

Reviewer #1:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I would like to thank the authors for their efforts in collecting evidence about outcomes of TIPS in advanced liver cirrhosis patients. I do agree with them about the limitations of retrospective studies but mortality even in the next 6 months of the procedure could be reached from the databases to potentiate the conclusions.

We thank the reviewer for this comment.

This issue was also raised by reviewer 4. We have to deal with the limitations of retrospective data acquisition and analysis. Complete data on survival beyond the inpatient stay were only available for patients in the TIPS group. Therefore, a comparison of survival data over *e.g.* 6 months was not possible because of the incomplete data of the No TIPS group.

We have modified the discussion accordingly – paragraph 5, sentence 2 in the discussion.

Reviewer #2:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Minor revision

Specific Comments to Authors: I congratulate the authors on their study. It is relevant and of high quality. I believe it should be accepted after some minor modifications, as follows:

- the title does not reflect the main subject. Here are some suggestions. “Transjugular intrahepatic portosystemic shunt versus conservative treatment for refractory ascites: a propensity score matching comparison”; “Does Transjugular intrahepatic portosystemic shunt increase ACLF risk? A propensity score matching comparison versus conservative treatment for refractory ascites.

We have changed the title accordingly.

- non-significant tendencies are better not mentioned on the abstract results (“The prognosis of ACLF tended to be better in the TIPS group”)

We have removed this sentence from the abstract.

- introduction, first paragraph, line 4: More recent studies had (reached, shown) more promising results...

Corrected.

- introduction, second paragraph, line 2: which kind of bleeding are you referring to? it should be explained

We thank the reviewer for this comment. We are referring to intraabdominal bleedings. In our experience, intra-abdominal bleeding after TIPS placement is a rare but relevant problem. We have changed “bleedings” to “bleeding complications due to the placement procedure“.

Reviewer #3:

Scientific Quality: Grade B (Very good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I consider that this paper included some interesting clinical points. The manuscript is well constructed and written. However, I have some concerns:

1) They described 'Cases of patients who had liver cirrhosis and significant ascites, but did not undergo TIPS placement were selected for comparison (No TIPS group)'. Kindly mention significant ascites is not equivalent to refractory ascites. In addition, they should add how they diagnosed the refractory ascites.

We thank the reviewer for this very important comment. This issue was also raised by reviewer 4.

The strict diagnosis of refractory ascites includes recurrent ascites despite low sodium diet and maximal doses of diuretics. This is rarely the case, as it was in our patients; more often, the diuretic dose is limited by impaired renal function and mobilization of ascites is unsuccessful because a sufficiently high dose cannot be given (intractable ascites). We included the following patients in the TIPS and No-TIPS group:

Patients in the TIPS group: we included patients whose TIPS indication was recurrent tense ascites according to patient records. Patient records were double checked to ensure that all cases had a history of recurrent paracentesis.

Patients in the No-TIPS group: patients with liver cirrhosis and tense ascites that required paracentesis during hospital stay.

Taken together, recurrent tense ascites describes the situation of our patients better than refractory/intractable/significant ascites. We have adjusted the entire text and figure 1 accordingly.

2) Totally 214 patients received TIPS in this retrospectively observational study. Kindly mention how they underwent TIPS procedures, especially the type and size of stents, which were found to be the most commonly reported risk factors of postoperative complications.

From 2007 to 2017, both covered and uncovered stents were used for TIPS placements at our institution. Uncovered stents were placed in 42% of cases and covered stents were placed in 58% of cases. The stents were mostly dilated to 7-8 mm. Smaller or larger diameters were rarely chosen (6 mm in 2 patients, 9 or 10 mm in 15 patients). No effect of stent type or stent diameter on any of our endpoints was found in either univariate or multivariate analyses (data not shown).

Reviewer #4:

Scientific Quality: Grade D (Fair)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: this was an interesting paper on TIPSS placement in high risk patients. The topic is of interest, although not novel. The manuscript has been designed as a single center, retrospective, observational study. The Authors compared patients who underwent TIPSS for ascites with a matched cohort of patients who did not. My comments

- there is a debate on the "degree" (or severity) of ascites that should be considered for TIPSS. what was the definition of refractory ascites used before considering TIPSS placement in patients with ascites? Did the Authors strictly follow this definition?

Patients in the control group were defined as having "significant ascites". What do these terms mean? Notably, in the abstract section, they used different terms (i.e., recurrent tense ascites)

We thank the reviewer for this very important comment. This issue was also raised by reviewer 3. Considering the available data and the selection criteria of the TIPS and the No-TIPS group "recurrent tense ascites" is the appropriate term.

We have adjusted the entire text and figure 1 accordingly.

- Table 1: TIPSS group: there are several uncommon values, for instance serum creatinine going up to 700 $\mu\text{mol/l}$, or haemoglobin of 2 g/dL, or MELD up to 40. This point should be discussed. Was ascites the only (and main) indication for TIPSS placement in such patients?

The table shows the median and extreme values in the respective group. The abnormal extreme values were double-checked and confirmed. The extreme values are comparable in both groups after propensity score matching (Table 2). All patients in the TIPS group in this study received TIPS for recurrent tense ascites. The laboratory findings mentioned are laboratory findings at hospital admission. In patients with very high MELD scores on hospital admission, TIPS placement was performed only after stabilization and after MELD had improved.

We have added this information to Discussion, paragraph 7.

- what was the cause of ACLF? what organ(s) was/were involved?

The majority of patients in both groups had ACLF 1, which was due to renal failure. This was to be expected in patients with recurrent tense ascites. Organ systems affected in patients with ACLF >1

were brain (HE 3-4) and/or liver function based on bilirubin. ACLF > 1 was mostly due to acute infections.

We have added this information to the end of Results – Incidence of ACLF and in-hospital mortality – paragraph 1 and to Discussion paragraph 2.

- the fact that many patients already had ACLF before TIPSS placement represents a pitfall of this study in my opinion.

In the No-TIPS-group were patients with more advanced liver cirrhosis and therefore a higher prevalence of ACLF (Table 1). For this reason, a propensity score matching was carried out. After matching, the prevalence and distribution of ACLFs at the time of hospital admission was identical in both groups (Table 2). A strong distortion of the results is therefore not to be expected. Of course, the causal attribution of ACLFs to TIPS is difficult in this situation. However, this is a general problem of retrospective studies.

We have added a paragraph (paragraph 6) on this topic to Discussion.

Who is the patient that requires TIPSS for refractory ascites during an ACLF? - The Authors said that "TIPS is more capable to overcome an ACLF than causing it". This is a true sentence for instance in patients with acute variceal bleeding causing haemodynamic failure. I do not understand the role of TIPS in patients with ACLF determined by bacterial infection, or when alcohol is the causative factor.

Our study did not aim to treat ACLF with TIPS but retrospectively analyzed the relationship between TIPS and ACLF. While doing so, we found that many ACLFs improved after TIPS placement. In fact, a TIPS is unlikely to improve an ACLF caused by a bacterial infection or excessive alcohol consumption. However, these were not the typical triggers of an ACLF in our patients. We have studied patients with recurrent tense ascites. The most common cause of ACLF within this group was kidney failure. It is plausible that a TIPS can improve such an ACLF, *e.g.* since dose of diuretics can be lowered or diuretics can be discontinued altogether.

We have added this aspect to the end of paragraph 3 of Discussion.

- I agree with the Authors when they said that the effectiveness of TIPSS should be measured beyond the hospitalization therefore I think that the endpoint was not so appropriate.

We wanted to investigate the question of whether a patient with refractory ascites has a better chance of surviving the inpatient stay with or without TIPS. Furthermore, we were interested in the risk of serious complications (ACLF) during inpatient stay with or without TIPS. Both questions are clinically relevant. Therefore, we have chosen “highest ACLF during inpatient stay” and “death during inpatient stay” as endpoints. Since this is a retrospective study, many patients in the No TIPS group lack data on the further course after hospital discharge. For the selected endpoints, however, complete data are available in both groups.

We have added a discussion of this topic to paragraph 5, sentence 2 in Discussion]

Reviewer #5:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: Cirrhotic patients with refractory ascites and impaired liver function were generally excluded from TIPS placement due to the fear of increased post-TIPS complication, including HE and ACLF. The current study found that elevated incidence of post-TIPS ACLF did not result in a higher in-hospital mortality. I like the manuscript study in its current form. It is well written and easy to follow. It would be better if the authors analyse and discuss why the positive effect of TIPS on mortality was not found, unlike the previous several RCTs.

Our TIPS patients had a comparatively poor liver function (MELD median 14, mean 15.2), while most of the randomized controlled trials (RCT) have been performed in patients with good liver function. This applies in particular to the RCTs that have shown a survival benefit. In these studies the mean MELD was 9.6 to 12.1). We only evaluated the short-term outcome during hospital stay. Some studies have observed an increased mortality after TIPS placement during the first few weeks. Therefore, positive effects of TIPS on survival might be underestimated.

We have added a sentence on this topic at the end of paragraph 8 of Discussion.

Round 2

Dear Yu-Lu Chen,

unfortunately we were unable to reply to your request within the F6Publishing System. Therefore, we are answering by mail.

The reviewer asks why we conclude from our data that TIPS may also be a viable option in patients with high Child scores, although we found an increased incidence of ACLF in patients with Child scores ≥ 11 points.

Indeed, our data show a significantly increased incidence of ACLF associated with TIPS placement in patients with high Child scores compared to conservatively treated patients. In contrast, hospital mortality was not increased in these patients compared to conservatively treated patients (see figure 2, panel B).

In patients with advanced cirrhosis, recurrent ascites is often the dominant symptom. It is known that TIPS is an effective therapy for ascites. Since adequate diuretic therapy is often not possible in these patients due to impaired renal function, the only alternative is repeated paracentesis. This is considered very burdensome by many patients.

According to our data, TIPS does not increase mortality. Therefore, the increased ACLF incidence is manageable, and a high Child score alone should not be considered as an absolute contraindication to TIPS placement.

We agree with the reviewer that the first two sentences of our conclusion better fit in the discussion section.

The following changes could be made to the current version of the manuscript to address the reviewer's concerns. To illustrate these changes we have modified the manuscript accordingly; it is attached to this mail.

- The current conclusion was moved back to the discussion section as suggested by the reviewer. The last sentence was modified to address the reviewer's concerns.
- New conclusion: "TIPS placement for recurrent tense ascites is associated with an increased incidence of ACLF. This effect occurs only in patients with severely impaired liver function (Child score ≥ 11) and does not lead to a higher in-hospital mortality compared with conservative treatment."

We hope that the manuscript is now acceptable for publication. Because we could not respond via the submission system we are kindly asking to acknowledge this mail