intrahepatic portosystemic shunt creation? A proposed definition and grading system

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## ABSTRACT

**Background and rationale for the study.** There is currently no definition of post-transjugular intrahepatic portosystemic shunt (TIPS) liver failure (PTLF), which constitutes a barrier to standardization of TIPS results reporting and limits the ability to compare liver failure incidence across clinical studies. This descriptive study proposes and preliminarily tests the performance of a PTLF definition and grading system. **Results.** PTLF was defined by  $\geq 3$ -fold bilirubin and/or  $\geq 2$ -fold INR elevation associated with clinical outcomes of prolonged hospitalization/increase in care level (grade 1), TIPS reduction or liver transplantation (grade 2), or death (grade 3) within 30-days of TIPS. PTLF incidence was 20% (grades 1, 2, 3: 10%, 3%, 8%) among 270 TIPS cases, and the scheme identified patients at increased risk for morbidity and mortality with a statistically significant difference in clinical outcomes between PTLF and non-PTLF groups ( $P < 0.0001$ ). **Conclusions.** In conclusion, the PTLF definition and classification scheme put forth distributes patients into unique risk groups. PTLF grading may thus be useful for standardization of TIPS results reporting.

**Key words.** Hepatic insufficiency. Classification. Portosystemic shunting.

## INTRODUCTION

Transjugular intrahepatic portosystemic shunt (TIPS) creation results in diversion of 80-100% of portal venous blood flow into the systemic circulation,<sup>1</sup> and may predispose patients to risk for hepatic insufficiency.<sup>2</sup> Post-TIPS liver decompensation may negatively impact clinical outcome, and although rare, fulminant hepatic failure can precipitate need for invasive management with TIPS reduction or liver transplant, and can even cause death. While rising bilirubin and international normalized ratio (INR) levels following TIPS may be a sign of liver failure, the degree and duration of lab elevation may be variable, and not all such abnormalities are associated with adverse sequela. At present, available Interventional Radiology (IR) clinical practice guidelines do not offer any explicit definition of post-TIPS liver failure (PTLF) to formally diagnose or classify patients with PTLF or identify those patients most likely to have poor

outcomes.<sup>3,4</sup> Such ambiguity presents a barrier to standardization of TIPS results reporting and may undermine the ability to compare liver failure incidence across clinical studies.

Recently, the International Study Group of Liver Surgery (ISGLS) designed and validated a definition and grading scale for post-hepatectomy liver failure (PHLF), diagnosed by an abnormal or increasing serum bilirubin and INR on or after postoperative day 5, and further stratified into subgroups based on clinical outcomes.<sup>5,6</sup> A similar model aimed at defining and classifying PTLF would ideally serve to simply and objectively detect patients with shunt related liver insufficiency associated with consequential adverse clinical outcomes, and would form a foundation for consistent reporting of shunt induced hepatic failure. The current study was thus undertaken with the aim of proposing and preliminarily evaluating the performance of a prototype descriptive PTLF definition and grading system.

## MATERIALS AND METHODS

Institutional review board approval was granted for this study. Informed consent was obtained for TIPS procedures.

### PTLF scheme development

Development of a PTLF system was undertaken with intent for the scheme to be simple, objective, and TIPS specific. A lab-based system with clinical outcome correlates was thus pursued. Lab values employed –namely bilirubin and INR– were selected because both are widely accepted surrogate markers of hepatic function commonly used in clinical practice, and these parameters were solely employed with the intention of most closely paralleling the validated ISGLS definition of post-operative liver failure but in the setting of an IR procedure, and to ensure optimal liver/TIPS specificity of the scheme. Furthermore, limiting the classification scheme to only two lab measures ensured simplicity of the model. Inclusion of other parameters, such as measures of renal or pulmonary function, was deferred given potential to stray from the analogous ISGLS scheme and reduce the liver/TIPS specificity of the system; inclusion of additional parameters would also increase the complexity of the model.

Table 1 summarizes the PTLF definition and grading scheme. Abnormal lab elevation post-TIPS was defined

on the basis of prior study results delineating early progression of liver related lab parameters<sup>7</sup> as a 3-fold or greater increase in bilirubin and/or a 2-fold or greater increase in INR (based on peak laboratory values) compared to baseline within 30-days of TIPS, excluding other identifiable causes for the observed alterations (such as biliary obstruction or suspected biliary vascular fistula). The selected bilirubin and INR levels represented useful threshold values for differentiating surviving *vs.* dying patients within 90-days of TIPS.<sup>7</sup> Clinical outcomes were defined analogously to those demarcated by the ISGLS for PHLF,<sup>5</sup> but modified to enhance TIPS specificity through correlation with liver function and also adjusted to include a mortality endpoint. PTLF was defined as an abnormal lab elevation associated with an escalation of clinical care or liver specific adverse clinical outcome within 30-days of TIPS, a time frame routinely applied to IR adverse event reporting.

### PTLF scheme performance

The performance of the proposed PTLF system –defined by its capability to stratify patients into risk groups associated with worsening morbidity and mortality outcomes– was preliminarily tested using a retrospective cohort of TIPS patients accrued from a database of 300 patients who underwent technically successful TIPS

**Table 1.** PTLF classification scheme.

		Clinical outcome levels and criteria					
		Level 1	Level 2	Level 3	Level 4		
Hepatic function		<ul style="list-style-type: none"> <li>Adequate coagulation</li> <li>No HE or stable HE</li> </ul>	<ul style="list-style-type: none"> <li>Coagulopathy</li> <li>New onset or worsening HE</li> </ul>		<ul style="list-style-type: none"> <li>Death within 30-days</li> </ul>		
Specific treatment		<ul style="list-style-type: none"> <li>No unanticipated alteration to medical management after TIPS</li> <li>Standard, timely hospital discharge without specific therapy required</li> </ul>	<ul style="list-style-type: none"> <li>Prolonged hospital stay</li> <li>Unplanned increase in level of care (need for FFP, readmission to hospital or ICU within 30 days for management of liver complications such as HE)</li> </ul>	<ul style="list-style-type: none"> <li>Invasive management with TIPS reduction or liver transplantation due to liver failure or side effect of hepatic insufficiency within 30-days</li> </ul>	<ul style="list-style-type: none"> <li>Not applicable</li> </ul>		
Lab categories and criteria	Level 1	< 3.0x bilirubin and/or < 2.0 x INR	No PTLF	No PTLF	No PTLF	No PTLF	PTLF presence and grade
	Level 2	≥ 3.0 x bilirubin and/or ≥ 2.0 x INR	No PTLF	PTLF grade 1	PTLF grade 2	PTLF grade 3	

PTLF: post-transjugular intrahepatic portosystemic shunt (TIPS) liver failure. HE: hepatic encephalopathy. FFP: fresh frozen plasma. ICU: Intensive Care Unit. TIPS: transjugular intrahepatic portosystemic shunt.

procedures between November 1998 and June 2014 at a single tertiary care hospital. TIPS were created for multiple clinically established indications,<sup>8</sup> and the technique for TIPS creation has been described in detail.<sup>9</sup>

Inclusion criteria for the analysis included lab and clinical follow-up to 30-days post-TIPS in the medical record. Heterogeneity in post-TIPS lab follow-up times with minor differences in exact lab time points and number of lab checks between patients was allowed. Patients without sufficient follow-up were excluded.

### Lab values and clinical outcomes

Baseline (within 24 h of TIPS creation) and peak (highest value within 30-days post-procedure) bilirubin and INR levels were collected for each case. Patients were assigned into a lab elevation category based on the ratio of peak to baseline bilirubin and INR. Medical record review was performed to collect information on clinical outcomes such as hospital stay and interventions performed, and patients were classified into a defined clinical outcome category. With regard to clinical outcomes, those patients who underwent liver transplant within 30-days for causes unrelated to liver failure or hepatic insufficiency were not categorized as having a TIPS related adverse (level 3) outcome.

### Measured outcomes

The primary outcome measures of this study were lab and clinical risk group stratification as well as PTLF incidence and association with clinical outcomes.

### Statistical analysis

Descriptive statistics were used to characterize patient demographics and TIPS procedure outcomes. The Pearson's  $\chi^2$ , Fisher Exact, or Student's *t*-tests were applied to evaluate risk group distribution and to determine differences in baseline features among different groups. Statistical analyses were implemented using Excel (Microsoft Inc., Redmond WA) and SPSS version 22 (SPSS Inc., Chicago IL), with P-values  $\leq 0.05$  considered as significant.

## RESULTS

### Patient and TIPS procedures

Two hundred sixty eight patients who underwent 270 TIPS (2 patients underwent two TIPS procedure each: a primary TIPS and then a second, parallel TIPS) comprised the study cohort. Baseline patient demographics, liver disease characteristics, and indication for TIPS procedures are summarized in table 2.

**Table 2.** Study population features.<sup>a</sup>

Measure	Value <sup>b</sup>
Age (years)	55 $\pm$ 10
Gender (n = 268)	
Male	167 (62%)
Female	101 (38%)
Ethnicity (n = 268)	
Caucasian	140 (52%)
Hispanic	72 (27%)
African-American	40 (15%)
Other	16 (6%)
Liver disease etiology (n = 268)	
Alcohol or other	191 (71%)
HBV or HCV	77 (29%)
Prior liver transplantation	11 (4%)
Baseline lab values	
Bilirubin (mg/dL)	3.2 $\pm$ 5.2
INR	1.6 $\pm$ 0.9
MELD score	17 $\pm$ 7
Child-Pugh score	9 $\pm$ 2
Class A	17 (6%)
Class B	148 (56%)
Class C	103 (38%)

HBV: hepatitis B virus. HCV: hepatitis C virus. INR: international normalized ratio. MELD: Model for End Stage Liver Disease. <sup>a</sup> Study cohort consists of 268 patients and 270 TIPS procedures. <sup>b</sup> Values reported as number (percent) or mean  $\pm$  standard deviation.

TIPS hemodynamic success was achieved in 260/270 (96%) procedures, with a mean portosystemic pressure gradient (PSG) reduction of 13  $\pm$  6 mmHg. Of the 270 procedures, 220 (82%) underwent covered stent-graft TIPS and 50 (19%) underwent bare metal stent TIPS.

### Lab outcomes

Lab and clinical outcomes are summarized in table 3. Of the 270 cases, 257 (95%) had a bilirubin or INR increase compared to baseline, while 13 (5%) had no bilirubin or INR increase compared to baseline. The mean peak bilirubin and INR levels for the entire cohort showed a statistically significant increase compared to baseline levels, with bilirubin usually doubling (6.6 *vs.* 3.2 mg/dL,  $P < 0.001$ ) and INR increasing 1.5-fold (2.3 *vs.* 1.6,  $P < 0.001$ ). Among 270 TIPS cases, 79 (29%) showed abnormal lab elevation ( $\geq 3$ -fold bilirubin and  $\geq 2$ -fold INR) post-procedure. Peak bilirubin and INR levels were significantly higher in the level 2 lab group compared to the level 1 lab group (bilirubin: 12.8  $\pm$  10.5 *vs.* 4.0  $\pm$  4.4 mg/dL,

**Table 3.** Post-TIPS lab and clinical outcomes.<sup>a</sup>

Category	Outcome level 1	Outcome level 2	Outcome level 3	Outcome level 4
Lab level 1	146 (77%)	22 (11%)	6 (3%)	17 (9%)
Lab level 2	24 (30%)	26 (33%)	8 (10%)	21 (27%)
Total	170 (63%)	48 (18%)	14 (5%)	38 (14%)

TIPS: transjugular intrahepatic portosystemic shunt. <sup>a</sup> For 270 TIPS procedures performed in 268 patients.

$P < 0.001$ ; INR:  $3.4 \pm 2.3$  vs.  $1.8 \pm 0.6$ ,  $P < 0.001$ ) despite similar baseline levels (bilirubin:  $3.8 \pm 5.7$  vs.  $3.0 \pm 4.0$  mg/dL,  $P = 0.214$ ; INR:  $1.6 \pm 0.6$  vs.  $1.6 \pm 1.0$ ,  $P = 0.986$ ).

There were no other differences in baseline characteristics between patients in the different lab level groups, including age ( $54.3 \pm 9.2$  vs.  $55.1 \pm 10.3$  years,  $P = 0.540$ ), gender (M/F: 125:66 vs. 44:35,  $P = 0.920$ ), baseline Model for End-stage Liver disease (MELD) score ( $16 \pm 7$  vs.  $18 \pm 8$ ,  $P = 0.060$ ), TIPS clinical indication (bleed/other = 90:101 vs. 46:33,  $P = 0.127$ ), type of stent used (covered stent-graft/bare metal = 154:37 vs. 66:13,  $P = 0.699$ ), or PSG reduction ( $13 \pm 6$  vs.  $14 \pm 5$  mm Hg,  $P = 0.513$ ).

### Clinical outcomes and PTLF scheme performance

Of the 270 TIPS procedures performed, 170 (63%) fell into the level 1 clinical outcome group, 48 (32%) were level 2, 14 (5%) were level 3, and 38 (14%) were level 4. The rates of TIPS reduction, liver transplantation, and overall mortality at 30-days following TIPS were 6 (2%), 8 (3%), and 38 (14%), respectively. Mortality was attributable to liver insufficiency or a complication thereof in most cases.

The proposed lab and clinical outcome classification system successfully stratified patients into different risk groups with a statistically significant difference in clinical outcome distribution between groups ( $P < 0.0001$ ) (Table 3). Nearly 80% of cases showing level 1 post-procedure lab alterations had an unremarkable post-TIPS clinical course, while 70% of cases with level 2 lab changes following TIPS had a complicated post-TIPS clinical course with higher rates of level 2, 3, and 4 clinical outcomes. The overall incidence of PTLF was 20% ( $n = 55$ ), and the overall frequencies of grades 1, 2, and 3 PTLF were 10% ( $n = 26$ ), 3% ( $n = 8$ ), and 8% ( $n = 21$ ), respectively. The presence of PTLF was associated with a 3-fold increase in level 2, 3, and 4 adverse clinical outcomes.

## DISCUSSION

Although TIPS can acutely decrease portal perfusion and precipitate hepatic insufficiency, post-TIPS liver failure is not well enumerated in the medical literature, and there is currently no explicit definition or reporting meas-

ure offered for this significant clinical outcome in IR standards documents.<sup>3,4</sup> This paper attempts to address this unmet need through the proposal of a prototype classification scheme for PTLF based on peak bilirubin and INR values correlated with 30-day clinical outcomes. In applying the suggested system to 270 TIPS cases, patients were distributed into distinct post-procedure outcome groups bearing markedly divergent 30-day adverse event incidence, confirming the scheme's discriminative capacity for stratification of patients according to morbidity and mortality risk. Specifically, patients with abnormal post-TIPS lab elevation had a 3-fold higher frequency of clinical care escalation, TIPS reduction or liver transplantation, and death in our cohort. In unambiguously defining PTLF as an abnormal lab elevation associated with an adverse 30-day outcome, the proposed system displays attributes of effective classification schemes, in that it is simple, objective, unambiguous, exhaustive, and mutually exclusive. It may thus prove useful for standardized reporting of TIPS adverse events, allowing for improved comparison across TIPS clinical studies.

The proposed scheme utilized a tiered system of lab elevation to help define patients with PTLF. An abnormal post-TIPS lab course was felt to be an essential component of the PTLF definition given that the clinical hallmark of liver failure is hepatocellular dysfunction resulting in impaired bilirubin metabolism and excretion as well as reduced clotting factor synthesis manifested by hyperbilirubinemia and coagulopathy; presence of these lab abnormalities supports the basis of adverse events in hepatocellular injury. The threshold levels for abnormal bilirubin and INR elevation were extrapolated from a prior study delineating "expected" and "abnormal" lab parameter alterations post-TIPS, in which the 3-fold bilirubin increase and 2-fold INR increase heralded adverse clinical outcomes, while hyper acute (within 7 days) 2-fold increase in bilirubin was more of an expected finding.<sup>7</sup> In that study, bilirubin rose to at least triple baseline value in approximately 50% of patients expiring vs. only 20% of patients surviving to 90-days.<sup>7</sup> A possible short coming of the proposed PTLF system is the potential inability of patients with markedly elevated baseline bilirubin to achieve PTLF status due to a physiologic "ceiling" for bilirubin elevation, precluding capability to triple initial

levels. However, not only are such patients probably better classified as having preexisting liver failure rather than TIPS induced liver failure, such cases typically constitute a minority of TIPS procedures because most patients with marked baseline bilirubin elevation are not TIPS candidates (outside of emergent scenarios) due to high risk. Only 14 (5%) TIPS patients in the current series had a baseline bilirubin  $\geq 10$  mg/dL. In addition, the current system attempted to account for this idiosyncrasy by utilizing INR elevation as a secondary marker of lab abnormality in order to allow PTLF classification in cases not meeting bilirubin elevation criteria.

The current report has several limitations. First, the study is a single-institution, retrospective investigation with heterogeneous lab follow-up and clinical outcome assignment dependent on medical record documentation. Second, PTLF is an admittedly difficult entity to define due to multifactorial nature, with basis in patient MELD score (including creatinine), shunt diameter and PSG reduction, and comorbid conditions (such as pulmonary function),<sup>3</sup> and all of these parameters were not accounted for in the simple definition put forth. Third, the proposed system does not have perfect sensitivity for detection of adverse events, as unfavorable outcomes do transpire in the absence of abnormal lab elevation. However, this occurrence is an exception rather than the rule, as the incidence of clinical care escalation or adverse outcome approximates 70% in patients with abnormal lab elevation *vs.* around 20% in patients with an “expected” lab course post-TIPS. Fourth, the grading scheme proposed considers the highest lab levels attained and does not take into account their trend. While PTLF may be better assessed using temporal evolution of laboratory findings, a single point assessment was used in order to maintain simplicity of the grading criteria. Fifth, we utilized all-cause 30-day mortality in assessing adverse outcomes, although mortality was attributable to liver insufficiency or a complication thereof in most cases. Regardless, overall mortality may likely still be a valid end point for the proposed classification system because it only results in the designation of PTLF when accompanied by concurrent lab abnormality. Sixth hepatic encephalopathy—which was used as an adverse clinical outcome metric—may not always be due to liver insufficiency, but can also be related to portosystemic over shunting of blood flow; the number of individuals with grade 2 PTLF may thus be somewhat exaggerated. Lastly, the current study was inherently descriptive in nature, and the prognostic value of the proposed classification scheme cannot be established without further investigation in larger scale studies.

In summary, PTLF is poorly defined in the current literature. The PTLF definition and classification scheme put forth in the present study capably distributes patients into unique risk groups and forms a foundation for stand-

ardized results reporting across TIPS clinical studies. Further investigations with larger sample sizes are necessary to confirm the findings herein, test the PTLF definition and grading scheme in different patient populations, and further refine the PTLF scheme put forth.

## ABBREVIATIONS

- **INR:** international normalized ratio.
- **IR:** Interventional Radiology.
- **ISGLS:** International Study Group of Liver Surgery.
- **MELD:** Model for End-stage Liver disease.
- **PHLF:** post-hepatectomy liver failure.
- **PSG:** portosystemic pressure gradient.
- **PTLF:** post-TIPS liver failure.
- **TIPS:** transjugular intrahepatic portosystemic shunt.

## FINANCIAL SUPPORT, DISCLOSURES, AND CONFLICTS OF INTEREST

None.

## REFERENCES

1. Walser EM, Harris VM, Harman JT, Park HM, Siddiqui AR. Quantification of intrahepatic portosystemic shunting after placement of a transjugular intrahepatic portosystemic shunt. *J Vasc Interv Radiol* 1996; 7: 263-7.
2. Zipprich A. Hemodynamics in the isolated cirrhotic liver. *J Clin Gastroenterol* 2007; 41(Suppl. 3): S254-S258.
3. Haskal ZJ, Martin L, Cardella JF, Cole PE, Drooz A, Grassi CJ, McCowan TC, et al. Quality improvement guidelines for transjugular intrahepatic portosystemic shunts. *J Vasc Interv Radiol* 2003; 14: S265-S270.
4. Krajina A, Hulek P, Fejfar T, Valek V. Quality improvement guidelines for Transjugular Intrahepatic Portosystemic Shunt (TIPS). *Cardiovasc Intervent Radiol* 2012; 35: 1295-300.
5. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R, Koch M, et al. Post-hepatectomy liver failure: A definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery* 2011; 149: 713-24.
6. Reissfelder C, Rahbari NN, Koch M, Kofler B, Sutudja N, Elbers H, Buchler MW, et al. Postoperative course and clinical significance of biochemical blood tests following hepatic resection. *Br J Surg* 2011; 98: 836-44.
7. Casadaban LC, Parvinian A, Couture PM, Minocha J, Knuttinen MG, Bui JT, Gaba RC. Characterization of liver function parameter alterations after transjugular intrahepatic portosystemic shunt creation and association with early mortality. *AJR* 2014; 203: 1363-70.
8. Boyer TD, Haskal ZJ, American Association for the Study of Liver D. The Role of Transjugular Intrahepatic Portosystemic Shunt (TIPS) in the Management of Portal Hypertension: update 2009. *Hepatology* 2010; 51: 306.
9. Gaba RC, Omene BO, Podczerwinski ES, Knuttinen MG, Cotler SJ, Kallwitz ER, Berkes JL, et al. TIPS for treatment of variceal hemorrhage: clinical outcomes in 128 patients at a single institution over a 12-year period. *J Vasc Interv Radiol* 2012; 23: 227-35.

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