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Impact of Pre-Heart Transplant Levosimendan Administration on Post-Transplant Vasoplegia and Primary Graft Dysfunction

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ABSTRACT

Introduction: Levosimendan, a calcium-sensitizing inotropic agent, is used in patients with advanced heart failure (HF) awaiting heart transplantation (HT). Its prolonged effects, due to an active metabolite, may influence post-transplant vasodilation, particularly when administered shortly before HT. However, its impact on post-HT complications such as vasoplegia and primary graft dysfunction (PGD) remains unclear. This study aimed to evaluate whether preoperative levosimendan affects these outcomes.

Methods: This retrospective, multicenter observational study included adult HT recipients from 2010 to 2022 across three Spanish centers. Patients were grouped based on whether they received levosimendan within 1 month prior to HT. Main outcomes were post-HT vasoplegia (defined as cardiac index ≥2.5 L/min/m^2, systemic vascular resistance <1000 dyn·s·cm^{-5}, and either a vasoactive-inotropic score (VIS) > 20 or norepinephrine administration >0.1 μg/kg/min at 24 h post-HT) and severe PGD, as defined by the 2014 ISHLT criteria. Secondary outcomes included all-cause mortality. Subgroup analyses were performed for patients receiving levosimendan within 1 week of HT and by sex. Statistical analyses included propensity score (PS) matching, Kaplan–Meier curves, and multivariate Cox regression models.

Results: Among 598 HT recipients, 94 (15.7%) received levosimendan preoperatively. After PS adjustment, no significant differences were found in the incidence of vasoplegia (40.0% vs. 39.2%, OR 0.99, $p = 0.98$) or severe PGD (10.6% vs. 10.3%, OR 1.25, $p = 0.63$) between groups. Post-HT mortality was also not different (HR 0.78, $p = 0.37$). Vasoplegia did not affect mortality, while severe PGD was linked to higher mortality. Subgroup and sex-based analyses revealed no significant outcome differences.

Conclusions: Pre-HT levosimendan use was not associated with increased early post-transplant complications and appears to be a safe strategy.

Abbreviations: BMI, body mass index; CI, confidence interval; ECMO, extracorporeal membrane oxygenation; HF, heart failure; HR, hazard ratios; HT, heart transplant; ISHLT, International Society for Heart and Lung Transplantation; LVAD, left ventricular assist device; MCS, mechanical circulatory support; OR, odds ratio; PGD, primary graft dysfunction; PS, propensity score; PWCP, pulmonary wedge capillary pressure; RAP, right atrial pressure; sPAP, systolic pulmonary artery pressure; SVR, systemic vascular resistance; VIS, vasoactive-inotropic score.

Summary

This study evaluated whether giving levosimendan before HT affects early post-transplant complications. Among 598 patients, 94 received levosimendan within a month before surgery. Results showed no significant differences in rates of vasoplegia, severe primary graft dysfunction, or mortality. Levosimendan use appears safe in the immediate pre-transplant setting.

1 | Introduction

Advanced heart failure (HF) affects 1%–10% of the overall HF population and is associated with a poor prognosis [1, 2]. Although studies on inotropes have not demonstrated significant improvements in clinical outcomes at this stage [3–5], the current position statement of the Heart Failure Association of the European Society of Cardiology acknowledges that inotropic support may be necessary in advanced HF patients as a bridge to definitive therapies, such as long-term mechanical circulatory support (MCS) or heart transplantation (HT) [6].

Levosimendan is a calcium-sensitizing inotropic agent that enhances cardiac output by increasing myofilament sensitivity to calcium, reducing pulmonary capillary wedge pressure, and exerting vasodilatory effects [7]. In patients with advanced HF, levosimendan has been shown to improve peak oxygen consumption and increase cardiac output [8].

Its active metabolite extends the drug's hemodynamic effects [9]. Although the cardiovascular effects of levosimendan may persist for up to 30 days in real-world clinical settings, prior studies have demonstrated that its effects on objective echocardiographic measures [10, 11], NT-proBNP levels [10, 11], and hemodynamic parameters [11] generally last between 7 and 13 days, with values returning to baseline by Day 30.

Despite these physiological benefits, randomized clinical trials investigating levosimendan in the advanced HF setting have reported conflicting results regarding clinical outcomes [12–16]. However, two meta-analyses have suggested a survival benefit with levosimendan use [17, 18]. In the specific subset of patients awaiting HT, retrospective analyses have not demonstrated a survival advantage [19]. However, although patients receiving levosimendan were more severely ill, post-HT outcomes were comparable, suggesting a potential benefit and it is considered a safe strategy that may reduce HF-related hospitalizations [19].

Given its prolonged hemodynamic effects—vasodilation and inotropism—mediated by its active metabolite, pre-HT administration of levosimendan may influence the incidence of post-HT vasoplegia. Furthermore, its role in the development of severe primary graft dysfunction (PGD), whether as a risk or protective factor, has not yet been investigated.

Vasoplegia is a common complication following HT, characterized by severe vasodilatory shock after cardiac surgery [20]. Reported incidence rates exceed 30% [20–23]. Identified risk factors include advanced age, chronic kidney disease, MCS, and prolonged cardiopulmonary bypass time [20, 21]. The relationship between vasoplegia and mortality remains inconclusive. Although some recent studies have not found increased 30-day or 1-year mortality, they have noted associations with prolonged hospitalization [20, 21]. In contrast, a recent meta-analysis reported a significant association between vasoplegia and increased mortality [23]. Despite its frequency, a consensus definition for vasoplegia is still lacking.

PGD, as defined by the International Society for Heart and Lung Transplantation (ISHLT) consensus [24], is a severe early post-HT complication that significantly increases short-term mortality [25, 26]. Although multiple risk factors for PGD have been identified, a recent large retrospective analysis of over 2700 HT recipients found that only acute preoperative dialysis, durable left ventricular assist device (LVAD) support, and ischemic time remained independent predictors of PGD [27].

The potential impact of preoperative levosimendan administration on the incidence of vasoplegia following HT has not been specifically investigated. Similarly, its role as either a protective or risk factor for severe PGD remains unexamined.

2 | Materials and Methods

2.1 | Study Design and Patient Population

This retrospective, observational, and multicentric study included all consecutive adult HT recipients between 2010 and 2022 across three Spanish centers. The study was approved by the institutional ethics committees of each participating site, with a waiver of informed consent granted due to its retrospective nature.

2.2 | Study Data

Data collection and management were conducted using a secure Research Electronic Data Capture (REDCap) [28, 29]. Retrospective data focused on recipient demographics, medical history, laboratory values, and MCS and inotropic therapy at the time of transplantation. Specific attention was given to levosimendan administration during the HT waiting period, with detailed recording of its use within the month and week preceding transplantation. Post-transplant data encompassed hemodynamic parameters, laboratory results, MCS and inotropic requirements at 24 h post-HT, as well as surgical complications. Additionally, available donor characteristics were documented.

The analyzed intervention was the administration of at least one complete levosimendan dose (12.5 mg) within the 30 days preceding HT.

The outcomes of interest were the incidence of post-HT vasoplegia and the incidence of severe PGD. Secondary outcomes included overall mortality in patients who received levosimendan prior to HT compared to those who did not, as well as mortality among patients who developed post-HT vasoplegia and severe PGD.

A subanalysis was conducted on patients who received levosimendan exclusively within 1 week prior to HT, based on the previously mentioned available data for objective echocardiographic, NT-proBNP, and hemodynamic parameters [10, 11]. Due to uncertainties about the exact duration of its effects (lasting between 7 and 13 days, with values returning to baseline by Day 30), we conducted this subgroup analysis using a 7-day cutoff to ensure that patients were very likely still under the drug's influence. The comparison group comprised all patients who did not receive levosimendan during the last 7 days preceding HT.

Additionally, a sex-based subanalysis was performed to investigate potential interactions between sex differences and post-HT outcomes.

2.3 | Definition of Vasoplegia and Severe PGD

A consensus definition for vasoplegia remains lacking. In this study, we aimed to define vasoplegia based on the hemodynamic profile within the first 24 h after HT. In concordance with previous literature [20], vasoplegia was identified by a cardiac index $\geq$ 2.5 L/min/m^2, a systemic vascular resistance (SVR) < 1000 dyn·s·cm^{-5}, and either a vasoactive-inotropic score (VIS) > 20 or norepinephrine administration > 0.1 μg/kg/min at 24 h post-HT.

The definition of severe PGD was consistent with the 2014 ISHLT consensus conference document [24]. Severe PGD was characterized by significant left, right, or biventricular dysfunction requiring MCS, such as extracorporeal membrane oxygenation (ECMO) or a ventricular assist device, within the first 24 h after HT. Secondary causes of graft dysfunction—including hyperacute rejection, pulmonary hypertension, and surgical complications—were systematically excluded.

In this study, by applying strict hemodynamic criteria, there was no overlap between the two conditions by definition.

2.4 | Statistical Methods

Categorical variables are presented as counts and percentages, while continuous variables are expressed as medians with interquartile ranges (Q1–Q3) in the baseline characteristics table. Group comparisons were performed using the Chi-squared test for categorical variables and the Wilcoxon rank-sum test for continuous variables.

A propensity score (PS) method was applied to assess the association between the intervention and the outcomes by including as covariates all variables with a p value < 0.10 in the univariate analysis with the outcome. Specifically, for the vasoplegia analysis, adjustment variables were recipient age and sex; recipient diabetes, hypertension, body mass index (BMI), HF etiology, resternotomy, renal function, and bilirubin levels; pre-HT use of amiodarone, sacubitril/valsartan, or pulmonary vasodilators; pre-HT right atrial pressure (RAP) and cardiac index; use of MCS, LVAD or inotropes pre-HT; transplant status (urgent vs. elective) and ischemic time. Similarly, for the severe PGD analysis, adjustments included: recipient age and sex; recipient diabetes, BMI, HF etiology, resternotomy, renal function, and bilirubin levels; pre-HT use of amiodarone; pre-HT RAP, systolic pulmonary artery pressure (sPAP), and cardiac index; use of MCS or LVAD pre-HT; transplant status, and ischemic time.

PSs were fitted using logistic regression. Interaction models were applied to examine potential treatment effect heterogeneity by recipient sex. Treatment effect estimation was reported as odds ratios (OR) with 95% confidence intervals (CI).

Survival analyses were conducted using Kaplan–Meier curves, with follow-up starting on the day of HT and concluding at the time of death. Cox proportional hazards regression models were used to estimate hazard ratios (HR) with 95% CIs for all-cause mortality in patients receiving levosimendan, development of post-HT vasoplegia or severe PGD. Comparisons of mortality between patients who received levosimendan prior to HT and those who did not were adjusted for relevant confounders, including recipient and donor age, pre-HT recipient sex, diabetes, renal function, bilirubin levels, resternotomy, HF etiology, pre-HT use of MCS, LVAD or inotropes, pre-HT RAP and pulmonary pressures; transplant status, and ischemic time.

A p value < 0.05 was considered statistically significant. All analyses were performed using R version 4.2.2 on a Windows 11 platform.

3 | Results

3.1 | Baseline Characteristics

The registry included 624 consecutive HT recipients, from which 598 patients had adequately captured data on pre-HT levosimendan administration. Among these, 94 patients received levosimendan within 30 days before HT, while 504 did not. Post-transplant hemodynamic data were available for 239 patients. Baseline characteristics of both groups are summarized in Table 1.

Patients in the levosimendan group were older (59 vs. 56 years, $p = 0.033$), with no significant difference in sex distribution (male: 76% vs. 77%, $p = 0.7$) or blood group. Levosimendan recipients had a lower BMI prior to HT (23.1 vs. 25.1 kg/m^2, $p < 0.001$). Other comorbidities, such as hypertension, diabetes mellitus, and prior cardiac surgery, were comparable between groups. However, HF etiology differed, with a higher prevalence of dilated cardiomyopathy and congenital HF, and a lower proportion of ischemic, restrictive, and hypertrophic cardiomyopathy in the levosimendan group ($p = 0.04$).

Laboratory results prior to HT were largely similar, with no differences in creatinine (1.2 vs. 1.1 mg/dL, $p = 0.4$) or bilirubin levels (1.3 vs. 1.1 mg/dL, $p = 0.061$). However, sodium levels were significantly lower in the levosimendan group (137 vs. 139 mmol/L, $p < 0.001$).

Hemodynamic profiles revealed notable differences: patients receiving levosimendan had higher sPAP (49 vs. 42 mm Hg, $p = 0.01$) and pulmonary capillary wedge pressure (PCWP) (24 vs.

TABLE 1 | Baseline characteristics stratified by levosimendan administration in the 30 days prior to heart transplant.

	Total	No levosimendan	Levosimendan	
	***N* = 598**	***N* = 504**	***N* = 94**	***p* value**
Recipient characteristics				
Age (years)	57 (47–63)	56 (46–63)	59.0 (50–65)	0.033
Male sex (%)	460 (77)	389 (77)	71 (76)	0.7
Blood group				
A (%)	284 (47)	238 (47)	46 (49)	> 0.9
B (%)	59 (9.9)	50 (9.9)	9 (9.6)	
AB (%)	25 (4.2)	21 (4.2)	4 (4.3)	
0 (%)	230 (38)	195 (39)	35 (37)	
HF etiology				
Ischemic (%)	150 (25)	130 (26)	20 (21)	0.04
DCM (%)	304 (51)	247 (49)	57 (61)	
Congenital (%)	20 (3.3)	15 (3.0)	5 (5.3)	
HCM or restrictive (%)	78 (13.0)	73 (14)	5 (5.3)	
Retransplant (%)	3 (0.5)	2 (0.4)	1 (1.1)	
Other (%)	43 (7.2)	37 (7.3)	6 (6.4)	
BMI (kg/m^2)	24.8 (22.3–28.1)	25.1 (22.6–28.4)	23.1 (21.0–26.0)	<0.001
Diabetes (%)	162 (27.0)	130 (26.0)	32 (34.0)	0.1
Hypertension (%)	219 (37.0)	187 (37.0)	32 (34)	0.6
Prior sternotomy (%)	186 (31.0)	152 (30.0)	34 (36.0)	0.2
Creatinine (mg/dL)	1.1 (0.9–1.5)	1.1 (0.9–1.5)	1.2 (0.9–1.6)	0.4
INR	1.3 (1.1–1.8)	1.3 (1.1–1.8)	1.3 (1.2–1.8)	0.3
Bilirubin (mg/dL)	1.2 (0.7–1.9)	1.1 (0.7–1.9)	1.3 (0.9–2.2)	0.061
Sodium (mEq/L)	139 (136–141)	139 (136–141)	137 (132–141)	<0.001
Sacubitril-Valsartan (%)	37 (6.2)	31 (6.2)	6 (6.4)	>0.9
Amiodarone (%)	146 (24)	119 (24)	27 (29)	0.3
Pulmonary vasodilators (%)	85 (14)	64 (13)	21 (22)	0.014
LVAD bridge (%)	29 (4.8)	28 (5.6)	1 (1.1)	0.068
RAP (mm Hg)	11 (6–15)	10 (6–15)	11 (7–16)	0.2
sPAP (mm Hg)	43 (33–55)	42 (32–55)	49 (37–60)	0.01
dPAP (mm Hg)	21 (16–28)	21 (16–27)	24 (17–30)	0.07
PCWP (mm Hg)	21 (15–27)	21 (15–27)	24 (18–30)	0.006
CI (L/min/m^2)	2.3 (1.9–2.7)	2.3 (1.9–2.7)	2.3 (1.9–2.7)	0.3
IABP support (%)	71 (20)	55 (19)	16 (25)	0.2
ECMO support (%)	51 (8.5)	43 (8.5)	8 (8.5)	>0.9
Short term MCS (%)	130 (22)	103 (20)	27 (29)	0.075
Mechanical ventilation (%)	106 (18)	86 (17)	20 (21)	0.3
Pre-HT RRT (%)	32 (5.4)	29 (5.8)	3 (3.2)	0.3
Donor and surgical characteristics				
Age (years)	47 (38–54)	47 (38–54)	47.5 (38–55)	0.6
Male sex (%)	385 (65)	325 (65)	60 (64)	0.8
BMI (kg/m^2)	25.7 (23.7–28.4)	25.7 (23.8–28.7)	25.7 (23.5–28.1)	0.8

(Continues)

TABLE 1 | (Continued)

	Total $N = 598$	No levosimendan $N = 504$	Levosimendan $N = 94$	p value
Sex mismatch (%)	167 (28)	140 (28)	27 (29)	0.9
Cause of death				
Stroke (%)	375 (63)	310 (62)	65 (71)	0.2
Anoxia (%)	30 (5.1)	24 (4.8)	6 (6.6)	
Head trauma (%)	135 (23)	123 (25)	12 (13)	
Drug intoxication (%)	6 (1.0)	5 (1.0)	1 (1.1)	
Other (%)	44 (7.4)	37 (7.4)	7 (7.7)	
Ischemic time (min)	205.5 (138–246)	209.5 (140–250)	194.5 (127–240)	0.2
Transplant status				
Elective (%)	306 (53)	268 (55)	38 (41)	0.02
Urgent (%)	273 (47)	218 (45)	55 (59)	
Post-HT (24 h)				
IABP (%)	78 (13)	68 (14)	10 (11)	0.5
Short-term LVAD (%)	4 (0.8)	2 (0.5)	2 (2.6)	0.12
ECMO (%)	41 (6.9%)	35 (6.9)	6 (6.4)	0.8
VIS	25.4 (10–55)	24.6 (10–55)	27.3 (10.8–54.9)	0.56
Need for RRT (%)	119 (20)	95 (19)	24 (26)	0.15

Note: Median (Q1–Q3) or *n* (%).

Abbreviations: BMI, body mass index; CI, cardiac index; DCM, dilated cardiomyopathy; dPAP, diastolic pulmonary arterial pressure; ECMO, extracorporeal membrane oxygenation; HCM, hypertrophic cardiomyopathy; HF, heart failure; HT, heart transplant; IABP, intra-aortic balloon pump; INR, international normalized ratio; LVAD, left ventricle assist device; MCS, mechanical circulatory support; PCWP, pulmonary capillary wedge pressure; RAP, right atrial pressure; RRT, renal replacement therapy; sPAP, systolic pulmonary arterial pressure; VIS, vasoactive-inotropic score.

21 mm Hg, $p = 0.006$), with no differences on RAP and cardiac index.

Cardiologic treatments, including sacubitril-valsartan and amiodarone, did not differ between groups, although patients on levosimendan were more frequently treated with pulmonary vasodilators (22% vs. 13%, $p = 0.014$). Although the use of LVAD was low across both groups, no significant difference was noted.

Donor characteristics, including sex, age, BMI, sex mismatch, and cause of death, were not different between the groups. Ischemic time during HT also showed no difference (194.5 vs. 209.5 min, $p = 0.2$). However, the levosimendan group had a higher transplant urgency status, with significantly fewer patients undergoing elective HT ($p = 0.02$). Use of temporary MCS prior to HT did not differ.

Postoperative support at 24 h post-HT was not different between groups, including MCS use, VIS, and the need for renal replacement therapy.

3.2 | Post-HT Vasoplegia and Severe PGD

The outcomes analyses are presented in Table 2. The vasoplegia analysis was conducted on 239 patients due to missing hemodynamic data. A total of 94 cases (39.3%) of vasoplegia were identified, with 18 cases (40%) occurring in the levosimendan group and 76 cases (39.2%) in the non-levosimendan group. No significant differences were observed between the groups (OR 1.04, 95% CI 0.53–2.01, $p = 0.92$), and these results remained consistent after PS adjustment (OR 0.99, 95% CI 0.4–2.43, $p = 0.98$).

Severe PGD was evaluated in the entire cohort ($N = 598$), with 62 cases identified (10.4%). Among these, 10 cases (10.6%) occurred in the levosimendan group, while 52 cases (10.3%) were observed in the non-levosimendan group. No significant differences were found between the two groups (OR 1.03, 95% CI 0.51–2.12, $p = 0.93$), even after PS adjustment (OR 1.25, 95% CI 0.5–3.16, $p = 0.63$).

3.3 | Survival Analyses

Survival analysis is graphically presented in Figure 1. With a median follow-up of 4.9 years (interquartile range [IQR], 1.6–7.4 years), there was no significant difference in overall mortality between patients who received levosimendan prior to HT and those who did not (unadjusted HR, 1.02; 95% CI, 0.66–1.57; $p = 0.94$; adjusted HR, 0.78; 95% CI, 0.44–1.36; $p = 0.37$). One-month post-transplant survival was not different between both groups: 93.4% (95% CI 89.8%–97.0%) in the levosimendan group

TABLE 2 | Outcomes analysis stratified by levosimendan administration in the 30 days and 7 days prior to heart transplant.

	N	No levosimendan	Levosimendan	PS OR (95% CI)	*p* value
30 days pre-HT	598	504	94		
Vasoplegia	239	76 (39.2)	18 (40)	0.99 (0.4–2.43)	0.98
Severe PGD	598	52 (10.3)	10 (10.6)	1.25 (0.5–3.16)	0.63
7 days pre-HT	598	572	26		
Vasoplegia	239	88 (39.5)	6 (37.5)	0.93 (0.27–3.21)	0.91
Severe PGD	598	59 (10.3)	3 (11.5)	1.25 (0.27–5.81)	0.77

Note: n (%) or OR (CI).

Abbreviations: CI, confidence interval; HT, Heart Transplantation; OR, odds radio; PGD, primary graft dysfunction; PS, propensity score.

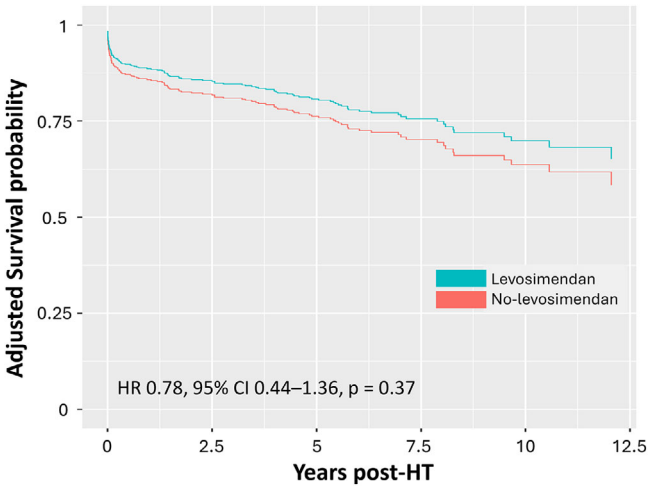

FIGURE 1 | Adjusted survival analysis for patients with or without levosimendan administration prior to heart transplant.

versus 91.6% (95% CI 89.0%–94.3%) in the non-levosimendan group.

The occurrence of post-HT vasoplegia was not associated with a significant difference in mortality (HR 0.75, 95% CI 0.43–1.34, $p = 0.34$). In contrast, the development of severe PGD was strongly associated with increased mortality (HR 4.68, 95% CI 3.65–6.72, $p < 0.001$).

3.4 | Outcomes Subanalysis

A subanalysis was performed focusing on patients who received levosimendan within 1 week prior to HT (Table 2). This subgroup included 26 patients (4.4%). The vasoplegia analysis was conducted on 16 patients due to missing hemodynamic data of whom six (37.5%) developed post-transplant vasoplegia, compared to 88 (39.5%) in the control group. No significant differences were observed between the two groups after PS adjustment (OR 0.93, 95% CI 0.27–3.21, $p = 0.91$). Regarding severe PGD, three (11.5%) patients in this subgroup developed the complication, compared to 59 (10.3%) in the control group. Again, no significant differences were observed after PS analysis (OR 1.25, 95% CI 0.27–5.81, $p = 0.77$).

Finally, the distribution of post-HT vasoplegia and severe PGD among male and female recipients, stratified by pre-transplant levosimendan administration, is shown in Figure 2. In this subgroup analysis, the interaction model assessing treatment effect by sex did not identify a significant interaction for vasoplegia ($p = 0.44$) or severe PGD ($p = 0.51$).

4 | Discussion

Levosimendan administration is used in some patients awaiting HT and is considered a safe strategy in our setting [30]. Due to its prolonged hemodynamic effects, mediated by an active metabolite, its impact may extend beyond transplantation when administered shortly before HT. This could potentially increase post-HT vasoplegia due to its vasodilatory properties or influence the incidence of severe PGD.

In our retrospective cohort, patients who had received levosimendan exhibited lower BMI, higher urgency status for HT, higher pulmonary pressures, greater use of pulmonary vasodilators, and lower sodium levels. These characteristics reflect more advanced HF [6], pulmonary hypertension, and a higher degree of congestion [30]. Differences in HF etiology were primarily due to a lower prevalence of restrictive cardiomyopathy and hypertrophic cardiomyopathy, less frequently treated with inotropes.

With regard to vasoplegia following HT, contemporary studies have identified pre-HT MCS, prolonged ischemic time, increased blood product transfusion, impaired renal function, and thyroid disease as risk factors for its development [20, 21, 31]. Notably, vasodilator agents like sacubitril/valsartan have not been associated with an increased incidence of post-HT vasoplegia [32, 33]. Despite the long-lasting vasodilatory effects of levosimendan, its preoperative administration was not associated with an increased incidence of vasoplegia in our study, even in the subgroup that received levosimendan within 1 week prior to HT. These findings align with previous research evaluating levosimendan in cardiac surgery. Two randomized clinical trials failed to demonstrate a mortality benefit with prophylactic levosimendan use but did not report significant differences in safety outcomes, such as hypotension or the need for high-dose vasopressors [34, 35].

Although extensive literature exists on PGD risk factors [36–40], this study is the first to assess levosimendan as a potential

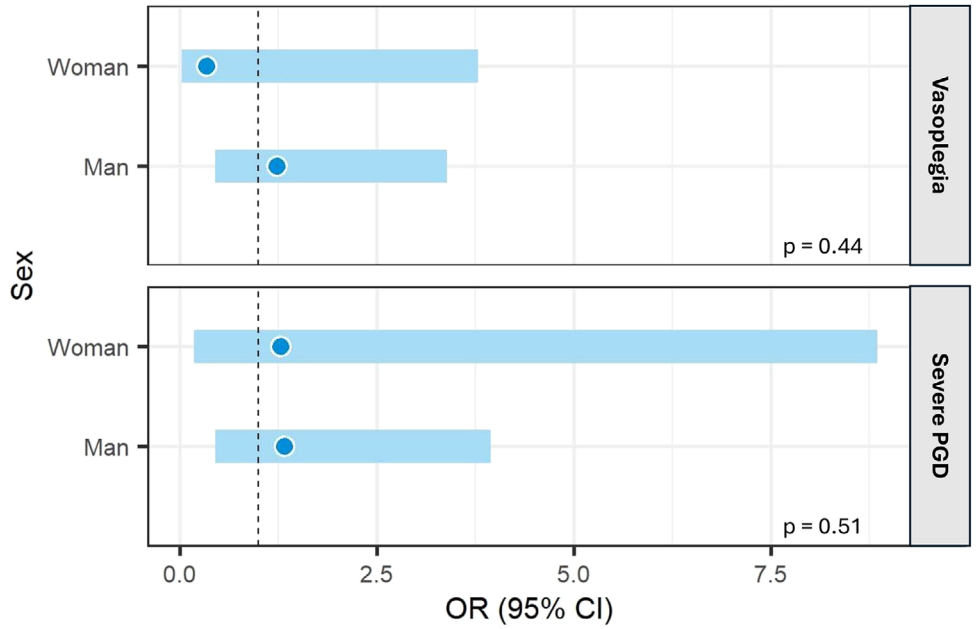

FIGURE 2 | Analysis of sex interaction with the outcomes stratified by levosimendan administration in the 30 days prior to heart transplant.

risk or protector factor, without finding a significant impact—even in the subgroup that received levosimendan within 1 week prior to HT. The neutral effect may be attributed to two opposing factors. On the one hand, patients receiving levosimendan tend to be more critically ill, potentially increasing the likelihood of severe PGD after HT. On the other hand, improvements in hemodynamic status following inotropic support and other indirect factors—such as the withdrawal of prognostic HT medications—could mitigate this risk. Notably, analysis of the first report from the PGD consortium indicated that prior treatment with inotropes had a mild protective effect against severe PGD development [27].

We also conducted a survival analysis of pre-HT levosimendan administration, which revealed no significant differences—findings that may align with results from trials investigating preoperative levosimendan use in cardiac surgery [34, 35].

Moreover, although the relationship between vasoplegia and mortality remains inconclusive—with conflicting results reported in previous studies [20–22] and a meta-analysis by Kumar et al.—our study found that patients who developed vasoplegia early in the postoperative period did not exhibit reduced survival. In contrast, we observed a significantly higher mortality risk among patients who developed severe PGD, consistent with findings from recent literature [41–43].

Finally, the interaction model assessing the effect of levosimendan treatment by sex did not demonstrate a statistically significant association with vasoplegia or severe PGD

A final general consideration regarding early hemodynamic complications following HT warrants attention. In the present study, vasoplegia and severe PGD were treated as distinct hemodynamic entities, primarily based on differences in cardiac index, with no possible overlap. However, we acknowledge that in clinical practice, the distinction between vasoplegia and PGD is often less clear, and both conditions may coexist to varying degrees in the same patient.

Notably, the diagnosis of severe PGD is defined by the need for MCS [24], which complicates differentiation, as MCS is also a standard intervention for severe vasoplegia [23]. Some studies suggest that PGD may confound the assessment of vasoplegia and its impact on outcomes [44]. A recent study further stratified severe PGD by timing of MCS initiation, revealing higher mortality in patients requiring immediate MCS—where a vasoplegic pathophysiology predominated—compared to those with delayed support [45]. These findings highlight the need for further research to clarify the pathophysiological overlap, refine the definition of severe PGD, and establish a consensus definition for vasoplegia in the context of HT.

5 | Limitations

This study has several inherent limitations due to its retrospective design, which introduces potential selection bias. Although severe PGD outcomes were assessed in the entire cohort, the evaluation of vasoplegia outcomes was limited by missing hemodynamic data. Similarly, the assessment of mild and moderate PGD was not conducted due to missing hemodynamic data and the low incidence rates. The primary reasons for these data gaps include the non-systematic use of pulmonary artery catheters following HT across centers, as well as the lack of electronic medical records in the initial years of study. The subgroup analysis of patients receiving levosimendan within 1 week prior to transplantation was further limited by the small sample size, reducing the statistical power of these findings. We acknowledge that the distinction between vasoplegia and PGD in real-world practice is not always clear and both conditions may partially overlap in the same patient. Although we adjusted the outcomes using PS analysis, adjusting for variables identified as significant

in univariate analysis, the influence of unmeasured confounders cannot be entirely excluded.

6 | Conclusions

In this study, preoperative administration of levosimendan was not associated with an increased incidence of post-transplant vasoplegia, despite its prolonged hemodynamic effects. Although patients who received levosimendan tended to be more critically ill—reflecting advanced stages of HF—they exhibited comparable rates of severe PGD and short-term survival following HT. Vasoplegia was not linked to increased mortality, whereas severe PGD was associated with a higher risk of death. These findings suggest that preoperative levosimendan administration is a safe strategy that does not significantly alter post-HT outcomes. Further research is required to more clearly define and differentiate vasoplegia and PGD, particularly given their potential overlap in clinical practice.

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Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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