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ORIGINAL ARTICLE

Liver transplantation and hepatocellular carcinoma: is TIPS deleterious? A multicentric retrospective study of the ARCHET research group with propensity score matching

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Abstract

Purpose A transjugular intrahepatic portosystemic shunt (TIPS) before the liver transplantation (LT) has been considered a contraindication in cases of hepatocellular carcinoma (HCC) because of the risk of tumour growth.
We aimed to assess the impact of TIPS on incidental HCC and oncological outcomes in transplanted patients with pre-existing HCC.

Methods All consecutive transplanted patients for cirrhosis who had a previous TIPS with or without HCC were included. Between 2007 and 2014, 1912 patients were transplanted. We included 122 (6.3%) patients having TIPS before LT. A 1:3 matched cohort of 366 patients (18.9%) having LT without previous TIPS was selected using a propensity score. Incidental HCC rate and risk factor of HCC recurrence were evaluated using multivariate analysis with a competing risk model.

Results Before LT, in the TIPS group, 27 (22.1%) had an HCC vs. 81 (22.1%) in the control group ($p = 1$). The incidental HCC rate was similar: 10.5% (10/95) in the TIPS group vs. 6.3% (18/285) in the control group ($p = 0.17$). Recurrence occurred in 1/27 (3.7%) patient in the TIPS group and in 7/81 (8.6%) patients in the control group, without significant difference ($p = 0.51$). After multivariate regression, patient's gender ($p < 0.01$) was significantly associated with HCC recurrence while a tumour within Milan criteria ($p = 0.01$, sHR: 0.17 [0.04; 0.7]) and an incidental HCC ($p<0.01$) were found to be protector factors against HCC recurrence.

Conclusion TIPS did not worsen the prognosis of transplanted patients for HCC. TIPS should no longer be contraindicated for oncological reasons in patients with HCC waiting for an LT.

Keywords Liver · Liver transplantation · TIPS · Hepatocellular carcinoma · Cirrhosis · Survival

Abbreviations

TIPS	Transjugular intrahepatic portosystemic shunt
LT	Liver transplantation
HCC	Hepatocellular carcinoma
CT scan	Computed tomography scan
MRI	Magnetic resonance imaging
ICU	Intensive care unit
BMI	Body mass index
MELD	Model for end-stage liver disease
AFP	Alpha-foetoprotein
sHR	Sub-hazard ratio

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Introduction

Two main complications of cirrhosis are symptomatic portal hypertension and the emergence of hepatocellular carcinoma (HCC) [1]. A transjugular intrahepatic porto-systemic shunt (TIPS) is a widely used treatment for portal hypertension and its complications (refractory ascites, hepatorenal and hepatopulmonary syndrome and variceal bleeding) [2, 3]. However, some authors have suggested an increasing risk of neo-HCC in patients who undergo TIPS [4, 5]. Indeed, TIPS can generate changes in the liver, such as an increase in hepatic arterial blood flow [6], an increase in hepatocyte proliferative activity [7, 8] and pseudo-intima development stimulated by transforming growth factor-beta [9, 10]. These different physiological responses to TIPS can strongly affect liver carcinogenesis and promote the progression of HCC. However, these considerations have not been confirmed by others [11, 12]. In some cases, patients with HCC complicated by portal hypertension need TIPS to manage the waiting period before liver transplantation (LT) [2]. Few studies have been published on this specific population showing that inserting TIPS does not increase the risk of HCC development [13, 14]. However, the oncological impact of TIPS in patients with HCC on the waiting list for LT is unclear. In a recent review, the presence of HCC was considered a relative contraindication for TIPS, for complicated portal hypertension [3], and TIPS is not used in several liver transplant centres if the patient has HCC.

The aim of this study was to assess the impact of TIPS on liver carcinogens by investigating the rate of incidental HCC and the oncological outcomes of transplanted patients with pre-existing HCC.

Material and methods

Population study

This retrospective multicentric study was conducted from January 2007 to December 2014 and included five French liver transplant centres (Bordeaux, Lyon, Marseille, Rennes and Toulouse). During this period, 1912 LT procedures were performed, with a graft from deceased donor in all cases.

All consecutive transplanted patients who had a previous TIPS with or without HCC were included. Patients who had TIPS inserted < 3 months before LT were excluded from the study. In order to efficiently evaluate the impact of TIPS, a control group of patient having LT without previous TIPS was selected using a propensity score matching (1:3 ratio) among patients transplanted in the same period.

TIPS procedure

The indications for TIPS placement were refractory ascites, recurrent variceal bleeding and hepatopulmonary syndrome. Central HCC close to the right sus-hepatic vein was a contraindication for TIPS. TIPS was performed by a specialised radiologist using a classically covered stent following a standardised technique [14]. Patency of the TIPS was assessed by routine Doppler ultrasound during the waiting time. Final patency of the TIPS prior to liver transplantation was retrospectively assessed on the most recent preoperative injected CT scan and Doppler ultrasound. In case of TIPS occlusion, we evaluated the time when the TIPS was patent.

Waiting list management

The pre-transplantation assessment included a computed tomography (CT) scan and magnetic resonance imaging (MRI) of the liver. The imaging was discussed in a multidisciplinary meeting to assess the presence of HCC according to current recommendations at the time of diagnosis [15–17]. Patients with HCC who were candidates for transplantation were selected on the basis of their AFP blood level, allowing calculation of the AFP score [18], a predictive model allowing access to transplantation when it is less than or equal to two. During the waiting period, each patient was systematically followed up every 3 months with a laboratory evaluation, abdominal ultrasonography or CT scan and, alternatively, MRI and AFP dosage.

Surgical technique and post-operative care

The surgical procedure was similar in all centres and was an orthotopic liver transplantation with inferior vena cava preservation. Briefly, after a standard wound incision and exposure, the liver pedicle was dissected. A temporary porto-caval shunt was performed depending on the surgeon's preference. The native liver was then removed and careful haemostasis was performed. Graft implantation was started with caval anastomosis: original or modified (i.e. side-to-side) piggy-back technique. End-to-end portal vein anastomosis was performed followed by the arterial anastomosis and then the biliary anastomosis.

After the procedure, patients were transferred to the intensive care unit (ICU) until graft function was satisfactory. Routine immunosuppression was similar in the five centres and based on calcineurin inhibitors (mostly tacrolimus), mycophenolate mofetil and a short course of corticosteroids (4-6 months).

After discharge, patients were followed up according to centre policy. AFP dosage and systematic imaging (i.e. Doppler ultrasound or CT scan) were carried out at least every 6 months in the first 3 years, and yearly thereafter.

No significant change regarding the surgical procedure or the post-operative medical care was observed during the study period.

Pathological study

Macroscopic features of the tumour, including size, number, tumour capsule and vascular invasion, were recorded. Haematoxylin and eosin, Masson's trichrome, reticulin and Perl's stains were available for all tumoural and non-tumoural tissue samples. A minimum of four different sections for each tissue sample was examined. HCC was graded using the classification proposed by Edmonson and Steiner and the presence of lymphatic or vascular invasion was noted. Incidental HCC was defined using the classification tool based on a systematic and balanced assessment of the 10 histological features proposed by Quaglia et al. [19].

Data collection

Demographic, clinical and biological data were collected, including gender, age, body mass index (BMI), cause of cirrhosis, model for end-stage liver disease (MELD) and alpha-foetoprotein (AFP) level [18, 20], number and size of HCC as well as reaching the "Milan criteria" [21] and histological features of HCC. In line with the retrospective nature of this work and the section R1121-1 from the French Public Health Code, no institutional review board was required.

Statistical analysis

Quantitative variables were expressed as mean values ± standard deviation or as medians with extreme values (range) and compared using Student's *t*-test or Wilcoxon's test as appropriate. Qualitative variables were expressed as numbers and percentages and compared using Chi-square or Fisher's exact tests, as appropriate.

Competing risk analysis and survival analysis

Patients undergoing OLT for HCC are at risk of presenting mutually exclusive events since the occurrence of death (not related to HCC recurrence) precludes HCC recurrence. Therefore, the usual Kaplan Meier model is inappropriate to correctly estimate the HCC recurrence rate. A competitive risk analysis using a Fine and Gray model [19] was then used in order to specifically evaluate the risk factors of HCC recurrence and estimate the cause specific hazard also called sub-hazard ratio (sHR).

All variables with a p-value < 0.2 in univariate competing risk analysis were included in a mutivariable competing risk model. The final multivariable model was selected using a descending stepwise method retaining only significant variables. The date of last follow-up was April 30, 2022.

Propensity score matching

The following variables were used for the propensity score calculation: patient's age, gender, BMI, MELD score, underlying liver disease, diagnosed HCC at time of LT and tumour within the "Milan criteria" (when HCC was known at time of LT). Exact matching was given priority and the maximum distance allowed between two matched patients was set at 0.2 (calliper restriction).

A $p < 0.05$ was considered significant. All statistical analyses were performed on the R software version 3.1.3. using the "Matching" v4.9-3 and "survival" v3.1-12 packages.

Results

Patient characteristics

During the study period, 122 patients (6.3%) were transplanted for liver cirrhosis with TIPS. Among them, 27 (22.1%) had initial HCC at the time of TIPS placement and 95 (77.9%) had not. The indications for TIPS placement were refractory ascites (60.6%), recurrent variceal bleeding (29.5%), hepatopulmonary syndrome (4.9%) and others (5%). No complications related to TIPS were reported. The median age of the transplanted patients was 56 (24–68) years, and 70.5% were male. The aetiology of cirrhosis was alcoholic (51.6%), post-viral hepatitis (23.8%), non-alcoholic steatohepatitis (4.1%) and others (7.4%). The median MELD score was 16 (4–40). The median time between TIPS placement and LT was 10.7 [3.1; 99] months. At the time of liver transplantation, the TIPS was patent in 117 patients (95.9%). For the 5 patients having occlusion of the TIPS before the LT, they had a median time of TIPS patency of 6.5 months.

The control group was formed by 366 (19.1%) patients transplanted during the same period without TIPS.

A comparison of the demographic and HCC characteristics between the TIPS group and the control group is reported in Table 1. There were no significant differences between the 2 groups regarding the patient's or the HCC characteristics. Concerning details of loco-regional treatments before LT, 13 (48.1%) patients in the TIPS group and 27 (33.3) in the control group had tumoural radiofrequency ($p = 0.17$), while 10 (37%) patients in the TIPS group and 39 (48.1%) patients in the control group had arterial chemoembolization ($p = 0.43$).

Table 1 Characteristics of the study population including 122 patients having a TIPS before liver transplantation and the control group (without TIPS)

Variables	TIPS group $n = 122$ (%)	Control group $n = 366$ (%)	p-value
Recipient characteristics			
Gender (male)	86 (70.5%)[†]	256 (69.9%)	0.91
Age (years)	56 [24; 68] [‡]	56 [17; 73]	0.55
BMI (kg/m2)	24.05 [18; 43.09]	24.86 [17.30; 40.90]	0.86
Liver disease aetiology			0.72
Viral	29 (23.8%)	77 (21%)	
Alcohol	63 (51.6%)	207 (56.6%)	
NASH	5 (4.1%)	9 (2.5%)	
Biliary and autoimmune	16 (13.1%)	42 (11.5%)	
Others	9 (7.4%)	31 (8.5%)	
MELD score	16 [4; 40]	18.44 [4; 40]	0.57
Waiting time before LT [‡] (months)	3.46 [0.85–7.67]	2.76 [0.70–7.92]	0.44
HCC characteristics			
At time of TIPS/before liver transplantation	27 (22.1%)	81 (22.1%)	1
Within MILAN criteria	23 (85.2%)	68 (84%)	1
Number of nodules	1 [1; 5]	2 [1; 6]	0.34
Maximum size (cm)	2.1 [1; 5]	2.3 [1; 6]	0.76
Alpha foetoprotein (ng/mL)	5 [1.6; 1068]	5 [1.2; 2336]	0.88
Loco-regional treatments	16 (59.3%)	56 (69,1%)	0.35
On final specimen analysis	37 (30.3%)	99 (27%)	0.48
Incidental HCC**	10 (10.5%)	18 (6.3%)	0.17
Number of nodules	2 [1; 11]	2 [1; 20]	0.98
Maximum size (cm)	1.85 [1; 8]	2 [0.5; 9]	0.13
Edmonson grade			
0-2	22 (59.5%)	73 (73.7%)	0.16
3-4	15 (40.5%)	26 (26.3%)	
Vascular invasion	5 (13.5%)	5 (5.1%)	0.13

BMI body mass index, *NASH* non-alcoholic steatohepatitis, *MELD* model for end-stage liver disease, *HCC* hepatocellular carcinoma

[†]Number of cases (percentages of cases)

[‡]Median (range)

**Ratio calculated for patient without diagnosed HCC at time of LT ($n = 95$ for TIPS group and $n = 285$ for control group)

Surgical data of the liver transplantation

The surgical data for liver transplantation have been reported in Table 2. Significant differences were found for cold ischaemia which was 480 min in median for the TIPS group and 532 min for the control group ($p = 0.03$) and the median number of transfusions which was 6 for the TIPS group and 5 for the control group ($p = 0.005$). No significant differences were found for morbidity and mortality on POD 90 and graft failure.

Pathological analysis and incidental HCC occurrence

Pathological analysis of all explanted livers revealed that an incidental HCC was observed in 10 of 95 (10.5%) patients from the TIPS group and 18 of 285 (6.3%) patients from the control group, without any difference ($p = 0.17$). Seven patients (7.1%) in the control group had a cholangiocarcinoma coexistence with the HCC on final pathological examination, whereas they were none in the TIPS group ($p = 0.19$). Median size of these cholangiocarcinoma was 7 mm [5; 9] and no recurrence of cholangiocarcinoma happened in these patients with a mean follow-up of 77 months.

Survival analysis

The median follow-up in months was similar between the two groups (93 months [0; 177] in the TIPS group vs. 85 months [0; 178] in the control, $p = 0.31$). The overall survival rates in the TIPS group at 1, 3 and 5 years were 84.4%, 78.7% and 73.8% respectively, compared to 86.9%, 82.8% and 73.8% in the control group ($p = 0.3$) (Fig. 1).

Table 2 Surgical data of the liver transplantation in the TIPS group and the control group (without TIPS)

Variables	TIPS group $n = 122$ (%)	Control group $n = 366$ (%)	p-value
Surgical data			
Cold ischaemia, minutes	480 [395–577] ‡	532 [397–662]	*0.03*
Transfusions	6 [4–9]	5 [3-8]	*0.005*
Operating time, minutes	360 [307–425]	380 [300–455]	0.3
			0.72
Morbidity on POD 90		77 (21%)	
Dindo-Clavien I	29 (23.8%)†	207 (56.6%)	
Dindo-Clavien II	5 (4.1%)	9 (2.5%)	
Dindo-Clavien III	16 (13.1%)	42 (11.5%)	
Dindo-Clavien IV	9 (7.4%)	31 (8.5%)	
Reoperation	9 (7.38%)	20 (5.46%)	0.44
Graft failure	5 (4.10%)	6 (1.64%)	0.15
Length of stay, days	24 [16–32]	23 [16-36]	0.65
Mortality on POD 90	11 (9.01%)	38 (10.38%)	0.48

†Number of cases (percentages of cases)

‡Median (range)

Among patients with HCC known at time of LT, a recurrence was observed in 1/27 (3.7%) patients of the TIPS group and in 7/81 (8.6%) of the control group. In competing risk analysis, there was no difference in recurrence rate between the 2 groups ($p = 0.45$) (Fig. 2A).

When considering all patients presenting an HCC on specimen analysis, a recurrence was observed in 1/37 (2.7%) patients of the TIPS group and in 7/99 (7.1%) of the control group. In competing risk analysis, there was no difference in recurrence rate between the 2 group ($p = 0.38$) (Fig. 2B).

Risk factor of HCC recurrence

Univariate competing risk analysis of HCC recurrence was realised in Table 3. When comparing AFP median levels between patients having an HCC and a recurrence and patients with HCC but without recurrence, no difference was found (3.3 [2.25–9.15] vs. 4.6 [2.99–12.93], $p = 0.38$).

After multivariate regression, patient's gender was significantly associated with HCC recurrence. Although the sHR could not be estimated because of the lack of convergence of the model due to the absence of HCC recurrence in women, it could be considered a risk factor because the sHR was extremely greater than 1, while a tumour in the Milan criteria ($p = 0.01$ sHR: 0.17 [0.04; 0.7]) and incidental HCC ($p < 0.01$) were considered protective factors of HCC recurrence. For the latter, the model still lacked convergence as no HCC recurrence occurred in patients with incidental HCC despite the long follow-up of our population. However, given that the sHR was much lower than 1, a patient with incidental HCC can be considered to have significantly less risk of long-term recurrence than a patient with known HCC before transplantation.

Discussion

TIPS may be necessary to treat severe complications related to portal hypertension in cirrhotic patients and to avoid LT. However, LT is indicated in a small percentage of those patients because of TIPS failure or impaired liver function. On the other hand, TIPS is indicated in liver transplant candidates to facilitate LT or to treat a portal hypertension-related complication during the waiting period. Actually, we observed that TIPS was not a common feature, as only 6.3%

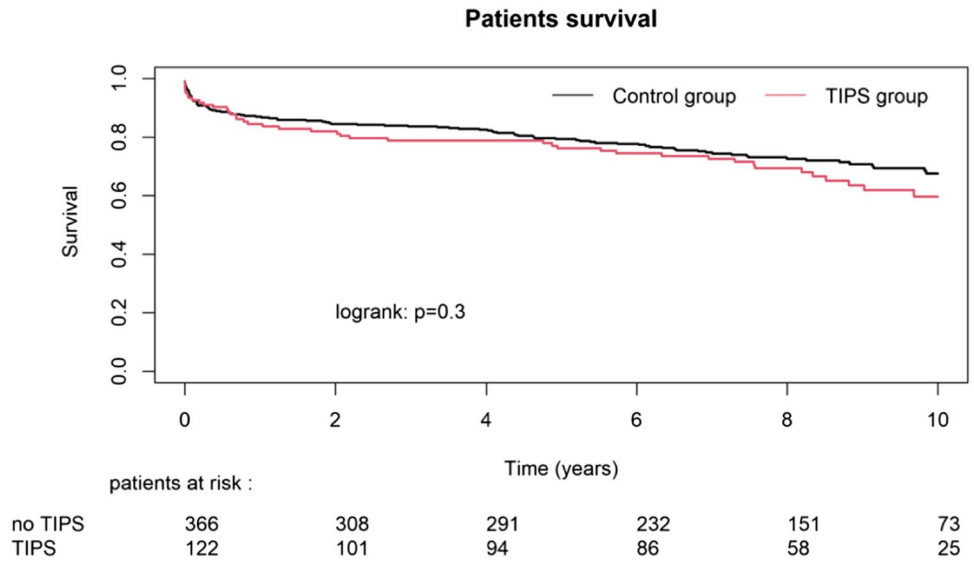

Fig. 1 Patient's overall survival

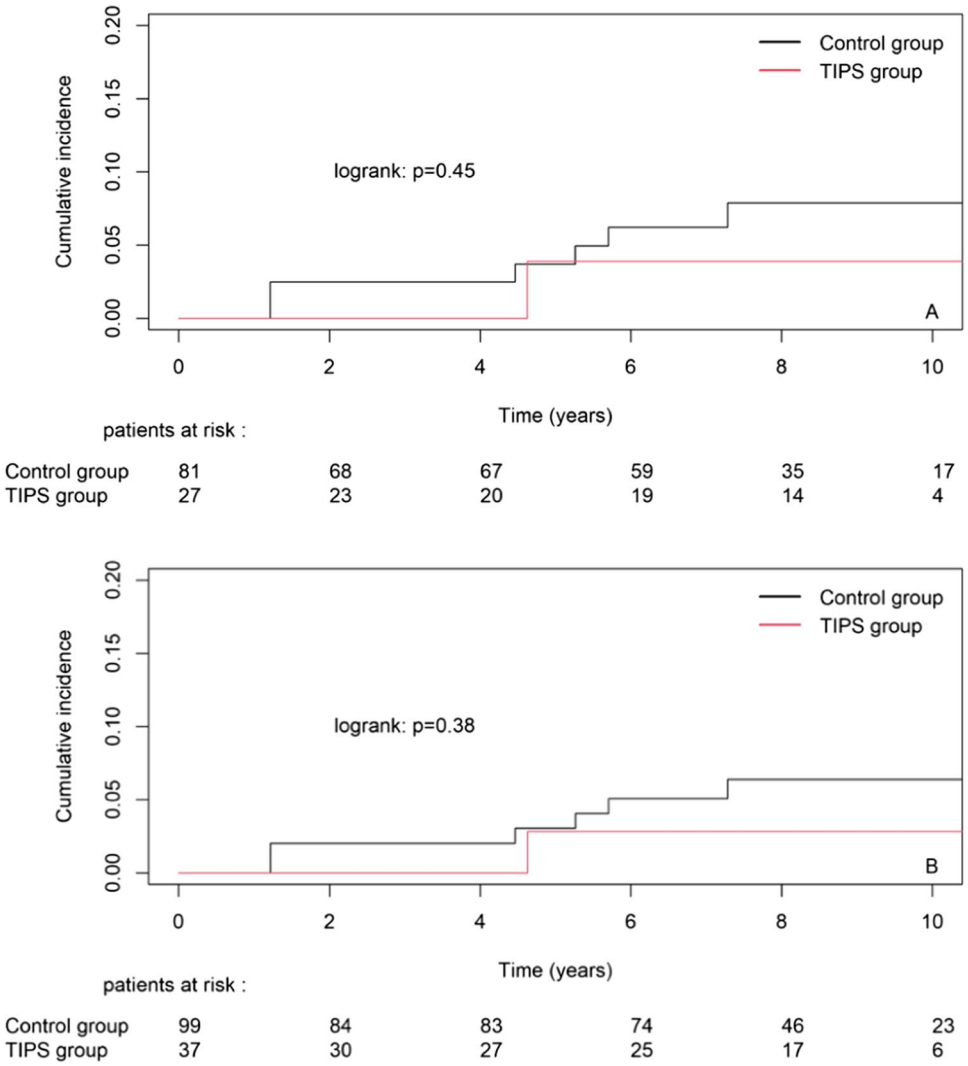

Fig. 2 Cumulative incidence of HCC recurrence (competing risk analysis) in (**A**) patients with HCC diagnosed before LT; **B** patients with HCC found on specimen analysis

of liver transplant candidates underwent TIPS at our five centres. Even if the presence of a TIPS is not a contraindication for LT [22], this low percentage may be partly due to a reluctance of transplant teams to use TIPS because of the putative impact on HCC genesis. Some authors have demonstrated an increase in neo-HCC associated with TIPS [4, 5]. The physiological explanation is more or less convincing based on the increase of arterial flow after TIPS, which is involved in carcinogenesis [6–10]. Nevertheless, few data are available in the literature on this topic considering the small number of transplant patients with TIPS. In one study focusing on the rate of incidental HCC in explanted livers with TIPS [13], the authors reported that TIPS was a risk factor for liver dysplasia but not HCC. Our study is one of the larger analysing the oncological impact of TIPS in cases of pre-existing HCC.

Looking at our results on the surgical data, there was no more post-operative morbidity when transplanting with TIPS in place or when transplanting without TIPS. This had also been shown by others [23–25] although Barbier et al. [26] found that the presence increased post-operative ascites rates. However, we found that in cases of transplantation with TIPS, the number of transfusions was higher, which may be an indirect indicator of intraoperative difficulty and higher bleeding. Others had the same observation [24, 27]. Although the majority of our TIPS were patent pre-operatively, this suggests that alleviating portal hypertension by TIPS does not facilitate the procedure itself.

We showed that incidental HCC was not more frequent in patients with TIPS, although it should be mentioned that the median time between TIPS and LT was rather short (10.7 months) to definitively exclude a carcinogenic potential of TIPS, but this confirms data of Borentain et al. who had an equal TIPS duration [13]. The most interesting point concerns patients with pre-existing HCC; we showed that TIPS had no impact on the recurrence rate. Even if some prospective studies should confirm these results, the hypothesis of a carcinologic "boost" by the TIPS should not be retained

Table 3 Risk factors of HCC recurrence (competing risk analysis)

Variables	Univariate (competing risk)	Multivariate (competing risk)	
	p	*p*	sHR [CI 95%]
Recipient characteristics			
Gender	*<0.01*	*<0.01*	*
Age	*0.74*		
BMI	0.55		
TIPS	0.42		
Liver disease aetiology	0.66		
MELD score	*0.29*		
Tumour characteristics			
Within MILAN criteria (at listing)	*0.02*	*0.01*	*0.17 [0.04; 0.7]*
Alpha foetoprotein (ng/mL)	*0.29*		
Incidental tumour on specimen	*<0.01*	*<0.01*	*
Number of nodules on specimen	*<0.01*		
Maximum size on specimen (cm)	*0.23*		
Edmonson grade			
0-2	*0.89*		
3-4			

sHR sub-hazard ratio provided by competing risk analysis, *MELD* model for end-stage liver disease

*sHR cannot be estimated due to absence of convergence of the statistical model

to contraindicate TIPS in patients with Milan HCC. To perform TIPS may avoid some drop out in portal hypertension complications in patients with HCC. Moreover, we should not hesitate to put TIPS in a patient with HCC because of refractory ascites, as this is not deleterious to the oncological outcome [28] and may avoid transplantation if the HCC becomes treatable (radiofrequency, liver resection). Indeed, as proposed by Larrey et al., TIPS in patient with HCC and symptomatic portal hypertension could be considered a bridge to liver transplantation [29].

However, while the placement of a TIPS does not seem to promote increased carcinogenesis of HCC, its presence may hinder the pre-operative detection of HCC. Indeed, Krumeich et al. [14] showed in a series of 40 patients with TIPS an almost 2-fold higher rate of occulted HCC compared to non-TIPS transplanted patients. As we found, they assessed that the presence of TIPS itself was not an independent factor reducing DFS and OS. Nevertheless, they concluded that the presence of TIPS may limit the sensitivity of HCC detection on preoperative imaging and that caution should be adopted if a suspicion arises. However, as proposed by Zhou et al. [30], the advantages of the TIPS over portal hypertension before pre-LT outweigh any disadvantages of incidental HCC findings, as these have no oncological impact in terms of survival. In addition to current diagnostic imaging test, contrast enhanced ultrasound (CEUS) is one accurate diagnostic tool which should be useful in these specific patients with TIPS inducing increased arterial blood flow [31]. As shown by Chang et al. [32], CEUS takes advantage of the change in blood flow by allowing a diagnosis of HCC with a sensitivity of 90.9% in case of TIPS, close to the 93.3% obtained on patients without TIPS.

Regarding at the risk factors for recurrence obtained, there were some elements to consider. The AFP rate did not appear to be a risk factor for recurrence, although it is a well-established risk factor in the literature. Indeed, as reported by Duvoux et al. [18] and others [33, 34], AFP is independently predictive of the risk of HCC recurrence. This is why it is included in France in the predictive model: "AFP score", selection criterion for patients with HCC who are candidates for liver transplantation. Our hypothesis for its absence in our univariate and multivariate analysis models was that we had too few HCC recurrences in the follow-up to have a sufficient number of patients to obtain a difference on this precise criterion.

A tumour in the Milan criteria appeared to be a protective factor for recurrence in our results with a hazard ratio of 0.17 [0.04; 0.7]. Indeed, being outside the Milan criteria at the time of registration on the waiting list for liver transplantation is known to be a risk factor for recurrence after transplantation [21, 35]. Indeed, patients belonging to these Milan criteria have a very low risk of recurrence evaluated at 8% at 4 years after transplantation [21]. However, some limitations have appeared for these criteria, notably due to the fact that the determination of these criteria varied according to the precision of the radiological tests. This is in addition to the reason for the choice of the AFP score in France to select the criteria at transplantation.

Incidental HCC appeared to be a protective factor for recurrence compared to pre-transplant HCC. Although due to the lack of convergence of the model we could not clearly define the confidence interval, this finding was reinforced by the long median follow-up of this study, more than 8 years, and the data in the literature. Indeed, recently Leon et al. reported 216 liver transplants with 4.18% incidental HCC without recurrence after a median follow-up of 61 months [36]. Similarly, El Moghazy et al. [37] reported no recurrence of incidental HCC in 887 liver transplants with a prevalence of incidental HCC of 3.6% and a median follow-up of 54 months. This interesting finding needs to be confirmed by further prospective studies.

Although our "gender" criterion was also difficult to interpret because the patients who recurred were only men, it seemed to be a risk factor for HCC recurrence after liver transplantation. This is in line with the data in the literature that find male gender as a risk factor for recurrence after HCC treatment [38], especially after liver transplantation [39].

This study had some bias. It was a retrospective study from 5 centres. This inevitably induced bias in the collection of data as our lack of data concerning donor characteristics on the one hand and on the other hand, and all centres do not have exactly the same procedures limiting the exhaustiveness of the data; for example, not all of them perform a biopsy of the liver graft after implantation or discrepancy in the way loco-regional treatments was delivered could be found. However, we have tried to be as precise as possible in the collection of data and the number of patients allows us to obtain robust data for the variables obtained. We compared patients with and without TIPS. Obviously, it was not a randomised study but the two groups were comparable thanks to matching process using a propensity score. Ideally, it would be very interesting to build a prospective observational cohort of patients with HCC requiring TIPS before LT, to collect more precise information on the growing HCC curve, the histological specificities and liver dysplasia, which are all data that we were unable to report in this retrospective multicentric series. According to ex-post statistical power calculations, a number of 377 subjects having an HCC in a TIPS group and a control group respectively could show a difference if it exists.

In conclusion, TIPS can be done in cirrhotic patients awaiting LT or in potential LT candidates without increasing the risk of HCC. TIPS does not seem to be deleterious in patients with HCC, so patients with HCC should not be contraindicated for TIPS, as some have indicated.

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Authors' contributions Study conception and design: CL, AM, MR. Acquisition of data: CL, AM, LC. Analysis and interpretation of data: CL, AM, MR, CM. Drafting of manuscript: CL, AM, LC, MR. Critical revision of manuscript: CL, AM, MR, FM, KM, EG, CM, JYM, KD, KB, ML, JPA, LC. All authors reviewed and approved the manuscript.

Declarations

Competing interests The authors declare no competing interests.

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