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ORIGINAL ARTICLE

Therapeutic anticoagulation after liver transplantation is not useful among patients with pre-transplant Yerdel-grade I/II portal vein thrombosis: A two-center retrospective study

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Abstract

Background: Portal vein thrombosis (PVT) is no longer a contraindication for liver transplantation (LT). While therapeutic anticoagulation (tAC) is recommended during the waiting period, there is no evidence for its usefulness in the prevention of PVT recurrence after LT.

Objectives: The aim of our study was to evaluate the role of tAC post-LT in the prevention of PVT recurrence.

Patients/methods: All adult LTs performed in two high-volume centers between 2003 and 2018 were retrospectively analysed. Only patients with PVT classified as Yerdel grade I or II and with standard portal reconstruction were included. PVT recurrence and tAC-associated morbidity within 1 year were compared between patients receiving tAC or not.

Results: During the study period, of 2612 LTs performed, 235 (9%) patients with PVT were included; 113 patients (48.1%) received post-LT tAC (tAC group) while 122 (51.9%) did not (non-tAC group). The incidence of bleeding events was significantly higher in the tAC group (26 [23%] vs. 5 [4.1%], $P < .01$) and the initial hospitalization duration was longer (21 vs. 17.5 days, $P < .01$). Within the first year, PVT recurrence was observed for 9 (3.8%) patients without any difference between the tAC and non-tAC groups (6 [5.1%] vs. 3 [2.5%], $P = .39$). The only identified risk factor for PVT recurrence was the recipients' age (odds ratio= 0.94, $P = .03$). Graft ($P = .11$) and patient ($P = .44$) survival were similar between the two groups.

Conclusion: Therapeutic anticoagulation is not necessary in the prevention of grade I/II PVT recurrence and is associated with higher morbidity and longer hospital stay.

KEYWORDS
liver transplantation, portal vein thrombosis, recurrence, therapeutic anticoagulation, Yerdel

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1 | INTRODUCTION

Portal vein thrombosis (PVT) is encountered in 10% to 25% of cirrhotic patients awaiting liver transplantation (LT).[1-3] With improvements in surgery, PVT is no longer a technical contraindication and can be managed intraoperatively in almost all cases.[4]

Although PVT management during the waiting period before LT is well codified[2,5] with a recommendation to administer therapeutic anticoagulation (tAC) when possible, there is only limited evidence supporting its usefulness in the post-transplant period for the prevention of PVT recurrence.

Consequently, most liver transplantation centers have developed their own protocols, which mostly consist in administering tAC for a period of 3 to 6 months,[6-8] although it can increase the incidence of bleeding events among patients already considered at increased risk during the early postoperative course.[9]

The aim of the present study was, in two tertiary high-volume liver transplantation centers, to evaluate the usefulness of tAC administered after LT in the prevention of PVT recurrence at 1 year after the procedure, and any potential side effects.

Essentials

- Interest of therapeutic anticoagulation (tAC) after liver transplantation (LT) is not established.
- Patients with grade I/II portal vein thrombosis (PVT) receiving tAC or not after LT were compared.
- tAC did not reduce PVT recurrence and is associated with higher bleeding events.
- Therapeutic anticoagulation is not necessary in prevention of grade I/II PVT.

2 | PATIENTS AND METHODS

2.1 | Patient selection

All adult LTs performed between January 2003 and December 2018 in two European high-volume LT centers (University Medical Center Groningen, the Netherlands, and Rennes University Hospital, France) were retrospectively analyzed ($n = 2502$).

All patients who were known to have PVT (diagnosed on imaging) while on the waiting list or discovered during the LT procedure (mentioned in the operative report) were reviewed.

Patients transplanted with a graft from a living donor or a split liver graft ($n = 26$), with other associated organs ($n = 14$), re-transplantations ($n = 50$), without cirrhosis or having a coagulation disorder requiring tAC after LT ($n = 7$), were excluded from the analysis. Patients with complex portal reconstruction (i.e., reno- or cavo-portal anastomosis, using conduit; $n = 15$), or having Yerdel grade III/IV PVT ($n = 5$) were also excluded. Patients with tumoral thrombosis ($n = 1$), intraoperative death ($n = 5$), or presenting primary graft non-function ($n = 11$) leading to death or re-transplantation in the first 7 postoperative days (PODs) were also excluded (Figure 1).

Hence, our study population only included patients with cirrhosis and thrombosis of the portal vein, without complete extension into the spleno-mesenteric confluence or superior mesenteric vein (i.e., Yerdel grade I or II). In addition, for all patients, the portal inflow to the liver graft was achieved by regular direct end-to-end portal vein anastomosis. The analysis compared patients receiving or not receiving tAC postoperatively.

2.2 | Perioperative management and surgical procedure

Before LT, all patients with a known PVT received therapeutic anticoagulation (mostly vitamin K antagonists), in the absence of contraindication, until transplantation.

Orthotopic LT with inferior vena cava preservation was performed in all cases. During the hepatectomy, the PVT was removed by surgical eversion thrombectomy maneuver[10] allowing a direct end-to-end portal anastomosis to be conducted, once the portal flow was judged satisfactory by the surgeon. Graft implantation was started with caval anastomosis, which was performed with an original or modified (i.e., side-to-side) piggy-back technique followed by an end-to-end portal vein anastomosis. The graft was then vascularized prior to arterial anastomosis and subsequent biliary anastomosis.

After the procedure, patients were transferred to the intensive care unit (ICU) until graft and recipient functions were satisfactory. Routine immunosuppression was similar in the two centers and based on calcineurin inhibitors (mostly tacrolimus) associated with mycophenolate mofetil and a short course of corticosteroids. Systematic Doppler ultrasound was routinely performed at POD 1 and 7 and repeated or completed by a contrast-enhanced computed tomography (CT) scan according to the clinical course.

After discharge, patients were followed up according to center policies. Systematic imaging (i.e., Doppler ultrasound or CT scan) was performed at least every 6 months during the first year, and yearly thereafter.

2.3 | Therapeutic anticoagulation

The decision to administer tAC varied with center policies and the time period concerned. Indeed, while it was systematically provided in both centers in the early period, it was largely abandoned in the French center from 2012 onward due to changes in practice, unless it was required for another reason (e.g., cardiac rhythm disorder). Therapeutic

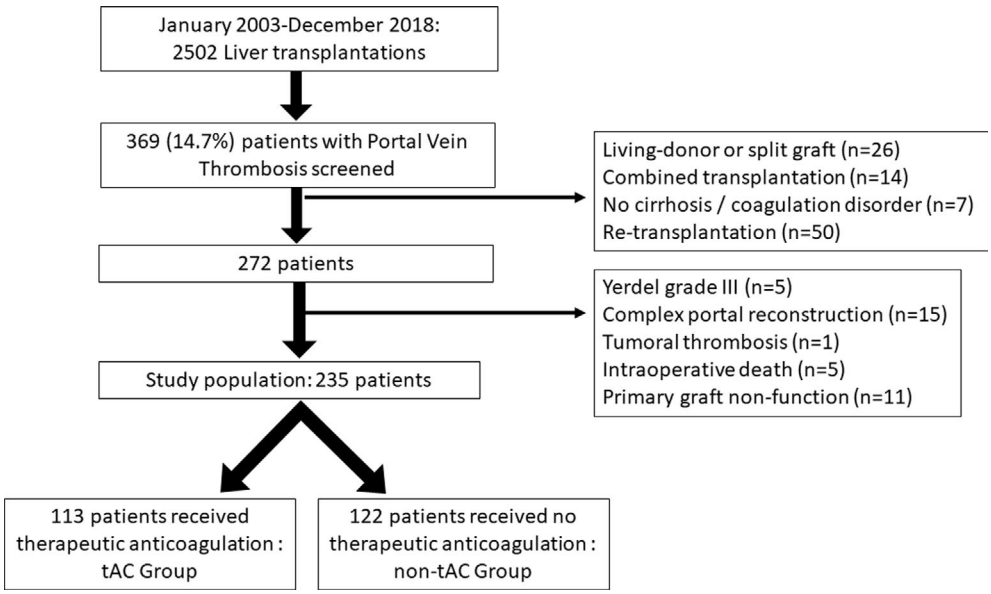

FIGURE 1 Flowchart of the study. tAC, therapeutic anticoagulation treatment

anticoagulation consisted of a short initial administration of heparin (started in the ICU as soon as possible), and quickly switched to oral administration of vitamin K antagonist, with an international normalized ratio (INR) target between 2 and 3, for a duration of 3 months in most cases. No direct-acting oral anticoagulants were used.

2.4 | Data collection

The following variables were collected from a prospective database and analyzed:

1. Recipient characteristics: age, gender, body mass index (BMI), underlying liver disease, Child-Pugh score, and Model for End-Stage Liver Disease (MELD) score.
2. PVT characteristics: all available pre-operative images (CT scans or magnetic resonance imaging [MRI]) were systematically reviewed by two senior surgeons (MR and VdM) as were LT procedure reports for PVT grading according to the Yerdel classification.[11] Persistence of residual thrombus after intraoperative thrombectomy was derived from the surgical reports and postoperative Doppler ultrasound examinations.
3. Donor characteristics: age, gender, BMI, type of donor (brain death donor [DBD] or circulatory death donor [DCD]), cold ischemia time.
4. Outcomes: recurrence of PVT at 1 year after LT as well as other vascular complications; postoperative outcomes during the initial hospitalization, especially bleeding events (defined by the exteriorization of blood through abdominal wounds or drains, perihepatic hematoma or voluminous abdominal blood accumulation diagnosed by imaging); need for surgical revision; hospitalization duration; graft and patient survival. Severity of complications during the initial hospitalization was scored by the Clavien-Dindo grade.

2.5 | Ethics

For University Medical Center Groningen, patient data were derived from a post hoc analysis of an observational cohort study (www.trialregister.nl – Trial NL6334), which was approved by the Medical Ethical Committee (METc 2014/77).

For Rennes University Hospital, formal approval from the local ethics committees was obtained (avis n°21.49).

Data were retrieved from each center database and made anonymous prior to analysis.

The study adhered to the Declaration of Helsinki and the Declaration of Istanbul.

2.6 | Statistical analysis

Quantitative variables were expressed as medians with extreme values (range) and compared using Student's *t*-test or Wilcoxon test as appropriate.

Qualitative variables were expressed as numbers and percentages and compared using Chi-square or Fisher's exact tests, as appropriate.

Risk factors for PVT recurrence were sought using a logistic regression model.

In order to carry out efficient analyses of graft and patient survival according to the administration or not of tAC and correcting for bias due to population heterogeneity and the small sample size in the subgroup analyses, a survival analysis with stabilized inverse

probability weighting (IPW)[12] was performed, and a comparison was made using an adjusted log-rank test.[13]

Briefly, the IPW method aims to reduce bias by weighting the contribution of each subject according to confounding factors. The weight of each subject is calculated based on a propensity score (i.e., logit mode estimating the probability of belonging to a group according to the confounding factors) and corresponds to the inverse probability of belonging to the group. Consequently, the contribution of subjects presenting very different characteristics is ponderate (because they have a high probability of belonging to a group) which makes groups more comparable by reducing the variance.

Only the most impactful variables were selected for the propensity score calculation: the Yerdel grade of the PVT (because it can be the most significant difference in characteristics between the two groups), the type of donor (DBD or DCD), and the occurrence of arterial thrombosis within the first year after transplantation (because these two variables are well known to have a significant impact on graft survival). The other variables were considered less important and were not included in the propensity score calculation.

A *P*-value <.05 was considered significant. All statistical analyses were performed on R software version 3.1.3 using the "survival" v3.1–12 and "cmprskcoxmsm" v0.1.0 packages.

3 | RESULTS

3.1 | Population characteristics

Between 2003 and 2018, among the 2502 LT performed, 369 (14.7%) patients had a PVT prior to or at the time of the transplantation. After the selection process, 235 patients were included in the study (Figure 1). tAC was administered to 113 (48.1%) patients (tAC group) with a median duration of 3 months (95% confidence interval [CI: 0; 169]) while 122 (51.9%) patients did not receive tAC (non-tAC group).

The main characteristics of the two study groups are summarized in Table 1.

The recipients' median age (58 vs. 60 years, $P = .045$) and the donors' median age (55 vs. 61 years, $P < .01$) were significantly younger in the tAC group, while the proportion of DCD donors was significantly higher (6 [4.9%] vs. 25 [22.1%], $P < .01$) than in the non-tAC group.

3.2 | PVT characteristics

According to the Yerdel classification, PVT was grade I in 147 cases (62.6%) and grade II in 88 (37.4%). The proportion of grade II was significantly higher in the tAC group (33 [27%] vs. 55 [48.7%], $P < .01$).

PVT was diagnosed before LT in 164 cases (69.8%) and discovered during surgery in 71 cases (30.2%). Among patients with known PVT before LT, therapeutic anticoagulation treatment was administered during the waiting period to 106/164 (64.6%), resulting in complete resolution of the thrombus in 40/106 (37.7%) cases. No spontaneous thrombus resolution was observed.

For patients with a persistent thrombus at the time of LT ($n = 195$, 83%), a surgical thrombectomy was performed intraoperatively enabling satisfactory portal flow to be restored in all cases. However, the thrombectomy was not complete (i.e., persistence of residual thrombus despite thrombectomy) for 34 patients, without any difference between groups (19 [16.8%] vs. 15 [12.3%], $P = .33$).

3.3 | Impact of post-transplant therapeutic anticoagulation management on outcomes

3.3.1 | Post-transplant morbidity

During the initial hospitalization, the median duration in the ICU did not differ between the tAC and non-tAC groups (4 vs. 4 days, $P = .42$). However, the total hospital duration was significantly longer in the tAC group (21 vs. 17.5 days, $P < .01$). The incidence of bleeding events, during the initial hospitalization, was significantly higher in the tAC group (26 [23%] vs. 5 [4.1%], $P < .01$) as was the related surgical revision (13 [11.5%] vs. 4 [3.3%], $P = .02$). The proportion of Clavien-Dindo grade ≥ 3 was significantly higher in the tAC group (54 [47.8%] vs. 32 [26.2%], $P < .01$).

During the study period, tAC treatment was prematurely and definitively stopped due to a related complication for 10 (8.8%) patients in the tAC group.

3.3.2 | Incidence of vascular complications at 1 year

During the first year after LT, there was a PVT recurrence in (3.8%) cases with no difference between the tAC group and the non-tAC group (6 [5.1%] vs. 3 [2.5%], $P = .39$). In 7 patients (4 in the tAC and 3 in the non-tAC group), a residual thrombus was diagnosed fortuitously on a CT scan (i.e., partial thrombus in the mesenteric or splenic veins and not involving the portal vein). None of them presented a PVT recurrence later.

Arterial complications were observed in 25 (10.6%) cases. Because 3 patients from the tAC group presented an arterial thrombosis before tAC treatment initiation, they were counted in the non-tAC group. There was no difference in the occurrence of arterial complications between the two groups (11 [12.4%] vs. 14 [9%], $P = .83$).

Venous complications other than PVT recurrence (i.e., PV stenosis of hepatic vein thrombosis) were observed in 5 (2.1%) patients with no difference between the two groups (3 [2.7%] vs. 2 [1.6%], $P = .67$).

3.3.3 | Graft and patient survival

The median follow-up was 59.8 months (95% CI [0.4; 189.2]) for the overall population without any difference between the tAC and non-TAC groups (72.3 vs. 49.4 months, $P = .34$).

After weighting using the IPW technique, graft ($P = .11$) and patient survival ($P = .44$) were not significantly different between the two groups (Figure 2).

TABLE 1 Characteristics and outcomes of the overall study population

Variables	Overall population *n* = 235 (%)	tAC group *n* = 113 (%)	Non-tAC group *n* = 122 (%)	*P*-value
Recipient characteristics				
Gender (male)	187 (79.6%)	86 (76.1%)	101 (82.8%)	.20
Age (years)	59 [16; 73]	58 [16; 73]	60 [26; 68]	.045
BMI (kg/m^2)	26.7 [18; 46.2]	26.6 [18.8; 46.2]	26.9 [18; 45.7]	.63
Liver disease etiology				
Alcohol	109 (46.4%)	44 (38.9%)	65 (53.3%)	<.01
Viral	39 (16.6%)	14 (12.4%)	25 (20.5%)	
NASH	38 (16.2%)	26 (23%)	12 (9.8%)	
Biliary & autoimmune	26 (11.1%)	17 (15%)	9 (7.4%)	
Others	23 (9.8%)	12 (10.6%)	11 (9%)	
Hepatocellular carcinoma	88 (37.4%)	37 (32.7%)	51 (41.8%)	.15
Child-Pugh score	9 [5; 15]	9 [5; 15]	9 [5; 14]	.64
MELD score	16 [6.3; 40]	16.3 [6.4; 40]	14.6 [6.3; 40]	.10
PVT characteristics				
Diagnosed before OLT	164 (69.8%)	91 (80.5%)	73 (59.8%)	<.01
Treated by tAC before OLT	106 (64.6%)	58 (63.7%)	48 (65.8%)	.8
Complete resolution before OLT	40 (17%)	14 (12.4%)	26 (21.3%)	.07
Yerdel classification				
Grade 1	147 (62.6%)	58 (51.3%)	89 (73%)	<.01
Grade 2	88 (37.4%)	55 (48.7%)	33 (27%)	
Residual thrombus after procedure	34 (14.5%)	19 (16.8%)	15 (12.3%)	.33
Donor characteristics				
Gender (male)	113 (48.1%)	52 (46%)	61 (50%)	.54
Age (years)	59 [10; 90]	55 [16; 90]	61 [10; 89]	<.01
BMI (kg/m^2)	25.1 [15.4; 53.2]	24.5 [17; 43.2]	25.4 [15.4; 42.1]	.61
Donor type				
DBD	204 (86.8%)	88 (77.9%)	116 (95.1%)	<.01
DCD	31 (13.2%)	25 (22.1%)	6 (4.9%)	
Cold ischemia time (min)	504 [58; 910]	496 [58; 910]	506.5 [295; 909]	.29
Outcomes				
ICU duration (days)	4 [1; 161]	4 [1; 161]	4 [1; 122]	.42
Total hospital duration (days)	19 [9; 195]	21 [10; 195]	17.5 [9; 123]	<.01
Bleeding events	31 (13.2%)	26 (23%)	5 (4.1%)	.03
Requiring surgical revision	17 (7.2%)	13 (11.5%)	4 (3.3%)	.02
Clavien-Dindo grade ≥3	88 (37.4%)	55 (48.7%)	33 (27%)	<.01
PVT recurrence (at 1 year)	9 (3.8%)	6 (5.3%)	3 (2.5%)	.32
Other venous complications (at 1 year)	5 (2.1%)	3 (2.7%)	2 (1.6%)	.67
Portal vein stenosis	4 (1.7%)	2 (1.8%)	2 (1.6%)	
Hepatic veins thrombosis	1 (0.4%)	1 (0.9%)	0 (0%)	
Arterial complications (at 1 year)[a]	25 (10.6%)	11 (12.4%)	14 (9%)	.83
Thrombosis	10 (4.3%)	5 (4.5%)	5 (4%)	
Stenosis	12 (5.1%)	5 (4.5%)	7 (5.6%)	
Other	3 (1.3%)	1 (0.9%)	2 (1.6%)	

Abbreviations: BMI, body mass index; DBD, brain death donor; DCD, circulatory death donor; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; PVT, portal vein thrombosis; tAC, therapeutic anticoagulation treatment.

[a]Calculated for a population size of the tAC group of 110 patients and of the non-tAC group of 125 because 3 patients in the tAC group presented thrombosis before tAC initiation.

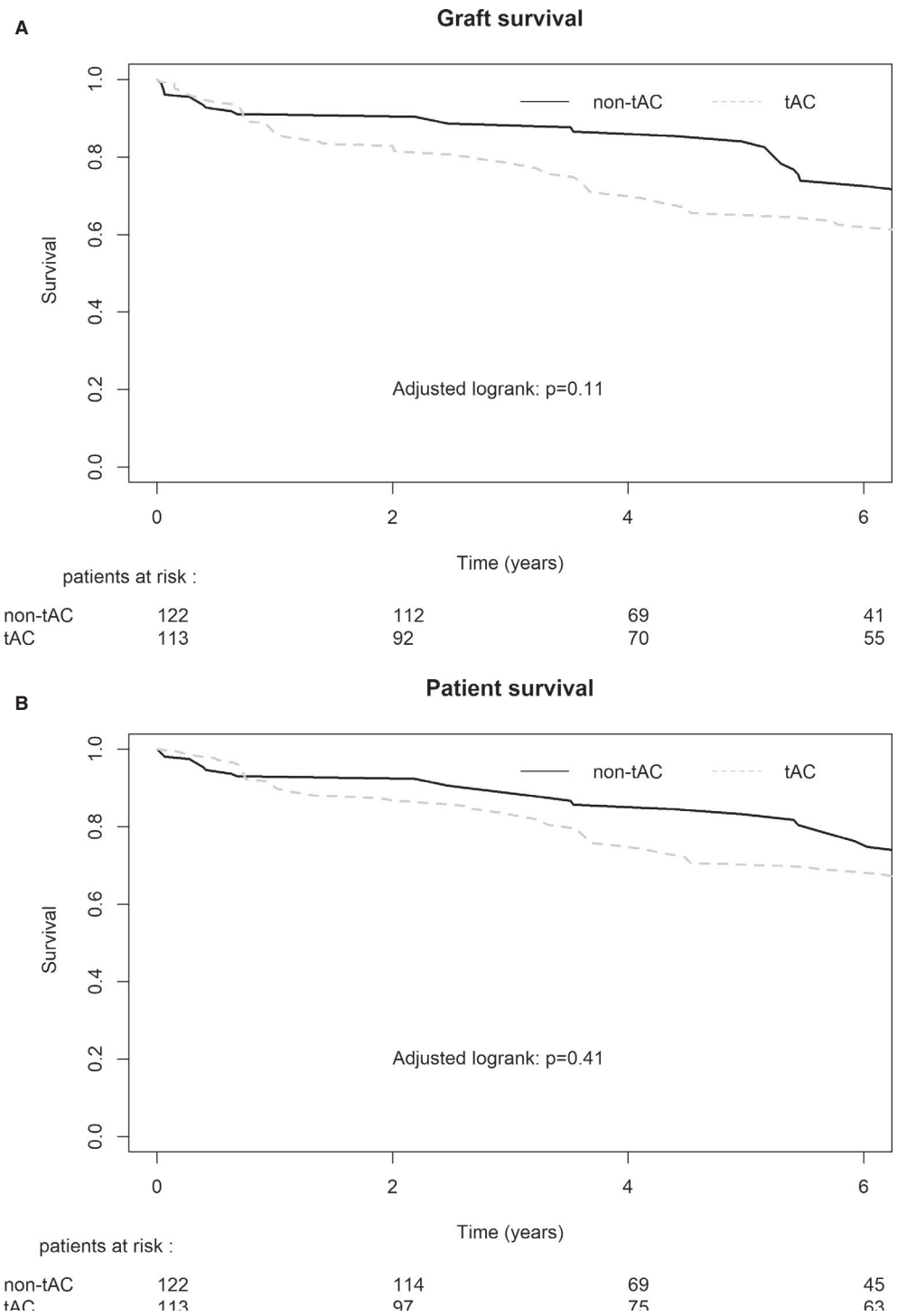

FIGURE 2 Graft (A) and patient (B) survival, with inverse probability weighting, on the overall study population. tAC, therapeutic anticoagulation treatment

3.4 | Risk factors for PVT recurrence

The only risk factor for PVT recurrence identified in univariate analysis was recipient age (odds ratio [OR]: 0.94, 95% CI [0.89; 0.99], P = .03). Because no other variables were found to have a P-value <.2, no multivariate analysis could be performed.

3.5 | Subgroup analyses

3.5.1 | Subgroup of patients presenting Yerdel grade II PVT

When considering only patients presenting Yerdel grade II PVT (n = 88), 55 patients (62.5%) received tAC while 33 patients (37.5%) did not (Table 2).

TABLE 2 Characteristics and outcomes of patients presenting Yerdel grade II PVT

Variables	Overall population *n* = 88 (%)	tAC group *n* = 55 (%)	Non-tAC group *n* = 33 (%)	*P*-value
Recipient characteristics				
Gender (male)	71 (80.7%)	44 (80%)	27 (81.8%)	.83
Age (years)	57.5 [30; 73]	58 [30; 73]	56 [40; 68]	.76
BMI (kg/m^2)	27.1 [19; 45.7]	26.1 [19; 38.8]	28.6 [19.6; 45.7]	.05
Liver disease etiology				
Alcohol	43 (48.9%)	27 (49.1%)	16 (48.5%)	.09
Viral	13 (14.8%)	4 (7.3%)	9 (27.3%)	
NASH	14 (15.9%)	11 (20%)	3 (9.1%)	
Biliary & autoimmune	13 (14.8%)	10 (18.2%)	3 (9.1%)	
Others	5 (5.7%)	3 (5.5%)	2 (6.1%)	
Hepatocellular carcinoma	33 (37.5%)	18 (32.7%)	15 (45.5%)	.23
Child-Pugh score	9 [5; 14]	9 [5; 13]	8 [5; 14]	.86
MELD score	16 [6.4; 40]	16.1 [6.4; 39]	14.3 [6.9; 40]	.42
PVT characteristics				
Diagnosed before OLT	70 (79.5%)	45 (81.8%)	25 (75.8%)	.50
Treated with tAC before OLT	37 (52.9%)	24 (43.6%)	13 (39.4%)	.91
Complete resolution before OLT	4 (4.5%)	1 (1.8%)	3 (9.1%)	.15
Residual thrombus after procedure	22 (25%)	12 (21.8%)	10 (30.3%)	.37
Donor characteristics				
Gender (male)	36 (40.9%)	22 (40%)	14 (42.4%)	.82
Age (years)	59 [10; 90]	59 [17; 90]	62 [10; 87]	.44
BMI (kg/m^2)	25.6 [17; 39]	25.6 [17; 39]	26 [17.1; 34.7]	.94
Donor type				
DBD	75 (85.2%)	43 (78.2%)	32 (97%)	.03
DCD	13 (14.8%)	12 (21.8%)	1 (3%)	
Cold ischemia time (min)	524 [305; 910]	520 [324; 910]	540 [305; 909]	.80
Outcomes				
ICU duration (days)	5 [1; 51]	5 [1; 19]	5 [2; 51]	.192
Total hospital duration (days)	22 [10; 74]	23 [11; 74]	21 [10; 66]	.19
Bleeding events	16 (18.2%)	15 (27.3%)	1 (3%)	<.01
Requiring surgical revision	7 (8%)	6 (10.9%)	1 (3%)	.25
Clavien-Dindo grade ≥3	36 (40.9%)	25 (45.5%)	11 (33.3%)	.26
PVT recurrence (at 1 year)	5 (5.7%)	3 (5.5%)	2 (6.1%)	1
Other venous complications (at 1 year)	2 (2.2%)	2 (3.6%)	0 (0%)	.53
Portal vein stenosis	1 (1.1%)	1 (1.8%)	0 (0%)	
Hepatic veins thrombosis	1 (1.1%)	1 (1.8%)	0 (0%)	
Arterial complications (at 1 year)[a]	14 (15.9%)	8 (14.8%)	6 (17.6%)	.72
Thrombosis	7 (8%)	4 (7.4%)	3 (8.8%)	
Stenosis	7 (8%)	4 (7.4%)	3 (8.8%)	
Other	0(0%)	0 (0%)	0 (0%)	

Abbreviations: BMI, body mass index; DBD, brain death donor; DCD, circulatory death donor; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; PVT, portal vein thrombosis; tAC, therapeutic anticoagulation treatment.

[a]Calculated for a population size of the tAC group of 54 patients and the non-tAC group of 33 patients because 1 patient in the tAC groups presented thrombosis before tAC initiation.

There were significantly more bleeding events in the tAC group (15 [27.3%] vs. 1 [3%], $P < .01$) but without differences in the need for surgical revision (6 [10.9%] vs. 1 [3%], $P = .25$). The total duration of hospitalization (23 vs. 21, $P = .19$) and the proportions of Clavien-Dindo grade ≥ 3 (25 [45.5%] vs. 11 [33.3%], $P = .26$) were not different between the two groups.

At 1 year, 5 (5.7%) patients presented PVT recurrence with no difference between the tAC and non-tAC groups (3 [5.5%] vs. 2 [6.1%], $P = 1$). Likewise, the proportions of arterial (8 [14.8%] vs. 6 [17.6%], $P = .88$) and venous (2 [3.6%] vs. 0 [0%], $P = .53$) complications did not differ between the two groups.

Graft ($p = .13$) and patient ($p = .58$) survival did not differ between the tAC and non-tAC groups (Figure 3).

3.5.2 | Subgroup of patients with persistent PVT at the time of LT

If only patients with persistent PVT at the time of LT ($n = 195$) are considered, 99 (50.8%) received tAC while 96 (49.2%) did not (Table 3).

There were significantly more bleeding events in the tAC group (23 [23.2%] vs. 5 [5.2%], $P < .01$) but no difference in the need for surgical revision (11 [11.1%] vs. 4 [4.2%], $P = .07$).

The total duration of hospitalization was significantly longer in the tAC group (22 vs. 18 days, $P < .01$) and the proportion of Clavien-Dindo grade ≥ 3 was higher (45 [45.5%] vs. 28 [29.2%], $P = .02$).

At 1 year, 9 patients (4.6%) presented PVT recurrence with no difference between the tAC and non-tAC groups (6 [6.1%] vs. 3 [3.1%], $P = .50$). The incidence of arterial complications (8 [8.2%] vs. 12 [12.4%], $P = .29$) and venous complications (3 [3%] vs. 1 [1%], $P = .62$) did not differ either.

Graft ($P = .052$) and patient ($P = .34$) survival did not differ between the two groups (Figure 4).

4 | DISCUSSION

To our knowledge, this is the first study evaluating tAC for the prevention of PVT recurrence after LT, comparing patients who received it and those who did not.

We found that tAC administration was not useful in the prevention of PVT recurrence, which was found to be low (3.8%). This finding was also confirmed in the analysis of subgroups that could be considered at higher risk of recurrence (i.e., Yerdel grade II or persistence of PVT at the time of transplantation). We also found that tAC did not reduce the incidence of vascular complications such as arterial or hepatic vein thrombosis.

In addition, we found that tAC significantly increased the number of bleeding events and the need for secondary surgery for bleeding during the initial hospitalization, resulting in a longer hospitalization duration.

PVT incidence among cirrhotic patients has been reported to be as high as 5% to 26%[1-4] and it is reported to be discovered during the LT procedure in 30% to 50% of cases.[8,14] This high incidence could be explained by an association of complex hemostatic disorders leading to simultaneous hypo- and hypercoagulation states,[15] a decrease in the portal blood velocity,[16] and the development of collateral circulation.

Initially considered a contraindication for LT,[17] PVT can now be managed intraoperatively in all cases and does not affect patient survival any longer, as has been recently reported.[4,18] During the waiting period, tAC is recommended to prevent PVT extension or at best for complete recanalization.[2,19] In our study, we found that pre-transplant tAC enabled complete resolution of PVT in 37.7% of cases, which is in line with previous reports.[14,20]

However, the role of tAC in the post-transplant period is not well documented and there are currently no guidelines. Consequently, most liver transplantation centers have developed their own protocol. Indeed, some centers prescribe oral tAC for a period of 3 to 6 months,[3,7,14] some use an implantable portal vein pump,[21] or they prescribe aspirin.[22,23] In all cases, when a physiological reconstruction is performed, the reported PVT recurrence rate is low, ranging from 0% to 7%,[2,3,8,14] which is in line with our findings.

On the other hand, Rodríguez-Castro et al.[24] in their meta-analysis reported that "the absence of prevention strategies" is associated with a pooled rate of 10.3% of secondary thrombosis. However, while the absence of anticoagulation is not clearly mentioned in most of the studies analyzed by Rodríguez-Castro et al., most of these secondary occurrences of thrombosis concern grade III and IV PVT with complex portal reconstruction.

Our study clearly suggests that tAC is ineffective in the prevention of PVT recurrence when a "standard" (i.e., end-to-end without use of conduit) portal vein anastomosis is performed, even if the thrombectomy remains incomplete once the portal flow is restored. Our results could be explained by the resolution of all PVT risk factors by the liver transplantation. Indeed, the replacement of the native cirrhotic liver by the graft will quickly restore the physiological hemostatic balance as well as normal hemodynamic parameters (intrahepatic resistance, portal flow, and portal hypertension). Even in the case of incomplete thrombectomy, normalization of the endogenous fibrinolytic system will "finish the job" initiated by the surgeon during the procedure and residual thrombus (i.e., only present in splenic or mesenteric veins and not involving the portal vein) should not be treated or considered a PVT recurrence, which may explain the difference in PVT recurrence rate between our study and other reports.[25]

Thus, we think that liver transplantation is the best and only necessary treatment in the prevention of PVT recurrence.

In addition to this, liver transplant recipients are considered at high risk of bleeding; prophylactic anticoagulation has been debated since it was found to be associated with an increased risk of haemorrhagic complications.[26,27] Therefore, it is quite clear that anticoagulation administered at therapeutic doses should be avoided as far as possible, especially in the early postoperative period when hemostatic disorders can persist, thus explaining the more frequent bleeding events in our tAC group (reaching 23%).

There are, however, some limitations to our study.

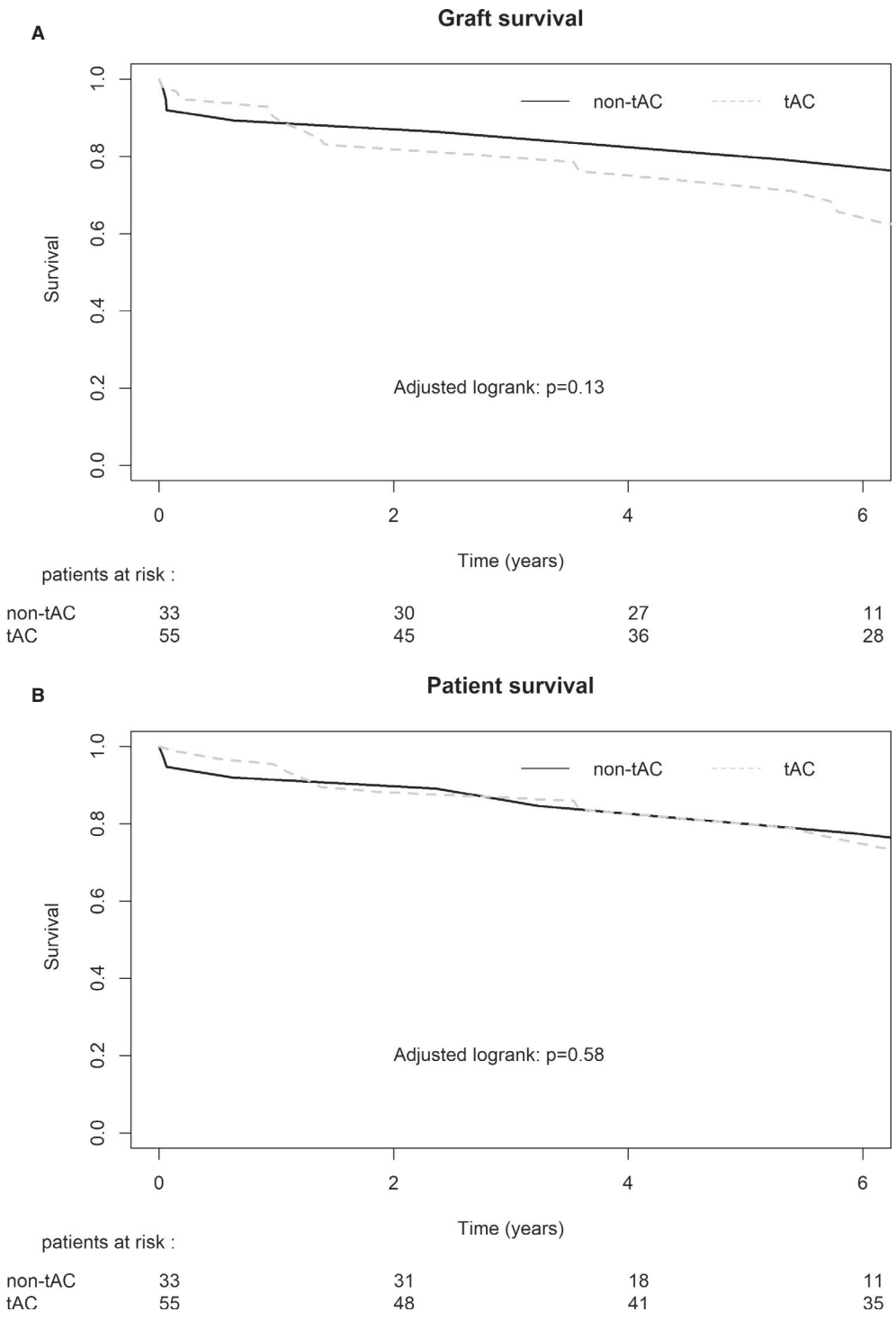

FIGURE 3 Graft (A) and patient (B) survival, with inverse probability weighting, among patients presenting Yerdel grade II portal vein thrombosis. tAC, therapeutic anticoagulation treatment

First, the retrospective nature of our study entailed several differences in recipient and graft characteristics between our two groups, especially regarding the type of donor (DBD or DCD). In addition, the absence of clear guidelines for post-transplant tAC indications was also responsible for differences regarding the characteristics of the PVT, with more Yerdel grade II PVT in the tAC group. Indeed, a clinician is intuitively inclined to administer tAC to patients he considers as having a more severe PVT (i.e., grade II) and therefore at a higher risk of PVT recurrence. However, our subgroup analysis showed that PVT recurrence was also low among patients who were supposedly at high risk, and our logistic regression analysis did not find these parameters as risk factors for PVT recurrence.

Second, we decided to analyze grade I/II PVT with standard portal vein anastomosis only. Indeed, extensive PVT (i.e., grade III/IV) remains a technical and medical challenge, usually requiring complex

TABLE 3 Characteristics and outcomes of patients presenting PVT at the time of LT

Variables	Overall population *n* = 195(%)	tAC group *n* = 99 (%)	Non-tAC group *n* = 96 (%)	*P*-value
Recipient characteristics				
Gender (male)	159 (81.5%)	77 (77.8%)	82 (85.4%)	.17
Age (years)	58 [16; 73]	58 [16; 73]	58.5 [26; 68]	.23
BMI (kg/m^2)	27.2 [18; 46.2]	26.8 [18.8; 46.2]	27.7 [18; 45.7]	.46
Liver disease aetiology				
Alcohol	91 (46.7%)	40 (40.4%)	51 (53.1%)	.03
Viral	31 (15.9%)	12 (12.1%)	19 (19.8%)	
NASH	34 (17.4%)	24 (24.2%)	10 (10.4%)	
Biliary & autoimmune	20 (10.3%)	13 (13.1%)	7 (7.3%)	
Others	19 (9.7%)	10 (10.1%)	9 (9.4%)	
Hepatocellular carcinoma	68 (34.9%)	33 (33.3%)	35 (36.5%)	.65
Child-Pugh score	9 [5; 15]	9 [5; 15]	9 [5; 14]	.88
MELD score	16 [6.3; 40]	16.1 [6.4; 40]	15.6 [6.3; 40]	.71
PVT characteristics				
Diagnosed before OLT	124 (63.6%)	77 (77.8%)	47 (49%)	<.01
Treated with tAC before OLT	75 (60.5%)	45 (60%)	30 (63.8%)	.55
Yerdel classification				
Grade 1	111 (56.9%)	45 (45.5%)	66 (68.8%)	<.01
Grade 2	84 (43.1%)	54 (54.5%)	30 (31.2%)	
Residual thrombus after procedure	34 (17.4%)	19 (19.2%)	15 (15.6%)	.51
Donor characteristics				
Gender (male)	92 (47.2%)	46 (46.5%)	46 (47.9%)	.84
Age (years)	59 [10; 90]	55 [16; 90]	61.5 [10; 89]	<.01
BMI (kg/m^2)	25.7 [15.4; 43.2]	25.4 [17; 43.1]	26.2 [15.4; 42.1]	.41
Donor type				
DBD	167 (85.6%)	77 (77.8%)	90 (93.8%)	<.01
DCD	28 (14.4%)	22 (22.2%)	6 (6.2%)	
Cold ischemia time (min)	508 [58; 910]	496 [58; 910]	509 [295; 910]	.37
Outcomes				
ICU duration (days)	4 [1; 161]	4 [1; 161]	4 [1; 51]	.68
Total hospital duration (days)	20 [10; 195]	22 [10; 195]	18 [10; 74]	<.01
Bleeding events	28 (14.4%)	23 (23.2%)	5 (5.2%)	<.01
Requiring surgical revision	15 (7.7%)	11 (11.1%)	4 (4.2%)	.07
Clavien-Dindo grade ≥3	73 (37.4%)	45 (45.5%)	28 (29.2%)	.02
PVT recurrence (at 1 year)	9 (4.6%)	6 (6.1%)	3 (3.1%)	.50
Other venous complications (at 1 year)	4 (2.1%)	3 (3%)	1 (1%)	.62
Portal vein stenosis	1 (0.5%)	2 (2%)	1 (1%)	
Hepatic veins thrombosis	3 (1.5%)	1 (1%)	0 (0%)	
Arterial complications(at 1 year)[a]	20 (10.3%)	8 (8.2%)	12 (12.4%)	.29
Thrombosis	7 (3.6%)	4 (4.1%)	3 (3.1%)	
Stenosis	11 (5.6%)	4 (4.1%)	7 (7.2%)	
Other	2 (1%)	0 (0%)	2 (2.1%)	

Abbreviations: BMI, body mass index; DBD, brain death donor; DCD, circulatory death donor; ICU, intensive care unit; MELD, Model for End-Stage Liver Disease; NASH, non-alcoholic steatohepatitis; OLT, orthotopic liver transplantation; PVT, portal vein thrombosis; tAC, therapeutic anticoagulation treatment.

[a]Calculated for a population size of the tAC group of 98 patients and the non-tAC group of 97 patients because 1 patient in the tAC group presented thrombosis before tAC initiation.

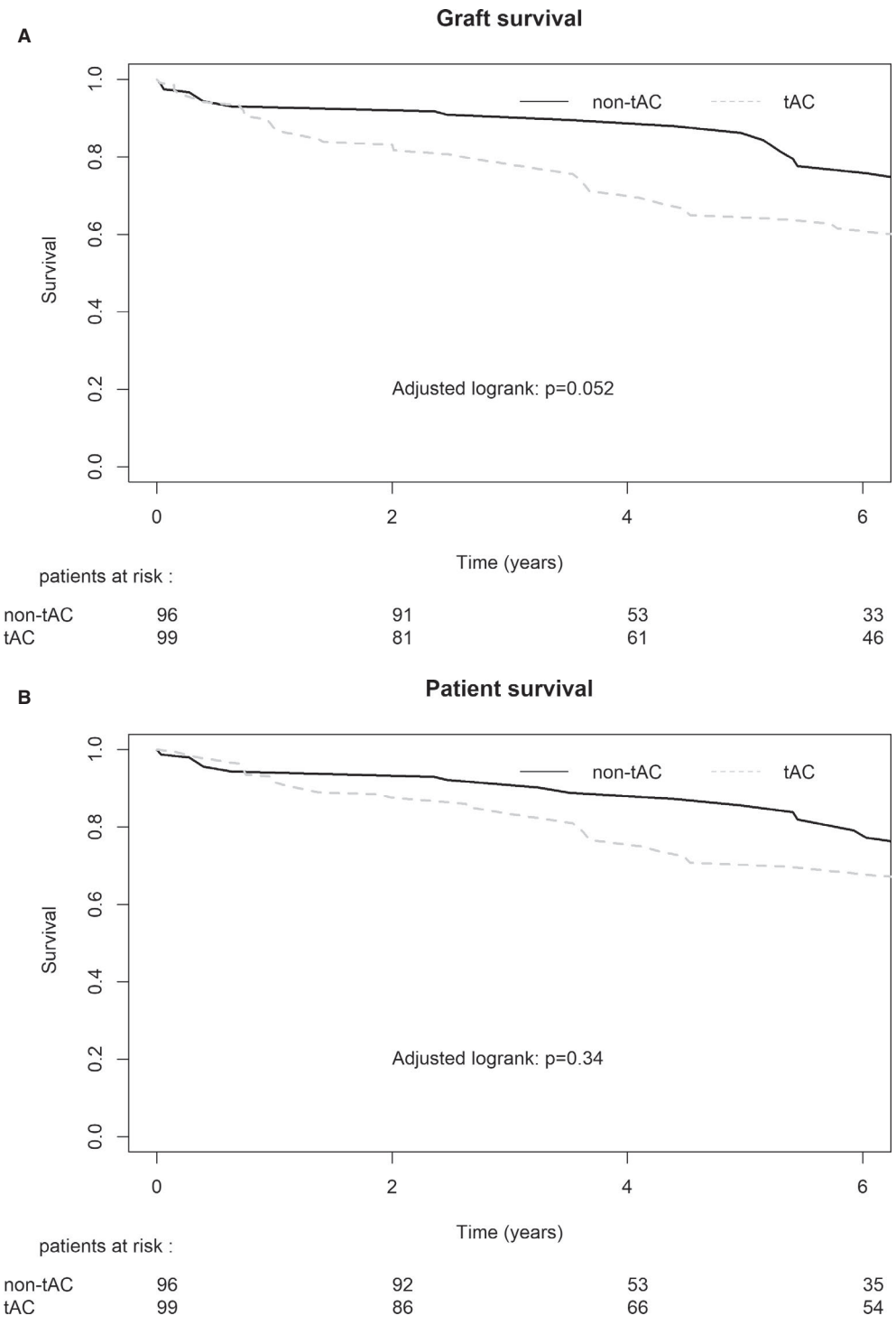

FIGURE 4 Graft (A) and patient (B) survival, with inverse probability weighting, among patients with persistent portal vein thrombosis at the time of liver transplantation. tAC, therapeutic anticoagulation treatment

reconstruction, which is associated with higher postoperative complication rates.[28,29] Because all these patients received tAC in the postoperative period, to have included them in the study would, to our mind, have induced a major bias by penalizing the tAC group. Furthermore, patients with grade I to II PVT and with physiological portal vein reconstruction were the most common cases.[24] Therefore, our study population was representative of a very large majority of these occurrences.

Third, portal flow was not measured after the thrombectomy but only subjectively assessed by the surgeon (which is standard practice in real life). However, while measures of the portal vein flow have been found to predict graft survival, they were not found to be predictive of PVT recurrence.[22] In addition, portal flow measurement can only be performed after graft reperfusion (i.e., after carrying out portal vein anastomosis). Thus, the surgeon cannot use it to

evaluate portal flow immediately after the thrombectomy has been performed.

Despite these limitations, we believe that our study will provide valuable data regarding the usefulness of tAC in the pre- and post-transplant period that will help clinicians in their decisions.

In conclusion, our study has shown that tAC is not necessary in the prevention of grade I/II PVT recurrence when thrombectomy and classic portal vein anastomosis are performed. We have also shown that it is associated with higher risk of bleeding.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest regarding this study.

AUTHOR CONTRIBUTIONS

M. Rayar, R.J. Porte, and V. de Meijer designed the study. M. Rayar, I. Bos, D. Wouters, M. Blondeau, W.S van der Plas, L.M. Nieuwenhuis, and C. Camus collected the data. M. Rayar, I. Bos, and D. Wouters drafted the manuscript. All authors reviewed and approved the manuscript.

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REFERENCES

1. Violi F, Corazza GR, Caldwell SH, et al. Portal vein thrombosis relevance on liver cirrhosis: Italian Venous Thrombotic Events Registry. *Intern Emerg Med*. 2016;11:1059-1066.
2. Northup PG, Garcia-Pagan JC, Garcia-Tsao G, et al. Vascular Liver Disorders, Portal Vein Thrombosis, and Procedural Bleeding in Patients With Liver Disease: 2020 Practice Guidance by the American Association for the Study of Liver Diseases. *Hepatology*. 2021;73:366-413.
3. Francoz C, Valla D, Durand F. Portal vein thrombosis, cirrhosis, and liver transplantation. *J Hepatol*. 2012;57:203-212.
4. Bhangui P, Lim C, Levesque E, et al. Novel classification of non-malignant portal vein thrombosis: A guide to surgical decision-making during liver transplantation. *J Hepatol*. 2019;71:1038-1050.
5. Loffredo L, Pastori D, Farcomeni A, et al. Effects of anticoagulants in patients with cirrhosis and portal vein thrombosis: a systematic review and meta-analysis. *Gastroenterology*. 2017;153:480-487.e1.
6. Liou P, Kato T, Fishbein T. Surgical perspectives on the American Association for the Study of Liver Diseases Guideline for Anticoagulation and Implications for Liver Transplantation. *Liver Transpl*. 2021;27(4):580-583.
7. Conzen KD, Pomfret EA. Liver transplant in patients with portal vein thrombosis: Medical and surgical requirements: Conzen and Pomfret. *Liver Transpl*. 2017;23:S59-S63.
8. Sanchez-Ocaña R, Tejedor-Tejada J, Cimavilla-Roman M, et al. Utility of oral anticoagulants as prophylaxis of recurrent portal thrombosis after liver transplantation. *Transplant Proc*. 2019;51:83-86.
9. Hendriks HGD, van der Meer J, de Wolf JTM, et al. Intraoperative blood transfusion requirement is the main determinant of early surgical re-intervention after orthotopic liver transplantation. *Transpl Int*. 2005;17:673-679.
10. Dumortier J, Czyglik O, Poncet G, et al. Eversion thrombectomy for portal vein thrombosis during liver transplantation. *Am J Transplant*. 2002;2:934-938.
11. Yerdel MA, Gunson B, Mirza D, et al. Portal vein thrombosis in adults undergoing liver transplantation: risk factors, screening, management, and outcome. *Transplantation*. 2000;69:1873-1881.
12. Cole SR, Hernán MA. Adjusted survival curves with inverse probability weights. *Comput Methods Programs Biomed*. 2004;75:45-49.
13. Xie J, Liu C. Adjusted Kaplan-Meier estimator and log-rank test with inverse probability of treatment weighting for survival data. *Stat Med*. 2005;24:3089-3110.
14. Chen H, Turon F, Hernández-Gea V, et al. Nontumoral portal vein thrombosis in patients awaiting liver transplantation: Nontumoral Portal Vein Thrombosis. *Liver Transpl*. 2016;22:352-365.
15. Lisman T, Porte RJ. Rebalanced hemostasis in patients with liver disease: evidence and clinical consequences. *Blood*. 2010;116:878-885.
16. Stine JG, Wang J, Shah PM, et al. Decreased portal vein velocity is predictive of the development of portal vein thrombosis: a matched case-control study. *Liver Int*. 2018;38:94-101.
17. Van Thiel DH, Schade RR, Starzl TE, et al. Liver transplantation in adults. *Hepatology*. 1982;2:637-640.
18. Ravaioli M, Zanello M, Grazi GL, et al. Portal vein thrombosis and liver transplantation: evolution during 10 years of experience at the University of Bologna. *Ann Surg*. 2011;253:378-384.
19. Simonetto DA, Singal AK, Garcia-Tsao G, et al. ACG clinical guideline: disorders of the hepatic and mesenteric circulation. *Am J Gastroenterol*. 2020;115:18-40.
20. Francoz C, Belghiti J, Vilgrain V, et al. Splanchnic vein thrombosis in candidates for liver transplantation: usefulness of screening and anticoagulation. *Gut*. 2005;54:691-697.
21. Shi Z, Yan L, Zhao J, et al. Prevention and treatment of rethrombosis after liver transplantation with an implantable pump of the portal vein. *Liver Transpl*. 2010;16:324-331.
22. Draoua M, Titze N, Gupta A, et al. Significance of measured intraoperative portal vein flows after thrombendvenectomy in deceased donor liver transplantations with portal vein thrombosis. *Liver Transpl*. 2017;23:1032-1039.
23. Rizzari MD, Safwan M, Sobolic M, et al. The impact of portal vein thrombosis on liver transplant outcomes: does grade or flow rate matter? *Transplantation*. 2020;105(2):363-371. https://doi.org/10.1097/TP.0000000000003235
24. Rodríguez-Castro KI, Porte RJ, Nadal E, et al. Management of nonneoplastic portal vein thrombosis in the setting of liver transplantation: a systematic review. *Transplantation*. 2012;94:1145-1153.
25. Blasi A, Hernandez V, Fernandez J, et al. Venous thrombotic events after liver transplantation. *Clin Appl Thromb*. 2018;24:317-322.
26. Mukerji AN, Karachristos A, Maloo M, et al. Do postliver transplant patients need thromboprophylactic anticoagulation? *Clin Appl Thromb*. 2014;20:673-677.
27. Kaneko J, Sugawara Y, Tamura S, et al. Coagulation and fibrinolytic profiles and appropriate use of heparin after living-donor liver transplantation. *Clin Transplant*. 2005;19:804-809.
28. Bhangui P, Lim C, Salloum C, et al. Caval inflow to the graft for liver transplantation in patients with diffuse portal vein thrombosis: a 12-year experience. *Ann Surg*. 2011;254:1008-1016.
29. Hibi T, Nishida S, Levi DM, et al. When and why portal vein thrombosis matters in liver transplantation: a critical audit of 174 cases. *Ann Surg*. 2014;259:760-766.

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