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Authors

Yang, Jun
Rao, Zhuqing
Hong, Fu
et al.

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ORIGINAL ARTICLE

Takotsubo syndrome after liver transplantation: An association with intraoperatively administered epinephrine and fentanyl

Jun Yang[1,2] | Zhuqing Rao[3] | Fu Hong[4] | Vatche Agopian[5] | Jennifer Nguyen-Lee[2] | Randolph H. Steadman[6] | Christopher Wray[2] | Victor W. Xia[2]

[1] Department of Critical Care Medicine, Shandong Provincial Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, China

[2] Department of Anesthesiology and Perioperative Medicine, Ronald Reagan UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[3] Department of Anesthesiology, Jiangsu Province Hospital, The First Affiliated Hospital of Nanjing Medical University, Nanjing, China

[4] Department of Anesthesiology, Chongqing University Central Hospital, Chongqing, China

[5] Department of Surgery, Ronald Reagan UCLA Medical Center, David Geffen School of Medicine at UCLA, Los Angeles, California, USA

[6] Department of Anesthesiology and Critical Care, Houston Methodist Hospital, Houston, Texas, USA

Correspondence
Victor W. Xia, Department of Anesthesiology and Perioperative Medicine, Ronald Reagan UCLA Medical Center, David Geffen School of Medicine at UCLA, University of California, Los Angeles, 757 Westwood Plaza, Suite 3325, Los Angeles, CA 90095–7430, USA.
Email: vxia@mednet.ucla.edu

Abstract

Takotsubo syndrome (TTS) can develop after liver transplant (LT), but its predisposing factors are poorly understood. In this study, we aimed to determine if perioperative factors were associated with posttransplant TTS. Adult patients who underwent primary LT between 2006 and 2018 were included. Patients with and without TTS were identified and matched by propensity scores. Of 2181 LT patients, 38 developed postoperative TTS with a mean left ventricular ejection fraction of 25.5% (±7.8%). Multivariable logistic regression revealed two preoperative risk factors (alcoholic cirrhosis and model for end-stage liver disease-sodium scores) for TTS. Post-propensity match analyses showed that TTS patients had significantly higher doses of epinephrine and lower doses of fentanyl during LT compared with non-TTS patients. A higher dose of epinephrine and a lower dose of fentanyl was associated with a higher predicted probability of TTS. All TTS patients had full recovery of cardiac function and had comparable 1-year survival. In conclusion, TTS occurred at a rate of 1.7% after LT and was associated with two pretransplant risk factors. The higher doses of epinephrine and lower doses of fentanyl administered during LT were associated with posttransplant TTS. More studies on the relationship between intraoperative medications and TTS are warranted.

KEYWORDS
cardiovascular disease, complication, heart (native) function / dysfunction

1 | INTRODUCTION

Takotsubo syndrome (TTS) is a clinical condition characterized by an acute development of severe left ventricular dysfunction triggered by intense emotional, pathophysiological, or surgical stress.[1] Although TTS is often described as having a transient clinical course, it is associated with substantial morbidity and mortality.[2] During the acute phase, TTS patients can present with hemodynamic and electrical instability due to cardiogenic shock, ventricular arrhythmias, heart failure, pulmonary edema and are at increased risk of cardiac death.[1,3–5] Life-saving invasive interventions such as intra-aortic balloon pump, ventricular assist devices, and extracorporeal membrane oxygenation are often required to mitigate the serious complications.[6,7]

Postoperative TTS has been documented after a wide range of surgical procedures including liver transplantation (LT).[8] Patients undergoing LT appear to have a higher risk of developing postoperative TTS

compared with non-LT patients.[1,8] Transplantation presents tremendous perioperative stress to patients. Underlying advanced liver disease and cirrhotic cardiovascular disease in LT patients increase the risk for the development of postoperative TTS. In addition, LT candidates may experience significant emotional stress while waiting for a donor organ since the wait is often long and unpredictable. Furthermore, chronic multiorgan dysfunction, the mental and physical burden of chronic medical conditions add to an overall lack of reserve to buffer the stress of LT. These preoperative conditions combined with the intraoperative insult and frequent hemodynamic instability of surgery make it less surprising that LT patients have a higher rate of TTS.

Maintaining adequate anesthesia depth and stable hemodynamics during major surgery is challenging, and perioperative management choices may contribute to the development of TTS. In non-LT surgery, postoperative TTS has been reported as a result of excessive catecholamine administration and inadequate depth of anesthesia.[9,10] Perioperative risk factors for TTS in LT are poorly understood. Our understanding of TTS after LT mostly relies on analyses from underpowered single case reports or small case series or from poorly controlled groups.[8,11] Identifying perioperative risk factors associated with TTS in LT patients is important, since it may provide guidance to improve the perioperative management in these critically ill patients.

In this retrospective study, we aimed to investigate the incidence of TTS in a large, single-center cohort of consecutive adult LT patients. We also planned to identify preoperative and intraoperative risk factors for the development of TTS. We specifically focused on the intraoperative use of catecholamine and opioid medications to determine if there was any association between their use and the development of TTS after LT.

2 | METHODS

We conducted a retrospective study after receiving approval from the institutional review board and waiver of informed consent from the University of California, Los Angeles (UCLA). Adults (≥18 years of age) who underwent primary LT between January 2006 and December 2018 at UCLA Medical Center were included. Patient demographics, comorbidity, etiology of liver disease, MELD-Na scores, baseline laboratory values, and intraoperative requirements for transfusion of red blood cells and frozen fresh plasma were prospectively collected. Preoperative and postoperative echocardiographic data, cardiology notes, and cardiac diagnostic tests were collected retrospectively. Total doses of intraoperative vasopressors, anesthetics, and opioids were also recorded retrospectively based on the anesthetic records.

All LT patients underwent preoperative cardiac screening including transthoracic echocardiography, stress test, and/or coronary artery angiogram. Anesthesia management followed our institution standard as previously reported.[12] In brief, patients received intravenous anesthetics for induction and combined inhalational and intravenous anesthetics for maintenance. Vasopressors were administered for hemodynamic support and the choice and dosing of vasopressors were selected according to patient's needs and anesthesiologist preference. Anesthetics including inhalational agents and opioids were used to maintain patients under general anesthesia and titrated according to levels of surgical stimulation and patient responses. Isoflurane was the most commonly used inhalational agent during the study period and fentanyl was the primary opioid used for analgesia and sympatholysis. Postoperatively, patients were transferred to the intensive care unit and managed by a multidisciplinary team.

Patients with TTS were identified by reviewing medical records, cardiology consultant notes, electrocardiograms, echocardiographic reports, and angiographic reports. We used the 2018 consensus criteria to define TTS.[13] In brief, TTS was diagnosed when significant left ventricular dysfunction occurred within 30 days after LT in the absence of significant coronary artery disease or infectious myocarditis. Patients were divided into two groups: non-TTS and TTS.

Statistical analysis

Data were presented as a mean ± standard deviation (SD) or median (interquartile range, IQR) for continuous variables, and as a percentage for categorical variables. Statistical analysis comparing the two groups was performed using Student t, Wilcoxon rank, Mann-Whitney, Pearson's chi-square, or Fisher tests. Independent preoperative risk factors for TTS were identified using multivariate logistic regression analysis. Prior to comparing intraoperative variables between patients with and without TTS, the two groups underwent propensity score matching (PSM). The propensity scores were first generated using preoperative factors that showed statistical significance between the two groups in univariate analysis. Patients were matched in a 1:4 ratio with the closest propensity scores using a .2 width caliper. Intraoperative variables between the two groups were compared using post-PSM data. Odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. Survival analysis was performed using the Kaplan–Meier method with a log-rank test. All statistical analyses were performed with SPSS, version 26.0 for Windows (IBM, Armonk, NY) with a P value of less than .05 considered statistically significant.

3 | RESULTS

A total of 2181 adult patients underwent LT at our institution during the study period. Mean age was 54.4 (±11.5) years old and 61.7% were male. Mean MELD-Na score was 33.0 (±8.3). The percentages of patients needing preoperative intubation, vasopressors, and hemodialysis were 22.4%, 18.3%, and 39.5%, respectively.

Of the 2181 adult patients, 38 developed TTS after LT with an incidence of 1.7%. Mean age of TTS patients was 54.4±10.7 and 60.1% were male. The majority of TTS cases (71%) occurred in the first 5 days after LT (Figure 1). Preoperative echocardiograms showed that mean ejection fraction (EF) of the left ventricle was 62.0% (± 3.8%) in TTS patients with no significant difference compared with non-TTS patients (61.4% ± 6.3%, P = .282). EF of the TTS patient decreased to 25.5% (±7.8%) at the time of the diagnosis (Figure 2).

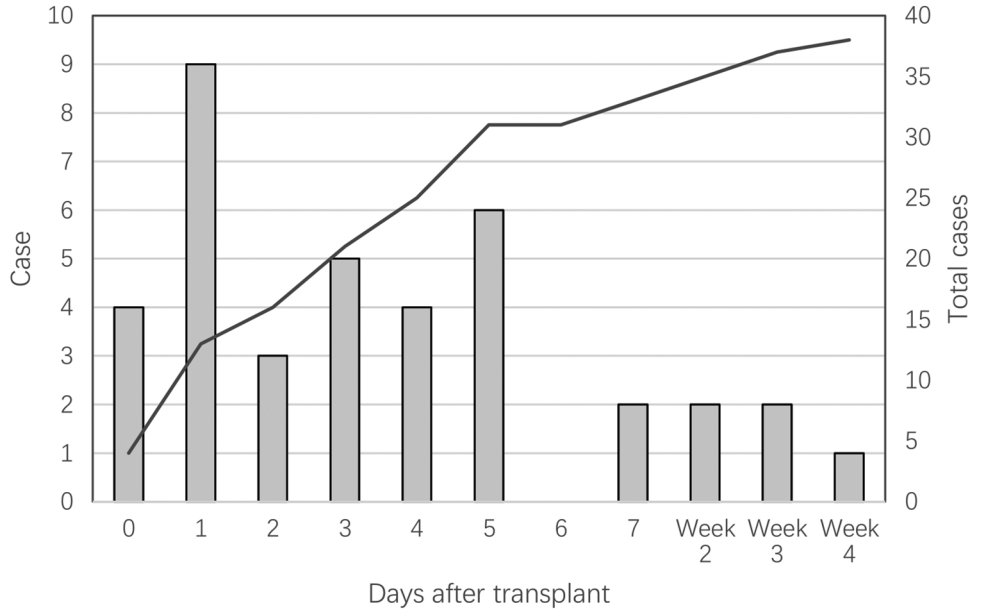

FIGURE 1 The number of TTS cases (bars, values on the left axis) and the accumulated TTS cases (line, values on the right axis) occurred on postoperative days

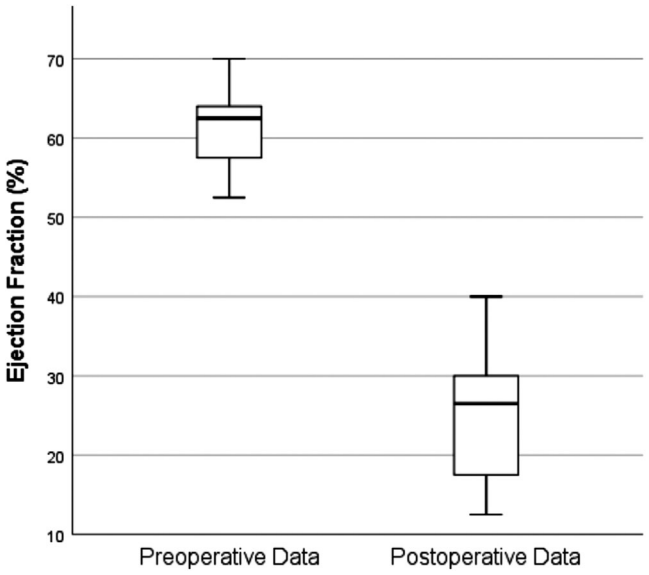

FIGURE 2 Ejection fraction of the left ventricle of TTS patients before liver transplantation and at time of the diagnosis after transplantation

Comparison of preoperative variables between patients with and without TTS is shown in Table 1. Patients in the TTS group had a higher percentage of alcoholic cirrhosis as the underlying etiology of liver failure and a lower percentage of hepatocellular carcinoma. In addition, TTS patients had a higher incidence of ascites at the time of LT, higher requirements for vasopressors and lower baseline hematocrit values before LT (Table 1). Notably, patients in the TTS group had higher MELD-Na scores compared with non-TTS patients. Using MELD-Na scores, patients were divided into three groups using quartiles. The incidences of TTS were .4%, 2.0%, and 2.8% in patients with MELD-Na scores < 27, 27–39 and ≥ 40 (representing the 1st, the 2nd/3rd, and the 4th quartiles, $P = .016$), respectively. Multivariable logistic regression showed that two factors (alcoholic cirrhosis and higher MELD-Na scores) were independent risk factors for postoperative development of TTS. Patients with alcoholic cirrhosis had twice the odds of developing TTS compared with those without alcoholic cirrhosis (OR 2.13, 95% CI 1.11–4.08, $P = .023$). Patients with MELD-Na scores 27–39 and ≥ 40 had 4.33 (95% CI 1.01–18.64, $P = .049$) and 6.18 (95% CI 1.41–27.08, $P = .016$) fold higher odds of developing postoperative TTS compared with patients with MELD-Na score < 27.

Since there were significant differences in multiple preoperative variables between the two groups, PSM was used to generate a data set for intraoperative factor analysis between patients with and without TTS. Six preoperative variables showing significant differences by the univariate analysis were selected to generate propensity scores. Post-PSM analyses showed that significant differences between the 2 groups were eliminated (Table 2).

Table 3 illustrates results of comparing intraoperative variables between the two groups using post-PSM data. Transfusion of blood products was not significantly different between the non-TTS and TTS groups. Utilization of venovenous bypass, intraoperative dialysis and piggyback technique were also similar. Other variables including cold and warm ischemia times and isoflurane measured by maximum concentration were not significantly different between the two groups. Administration of vasopressin and norepinephrine, both measured by use (vs. non-use) and total doses, were also not significantly different between the non-TTS and TTS groups. Median dose of epinephrine administered during LT surgery was significantly higher in the TTS group (30 mcg, IQR 0–1104 mcg) compared to the non-TTS group (0 mcg, IQR 0–20 mcg, $P = .008$). In contrast, median dose of fentanyl

TABLE 1 Comparison of preoperative variables

Variables	Non-TTS ($n = 2143$)	TTS ($n = 38$)	P
Age	54.4±11.5	54.4±10.7	.988
Gender (male)	61.8	60.1	.602
Height (cm)	169.1±10.6	168.1±12.7	.590
Weight (kg)	80.1±20.2	77.8±25.6	.500
MELD-Na score	32.9±8.3	36.5±6.5	.002
Encephalopathy	47.3	62.2	.073
Preoperative intubation	23.6	32.4	.208
History of hypertension	31.9	25.0	.375
Coronary artery disease	9.4	8.3	.821
Preoperative pressors	19.5	34.2	.049
Preoperative dialysis	42.0	55.3	.143
Diabetes mellitus	28.2	18.9	.246
Gastroesophageal bleeding	35.7	38.9	.693
Ascites (> 1L)	43.6	65.8	.002
Hepatitis B	6.3	2.7	.375
Hepatitis C	29.4	18.9	.165
Alcoholic cirrhosis	27.1	44.7	.016
Non-alcoholic steatohepatitis	10.3	13.5	.521
Hepatocellular carcinoma	31.3	15.8	.050
Baseline laboratory values			
Hematocrit (%)	28.2±7.8	24.5±5.5	.003
International normalization ratio	1.8±.7	2.0±.6	.144
Creatinine (mg/dl)	1.7±1.4	1.6±1.4	.662
Sodium (mmol/L)	137.0±6.5	136.4±5.9	.566
Total bilirubin (mg/dl)	15.7±16.1	13.9±13.8	.420

TABLE 2 Comparison of preoperative variables between the non-TTS and TTS groups before and after propensity score match (PSM)

Variables	Non-TTS ($n = 152$)	TTS ($n = 38$)	P
Age	55.4±10.9	54.4±10.7	.611
Gender (male)	70.4	68.4	.812
Height (cm)	168.7±10.5	168.1±12.7	.804
Weight (kg)	81.9±17.9	77.8±25.6	.364
MELD-Na score	36.0	36.5±6.5	.689
Encephalopathy	56.6	62.2	.538
Preoperative intubation	26.5	32.4	.469
History of hypertension	28.7	25.0	.660
Coronary artery disease	9.5	8.3	.834
Preoperative pressors	31.6	34.2	.756
Preoperative dialysis	53.3	55.3	.827
Diabetes mellitus	31.8	18.9	.141
Gastroesophageal bleeding	46.3	38.9	.425
Ascites (>1L)	67.8	65.8	.816
Hepatitis B	3.9	2.7	.719
Hepatitis C	21.7	18.9	.709
Alcoholic cirrhosis	41.4	44.7	.713
Non-alcoholic steatohepatitis	12.5	13.5	.868
Hepatocellular carcinoma	16.4	15.8	.922
Baseline laboratory values			
Hematocrit (%)	24.3±6.0	24.5±5.5	.873
International normalization ratio	2.1±.6	2.0±.6	.416
Creatinine (mg/dl)	1.8±1.4	1.6±1.4	.519
Sodium (mmol/L)	136.0±5.5	136.4±5.9	.717
Total bilirubin (mg/dl)	21.5±16.2	13.9±13.8	.209

used during LT was significantly less in the TTS group (250 mcg, IQR 137.5–558.8 mcg) compared with that in the non-TTS group (400 mcg, IQR 250.0–800.0 mcg, $P = .043$).

In order to delineate the relationship between epinephrine and fentanyl administered intraoperatively, several logistic regression models of the predicted probability of TTS were constructed. The higher doses of epinephrine and the lower doses of fentanyl was associated with a higher probability of TTS (Figure 3A and 3B). The higher dose of epinephrine was associated with the higher probability of TTS regardless of patients receiving fentanyl or not (Figure 3C). At any given dose of epinephrine, the probability of TTS was lower in patients who received fentanyl compared with those who did not receive fentanyl (Figure 3C). In patients who did not receive epinephrine, there was no relationship between the fentanyl dose used during LT and the predicted probability of TTS (Figure 3D). However, in patients who received epinephrine, there was a negative relationship between the TTS probability and dose of fentanyl. The lower doses of fentanyl were associated with a higher predicted probability of TTS (Figure 3D).

All TTS patients received aggressive pharmacologic therapy. Of the 38 patients, seven patients required invasive interventions (five intra-aortic balloon pump and two venoarterial extracorporeal membrane oxygenation). All TTS patients had full recovery of cardiac function as measured by postoperative echocardiography (LVEF, 54.3% ± 12.6%). Patients with and without TTS had comparable 1-year survival (18.4% vs. 21.1%, Log-rank test, $P = .698$).

4 | DISCUSSION

In this large retrospective study of 2181 adult patients, we found that TTS occurred at a rate of 1.7% after LT. The majority of TTS occurred within 5 days after LT. Alcoholic cirrhosis and high MELD-Na score were independent preoperative risk factors for TTS. Intraoperatively, higher doses of epinephrine and lower doses of fentanyl were associated with the development of TTS. Seven out of the 38 patients required invasive mechanical cardiac support. TTS

TABLE 3 Comparison of intraoperative and donor variables between the non-TTS and TTS groups using post-match data

	Non-TTS (n = 152)	TTS (n = 38)	*P*
Red blood cells (unit)	25.8±20.5	27.0±18.9	.743
Fresh frozen plasma (unit)	28.9±21.6	30.9±22.5	.615
Cryoprecipitate (unit)	1.8±1.9	1.8±1.5	.958
Platelet (unit)	1.6±1.3	1.6±1.1	.757
Hemodialysis (%)	20.3	24.3	.589
Venoveous bypass (%)	53.6	43.2	.257
Piggyback technique (%)	4.2	2.9	.720
Antifibrinolytics (%)	25.7	22.2	.668
Postreperfusion syndrome (%)	17.7	22.2	.531
Isoflurane, highest concentration (%)	.9 (.8–1.0)	1.0 (.8–1.0)	.545
Fentanyl use (yes vs. no)	95.2	89.5	.180
Fentanyl (total dose in mcg)	400.0 (250.0–800.0)	250.0 (137.5–558.8)	.043
Epinephrine use (yes vs. no)	35.5	52.6	.053
Epinephrine (total dose in mcg)	0 (0–20.0)	30 (0–1104.8)	.008
Vasopressin use (yes vs. no)	77.6	76.3	.862
Vasopressin (total dose in unit)	7.1 (1.5–23.1)	12.5 (.8–38.5)	.486
Norepinephrine use (yes vs. no)	60.5	68.4	.370
Norepinephrine (total dose in mcg)	1145.5 (0–3775.8)	1236.4 (0–5098.3)	.623
Donor factors			
Age (year)	37.3±15.1	39.2±15.1	.507
Gender (male, %)	63.2	71.1	.606
Donation after cardiac death (%)	4.6	10.5	.336
Extended criteria donor (%)	17.2	21.1	.582
Cold ischemia time (min)	445.3±153.3	406.4±135.9	.192
Warm ischemia time (min)	48.3±16.5	44.4±10.4	.202

patients had similar 1-year survival compared with those without TTS after LT.

TTS was first reported in LT patients in 2007. Since then, at least 97 post-LT TTS cases (including this study) have been reported.[11,14–16] Compared to non-LT surgery, LT patients appear to be at a higher risk for the development of TTS. In a single-center study, six patients (.8%) developed TTS after 734 LTs compared to 1 TTS case (.04%) after 2303 kidney transplants.[1] In a systemic review of all reported perioperative TTS cases in 2017, LT patients represented 9% of all postoperative TTS cases, whereas TTS after vascular or orthopedic surgery was only around 5%.[8]

Our study suggests that patients with high MELD-Na scores have a significantly higher risk of developing TTS than those with lower MELD-Na scores. This is likely due to the known extensive interactions between the hepatic and cardiovascular systems.[17] When cirrhosis develops, so does cardiovascular dysfunction. As an index of severity of liver disease, the higher MELD-Na score correlates with severe liver disease and multiorgan dysfunction and an increased posttransplant cardiac structural and functional abnormalities.[18] In addition, preoperative cardiac dysfunction has been shown to be a risk factor for post-LT cardiac dysfunction.[19] Intraoperatively, a high MELD-Na score is associated with a more difficult intraoperative course and higher requirements for blood transfusion.[12] Since MELD-Na scores of LT candidates are continuing to trend up in the United States, (https://srtr.transplant.hrsa.gov/annual_reports/2019/Liver.aspx) (UNOS annual report 2019) TTS cases is likely to increase in the future.

In addition to MELD-Na scores, alcohol consumption significantly affects the cardiovascular systems and hemodynamics of patients. Excessive alcohol consumption is associated with an increased risk of cardiovascular diseases including alcoholic cardiomyopathy, elevated blood pressure, atrial arrhythmias, and stroke. Mechanisms by which alcohol causes cardiomyopathy are likely multifactorial. Patients with alcohol abuse often have a thiamine deficiency, which is associated with hyperdynamic cardiomyopathy. Alcohol consumption may lead to transient hypotension and long-term hypertension mediated by the renin-aldosterone system and plasma vasopressin. In addition, alcohol has direct toxic effects on cardiomyocytes.[20,21] Therefore, it is reasonable to postulate that patients with a preoperative history of alcohol abuse can be a predisposition to postoperative TTS.

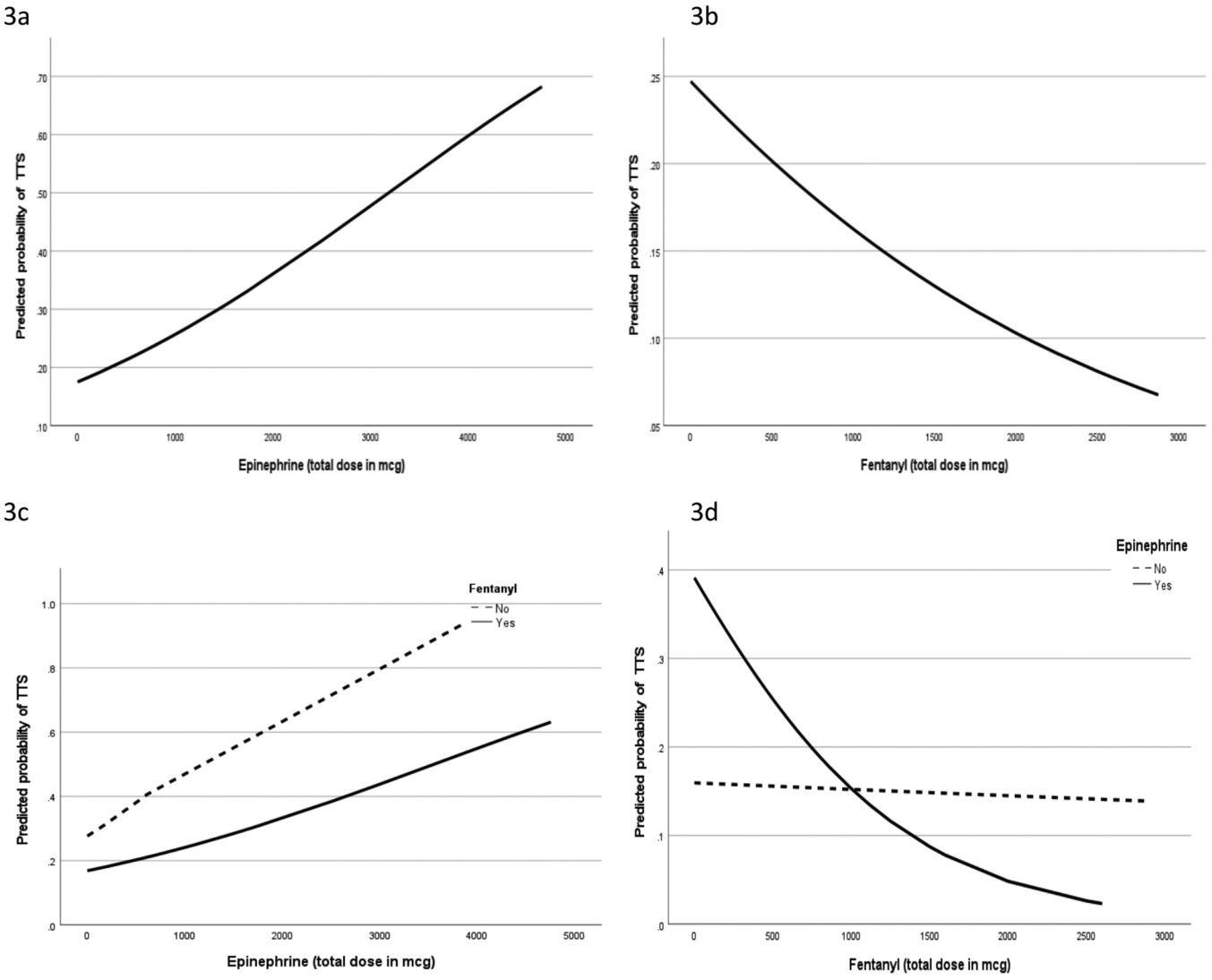

FIGURE 3 Mean predicted probability of TTS in a relationship with epinephrine and fentanyl used during liver transplantation. A higher dose of epinephrine was associated with a higher predicted probability of TTS (A). In contrast, a lower dose of fentanyl was associated with a higher predicted probability of TTS (B). Predicted probability of TTS in a relation with epinephrine, fentanyl and their interactions during liver transplantation are constructed by following logistic regression models. Model 1 (C). TTS = a + b1* epinephrine (in mcg) + b2*the use of fentanyl + b3*epinephrine (in mcg)*the use of fentanyl. At any given epinephrine dose, the use of fentanyl was associated with a lower probability of TTS. Model 2 (D). TTS = a + b1* fentanyl (in mcg) + b2*the use of epinephrine + b3*fentanyl (in mcg)*the use of epinephrine. The lower dose of fentanyl was associated with a higher probability of TTS in patients who received epinephrine

The role of catecholamines in the development of TTS has been documented in both experimental studies and clinical observations.[7] Elevated catecholamine levels have often been found in patients with TTS. In patients with pheochromocytoma and central nervous system disorders, elevated levels of catecholamines and TTS are commonly encountered together. In addition, many TTS cases have been reported after administration of catecholamines.[1] Excessive catecholamines have direct effects on cardiomyocytes, causing myocardial stunning, coronary artery spasm, myocardial ischemia, microcirculation dysfunction, and LV dysfunction. In patients undergoing major surgery, intrinsic catecholamine concentrations are commonly increased.

Catecholamines are frequently required during LT to maintain hemodynamic stability. Common catecholamines used during LT include norepinephrine and vasopressin. Epinephrine is infrequently used at our institution since low systemic vascular resistance is the most common factor contributing to hemodynamic instability during LT. Although all catecholamines have the potential to induce TTS in both animal models and clinical studies,[22] epinephrine was the only catecholamine found to have an association with the development of TTS in our study. Compared with other catecholamines, epinephrine enhances contractility of myocytes by acting on the beta 2 receptor. This inotropic effect may induce myocardial ischemia in a patient by altering the myocardial supply/demand balance, particularly when combined with severely depleted intravascular volume, hypotension and tachycardia. In our study, epinephrine was administered differently from other catecholamine mediations. More than 60% of patients in

our study received both norepinephrine and vasopressin by continuous infusion. In contrast, only 38.9% of LT patients received epinephrine intraoperatively. In addition, the dose range of epinephrine was significantly wider compared with those of norepinephrine or vasopressin, indicating that epinephrine was administered more often by intravenous blousing compared to other catecholamines.

The depth of anesthesia, determined by a balance between surgical stimulation and anesthetics, is important to consider in the development of TTS. Inadequate anesthetic depth has been suspected to play a role in the development of TTS after surgery.[1,23] In this study, we demonstrated that a lower cumulative dose of fentanyl, a main analgesic agent used during LT surgery, was associated with the development of TTS. Fentanyl can blunt responses to surgical and other stressful sympathetic stimulations, preventing the development of tachycardia and hypertension that may have deleterious defects on the cardiovascular system. Fentanyl may protect against catecholamine-induced cardiac injury by reducing the overall inotropic and chronotropic cardiac responses over an extended period. However, excessive fentanyl can suppress cardiac output and exacerbate hypotension and hemodynamic instability. Since complex interactions can occur between catecholamines and fentanyl, risk and benefit need to be carefully considered before their use.

Our study has several limitations. First, this was a retrospective study with inherent shortcomings. Second, although we used PSM to adjust for the imbalances in preoperative variables between the two groups, we could not control for unmeasured variables. Third, we were unable to account for all intraoperative medications that were administered in our study. These medications could have impacted in the occurrence of TTS. Fourth, perioperative episodic events resulting in severe hemodynamic instability requiring epinephrine administration may have contributed to the development of TTS. These episodes may not have been detected by our methods. Finally, as in any retrospective study, the associations found in this study cannot be interpreted as causal relations. Despite these limitations, this is the first large database study to identify important preoperative and intraoperative risk factors for the development of postoperative TTS in patients undergoing LT.

In summary, in this large retrospective study, we found that TTS occurred in 1.7% of patients after LT. Patients with alcoholic cirrhosis and higher MELD-Na score were at risk of developing posttransplant TTS. Furthermore, we found that higher doses of epinephrine and lower doses of fentanyl intraoperatively were associated with postoperative TTS in LT. Our findings extend the current understanding of postoperative TTS and may help guide the development of prophylactic or therapeutic strategies for TTS in LT. Further studies are warranted.

AUTHOR CONTRIBUTION

Jun Yang: substantial contribution to the design of the work, acquisition, analysis, and interpretation of data, drafting and revising the work and final approval of the work to be published. Dr. Yang attests to the integrity of the original study data and the analysis reported in this manuscript. **Zhuqing Rao**: substantial contribution to the design of the work, acquisition, analysis, and interpretation of data, drafting and revising the work and final approval of the work to be published. **Fu Hong**: substantial contribution to the design of the work, acquisition, analysis, and interpretation of data, and final approval of the work to be published. **Vatche G. Agopian**: substantial contribution to the design of the work, acquisition, and interpretation of data, revising the work and final approval of the work to be published. **Jennifer Nguyen-Lee**: substantial contribution to the acquisition of data and drafting and final approval of the work to be published. **Randolph H. Steadman**: substantial contribution to the design of the work and revising the work and final approval of the work to be published. **Christopher Wray**: substantial contribution to the design of the work and revising the work and final approval of the work to be published. **Victor W. Xia**: substantial contribution to the design of the work, acquisition, analysis, and interpretation of data, drafting and revising the work and final approval of the work to be published. Dr. Xia attests to the integrity of the original study data and the analysis reported in this manuscript.

CONFLICT OF INTEREST

None.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

ORCID

Jun Yang https://orcid.org/0000-0003-2925-7478
Victor W. Xia https://orcid.org/0000-0003-1182-3179

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