



IMPACT OF STENT TYPE ON OUTCOME OF CIRRHOTIC PATIENTS TREATED WITH TRANSJUGULAR INTROHEPATIC PORTOSYSTEMIC SHUNT

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IMPACT OF STENT TYPE ON OUTCOME OF CIRRHOTIC PATIENTS TREATED
WITH TRANSJUGULAR INTROHEPATIC PORTOSYSTEMIC SHUNT

by

Jiangtao Liu

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I have reviewed this thesis. It represents work done by the author under my
guidance/supervision.

Primary Mentor: Dr. Wehrenberg-Klee, Eric Paul

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Overview of the thesis papers

Hepatic encephalopathy (HE) following transjugular intrahepatic portosystemic shunt (TIPS) placement remains a leading adverse event. Controversy remains regarding diameter selection of 8-mm vs. 10-mm stent. We aim to provide meta-analysis-based evidence regarding the safety and efficacy of 8-mm vs. 10-mm stents during TIPS placement. Five studies with a total sample of 489 cirrhotic patients were recruited in the present study. The pooled hazard ratio (HR) of post-TIPS HE was 32% lower in patients in the 8-mm stent group than in the 10-mm stent group. The combined HR of post-TIPS rebleeding/need for paracentesis was 76% higher in patients in the 8-mm stent group than in the 10-mm stent group. There was no statistically significant difference in the overall survival between the 8-mm and 10-mm stent groups. The combined risk of HE in the variceal bleeding subgroup was 48% lower with 8-mm stent compared with 10-mm stent. The combined risk of both rebleeding/paracentesis and survival was not statistically significant between 8-mm and 10-mm stent use in subgroup analysis.

While multiple advantages of Viatorr stents relative to bare-metal stents (BMS) have been identified, the mortality benefit of covered stents has not been clearly demonstrated. We performed a retrospective cohort study of patients receiving TIPS between 1995 and 2018. A total of 427 patients were eligible for the study with 312 in Viatorr groups and 115 in BMS group. Multivariate logistic regression analysis revealed that the covered stent placement was associated with significantly reduced odds of mortality by 58% at 1-year post TIPS. With subgroup analysis, use of covered stent was associated with decreased odds of mortality by 88% in patients with refractory ascites in the multivariate model.

Transjugular Intrahepatic Portosystemic Shunt Placement for Portal Hypertension:

Meta-analysis of Safety and Efficacy of 8 mm vs. 10 mm Stents

Abstract

Introduction: Hepatic encephalopathy (HE) following transjugular intrahepatic portosystemic shunt (TIPS) placement remains a leading adverse event. Controversy remains regarding optimal stent diameter given that smaller stents may decrease the amount of shunted blood and decrease the risk of HE, but stent patency and/or clinical adequacy of portal decompression may also be affected. We aim to provide meta-analysis-based evidence regarding the safety and efficacy of 8-mm vs. 10-mm stents during TIPS placement.

Methods: PubMed, EMBASE, Cochrane Library and Web of Science were searched for studies comparing 8-mm and 10-mm stents during TIPS placement for portal hypertension decompression in cirrhotic patients. Randomized controlled trials and cohort studies were prioritized for inclusion. Overall evaluation of quality and bias for each study was performed. The outcomes assessed were prevalence of HE, rebleeding or failure to control refractory ascites, and overall survival. Subgroup analysis based on TIPS indication was conducted.

Results: Five studies with a total number of 489 cirrhotic patients were identified. The pooled hazard ratio (HR) of post-TIPS HE was significantly lower in patients in the 8-mm stent group than in the 10-mm stent group (HR:0.68, 95% CI:0.51~0.92, p value<0.0001). The combined HR of post-TIPS rebleeding/need for paracentesis was significantly higher in patients in the 8-mm stent group than in the 10-mm stent group (HR:1.76, 95% CI:1.22~2.55, p value<0.0001). There

was no statistically significant difference in the overall survival between the 8-mm and 10-mm stent groups. The combined risk of HE in the variceal bleeding subgroup was statistically lower (HR:0.52, CI: 0.34-0.80) with an 8-mm stent compared with a 10-mm stent. The combined risk of both rebleeding/paracentesis and survival was not statistically significant between 8-mm and 10-mm stent use in subgroup analysis.

Conclusion: 8-mm stents during TIPS placement are associated with a significant lower risk of HE compared to 10-mm stents (32% decreased risk), but also a 76% increased risk of rebleeding/paracentesis. Meta-analysis results suggest that there is not one superior stent choice for all clinical scenarios, and that the TIPS indication of variceal bleeding or refractory ascites might have different appropriate selection of shunt diameter.

Key words: Transjugular Intrahepatic Portosystemic Shunt; Portal hypertension; Stent; Diameter

1. Introduction

Transjugular intrahepatic portosystemic shunt (TIPS) placement for portal pressure decompression is a well-established treatment for complications of portal hypertension in cirrhotic patients[1-4]. New or worsened hepatic encephalopathy (HE) is one of the main adverse events after TIPS, with no pharmacological treatment able to completely prevent its incidence[5]. TIPS placement affects hepatic hemodynamics by reducing portal blood inflow to hepatocytes, decreasing hepatic portal perfusion and increasing ischemic injury with decreased hepatic function[6]. The amount of portal blood shunting also prevents hepatic detoxication of the blood, and is closely related to post-TIPS HE[7]. The choice of stent diameter, and therefore the shunt size, balances the demands of portal decompression to prevent portal hypertension complications and shunt-related encephalopathy. Controversary remains regarding the optimal stent diameter owing to the theory that smaller stents may decrease the amount of shunting blood and decrease the risk of HE, but stent patency and/or clinical adequacy of portal decompression is also affected[8].

In the past decade, 10-mm-diameter stents have been used most frequently during TIPS procedures, with reported HE rates of nearly 40% [2, 9]. Under dilation of 10-mm stents at the time of TIPS creation, to 8-mm for example, is a utilized technique to decrease HE incidence, but this technique has not proven to be long-lasting[10-12]. Riggio et al was the first to compare TIPS placement with 8-mm and 10-mm stents, showing that 8-mm stents lead to significantly less efficient control of portal hypertension with recurrence or persistence of portal hypertension complications in the majority of patients[13]. Another study comparing small diameter (majority of 8-mm) TIPS with standard treatment for prevention of variceal rebleeding revealed a significant lower incidence of rebleeding in the 8-mm group, with just a slightly higher

prevalence of HE[14]. Other prospective and retrospective studies comparing 8-mm to 10-mm stents in relation to HE, rebleeding, ascites and survival have shown mixed results in favor of 8-mm or 10-mm stents[15, 16]. Given this controversy, this study aims to provide meta-analysis-based evidence regarding the efficacy of 8-mm vs. 10-mm stents during TIPS placement on HE incidence, control of portal hypertension, and overall survival (OS).

2. Materials and Methods

2.1 Search method and selection of studies

PubMed, EMBASE, Cochrane Library and Web of Science were searched for eligible studies from 1988 (the initial year in which metal stent TIPS procedures were performed) to January 2020. Web of Science search engine was also used for peer reviewed publications and conference papers or abstracts to ensure full coverage of information to reduce selection bias. The following key words were included: “transjugular intrahepatic portosystemic shunt”, “TIPS”, “diameter”, “shunt”, “8-mm” and “10-mm”. The cited references of original studies and reviews were also searched. The following criteria were employed for study selection: (1) study with full-text in English; (2) study design: randomized controlled trial (RCT) or retrospective observational study; (3) study participants: cirrhotic patients receiving TIPS for variceal bleeding and/or refractory ascites; (4) study interventions: TIPS with different stent diameters including 8-mm and 10-mm; and (5) at least one of the following outcomes reported: overall survival (OS), number or prevalence of post-TIPS HE; number or rate of post-TIPS rebleeding; number or rate of post-TIPS failure to control ascites or paracentesis; number or rate of post-TIPS stent dysfunction. Exclusion criteria included: (1) non-cirrhotic portal hypertension; (2) Budd-Chiari syndrome or hepatic veno-occlusive diseases and (3) case-series studies. This study has been

registered at the international prospective register of systematic reviews (registration number: CRD42020168695).

2.2 Outcome definitions

We acknowledge that end point and adverse event reporting metrics might not be uniform across studies, and often include rates or time-to-event results. Given this, the outcomes utilized in this meta-analysis were based on the results of data extraction. The study outcome includes the prevalence of HE or time to HE, the prevalence of rebleeding or need for paracentesis, time to rebleeding or need for paracentesis, mortality, or OS. The prevalence of HE was defined as the number of patients who presented with encephalopathy symptoms during follow-up after TIPS. Rebleeding rate was defined as the number of cases who presented with variceal bleeding during follow-up after TIPS. The need for paracentesis was defined as the number of patients with refractory ascites who still required paracentesis during follow-up after TIPS. The rebleeding prevalence and need for paracentesis were combined to create the category of “rebleeding/paracentesis”. OS was defined as the length of time that the patients were still alive after the date of TIPS or to the endpoint of study. Mortality was defined as the number of patients who died from any reason during follow-up after TIPS.

2.3 Risk of bias assessment

Two investigators (JL and EWK) independently assigned an overall evaluation of quality and bias for each study with the “Revised cochrane risk of bias tool for randomized trials” (RoB 2.0)[17] or the “risk of bias in non-randomized studies of interventions” (ROBINS-I) for observational cohort studies[18]. The RoB 2.0 tool evaluated the randomization process,

deviation from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results with the overall risk-of-bias judgment as “low risk of bias”, “some concerns”, and “high risk of bias”. The overall evaluation with ROBINS-I criteria was “Low”, “Moderate”, “Serious”, “Critical” and “No information” based on the seven domains evaluated. Any differences in evaluation were resolved with a consensus between the two investigators.

2.4 Data extraction

The trial eligibility determination and extraction of data were performed independently by the two investigators. Agreements were made through consensus discussion. Data were extracted with study-features and clinical information levels, respectively. Study-feature information included: study year, study design, sample size and allocation, stent type, mean follow-up time and bias risk score. Clinical information included: treatment group, age, gender, etiology of cirrhosis, history of HE, ascites, Child-Pugh score or class, portosystemic pressure gradient (PSG) before and after TIPS and indication of RA placement. The time-event information in each study was pooled if accessible. The hazard ratio (HR) and its standard error (SE) were pooled directly if they were reported in the publication. Another method for calculation was to use the data available in the report and back-calculate the values with the Mantel-Haenszel method[19]. For outcomes with binary variables, the numbers of observed events were extracted directly or based on the information reported or, if necessary, by contacting the authors for possible data. The risk ratio (RR) was used to evaluate the pooled effect of binary outcomes.

2.5 Statistical analysis

Heterogeneity was assessed by the I^2 index. Data was pooled with a fixed-effect model if $I^2 \leq 50\%$, indicating insignificant heterogeneity. Otherwise, the results of both the fixed-effect and random effect models were reported. The visualization of publication bias of the included studies was evaluated using the funnel plot if the sample size was over 10. The Z-test was performed to evaluate the significance of the combined HR or RR estimate. Subgroup analysis was conducted based on TIPS indication (variceal bleeding or refractory ascites). A p value of 0.05 was set as the threshold for statistical significance. All analyses were performed using free software R (R Foundation for Statistical Computing; Vienna, Austria) with a “meta” and “dmetar” package.

3. Results

Utilizing the described search strategy, a total of 113 publications were identified. 108 of the identified papers were abandoned with the preset inclusion and exclusion criteria. Five studies including 2 RCTs[13, 16] and 3 retrospective cohort study[15, 20, 21] from 2010 to 2019 were included into the meta-analysis. Figure 1 provides the flow diagram of publication retrieval, screening, and resulting study selection. Data from Trebicka et al[20] was retrieved based on a multicenter RCT and propensity score matching for known confounders, so this study was categorized as an observational feature[20]. The total number of patients reported in the five studies was 489.

3.1 Study characteristics

The five included studies are summarized in Table 1. The two arms for treatment comparisons in all five studies were defined as TIPS placement with 8-mm vs.10-mm stents. All

studies used self-expandable PTFE-covered stents (Viatorr; Gore, Newark DE or Fluency; Becton Dickinson, East Rutherford, NJ). The indications for TIPS was variceal bleeding in two studies[16, 21] refractory ascites (RA) in one study[15], and both variceal bleeding and RA in two studies[13, 20]. Rebleeding was reported as the probability of remaining free of recurrence and/or persistence of complications due to portal hypertension in one study[13] and as the cumulative incidence of variceal rebleeding in two studies[16, 21]. One study reported the cumulative probability of remaining free from paracentesis for RA[15]. Event-time analysis of HE was reported in four studies[13, 15, 16, 21]. Survival analysis with log-rank test was reported in three studies[13, 16, 21]. Information on OS was accessed by contacting the authors of Miraglia et al[15]. The HR and the corresponding standard error were calculated based on information retrieved in context of Trebicka et al[20], where two arms of data were retrieved with the subgroup of 8-mm vs. 10-mm stents (fully-dilated plus under-dilated). In all the 3 studies with observational features[15, 20, 21], propensity score matching (PSM) was applied to reduce the bias due to confounding variables that could be found in non-randomized trials. The two RCTs[13, 16] were evaluated with the RoB 2.0 tool and the three observational cohort studies[15, 20, 21] were evaluated with the ROBINS-I criteria. The risk of bias assessment information is summarized in Table 1.

3.2 Patient characteristics

Table 2 summarizes the characteristics of the patients in the five studies. Most of the baseline variables were balanced between the 8-mm and 10-mm groups. Patient age in one study[16] had a slight statistical difference between the two groups (49.4 in 8-mm vs. 52.0 years in 10-mm, $p < 0.001$). In Trebicka et al[20], presence of ascites (no/yes; 22/19 in 8-mm vs. 6/35

in 10-mm, $p < 0.01$), Child-Pugh class (A/B/C; 19/18/4 in 8-mm vs. 3/27/11 in 10-mm, $p < 0.01$) and indication for TIPS (bleeding/RA; 29/12 in 8-mm vs. 6/35 in 10-mm, $p < 0.01$) had a statistical difference.

3.3 Technical results

The technical success rate was reported as 100% in all the studies except for Riggio et al[13], in which an incorrect placement of a stent was subsequently corrected with a second stent. Of all the studies, significant reduction of portal-systemic gradient (PSG) was observed in both the 8-mm and 10-mm stent groups. In Riggio et al[13], the post TIPS PSG of the 10-mm group was lower than that of the 8-mm group (6.5 ± 2.7 vs. 8.9 ± 2.7 mmHg, p value: 0.0007). Percentages of HE, rebleeding/paracentesis and mortality were calculated based on the data available in the corresponding studies. The prevalence of post-TIPS HE was between 35.9% and 48.9%, with prevalence of 25%-50% in the 8-mm group, and 46.9%-50% in the 10-mm group. The prevalence of rebleeding/paracentesis ranged from 18.1% to 33.3%, with prevalence of 20.3%-54.5% in the 8-mm group, and 8.7%-15.5% in the 10-mm group. The mortality rate during follow-up was from 17.8% to 40.2%, with a rate of 20.3%-22.7% in the 8-mm group, and 13.0%-27% in the 10-mm group.

3.4 Meta-analysis

According to the heterogeneity analysis, the I^2 of both HE and rebleeding/paracentesis was less than 50%. The HR of time to HE or rebleeding/paracentesis amongst the studies was combined with the fixed-effect model. The pooled HR of post TIPS HE was significantly lower in patients in the 8-mm stent group than the 10-mm stent group (HR:0.68, 95% CI:0.51~0.92, p

value<0.0001) (Figure 2). The 8-mm stent group had a 32% decreased risk in HE compared to the 10-mm stent group. Compared to the 10-mm stent group, the HR of HE in the 8-mm stent group for four of the studies was between 0.51 and 1.34. Two studies had a statistically significant difference[16, 21], and the other two studies[13, 15] did not show significant differences.

The pooled HR of post-TIPS rebleeding/paracentesis was significantly higher with the 8-mm stent compared with the 10-mm stent (HR:1.76, CI:1.22~2.55, p value<0.0001), with the 8-mm stent group having a 76% increased risk in rebleeding/paracentesis compared to the 10-mm stent group (Figure 3). Compared with the 10-mm stent group, the HR of rebleeding/paracentesis in the 8-mm stent group was between 1.21 and 3.10, with only Riggio et al[13] showing a statistically significant difference in favor of the 10-mm group.

The I^2 of the HR for OS was above 50% between studies so the HR was reported with both fixed and random-effect models, and the latter was preferred as the final impression. The pooled HR of OS between the 8-mm and 10-mm stent group in the included five studies was 0.98 (95% CI: 0.76~1.26, p value:0.859) with the fixed effect model and 0.81 (95% CI: 0.49~1.34, p value:0.411) with the random-effect models. There was no statistically significant difference in the risk of death between the 8-mm and 10-mm stent groups (Figure 4). The HR of the 5 studies was between 0.44 to 1.51 with only Trebicka et al[20] showing a statistically significant difference in survival (HR: 0.44, p value: 0.025) in favor of 8-mm stent group.

Of the 5 studies included in the meta-analysis, Riggio et al[13] [13] and Trebica et al[20] included both variceal bleeding and refractory ascites, Wang et al[16] and Luo et al[21] included only variceal bleeding, and Miraglia et al[15] focused only on refractory ascites patients. The outcome information corresponding specifically to bleeding or refractory ascites patients is limited. Given this, subgroup analysis was conducted within studies recruiting either variceal bleeding or refractory ascites[15, 16, 21]. Results demonstrated that the pooled risk of HE was statistically lower (HR:0.62, CI: 0.45-0.85) in the 8-mm stent group compared with the 10-mm stent group in the three studies. In the variceal bleeding subgroup, the pooled risk of HE was also statistically lower (HR:0.52, CI: 0.34-0.80) in the 8-mm stent group compared with the 10-mm stent group. There was only one study with refractory ascites[15]. It did not demonstrate a significant difference of risk of HE between 8-mm and 10-mm stent use (Figure 5). The pooled risk of both rebleeding/paracentesis and survival was not statistically significant between the 8-mm stent and the 10-mm stent group in subgroup analysis (Figure 6, 7). The risk of need for paracentesis with the 8-mm stent group compared to the 10-mm stent group in Miraglia et al[15] demonstrated marginal significance (HR:1.63, CI: 0.92-2.88).

4. Discussion

The primary result of this meta-analysis shows that the incidence of post TIPS HE is significantly lower in patients with 8-mm versus 10-mm stents. The 8-mm stent group had a 32% decreased risk of HE compared to the 10-mm stent group. This was in concordance with both Wang et al and Luo et al[16, 21], which had statistically significant lower incidences of HE in 8-mm stents, with a HR of 0.53 and 0.51, respectively[16, 21]. Early studies suggested that a stent diameter greater than 12-mm resulted in excessive risk of HE, without additional portal

decompression benefits. Further studies established the superiority of 10-mm to 12-mm stents for TIPS procedures in various clinical outcomes, including HE[22]. Meanwhile, a relationship between smaller shunt diameter and lower incidence of HE has been documented with surgical shunts[23]. In subgroup analysis, the risk of HE of 8-mm stents compared to 10-mm stents remained significant in the variceal bleeding subgroup. Miraglia et al[15] focused on refractory ascites and did not show a statistical difference between 8-mm and 10-mm stents. To date, there is no definitive statement on the overall superiority of 8-mm versus 10-mm shunts. The challenge in identifying the optimal diameter relates to individual patient characteristics, including the need to balance the necessity of absolute portal pressure reduction against HE risk. What we can report from our present analysis is the superiority of 8-mm stents to 10-mm stents in decreasing post-TIPS HE in portal hypertension-related complications.

Post-TIPS PSG is a critical determinant for the occurrence of HE[24]. In this study, the post-TIPS PSG as well as the extent of decreasing pre-TIPS PSG were comparable between each group in all the recruited studies except for Miraglia et al[15]. In that study, the post TIPS PSG was 7.5 ± 2.6 in the 8-mm group vs. 6.5 ± 3.4 mmHg in the 10-mm group ($P = 0.039$). The decrease in PSG was $8.7 \text{ mm} \pm 3.5$ mmHg in the 8-mm group vs. 10.4 ± 4.2 mmHg in the 10-mm group ($P = 0.004$). Like most of the recruited studies, previous studies comparing 12-mm and 10-mm stents have not shown a difference of post-TIPS PSG between the two groups[22]. This may be because the subtle decreases in diameter may not cause remarkable differences in pressure gradient between the portal and hepatic veins. In other words, the pressure gradient might not linearly decrease with increased shunt diameter after a certain threshold, and the TIPS has

reached its maximum effect of decreasing portal pressure. Further increasing the stent diameter may not enhance this effect.

With comparable pressure gradients, a 10-mm stent will receive more portal flow compared to an 8-mm stent, and more unfiltered portal blood will flow directly into the systemic circulation, resulting in an increased risk of HE. In fact, despite the quality of life detriment reported in patients with HE[25], it has been reported as inversely associated with chance of survival[26]. The use of the 8-mm stent in the present analysis leads to decreased incidence of HE. A recent single arm study[27] of a new controlled expansion stent revealed that most of patients (92%) reached the PSG target (<12 mmHg) with the diameter of 8-mm. With the emerging application of new controlled expansion stents, the choice between 8-mm and 10-mm diameter may be more flexible during TIPS procedures[27, 28], and chosen on a case-by-case basis. However, an 8-mm shunt can be considered when the aim of a PSG of 12 mmHg or a 20% reduction in PSG[29, 30] is satisfactory for clinical indications.

Our study demonstrated a significant difference in risk of rebleeding/paracentesis between the two groups. The 8-mm stent group had a higher risk of rebleeding or need for subsequent paracentesis. Riggio et al[13] reported a higher rebleeding rate in patients from the 8-mm stent group, which had a higher post-TIPS PSG than the 10-mm stent patients at the onset of rebleeding event. Interestingly, the other three studies also reported a trend to higher risk of rebleeding or refractory ascites in the 8-mm stent group with a HR of 1.21-1.63, although without statistical significance. The PSG post-TIPS were similar between both groups and both were below the recommended threshold of 12 mmHg in the three studies. In Riggio et al[13],

most cases with recurrence and/or persistence of portal hypertension in the 8-mm stent group did not have obvious stenoses on venography, but with an obvious elevated PSG (17.5 ± 5.4 mmHg) compared to immediate TIPS placement. Although the information of PSG was not mentioned in the 10-mm stent group, all cases with recurrence and/or persistence of portal hypertension were shown to have restenosis. The higher rebleeding rate or need of paracentesis of the combined studies in the 8-mm group might not be related directly to the immediate post TIPS PSG but may represent failure of long-term persistence of decreased portal pressure.

The RCT conducted by Wang et al[16] demonstrated that TIPS with 8 mm covered stents did not compromise shunt patency compared with 10 mm stents in patients with variceal bleeding. Accordingly, in our subgroup analysis of variceal bleeding indication, the pooled risk of rebleeding did not show a significant difference between 8-mm and 10-mm stents. Miraglia et al, focusing on refractory ascites, did reveal a marginal significance of increased risk of paracentesis requirements in the 8-mm stent group compared with the 10-mm stent group. This suggests that an 8-mm stent does not compromise shunt patency in patients with variceal bleeding but may not be satisfactory for patients with refractory ascites. In fact, the clinical requirements of appropriate post-TIPS PSG may be different between recurrent variceal bleeding and refractory ascites[31, 32] indications, which in turn might have different optimal stent diameters. Although the selection of patients might explain the reason for increased rebleeding or RA incidence in the 8-mm group, it is not definitive.

All-cause mortality is a tangible and clinically relevant outcome. Although different endpoints were reported in the studies, we preferred to combine the time-to-event information

between them. The combined HR of OS between the 8-mm stent and 10-mm stent groups was 0.81, and did not reach statistical significance. The heterogeneity of HR for OS within the recruited studies is high. This may be the result of wide confidence intervals in each study, indicating that the pooled result of HR is associated with high uncertainty.

We acknowledge some study limitations. The first is the small sample sizes (5 studies). This might weaken the statistical power of meta-analysis. Secondly, all three retrospective observational studies have conducted propensity score matching (PSM), by which most of the known baseline characteristics in the studies were matched between groups and balanced. But unlike RCT, it may not eliminate the potential bias that arises from any unknown confounders. Due to their study designs, the risk of bias remains moderate to severe in the three studies. A third limitation is the subgroup analysis, which was conducted with only 3 studies recruiting either variceal bleeding or refractory ascites due to specific outcome information inaccessibility. This weakens the persuasive power of the results. Fourth, all the retrieved studies used covered stents, which limits the generalizability of the conclusion. Although bare stents are used much less for TIPS in the era of covered stents, this should be noted because the difference between covered and bare stents is popularly regarded as significant[33]. Lastly, post-TIPS HE is often associated with multiple factors including age, prior HE and liver function[34]. The shunt diameter should only be included into consideration amongst other important factors that influence the post-TIPS HE.

In conclusion, this meta-analysis demonstrated that 8-mm stents during TIPS placement are associated with a significantly lower risk of HE, but a higher risk of rebleeding and/or

uncontrolled refractory ascites when compared to 10-mm stents. The OS between 8-mm and 10-mm stents is similar. Based on the limited information in the present analysis, we deduce conservatively that the indication of RA may indicate specific selection of shunt diameter, with variceal bleeding being prone to 8-mm stent placement and refractory ascites to 10-mm stent placement. Furthermore, well-designed clinical trials with sub-group TIPS indications should be encouraged to further reveal the optimal choice of 8-mm or 10-mm stents in clinical practice.

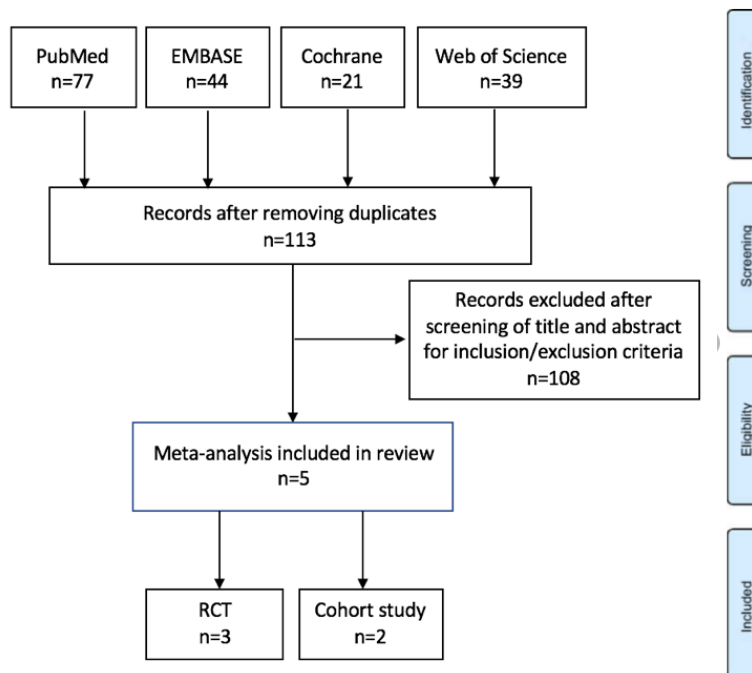


Fig 1: Flow Diagram of Meta-Analysis Study Selection Process

Table 1: Study Characteristics

Reference	Year	Study design	Sample size (8mm/10mm)	Stent Type (PTFE-covered)	Mean Follow-up time in months (8mm/10mm)	Bias risk evaluation**
Riggio et al [13]	2010	Randomized Control Trial	22/23	Viatorr; Gore	12/15.7	Some concerns
Miraglia et al [15]	2017	Retrospective Cohort study	111/60	Viatorr; Gore	71.7/74.8	Moderate risk
Wang et al [16]	2017	Randomized Control Trial	64/63	Fluency; Bard	26.9*	Low risk
Trebicka et al [20]	2019	Retrospective Cohort study#	41/41	Viatorr; Gore	NA	Serious risk
Luo et al [21]	2019	Retrospective Cohort study	32/32	Fluency; Bard	38.7/22.5	Moderate risk

#: sub-group cohort data within a randomized controlled trial

*: reported with overall follow-up time

** : RCT were evaluated with RoB2; cohort studies were evaluated with ROBINS-I

Table 2: Patient characteristics

Reference	Treatment Group	Age (years)	Gender (male/female)	Etiology (viral/non-viral)	History of HE (Yes/No)	Ascites (Yes/No)	Child-Pugh class (A/B/C)	PSG baseline (mmHg)	PPG post TIPS (mmHg)	TIPS indication (Bleeding/RA)
Riggio et al[13]	8mm	53.1 ± 11.3	15/7	13/9#	6/16	15/7	5/10/7	21.3 ± 4.9	8.9 ± 2.7*	12/10
	10mm	57.1 ± 9.9	13/10	14/9#	3/20	18/5	5/15/3	22.1 ± 7.1	6.5 ± 2.7*	9/14
Miraglia et al[15]	8mm	58.6±10.6	76/35	63/51	36/75	111/0	0/71/40	16.1±3.7	7.5±2.6	0/111
	10mm	59.0±10.0	36/24	40/20	20/40	60/0	0/35/25	17.0±4.2	6.5±3.4	0/60
Wang et al[16]	8mm	49.4 ± 11.0*	41/23	54/10	NA	32/32	36/25/3	26.2 ± 4.3	8.2 ± 3.0	64/0
	10mm	52.0 ± 9.7*	37/26	47/16	NA	35/28	35/25/3	24.9 ± 4.3	7.4 ± 3.0	63/0
Trebicka et al[20]	8mm	56 (33~81) **	29/12	25/16	11/30	19/22*	19/18/4*	NA	NA	29/12*
	10mm	56 (41~71) **	29/12	31/10	14/27	35/6*	3/27/11*	NA	NA	6/35*
Luo et al[21]	8mm	52 ± 12	20/12	25/7	0/32	21/11	10/18/4	23.9 ± 6.3	9.2 ± 3.5	32/0
	10mm	51 ± 11	20/12	23/9	0/32	21/11	12/16/4	24.6 ± 7.3	7.4 ± 3.7	32/0

#: reported as Alcoholic/Non-alcoholic

*: variables of 8mm vs. 10mm groups with significant difference

** : expressed as median (range)

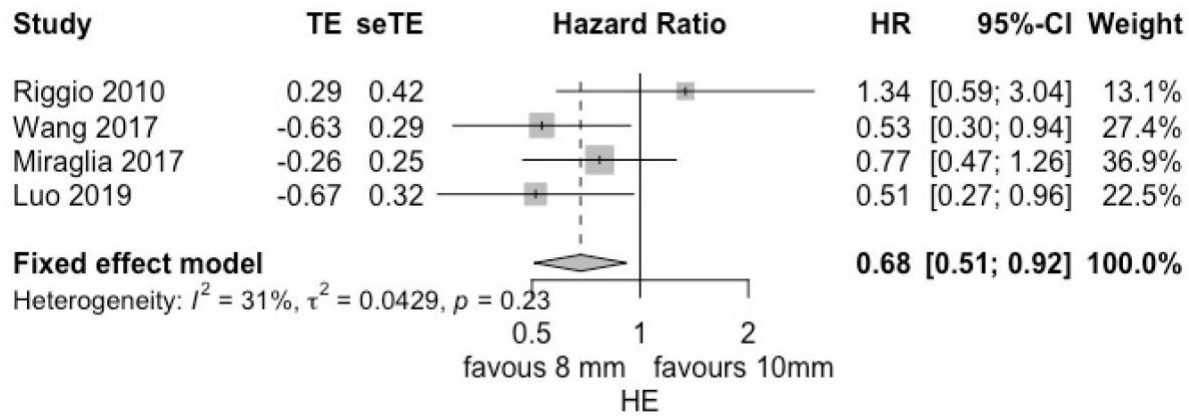


Fig.2 meta-analysis of HR of HE: 8-mm vs. 10-mm

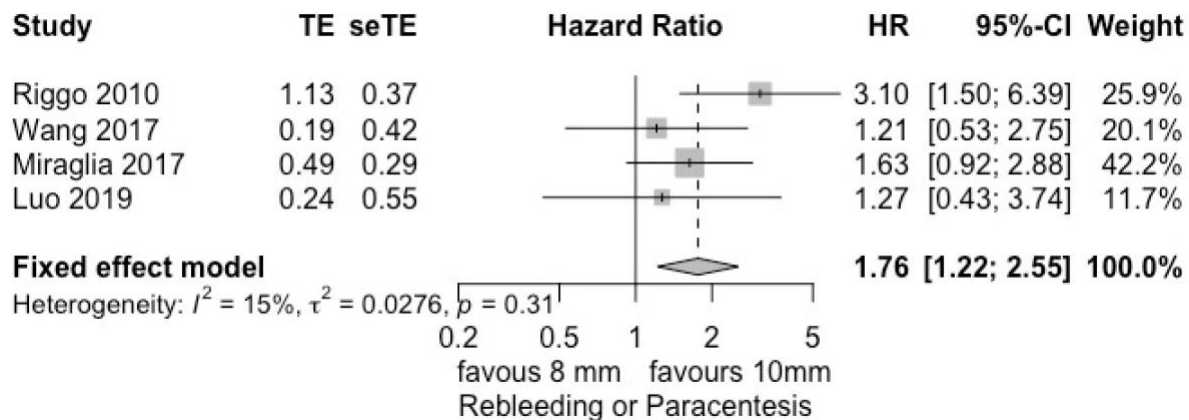


Fig.3 meta-analysis of HR of Rebleeding or Paracentesis: 8-mm vs. 10-mm

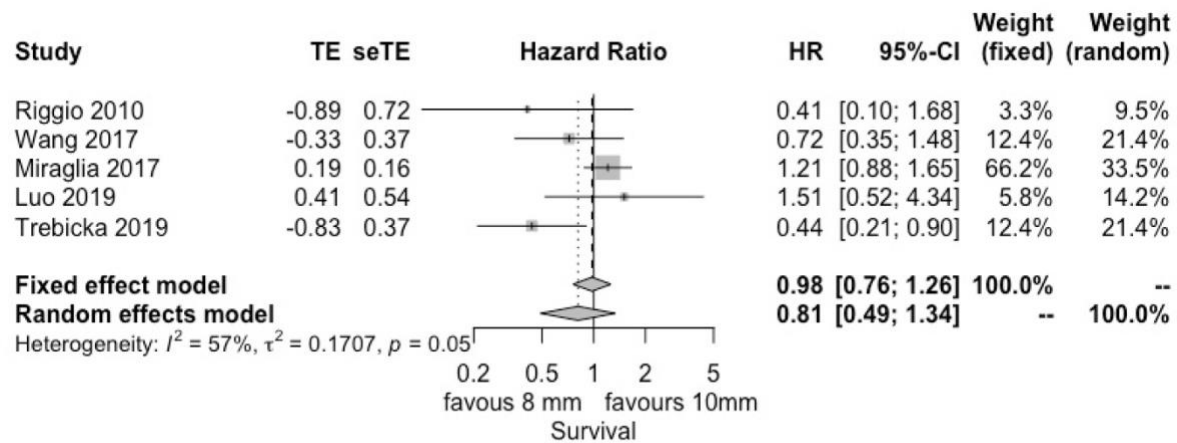


Fig.4 meta-analysis of HR of survival: 8-mm vs. 10-mm

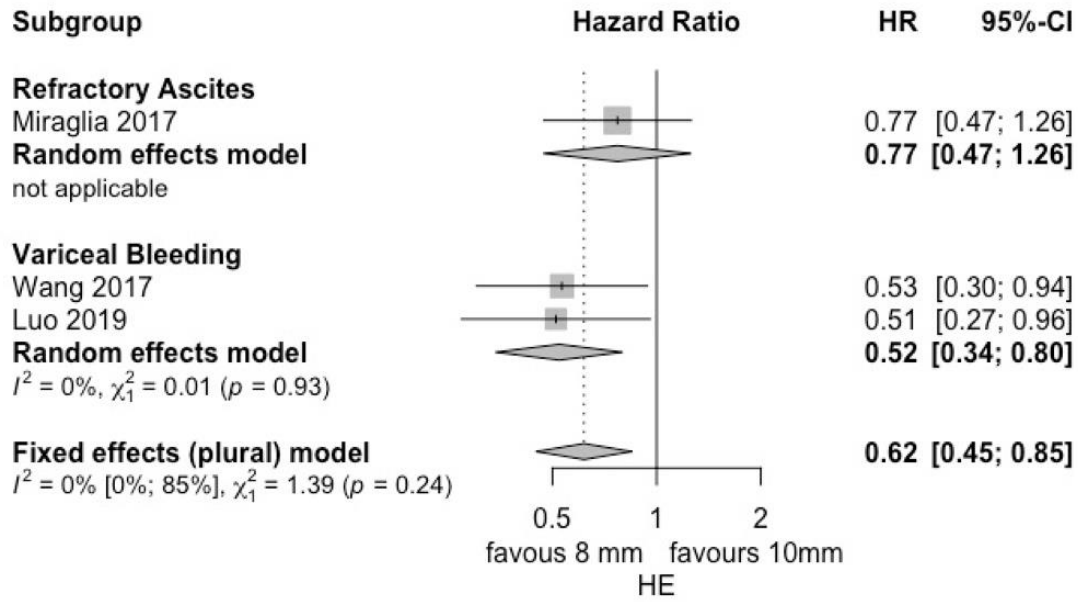


Fig 5: Subgroup Meta-analysis of HR of HE in Variceal Bleeding and Refractory Ascites: 8-mm vs. 10-mm

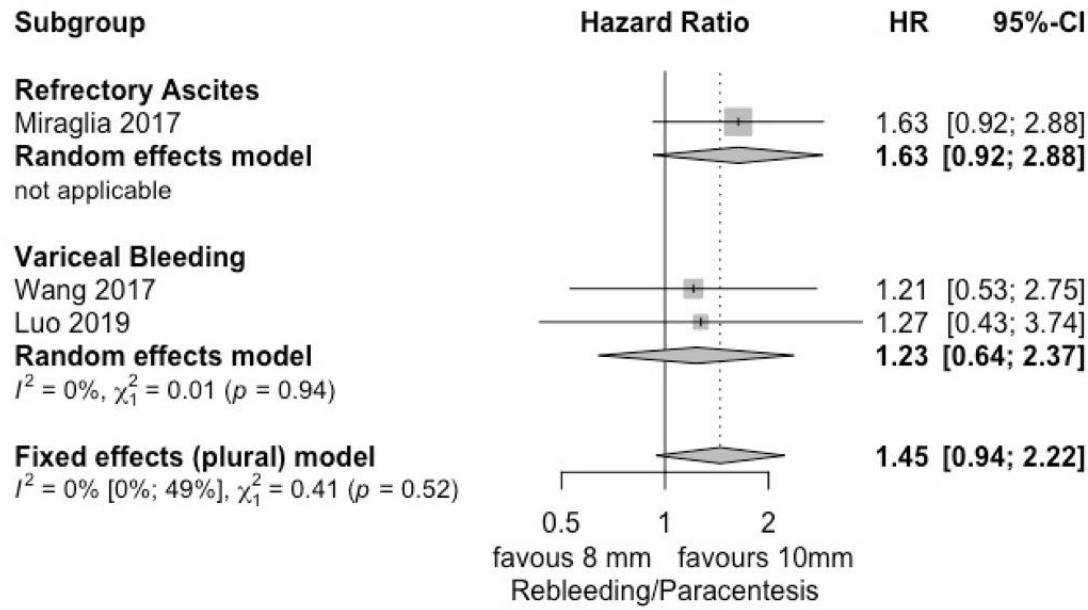


Fig 6: Subgroup Meta-analysis of HR of Rebleeding or Paracentesis in Variceal Bleeding and Refractory ascites: 8-mm vs. 10-mm

The HR of Paracentesis was reported in the Refractory ascites group. The HR of Rebleeding was compared in the subgroup of Variceal Bleeding.

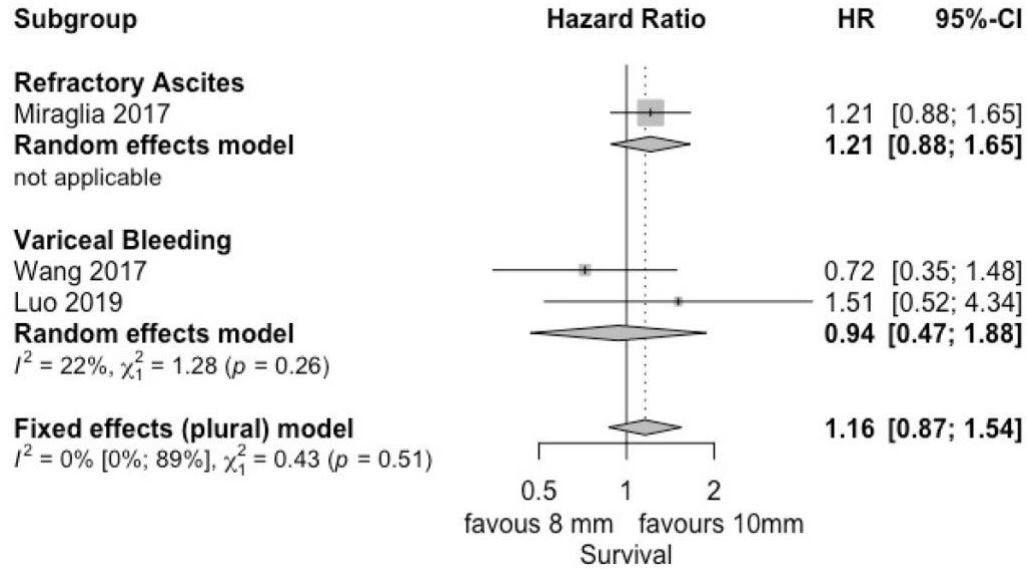


Fig 7: Subgroup Meta-analysis HR of Survival in Variceal Bleeding and Refractory Ascites Group.

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**Survival Benefit of Covered Stent Placement in Patients with Cirrhotic Portal Hypertension Treated with Transjugular
Intrahepatic Portosystemic Shunt:
A Retrospective Cohort Study**

Abstract:

Background and Aims: The survival benefit of covered stents in transjugular intrahepatic portosystemic shunt (TIPS) placement has not been clearly demonstrated. The aim of this study was to investigate whether covered stents offer a survival benefit relative to bare-metal stents (BMS) in general cirrhotic population as well as in subgroup patients stratified with TIPS indication.

Methods: We performed a retrospective cohort study of all patients who had a first-time TIPS between 1995 and 2018. A multivariate logistic model including the type of stent, age, portosystemic gradient (PSG) pre-and post-TIPS creation, indication for TIPS (variceal bleeding /refractory ascites), TIPS urgency (selective/emergency), any degree of hepatic encephalopathy (HE), etiology of cirrhosis, model for end-stage liver disease (MELD) score and year of TIPS were used to identify relationship between covered stent and 1-year mortality in general cirrhotic population as well as sub-group of variceal bleeding and refractory ascites.

Results: A total of 427 patients were eligible for the study with 312 in covered-stent group and 115 in BMS group. Covered stent placement was associated with significantly reduced odds of mortality by 58% at 1-year post TIPS in multivariate regression model (OR=0.42; p=0.001). The use of a covered stent was associated with decreased odds of mortality by 88% in patients with refractory ascites (OR=0.12; p<0.001).

Conclusions: PTFE-covered stent placement was associated with reduced 1-year mortality compared to BMS in general cirrhotic population. The benefit effect was more remarkable in the subgroups of patients with refractory ascites. Further large-scale hypothesis-driven studies with comparative effectiveness analysis are needed to confirm the present conclusion.

Key words: Bare-metal stent; Covered stent; Transjugular intrahepatic portosystemic shunt

Background:

Transjugular intrahepatic portosystemic shunt (TIPS) placement has been increasingly used for the treatment of complications related to portal hypertension in patients with liver diseases [1]. A major limitation of the technique is shunt dysfunction from stent stenosis or occlusion, which occurs in more than 50% of patients treated with conventional bare-metal stents (BMS) during the first year [2]. Covered stents made from polytetrafluoroethylene (PTFE) (Viatorr, Gore Medical) were introduced in an effort to overcome the shunt dysfunction known to occur with BMS by avoiding pseudointimal hyperplasia within the stent [3]. Based on the results of several trials conducted in the early 2010's[4], covered stents were shown to significantly decrease the incidence of shunt dysfunction and recurrence of portal hypertension-related complications[5-7]. During the last decade, the use of covered stents has become the first choice for TIPS creation. The decreased need for intervention to dilate the stents provides a strong rationale for the use of covered stent for TIPS and is now widely accepted.

Despite the demonstrated advantages of covered stent placement, a mortality benefit has not consistently been shown. A 2010 meta-analysis of studies including 1275 patients (346 with covered stent and 929 with BMS) showed significantly better survival with covered stent placement [7]. A 2015 meta-analysis of two RCTs including 209 patients (101 with covered stent and 108 with BMS) showed a trend towards survival benefit with covered stent placement [8]. In 2018, a meta-analysis including 4 RCTs and 8 observational studies including a total of 2152 patients (739 with covered stent and 1413 with BMS) showed that covered-stents group had significantly improved overall survival[6]. However, the individual studies upon which these meta-analyses based were not

appropriately designed to rigorously answer the issue of mortality and survival benefits have been reported with controversial results – and only one randomized controlled trial [9] and two observational studies [4, 10] have demonstrated survival benefit whereas no survival difference has been shown in two RCTs [11, 12] and in a majority of observational studies [13-17]. These previous reports have included subjects with both refractory ascites and variceal bleeding, which might obscure the possible difference of mortality benefits in sub-group population and liver stratification. We aim to contribute another large database analysis to reveal the efficacy of covered stent in improving mortality relative to BMS overall as well as in clinically relevant subgroups, guiding clinicians in their understanding or approach of the procedure. As covered stents are significantly more expensive than BMS, these findings may additionally inform on cost-effectiveness decision, especially in developing regions.

Material and methods:

We integrated a database between 1995 to 2015 previously established by Allegretti et al in a 2019 report evaluation of model performance to predict 90-day survival after TIPS placement [18] and a updated consecutive database between 2016 to 2018 within a network of acute care hospitals (Mass General Brigham, Massachusetts, USA). The majority of TIPS cases were performed at Massachusetts General Hospital, Boston, MA. Briefly, data were identified using a centralized clinical data warehouse designed for research and quality improvement purposes [13, 14]. TIPS recipients were identified using the ICD-9 code “39.1 –intra-abdominal venous shunt” (or related ICD-10 codes) as well as review of TIPS procedure censuses. At least two authors manually identified all

TIPS recipients to confirm the ICD-9/10 code corresponded to a new TIPS placement and the indication was consistent with guideline definitions.[15]. Patients with portal vein thrombosis, post-sinusoidal portal hypertension or history of surgical or interventional portosystemic shunt were excluded.

TIPS placement was performed according to standard technique, in angiography suites under general anesthesia. Following TIPS creation, patients were admitted for 24 hours of observation. Outpatient care was performed in interventional radiology or hepatology clinics. All clinical and laboratory data obtained for this study was sourced from the longitudinal electronic medical record.

Laboratory data were taken from the most recent values prior to TIPS. All subjects with missing values were excluded. To estimate the effect of liver transplantation on survival, A competing risk analysis was performed if the percentage of liver transplantation within 1 year was higher than 10%. Subjects who received liver transplantation within 1 year post TIPS placement were excluded from the dataset if the percentage was equal or lower than 10%.

Primary analysis included differences in 1-year mortality between BMS and covered stent groups. The clinical information collected included age, gender, indication for TIPS (VB/RA), TIPS urgency (selective/emergent), presence of any degree of hepatic encephalopathy (HE) prior to TIPS, etiology of cirrhosis, portosystemic gradient (PSG) before and after shunt creation and year of TIPS (pre-2005/post-2005). Hematological tests including international normalized ratio (INR), serum creatinine (Cr), and total

bilirubin were recorded. Model for end-stage liver disease (MELD) score was calculated according to the following formula as:

$$\text{MELD} = 9.57 \log(\text{Cr}) + 3.78 \log(\text{total bilirubin}) + 11.2 \log(\text{INR}) + 6.43 [19].$$

Means and standard deviation (SD) were provided for continuous variables and values with percentages are provided for categorical variables. To see baseline balance, continuous variables prior to TIPS creation were compared between BMS and covered stent groups using independent one-sample t-test. Categorical variables were compared with Chi-Square (χ^2) test. To see the relationship of stent type (BMS/covered) and outcomes with potential confounders balanced, we used a multivariate logistic model (forward selection) including the treatment group and other variables including age, PSG pre-TIPS creation, PSG post-TIPS creation, any degree of HE, indication for TIPS (VB/RA), TIPS urgency (selective/emergent), etiology of cirrhosis, MELD score and year of TIPS (pre-2005/post-2005). Etiology of cirrhosis was categorized into nonalcoholic steatohepatitis (NASH), ethyl alcohol-related (EtOH), Viral-related or other miscellous origin. This Akaike information criterion (AIC)-based approach starts with no variables in the model and all predictors are entered individually into the model. By repeatedly comparing AIC of each model with previous one, the finally selected variables in the model corresponding to smallest AIC were statistically associated with the outcome (1-year mortality). Association with significance are reported as odds ratio (OR) with 95% confidence interval (CI). Factors with $\text{OR} > 1$ are associated with a higher risk of the outcome and vice versa.

We performed sub-group analysis of impact of stent type on 1-year mortality by stratifying patients based on indication for TIPS (VB/RA) with above multivariate model. Independent sample T-test was conducted to compare the difference of PSG pre-TIPS creation, post-TIPS creation and MELD score between sub-groups of indication of TIPS (VB/RA).

R software (R Foundation for Statistical Computing, Vienna, Austria; Version 3.6.1) was used for all analysis. A threshold of $p < 0.05$ was used to determine statistical significance in comparative and univariate regression analysis. For forward selection in multivariate logistic model in R, the lowest AIC was used as criteria of variable selection.

Results:

Retrospective review of records identified a total of 457 subjects. 55 (12.0%) subjects with missing values distributed among variables of etiology of cirrhosis, PSG pre-TIPS, PSG post-TIPS and HE before TIPS were eliminated from the dataset. 30 (6.6%) patients (6.6%) received liver transplantation within 1 year post TIPS placement, which were eliminated from the dataset. A total 427 patients were finally included into the study (Fig. 1). Of all the 427 patients, 115 patients (26.9%) received BMS and 312 patients (73.1%) received a covered stent. Age, indication of TIPS, TIPS urgency, PSG pre- and post-TIPS, MELD score, encephalopathy pre-TIPS and year of TIPS showed significant difference between BMS and covered stent group (Table.1). As univariate analysis revealed (Table.2), the age, indication for TIPS placement of RA, TIPS urgency (selective vs emergency), PSG pre-TIPS, PSG post-TIPS,

MELD score and year of TIPS were statistically different between the BMS group and covered stent group. Among all patients, 155 (36.3%) died within 1-year post TIPS. The crude incidence of 1-year mortality was lower in the covered stent group than the BMS group (30.1% vs. 53.0%). In the univariate analysis, the age, emergency TIPS, MELD score, TIPS post-2005 and covered stent were significantly associated with 1-year mortality post-TIPS. In the multivariate logistic regression model (Table.2), the significantly reduced odds of 1-year mortality by 58% were associated with covered stent compared to BMS with potential confounders constant. Other variables associated with 1-year mortality included age, PSG post-TIPS, MELD score and HE pre-TIPS.

Sub-group analysis demonstrated that the use of covered stent was associated with decreased odds of 1 year mortality by 88% in patients with refractory ascites in the multivariate model (OR=0.12) (Table.3). The use of covered stent was not associated with an improvement in 1-year mortality in variceal-bleeding sub-group patients (Table.4). The mean PSG pre-TIPS (14.72 vs. 15.18 mmHg; p value=0.547), post-TIPS (6.49 vs.6.66mmHg; p value:0.578) and MELD score (17.88 vs. 17.13; p value=0.241) pre-TIPS creation did not show significant difference between sub-group of RA and VB.

Discussion:

Previous studies have repeatedly shown that the use of stents covered with polytetrafluoroethylene (PTFE) could improve shunt patency by avoiding the pseudointimal hyperplasia[20, 21]. Implantation of a covered TIPS led to reduction of rebleeding and reduced

shunt dysfunction in nearly all published series[6]. Despite the therapeutic benefit of shunt patency on rebleeding, whether this advantage transfers naturally to a survival benefit remains controversial. Although a recent meta-analysis including a total of 2152 patients have shown that patients with covered stents had improved overall survival compared to those with BMS [6], the survival benefit remains controversial based on individual studies, which favors covered stent in 1 RCT[9] and 2 observational studies[4, 10]. In the majority of previous observational [13-17] or RCT studies[11, 12, 22], however, no survival differences between covered stent and BMS were revealed.

We have endeavored to help resolve this controversy through the analysis of a large sample data set representing real-world experience with an increased number of patients with covered stents relative to previous studies. In our retrospective cohort analysis of patients undergoing TIPS creation for either variceal bleeding or refractory ascites we found an overall 1-year mortality of 36.3%. After adjusting for potential confounders, the risk of mortality post-TIPS associated with covered stents was reduced by 58% at 1-year relative to the BMS group. Our associated benefit result of covered stent over BMS is consistent with the findings of a few previous studies. One multi-center retrospective study of 508 patient showed that the 3-months, 1-year and 2-year survival rates were all significantly higher in covered stent group (89 patients) than in the BMS group (419 patients) [4]. In another retrospective study, the covered stent group (32 patients) showed a significantly improved 2-year survival associate with covered stent compared with the BMS group (sample of 104) (85.9% versus 69.5%)[10]. The only RCT showing a mortality benefit of covered stents demonstrated

similar mortality between stent types at 1, 2, and 3 years. However, the 4-year (83.2%) and 5-year survival rates (76.3%) in the covered TIPS group were slightly higher than those in the BMS TIPS group (71.7% and 62.2%, respectively) [9].

A counterfactual result is that the history of any degree of hepatic encephalopathy was negatively associated with 1-year mortality in overall analysis as well as in RA sub-group patients, which did not in accordance with previous reports. One explanation is that patients who had a history of HE was not likely to be referred to TIPS unless all other selection criteria are optimal that leading to better outcomes. Another reason, alternatively, is that these HE episodes were mild/distant and do not suffer ongoing high grade HE, which would be a relative contraindication. Other factors including Child-Pugh stage and MELD score are known independent predictors of survival post TIPS [4]. Our study confirmed that variables other than stent type associated with 1-year mortality included age, PSG post-TIPS, and MELD score, which was in accordance with previous reports in decompensated cirrhotic patients [23, 24]. MELD score was calculated according to the serum creatine, total bilirubin and INR. Although it is far from perfect in the performance predicting post TIPS mortality, it is by far the most widely used index for patient prognosis prediction. There should be plenty of other factors that might affect mortality of cirrhotic patients. We just selected the most suggestive variables that we believe would have main influence on the outcome. These factors collectively determine mortality outcome of patients receiving TIPS and the positive effect of covered stent placement on mortality through reduction of rebleeding and reduced shunt dysfunction might be masked by these factors.

Subgroup analysis based on indication for TIPS placement identified a decrease in the odds of 1-year mortality by 88% among patients with refractory ascites, but not among the variceal bleeding subgroup of patients. Of note, within our overall patient population, variceal bleeding was not shown to be an independent predictor of mortality compared to refractory ascites and the mean PSG and MELD scores of the variceal-bleeder sub-group was not significantly different than the refractory ascites subgroup. We believe that the difference in mortality benefit is due to the differing requirements for PSG-reduction to improve mortality. While a significant reduction in the PSG is required for improvement in ascites, variceal bleeding patients might require a comparatively lower reduction in the PSG to prevent ‘life-threatening’ episodes of bleeding – as distinct from ‘recurrent bleeding’ episodes. As TIPS placement for bleeding is often accompanied by adjunctive varix embolization in our institution, less effective reduction of the PSG by BMS over time may also have lesser impact on ‘life-threatening’ bleeds. Unfortunately, most studies do not routinely report on the use of varix embolization as part of TIPS placement and thus its impact remains incompletely understood. With limited information as to the incidence of varix embolization, shunt patency and follow-up PSG measurements acquired in the present study, it is hard to prove the above hypothesis. Further prospective study with consistent follow-up information focusing on shunt patency and PSG would be necessary to verify our finding that there is no significant difference in 1-year mortality between BMS and covered stents in the variceal-bleeder population.

Limitations:

Due to the retrospective nature of the present study, both known and unknown confounders may limit conclusions. Although we have used a regression model to minimize the effect of known confounders and used propensity scores in sensitivity analysis, the chances of unknown confounders, such as shunt revision, adherence to medication or technique improvement, biasing the main result might still exist. Secondly, the relatively short span of follow-up confined the generalization of the main result to a longer time span post-TIPS. Thirdly, we abandoned all the subjects with missing data and who received liver transplantation, which might lead to selection bias, in which the patients with incomplete characteristic information or outcome might differ with patients of full data. Since the percentage of missing value and liver transplantation is relatively low, the risk of bias originated from sample selection should be minimal.

Conclusion:

Based on the result of the retrospective cohort study, covered stents were associated with significantly reduced risk of 1-year mortality in the entire population. The benefit effect was more remarkable in the subgroups of patients with refractory ascites. Further hypothesis-driven studies to validate the observational results as well as to better understand the mechanisms underlying them would be needed to confirm the present conclusion. Since shunt patency and portal pressure post TIPS establishment would be associated with clinical control of portal hypertension and accordingly with mortality, to confirm the actual effectiveness of covered stent on mortality, prospective study with consistent information of fluoroscopic or ultrasonic shunt patency as well as PSG measurement during follow-up would be necessary.

Fig 1. Flow chart of patient selection

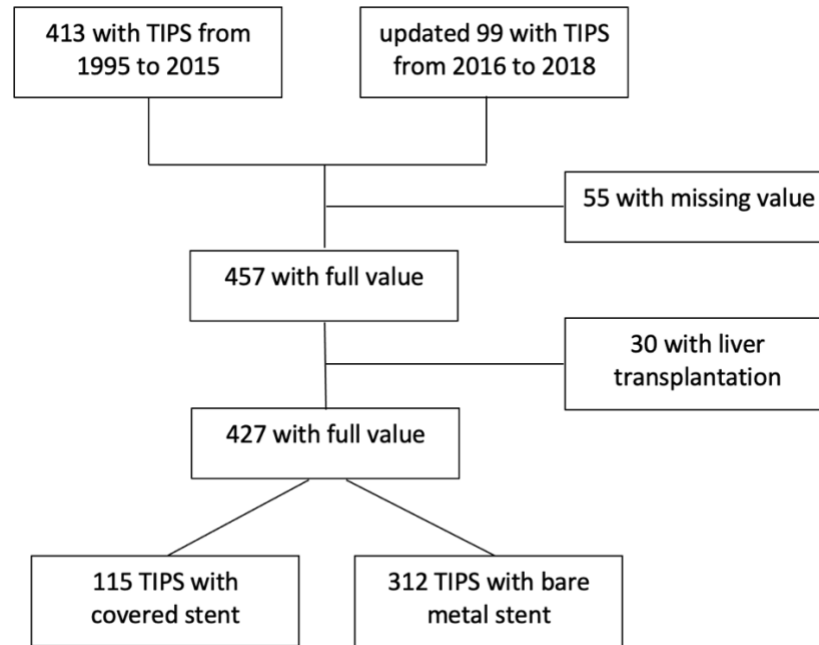


Table.1 Baseline and primary characteristics of patients with BMS and covered stent

	All Patients n=427	BMS n=115	Covered stent n=312	p value
Female (%)	127 (29.7)	28 (24.3)	99 (31.7)	0.173
Age (mean (SD))	56.5 (11.7)	54.6 (11.8)	57.3 (11.6)	0.033
Etiology of cirrhosis (%)				0.103
0: NASH	49 (11.5)	8 (7.0)	41 (13.1)	
1: EtOH	162 (37.9)	49 (42.6)	113 (36.2)	
2: Virus	146 (34.2)	44 (38.3)	102 (32.7)	
3: Other	70 (16.4)	14 (12.2)	56 (17.9)	
Indication of RA (%)	146 (34.2)	29 (25.2)	117 (37.5)	0.024
Emergency TIPS (%)	58 (13.6)	31 (27.0)	27 (8.7)	<0.001
PSG pre-TIPS (mean (SD))	17.6 (7.09)	20.1 (7.37)	16.7 (6.77)	<0.001
PSG post-TIPS (mean (SD))	6.55(3.23)	7.53(4.09)	6.18(2.78)	<0.001
MELD (mean (SD))	14.9 (7.65)	17.8 (8.70)	13.8 (6.94)	<0.001
Encephalopathy pre-TIPS (%)	139 (32.6)	43 (37.4)	96 (30.8)	0.238
TIPS post-2005 (%)	306 (71.7)	12 (10.4)	294 (94.2)	<0.001
Mortality_1year (%)	155 (36.3)	61 (53.0)	94 (30.1)	<0.001

Table.2: Variables in Univariate Analysis Associated with 1-year mortality post TIPS

Variables	Univariate analysis		Multivariate analysis	
	Odds Ratio (OR)	p value	Odds Ratios (OR)	p value
Age	1.02 (1.01~1.03)	0.042	1.19 (1.16~1.21)	<0.001
Female	0.74 (0.59~0.93)	0.180		
Etiology of Cirrhosis	1.13 (1.01~1.27)	0.263		
Indication of RA	1.09 (0.89~1.35)	0.671		
Emergency TIPS	2.46 (1.85~3.28)	0.002		
PSG pre-TIPS	1.01 (1.00~1.03)	0.327		
PSG post-TIPS	0.98 (0.95~1.01)	0.563	0.93 (0.90~0.97)	0.009
MELD score	1.17 (1.14~1.19)	<0.001	1.19 (1.16~1.21)	<0.001
HE pre-TIPS	0.98 (0.79~1.21)	0.922	0.56 (0.43~0.73)	0.026
TIPS post-2005	0.38 (0.30~0.47)	<0.001		
Covered stent	0.38 (0.31~0.48)	<0.001	0.42 (0.32~0.57)	0.001

Table.3: Variables selected with multivariate analysis associated with 1-year mortality post TIPS in subgroup of patients with refractory ascites

Variables	Odds Ratio (Confidential Interval)	p value
Age	1.05 (1.03~1.08)	0.03
Encephalopathy pre-TIPS	0.31(0.19~0.50)	0.014
MELD score	1.16(1.12~1.21)	<0.001
PSG pre-TIPS	1.07 (1.02~1.12)	0.141
PSG post-TIPS	0.79 (0.72~0.86)	0.008
Covered stent	0.12(0.07~0.23)	<0.001

Table.4: Variables selected with multivariate analysis associated with 1-year mortality post TIPS in subgroup of patients with variceal bleeding

Variables	Odds Ratio (Confidential Interval)	p value
Age	1.03(1.02~1.05)	0.007
Emergency TIPS	1.98(1.38~2.85)	0.059
MELD score	1.18(1.15~1.21)	<0.001

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Summary of Paper 1 and Paper 2 conclusions (1 page)

The present meta-analysis demonstrated that 8-mm stents during TIPS placement are associated with a significantly lower risk of HE, but a higher risk of rebleeding and/or uncontrolled refractory ascites when compared to 10-mm stents. The OS between 8-mm and 10-mm stents is similar. Based on the limited information in the present analysis, we deduce conservatively that the indication of TIPS may indicate specific selection of shunt diameter, with variceal bleeding being prone to 8-mm stent placement and refractory ascites to 10-mm stent placement.

Based on the result of the retrospective cohort study, Viatorr stents significantly reduced the risk of 1-year mortality in the entire population as well as subgroup patients with refractory ascites. Further hypothesis-driven studies to validate the observational results as well as to better understand the mechanisms underlying them would be needed to confirm the present conclusion.

Discussion and Perspectives (1 page)

Paper 1: The meta-analysis with registered protocol revealed that the 8-mm stent group had decreased risk of HE as well as a higher risk of rebleeding or need for subsequent paracentesis compared to the 10-mm stent group, which was in concordance with previous individual reports. Subgroup analysis of variceal bleeding indication showed that the risk of rebleeding did not show a significant difference between 8-mm and 10-mm stents, suggesting that an 8-mm stent does not compromise shunt patency in patients with variceal bleeding.

The small sample sizes, observational feature of some of the recruited studies were main limitations of the analysis. All the retrieved studies used covered stents, which limits the generalizability of the conclusion.

Paper 2: The main strength of the study is the sub-group analysis with stratification with indication of RA. Covered stents was associated with significantly reduced risk of 1-year mortality in the entire population as well as in RA subgroup patients. This raised the question whether BMS should be considered as an alternative in particular circumstances regarding the availability of covered stent as well as interventional costs.

Due to the observational and retrospective nature of the present study, both known and unknown confounders may limit conclusions. The relatively short span of follow-up data confined the generalization of the main result.

Future directions: Based on what is known in the above Meta-analysis and retrospective study, well-designed hypothesis-driven studies with sub-group stratification should be encouraged to further reveal the optimal choice of type of stents in clinical practice.