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Salvage transjugular intrahepatic portosystemic shunt in patients with cirrhosis and refractory variceal bleeding: A systematic review with meta-analysis

Laura Weichselbaum[1,2] | Antonia Lepida[2] | Astrid Marot[3] | Eric Trépo[2,4] | Christophe Moreno[2,4] | Pierre Deltenre[1,2,3]

[1]Department of Gastroenterology and Hepatology, Clinique St Luc, Bouge, Belgium

[2]Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, CUB Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium

[3]Department of Gastroenterology and Hepatology, CHU UCL Namur, Université Catholique de Louvain, Yvoir, Belgium

[4]Laboratory of Experimental Gastroenterology, Université Libre de Bruxelles, Brussels, Belgium

Correspondence
Pierre Deltenre, Department of Gastroenterology, Hepatopancreatology, and Digestive Oncology, C.U.B. Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.
Email: pierre.deltenre01@gmail.com

Abstract

Background: Transjugular intrahepatic portosystemic shunt (TIPS) may be used as a salvage treatment in patients with cirrhosis and refractory variceal bleeding.

Aim: To synthesize the available evidence on the efficacy of TIPS in patients with cirrhosis and refractory variceal bleeding.

Methods: Meta-analysis of trials evaluating TIPS in patients with cirrhosis and refractory variceal bleeding, including subgroup analysis to assess the impact of recent changes in the management of variceal bleeding (i.e., the use of Polytetrafluoroethylene-covered TIPS and the availability of pre-emptive TIPS as a first-line treatment for acute variceal bleeding).

Results: Twenty-three studies with 1430 patients were included. The pooled estimate rates were 0.33 (95% CI = 0.29–0.37) for death at 1 month–6 weeks, 0.46 (95% CI = 0.40–0.52) for death at 1 year, and 0.09 (95% CI = 0.06–0.11) for death due to rebleeding in the follow-up. The pooled estimate rates for death at 1 month or 6 weeks were similar in subgroup analyses including studies that did not use covered TIPS or that did not include patients after the pre-emptive TIPS area compared to the ones that did (pooled estimate rate 0.33 [95% CI = 0.28–0.38] and 0.32 [95% CI = 0.25–0.39], respectively). The pooled estimate rates were 0.16 (95% CI = 0.13–0.18) for rebleeding, 0.25 (95% CI = 0.17–0.36) for occurrence of hepatic encephalopathy, and 0.08 (95% CI = 0.05–0.13) for access to liver transplantation after TIPS insertion.

Conclusions: One third of patients with cirrhosis and refractory variceal bleeding treated with salvage TIPS died within the first 6 weeks. Recent improvements in the management of variceal bleeding did not improve the survival of patients presenting with refractory variceal bleeding.

Laura Weichselbaum and Antonia Lepida have contributed equally to the presented work and share first authorship.

KEYWORDS
cirrhosis, portal hypertension, refractory variceal bleeding, transjugular intrahepatic portosystemic shunt

INTRODUCTION

Acute variceal bleeding is one of the most common life-threatening complications in patients with cirrhosis. Current standard-of-care treatment includes the combination of vasoactive drugs, band ligation and antibiotics.[1] During the last 2 decades, this combination therapy has markedly improved patient outcome. However, 6-week mortality is still estimated at around 20%.[2] Several therapeutic alternatives have been proposed to further reduce mortality. The most promising approach is the placement of a pre-emptive transjugular intrahepatic portosystemic shunt (TIPS) which has proven effective when placed within 72 h of acute variceal bleeding in patients with high portal pressure as well as in those with Child–Pugh class C up to 13 points or with class B and active bleeding at initial endoscopy.[3–5] However, the pre-emptive use of TIPS faces several challenges. First, although a recent study suggested that the use of a modified model for end-stage liver disease (MELD) score may help to evaluate the prognosis of patients with variceal bleeding,[2] accurate predictive models able to precisely assess the prognosis of patients with acute variceal bleeding are lacking. Second, even if the use of pre-emptive TIPS is effective at reducing mortality of patients with acute-on-chronic liver failure,[6] pre-emptive TIPS can be harmful in patients with severe liver failure and should be considered with caution in those patients.[7] Third, only a minority of eligible patients with acute variceal bleeding actually receive pre-emptive TIPS in real-life settings.[8,9] As a consequence, a significant proportion of patients do not have access to pre-emptive TIPS and, if standard-of-care treatment fails to control bleeding, TIPS may be considered as a salvage therapeutic option.[10]

In the last 2 decades, many studies reported the outcomes of salvage TIPS for patients with cirrhosis and refractory variceal bleeding. Meta-analysis is a quantitative technique that allows to pool data from multiple trials in order to decrease random errors. It also allows to evaluate the magnitude of impact of a given factor.[11,12] In this study, we perform a meta-analysis of studies evaluating TIPS as a salvage therapy in patients with cirrhosis and refractory variceal bleeding. Our aim is to assess the efficacy and safety of this treatment in this context.

Key summary

- Despite recent advances in the management of variceal bleeding, number of patients still present with refractory variceal bleeding. The efficacy of salvage Transjugular intrahepatic portosystemic shunt (TIPS) in these patients has currently not been assessed in a meta-analysis.
- A meta-analysis of 23 studies shows that mortality after TIPS placement as a salvage therapy for refractory variceal bleeding is associated with a high mortality of 33% at 6 weeks and 46% at 1 year.
- Only 9% of these deaths were due to rebleeding.
- Advances such as the use of PTFE-covered TIPS and recommendations to place TIPS pre-emptively in selected patients did not improve these outcomes.

MATERIALS AND METHODS

This systematic review is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[13]

Literature search

Medline (PubMed), Cochrane library and manual searches were combined and last performed on 11 February 2022. Key search terms were “transjugular intrahepatic portosystemic shunt”, “TIPS”, “refractory variceal bleeding”, “variceal bleeding”, “emergency TIPS”, “salvage TIPS” and “hemorrhage”. Terms were combined within each database. General reviews and references from published trials were also used. The exact search term combinations can be found in Appendix S1. Duplicate publications were excluded. Only articles published in English were considered. Two observers (L.W. and A.L.) also screened all abstracts presented between 2018 and 2021 at the Liver Meeting of the American Association for the Study of Liver Diseases and the International Liver Congress of the European Association for the Study of the Liver.

Criteria for inclusion and exclusion of studies

Randomized controlled trials and single arm observational studies were included. In order to reduce risks of bias, strict inclusion and exclusion criteria were defined prior to the literature search. To be considered, a study had to: a) include patients with cirrhosis; b) include patients with refractory variceal bleeding from esophageal or gastric varices. Refractory variceal bleeding was defined as failure to achieve hemostasis despite adequate pharmacological and endoscopic

therapy.[5] A study that included patients with and without refractory variceal bleeding was included in the present meta-analysis if more than 50% of patients received TIPS for refractory bleeding and if this information was clearly stated; c) use salvage TIPS to control variceal bleeding in at least 50% of the cases. When several publications existed covering the same study population, only the most recent was included. Studies were excluded when the manuscript or a summary was not available (NA) and when useful data could not be retrieved.

Endpoints and criteria for combinability

Endpoints were defined prior to the beginning of the meta-analysis. Primary endpoints were death occurring 1 month or 6 weeks after TIPS insertion, death occurring 1 year after TIPS insertion and death from rebleeding. Secondary endpoints were occurrence of rebleeding at 6 weeks, the successful placement of TIPS, occurrence of hepatic encephalopathy after TIPS insertion and access to liver transplantation.

Data extraction

Data extraction was performed independently by two investigators (L. W. and A.L.) using standardized data collection forms. Discrepancies in data interpretation were resolved by discussion, re-review of the studies and consultation with one other author (P.D.) when necessary.

Quality score

The methodological quality of the studies was assessed using the National Institute of Clinical Excellence checklist.[14]

Statistical analysis

We used a random effects model to obtain a summary estimate of primary outcomes (using the inverse variance method) among patients treated with TIPS.[15] The random model was chosen because it takes into account the possibility of heterogeneity between studies.[16] Data on all patients were extracted to allow intention-to-treat analyses. The overall treatment effect was expressed as event rate, a measure of how often a particular statistical event occurs within a group of patients, with 95% confidence intervals (95% CI), or as mean difference with 95% CI.

As a first step, an overall meta-analysis was performed. This analysis included studies that followed different guidelines over time for the management of variceal bleeding. More specifically, these differences concern the use of Polytetrafluoroethylene-covered TIPS and the availability of pre-emptive TIPS as a first-line treatment for acute variceal bleeding.[1] Therefore, subgroup analyses were run to account for the fact that the use of PTFE-covered TIPS could influence outcomes such as survival,[17] or that the use of pre-emptive TIPS might lead to differences within the populations exposed to the risk of refractory variceal bleeding.[18] Two additional subgroup analyses were also performed. The first was done in studies that exclusively used covered stents and the second was done among studies published before and after 2010.

The methodological section of each study was reviewed to determine whether any discrepancies could be identified. When a discrepant study was identified, sensitivity analyses excluding this study were performed. Heterogeneity was assessed using Cochran's Q test[19] and the I^2 statistic. More specifically, the I^2 statistic was used to estimate inconsistency in meta-analyses, representing the percentage of the between-study variability due

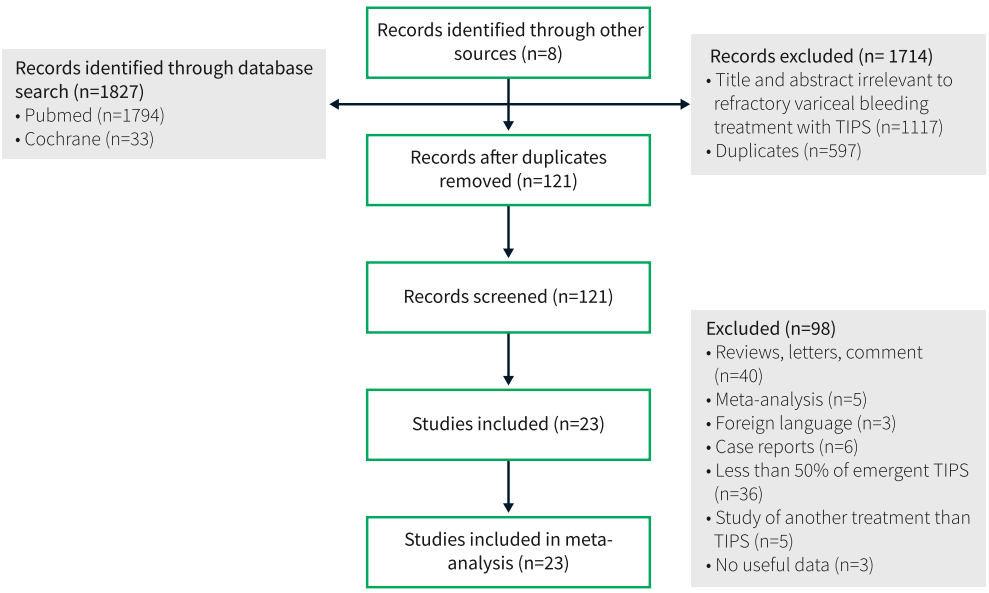

FIGURE 1 Flow chart of the selection of studies for inclusion in the meta-analysis

to heterogeneity rather than chance.[20] A significant Cochran's Q-statistic (below 0.10) was chosen as a threshold for significant heterogeneity across studies. The following cut-offs were used to quantify heterogeneity with the I^2 statistic: 0%–25%, low; 25%–50%, moderate; >50%, high heterogeneity.[20] To assess the extent of publication bias, the Egger test and the Begg and Mazumdar test were used. A p-value <0.05 was considered statistically significant. All statistical analyses were performed using Comprehensive Meta-analysis (Biostat, Englewood, NJ).

RESULTS

Study population

Figure 1 summarizes the flow chart of the selection of studies to be included in this meta-analysis. We screened 1835 references; 121 were selected for full-text retrieval. Of these, 23 were included in the analysis.[21–43] Of note, the Lemoine study[44] was not included because only 4 patients out of 24 were treated with a TIPS emergently, the Orloff study[45] was not included because the study did not meet our inclusion criteria of variceal bleeding refractory to standard-of-care treatment since all patients with variceal bleeding were randomized to TIPS versus surgical shunt before assessing their response to endoscopic treatment, and the Choudhury and Singh studies[46,47] were not included because no relevant information regarding our chosen outcomes could be retrieved. All studies were published as full-text articles. Twenty-one studies were case series, two studies did not specify the study design (Table 1).

A total of 1430 patients with refractory variceal bleeding were included in the meta-analysis. Follow-up of each study ranged between 4 and 31 months. Fifty-six percent of the patients had alcoholic cirrhosis. Percentage of patients with Child-Pugh stage C ranged between 29% and 100% (Table 1).

Study quality

All studies were observational. Table S1 summarizes the quality of the studies included in the analysis.

Assessment of differences in baseline study characteristics that may influence outcomes

The methodological analysis of each study identified discrepancies in 1 study[37] in which salvage TIPS was performed only in patients with a Child-Pugh score ≥14 (Table 1). As Child-Pugh score might influence the rate of adverse events related to the procedure, sensitivity analyses excluding the Rudler study[37] were performed.

Outcomes

Primary endpoints–Death 1 month to 6 weeks after Transjugular intrahepatic portosystemic shunt insertion

Data on short-term mortality were available for 1398 patients. The pooled estimate rate for death 1 month or 6 weeks after TIPS insertion was 0.33 (95% CI = 0.29–0.37, Figure 2a and Table 2). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 52\%$). No publication bias was detected by the Egger test ($p = 0.8$) or by the Begg and Mazumdar test ($p = 0.9$).

In sensitivity analysis excluding the Rudler study,[37] the pooled estimate rate for death 1 month or 6 weeks after TIPS insertion was 0.32 (95% CI = 0.29–0.36). There was moderate heterogeneity between studies ($p = 0.01$, $I^2 = 49\%$).

Rates for death 1 month or 6 weeks after TIPS insertion were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Primary endpoints–Death 1 year after Transjugular intrahepatic portosystemic shunt insertion

Data on 1-year mortality were available for 1207 patients. The pooled estimate rate for death 1 year after TIPS insertion was 0.46 (95% CI = 0.40–0.52, Figure 2b and Table 2). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 71\%$). No publication bias was detected by the Egger test ($p = 0.8$) or by the Begg and Mazumdar test ($p = 0.9$).

In sensitivity analysis excluding the Rudler study,[37] the pooled estimate rate for death 1 year after TIPS insertion was 0.45 (95% CI = 0.39–0.51). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 71\%$).

Rates for death 1 year after TIPS insertion were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Primary endpoints–Death from rebleeding in follow-up

Data on mortality from rebleeding were available for 890 patients. The pooled estimate rate for death from rebleeding in the follow-up after TIPS insertion was 0.09 (95% CI = 0.06–0.11, Figure 3a and Table 2). There was moderated heterogeneity between studies ($p = 0.14$, $I^2 = 28\%$). No publication bias was detected by the Begg and Mazumdar test ($p = 0.3$) but a publication bias was detected by the Egger test ($p = 0.03$).

In sensitivity analysis excluding the Rudler study,[37] the pooled estimate rate for death from rebleeding in the follow-up after TIPS

TABLE 1 Characteristics of the 23 included studies

Authors	Study design	*N*	Age (years, mean)	Alcoholic cirrhosis *n* (%)	Male *n* (%)	Esophageal varices (%)	Child-Pugh score (mean/% of child-Pugh class C)	MELD score (mean)	% Of patients with patients with indication for salvage TIPS	Type of antibiotic treatment	Type of TIPS used	Recruitment period
McCormick 1994[21]	Case series prospective	20	52	55	85	85	NA/60	NA	100	NA	Non-covered stent	1991–1994
Rubin 1995[22]	Case series prospective	49	53	51	59	82	NA/47	NA	94	NA	Non-covered stent	1991–1993
Jalan 1995[23]	Case series retrospective	19	57.1	79	42	100	NA/68	NA	100	Prophylactic before TIPS	Non-covered stent	1988–1994
Sanyal 1996[24]	Case series prospective	30	52	63	67	87	NA/73	NA	100	NA	Non-covered stent	1991–1994
Tyburski 1997[25]	Case series retrospective	33	52	97	61	NA	NA/85	NA	100	NA	Non-covered stent	1992–1995
Patch 1998[26]	NA	54	48.6	61	72	52	9.6/54	NA	100	NA	Non-covered stent	1992–1995
Banares 1998[27]	Case series prospective	56	57	59	70	66	NA/41	NA	100	NA	Non-covered stent	1992–1996
Gerbes 1998[28]	Case series prospective	11	46	55	73	73	10.5/64	NA	100	100%, 1 dose pre TIPS (3rd gen Cephalo)	Non-covered stent	1993–1995
Chau 1998[29]	Case series prospective	112	49	60	70	75	NA/71	NA	100	NA	Non-covered stent	1992–1997
Williams 1998[30]	NA	67	54	67	79	72	NA/48	NA	63	NA	Non-covered stent	1991–1995
Barange 1999[31]	Case series prospective	32	54	59	72	0	NA/47	NA	63	100%, NA	Non-covered stent	1992–1997
Bizollon 2001[32]	Case series prospective	28	52	71	71	93	NA/61	NA	100	100%, just before and for 48h after TIPS	Non-covered stent	NA
Azoulay 2001[33]	Case series prospective	58	54	79	76	78	10.6/81	NA	100	100%, Amoxiclav	Non-covered stent	1993–2000
Abujudeh 2005[34]	Case series retrospective	16	NA	NA	NA	NA	NA	NA	100	NA	NA	2000–2004
Tzeng 2009[35]	Case series retrospective	107	55.5	24	69	NA	NA/NA	NA	100	Only if signs of infection	Non-covered stent	1995–2006
Gazzera 2012[36]	Case series prospective	82	55	24	67	NA	NA/NA	NA	100	NA	94% non-covered, 6%	1992–2009

TABLE 1 (Continued)

Authors	Study design	*N*	Age (years, mean)	Alcoholic cirrhosis *n* (%)	Male *n* (%)	Esophageal varices (%)	Child-Pugh score (mean/% of child-Pugh class C)	MELD score (mean)	% Of patients with patients with indication for salvage TIPS	Type of antibiotic treatment	Type of TIPS used	Recruitment period
											PTFE-covered stents	
Rudler 2013[37]	Case series retrospective	5	51.2	60	100	NA	NA/100	31.5	100	100	PTFE-covered stent	2004–2007
Casadaban 2015[38]	Case series retrospective	101	51[a]	38	68	48	NA/52	18[a]	100	100%, prophylaxis	41% non-covered, 59% PTFE-covered stents	1998–2013
Zhu 2019[39]	Case series retrospective	58	52	7	67	100	8.7/29	10.5	100	100%, prophylaxis	95% PTFE-covered stents	2009–2017
Maimone 2019[40]	Case series retrospective	144	51	58	66	79	10/54	18.5	100	53%, 3rd gen Cephalo or Pip/Tazo (or Amoxiclav) for those on Quinolones	56% non-covered, 44% PTFE-covered stents	1992–2008
Bouzbib 2021[41]	Case series retrospective	106	54	70	82	NA	10.7/63	20.2	100	100%, 3rd gen Cephalo or Quinolones	PTFE-covered stent	2002–2017
Walter 2021[42]	Case series retrospective	164	55 for 83 patients and 54 for 81 patients[a]	79	79	81	NA/50[b]	19[a]	100	3rd gen Cephalo (84%), Quinolones (8.6%), Pip/Tazo (7.4%)	PTFE-covered stent	2007–2017
Kumar 2021[43]	Case series retrospective	78	50.2	73	76	NA	NA/65	18[a,c]	100	100	PTFE-covered stent	2005–2015

Abbreviations: NA, not available; PTFE, Polytetrafluoroethylene; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Expressed as median.

[b]Available for 156 patients.

[c]MELD-Na.

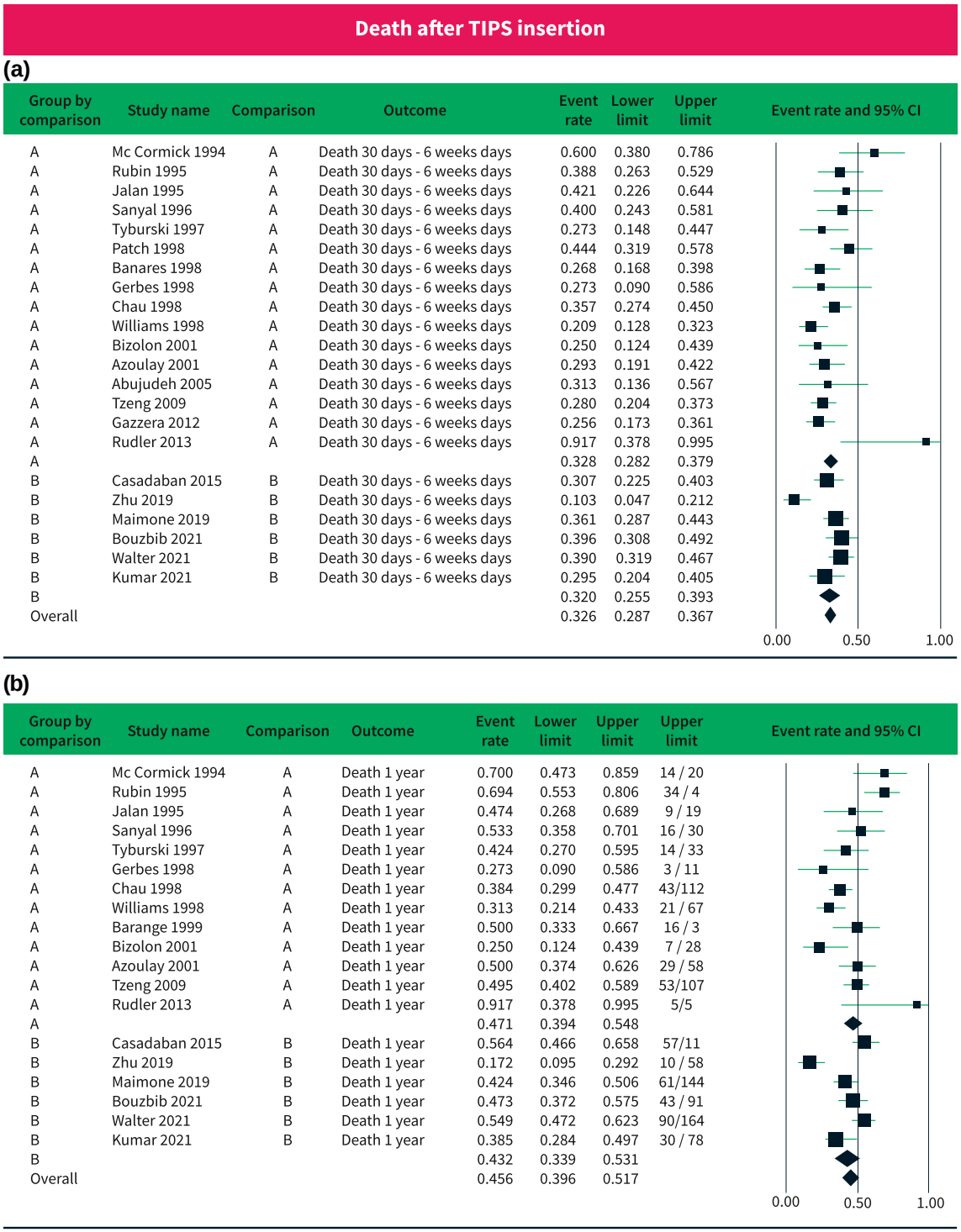

FIGURE 2 Death after transjugular intrahepatic portosystemic shunt (TIPS) insertion: Pooled estimate rate for death 1 month–6 weeks (a) or 1 year (b) after TIPS insertion in patients with cirrhosis and refractory variceal bleeding. Studies before (group A) or after (group B) the use of PTFE-covered TIPS and the pre-emptive TIPS recommendation. TIPS, transjugular intrahepatic portosystemic shunt

insertion was 0.08 (95% CI = 0.06–0.12). There was moderate heterogeneity between studies ($p = 0.1$, $I^2 = 33\%$).

Rates of death from rebleeding in follow-up were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Secondary endpoints–Occurrence of rebleeding at 6 weeks

Data on occurrence of rebleeding at 6 weeks were available for 1149 patients. The pooled estimate rate for rebleeding at 6 weeks was

TABLE 2 Endpoints among the 23 included studies

Authors	*N*	Technical Success (*n* patients)	Follow-up (mean, months)	Deaths at 1 month–6 weeks (*n* patients)	Deaths at 1 year (*n* patients)	Deaths due to rebleeding (*n* patients)	Rebleeding at 6 weeks (*n* patients)	Occurrence of hepatic encephalopathy (*n* patients)	Access to liver transplantation (*n* patients)
McCormick 1994[21]	20	20	8[a]	11 (30 days)–12 (6w)	14	NA	7	NA	1
Rubin 1995[22]	49	48	8.4	19	34[f]	7	8	3	4
Jalan 1995[23]	19	17	"Up to 20"	8	9	0	3	2	1
Sanyal 1996[24]	30	29	31[a]	12	16	0	6[g]	8	3
Tyburski 1997[25]	33	NA	"Up to 18"	9	14	5	6	NA	NA
Patch 1998[26]	54	54	5.7[a]	24	NA	2	11	NA	8
Banares 1998[27]	56	55	NA	15	NA	3	8[h]	NA	NA
Gerbes 1998[28]	11	11	18.3	3	3	1	3	2	NA
Chau 1998[29]	112	112	7[a]	40	43[i]	5	15[j]	7	NA
Williams 1998[30]	67	65	12[a]	14	21	3	14[g]	28	1
Barange 1999[31]	32	32	17[a]	NA	16	6	NA	5	1
Bizollon 2001[32]	28	26	24	7	7	1	2[g]	4	8
Azoulay 2001[33]	58	58	16[a]	17	29	4	2	2	6
Abujudeh 2005[34]	16	14	NA	5	NA	NA	NA	NA	NA
Tzeng 2009[35]	107	NA	"Up to 12"	30	53	NA	NA	NA	NA
Gazzera 2012[36]	82	77	NA	21	NA	NA	NA	NA	NA
Rudler 2013[37]	5	5	NA	5	5	0	NA	NA	0
Casadaban 2015[38]	101	NA	NA	31	57	NA	16[h]	33	NA
Zhu 2019[39]	58	57	17.3[a]	6	10	5	6	19	3
Maimone 2019[40]	144	137	3.9[a]	52	61	NA	23	22	NA
Bouzbib 2021[41]	106	106	NA	42	43[b]	11[b]	14[c]	61[d]	10
Walter 2021[42]	164	164	NA	64	90	16	26	74[e]	4
Kumar 2021[43]	78	78	NA	23	30	1	7	NA	NA

Abbreviations: NA, not available; TIPS, transjugular intrahepatic portosystemic shunt.

[a]Expressed as median.

[b]Available in 91 patients.

[c]Available in 84 patients.

[d]Available in 104 patients.

[e]Available in 161 patients.

[f]At 8.4 months.

[g]At 2 weeks.

[h]At 1 month.

[i]At 6 months.

[j]At 7 days.

TABLE 3 Subgroup analyses according to the use of covered Transjugular intrahepatic portosystemic shunt (TIPS) and to the recommendation of using pre-emptive TIPS in the management of acute variceal bleeding

	Non-covered TIPS and before pre-emptive TIPS recommendation		PTFE-covered TIPS and after pre-emptive TIPS recommendation	
Endpoints	**Pooled estimate rate**	**95% CI**	**Pooled estimate rate**	**95% CI**
Death (1 month - 6 weeks after TIPS)	0.33	0.28–0.38	0.32	0.26–0.39
Death (1 year after TIPS)	0.47	0.39–0.55	0.43	0.34–0.53
Death from rebleeding	0.08	0.05–0.12	0.09	0.06–0.14
Rebleeding (6 weeks after TIPS)	0.17	0.13–0.21	0.15	0.12–0.18
Hepatic encephalopathy after TIPS	0.14	0.07–0.26	0.36	0.23–0.52
Successful placement of TIPS	0.96	0.93–0.97	0.99	0.95–1.00
Access to liver transplantation	0.10	0.06–0.17	0.05	0.02–0.12

Abbreviation: CI, confidence interval.

0.16 (95% CI = 0.13–0.18, Figure 3b and Table 2). There was low heterogeneity between studies ($p = 0.2$, $I^2 = 21\%$). No publication bias was detected by the Egger test ($p = 0.3$) or by the Begg and Mazumdar test ($p = 0.4$).

Rates for occurrence of rebleeding 6 weeks after TIPS insertion were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Secondary endpoints–Occurrence of hepatic encephalopathy after Transjugular intrahepatic portosystemic shunt

Data on occurrence of hepatic encephalopathy were available for 958 patients. The pooled estimate rate for hepatic encephalopathy after TIPS insertion was 0.25 (95% CI = 0.17–0.36, Figure 4 and Table 2). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 89\%$). No publication bias was detected by the Begg and Mazumdar test ($p = 0.1$) but a publication bias was detected by the Egger test ($p = 0.005$).

Rates for occurrence of hepatic encephalopathy after TIPS were quantitatively lower in studies that did not use covered TIPS or that included patients without considering pre-emptive TIPS in the management of acute variceal bleeding (Table 3).

Secondary endpoints–Successful placement of Transjugular intrahepatic portosystemic shunt

Data on TIPS feasibility were available for 1183 patients. The pooled estimate rate for successful placement of TIPS was 0.96 (95% CI = 0.94–0.98, Figure S1 and Table 2). There was low heterogeneity between studies ($p = 0.2$, $I^2 = 18\%$). No publication bias was detected by the Begg and Mazumdar test ($p = 0.2$) but a publication bias was detected by the Egger test ($p = 0.001$).

Rates of successful placement of TIPS were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Secondary endpoints–Access to liver transplantation

Data on access to liver transplantation were available for 670 patients. The pooled estimate rate for access to liver transplantation after TIPS insertion was 0.08 (95% CI = 0.05–0.13, Figure S2 and Table 2). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 69\%$). No publication bias was detected by the Egger test ($p = 0.1$) or by the Begg and Mazumdar test ($p = 0.2$).

In sensitivity analysis excluding the Rudler study,[37] the pooled estimate rate for access to liver transplantation after TIPS insertion was 0.08 (95% CI = 0.05–0.13). There was high heterogeneity between studies ($p < 0.01$, $I^2 = 63\%$).

Rates of access to liver transplantation after TIPS insertion were not quantitatively different in subgroup analyses based on the type of TIPS or the recommendation to use pre-emptive TIPS in eligible patients (Table 3).

Results of additional subgroup analyses among studies that exclusively used covered stents and among those published before and after 2010 are reported in Supplementary information (Supp 1 and 2).

DISCUSSION

In patients with cirrhosis and variceal bleeding, TIPS may be used in three different circumstances: immediately in case of acute variceal bleeding as a pre-emptive treatment in patients at high risk of rebleeding; as a secondary prophylaxis in patients who stopped bleeding after a first episode of acute variceal bleeding and then rebled; or as a salvage therapy in patients with refractory variceal bleeding. The first 2 situations have already been largely studied

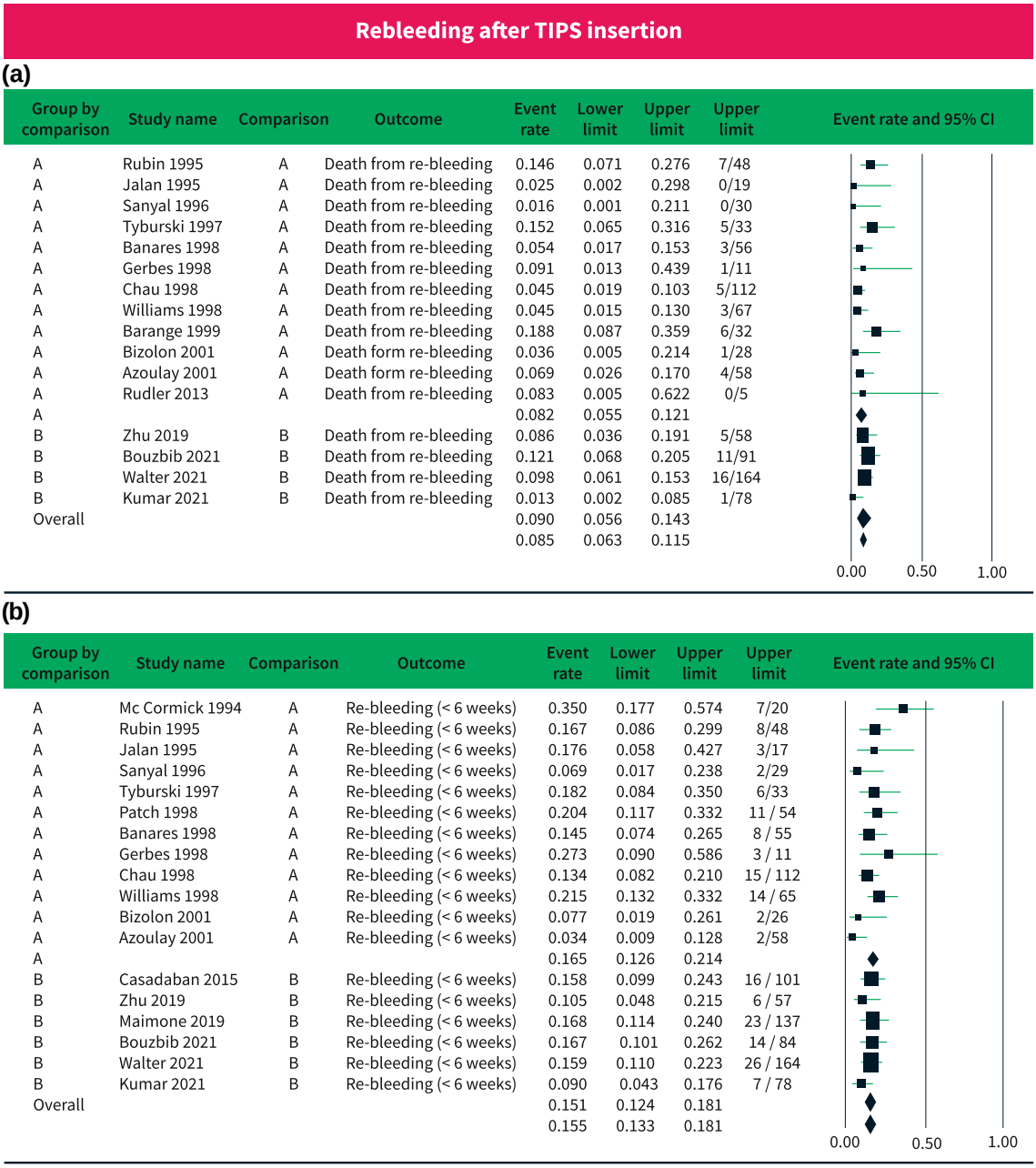

FIGURE 3 Rebleeding after transjugular intrahepatic portosystemic shunt (TIPS) insertion: Pooled estimate rate for death from rebleeding (a) or occurrence of rebleeding at 6 weeks (b) in patients with cirrhosis and refractory variceal bleeding. Studies before (group A) or after (group B) the use of PTFE-covered TIPS and the pre-emptive TIPS recommendation. TIPS, transjugular intrahepatic portosystemic shunt

and evaluated in several meta-analyses.[7,48,49] Regarding refractory variceal bleeding, a number of reports have provided results for patients treated with salvage TIPS. These individual publications often address only a limited number of patients. Hence, a meta-analysis was needed to synthesize the data available on the efficacy of TIPS as a salvage therapy in this setting to assess the impact of recent management changes given the dire outcome for those patients.

The main result of the present meta-analysis is that 33% of patients treated with salvage TIPS died 1 month to 6 weeks after TIPS insertion. This percentage increases to 46% at 1 year. Of note, only 15% of patients rebled in the follow-up after TIPS placement and 9% died from uncontrolled rebleeding. We acknowledge that studies included in this meta-analysis were performed over a long period of time within which the standard-of-care for acute variceal bleeding has changed. More specifically, PTFE-covered stents have been used since the end of the 2000s after the publication of a first study showing that PTFE-covered TIPS were associated with reduced rates of stent dysfunction and improved clinical outcomes in patients with cirrhosis and uncontrolled bleeding, recurrent bleeding or refractory ascites.[17] Another important change in the management of patients with cirrhosis and acute variceal bleeding is the recommendation to

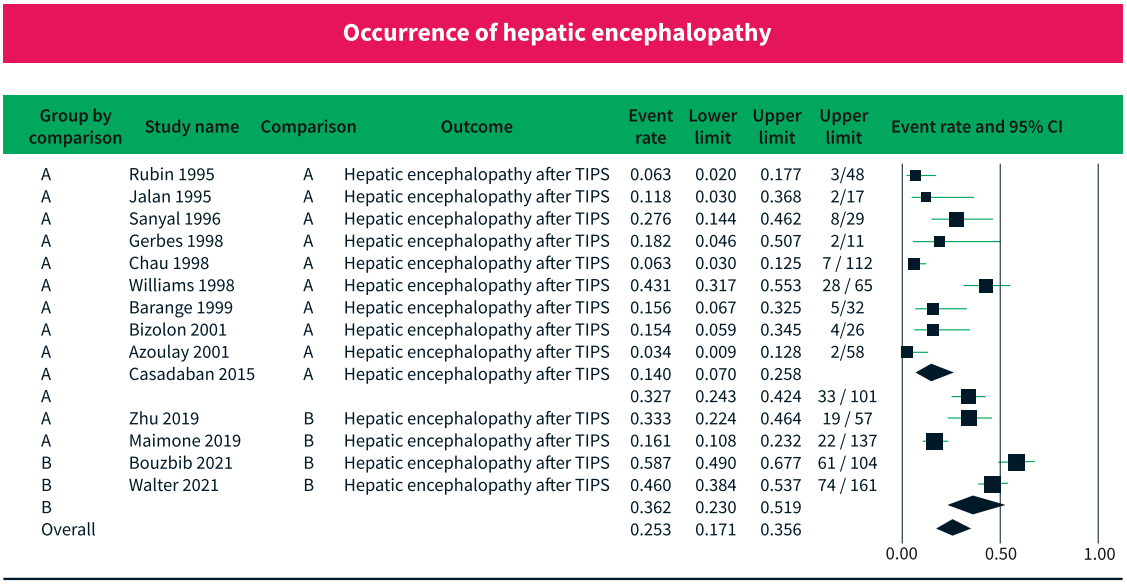

FIGURE 4 Occurrence of hepatic encephalopathy: Pooled estimate rate for hepatic encephalopathy after transjugular intrahepatic portosystemic shunt (TIPS) insertion in patients with cirrhosis and refractory variceal bleeding. Studies before (group A) or after (group B) the use of PTFE-covered TIPS and the pre-emptive TIPS recommendation. TIPS, transjugular intrahepatic portosystemic shunt

use pre-emptive TIPS as a first-line treatment in patients at high risk of rebleeding. This followed the publication of a randomized controlled trial showing a survival benefit for patients treated with pre-emptive TIPS compared to controls receiving standard-of-care.[18] Hence, compared to recent studies, older studies may have included patients with refractory variceal bleeding who would have been eligible for pre-emptive TIPS, which may result in different study populations exposed to the risk of refractory variceal bleeding. To overcome these limitations, we decided prior to the beginning of the meta-analysis to perform 2 subgroup analyses according to these two important changes in patient management.

Of note, pooled estimate rates for early death (i.e., death occurring within 1 month or 6 weeks), the most important endpoint in this study population, were not different between older studies (0.33, 95% CI: 0.28–0.38) and more recent ones (0.32, 95% CI: 0.26–0.39). One possible explanation for this unexpected finding could be that only a minority of eligible patients with acute variceal bleeding actually receive pre-emptive TIPS in real-life settings.[8,9] Thus, the recommendation to use pre-emptive TIPS in patients at high risk of rebleeding is unlikely to have significantly changed the selection of patients exposed to the risk of refractory variceal bleeding. Furthermore, a recent prospective randomized trial showed that the main benefit of PTFE-covered stents is the reduced rate of long-term stent dysfunction, that is, 2 years after TIPS insertion.[51] This delay is much longer than the one during which patients with refractory variceal bleeding are at risk of dying, which could at least partially explain why using PTFE-covered stents did not translate into lower death rates. Of note, we also ran a subgroup analysis in studies that only used covered stents[41–43,50] and reached similar results for the various outcomes we studied (Supp 2). Likewise, since the management of patients with variceal bleeding and decompensated cirrhosis or Acute-on-Chronic Liver Failure has significantly improved in recent years, we performed subgroup analyses comparing studies published before or after 2010 and the results reflected those reached in the first subgroup analysis we did (Supp 3). Thus, the management of patients with acute variceal bleeding has undoubtedly improved during the last decade and this may result in fewer patients suffering from refractory variceal bleeding. Yet, once the variceal bleeding becomes refractory, the outcomes for patients requiring the placement of a TIPS as salvage therapy remains unchanged.

Another important finding of this meta-analysis is the occurrence of hepatic encephalopathy in a significant proportion of patients (25%), a percentage that needs to be balanced with the very high risk of dying if TIPS is not offered as a salvage therapy. In line with these results, it should be outlined that 8% of patients had access to liver transplantation after emergency TIPS. As patients with refractory variceal bleeding often have severe liver dysfunction, reducing the rate of rebleeding (and consequently short-term mortality) allows some patients with severe cirrhosis who were not identified earlier using conventional criteria to be listed and transplanted within a short time.

Although randomized controlled trials are considered the best way for assessing a treatment effect, this does not fully apply to patients with cirrhosis and refractory variceal bleeding treated with salvage TIPS for a number of reasons. First, blinding the therapeutic intervention would not be possible. Second, there is no satisfactory control group to compare to patients treated with salvage TIPS. Third, it is likely that patients who could be enrolled in a randomized trial would differ from the average patients seen in daily practice. Hence, the results of observational studies appear to be more relevant to clinical practice.[52] Currently, self-expanding metal stents are the only alternative as an emergency treatment for refractory

variceal bleeding when patients have a quick prospect of liver transplantation or as a bridge to TIPS in centers where salvage TIPS placement is not an option.[11] Overall, this meta-analysis underlines that further studies in this field could be useful for determining the role of other treatments susceptible of improving the prognosis of patients with refractory variceal bleeding, such as a prolonged use of antibiotics for the prevention of septic complications.

This study has several limitations. A classical drawback of meta-analyses is related to the presence of heterogeneity that may prevent making robust conclusions and recommendations. This reflects the fact that a substantial proportion of the difference in the effect between studies may be explained not only by random sampling but because of true differences between studies. In this meta-analysis, moderate to high heterogeneity was found for several analyses, suggesting that other factors than those taken into account in these analyses may have influenced the outcomes. On the other hand, low heterogeneity was observed for several endpoints, suggesting a robust and reproducible effect. Specific data according to Child-Pugh or MELD score would be of interest. However, this information was NA for most studies. No publication bias was identified using the Egger test and the Begg and Mazumdar test for most endpoints. However, these tests do not guarantee the lack of publication bias. Another limitation of this meta-analysis is related to the limited quality of the included studies.

In summary, this meta-analysis indicates that one third of patients with cirrhosis and refractory variceal bleeding treated with salvage TIPS died within the first 6 weeks, a result consistent in subgroup analyses regrouping old or recent studies. These findings suggest that the recent improvements made in the management of patients with acute variceal bleeding do not translate into survival benefits once patients present refractory variceal bleeding. New public health strategies promoting the screening for cirrhosis in patients at risk and a close monitoring of cirrhotic patients with non-invasive methods such as transient elastography are required to reduce the incidence of refractory variceal bleeding through allowing early identification of patients at risk of bleeding.[5] Additional studies are also required to identify potential risk factors leading to a poor prognosis after salvage TIPS in patients with refractory variceal bleeding and to determine the impact of the degree of liver failure on the patients' prognosis.

AUTHOR CONTRIBUTIONS

Laura Weichselbaum: acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content. Antonia Lepida: acquisition of data; analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Astrid Marot: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Eric Trépo: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Christophe Moreno: analysis and interpretation of data; critical revision of the manuscript for important intellectual content. Pierre Deltenre: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; study supervision. All authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

No conflicts of interest exist for any of the authors in relation to this study.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

ORCID

Laura Weichselbaum https://orcid.org/0000-0001-8869-944X
Antonia Lepida https://orcid.org/0000-0002-6578-3726
Pierre Deltenre https://orcid.org/0000-0002-4253-6028

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