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Performance of a Prospective Anticoagulation Stratification Algorithm After Liver Transplantation

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Background. Venous thromboembolism (VTE) occurs in 0.4% to 15.5% and bleeding occurs in 20% to 35% of patients after liver transplantation (LT). Balancing the risk of bleeding from therapeutic anticoagulation and risk of thrombosis in the postoperative period is challenging. Little evidence exists regarding the best treatment strategy for these patients. We hypothesized that a subset of LT patients who develop postoperative deep vein thromboses (DVTs) could be managed without therapeutic anticoagulation. We implemented a quality improvement (QI) initiative using a standardized Doppler ultrasound-based VTE risk stratification algorithm to guide parsimonious implementation of therapeutic anticoagulation with heparin drip. **Methods.** In a prospective management QI initiative for DVT management, we compared 87 LT historical patients (control group; January 2016–December 2017) to 182 LT patients (study group; January 2018–March 2021). We analyzed the rates of immediate therapeutic anticoagulation after DVT diagnosis within 14 d of LT, clinically significant bleeding, return to the operating room, readmission, pulmonary embolism, and death within 30 d of LT before and after the QI initiative. **Results.** Ten patients (11.5%) in the control group and 23 patients (12.6%; $P=0.9$) in the study group developed DVTs after LT. Immediate therapeutic anticoagulation was used in 7 of 10 and 5 of 23 patients in the control and study groups, respectively ($P=0.024$). The study group had lower odds of receiving immediate therapeutic anticoagulation after VTE (21.7% versus 70%; odds ratio = 0.12; 95% confidence interval, 0.019-0.587; $P=0.013$) and a lower rate of postoperative bleeding (8.7% versus 40%; odds ratio = 0.14, 95% confidence interval, 0.02-0.91; $P=0.048$). All other outcomes were similar. **Conclusions.** Implementing a risk-stratified VTE treatment algorithm for immediate post-LT patients appears to be safe and feasible. We observed a decrease in the use of therapeutic anticoagulation and a lower rate of postoperative bleeding without adverse impacts on early outcomes.

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The incidence rate of deep vein thrombosis (DVT) and pulmonary embolism (PE) is 2.7% to 15.5% and 0.4% to 1.3%, respectively,[1-8] whereas that of bleeding ranges from 20% to 35% after liver transplant (LT).[9,10] Anticoagulation is

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the cornerstone of treatment for acute venous thromboembolism (VTE). LT is a complex and long procedure during which intraoperative and postprocedure coagulopathies,[11] such as prolonged clotting time and increased international normalized ratio (INR), exist. Thus, in the acute postoperative setting, therapeutic anticoagulation for the treatment of acute VTE can lead to serious complications, including hemorrhage, graft failure, and even death. Because it is possible that some VTE may resolve spontaneously, we hypothesized that a subset of LT patients who experience postoperative VTE in the first 14 d of LT may be safe to be managed without therapeutic anticoagulation, thus averting the risks of anticoagulation. Therefore, a Doppler ultrasound (D-US) algorithm was developed to standardize surveillance for immediate posttransplant patients upon diagnosis of VTE. This algorithm attempts to minimize anticoagulation therapy in patients with low risk of embolism. The goal of this quality improvement (QI) initiative was to minimize the risk of postoperative hemorrhage without a concomitant increase in VTE morbidity. In this study, we report the feasibility and results of a VTE risk stratification algorithm refraining from therapeutic anticoagulation among LT patients diagnosed with acute DVT estimated to be at low risk for progressive thrombosis and high risk for postoperative hemorrhage.

MATERIALS AND METHODS

Study Population

This single-center study included LT patients managed before implementation of the QI initiative (control group reviewed retrospectively: January 2016–December 2017) and LT patients after implementation (study group with prospective data collection: January 2018–March 2021). This project was defined as a non–human subject research by our institution's institutional review board (IRB) Committee and, therefore, not subject to IRB oversight (IRB # 1051141). A standardized VTE risk stratification algorithm (Figure 1) was created as part of this QI initiative to tailor management according to the severity of the DVT and risk of embolization.

The following information was recorded for each subject: demographics; disease cause; Model for End-stage Liver Disease Sodium (MELD-Na) calculated at the time of LT; history of portal vein thrombosis (PVT), DVT, or hypercoagulable disorder diagnosis; and type and location of central venous lines placed before transplant. Types of central venous catheters used included peripherally inserted central catheters, triple lumen catheters, cordis, and hemodialysis lines. Diagnosis of DVT was pursued if clinical signs or symptoms presented within the patient, such as swelling in an extremity. Any DVT within 14 d after LT was recorded. Length of stay (LOS) was calculated from the day of transplantation to the day of discharge or date of death.

Primary endpoints included initiation of immediate anticoagulation after diagnosis of DVT by D-US and clinically significant bleeding (defined as a drop in hemoglobin ≥2 g/dL, transfusion of ≥2 units of blood, or bleeding into a critical space) after DVT diagnosis.[12]

Safety outcomes included death, PE (diagnosed by computed tomography, pulmonary angiography, or ventilation/perfusion scan), return to operating room for bleeding after DVT diagnosis, and 30-d readmission for any cause. Although PE and DVT are both considered as VTE, we considered the development of PE as a safety outcome because it represented DVT progression or treatment delay.

DVT Diagnosis and Treatment

This QI initiative to selectively anticoagulate and use D-US surveillance was created in collaboration with the expertise and guidance of our institution's thrombosis physicians (S.M.S., S.C.W.). The VTE risk stratification algorithm was

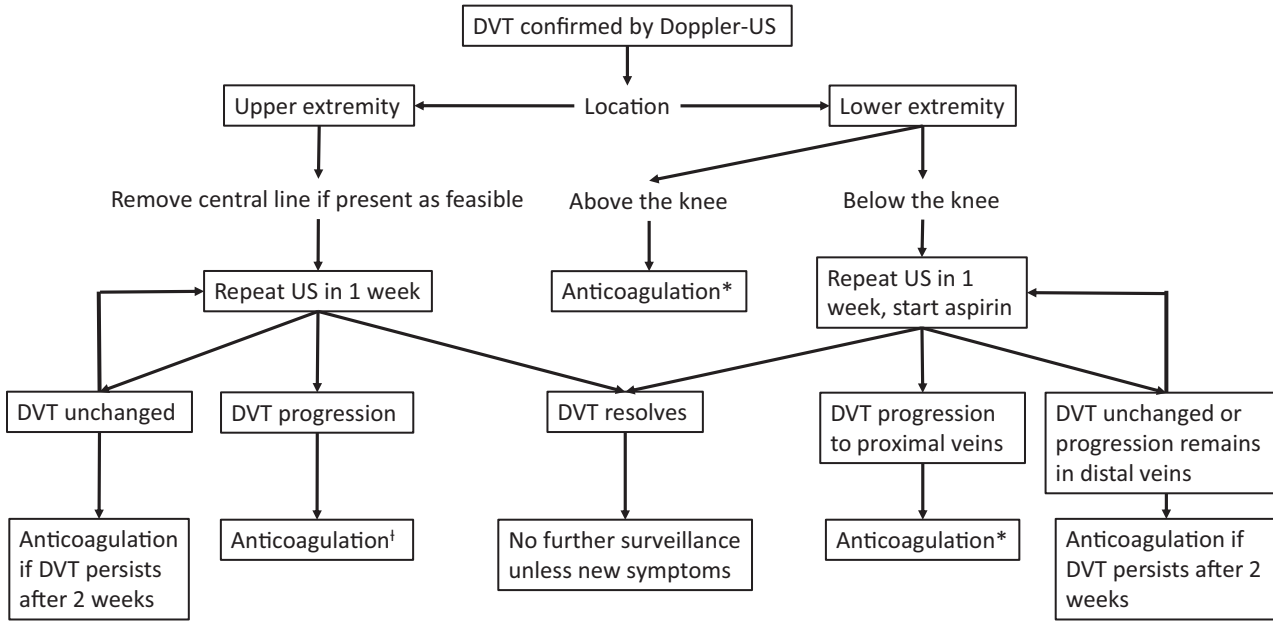

FIGURE 1. Stratified venous thromboembolism algorithm for immediate therapeutic anticoagulation in the postoperative in liver transplant. DVT, deep vein thrombosis; IVC, inferior vena cava; US, ultrasound.

applied to patients with DVT identified on the basis of clinical symptoms suggestive of thrombosis and corroborated by D-US in the first 14 d posttransplant. Because posttransplant coagulopathy was assumed for the first 2 wk postprocedure, patients presenting with DVT beyond 14 d were excluded from this QI initiative.

In the control group, patients diagnosed with DVT were treated with immediate therapeutic anticoagulation unless contraindicated. Based on our stratified algorithm, the study group was treated as follows: if DVT of the upper extremity was found in the setting of an indwelling venous catheter, the catheter was removed when clinically feasible. The DVT was then monitored with weekly D-US. If serial D-US showed DVT propagation or persistence of DVT after 2 wk, then therapeutic anticoagulation was prescribed. If the thrombosis had resolved, then no further surveillance was used. The anticoagulant regimen consisted of a low-dose heparin infusion with the goal of partial thromboplastin times of 50 to 70. Once clinically appropriate, the patient was then transitioned to warfarin with an INR goal of 2.0 to 3.0.

Lower extremity DVT was categorized as occurring in the isolated distal circulation (veins inferior to the popliteal vein) or the proximal circulation (thrombosis involving the popliteal or proximal veins). If DVT occurred in the proximal circulation, then therapeutic anticoagulation was ordered (or a retrievable inferior vena cava filter was placed if anticoagulation was contraindicated). If DVT was isolated to the distal lower extremity, then anticoagulation was withheld, and repeat D-US was ordered within a week, as advised in a major guidance statement.[13,14] If DVT propagated into the proximal veins, then therapeutic anticoagulation was prescribed. If DVT was unchanged or progression included only the isolated distal circulation, then anticoagulation was withheld and repeat D-US occurred a week later. If DVT persisted on the second surveillance D-US, then therapeutic anticoagulation was prescribed. If the thrombosis had resolved, then no further surveillance was used.

Independently of the group, patients who required therapeutic anticoagulation were treated with a low-dose heparin drip with the goal of partial thromboplastin times of 50 to 70. Once clinically appropriate, the patient was then transitioned to warfarin with an INR goal of 2.0 to 3.0.

Statistical Analysis

Descriptive results are shown as number and percentages for categorical data. Continuous variables are reported as median and interquartile range. Sample size was calculated at 52 patients in each group for 80% power, significance level of 0.05, and effect size of 0.5. The method for sample size calculation in the context of this study design followed the technique described by Cohen et al.[15] To determine differences between groups, Student *t* test or Mann-Whitney test was performed. Categorical variables were compared using the χ^2 test or the Fisher exact test. Linear regression was performed with laboratory values (fibrinogen, INR, and platelet count) 14 d after LT. Univariate logistic regression analysis was performed to evaluate whether implementation of the QI initiative was associated with decreased odds of therapeutic anticoagulation and bleeding; no other variable was associated with the primary endpoints; thus, multivariate analysis was not reported. Univariate Cox regression was performed to assess any DVT predictor. Multivariate Cox regression models were performed using variables with a P value of <0.05 on the univariate analysis. Time to event was analyzed with the use of Kaplan-Meier curves with a log-rank test for cumulative hazard ratio. All analyses were 2-tailed, and the threshold of significance was assessed at a P value of <0.05. The statistical analysis was performed using R software version 4.0.3 (R Core Team, 2020).

RESULTS

Among the 269 LT patients enrolled, 58.4% were male, with a median age of 57. Eighty-seven patients were in the control group, and 182 were in the study group. Demographics, history of hypercoagulable disorder, PVT or DVT, and number and type of intraoperative lines (Table 1) were similar between groups. The study group had lower median MELD-Na scores at the time of LT (24 versus 31; $P<0.0001$), lower rate of peripherally inserted central catheter line placement (20.9% versus 63.2%; $P<0.0001$), and a higher rate of intrajugular central line (100% versus 94.3%; $P=0.005$) when compared with the control group.

Patients Diagnosed With DVT

Among the 33 patients (12.3%) who developed DVT, 23 patients (12.6%) were in the study group, and 10 patients (11.5%; $P=0.9$) were in the control group. These patients had similar demographics and characteristics (Table 2). Preoperative thromboelastography (citrated kaolin R time [median: 5.2 versus 5.2; $P=0.5$], citrated kaolin 30 min [mean: 2.9 versus 2; $P=0.6$], citrate kaolin R time [median: 51.9 versus 51.8; $P=0.8$], and citrate functional fibrinogen [median: 34.9 versus 20.1; $P=0.5$]) results were similar between the patients who developed DVT and those without DVT. Additionally, fibrinogen, platelets, and INR at the time of DVT diagnosis were similar between those who developed DVT and those who did not (Table 3) or the posttransplant slope values were similar (**Figures S1–S3, SDC**, http://links.lww.com/TXD/A506). There was no difference in the rate of DVT between groups (12.6% in the study group versus 11.5% in the control group, $P=0.9$ by the χ^2 test, and $P=0.8$ by the log-rank test; Figure 2). One patient in the control group without DVT had a complicated postoperative course because of aspiration and long LOS (188 d) and was considered an outlier for LOS (<90 d in the cohort) and removed from the LOS analysis. LOS was longer among patients who developed DVT (14 versus 10 d; $P<0.001$; **Figures S4 and S5, SDC**, http://links.lww.com/TXD/A506) and in those with postoperative bleeding (20 versus 10 d; $P=0.03$; **Figures S6 and S7, SDC**, http://links.lww.com/TXD/A506).

Higher MELD-Na scores (30 versus 26; $P=0.014$; odds ratio [OR] = 1.06; 95% confidence interval [CI], 1.01-1.11; $P=0.01$) and number of operative lines (3 versus 2; $P=0.031$; OR = 1.35; 95% CI, 1.03-1.78; $P=0.033$) were associated with the development of DVT. But only MELD-Na score (OR = 1.05; 95% CI, 1.01-1.1; $P=0.04$) remained significant in the multivariate Cox model.

Primary Endpoint

Upon surveillance D-US, treatment with anticoagulation was initiated in 5 patients (21.7%) with high risk of embolization because of DVT progression in the study group patients and in 7 (70%) control group patients ($P=0.024$), whereas the remainder in each group completed serial D-US follow-up

TABLE 1.

Demographic data of the cohort

Variable	Total (N = 269)	Control group (N = 87)	Study group (N = 182)	*P*
Female, n (%)	112 (41.6)	38 (43.7)	74 (40.7)	0.7
Age, median (IQR), y	57 (45–64)	57 (47–62.5)	56 (44–64)	0.9
Body mass index, median (IQR), kg/m^2	27 (24–32)	28 (24–32)	27 (24–32)	0.9
Caucasian, n (%)	244 (90.7)	82 (94.3)	162 (89)	0.3
Reason for transplant, n (%)				0.3
NASH	61 (22.7)	23 (26.4)	38 (20.9)	
ETOH	52 (19.3)	12 (13.8)	40 (22)	
Viral	38 (14.1)	17 (19.5)	21 (11.5)	
Malignancy	13 (4.8)	4 (4.6)	9 (4.9)	
AIH	14 (5.2)	5 (5.7)	9 (4.9)	
PSC	44 (16.4)	13 (14.9)	31 (14.9)	
Other	38 (14.1)	13 (14.9)	25 (13.7)	
History of PVT, n (%)	64 (23.8)	18 (20.7)	46 (25.3)	0.5
History of DVT, n (%)	22 (8.2)	7 (8)	15 (8.2)	1
History of hypercoagulable disorder, n (%)	5 (1.9)	0	5 (2.7)	0.3
MELD-Na score, median (IQR)	27 (22–33)	31 (28–37)	24 (20–30)	<0.001
Living donors, n (%)	11 (4.1)	0	11 (6)	0.06
Donation after circulatory death, n (%)	38 (15.1)	9 (10.6)	29 (17.4)	0.2
Operative lines, median (IQR)	2 (1–3)	2 (2–3)	2 (1–3)	0.3
Intrajugular, n (%)	264 (98.1)	82 (94.2)	182 (100)	0.005
PICC, n (%)	93 (34.6)	55 (63.2)	38 (20.9)	<0.001
LOS, median (IQR), d	10 (7–15)	10 (8–15)	10 (7–15)	0.2

AIH, autoimmune hepatitis; DVT, deep vein thrombosis; ETOH, alcohol cirrhosis; IQR, interquartile range; LOS, length of stay; MELD-Na, Model for End-stage Liver Disease Sodium; NASH, nonalcoholic steatohepatitis; PICC, peripherally inserted central catheter; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis.

TABLE 2.

Demographic data of patients with thrombosis

Variable	Total (N = 33)	Control group (N = 10)	Study group (N = 23)	*P*
Female, n (%)	16 (48.5)	6 (60)	10 (43.5)	0.6
Age, median (IQR), y	54 (45–61)	57 (48–62)	52 (41–60)	0.5
Body mass index, median (IQR), kg/m^2	27 (23–32)	28 (27–35)	27 (22–31)	0.5
Caucasian, n (%)	30 (90.9)	9 (90)	21 (91.3)	1
Reason for transplant, n (%)				0.5
NASH	6 (18.2)	3 (30)	3 (13)	
ETOH	9 (27.3)	2 (20)	7 (30.4)	
Viral	4 (12.1)	2 (20)	2 (8.7)	
AIH	2 (6.1)	0	2 (8.7)	
PSC	5 (15.2)	2 (20)	3 (13)	
Other	7 (21.2)	1 (10)	6 (26.1)	
History of PVT, n (%)	8 (24.2)	3 (30)	5 (21.7)	0.9
History of DVT, n (%)	2 (6.1)	1 (10)	1 (4.3)	1
History of hypercoagulable disorder, n (%)	1 (3)	0	1 (4.3)	1
MELD-Na score, median (IQR)	30 (25–37)	32 (28–36)	28 (25–39)	1
Donation after circulatory death, n (%)	4 (12.1)	0	4 (17.3)	0.4
Operative lines, median (IQR)	3 (2–3)	3 (2–3)	3(2–3)	0.8
Intrajugular, n (%)	32 (97)	9 (90)	23 (100)	0.7
PICC, n (%)	15 (45.5)	7 (70)	8 (34.8)	0.1

AIH, autoimmune hepatitis; DVT, deep vein thrombosis; ETOH, alcohol cirrhosis; IQR, interquartile range; MELD-Na, Model for End-stage Liver Disease Sodium; NASH, nonalcoholic steatohepatitis; PICC, peripherally inserted central catheter; PSC, primary sclerosing cholangitis; PVT, portal vein thrombosis.

without progressive thrombosis. Of the patients receiving immediate anticoagulation, 2 (8.7%) and 4 (40%) patients ($P = 0.1$) had postoperative bleeding, respectively. The study group had an observed decreased odds of receiving immediate therapeutic anticoagulation after DVT (21.7% versus 70%; OR = 0.12; 95% CI, 0.02-0.59; $P = 0.013$) and deceased odds in bleeding (8.7% versus 40%; OR = 0.14; 95% CI, 0.02-0.91; $P = 0.048$) when compared with the control group.

In the control group, 3 patients developed DVTs but had unique medical circumstances that influenced their anticoagulation status postoperatively. One patient developed a DVT in the distal lower extremity, and a multidisciplinary team decision was made to pursue surveillance; this patient was counted as developing a DVT but not receiving immediate therapeutic anticoagulation. The second patient had both a DVT and new atrial fibrillation postoperatively, and anticoagulation for the

TABLE 3.

Thrombosis characteristics

Variable	Total (N = 33)	Control group (N = 10)	Study group (N = 23)	*P*
Time to DVT, median (IQR), d	5 (3–7)	6 (5–11)	5 (3–7)	0.2
Site of thrombosis, n (%)				0.4
Upper extremity	25 (75.8)	6 (60)	19 (82.6)	
Above the knee	4 (12.1)	2 (20)	2 (8.7)	
Below the knee	4 (12.1)	2 (20)	2 (8.7)	
Catheter related, n (%)	23 (69.7)	7 (70)	16 (69.7)	1
Initial anticoagulation, n (%)	12 (36.4)	7 (70)	5 (21.7)	0.024
Bleeding at 30 d, n (%)	6 (18.2)	4 (40)	2 (13.3)	0.099
Reoperation	4 (12.1)	2 (20)	2 (8.7)	0.7
Platelets at diagnosis, median (IQR)	82 (49–143)	129 (89–154)	61 (44–110)	0.1
INR at diagnosis, median (IQR)	1.2 (1.1–1.4)	1.2 (1.1–1.6)	1.2 (1.1–1.3)	0.6

DVT, deep vein thrombosis; INR, international normalized ratio; IQR, interquartile range.

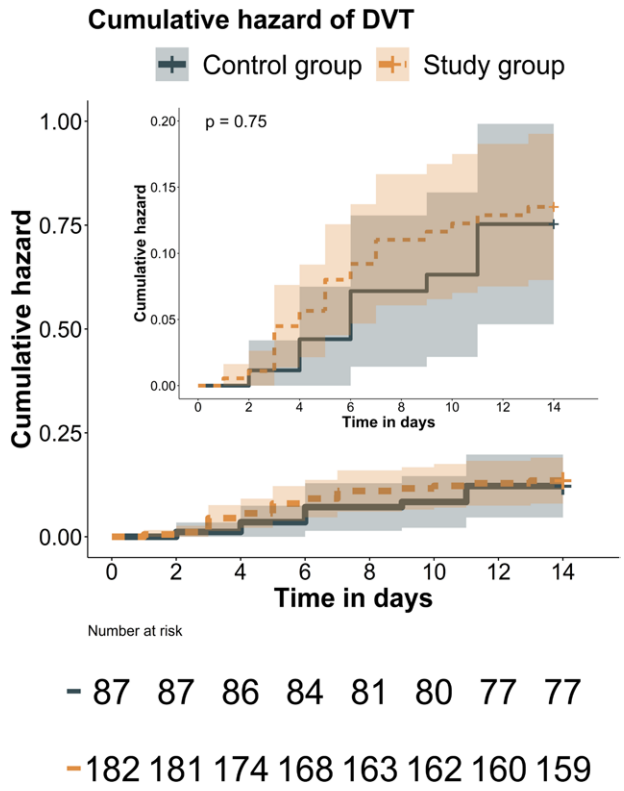

FIGURE 2. Cumulative hazard of DVT within 14 d after liver transplantation using a 100% hazard ratio scale and zoom in to 20% hazard ratio scale. DVT, deep vein thrombosis.

DVT was delayed until after electrical cardioversion per recommendations from the cardiology service; this patient was counted as developing a DVT and not receiving immediate therapeutic anticoagulation. The third patient had a pretransplant PVT and was on chronic anticoagulation, which was held perioperatively. This patient developed a DVT postoperatively, and the anticoagulation was restarted postoperatively; this patient was counted as developing a DVT but not receiving immediate therapeutic anticoagulation.

Safety Outcomes

Within the first 30 d after LT, no significant differences were observed with respect to death (1.1% versus 0%; $P = 0.8$), PE (1.1% versus 0%; $P = 0.8$), reoperation because of bleeding after anticoagulation (1.1% versus 2.3%; $P = 0.8$), or readmission for any cause (25.8% versus 26.4%; $P = 1$) between study and control groups (Table 4).

The 2 patients in the study group who developed PEs had complicated postoperative courses. One patient developed disseminated intravascular coagulation with intra-abdominal hemorrhage and ultimately required retransplant. This patient developed a DVT on postoperative day 11, but a multidisciplinary discussion felt that the risk of bleeding was greater than the risk of thrombosis, and the decision was made to defer anticoagulation. On postoperative day 29, the patient developed symptoms of a PE, which was confirmed on imaging, and an infrarenal vena cava filter was placed until it was acceptable to initiate anticoagulation. The second patient was transplanted because of acute liver failure secondary to acute alcoholic hepatitis. The patient was treated with hemodialysis because of hepatorenal syndrome. DVT and PE were detected on postoperative day 3 and treated with unfractionated heparin targeting a partial thromboplastin time of 60 s. Of the deaths in the study group, 1 patient presented with acute respiratory distress syndrome because of aspergillosis and diffuse alveolar hemorrhage on postoperative day 2. She progressed to right ventricle failure—negative imaging for PE—and died on postoperative day 5. The second patient was transplanted for acute fulminant hepatitis. During the immediate postoperative care, the patient presented with clinical suspicion for brain death and brain imaging with severe cerebral edema with tonsillar herniation.

DISCUSSION

Coagulopathic bleeding in the post-LT patient is a significant complication associated with increases in recipient mortality, intensive care unit readmission, and resource utilization.[9,16,17] Bhutiani et al analyzed the Premier Perspective Hospital Database, which includes data from >700 hospitals in the United States (n = 2747 patients). Through this database, they demonstrated that postoperative bleeding is the second most common complication in LT (35%), and this complication alone is associated with an annual cost increase of approximately $1 886 322 in hospital costs.[10] Thus, minimizing postoperative bleeding could decrease the financial burden in the US healthcare system. A conundrum thus arises when weighing the risks of VTE treatment in the post-LT patient.

TABLE 4.

Safety outcomes

Variable, n (%)	Total (N = 269)	Control group (N = 87)	Study group (N = 182)	*P*
Pulmonary embolism	2 (0.7)	0	2 (1.1)	0.8
Reoperation because of bleeding	4 (1.5)	2 (2.3)	2 (1.1)	0.8
Readmission	70 (26)	23 (26.4)	47 (25.8)	1
Death within 30 d	2 (0.7)	0	2 (1.1)	0.8

In this QI initiative, we sought to safely decrease the incidence of postoperative bleeding by more selectively anticoagulating post-LT patients who developed VTEs. Our VTE risk stratification algorithm resulted in 88.1% decreased odds of receiving initial anticoagulation and 86% decreased odds of postoperative hemorrhage while preserving a similar cumulative hazard for VTE and safety outcomes when compared with immediate anticoagulation.

These data suggest that we may be overtreating post-LT patients who develop VTEs when applying the standard anticoagulation algorithms as is done in other surgical patients. We may instead be able to defer anticoagulation in low-risk patients with the obvious benefits of decreasing unnecessary postoperative bleeding, associated bleeding risks, and financial burden. Although our data do not show a significant decrease in reoperation for bleeding, which we suspect is because of the low number of events, this may change with a larger sample size. The benefits of the decreased incidence of anticoagulation have to be weighed against the possible increased incidence of PE. Our current data show no increased incidence of PE, but this may be related to the low number of events. More research is ultimately needed in this specific post-LT patient population.

Regarding risk factors for VTE, we observed that the indication for LT[4] and body mass index[18,19] do not increase the risk in the immediate posttransplant period. Despite our limited data, a higher MELD-Na score is associated with DVT after LT; further multivariate analysis should be performed to clarify the true impact on these patients.

Limitations inherent to this study include the retrospective design, the low number of events in each group, and few outcome events. Identifying risk factors may be biased because of the low number of events; nevertheless, our study was focused on reducing DVT therapeutic anticoagulation in patients with low risk of embolization according to our algorithm. A multicenter randomized control trial would help to delineate the risks and benefits of the algorithm.

In conclusion, our standardized VTE algorithm using D-US surveillance in the immediate post-LT period appears to be safe and feasible. We observed decreased anticoagulation rates and decreased bleeding rates without adversely affecting progressive DVT, PE, or mortality rates.

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