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ORIGINAL ARTICLE

Pretransplant left ventricular hypertrophy in association with postoperative myocardial injury in liver transplantation

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Abstract

Pretransplant left ventricular hypertrophy (LVH) is a common finding during preoperative cardiac evaluation. We hypothesized that patients with pretransplant LVH were associated with a higher risk of postoperative myocardial injury (PMI) in adult patients undergoing liver transplantation (LT). A retrospective cohort analysis was performed by reviewing the medical records of adult patients who underwent LT between January 2006 and October 2013. Of 893 patients, the incidences of mild, moderate, and severe LVH were 7.8%, 5.6%, and 2.5%, respectively. Propensity match was used to eliminate the pretransplant imbalance between the LVH and non-LVH groups. In after-match patients, 23.5% of LVH patients developed PMI compared to 11.8% in the control group (P = .011). The incidence of PMI in patients with moderate-severe degrees of LVH was significantly higher compared with that in patients with mild LVH (27.9% vs 19.1%, P = .016). When controlling intraoperative variables, patients with LVH had 4.5 higher odds of developing PMI (95% CI1.18-17.19, P = .028). Patients experiencing PMI had significantly higher 1-year mortality (37.5% vs 15.7%, log-rank test P < .001). Our results suggest that patients with pretransplant LVH were at a high risk of developing PMI and should be monitored closely in the perioperative period. More studies are warranted.

KEYWORDS

hypertrophy, left ventricular, liver transplantation, myocardial injury

1 | INTRODUCTION

Left ventricular hypertrophy (LVH), characterized by increased left ventricular mass, is a common finding during preoperative evaluation in candidates of liver transplantation (LT). Although LVH is a well-known risk factor for cardiovascular events in the general population and those with hypertension, myocardial infarction, end-stage renal disease, and valvular heart disease,[1-5] the relationship between preoperative LVH and outcomes after LT is not clear. Previous studies investigating such relationship have generated mixed results with some studies suggesting that LVH was associated with poor survival after LT and others opposing such an association.[6-8]

Recently, postoperative myocardial injury (PMI), defined as troponin elevations due to cardiac ischemia with or without clinical signs and symptoms, has been increasingly recognized as an important cardiac event. In the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) study involving more than 15 000 patients undergoing noncardiac surgery, myocardial injury is associated with substantially high risk of nonfatal cardiac arrest, congestive heart failure, stroke, and mortality.[9,10] In patients undergoing LT, PMI has also been shown to link to poor outcomes.[11,12] It

is believed that PMI is mainly caused by myocardial ischemia due to oxygen supply-demand mismatch.[13] In the setting of LVH, there is an increase in oxygen consumption and a decrease in capillary density, leading to increased myocardial vulnerability to ischemia.[14,15] Despite that, the vulnerability of PMI in patients with preoperative LVH has never been evaluated.

In this retrospective study, we investigated the relationship between pretransplant LVH and PMI in LT. We hypothesized that patients with pretransplant LVH were associated with a higher risk of post-transplant PMI in adult patients undergoing LT.

2 | PATIENTS AND METHODS

This retrospective single-center study was approved by the institutional review board (IRB) of the University of California, Los Angeles (UCLA #13-001697), and no executed donor organs were used for these patients. The requirement for informed consent was waived by the IRB based on the retrospective nature of the study and the minimum intrusion on participants' privacy. All adult (age ≥ 18) patients undergoing LT between January 2006 and October 2013 in our institution were included. Preoperative characteristics and intraoperative data of both recipients and donors were collected prospectively, stored in the transplant database, and retrieved for this study. Pretransplant transthoracic echocardiography (TTE) data, intraoperative variables, and post-transplant data were collected retrospectively from the electronic chart systems.

As part of the standardized preoperative cardiac evaluation, all adult patients underwent resting TTE prior to LT. Pretransplant TTE data were obtained by reviewing cardiologist's reports. If patients had more than one pre-LT TTE report available, the one closest to the transplantation date was selected. An investigator blinded to patient data extracted TTE data. LVH was determined by the left ventricular mass index ≥ 96 g/m^2 for women or ≥116 g/m^2 for men. Left ventricular mass was determined using the formula 0.8 × {1.04 × [(interventricular septal wall thickness in the end-diastole + left ventricular end-diastolic dimension + posterior wall thickness in the end-diastole)^3 − (left ventricular end-diastolic dimension)^3]} + 0.6 and was indexed to body surface area. The degree of LVH was classified into three categories according to left ventricular mass index: mild (116-131 for men and 96-108 for women), moderate (132-148 for men and 109-121 for women), and severe (≥149 for men and ≥122 for women).[16,17]

Anesthetic management followed the standard of care at our institution. Patients' anesthesia was induced and maintained with intravenous sedatives and inhalational anesthetics combined with analgesics. Muscle relaxants were administered to provide neuromuscular blockade for tracheal intubation and operation. Standard monitors were applied. Additionally, invasive blood pressure was monitored continuously and the pulmonary artery catheter was placed. Vasopressors and fluids were used as appropriate. Packed red blood cells (RBC) were transfused to maintain the hematocrit between 28% and 30% in our center.

After LT, patients were transferred to the intensive care unit where they were consecutively monitored and managed by a multidiscipline team. Postoperative troponin I was measured in selected patients if they were suspected to have cardiac ischemia. The suspected ischemia events included persistent hemodynamic instability, requirements of a large amount of blood products or vasopressors, electrocardiographic changes, or ischemic symptoms.[11] If the troponin I was elevated, a series of measurements were typically performed until the troponin levels trended downward. The peak value of troponin I within 30 days after LT was recorded. PMI was defined as peak troponin I concentration at least 0.1 ng/mL as we described in detail previously.[11] Postoperative atrial fibrillation (AF) was defined as new-onset AF within 30 days after LT in patients without AF at the time of LT surgery. Hospital days and 1-year all-cause mortality were evaluated in all patients.

Data that were normally distributed were expressed as a mean and standard difference (SD), while non-normally distributed data were expressed as median (interquartile range). Categorical variables were expressed as percentages. Student's *t*, Mann-Whitney *U* or Kruskal-Wallis tests were performed for continuous variables. The chi-square test or Fisher's test was performed for categorical variables as appropriate. Each LVH patient was matched with one non-LVH patient by propensity scores, and the caliper was defined as 0.2. Factors chosen to generate the propensity scores were those based on recommendations in the literature and whether they were thought to be associated with either LVH or the incidence of PMI. The following variables were included in the propensity score model: age, gender, weight, hypertension, diabetes mellitus, history of cardiac artery disease, pretransplant renal replacement therapy, preoperative intubation, and hematocrit. Standardized mean differences (SMDs) were calculated for each covariates to assess the balance between groups, and any covariate with SMD less than 0.1 was considered to be well balanced. Intraoperative characteristics were compared between groups after the match. Odds ratio (OR) and 95% confidence interval (CI) of PMI in the LVH group compared to the non-LVH group were calculated and were adjusted by intraoperative variables with $P < .1$ in univariate analysis, which could have potentially biased estimates. Survival analysis was achieved by the Kaplan-Meier method with a log-rank test. Statistical analyses were performed using SPSS v 20.0 (IBM Inc). A P value < .05 was considered significant.

3 | RESULTS

During the study period, 893 patients had complete pretransplant TTE reports and were included in the analysis. The mean age of the study population was 53.8 ± 11.6 years. Patients were predominantly male (61.7%) and white (54.2%). The most common etiology of liver disease was hepatitis C (37.8%), followed by alcoholic cirrhosis (22.1%), hepatitis B (7.2%), and nonalcoholic steatohepatitis (6.9%). The mean Model for End-Stage Liver Disease score at the time of transplantation was 32.7 ± 7.9 (Table 1).

TABLE 1 Baseline characteristics description (n = 893)

Variables	
Age (y)	53.8 ± 11.6
Gender (male, %)	61.7
Weight (kg)	79.7 ± 19.8
Body mass index (kg/m^2)	27.6 ± 6.1
Model for End-Stage Liver Disease score	32.7 ± 7.9
Etiology of liver disease	
Hepatitis C (%)	37.8
Alcoholic cirrhosis (%)	22.1
Hepatitis B (%)	7.2
Nonalcoholic steatohepatitis (%)	6.9
Hypertension (%)	30.9
Diabetes mellitus (%)	28.8
History of cardiac artery disease (%)	8.6
Pre-LT renal replacement therapy (%)	41.4
Preoperative intubation (%)	25.6
Preoperative pressor (%)	16.6
Laboratory values	
Hematocrit (%)	29.1 ± 5.5
Serum creatinine (mg/dL)	1.8 ± 1.4
International normalized ratio	1.8 ± 0.6

TABLE 2 Echocardiographic measurements (n = 893)

Variables	
Septal wall thickness (cm)	1.0 ± 0.2
Posterior wall thickness (cm)	1.0 ± 0.2
Left ventricular diastolic dimension (cm)	4.6 ± 0.6
Left ventricular mass (g)	166.1 ± 49.9
Left ventricular hypertrophy	
Mild	7.8
Moderate	5.6
Severe	2.5
Left ventricular ejection fraction (%)	61.2 ± 6.4
Diastolic dysfunction (%)	45.5
Diameter of the aortic root (cm)	3.0 ± 0.4
Diameter of the left atrium (cm)	3.8 ± 0.7
Right ventricular dimension (cm)	2.3 ± 0.8
Tricuspid regurgitation (%)	
Mild	35.2
Moderate	5.5
Severe	0.3
Pulmonary hypertension (%)	22.1
Right ventricular systolic pressure (mm Hg)	35.7 ± 10.4

Patients underwent TTE at a median 41 (9-169) days prior to LT. The mean ejection fraction was (61.2 ± 6.4) %, and the incidence of diastolic dysfunction and tricuspid regurgitation was 45.5% and 41.0% (Table 2). The mean left ventricular mass was 166.1 ± 49.9 g, and 142 patients (15.9%) were diagnosed as LVH. The incidences of mild, moderate, and severe LVH were 7.8%, 5.6%, and 2.5%, respectively. LVH was significantly associated with increased septal wall thickness, posterior wall thickness, and left ventricular diastolic dimension ($P < .001$). We also found that LVH was more likely to be accompanied by diastolic dysfunction (54.9% vs 43.7%, $P = .014$). The left ventricular ejection fraction was similar between LVH and non-LVH patients.

A total of 35.8% of patients in our cohort had troponins measured within 30 days postoperatievly. There was no significant difference in patient percentages of postoperative troponin measured between LVH and non-LVH groups (38.7% vs 35.3%, $P = .432$). The percentages of postoperative troponin measured in patients with no, mild, and moderate-severe LVH were 35.3%, 42.9%, and 34.7%, respectively. The comparisons of preoperative characteristics between patients with or without LVH are shown in Table 3. Patients with LVH were more likely to be female and had a higher incidence of preoperative intubation (Table 3).

A propensity score was generated for each participant, and 136 LVH patients were matched with non-LVH patients in a 1:1 manner. After the match, all the pretransplant significant differences between LVH patients and non-LVH patients were eliminated (Table 4). Intraoperative variables were compared between groups. LVH was associated with a longer surgery duration, while there was no difference in transfusion, vasopressor requirement, and postreperfusion syndrome occurrence (Table 5).

The overall incidence of PMI was 17.6% after the match. LVH patients had a significantly higher incidence of PMI compared to non-LVH patients (23.5% vs 11.8%, $P = .011$). The incidence of PMI increased with higher severity of LVH (19.1% for mild LVH and 27.9% for moderate-severe LVH, $P = .016$, Figure 1). The degree of LVH was also related to the rise of troponin I. Specifically, the average postoperative troponin I of no, mild, and moderate-severe LVH was 0.07 (0.04-0.16) ng/mL, 0.09 (0.04-0.23) ng/mL, and 0.20 (0.10-0.35) ng/mL, respectively ($P = .006$). The OR of PMI was 2.31 (1.20-4.44, $P = .012$) for LVH vs the non-LVH group. When controlling for intraoperative variables, the OR of PMI was 4.50 (1.18-17.19, $P = .028$) for LVH vs the non-LVH group.

Of the 272 propensity-matched patients, LVH was associated with longer hospital days compared to non-LVH patients (36 [19-78] vs 29 [16-55], $P = .026$). There was no significant difference in postoperative AF incidence and mortality between LVH and non-LVH patients. Developing of PMI was associated with significantly more postoperative AF occurrence (18.8% vs 3.1%, $P < .001$), prolonged hospital days (52 [23-89] vs 29 [17-57], $P = .002$), and higher 1-year mortality (37.5% vs 15.7%, log-rank test $P < .001$, Figure 2).

4 | DISCUSSION

In this large retrospective study, we found that pretransplant LVH was associated with PMI in adult patients undergoing LT. The

TABLE 3 Comparisons of baseline characteristics before matching (n = 893)

Patient characteristics	LVH (n = 142)	Non-LVH (n = 751)	*P*	SMD
Age (y)	54.1 ± 11.3	53.7 ± 11.7	.712	0.03
Gender (male, %)	47.9	64.3	<.001	0.34
Weight (kg)	78.9 ± 21.0	79.8 ± 19.6	.611	0.04
Body mass index (kg/m^2)	27.7 ± 7.4	27.6 ± 5.9	.870	0.01
Model for End-Stage Liver Disease score	33.2 ± 7.7	32.6 ± 7.9	.422	0.08
Hypertension (%)	34.3	30.3	.349	0.09
Diabetes mellitus (%)	28.2	28.9	.863	0.02
History of cardiac artery disease (%)	9.2	8.4	.765	0.03
Pre-LT renal replacement therapy (%)	46.0	40.5	.225	0.11
Preoperative intubation (%)	32.9	24.2	.031	0.19
Preoperative pressor (%)	19.4	16.0	.326	0.09
Laboratory values				
Hematocrit (%)	28.3 ± 5.3	29.2 ± 5.5	.088	0.17
Serum creatinine (mg/dL)	1.9 ± 1.5	1.8 ± 1.4	.933	0.07
International normalized ratio	1.8 ± 0.6	1.8 ± 0.6	.838	0.00

Abbreviations: LVH, left ventricular hypertrophy; SMD, standardized mean difference.

moderate-severe degree of LVH was associated with a higher incidence of PMI than the mild degree of LVH. Patients who developed PMI had the increased incidence of new-onset AF, prolonged hospital days, and increased mortality.

LVH is a common finding during preoperative cardiac screening for LT candidates.[18] It is reported the prevalence of LVH in LT candidates is two or three times higher than that in the general population.[6,7] The high prevalence of LVH found in LT candidates appears to be a result of responding of the heart to the hyperdynamic circulation, myocardial remodeling, and the activation of the neurohumoral systems in these patients.[19,20] The hypertrophic heart has undergone significant cardiac structural and functional alterations, which may have a negative impact on hemodynamics and post-transplant outcome.[5] Two previous studies had shown that pretransplant LVH was a risk factor of post-transplant mortality in LT.[6,7] However, another study suggested that if the preoperative troponin level was considered, the association between preoperative LVH and postoperative mortality was no longer significant.[21] In the current study, we could not establish a direct relationship between preoperative LVH and postoperative mortality. However, preoperative LVH was strongly associated with PMI and the latter was associated with poor outcomes. It is possible that the association between LVH and postoperative outcome may be caused by some indirect mechanisms. It is known that the hypertrophic heart is usually associated with the increased left ventricular mass, cardiac fibrosis, subendothelial edema, the increased myocardial wall stiffness, and high filling pressures of the left ventricle, all of which can lead to increased oxygen demand.[22,23] The increase in oxygen demand coupled with the decrease in oxygen supply predisposes these patients to a high vulnerability of developing ischemic myocardial injury.

Cardiac troponins are highly specific to cardiac tissues and the ideal markers for the detection of myocardial damage. The high-sensitivity troponin tests are widely used in clinical settings, making the detection of myocardial injury easy and widespread. Currently, the most common cause of troponin elevation is myocardial injury rather than myocardial infarction. The Fourth Universal Definition of Myocardial Infarction defines myocardial injury as troponin elevation. In contrast, diagnosis of myocardial infarction requires, in addition to troponin elevation, clinical evidence of myocardial ischemia (symptoms, ischemic electrocardiogram changes, pathological Q waves, imaging evidence, etc).[24] In the perioperative setting, the majority of myocardial injury is silent (having neither symptom nor sign) and a diagnosis can be easily missed if the troponin levels are not monitored. The elevation of troponin without symptoms or signs was traditionally considered a benign event. Recently, several large well-designed studies have linked PMI with significant mortality and morbidities following noncardiac surgery,[9,25] making more clinicians aware of this potentially deadly postoperative event.

TABLE 4 Comparisons of baseline characteristics after matching (n = 272)

Patient characteristics	LVH (n = 136)	Non-LVH (n = 136)	*P*	SMD
Age (y)	53.9 ± 11.2	54.5 ± 12.2	.693	0.05
Gender (male, %)	49.3	52.2	.628	0.06
Weight (kg)	79.2 ± 21.2	78.7 ± 19.1	.836	0.02
Body mass index (kg/m^2)	27.8 ± 7.6	27.7 ± 5.5	.723	0.02
Model for End-Stage Liver Disease score	33.1 ± 7.8	32.8 ± 8.0	.710	0.04
Hypertension (%)	33.8	36.0	.703	0.05
Diabetes mellitus (%)	27.9	29.4	.789	0.03
History of cardiac artery disease (%)	9.6	10.3	.839	0.02
Pre-LT renal replacement therapy (%)	45.6	45.6	1.000	0.00
Preoperative intubation (%)	31.6	34.6	.606	0.06
Preoperative pressor (%)	19.9	18.4	.758	0.04
Laboratory values				
Hematocrit (%)	28.4 ± 5.4	28.5 ± 5.0	.850	0.02
Serum creatinine (mg/dL)	1.8 ± 1.4	1.8 ± 1.2	.756	0.00
International normalized ratio	1.8 ± 0.6	1.8 ± 0.5	.918	0.00

Abbreviations: LVH, left ventricular hypertrophy; SMD, standardized mean difference.

TABLE 5 Comparisons of intraoperative characteristics after propensity match (n = 272)

	LVH (n = 136)	Non-LVH (n = 136)	*P*
Cold ischemia time (min)	430.5 ± 149.9	401.3 ± 137.7	.100
Warm ischemia time (min)	42.4 ± 9.7	40.5 ± 9.2	.105
Surgery time (min)	368.5 ± 129.8	316.7 ± 93.8	.014
Requirement of vasopressors (%)	83.7	74.1	.053
Red blood cell transfusion (unit)	21.3 ± 16.1	18.8 ± 14.9	.184
Fresh-frozen plasma transfusion (unit)	25.4 ± 16.8	23.3 ± 16.6	.312
Postreperfusion syndrome (%)	17.4	13.2	.341

Abbreviations: LVH, left ventricular hypertrophy.

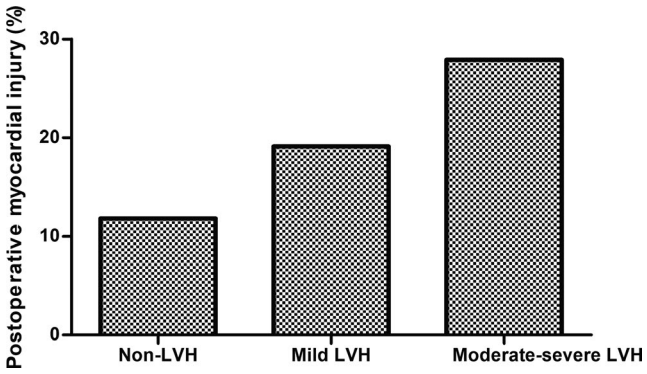

FIGURE 1 Degree of left ventricular hypertrophy (LVH) and postoperative myocardial injury. The incidence of postoperative myocardial injury increased along with the occurrence and severity of LVH (11.8% for non-LVH, 19.1% for mild LVH and 27.9% for moderate-severe LVH, *P* = .016)

Managing patients who develop PMI after LT faces many challenges. There is currently no effective treatment for PMI. Despite that, several pharmacologic regimens that have shown to reduce secondary ischemia can be considered. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and statins have shown to reduce secondary vascular complications in patients undergoing noncardiac surgery.[26] Aspirin and dabigatran have also been shown to reduce the risk of secondary infarction.[26] In an observational subanalysis of POISE patients, those who were started on aspirin and/or statins had a markedly lower risk of 30-day mortality.[27] However, several unique issues related to LT should be considered before implementing these regimen. Hypotension is not uncommon in the immediate postoperative period after LT; therefore, antihypertensive agents including angiotensin-converting enzyme inhibitors should

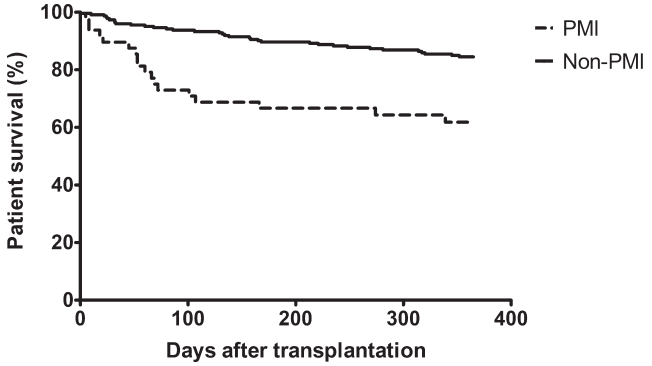

FIGURE 2 Kaplan-Meier survival analysis showed that the 1-y mortality in patients who developed postoperative myocardial injury (PMI) was significantly higher (37.5% vs 15.7%, log-rank test $P < .001$)

be considered only if the patient's hemodynamics are allowed. The use of antiplatelet and anticoagulant agents in the immediate postoperative period after LT is even more controversial. The risk of bleeding for these agents in patients who just receive the liver graft may be too high.

Although there is no effective prevention for PMI after LT, some lessons can be learned from those undergoing noncardiac surgery. Hypertension and cholesterol control should be included in pretransplant evaluation and education. This is particularly important in the current environment since today's LT patient population has been dominated by patients with nonalcoholic steatohepatitis and metabolic syndrome.[28] Beta blocker has been widely used to treat variceal bleeding in LT patients. From a cardiac standpoint, beta blocker significantly reduced postoperative myocardial infarction risk, but it also increases intraoperative bradycardia, postoperative stroke, and mortality.[27,29] Intraoperative hypotension is associated with PMI, acute kidney injury, and death[26]; therefore, severe and prolonged hypotension should be avoided during LT. Because LT patients usually have low systemic vascular resistance, the cutoff values of hypotension may be different compared with those undergoing noncardiac surgery. In this study, we have shown that preoperative LVH is a risk factor for post-transplant PMI, suggesting patients with pretransplant LVH may need preoperative education, lifestyle modification, and pharmacologic intervention. In addition, intraoperative monitoring should be tailored to the needs of these patients and severe and prolonged intraoperative hypotension should be avoided in LT.

Several limitations of this study are worth mentioning. First is the retrospective nature of this study. Although propensity-matched analysis and multivariate analysis were applied, some confounding factors were unable to obtain from medical records and were not adjusted. Those factors included pretransplant troponin and perioperative hemodynamic parameters. Besides, the absence of preoperative troponin levels made it impossible to distinguish patients with pretransplant existing myocardial injury. Secondly, postoperative troponin was measured in a selective group of patients according to clinical judgment, which might underestimate the incidence of PMI, especially missing those cases with asymptomatic PMI. Thirdly, patient demographics and management vary from centers to centers, so generalization of our findings requires caution. Despite these limitations, this is the first study to investigate the relationship between pretransplant LVH and PMI in adult patients undergoing LT.

In conclusion, this large retrospective study demonstrates that preoperative LVH is associated with PMI in LT. Patients with pretransplant LVH should be monitored closely in the perioperative period. Studies of further investigating pretransplant LVH in LT are warranted.

CONFLICT OF INTEREST

The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

AUTHOR CONTRIBUTIONS

Victor W. Xia: Designed the study; Yun Wang and Kai Sun: Contributed to acquisition of the data; Kai Sun and Victor W. Xia: Analyzed the data; Kai Sun, Min Yan, and Victor W. Xia: Drafted and revised the manuscript.

DISCLOSURE

This study was performed in Department of Anesthesiology and Perioperative Medicine, David Geffen School of Medicine at UCLA.

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