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Characteristics, Risk Factors, and Outcome of New-onset Systolic Heart Failure After Liver Transplantation: A Single-center Cohort

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Background. New-onset systolic heart failure (HF) after liver transplantation (LT) is a significant cause of morbidity and mortality; however, its characteristics are still insufficiently delineated. HF may involve the left ventricle (LV), right ventricle (RV), or both ventricles. We explored the incidence, characteristics, etiologies, risks, involved cardiac chambers, and outcomes of HF after LT. **Methods.** This study included 528 adult patients with preoperative LV ejection fraction ≥ 55% who underwent LT between 2016 and 2020. The primary outcome was new-onset systolic HF, defined by the presence of clinical signs, symptoms, and echocardiographic evidence of reduced LVejection fraction <50% and RV dysfunction within the first year after LT. **Results.** Thirty-one patients (6%) developed systolic HF within a median of 9 d (1–364). Of those, 23% of patients had ischemic HF, whereas 77% had nonischemic HF. Nonischemic HF was caused by stress (11), sepsis (8), or other factors (5). Nonischemic HF was secondary to isolated LV failure in 58% of patients or RV ± LV failure in 42% of patients. Recursive partitioning identified subgroups with varying risks and uncovered interaction between variables. HF risk increased from 4.2% to 13% when epinephrine and/or norepinephrine drips were used intraoperatively ($P < 0.01$). When no epinephrine and/or norepinephrine were used, HF risk increased from 3.1% to 38.5% if baseline hemoglobin was <7.2 g/dL ($P < 0.01$). When baseline hemoglobin was ≥7.2 g/dL, HF risk increased from 0% to 5.2% when ≥3500 mL crystalloid was used intraoperatively ($P < 0.01$). Posttransplant first-year survival and reversibility of HF depended on the etiology (stress, sepsis, ischemia, etc) and cardiac chamber involvement (isolated LV or RV ± LV). RV dysfunction was associated with inferior recovery of cardiac function and poorer survival than nonischemic isolated LV dysfunction (50% versus 70%, respectively). **Conclusions.** Posttransplant new-onset HF is mostly nonischemic in nature and is associated with increased morbidity and mortality.

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Retrospective study, which received institutional review board approval from the University of Miami.

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Cardiovascular complications are rampant after liver transplantation (LT).[1,2] Among this plethora of complications, systolic heart failure (HF) constitutes a distinct and important clinical entity in the first posttransplant year, with a reported incidence as high as 14% and associated mortality of 33%–45%.[3-5] Despite its devastating effect on the survival and quality of life of recipients, HF remains poorly understood. Regrettably, 2 decades of research into the diagnostic, therapeutic, and preventive strategies of post-LT myocardial dysfunction have provided scant data regarding its etiology, characteristics, and prognosis.[6,7] Thus, there remains a dire need to fill this knowledge gap so that the loss of both lives and grafts can be minimized.

Systolic HF is also aptly referred to as HF with reduced ejection fraction (EF). The new universal definition of HF requires the left ventricular EF (LVEF) to be <50%, which includes reduced (<40%) and mildly reduced EF (41%–49%) categories.[8] Nonetheless, right ventricular (RV) dysfunction also plays a crucial role in the hemodynamics and prognosis of HF.[9] Although several etiologies and predictors of HF after LT has been proposed,[3,5,10] these reports mainly focused on early nonischemic systolic LV dysfunction and overlooked the roles of ischemic etiologies and RV in post-LT HF.[3-5,7,10-14] An additional understanding of cardiac dysfunction after LT is

needed for the better identification of high-risk patients, treatments, and outcomes.

Therefore, this study aimed to identify the incidence, characteristics, etiologies, risk factors, and outcomes of new-onset HF within the first post-LT year, secondary to LV or RV dysfunction.

MATERIALS AND METHODS

Following approval from the institutional review board, the medical records of 537 adults' (≥18-y-old) LTs performed at the University of Miami/Jackson Memorial Hospital between January 2016 and December 2020 were reviewed. Excluded from the study were patients who died intraoperatively (n = 2) and patients with preexisting cardiomyopathy (LVEF < 50%; n = 7) resulting in 528 recipients as the study population.

Preoperative Variables

Preoperative data obtained from electronic medical records included recipient demographics, etiology of liver disease, need for renal replacement therapy, biologic Model End-stage Liver Disease (MELD) score, presence of portal vein thrombosis or transjugular intrahepatic portosystemic shunt, history of hepatopulmonary syndrome, portopulmonary hypertension, coronary artery disease (CAD), chronic or paroxysmal atrial fibrillation, diabetes, hypertension, smoking, pretransplant hospitalization and intensive care unit stay, mechanical ventilation, or vasopressor use before transplantation.

Preoperative Cardiac Workup

Preoperative routine cardiac testing included ECG, transthoracic echocardiography, and noninvasive cardiac stress tests. The QT interval, corrected for heart rate, was obtained from an electrocardiogram performed on the day of transplantation. Data retrieved from echocardiography included LVEF, diastolic dysfunction as defined by the American Society of Echocardiography and the European Association of Cardiovascular Imaging[15] (please see Figure 8 of Ref. 15 for details), RV size and function assessed via tricuspid annular plane systolic excursion, tissue Doppler imaging of the basal free lateral wall of the RV (S′) or visual gradation of the RV EF,[16] RV systolic pressure, pulmonary artery systolic pressure, and valvular abnormalities. Right heart catheterization was performed for recipients with a sonographically estimated pulmonary artery systolic pressure >45 mm Hg or if the RV systolic pressure was not measured. Recipients older than 40 y of age, as well as recipients younger than 40 y but with cardiovascular risk factors, underwent ischemic/coronary artery evaluation via a stress test within a year before transplantation. The preoperative test of choice to rule out CAD was the dobutamine stress test, with a target maximum age-predicted heart rate ≥85%. Single-photon emission computed tomography nuclear stress test was performed at the discretion of the transplant cardiologist. Left heart catheterization was reserved for recipients with a suboptimal heart rate on the screening stress test, stress-induced wall motion abnormalities, or a known history of CAD. When present, percutaneous coronary intervention was performed at the discretion of the interventional cardiologist based on the severity and location of the lesions.

Intraoperative Variables

All recipients underwent piggyback orthotopic LT without a venovenous bypass. The anesthesia protocol has been described[17] and included continuous transesophageal echocardiography and Kaolin/Kaolin-heparinase thromboelastography coagulation monitoring (Haemonetics, Braintree, MA). In 6% (34/528) of LTs, Swan-Ganz catheters were inserted intraoperatively, based on the clinical scenario at provider's discretion decision. Extracted intraoperative data included baseline thromboelastogram, coagulation laboratory values, duration of surgery, cold ischemia time, crystalloids and blood products administered, and donor risk index.[18] The severity of postreperfusion syndrome[19] and arrhythmia was also recorded. Continuous infusions of epinephrine or norepinephrine at doses >0.1 μg/kg/min, along with vasopressin at doses >2 units/h or phenylephrine at doses >1 μg/kg/min, administered for >1 h during the transplant procedure were also documented. All infusions were titrated according to the patient's hemodynamics.

Postoperative Cardiac Outcomes

The primary outcome was the development of new-onset systolic HF within the first posttransplant year, defined as signs and symptoms of HF and echocardiographic evidence of a decrease in LV or RV function. The LVEF was used to rank LV dysfunction as "mild" (41%–50%), "moderate" (30%–40%), or "severe" (<30%) irrespective of the LV size.[20] RV failure was defined by the American Heart Association because HF is caused by acute onset of moderate/severe RV dysfunction, irrespective of RV size,[21] whereas biventricular HF required the presence of both LV and RV failure. The clinical need for posttransplant echocardiographic evaluation was at the discretion of the clinicians, as per clinical symptomatology. The onset of systolic HF was defined as the time interval between transplantation and the diagnosis of HF. Full recovery was defined as an increase in LVEF to >50% or return to baseline RV function in any subsequent posttransplant echocardiogram.[14]

The etiology of new-onset systolic HF was determined following a comprehensive review of the electronic medical record, and classified as either "ischemic" or "nonischemic" as follows:

(1) The ischemic etiology of new-onset HF was diagnosed if significant CAD or demand ischemia occurred. When significant (≥70%) CAD was reported on posttransplant coronary angiography, the choice of treatment modalities was at the cardiologist discretion: coronary revascularization versus medical treatment. A diagnosis of myocardial infarction (MI) requires a troponin I level >0.119 ng/mL (normal 0.000–0.034 ng/mL) along with at least one of the following signs or symptoms: chest pain, ischemic changes on electrocardiogram: non-ST elevation MI (NSTEMI) versus ST-elevation MI (STEMI), and new wall motion abnormalities on echocardiography.[22] Demand ischemia (ie, type 2 MI) is defined as a mismatch between supply and demand for myocardial oxygen and attributed to pathophysiological mechanisms other than CAD.[23]

(2) Nonischemic etiology requires the absence of significant coronary artery stenosis on posttransplant coronary angiography.[24] In accordance with the specific etiology, nonischemic HF was consequently divided into 3 groups: (a) stress-induced/takotsubo cardiomyopathy; (b) sepsis-induced; and (c) other etiologies, such as pulmonary embolism (PE)-induced or de novo pulmonary hypertension,

have been previously described.[24-27] The diagnosis of PE was confirmed by positive computed tomography pulmonary angiography.[28] Septic patients were diagnosed by the infectious disease team based on the presence of at least 2 manifestations of systemic inflammatory response syndrome, along with an active source of infection, and proven by objective testing.[29] Patients with nonischemic HF were also grouped into "isolated left," "isolated right," or "biventricular groups," as per the dysfunctional ventricle(s). Postoperative troponin was drawn when clinically indicated. Patients with positive troponin but no CAD were labeled as nonischemic etiology.

Noncardiac Postoperative Outcomes

Renal replacement therapy, hepatic or extrahepatic venous thrombosis, time to extubation, tracheostomy, intensive care, and length of hospital stay were noted. Recorded postoperative surgical complications included hepatic artery thrombosis (early ≤1 mo; late >1 mo), re-exploration for bleeding within the first week, and biliary complications (eg, a leak or stricture within the first posttransplant month). Early allograft dysfunction was determined using a revised definition[30] and was used to analyze the groups.

Statistics

Categorical variables are presented as count and frequency (%), with differences between groups assessed using χ^2 or Fisher tests as appropriate. Continuous variables are presented as median and interquartile range (25%–75%), with differences between groups assessed using the Wilcoxon rank-sum test. Given the differences in timing and heterogeneous mechanism, we did not use logistic regression to identify risk factors associated with HF. As a practical alternative for heterogeneous causal effects, recursive partitioning was used.[31] The partition platform recursively partitions data according to a relationship between the predictors and response values, creating a decision tree (Overview of the Partition Platform at jmp.com). Predictors can be either continuous or categorical (nominal or ordinal). If a predictor is continuous, then the splits are created by a cutting value. The sample is divided into values below and above this cutting value. If a predictor is categorical, then the sample is divided into 2 groups of levels.[32] The tree-building process considered the statistically significant recipients' preoperative and intraoperative variables being potentially important when plotted against HF group.[33] The recursive partitioning procedure was repeated for each of the 2 subgroups that resulted from the first split. The process was repeated until no further partitioning was feasible because the subgroup contained fewer than 5 subjects (or contained only HF or non-HF patients).[31] G^2 likelihood ratio χ^2 for the best split and log-worth defined as –log10 (*P* value) were reported.[32] In recursive partitioning, a log-worth value >2 was considered significant at the <0.01 level. The c-index was calculated to measure the strength of the associations. Survival was estimated using the Kaplan-Meier survival method. All statistical analyses were performed using the JMP 15 software (SAS Institute, Cary, NC).

RESULTS

Characteristics of Posttransplant HF

Within the first year after LT, new-onset HF occurred in 6% (31/528) of recipients. Ischemic and nonischemic HF comprised 1% (7/528) and 5% (24/528) of the LTs, respectively (Figure 1). Nonischemic etiology was associated with significantly worse posttransplant LV dysfunction compared with ischemic etiology, with a decrease from baseline in EF of 25% (20–40) versus 15% (10–20), respectively ($\chi^2 = 5.3$, $P < 0.02$). LV dysfunction was mild in 13% (4/31), moderate in 58% (18/31), and severe in 23% (7/31) of the recipients with HF. Two recipients (6%) experienced isolated RV failure. A more detailed description of the 31 recipients with systolic HF is provided in Supplementary File 1 (**SDC**, http://links.lww.com/TXD/A538).

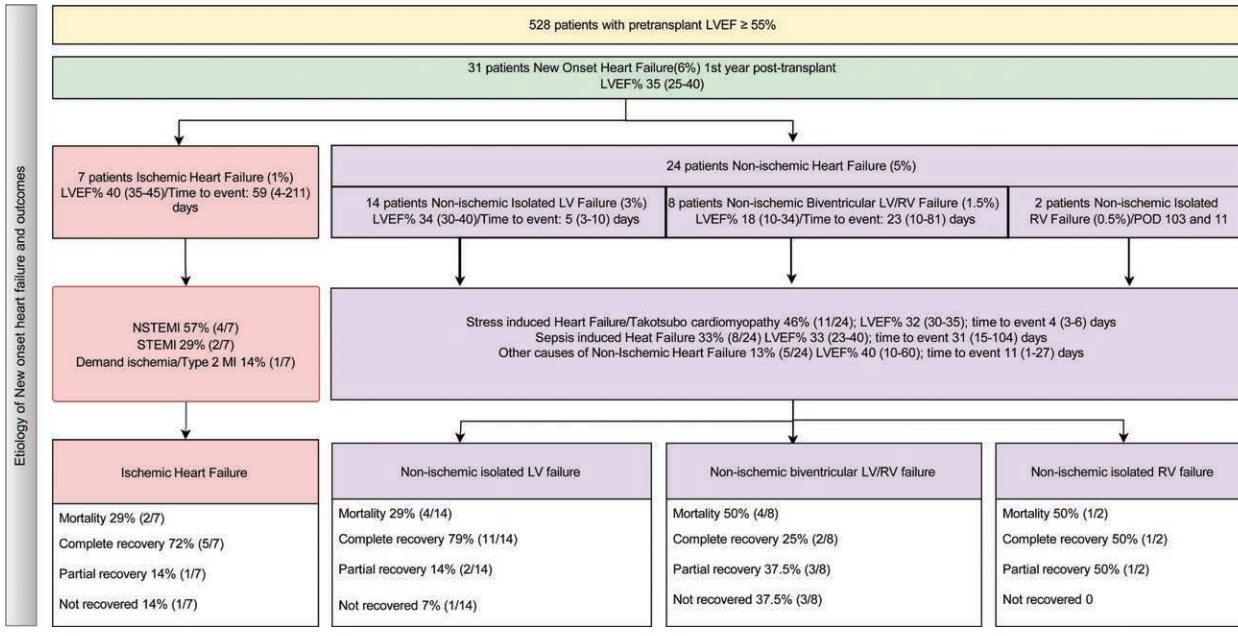

FIGURE 1. New-onset HF flowchart: etiologies and postoperative outcomes. Biventricular LV/RV failure, biventricular left and right ventricle failure; HF, heart failure; LVEF, left ventricular ejection fraction; NSTEMI, non-ST segment elevation myocardial infarction; POD, postoperative day; RV failure, right ventricle failure; STEMI, ST-segment elevation myocardial infarction; type 2 MI, type 2 myocardial infarction.

Ischemic HF

Ischemic HF comprised 23% (7/31) of the posttransplant HF cases (Figure 1). The etiology of ischemic HF was NSTEMI (4 patients), STEMI (2 patients), and demand ischemia/type 2 MI (1 patient). Details regarding the timing and type of intervention are documented in Supplementary File 1 (**SDC**, http://links.lww.com/TXD/A538). Of the 87 recipients with pretransplant CAD, 5 developed ischemic HF (6%) at a median of 5 (4–94) posttransplant days. Of the 5 patients with known significant CAD pretransplant, coronary revascularization was indicated in 2 patients, whereas 3 patients improved with medical treatment. De novo ischemic HF developed in 2 patients on postoperative days 211 and 365, despite normal preoperative cardiac workup; coronary revascularization was indicated (1 surgical and 1 stent) in both patients. Complete, partial, or no recovery of LV function was observed in 5-1-1 of 7 patients with ischemic HF, respectively. Two of the 7 recipients with ischemic HF died; the cause of death was sepsis (1/2) and HF (1/2) despite invasive cardiac interventions (angioplasty, stents, and intra-aortic balloon pump). Both deceased patients were preoperatively diagnosed with CAD.

Nonischemic HF

Nonischemic HF comprised 77% (24/31) of the posttransplant HF cases (Figure 1). Nonischemic HF was predominantly isolated LV failure (14/24), followed by biventricular LV/RV failure (8/24), and isolated RV failure (2/24). The etiology of nonischemic HF was stress-induced Takotsubo cardiomyopathy (11/24), sepsis (8/24), and other causes (5/24; see Supplementary File 1, **SDC**, http://links.lww.com/TXD/A538 for details). Compared to sepsis-induced cardiomyopathy, the median time for the onset of stress-induced HF was significantly shorter (31 [15–104] versus 4 [3–6] d, respectively; $\chi^2 = 11$, $P < 0.001$). Complete, partial, and no recovery of heart function was recorded in 14-6-4 of 24 patients, respectively. Nine of the 24 recipients with nonischemic HF perished: 6 due to sepsis and 3 due to HF.

Preoperative Characteristics

The demographics and preoperative variables of recipients with and without new-onset HF are presented in **Table S1, SDC**, http://links.lww.com/TXD/A539 and Table 1. Patients who developed posttransplant HF were significantly sicker

TABLE 1.

Preoperative variables in patients with and without new-onset HF

	HF, n = 31	Nonheart failure, n = 497	*P*
MELD biological	32 (22–36)	23 (16–32)	0.0239*
Pre-Tx RRT, n%	11 (35%)	93 (19%)	0.0227*
BMI, kg/m^2	24 (22–27)	26 (23–30)	0.0208*
HPS, n%	0	22	N/A
Mild, n	0	12	
Moderate, n	0	4	
Severe, n	0	6	
PPHTN, n%	1 (3%)	7 (1%)	0.3858
Mild, n	0	2	
Moderate, n	1	3	
Severe, n	0	2	
Pre-Tx CAD, n%	8 (26%)	79 (16%)	0.1490
CABG, n	1	5	
Stent, n	3	14	
CABG+ stent, n	0	2	
Nonobstructive/obstructive# CAD, n	4	58	
CAD (<50%; 50%–70%; >70%), n	(1/3/0)	(44/11/3)	
Atrial fibrillation, n%	6 (19%)	81 (16%)	0.6562
Diabetes, n%	16 (52%)	195 (39%)	0.1722
HTN, n%	17 (55%)	244 (49%)	0.5349
Smoking past/present, n%	12 (39%)	196 (39%)	0.9359
Diastolic dysfunction, n%	14 (45%)	144 (29%)	0.0471*
Grade I, n	12	106	
Grade II, n	2	37	
Grade III, n	0	1	
QTc ms	451 (425–494)	459 (442–481)	0.9143
RVSP, mm Hg	29 (26–39)	28 (24–33)	0.1723
Pre-Tx DVT/PE, n%	0	35 (7%)	N/A
Pre-Tx-hospitalization, n%	14 (45%)	124 (25%)	0.0130*
Pre-Tx hospitalization, days	15 (8–30)	14 (9–30)	0.7901
Pre-Tx ICU-admission, n%	9 (29%)	73 (15%)	0.0324*
Pre-Tx mechanical ventilation, n%	5 (16%)	27 (5%)	0.0155*
Pre-Tx vasopressors, n%	4 (13%)	34 (7%)	0.2051

Categorical variables are presented as count (n) and frequency (%); continuous variables are presented as median and interquartile ranges (25%–75%).
*$P < 0.05$ statistically significant.
BMI, body mass index; CAD, coronary artery disease; obstructive CAD, severe coronary lesion >70% not amendable for stenting; CABG, coronary artery bypass graft; DVT, deep vein thrombosis; HF, heart failure; HPS, hepatopulmonary syndrome; HTN, systemic hypertension; ICU, intensive care unit; MELD, Model End-stage Liver Disease score; PE, pulmonary embolism; pre-Tx, pretransplant; PPHTN, portopulmonary hypertension; RVSP, right ventricular systolic pressure; RRT, renal replacement therapy.

than their counterparts, as evident by their higher biological MELD score, presence of diastolic dysfunction, preoperative hospitalization, mechanical ventilation, renal replacement therapy, and reduced body mass.

Intraoperative and Donor Data

The intraoperative variables of the recipients with and without new-onset HF are presented in Table 2. The intraoperative course of recipients who developed posttransplant HF was accompanied by worse hemorrhage and hemodynamic instability, as reflected by the significantly higher need for fluids, blood products, and vasopressors. The groups were similar in surgical and cold ischemia times as well as donor variables.

Postoperative Outcomes and Survival

The postoperative outcomes of the recipients with and without new-onset HF are presented in Table 3. The HF group had a significantly higher incidence of atrial fibrillation, stroke, thrombotic events, and longer hospitalization. However, surgical complications and the incidence of early allograft dysfunction were similar. The HF group had a statistically significant decrease in the 1-y survival rate compared with the non-HF group (65% versus 94%, respectively; log-rank $P < 0.0001$; Figure 2A). Likewise, the nonischemic and ischemic HF groups had significantly lower 1-y survival rates than the non-HF group (63% and 75% versus 94%, respectively; log-rank $P < 0.0001$; Figure 2B). Recipients with biventricular LV/RV failure or isolated RV failure had lower 1-y survival rates of 56% and 50%, respectively, compared with 70% in the isolated LV failure group and 94% in the non-HF group (log-rank $P < 0.0001$; Figure 2C).

Regression Tree of HF After LT

Recursive partitioning was employed to explore the relationship of statistically significant recipients' variables (Tables 1 and 2), when plotted against HF group. The classification tree produced by recursive partitioning consisted of 3 main risk subgroups presented in Supplementary File 2 (**SDC**, http://links.lww.com/TXD/A538): (1) vasopressor (epi/norepinephrine) usage, (2) baseline hemoglobin of ≤7.2 g/dL, and (3) amount of ≥3500 mL crystalloids used

TABLE 2.

Intraoperative and donor factors

	HF, n = 31	Nonheart failure, n = 497	*P*
Intraoperative			
Swan-Ganz catheters, n%	3 (10%)	31 (6%)	0.4408
Thromboelastography			
R time, min	7.2 (6–9.7)	7.8 (5.9–9.8)	0.4843
K time	2.2 (1.9–3.8)	2.5 (1.8–3.2)	0.8641
α angle °	61.3 (48.8—64.5)	57.8 (50.3–64.6)	0.6053
Maximum amplitude, mm	49 (38–55)	52 (43–60)	0.1140
Fibrinogen baseline, mg/dL	160 (109–212)	179 (135–241)	0.0932
Platelets count baseline, x10^3 mm^3	72 (44–133)	69 (48–103)	0.7404
Hemoglobin baseline, mg/dL	9.2 (8–10.1)	9.8 (8.4–11.8)	0.0159*
INR baseline	1.9 (1.4–2.4)	1.7 (1.4–2.2)	0.2406
Surgery duration, h	4.2 (3.3–5.5)	4.3 (3.5–5.1)	0.9574
Cold ischemia time, h	5.5 (4.6–6.4)	5.5 (4.7–6.5)	0.7839
Crystalloids, L	4.7 (3.2–7.0)	4.0 (3.0–5.0)	0.0417*
Albumin 5%, mL	1000 (500–1500)	1000 (500–1500)	0.4310
Albumin 25%, mL	125 (100–200)	125 (100–200)	0.8967
pRBC, units	9 (6–14)	6 (3–11)	0.0078*
FFP, units	6 (3–10)	4 (1–8)	0.0308*
Platelets, units	2 (1–3)	1 (0–2)	0.0157*
Cryoprecipitate, units	1 (0–3)	1 (0–2)	0.0266*
Arrhythmias, n%	2 (6%)	18 (4%)	0.0899
Asystole, n	1	3	
Atrial fibrillation, n	0	11	
Ventricular tachycardia, n	1	2	
Ventricular fibrillation, n	0	2	
Epinephrine and/or norepinephrine infusion, n%	13 (42%)	87 (18%)	0.0008*
Vasopressin and/or phenylephrine infusion, n%	21 (68%)	300 (60%)	0.4142
Epinephrine and/or norepinephrine plus vasopressin and/or phenylephrine infusion, n%	11 (35%)	81 (16%)	0.0123*
Postreperfusion syndrome severe, n%	11 (35%)	113 (23%)	0.2508
Epinephrine bolus dose at the time of severe PRS, μg	110 (74–350)	100 (70–378)	0.8903
Donor characteristics			
Donor risk index	1.44 (1.33–1.70)	1.51 (1.33–1.73)	0.7235
Donation after cardiac death, n%	2 (6%)	63 (13%)	0.3061
Donor BMI > 30 kg/m^2	8 (26%)	121 (24%)	0.8593
Donor age, years	46 (28–58)	48 (31–59)	0.6506

Categorical variables are presented as count (n) and frequency (%); Continuous variables are presented as median and interquartile ranges (25%–75%).
*$P < 0.05$ statistically significant.
BMI, body mass index; FFP, fresh frozen plasma; HF, heart failure; pRBC, packed red blood cells; PRS, postreperfusion syndrome.

TABLE 3.

Postoperative outcomes

	HF, n = 31	Nonheart failure, n = 497	*P*
Myocardial ischemia first year, n%	7 (23%)	4 (1%)	<0.0001*
New-onset atrial fibrillation first year, n%	8 (26%)	38 (8%)	0.0005*
Time to atrial fibrillation, year	7 (3–31)	4 (2–11)	0.1826
Stroke first year	4 (13%)	15 (3%)	0.0177*
Ischemic, n	2	5	
Hemorrhagic, n	1	7	
Central pontine myelinolysis, n	1	3	
RRT first month, n%	8 (26%)	71 (14%)	0.0771
Thrombotic events 1st year, n%	7 (23%)	47 (9%)	0.0193*
DVT/PE, n	7	40	
PVT/IVC/HV thrombosis, n	0	7	
Time to extubation, hours	53 (23–119)	18 (10–48)	0.0003*
Tracheostomy, n%	8 (26%)	35 (7%)	0.0002*
ICU stay, days	12 (7–38)	6 (4–9)	<0.0001*
Hospital stay, days	20 (14–51)	13 (9–21)	<0.0001*
HAT first month, n%	1 (3%)	8 (2%)	0.4224
HAT > 1 month, n%	1 (3%)	4 (1%)	0.2619
Surgical bleeding first week, n%	5 (16%)	50 (10%)	0.2832
Biliary leak/stricture first month, n%	1 (3%)/1 (3%)	27 (5%)/35 (7%)	0.6030
Early allograft dysfunction, n%	4 (13%)	88 (18%)	0.4940

Categorical variables are presented as count (n) and frequency (%); continuous variables are presented as median and interquartile ranges (25%–75%).
*$P < 0.05$ statistically significant.
DVT, deep venous thrombosis; HAT, hepatic artery thrombosis; HF, heart failure; HV, hepatic vein thrombosis; IVC, inferior vena cava thrombosis; ICU, intensive care unit; PE, pulmonary embolism; PVT, portal vein thrombosis; RRT, renal replacement therapy.

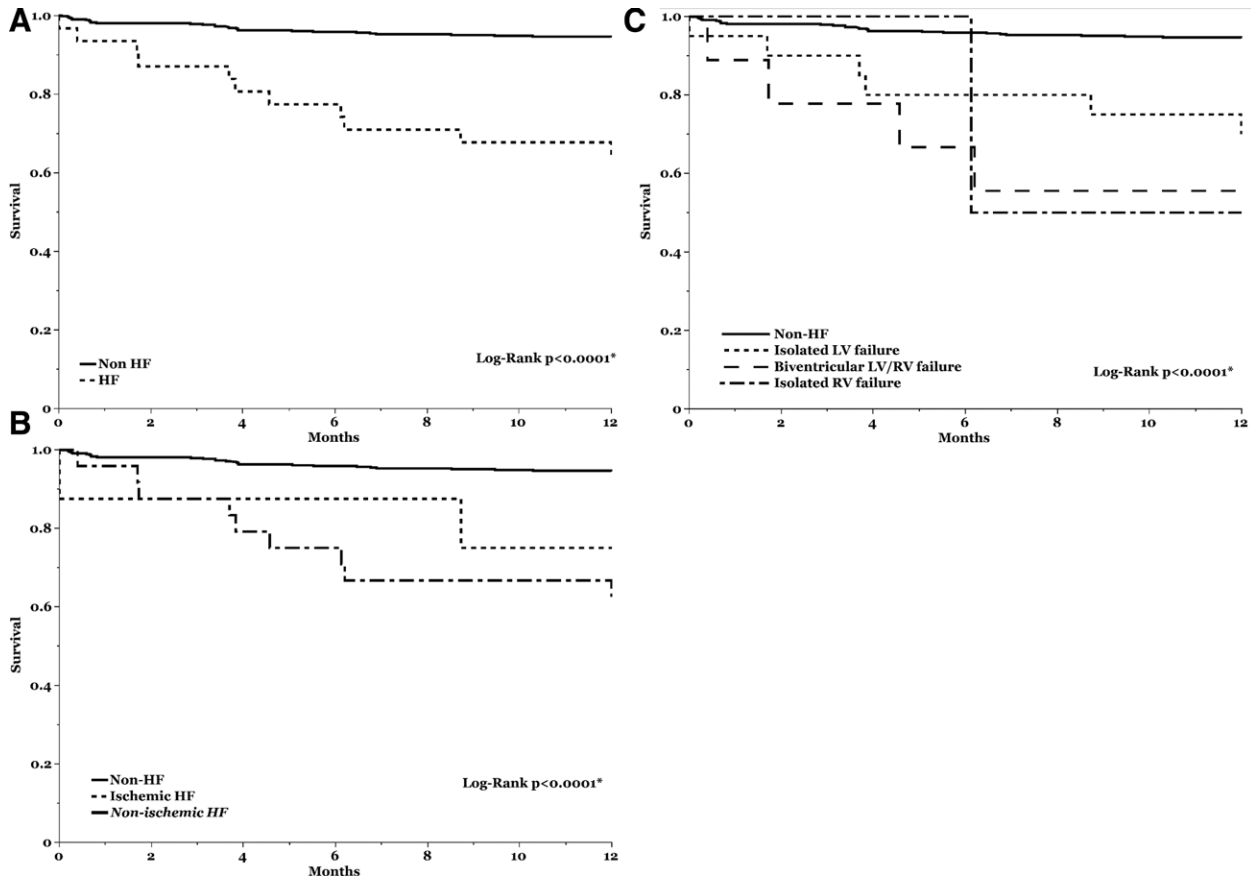

FIGURE 2. Kaplan-Meyer first-year survival curves. A, Patients with and without new-onset HF; B, patients with ischemic and nonischemic HF versus recipients without HF; C, patients with isolated left or RV failure and biventricular LV and RV failure versus recipients without new-onset HF. HF, heart failure; LV, left ventricle; RV, right ventricle.

intraoperatively. The risk of HF increased from 4.2% when no epi/norepinephrine drip was used intraoperatively to 13% when epi/norepinephrine was used (G^2 = 236, log-worth 2.6, $P < 0.01$). When no epi/norepinephrine drip was used intraoperatively, the risk of HF increased from 3.1% if baseline hemoglobin was ≥7.2 g/dL to 38.5% if hemoglobin was <7.2 g/dL (G^2 = 149, log-worth 3.1, $P < 0.01$). When baseline hemoglobin was ≥7.2 g/dL, the risk of HF increases from zero when <3500 mL crystalloids were used intraoperatively to 5.2% when ≥3500 mL crystalloid was used (G^2 = 116, log-worth 2.3, $P < 0.01$). A C-index of 0.77 was calculated for these risk subgroups.

DISCUSSION

The findings of this relatively large series of LT highlight the dire consequences of new-onset HF in the first posttransplant year as a substantial cause of morbidity, excess healthcare costs, and most importantly, loss of both allografts and recipients' lives. The study findings of 6% incidence of new-onset systolic HF, half thereof in the early posttransplant period (48% within 7 d, 68% within 30 d, and 90% within 120 d), are in agreement with previously reported incidences (1.2%–14%) as well as the median time to onset.[3,5,10,13,14]

Ischemic HF

Most previous analyses of posttransplant HF have excluded ischemic etiologies.[3,10-12,14,34] However, the current study underscores ischemic HF as an exigent etiology that accounts for nearly a quarter (23%) of all posttransplant HF cases. However, only 6% (5/87) of patients with a preoperative diagnosis of CAD suffered ischemic HF within the first 3 posttransplant months, despite the significantly perturbed supply-demand for myocardial oxygen that frequently transpires with LT, thereby supporting the applicability and sensitivity of the implemented pretransplant cardiac workup protocol.[4,14,35] The 2 recipients with newly diagnosed posttransplant CAD may have suffered from asymptomatic preoperative CAD that was not captured by the cardiac screening protocol because of its less-than-perfect sensitivity. Alternatively, accelerated posttransplant CAD may have developed,[36] a notion that is supported by the late onset of symptomatology (postoperative days 211 and 365).

Nonischemic HF

Consistent with previous reports,[3,4,12,14] this study attributed the majority (77%) of posttransplant HF cases to nonischemic etiology, with an overall incidence of 5%. RV dysfunction occurred in 42% (10/24) of nonischemic HF and compared with isolated LV dysfunction was associated with poorer first-year survival (50% versus 70%, respectively). RV failure in LT recipients remains poorly studied.[37] Biventricular dysfunction is more common in critically ill or septic patients and is associated with higher mortality.[13,38] Likewise, biventricular failure after LT caused by uncommon etiologies, such as portopulmonary hypertension, hemochromatosis, and cirrhotic cardiomyopathy, has been described, including dismal outcomes.[35]

Stress-induced cardiomyopathy, which accounts for 46% (11/24) of nonischemic HF, is believed to arise from increased levels of circulating catecholamines.[7,24,37] Its well-known variant, Takotsubo cardiomyopathy, has been previously reported in LT.[24,39] The sonographic appearance of stress-induced cardiomyopathy in our patients varied and included apical ballooning, global hypokinesis, or an LV resembling an inverted takotsubo. The median onset of stress-induced HF was 4 d, thereby underscoring intraoperative or immediate postoperative stress as the most significant contributor. Complete recovery of myocardial function occurred in all patients within a month, indicating the reversibility of this pathophysiology.[36,39] Nevertheless, the first-year survival for stress-induced etiology was 73% (8/11); mortality was attributed to sepsis/multisystem organ failure (see Supplementary File 1, **SDC**, http://links.lww.com/TXD/A538).

The second most frequent nonischemic HF etiology was sepsis, accounting for 33% (8/24). The dysfunctional chambers were LV (2 patients), RV (1 patient), and biventricular (5 patients, Figure 1). Compared with stress-induced etiology, the median onset time for sepsis-induced HF was much longer (31 d), arguably because infectious complications may arise throughout the postoperative period. Although sepsis-induced cardiomyopathy is presumed to be reversible,[40] we found partial or full recovery in only 75% of the cases, plausibly because of the dissimilar etiopathogenesis of sepsis-induced HF in LT recipients. The first posttransplant year survival of recipients with sepsis-induced HF was low (50%), conceivably because of the poorer outcome of sepsis in immunocompromised hosts.

Regression Tree of HF After LT

Recursive partitioning not only identifies subgroups with varying risks but may also uncover interactions between variables.[41] In agreement with Schnell et al,[13] our analysis demonstrated an independent association between the intraoperative administrations of vasopressors and posttransplant HF. However, other studies have not investigated this association.[3,10,14,37] It was hypothesized that high levels of circulating catecholamines via the β2-adrenoceptor trigger a switch in intracellular signal trafficking in ventricular cardiomyocytes, which ultimately leads to a negative inotropic effect.[42] Although anesthesiologists titrate vasopressors to achieve optimal patient hemodynamics, it is possible that patients predisposed to HF have higher catecholamine requirements during LT. This notion is reinforced by the observation that a significantly greater proportion of patients with HF received infusions of epinephrine or norepinephrine in combination with vasopressin or phenylephrine compared with those without HF (35% versus 16%; odds ratio 2.8; 95% confidence interval, 1.303-6.120).

Our finding that the severity of intraoperative anemia at baseline (hemoglobin ≤7.2 mg/dL) is associated with posttransplant HF is congruent with previous reports.[5,37] In our study, more patients with hemoglobin ≤7.2 mg/dL were inpatients at the time of transplant (46.7% versus 24.9%; $P < 0.0084$*; odds ratio 2.6; 95% confidence interval, 1.252-5.561) we do not think that this reflects preoperative transfusion practice but rather indicates the severity of the liver disease itself. The severity of anemia in cirrhosis correlates with the degree of hepatic dysfunction, portal hypertension, decompensation, and increased mortality.[43] Alternatively, baseline anemia is likely to necessitate a larger transfusion requirement during LT, with ensuing morbidity and mortality. The latter notion is supported by reports that a large intraoperative transfusion

requirement is predictive of posttransplant HF,[4,5,37] and may suggest that prevention of severe preoperative anemia may be an effective mitigation strategy.

In our study, a fluid regimen (≥3500 mL) was associated with an increased incidence of posttransplant HF in a subgroup of patients who did not receive intraoperative epinephrine/norepinephrine infusion and had a baseline hemoglobin level of ≥7.2 g/dL (Supplemental File 2, **SDC**, http://links.lww.com/TXD/A538). During the transplant procedure, fluid loading may aggravate portal hypertension and bleeding, especially during hepatectomy.[44] To our knowledge, no studies explored the association of perioperative fluid management and incidence of HF; a recent systematic review, however, evaluated the following postoperative outcomes: acute kidney injury, respiratory complications, operative blood loss/red cell units required, and intensive care length of stay.[44] Sustained hypervolemia, based on the absence of fluid responsiveness, elevated filling pressures, or echocardiographic findings, should be avoided (Quality of Evidence: Moderate | Grade of Recommendation: Weak for the restrictive fluid regime. Strong for the avoidance of hypervolemia).[44]

Postoperative Outcomes

As previously reported,[4,5,13,14] new-onset posttransplant systolic HF was associated with poorer outcomes (Table 3 and Figure 2). The novel findings of this comprehensive analysis are that both outcomes and reversibility of cardiac dysfunction after LT (Figure 1 and Supplementary File 1, **SDC**, http://links.lww.com/TXD/A538) depend on the etiology of HF (ie, ischemic versus nonischemic; stress-induced versus sepsis-induced) as well as the extent of cardiac chamber involvement (isolated LV or RV ± LV). RV dysfunction is associated with inferior recovery of cardiac function and poorer survival than nonischemic isolated LV dysfunction. Sepsis was the main cause of mortality in our series, even in patients whose EF recovered, whereas the remaining mortalities were directly attributed to refractory HF.

In patients with worsening organ function and delayed cardiac recovery after LT, early institution of an advanced hemodynamic support device, such as a ventricular assist device, intra-aortic balloon pump, or extracorporeal membrane oxygenator, should be considered.[3,35] However, experience suggests that hemodynamic support is frequently ineffective. In a series of adult LT recipients who received extracorporeal membrane oxygenator support for septic shock, only 2 of 8 patients survived.[45] After the institution of immediate hemodynamic support with an extracorporeal membrane oxygenator, a transition to continued circulatory support with a percutaneous ventricular assist device as a bridge to recovery has been successfully implemented in LT patients.[46]

Several preoperative, intraoperative, and postoperative strategies have been suggested for the prevention of HF in LT patients.[7] The threshold for ordering specialized cardiac studies in the intensive care unit (eg, troponins, brain natriuretic peptide, serial echocardiogram, pulmonary artery catheter, sepsis workup, and PE workup) and the efficacy of these modalities are yet to be determined. Although the majority of the aforementioned risk factors are nonmodifiable, their presence should trigger active surveillance for acute HF so that treatment can be instituted as early as possible.[7,14]

This study is limited by its retrospective single-center nature, which is based on an electronic review of medical records. The decision to perform echocardiography was based on clinical judgment; hence, not all patients underwent echocardiography during the first 12 mo after LT. The ensuing selection bias likely led to underdiagnoses of subclinical systolic dysfunction, with a resultant underestimation of the true incidence of HF after LT. Additionally, patients who died from any noncardiac causes within the first posttransplant year may have also underestimated the actual incidence of posttransplant HF.

In conclusion, posttransplant new-onset HF is mostly nonischemic in nature and is associated with increased morbidity and mortality. Survival and reversibility of cardiac dysfunction after LT depends on the etiology of HF as well as the cardiac chambers involved. RV dysfunction is associated with inferior recovery of cardiac function and poorer survival. Preoperative risk-mitigating "prehabilitation" and effective intensive postoperative strategies to prevent or minimize the risk of post-LT HF are yet to be determined.

REFERENCES

1. Raval Z, Harinstein ME, Skaro AI, et al. Cardiovascular risk assessment of the liver transplant candidate. *J Am Coll Cardiol.* 2011;58:223–231.
2. Sharma V, Cywinski JB, Menon KN, et al. Abstract 15563: impact of cardiovascular events on short and long-term mortality following liver transplantation. *Circulation.* 2019;140(Suppl_1):A15563–A15563.
3. Eyvazian VA, Gordin JS, Yang EH, et al. Incidence, predictors, and outcomes of new-onset left ventricular systolic dysfunction after orthotopic liver transplantation. *J Card Fail.* 2019;25:166–172.
4. Qureshi W, Mittal C, Ahmad U, et al. Clinical predictors of post-liver transplant new-onset heart failure. *Liver Transpl.* 2013;19:701–710.
5. Sakr AE, Fraser GE, Doctorian TP, et al. Predictors of systolic heart failure and mortality following orthotopic liver transplantation: a single-center cohort. *Transplant Proc.* 2019;51:1950–1955.
6. Guglin M, Nazif K. New onset nonischemic cardiomyopathy post liver transplantation. *Heart Fail Rev.* 2022;27:1829–1836.
7. Sharma S, Sonny A, Dalia AA, et al. Acute heart failure after liver transplantation: a narrative review. *Clin Transplant.* 2020;34:e14079.
8. Bozkurt B, Coats AJS, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure: Endorsed by the Canadian Heart Failure Society, Heart Failure Association of India, Cardiac Society of Australia and New Zealand, and Chinese Heart Failure Association. *Eur J Heart Fail.* 2021;23:352–380.
9. Voelkel NF, Quaife RA, Leinwand LA, et al.; National Heart, Lung, and Blood Institute Working Group on Cellular and Molecular Mechanisms of Right Heart Failure. Right ventricular function and failure: report of a National Heart, Lung, and Blood Institute working group on cellular and molecular mechanisms of right heart failure. *Circulation.* 2006;114:1883–1891.
10. Yataco ML, Difato T, Bargehr J, et al. Reversible non-ischaemic cardiomyopathy and left ventricular dysfunction after liver transplantation: a single-centre experience. *Liver Int.* 2014;34:e105–e110.
11. Dowsley TF, Bayne DB, Langnas AN, et al. Diastolic dysfunction in patients with end-stage liver disease is associated with development of heart failure early after liver transplantation. *Transplantation.* 2012;94:646–651.
12. Eimer MJ, Wright JM, Wang EC, et al. Frequency and significance of acute heart failure following liver transplantation. *Am J Cardiol.* 2008;101:242–244.
13. Schnell F, Donal E, Lorho R, et al. Severe left-sided heart failure early after liver transplantation. *Liver Transpl.* 2009;15:1296–1305.
14. Sonny A, Govindarajan SR, Jaber WA, et al. Systolic heart failure after liver transplantation: Incidence, predictors, and outcome. *Clin Transplant.* 2018;32:e13199.
15. Nagueh SF, Smiseth OA, Appleton CP, et al. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography

and the European Association of Cardiovascular Imaging. *J Am Soc Echocardiogr.* 2016;29:277–314.
16. Schneider M, Aschauer S, Mascherbauer J, et al. Echocardiographic assessment of right ventricular function: current clinical practice. *Int J Cardiovasc Imaging.* 2019;35:49–56.
17. Nicolau-Raducu R, Beduschi T, Vianna R, et al. Fibrinolysis shutdown is associated with thrombotic and hemorrhagic complications and poorer outcomes after liver transplantation. *Liver Transpl.* 2019;25:380–387.
18. Flores A, Asrani SK. The donor risk index: a decade of experience. *Liver Transpl.* 2017;23:1216–1225.
19. Hilmi I, Horton CN, Planinsic RM, et al. The impact of postreperfusion syndrome on short-term patient and liver allograft outcome in patients undergoing orthotopic liver transplantation. *Liver Transpl.* 2008;14:504–508.
20. Kosaraju A, Goyal A, Grigorova Y, et al. Left ventricular ejection fraction. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459131/. Accessed March 6, 2022.
21. Konstam MA, Kiernan MS, Bernstein D, et al.; American Heart Association Council on Clinical Cardiology; Council on Cardiovascular Disease in the Young; and Council on Cardiovascular Surgery and Anesthesia. Evaluation and management of right-sided heart failure: a scientific statement from the American Heart Association. *Circulation.* 2018;137:e578–e622.
22. Nicolau-Raducu R, Gitman M, Ganier D, et al. Adverse cardiac events after orthotopic liver transplantation: a cross-sectional study in 389 consecutive patients. *Liver Transpl.* 2015;21:13–21.
23. DeFilippis AP, Chapman AR, Mills NL, et al. Assessment and treatment of patients with type 2 myocardial infarction and acute nonischemic myocardial injury. *Circulation.* 2019;140:1661–1678.
24. Akashi YJ, Goldstein DS, Barbaro G, et al. Takotsubo cardiomyopathy: a new form of acute, reversible heart failure. *Circulation.* 2008;118:2754–2762.
25. Ellis ER, Josephson ME. What about tachycardia-induced cardiomyopathy? *Arrhythm Electrophysiol Rev.* 2013;2:82–90.
26. Koch DG, Caplan M, Reuben A. Pulmonary hypertension after liver transplantation: case presentation and review of the literature. *Liver Transpl.* 2009;15:407–412.
27. L'Heureux M, Sternberg M, Brath L, et al. Sepsis-induced cardiomyopathy: a comprehensive review. *Curr Cardiol Rep.* 2020;22:35.
28. Arrigo M, Huber LC. Pulmonary embolism and heart failure: a reappraisal. *Card Fail Rev.* 2020;7:e03.
29. Levy MM, Fink MP, Marshall JC, et al.; SCCM/ESICM/ACCP/ATS/SIS. 2001 SCCM/ESICM/ACCP/ATS/SIS International Sepsis Definitions Conference. *Crit Care Med.* 2003;31:1250–1256.
30. Nicolau-Raducu R, Cohen AJ, Bokhari A, et al. Predictive model and risk factors associated with a revised definition of early allograft dysfunction in liver transplant recipients. *Clin Transplant.* 2017;31:e13097.
31. Athey S, Imbens G. Recursive partitioning for heterogeneous causal effects. *Proc Natl Acad Sci U S A.* 2016;113:7353–7360.
32. JMP. Overview of the partition platform. Available at: https://www.jmp.com/support/help/en/17.1/index.shtml#page/jmp/overview-of-the-partition-platform.shtml. Accessed April 28, 2023.
33. Strobl C, Malley J, Tutz G. An introduction to recursive partitioning: rationale, application, and characteristics of classification and regression trees, bagging, and random forests. *Psychol Methods.* 2009;14:323–348.
34. Tandon M, Karna ST, Pandey CK, et al. Diagnostic and therapeutic challenge of heart failure after liver transplant: case series. *World J Hepatol.* 2017;9:1253–1260.
35. Sharma S, Karamchandani K, Wilson R, et al. Acute heart failure after orthotopic liver transplantation: a case series from one center. *BMC Anesthesiol.* 2018;18:102.
36. Fellström B, Backman U, Larsson E, et al. Accelerated atherosclerosis in the transplant recipient: role of hypertension. *J Hum Hypertens.* 1998;12:851–854.
37. Mandell MS, Seres T, Lindenfeld J, et al. Risk factors associated with acute heart failure during liver transplant surgery: a case control study. *Transplantation.* 2015;99:873–878.
38. Romero-Bermejo FJ, Ruiz-Bailen M, Gil-Cebrian J, et al. Sepsis-induced cardiomyopathy. *Curr Cardiol Rev.* 2011;7:163–183.
39. Aniskevich S, Chadha RM, Peiris P, et al. Intra-operative predictors of postoperative Takotsubo syndrome in liver transplant recipients—an exploratory case-control study. *Clin Transplant.* 2017;31:e13092.
40. Sato R, Nasu M. A review of sepsis-induced cardiomyopathy. *J Intensive Care.* 2015;3:48.
41. Nelson LM, Bloch DA, Longstreth WT, Jr, et al. Recursive partitioning for the identification of disease risk subgroups: a case-control study of subarachnoid hemorrhage. *J Clin Epidemiol.* 1998;51:199–209.
42. Lyon AR, Rees PS, Prasad S, et al. Stress (Takotsubo) cardiomyopathy—a novel pathophysiological hypothesis to explain catecholamine-induced acute myocardial stunning. *Nat Clin Pract Cardiovasc Med.* 2008;5:22–29.
43. Scheiner B, Semmler G, Maurer F, et al. Prevalence of and risk factors for anaemia in patients with advanced chronic liver disease. *Liver Int.* 2020;40:194–204.
44. Morkane CM, Sapisochin G, Mukhtar AM, et al.; ERAS4OLT.org Working Group. Perioperative fluid management and outcomes in adult deceased donor liver transplantation—a systematic review of the literature and expert panel recommendations. *Clin Transplant.* 2022;36:e14651.
45. Lee KW, Cho CW, Lee N, et al. Extracorporeal membrane oxygenation support for refractory septic shock in liver transplantation recipients. *Ann Surg Treat Res.* 2017;93:152–158.
46. Galvan NT, Kumm K, Kueht M, et al. Mending a broken heart: treatment of stress-induced heart failure after solid organ transplantation. *J Transplant.* 2018;2018:9739236.