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1. JYSELECA SmPC, May 2023; 2. Feagan BG, *et al. Lancet* 2021;397(10292):2372–2384; 3. Schreiber S, *et al. J Crohns Colitis* 2023;17(6):863–875.

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Transjugular intrahepatic portosystemic shunt in patients with hepatocellular carcinoma: A systematic review

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Abstract

Background/Aims: Transjugular intrahepatic portosystemic shunts (TIPS) in patients with hepatocellular carcinoma (HCC) may improve access to curative therapies, treat portal hypertension (PH)-related complications without worsening liver function, and increase overall survival. Data on the efficacy and safety of TIPS to treat PH complications in HCC patients, as well as the HCC treatment response, were evaluated.

Methods: Studies reporting efficacy in controlling bleeding/ascites or response to HCC therapy, safety, and survival in patients with HCC and TIPS were searched systematically on PubMed and Embase. An extraction of articles using predefined data fields and quality indicators was used.

Results: We selected 19 studies and found 937 patients treated for ascites/bleeding and 177 evaluating HCC treatment response. Over half were under 5 cm and solitary lesions, and most studies included tumours with portal vein thrombosis. Regarding PH studies, TIPS resolved bleeding/ascites in >60% of patients, more effective for bleeding. There were no lethal complications reported and procedural bleeding occurred in <5%. Hepatic encephalopathy occurred in 15%–30% within three months. In the HCC treatment-response studies, major complication rates were low with no mortality. In the studies that evaluated the response to transarterial chemoembolization, complete response rate of patients with TIPS varied from 16% to 75%. Liver transplantation rate varied from 8% to 80%, with >40% rate in half of the studies.

Conclusions: In the published studies, TIPS is effective in treating PH complications in patients with HCC. Prospective studies on TIPS placement in patients with HCC are urgently needed to evaluate the efficacy and safety of TIPS in this setting.

KEYWORDS
cirrhosis, HCC, hepatocellular carcinoma, liver cancer, portal hypertension, TIPS

INTRODUCTION

Hepatocellular carcinoma (HCC) and portal hypertension (PH)-related decompensation, mainly variceal bleeding (VB) and ascites, are the most common complications of liver cirrhosis and frequently coexist. In early HCCs, around 31%–45% of patients have clinically significant PH, defined by hepatic venous pressure gradient or clinical and noninvasive criteria, whilst its prevalence is likely higher but is unknown in advanced stages of HCC.[1–3] TIPS is an established therapy for severe cases of PH. Pre-emptive TIPS placed within the first 72 h of admission for acute VB improves survival in patients with cirrhosis Child-Pugh $B > 7$ and active bleeding and Child $C < 14$, and TIPS can increase survival rates in selected patients with recurrent or refractory ascites.[4–8]

PH-related complications can occur in patients with HCC, and HCC, per se, represents an independent risk factor for rebleeding after an index episode.[9,10] Short-term mortality in patients with VB and HCC depends on bleeding, and TIPS could be a potential life-saving procedure in these cases. However, in the past, the risks of post-TIPS liver failure and tumour dissemination, as well as the risk of limiting further local therapeutic options, contraindicated TIPS in patients with HCC.[11]

Transjugular intrahepatic portosystemic shunts diverts portal venous flow, leading to concerns of liver failure and tumour dissemination in patients undergoing transarterial chemoembolization (TACE),[11] but this has not been observed in other studies. Therefore, traditionally, HCC, particularly outside Milan criteria, has been considered an exclusion criterion in most randomized controlled trials and a relative contraindication, in clinical practice. Recently, diagnostic and therapeutic options for HCC have significantly increased, leading to an increase in overall survival ,OS, particularly in the late stages. Bleeding is a frequent cause of death in these patients[10] and ascites limits access to curative locoregional therapy, suggesting that an optimal treatment of PH might improve outcomes in patients with HCC. In some non-controlled retrospective cohorts, TIPS placement has shown to be safe and effective in patients with HCC.

Nevertheless, it is unestablished whether TIPS in patients with HCC can improve survival, and which patients would benefit the most. The aim of this systemic review is to synthesize the evidence on the efficacy and safety of TIPS in HCC patients to treat PH complications and as a bridge to other therapies and highlight the current gaps in knowledge.

METHODS

We performed a systematic review of the published studies in this field; the study search and selection, and data extraction were performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses recommendations.[12] Ethics approval was waived due to the nature of the study.

Key summary

Summarise the established knowledge on this subject

- Treatment of hepatocellular carcinoma (HCC) is limited in patients with portal hypertension-related complications.
- Although transjugular intrahepatic portosystemic shunt (TIPS) may be an effective treatment for ascites and bleeding and provide patients with HCC access to therapies, the current data is too scarce and inconsistent to recommend, globally, its use. Patients should be discussed on a case-by-case basis.

What are the significant and/or new findings of this study?

- This review demonstrates that TIPS in HCC is effective in treating PH with low procedural bleeding, but large prospective studies are required in order to better assess efficacy, safety and optimal patient selection for TIPS in the setting of HCC.

Definitions

Studies including patients with HCC who were submitted to TIPS were included if sufficient data regarding the main characteristics of patients, cirrhosis stage, HCC, and outcomes were provided. There was no minimum follow-up period defined for the outcomes. Sufficient baseline data was defined as follows: 1) at least 10 patients with HCC and TIPS; 2) available demographic and disease stage data (age, gender, aetiology, Child-Pugh or MELD score). Two types of studies were found; first those that assessed the use of TIPS to treat complications of PH (mostly VB and ascites) in patients with HCC and second those that assessed the effect of TIPS on patients' response to treatment for HCC (local or systemic therapy). The PH treatment studies will be referred to as "PH studies" and the latter studies as "HCC treatment response" studies. For the PH studies, sufficient outcome data was defined as follows: 1) rate of VB ascites resolution; 2) OS rate; and 3) overall complication rate. For the HCC treatment response studies, sufficient outcome data was defined as follows: 1) treatment type and response rate and 2) OS rate. The main outcomes assessed for the PH studies were technical feasibility, major procedural complication rate, efficacy in treating ascites or VB, and survival. The main outcomes assessed for the HCC treatment response studies were treatment response (RECIST criteria), major procedural complication rate, and survival. Regarding efficacy in treating VB and ascites, the reporting is inconsistent. Some studies defined this as absence of clinically detectable ascites with or without diuretic therapy or no need for further paracentesis and/or no further VB episodes after TIPS,[13,14] whereas others establish a specific time point for recurrence of gastroesophageal VB and ascites/hydrothorax, such as in 12 months.[15]

We used the following definitions. "Technical feasibility": successful access to the portal vein, and placement of TIPS. "Major procedural complication": serious or potentially life-threatening event because of endovascular treatment, for example, intraperitoneal bleeding or after locoregional therapy such as postembolization syndrome. "Technical follow-up complications": shunt-related complications such as stenosis, dysfunction or thrombosis of the stent. Stent dysfunction was reported as per authors' criteria. In most cases, TIPS was revised, if either changes in Doppler ultrasound or recurrent bleeding and/or ascites, and in some cases, it was undefined.

Search strategy and inclusion and exclusion criteria

Two electronic databases were searched: PubMed and Embase for articles in the English language that were published until 31 August 2022 (last search run). Randomised-controlled trials and prospective and retrospective cohort studies with original data and full text published were included. Search terms were ("hepatocellular carcinoma" or "HCC") and ("transjugular intrahepatic portosystemic shunt" or "TIPS") and ("cirrhosis" or "liver cirrhosis"). Search results were merged.

Exclusion criteria were case reports or studies with fewer than 10 patients and studies lacking the minimal data required for the analysis (see "data extraction"). Studies lacking data on efficacy and/or treatment response (for PH and HCC treatment response studies, respectively), complication rates and survival, in addition to providing baseline characteristics of the patients (age, sex, Child-Pugh or MELD score) were excluded. Abstracts were independently reviewed by two investigators (BN and SGR). In case of discrepancy regarding the eligibility for the analysis, a consensus was reached by another author (AB), and in the case of cohort overlap, the most recent publication was selected.

Data extraction

After selecting the studies, the authors separated them into PH and treatment response studies. General characteristics were collected: first author, year published, study design, age, sex, Child-Pugh Score, MELD Score, presence of portal vein thrombosis (PVT), alpha fetoprotein value, size, number and location of HCC, Barcelona Clinic Liver Cancer (BCLC) stage, whether HCC within Milan criteria, and TIPS indication and type of stent. Regarding outcome data extraction, in the PH studies, the following were extracted: efficacy in the treatment of PH, portal pressure gradient (PPG) change, major procedural and technical complications, further decompensation, survival/liver transplantation, and response to HCC therapy. For studies in the treatment response group, in addition to the baseline characteristics, the following data was obtained: the type of treatment used, systemic or local, and number of sessions, local response, major procedural complications, recurrence, and bridge to transplantation/survival.

Quality assessment from individual studies

Quality assessment was performed using the Newcastle-Ottawa Scale.[16] Studies were considered of high quality if ≥8 points (89), moderate quality, if 6–7 points, and low quality, if ≤5 points (Supplementary Tables 1 and 2). Ethical approval was not sought because of the study design.

RESULTS

Results of the study search are depicted in Figure 1. Among the final 34 excluded full texts, three studies were considered irrelevant due to insufficient outcome data. Of the 19 included studies, 11 dealt with HCC patients who received TIPS to treat PH-related complications, and the remaining eight evaluated the effect of TIPS on HCC treatment response. As clarified in the Methods section, the results of these two groups are presented separately.

Indication for TIPS: Treatment of portal hypertension-related complications

Study selection and characteristics of included studies

All 11 studies (Table 1) were retrospective of low to medium quality (Supplementary Table 1) and in total included 937 patients, 870 of which with TIPS placement after the diagnosis of HCC to treat the complications.[13–15, 17–24] Most studies originated from China and the majority had hepatitis B virus-associated cirrhosis and/or alcohol-related disease. Patients were mostly male (range: 57.9%–100%) and the mean age ranged from 46.3 to 63.5 years. Regarding Child-Pugh class, with the exception of one small study that evaluated patients in the palliative setting,[17] the majority of patients were Child-Pugh A (19.0%–61.5%) and B (34.4%–72.5%), with the latter group being the most frequent. In four studies, including 178 patients, the patients were in an advanced stage of HCC with PVT, considered tumoral thrombus. Seven out of 10 studies provided data regarding the number of lesions. Most were solitary, ranging from 33.8% to 77.8%. Six studies provided the average size or percentage of patients with lesions under 3 or 5 cm, in which 57.4%–97.1% were under 5 cm. Transjugular intrahepatic portosystemic shunts was indicated for VB (50%–100%) and/or ascites (7.7%–35%) One study specifically evaluated TIPS in patients with refractory ascites without bleeding.[25]

Outcomes: Feasibility, efficacy and survival

A summary of the outcomes reported is provided in Table 2.

It is impossible to evaluate the feasibility of TIPS placement in the setting of HCC, as most studies simply report the data on patients in whom TIPS was placed and provide no information on the number of attempted/failed cases.

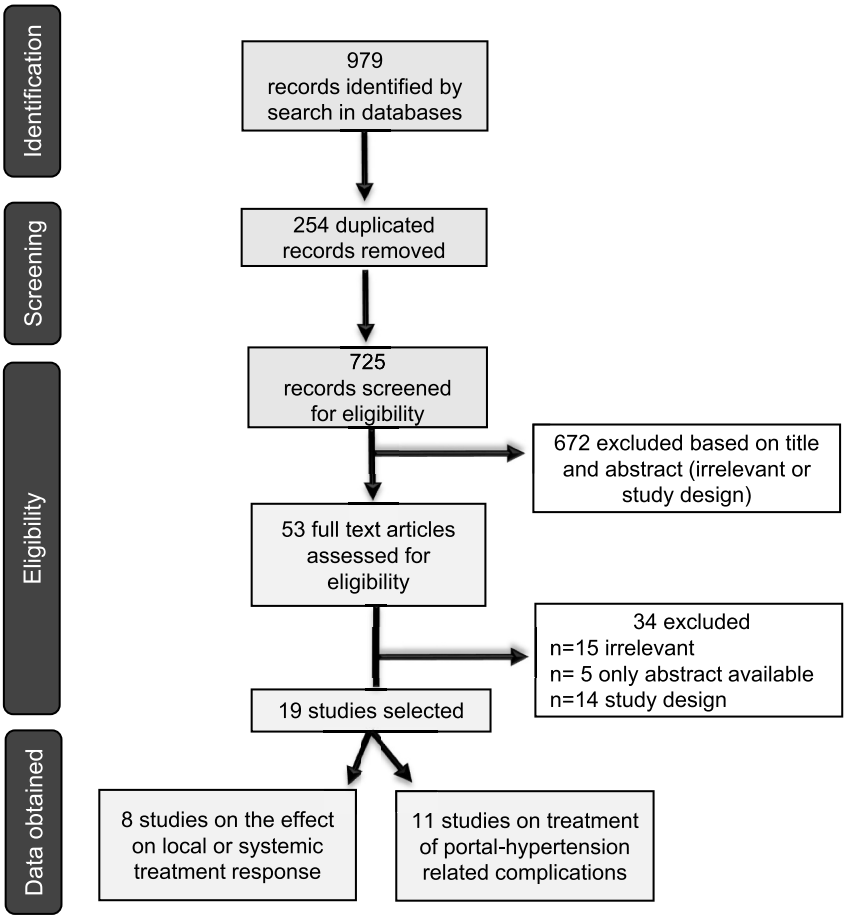

FIGURE 1 Flowchart of studies in the systematic review following PRISMA guideline and recommendation.

The absolute decrease in PPG varied from a reduction in 10–20 mmHg. However, only four studies reported average decrease in gradient to a level <12 mmHg.[13,14,17,20] Regarding PH-related complications, 56%–100% (in most studies >70%) of patients did not rebleed, and ascites resolved in 50%–95%.

Aside from TIPS for the PH-related complications, 30%–60% of patients received sessions of local (TACE and/or ablation) or systemic HCC-directed therapy. The OS varied greatly between 2.6 and 43.7 months. This depended on the stage of liver disease and HCC. In studies including exclusively patients without PV macrovascular invasion,[14,23] the OS ranged between 30 and 44 months. Better liver function, that is, lower Child-Pugh Score, absence of macrovascular invasion, solitary or smaller HCCs (<3 cm) and ALBI score were among the factors linked to better survival. Death was attributed predominantly to liver failure and tumour progression, and liver transplantation rate, was reported in only two studies from 1.6% to 5.9%.[14,24]

Complications

No lethal complications were reported. Bleeding rate was low (mostly <5%) and the rate of post-TIPS hepatic encephalopathy (HE) ranged from 13% to 55%, with most studies reporting an incidence between 15% and 30% within the first 3 months post-TIPS. Stent dysfunction in the follow-up was described within the first year, in most studies, and ranged 6%–38%, with one study reporting dysfunction in 58%.[15] In three studies with higher dysfunction rates (≥20%), the stents were bare and covered (vs. 100% covered),[13,19,23] or in an advanced HCC setting.[14]

Indication: Effect of transjugular intrahepatic portosystemic shunts on treatment response

Study selection and characteristics of included studies

All eight (Table 3) were retrospective of low to medium quality (Supplementary Table 2) and in total included 177 patients.[11, 26–32] Transarterial chemoembolization was the most frequent treatment, but some patients were treated with ablation,[28–30] radioembolization[28,32] and in one case stereotactic body radiotherapy.[30] Most studies originate from the United States. The aetiology in American studies was mostly alcohol or hepatitis C and hepatitis B in Asian countries. Patients were mostly males (range: 59%–90%) aged 51–73 years. Over 50% of the cases were in Child-Pugh B. MELD score was reported in six studies, from 7 to 25 points.

TABLE 1 Baseline characteristics: Treatment of portal hypertension.

Author	Year	Country	Design	Number of patients	Age (years)	Male sex (%)	Aetiology (%)	Child-Pugh class (%)	MELD	AFP (ng/mL)	PVTT (%)	Degree PVT (%)	Size HCC	Within Milan criteria (%)	Location	Solitary (%)	BCLC (%)
Jiang Z-B	2004	China	Retro	14 (10)[a]	56.3 (28–75)	92.9	NA	C 100	NA	NA	100	57.1 complete 42.9 partial	NA	None	NA	NA	D 100
Liu L	2014	China	Retro	58	51.7 (28–72)	86.2	98.2 HBV	A 19 B 59 C 22	NA	NA	100	44.8 complete 55.2 partial	8.87 cm (2.6–16)	NA	NA	1–2 lesions 65.5	C/D 60/40
Zhao J-B	2014	China	Retro	11	54.3 ± 12.7	100	100 HBV	A 54.5 B 45.5 C 0	NA	NA	100	100 complete	NA	NA	45% RL 27% LL 27% both	NA	NA
Qiu B	2015	China	Retro	261 (209)[a]	48.3 ± 12.5	57.9	86 HBV 5.7 HCV 1 both	A 39.7 B 34.4 C 25.8	NA	NA	14.8	NA	<3 cm: 24.8% 3–5 cm: 49% >5 cm: 25.8%	NA	NA	70.8	NA
Bettinger D	2015	Germany	Retro	40	63.5 (40–83)	87.5	62.5 alcohol; 27.5 HCV	A 7.5 B 72.5 C 20.0	13 (7–22)	6.7 (0.7–7125.0)	32.5	NA	3.7 ± 1.8	40	37.5% centrally	55	NA
Qiu B	2017	China/USA	Retro	95 (91)[a]	49.1 ± 11.5	59.0	NA	A 17 B 39 C 35	NA	NA	100	9 Vp1[b] 15 Vp2[b] 23 Vp3[b] 53Vp4[b]	<3 cm: 25.3% 3–5 cm: 54.8% >5 cm: 19.9%	NA	NA	73.6	NA
Luo S-H	2019	China	Retro	217 (212)[a]	46.32 ± 12.43	54.2	59 viral 31 alcohol	A 25 B 60.8 C 16	10.21 ± 5.25	468.53 ± 34.27	0	NA	NA	NA	NA	NA	A 8.4 B 50.4 C 25 D 16
Yan H	2020	China	Retro	68	58 (46–63)	89.7	97.1 HBV	A 10.3 B 72.1 C (17.6)	<15: 77.9% ≥15: 20.6%	>400 29.4%	66.2	NA	<5 cm: 57.4%	22.1	NA	33.8	A (14.7) B (14.7) C (52.9) D (17.6)
Luo J	2021	China	Retro	34	54.9 ± 8.5	91.2	91.2 HBV	7 (6–8) A 41.2 B 52.9 C 5.9	11.5 (9.75–13.25)	>100 14.7%	0	NA	<3 cm 97.1%	100	47.1%: Subcapsular; 23.5% Hilar; 5.9% Peri-diaphragm; 11.8% Peri-vascular	64.7	NA

(Continues)

TABLE 1 (Continued)

Author	Year	Country	Design	Number of patients	Age (years)	Male sex (%)	Aetiology (%)	Child-Pugh class (%)	MELD	AFP (ng/mL)	PVTT (%)	Degree PVT (%)	Size HCC	Within Milan criteria (%)	Location	Solitary (%)	BCLC (%)
Dong H	2021	China	Retro	13	58 (52.5–62.5)	61.5	92.3 HBV	A 61.5 B 38.5 C 0	NA	NA	0	NA	NA	NA	RL 100%	NA	A 61.5 B 38.5
Tsauo J	2021	China	Retro	126 (124)[a]	54.1 ± 10.2	87.3	81.7 HBV 7.9 HCV 3.2 alcohol 3.2 HBV + HCV; 4.0 other	7.2 ± 1.5	11.4 ± 3.3	NA	23.8	3.2 Vp1[b] 4.8 Vp2[b] 15.9 Vp3[b] 4.0 Vp4[b]	4.2 cm ± 3.0	NA	RL 49.2% LL 30.2% BL 20.6%	77.8	A 38.1 B 11.9 C 42.1 D 7.9

Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BL, bilobar; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LL, left lobe; MELD, model for end-stage liver disease; NA, not available; PVTT, portal vein tumour thrombosis; Retro, retrospective; RL, right lobe.

[a]Number of patients in which TIPS were placed.

[b]Liver Cancer Study Group of Japan (LCSGJ), distinguished four grades of portal vein tumour thrombosis.

Macrovascular invasion was reported in one study only for three patients[26] and PVT in 6/29 (21%) and 2/25 (8%) in two studies.[28,31] Most had a solitary HCC (56%–80%), with a mean size 1.2–8.8 cm. All had HCC treatment after TIPS placement, except in one,[26] where some underwent sessions of TACE before TIPS. Indications for TIPS were VB (43%–100%) and ascites (29%–56%). Regarding BCLC stage, patients were distributed heterogeneously: stage A 18.8%–50%, stage B 7.7%–36.8%, stage C 0%–52% and stage D 0%–26.3%.

Outcomes: Complications, survival and response to hepatocellular carcinoma therapy

Major complication rates were low with no mortality (Table 4).

In patients with TIPS who received locoregional treatment for HCC, evaluating the response to TACE,[11, 26–28] complete response was reported in 16%–75%, partial 6.3%–20%, stable 10%–26% and progressive 5%–42%.

Data on recurrence was scarce. The median follow-up periods varied from 12 to 33 months. Overall survival ranged between 23 and 75 months, with 1-year and 3-year rates of 85%–100% and 30%–67%, respectively. Seven studies reported liver transplantation rates from 8% to 80%, half reporting transplantation ≥40% of cases.

DISCUSSION

Transjugular intrahepatic portosystemic shunts is recognized as an effective and minimally invasive technique that improves survival in selected patients with cirrhosis and complications of PH.[7,33] HCC has been traditionally considered a relative contraindication, particularly if centrally located[34] mostly for fear of tumour spread, lung dissemination and liver failure, and concerns regarding the risks of portal flow diversion in HCC patients requiring TACE.[11]

As a result, most patients with HCC were denied TIPS, even with complications of PH, which have worse outcomes in HCC patients.[9,10] However, this was linked with inadequate treatment for the prevention of recurrent variceal hemorrhage.[10] Since TIPS has been proved life-saving when used early in high-risk patients, understanding the current status on TIPS for PH complications in HCC is a compelling question. We conducted this systematic review to assess data in the context of HCC and TIPS. As expected, the largest number of published studies reported TIPS to treat complications of PH, which are common in HCC. One important limitation is the lack of reporting on TIPS feasibility. This is clinically very relevant, in the setting of HCC, and authors do not report the limiting factors in TIPS placement, such as anatomical or technical restrictions. Furthermore, in the specific setting of PVT, authors refer to "tumoral thrombus" but do not define how the diagnosis was established between bland and tumoral thrombus. Overall, in >70% of patients, TIPS successfully reduced portal pressure and controlled VB and/or ascites. In studies with smaller HCCs, bleeding stopped in over 90% of cases, and ascites improved in over 70%.[13,14,19, 22–24] Even so, important technical details such as the method and timing of pressure gradient

TABLE 2 Outcomes: Treatment of portal hypertension.

Author	Indication (%)	Efficacy (%)/ feasibility (%)	Covered stent (%)/ Timing TIPS	PPG change (mmHg)	Other therapy (%)	Major procedural complications (%)	Further bleeding/ ascites	Technical follow-up complications (%)	Follow-up period	Survival	Factors linked better survival	Causes of death (%)	OLT (%)	Response to therapy (%)
Jiang Z-B	21.4 ascites; 71.4 VB+ ascites; 7.1 VB	NA/ 71.4 (cavernoma)	NA	37.2 to 18.2	0	Peritoneum puncture	NA	10 Dysfunction 15d 10 Dysfunction 30d	3 mo	132.3 d	Successful TIPS placed	100 Liver failure	NA	NA
Liu L	50 VB; 34.4 Ascites; 15.5 Diarrhoea	95 ascites; 100 hydrothorax; 100 VB; NA	39.7/ post-HCC	14	31.0 in 1-2 sessions TACE pre-TIPS; 34.5 TACE post-TIPS	20.7 HCC rupture 17 HE 30d 26 HE 90d	NA	91 patent 30d 79 patent 90d	78.5 d (range 11–1713);	OS: 77 d (48.4–105.6); 30 d 49% 90 d 27% 1y 3.4%	Higher degree of thrombosis, WBC and ascites	27.6 Bleeding; 43.1 liver failure; 15.5 MOF; 8.6 HCC rupture; 1.7 cerebral bleed	NA	15 CR; 80 PR 5 No response
Zhao J-B	81.8 VB; 18.2 ascites	100 VB; 50 ascites/NA	100/ post-HCC	32.0 to 11.8	63.6 TACE/ 27.3 RFA	54.5 HE	NA	NA	2-18 mo	1-y 18.2%	NA	100 MOF	NA	NA
Qiu B	87 VB; 18.6 ascites+VB; 5.7 ascites	56/NA	46.4/ pre + post-HCC	29.0 ± 4.1 to 18.1 ± 2.9	11.4 RFA, 45.9 TA(C)E/42.6 RFA + TA(C)E	39.2 HE	NA	Dysfunction 58.3	5 y	1y 91.4%; 2y 84.7%; 3y 71.8% 4y 51.2% 5y 38.8%	Child-Pugh, PVTT, size, fistulas, HCC diag. before or after TIPS, stent type, HE, other treatments	17.2 GI bleeding; 14.8 liver failure/MOF; 13.9 infection; 9.1 HCC progression	NA	NA
Bettinger D	57.5 refractory ascites, 35.0 VB; 7.5 ascites+VB	74 ascites, 100 bleeding;/NA	40/ post-HCC	20.0 (13.0–33.0) to 8.0 (2–16)	9 TACE 2 TAE	0 major; 40 HE	NA	20 dysfunction; 7.5 thrombosis	211 d	OS 180 d 1y 42.5%; 5y 7.5%	No PVTT	94.4 tumour progression; 5.6 MOF post TIPS	NA	n=1 CR, n=5 SD; n=2 PD
Qiu B	69.2 VB; 13.2 Ascites/ Hydrothorax 17.6 VB+Ascites	95.8 overall 100 bleeding 92.9 ascites/NA	57.1/ post-HCC	31.3 ± 2.6 to 20.8 ± 1.4	47.2 TACE 11 RFA 37 TACE+RFA 12 Systemic	2.1 major bleeding; 41.7 HE	17.9 recurrent ascites/ hydrothorax 39.2 bleeding	37.5 dysfunction	NA	6m 75.8% 1y 52.7%; 2y 26.4%	Covered stents, Vp2 PVTT, single HCC or <3 cm, Child-Pugh A	n=25 tumour progression, n=16 rebleeding, n=15 liver/MOF, n = 32, cardiovasc	NA	NA
Luo S-H	78.3 VB, 21.7 refractory ascites	91.0 at 30d 83.3 Overall bleeding 86.6 at 30d ascites 71.5 Overall ascites/NA	100/ post-HCC	23.37 ± 6.51 to 9.43 ± 3.14	212 TACE 133 TACE 1st 79 TIPS 1st 364 RFA sessions in total	17.1 HE	NA	29.54 recurrent ascites due to dysfunction	NA	OS 43.7 mo 5y 41.5%	Increased age, ALBI score, creatinine, and decreased sodium	7 from VB, 56 from hepatic tumour, 25 from hepatic failure, 24 MOF, and 12 other causes	NA	2.3 CR, 17.4 PR, 29 SD, 50.9 PD 49.1 Disease control rate
Yan H	100 ascites; 19.1 VB; 2.9 pain/diarrhoea	55.9 refractory ascites 30 Partially 13 No response/NA	100 16 also bare/ post-HCC	28.3 to 12.9	14.7 TACE, 30.9 TACE + MWA, 4.4 MWA, 47.1 Systemic, 14.7 systemic+ TACE	7.4 small hematoma; 1.5 hemobilia 13.2 HE; 1.5 ALF	NA	14.7 dysfunction	9.6 (0.5-49.6)	OS 8.7 mo (0.4-49.6)	Change in Child-Pugh Score and AFP >/> 400 – independent for OS	NA	NA	NA
Luo J	100 VB; 70.6 Ascites	94.1 control bleeding/NA	17 bare + covered 17 covered/ post-HCC	All <12 and reduced at 25%	21 TACE 2 RFA 2 TACE +RFA	23.5 HE at 1y	5.9 rebled	5.9 dysfunction	33.1 mo (8.6-95.3)	1y 82.4%, 2y 66.4%		n=6 HCC progression, n=6 liver failure, n=6 bleeding, n=1 lung metastasis, n=1 stroke	5.9	NA
Hong D	100 VB, 7.7 ascites	NA	100 covered +bare/ post-HCC	27.85 ± 7.02 to 16.23 ± 6.61	23 TACE and 14 MWA sessions 13 Systemic therapy	NA	NA	38.5 dysfunction		OS 29.8 ±11.5 mo PFS 20.2 mo +13.2		NA	NA	NA
Tsauo J	100 prevention of gastric VB	Rebleeding 20.6 overall 98.3 6-week 81.2 1y 72.5 3y/ NA	69.5/post-HCC		29.4 TACE ≥ 1 session (2.3 ± 1.5)	1.6 major: n=1 ALF, n=1 abdominal bleeding, 26.2 HE		6.3 shunt traversed HCC; 11.9 Shunt dysfunction	13.9 mo (0.1–102.5)	OS 61.2%, 6-w 98.4% 1-y 65.6% 3-y:53.8%	No PVTT, TACE post TIPS, no ascites		1.6	

Abbreviations: ALF, acute liver failure; CR, complete response; d, days; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; mo, months; MOF, multiorgan failure; MWA, microwave ablation; NA, not available; OLT, orthotopic liver transplantation; OS, overall survival; PD, progressive disease; PFS, progression free survival; PPG, portal pressure gradient; PR partial response; RFA, radiofrequency ablation; SD, stable disease; TA(C)E, transarterial (chemo)embolization; TIPS, transjugular intrahepatic portosystemic shunt; VB, variceal bleeding; w, weeks; WBC, white blood cell count; y, years.

measurement, and the type and size of stents used, are largely missing. In studies, excluding palliative stage of HCC, the OS rate at 1-year after TIPS ranged from 43% to 91%, which is similar to reported survival after TIPS without HCC.[5,8,35,36] The authors do not provide comparative data on the treatment of PH complications and survival in patients not submitted to TIPS, thus hampering analysis of outcomes with TIPS. According to published data, patients with acute VB and HCC, of all stages, have a higher 6-week mortality rate, 26.4%.[37] Future prospective studies/trials involving TIPS in HCC patients require a direct comparison with the standard of care to establish efficacy.

Interestingly, the rate of major complications and post-TIPS HE is also similar to that observed in patients without HCC and occurring in 20%–40% of patients.[38] A high incidence of stent dysfunction was noted, particularly in advanced HCC and PVT, in whom the rate of dysfunction was ≥50%. In the era of covered stents, as the standard of care, dysfunction is relatively infrequent in patients without HCC, about 24% at 2 years.[39] This contrasts sharply with the HCC setting between 12% and 59%. Nevertheless, the definition of stent dysfunction varied throughout the studies. We highlight the importance of consistent definitions when reporting outcome efficacy and procedural complications.

Kuo et al[11] suggested TIPS patients required more TACE sessions to achieve an objective response with a similar time to progression. Another study suggested that TIPS patients who submitted to TACE experienced more hepatotoxicity, although the transplantation rate within 1 year after TACE was 2.5 times higher in TIPS patients.[40] Even if this data has to be interpreted with caution, TIPS should not be considered a contraindication to superselective TACE.

This review highlights the incomplete and inconsistent evidence in this field, and calls for urgent prospective and well-designed studies in patients with HCC and PH complications. Most studies were retrospective and included a heterogeneous population, with some belonging to the palliative care setting. They did not stratify by tumour size and number, degree of liver failure and presence of PVT. Furthermore, >80% of the patients were Asian mainly with hepatitis B, and whether these findings can be generalized to other ethnicities and aetiologies is unclear. Regarding the studies assessing loco-regional treatment response in patients with TIPS and HCC, it is unclear whether current systemic treatment combinations, with

TABLE 3 Baseline characteristics: Treatment response.

Author	Year	Country	Design	Number of patients	Age	Male sex (%)	Aetiology (%)	Child-Pugh (%)	MELD	AFP (ng/mL)	PVTT (%)	Size HCC	Within Milan criteria (%)	Location (%)	Solitary (%)	BCLC (%)	Indication (%)
Kang JW	2012	Korea	Retro	20	56.6 + 10.7	75	Mixed, 70 HBV, 10 HCV	A 35 B 55 C 10	NA	Median 67.1	15	3.3 cm mean	NA	RL $n = 3$ LL $n = 2$ BL $n = 2$	65	NA	100 VB (10 prophylaxis)
Kuo Y-C	2013	USA	Retro	10	59 (51–72)	90		7 (5–11) A 50 B 30 C 20	14 (10–18)	NA	NA	2.7 (1.2–4.8)	NA	NA	80	0 10 A 50 B 20 C 0 D 20	NA
Wang Z	2014	China	Retro	19	54 (36–70)	89.5	94.7 HBV 5.3 HCV	8.11 ± 1.76 A 26.3, B 47.3, C 26.3	13.37 ± 2.57 (10–18)	NA	NA	3.72 ± 1.74 cm (2.0–8.8 cm)	NA	NA	63.2	A 36.8 B 36.8 D 26.3	100 VB (10.5 prophylaxis)
Padia SA	2015	USA	Retro	48 (29 local, 19 BSC) data on[a] 29	58 (42–73)	76	38 alcohol + HCV 28 HCV	B 66 C 34	12 (8–25)	>50: 11%	79	23 (11–55)	NA	Unilobar 79	69	A 34 B 14 C 52 D 0	71 VB 29 Ascites/ Hydrothorax
Park JK	2015	USA	Retro	19	62.2 (51–73)	79	57.9 viral 26.3 alcohol	A 5 B 69 C 26	NA	NA	NA	2.6 cm mean	NA	NA	NA	NA	NA
Miura JT	2015	USA	Retro	16	60.5 (52.5–67.5)	75	43.8 viral 31.2 alcohol	A 12.5 B 75 C 12.5	12.5 (7.5–13)	NA	NA	2.8 cm (1.9–4.5)	NA	NA	56.2	A 18.8 B 25 C 43.7 D 12.5	56.2 ascites 43.8 VB
Ruohoniemi DM	2020	USA	Retro	25	60.0 (57–63.5)	76	72 HCV	NA	13 (11–15) 13.2 + 2.7	NA	8	2.5 (1.8–3.2)	NA	Unilobar 84	76	NA	NA
Gordon AC	2021	USA	Retro	39	63.5 (61.5–66.6)	59	25.6 alcohol 25.6 HCV	A 10.3 B 61.5 C 28.2	18 (16.4–19.4)	<200 84.6%	0	2.9 cm (2.4–3.4)	NA	BL 20.5	66.7	A 35.9 B 7.7 C 43.6 D 12.8	41 ascites 59 VB 15.4 "emergent"

Abbreviations: AFP, alpha fetoprotein; BCLC, Barcelona Clinic Liver Cancer; BL, bilobar; BSC, best supportive care; HBV, hepatitis B virus; HCV, hepatitis C virus; HCC, hepatocellular carcinoma; LL, left lobe; MELD, model for end-stage liver disease; NA, not available; PVTT, portal vein tumour thrombosis; Retro, retrospective; RL, right lobe; VB, variceal bleeding.

[a]Number of patients in which TIPS were placed.

TABLE 4 Outcomes: Treatment response.

Author	Therapy	Number of sessions/timing	Response (%)	Major procedural complications (%)	Recurrence (%)	Further therapy	OLT (%)	Follow-up period	Survival	Causes of death
Kang JW	All TACE	After TIPS median 3 (1–13) Before TIPS 7 had 1–3 TACE sessions	CR 55 PR 15 SD 25 PD 5	35 postembolization syndrome; 5 major complication (fever, worsened ascites)	NA	NA	NA	32.6 months	OS 23 months (14.24–31.77) 1 year 85%, 2 years 50%, 3 years 30%, 5 year 15%, 7 years 10%	MOF (18), HCC metastases (9) LF (3) Pneumonia (3) VB (2) HCC rupture (1)
Kuo Y-C	All TACE	1.4 (1–3)	CR 30 PR 20 SD 40 PD 10 Objective response 50 disease control 90	70 ≥ 1 hepatobiliary SAE (*data extracted from other source*)	80 no recurrence (all OLT patients) Unclear 2 non OLT patients	2 patients ethanol injection	80	NA	3 years 60%	NA
Wang Z	54 TACE sessions	(Mean, 2.84 sessions; range, 1–7 sessions)	CR 16 PR 16 SD 26 PD 42	SAE grade 3–4: 31.6 5.2 VB	NA	NA	10.5	20.9 months (4.1–50.1)	1 year 88% 2 years 53% 3 years 32%	MTT 15.7% LF10.5 GIB 10.5 HCC rupture 5.2% Sepsis 5.2%
Padia SA	66 treatments, 59 ablation, 26 TACE, 15 Y^{90} RE (Ablation: 62 RFA, 36 PEI, 2 IRE)	NA	Of 48 lesions CR 75 PR 6.3 SD 12.5 PD 6.25	NA	NA	NA	40 (44.8 local therapy group)	23.5 months (1.2–112.5 months)	OS 75.5 months tx group OS 72%	NA
Park JK	RFA	25	Complete ablation 3 months: 68 Local progression 37	NA	NA	NA	58	25.5 ± 23.1 mo (Range 1–93)	Non-OLT group: 1 year 100% 2 years 80% 3 years 67% 45% OLT died in F/U	In OLT 5/11 deaths: 2 recurrent Hep. C 2 MOF 1 PE
Miura JT	TACE *n* = 16 RFA *n* = 1 SBRT + Systemic *n* = 1	27 TACE sessions Median 1 (1–3)	CR: 12.5 PR: 43.7 SD: 37.5 PD: 6.25	Clavien grade ≥III complication: 11.1 ascites 12.5 HE	NA	NA	18.8	11.5 months	PFS: 9 months OS 22 months	NA

(Continues)

TABLE 4 (Continued)

Author	Therapy	Number of sessions/timing	Response (%)	Major procedural complications (%)	Recurrence (%)	Further therapy	OLT (%)	Follow-up period	Survival	Causes of death
Ruohoniemi DM	TACE $n = 19$ DEE-TACE $n = 6$	40% 2 sessions 60% 1 session	CR 52 PR 28 SD 12 PD 8	1 SAE (CTCAE grade >2)	NA	40% systemic therapy	8	NA	OS 72 months	NA
Gordon AC	Y^{90} RE	Median total RE:1 (1.1–1.8)	1 month: CR 18 PR 42 SD 39 PD 0	Grade 3: 5%	NA	NA	53.8	NA	OS: 31.6 months (censored for OLT)	NA

Abbreviations: ALF, acute liver failure; CR, complete response; d, days; DEE-TACE, drug-eluting embolic-TACE; GI, gastrointestinal; HCC, hepatocellular carcinoma; HE, hepatic encephalopathy; mo, months; MOF, multiorgan failure; MWA, microwave ablation; NA, not available; OLT, orthotopic liver transplantation; OS, overall survival; PD, progressive disease; PFS, progression free survival; PPG, portal pressure gradient; PR partial response; RE, radioembolization; RFA, radiofrequency ablation; SAE, serious adverse event; SBRT, stereotactic body radiotherapy; SD, stable disease; TA(C)E, transarterial (chemo) embolization; TIPS, transjugular intrahepatic portosystemic shunt; VB, variceal bleeding; w, weeks; WBC, white blood cell count; y, years.

improved OS compared to sorafenib,[41] may or not reduce the need for TIPS to gain access to locoregional treatment, underlining the complexity and the lack of current data. Furthermore, tumour recurrence data in patients with HCC and TIPS is scant, and was stated in only one out of eight studies[11].

Transjugular intrahepatic portosystemic shunts insertion, in selected cases of patients with HCC, may be effective to control PH-related complications and allow for bridging to loco-regional and systemic therapy, eventually improving survival. On the other hand, and as expected, some studies[17,18,20] have shown that, in patients in an advanced stage (BCLC C and D), TIPS did not bring any survival benefit. Notwithstanding, data on tumoral characteristics, such as size, location and presence of PVT, is scarce and inconsistent and significantly hampers granularity and definitive conclusions. Another relevant aspect is that the studies did not use consistent endpoints, nor timeframes, for VB and ascites treatment response, such as those established by Baveno V (5-week treatment failure and 6-week mortality rate).[42] Harmonization of outcomes after TIPS is essential to construct prospective studies and trials in this setting.

It is still unclear whether TIPS in HCC patients could allow curative treatments in selected cases with good liver function, but with PH-related complications. Moreover, whether TIPS is an option to treat PH complications in selected patients, not transplant candidates, also remains open. Current evidence supports TIPS in patients with clear indications, that is, VB and recurrent/refractory ascites. In the setting of HCC, TIPS placement should be assessed case-by-case, until large, cooperative, prospective studies provide data on efficacy, safety and optimal patient selection.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

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

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