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ORIGINAL ARTICLE

Hemodynamic failure and graft dysfunction after lung transplant: A possible clinical continuum with immediate and long-term consequences

Vittorio Scaravilli[1,2] | Amedeo Guzzardella[3] | Fabiana Madotto[3] | Letizia Corinna Morlacchi[3,4] | Marco Bosone[3] | Claudia Bonetti[3] | Valeria Musso[3] | Valeria Rossetti[3,4] | Filippo Maria Russo[1] | Lorenzo Del Sorbo[5] | Francesco Blasi[3,4] | Mario Nosotti[3,6] | Alberto Zanella[1,3] | Giacomo Grasselli[1,3]

[1]Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda, Ospedale Maggiore Policlinico, Milan(MI), Italy

[2]Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan(MI), Italy

[3]Department of Pathophysiology and Transplantation, University of Milan, Milan(MI), Italy

[4]Department of Internal Medicine, Respiratory Unit and Cystic Fibrosis Center, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan(MI), Italy

[5]Interdepartmental Division of Critical Care Medicine, Toronto General Hospital, Toronto, Ontario, Canada

[6]Department of Cardio-thoraco-vascular diseases, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Milan(MI), Italy

Correspondence
Vittorio Scaravilli, Department of Anesthesia, Critical Care and Emergency, Fondazione IRCCS Ca' Granda – Ospedale Maggiore Policlinico, Via F. Sforza 35, 20122 Milan, MI, Italy.
Email: vittorio.scaravilli@gmail.com

Abstract

Introduction: The postoperative hemodynamic management after lung transplant (LUTX) is guided by limited evidence. We aimed to describe and evaluate risk factors and outcomes of postoperative vasoactive support of LUTX recipients.

Methods: In a single-center retrospective analysis of consecutive adult LUTX, two cohorts were identified: (1) patients needing prolonged vasoactive support (>12 h from ICU admission) (VASO+); (2) or not (VASO−). Postoperative hemodynamic characteristics were thoroughly analyzed. Risk factors and outcomes of VASO+ versus VASO− cohorts were assessed by multivariate logistic regression and propensity score matching.

Results: One hundred and thirty-eight patients were included (86 (62%) VASO+ versus 52 (38%) VASO−). Vasopressors (epinephrine, norepinephrine, dopamine) were used in the first postoperative days (vasoactive inotropic score at 12 h: 6 [4−12]), while inodilators (dobutamine, levosimendan) later. Length of vasoactive support was 3 [2−4] days. Independent predictors of vasoactive use were: LUTX indication different from cystic fibrosis ($p = .003$), higher Oto score ($p = .020$), longer cold ischemia time ($p = .031$), but not preoperative cardiac catheterization. VASO+ patients showed concomitant hemodynamic and graft impairment, with longer mechanical ventilation ($p = .010$), higher primary graft dysfunction (PGD) grade at 72 h (PGD grade > 0 65% vs. 31%, $p = .004$, OR 4.2 [1.54−11.2]), longer ICU ($p < .001$) and hospital stay ($p = .013$). Levosimendan as a second-line inodilator appeared safe.

Conclusions: Vasoactive support is frequently necessary after LUTX, especially in recipients of grafts of lesser quality. Postoperative hemodynamic dysfunction requiring vasopressor support and graft dysfunction may represent a clinical continuum

with immediate and long-term consequences. Further studies may elucidate if this represents a possible treatable condition.

KEYWORDS
hemodynamics, lung transplant, primary graft dysfunction, vasoactive support

1 | INTRODUCTION

Bilateral Lung transplantation (LUTX) is a viable option for selected patients with end-stage respiratory failure,[1] which is frequently complicated by pulmonary hypertension, right ventricular hypertrophy, and right heart failure.[2] The increasing age and comorbidities (i.e., ischemic heart disease) of LUTX candidates further enhance their pre-operative and intraoperative burden.[3] During the surgical operation, the pulmonary arteries are sequentially cross-clamped, while severe hypoxia and hypotension commonly occur.[4] These factors, together with fluid loss, may lead to hemodynamic instability and acute heart failure that can eventually persist into the postoperative period, resulting in the need of prolonged vasoactive support and even extracorporeal membrane oxygenation (ECMO).[5] Levosimendan is an innovative lusitropic vasoactive agent that has been proven helpful in the similar—but not equivalent—scenario of postoperative cardiac failure after cardiac surgery.[6]

Literature regarding the postoperative hemodynamic management of patients who have undergone LUTX is scarce,[7] and to our knowledge, no previous work has documented the postoperative use of vasoactive agents—particularly levosimendan—in this clinical situation. Moreover, to our knowledge, no study has assessed the association between hemodynamic impairment and graft function in the immediate postoperative period. We hypothesize that the prolonged need for vasoactive agents in the postoperative period may be related to primary graft dysfunction, owing to a multisystemic widespread endothelial barrier and inflammation due to ischemia-reperfusion injury.

Thus, with this retrospective single-center analysis, we want to thoroughly describe the need for postoperative vasoactive support in patients undergoing LUTX and evaluate the risk factors for prolonged vasoactive support and its impact on outcomes, particularly its association with graft function. Secondarily, we want to document the use of levosimendan in this particular scenario.

2 | METHODS

The Institutional Ethical Committee approved the study (Comitato Etico Milano Area 2, # 1183_2021), and informed consent was waived due to the retrospective observational nature of the study. The study was registered at clinicaltrials.gov with the identifier NCT05702333. The study complies with the most recent ISHLT ethics statement.[8] The STROBE guidelines[9] have been followed to report this study.

This study is a retrospective analysis of medical records of all consecutive adult patients who underwent LUTX at our Institution (Fondazione IRCCS Ca' Granda—Ospedale Maggiore Policlinico) from January 1, 2017 to May 31, 2022. Our Institution performs LUTX through sequential bilateral pneumonectomy and graft implantation, preferentially without ECMO support. No fixed protocol is utilized for the postoperative hemodynamic management of patients who have undergone LUTX, but general guidelines are followed[7] (see Additional Methods, Supplementary Material for further details). Specifically, hemodynamic management is guided by lactate, urinary output, invasive cardiac output monitoring, pulmonary artery pressure, wedge pressure, and mixed venous saturation measurement through an elective pulmonary artery catheter. We do not employ a specific hemodynamic protocol but follow the following general rules: filling optimization based on dynamic cardiac output indicators (Wedge pressure < 15 mm Hg), high-threshold red blood cell transfusions (i.e., Hb > 9 gr/L), and vasopressors are used to guarantee a mean arterial pressure in the 65–75 mm Hg range. Whence hypovolemia is ruled out, and euvolemia is guaranteed by judicious volume loads, norepinephrine is the vasopressor of choice whether cardiac output is in the normal range (i.e., cardiac index > 2.6 L/min/m^2). Additionally, whether cardiac output is impaired (i.e., cardiac index < 2.6 L/min/m^2), adrenaline and—less frequently—dopamine might be employed to both guarantee adequate perfusion pressures (in the 65–75 mm Hg range) and stabilize cardiac output and oxygen delivery.

Then, inodilators (i.e., dobutamine, levosimendan) might be introduced in patients showing—despite Hb > 9 gr/L, euvolemia, mean arterial pressure guaranteed by vasopressors—increasing lactate levels and reductions in mixed venous saturation (as per a reduction in oxygen delivery) are observed during weaning. The use of those inodilators is thoroughly avoided in patients with arrhythmic alterations, or high risk for rhythm disturbances. The occurrence of pulmonary hypertension is usually sequentially treated with inhaled nitric oxide and sildenafil.

All patients who had undergone LUTX during the study period were considered for inclusion. Exclusion criteria were: (1) single LUTX; (2) re-transplantation; and (3) missing medical records.

The following data at enlistment were collected: demographics, weight, height, comorbidities, lung allocation score (LAS) at transplantation, pulmonary arterial pressures and cardiac output (by invasive cardiac catheterization), pulmonary perfusion at scintigraphy, and ventricular ejection fraction at ventriculography. The following donor data were collected: donor after cardiac or brain death (DCD or DBD), need for ex-vivo lung perfusion (EVLP), and Oto Score.[10] The

following perioperative data were collected: time on the waiting list, need for ECMO bridge to LUTX, cold and warm ischemia time of graft, and need for ECMO for LUTX, reason for ECMO employment during surgery (i.e., respiratory, hemodynamic, mixed). The following postoperative data were collected at ICU admission, after 12 h, and then daily until ICU discharge: use and dosage (the maximum dosage of the assessed timeframe) of vasopressors, vasoactive-inotropic score (VIS),[11] hemodynamics (heart rate, mean arterial pressure (MAP), mean pulmonary arterial pressure (PAPm), central venous pressure (CVP), cardiac output (CO), mixed venous oxygen saturation (S_vO_2), systemic vascular resistances (SVR)), fluid balance, red blood cells transfusion needs, arterial lactate concentration, and ventilatory parameters (ventilatory mode, inspired fraction of oxygen (F_iO_2), oxygen arterial partial pressure (P_aO_2), tidal volume (TV), Positive End-Expiratory Pressure (PEEP), and plateau pressure (P_{plat})). Moreover, to better define the reason for vasoactive support, we assessed the occurrence of 1/ cardiac complications (i.e., cardiac ischemia, pericarditis, supraventricular tachyarrhythmias, and pulmonary venous anastomotic–related dysfunction or torsion); 2/ massive hemorrhage (i.e., need for surgical revision) and hemorrhagic shock; 3/ septic shock, defined upon the latest Surviving sepsis campaign guidelines; 4/ anaphylaxis and anaphylactic shock (e.g., thymoglobulin).

The patients' population was divided into two cohorts: (1) patients who needed vasoactive support (VASO+) after 12 h of ICU stay; (2) patients who did not require vasoactive support or patients whose vasoactive support was shorter than 12 h (VASO−). Moreover, the VASO+ cohort was sub-dived into two sub-cohorts: (1) patients treated with levosimendan (LEVO+) and (2) patients not treated with levosimendan (LEVO−).

The following outcomes were measured: ICU mortality, duration of mechanical ventilation, primary graft dysfunction (PGD) grade at 72 h from reperfusion,[12] need for renal replacement therapy (RRT), ICU length of stay (LOS), hospital LOS, hospital mortality, and overall mortality at follow-up (July 31, 2022).

2.1 | Statistical analysis

Continuous variables were reported using median and interquartile range (IQR), while discrete variables with absolute and relative frequency. The sample size was chosen based on available clinical data at our Institution. Differences between patients' cohorts were assessed using the chi-square test (or Fisher exact tests) and Student's t-test (or Wilcoxon rank-sum test) as appropriate. For binary outcome measures, odds ratios (OR) and the relative risk (RR), when appropriate, and associated 95% likelihood ratio-based confidence intervals were calculated. In addition, multivariate logistic regression was fitted to the data to evaluate variables independently associated with the need for prolonged vasoactive support. To evaluate the impact of treatment on outcomes, a propensity score matching procedure was applied to identify two matched cohorts of VASO+ versus VASO− patients. In detail, the propensity score was estimated using a multivariable logistic regression model with a

list of clinically relevant independent variables with a possible role of confounder in the relationship between treatment and mortality: age,[13] sex,[14] BMI,[15] lung transplantation disease reason,[16] presence of pulmonary hypertension,[17] Oto score,[18] cold ischemia time[19] and use of intraoperative ECMO.[4] Patients were matched (1:1 match without replacement) using sequential greedy matching with a caliper of .2 standard deviations of the logit of the propensity score. The similarity of the matched groups was assessed by standardized differences for each independent variable used in the propensity score estimation. Differences between groups after matching were assessed using the McNemar test and the Wilcoxon sign rank test, as appropriate. Kaplan–Meier survival curve analysis was used with the Klein and Moeschberger test to compare patients' cohorts' survival. The cox-proportional hazard models were utilized to evaluate the effects of vasoactive support upon survival. Observations were right censored. All tests were two-sided; $p < .05$ was chosen to indicate statistical significance. STATA 17.0 (StataCorp, TX, USA) and JMP 15.0 Pro (SAS Institute Inc., Cary, NC, USA) statistical programs were utilized. For further details, see Additional Methods, Supplementary Material.

3 | RESULTS

During the study period, 150 patients underwent LUTX at our Institution, and after the exclusion of 12 patients, 138 were included in the study (see Flowchart, Additional Results, Supplementary Material). Table 1 describes the overall patients' characteristics. Patients were primarily male ($n = 77$, 66%), with a median age of 41 [28–55] years old. The most common indication for LUTX was cystic fibrosis, followed by idiopathic pulmonary fibrosis. Among 138 patients, 76 patients had ECMO support during the surgical procedure. Of those, 12 were bridge to LUTX with ECMO, and continued venovenous-ECMO support in the intraoperative period. Of the remaining 64 patients, 34 (53%) hemodynamic, 15 (23%) respiratory, or 15 (23%) mixed reasons.

See Figure 1 for a detailed description of the vasoactive support needed in the postoperative period. At 12 h, the median dosage of norepinephrine was relatively high (i.e., .08 [.04–.14] mcg/kg/min), dobutamine was used at a moderate dosage (i.e., median dosage from day 3 to 7 was 3 [2–5] mcg/kg/min), with a median VIS of 6 [4–12]. As shown in the figure, epinephrine, dopamine, and norepinephrine were used in the first postoperative days, and a relatively constant fraction of patients needed dobutamine and levosimendan in the following days.

Eighty-six (62%) patients needed vasoactive support for >12 h after surgery termination and thus were defined as VASO+, while the other 52 (38%) patients—who did not require vasoactive support throughout the overall ICU stay or required vasoactive support just in the first 12 h after ICU admission—were defined as VASO− patients. Among the 86 VASO+ patients, we documented four cases of secondary shock. Respectively, two cases of postoperative sepsis, occurring on postoperative day 3 and 4, and two cases of surgical revision, which occurred both on day 2. Vasopressor support by means of noradrenaline and adrenaline were ongoing at ICU admission (i.e., prior to septic shock
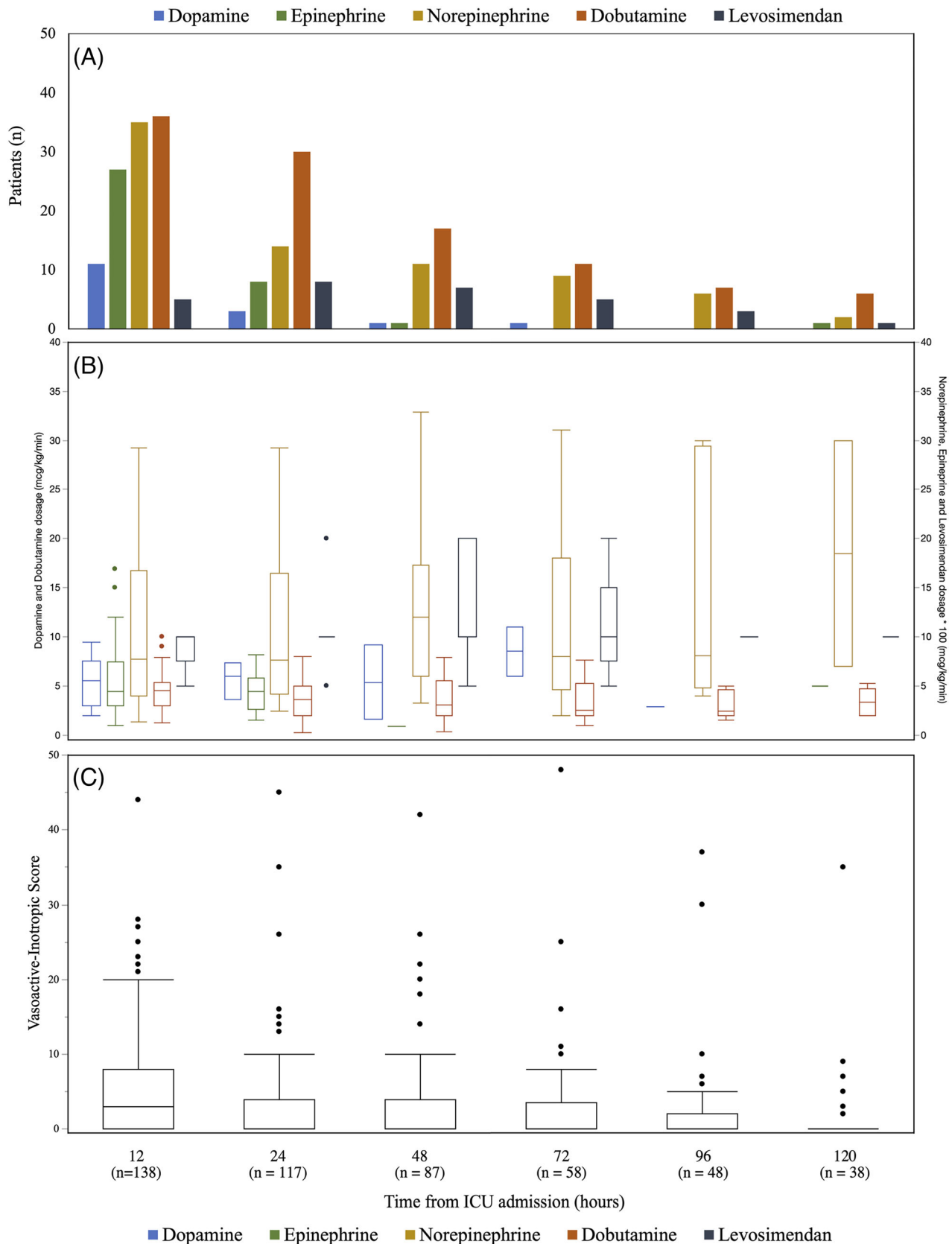
FIGURE 1 Vasoactive and Inotropic support after lung transplantation. Panel A. Number of patients treated with the different vasopressors. Each histogram represent the total number of patients treated with each vasopressor. Panel B. Vasopressor dosage. Box-plots (median, interquartile range, and outliers). Please refer to the left and right vertical axis, for dopamine and dobutamine versus norepinephrine, epinephrine, and levosimendan dosages, respectively. Panel C. Vasoactive-Inotropic score. Box-plots (median, interquartile range, and outliers). Data are represented until the 7th postoperative day. At-risk patients are in brackets.

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TABLE 1 Patients' characteristics.

		Overall (n = 138)	VASO+ (n = 86, 62%)	VASO− (n = 52, 38%)	p-value	OR (95% CI)
At enlistment for LUTX	Sex (female)	61 (44%)	38 (44%)	23 (44%)	.996	1.00 (.50–2.00)
	Age (years)	41 [28–55]	44 [32–57]	33 [25–48]	**.005**	**1.04 (1.01–1.06)**
	BMI (kg/m^2)	21.2 [18.7–24.5]	21.3 [19–25.2]	20.7 [18.3–23.5]	.123	1.07 (.97–1.17)
	Lung allocation score	40.81 [36.58–48.51]	42.62 [37.24–48.51]	39.68 [34.72–50.02]	.115	1.02 (.99–1.05)
	Cystic fibrosis	74 (54%)	37 (43%)	37 (71%)	**.001**	**.30 (.14–.63)**
	Heart rate (bpm)	80 [73–92]	80 [72–90]	80 [74–95]	.753	.99 (.97–1.02)
	Mean PAP (mm Hg)	22 [19–28]	22 [18–27]	23 [20–29]	.722	.99 (.94–1.03)
	Mean PAP ≥ 25 mm Hg	40 (29%)	25 (29%)	15 (29%)	.997	1.01 (.47–2.16)
	WP (mm Hg)	9 [6–12]	9 [6–12]	10 [7–13]	**.030**	**.90 (.81–.99)**
	Cardiac Index (lt/min/m^2)	3.2 [2.9–3.6]	3.1 [2.8–3.6]	3.2 [2.9–3.6]	.430	1.05 (.67–1.64)
	LVEF (%)	60 [57–65]	60 [57–64]	61 [58–67]	.062	.93 (.87–1.01)
	RVEF (%)	49 [41–55]	48 [41–55]	50 [42–55]	.131	.97 (.93–1.01)
	Left lung perfusion (%)	46 [37–56]	47 [39–57]	46 [33–56]	.259	1.01 (.99–1.03)
Surgery	Urgent LUTx	10 (7%)	7 (8%)	3 (6%)	.597	1.45 (.35–5.68)
	ECMO bridge	12 (9%)	8 (9%)	4 (8%)	.743	1.23 (.35–4.30)
	Waiting list time (days)	145 [59–314]	148 [62–270]	140 [53–358]	.122	.99 (.99–1.00)
	Intraoperative ECMO	76 (55%)	53 (62%)	23 (44%)	**.046**	**2.02 (1.01–4.07)**
	Cold ischemia time total (min)	887 [734–1094]	928 [775–1193]	802 [677–920]	**.005**	**1.01 (1.00–1.02)**
	Warm ischemia time total (min)	148 [129–165]	154 [132–170]	141 [124–158]	**.021**	**1.01 (1.00–1.02)**
Donor	OTO score	3 [1–5]	3 [2–5]	1 [1–3]	**<.001**	**1.26 (1.08–1.48)**
	Donor type (DCD) (n)	14 (11%)	11 (13%)	3 (6%)	.182	2.34 (.62–8.84)
	Ex vivo lung perfusion	27 (20%)	19 (22%)	8 (15%)	.329	1.55 (.62–3.87)
	ECMO needed after surgery	21 (15%)	18 (21%)	3 (6%)	**.010**	**4.32 (1.20–15.49)**

Note: Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. VASO+: patients treated with vasopressors; VASO−: patients not treated with vasopressors. Statistically significant differences are highlighted in bold.
Abbreviations: BMI, body mass index; CI, confidence interval; DCD, donor after cardiac death; ECMO, extracorporeal membrane oxygenation; LUTX, lung transplantation; LVEF, left ventricular ejection fraction; OR, odds ratio; PAP, pulmonary artery pressure; RVEF, right ventricular ejection fraction; WP, wedge pressure.

and hemorrhage), and thus were not excluded from the analysis. No case of anaphylactic shock was documented. No cardiac ischemia, pericarditis, or ventricular tachyarrhythmias, and pulmonary venous anastomotic–related dysfunction or torsion were documented. The remaining 82 patients did not have other apparent causes of hemodynamic impairment and subsequent need for vasopressor support. Finally, in seven (8%) patients we documented a simultaneous (i.e., occurring during the same 24 h timepoint) increase in PEEP—of a median of 2 (2–4) cm H_2O—and vasopressor introduction. Most of the VASO+ patients commenced vasoactive support at ICU admission (i.e., median time from ICU admission to vasoactive introduction of 0 [0–0] days, maximum 3 days). The median length of vasoactive support was 3 [2–4] days for VASO+ patients.

See Table 1 for a detailed description of the pre-operative and intraoperative characteristics of the two cohorts. VASO+ patients were older, less frequently affected by cystic fibrosis, received a less suitable graft (i.e., higher Oto score, longer ischemic times), and suffered a more complicated surgery (i.e., longer surgery, need for intraoperative ECMO support).

See Tables S1 and S2 (Additional Results, Supplementary Material) for a detailed description of the two cohorts at ICU admission and 12 h after admission. Of note, at ICU admission after surgery, VASO+ patients had lower arterial pressure and cardiac index with higher lactate concentration. After the first 12 h, hemodynamics was normalized, with VASO+ patients receiving higher—but still restrictive—fluid balance (i.e., 522 vs. 130 mL, p = .018). For a detailed longitudinal depiction of fluid balance, lactate concentration, and red blood cells use see Figure S1 (Additional Results, Supplementary Material), and for a detailed longitudinal depiction of major hemodynamic variables (i.e., cardiac output, mean arterial pressure, systemic vascular resistances, and mixed venous saturation) see Figure S2 (Additional Results, Supplementary Material)

Moreover, at both the timepoints, VASO+ had worse graft oxygenation. Indeed, PaO_2/FiO_2 was 253 [194–334] versus 334 [254–374] mm Hg (p = .002) at ICU admission and 273 [230–347] versus 326 [293–382] mm Hg at 12 h after ICU admission (p < .001), in VASO+ and VASO− patients, respectively. At 12 h, VASO + patients were more frequently ventilated in controlled mode and needed a higher level

TABLE 2 Risk factors analysis.

	Total (n = 138)	VASO + (n = 86, 62%)	VASO− (n = 52, 38%)	*p*-value	OR (95% CI)
Sex (female)	61 (44%)	38 (44%)	23 (44%)	.483	.74 (.32–1.72)
BMI (kg/m^2)	21.2 [18.7–24.5]	21.3 [19–25.2]	20.7 [18.3–23.5]	.970	1.00 (.89–1.12)
Lung allocation score	40.81 [36.58–48.51]	42.62 [37.24–48.51]	39.68 [34.72–50.02]	.723	.99 (.96–1.03)
Cystic fibrosis	74 (54%)	37 (43%)	37 (71%)	**.003**	**.24 (.09–.62)**
Oto score	3 [1–5]	3 [2–5]	1 [1–3]	**.020**	**1.22 (1.03–1.45)**
Cold ischemia time (min)	887 [734–1094]	928 [775–1193]	802 [667–920]	**.031**	**1.01 (1.00–1.02)**
Intraoperative ECMO	76 (55%)	53 (62%)	23 (44%)	.112	1.99 (.85–4.68)

Note: Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. VASO+: patients treated with vasopressors; VASO−: patients not treated with vasopressors. Statistically significant differences are highlighted in bold.
Abbreviations: BMI, Body Mass Index; CI, Confidence Interval; ECMO, Extracorporeal Membrane Oxygenation; OR, Odds Ratio.

TABLE 3 Patients' outcomes (matched cohorts).

		Total (n = 70)	VASO + (n = 35, 50%)	VASO− (n = 35, 50%)	*p*-value
Primary graft dysfunction	Grade 0	36 (51%)	12 (34%)	24 (68%)	**.015**
	Grade I	23 (33%)	14 (40%)	9 (25%)	
	Grade II	10 (14%)	8 (22%)	2 (6%)	
	Grade III	1 (1%)	1 (3%)	0 (0%)	
Mechanical ventilation duration (days)		1 [1–2]	1 [1–2]	1 [1–1]	**.010**
Atrial fibrillation		4 (6%)	2 (6%)	2 (6%)	1.000
Renal replacement therapy		2 (3%)	2 (6%)	0 (0%)	.500
ICU LOS (days)		3 [2–4]	3 [2–6]	2 [2–3]	**< .001**
Hospital LOS (days)		21 [19–26]	24 [19–31]	20 [19–22]	**.013**
In hospital mortality		3 (4%)	3 (9%)	0 (0%)	.250

Note: Data are presented as absolute frequency (% of the included patients) or as median and interquartile range. VASO+: patients treated with vasopressors; VASO−: patients not treated with vasopressors. Statistically significant differences are highlighted in bold.
Abbreviations: ICU, Intensive Care Unit; LOS, Length of Stay.

of PEEP (10 [8–12]) vs. 8 [7–10] cmH$_2$O, *p* = .015). Moreover, prolonged ECMO support after LUTX was necessary for 18 (21%) and 3 (6%) VASO+ and VASO− patients (*p* = .017, OR 4.3 (1.2–15.4)), respectively. For a detailed longitudinal depiction of ventilatory parameters (i.e., PEEP, plateau pressure, driving pressure) see Figure S3 (Additional Results, Supplementary Material).

See Table 2 for the risk factor analysis. At multivariate analysis, among the variable considered, the factors independently associated with vasoactive support need were higher Oto score and longer cold ischemia time. Being transplanted for cystic fibrosis was associated with a lesser risk for vasoactive/inotropic support after LUTX.

After the matching procedure, two cohorts of 35 patients each were identified. Tables S3–S5 (Additional Results, Supplementary Material) describe the matched cohorts' characteristics at enlistment and during surgery, at ICU admission, and 12 h after ICU admission, respectively. No clinically meaningful pre-operative and intraoperative difference in the two matched cohorts was documented.

Table 3 summarizes the outcomes of the two matched cohorts. Of note, patients suffering postoperative septic shock and surgical revision were excluded by the matching algorithm.

Three patients (4%) died before hospital discharge. All of them were VASO+ patients. VASO+ patients had a longer duration of mechanical ventilation, more prolonged ICU, and hospital LOS. No differences in adverse cardiac events were detected in the two groups, except for four cases of atrial fibrillation. VASO+ patients showed a higher risk of PGD. Indeed, 23 (65%) VASO+ patients versus 11 (31%) VASO− patients had PGD grade > 0 at 72 h (*p* = .004, OR 4.2 [1.54–11.2]).

Figure 2 represents Kaplan–Meier curves of the survival of the VASO+ versus VASO− matched cohorts (Klein and Moeschberger test *p* = .366). The cox-proportional hazard model did not show an increase in mortality in VASO+ patients (HR 1.19 (.40–3.55), *p* = .753).

In the VASO+ group, 28 out of 86 (33%) patients were treated with Levosimendan. Levosimendan infusion was started 3 [2–4] days after ICU admission. No initial bolus was ever administered, and levosimendan started as a continuous infusion at .10 mcg/kg/min rate that lasted 24 h in 19/28 (68%) patients. In four cases, it was administered at .20 and in five cases at .05 mcg/kg/min. In all patients except two, levosimendan infusion started after another inotropic drug was tested. Twenty-three patients (82%) were treated with dobutamine before levosimendan started.
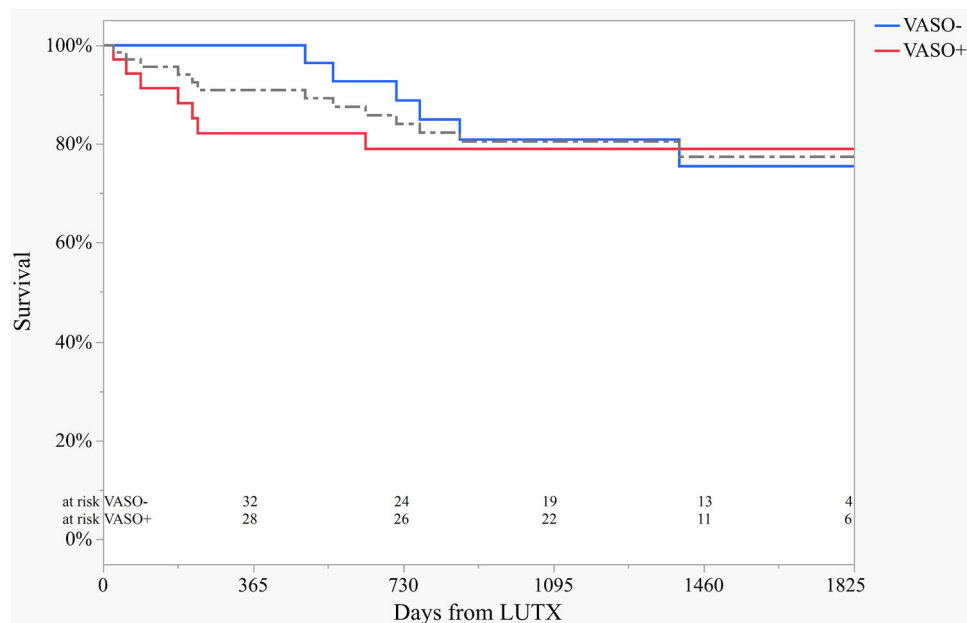
FIGURE 2   Probability of survival. Kaplan–Meier estimates of the unadjusted cumulative probability of survival among the two cohorts. Red and blue lines represent patients treated with vasopressors (VASO+) and patients not treated with vasopressors (VASO−), respectively. Grey dotted lines represent the overall population.

Twenty-one out of 28 (75%) LEVO+ versus 32 (55%) of LEVO— patients needed intraoperative ECMO support ($p = .071$). No other clinically relevant differences between LEVO + and LEVO− patients were recorded before and during surgery, at ICU admission, and 12 h after ICU admission (see Tables S6–S8, Additional Results, Supplementary Material). A matching procedure was attempted between LEVO+ and LEVO− cohorts, but only 11 viable couples were attained. Thus, analysis of the outcomes of the two cohorts was not considered appropriate. Notably, 11 (39%) LEVO+ versus 7 (12%) LEVO− suffered from atrial fibrillation during ICU stay ($p = .172$).

4 | DISCUSSION

This retrospective analysis described the postoperative vasoactive and inotropic needs after LUTX. We observed that vasoactive support after LUTX is frequent (i.e., >60%) and that both LUTX indication and receiving a graft of lesser quality independently increased the risk of postoperative vasoactive need. Furthermore, the need for vasoactive support was associated with worse gas exchanges at admission, higher incidence of PGD and worsened hospital survival. Finally, we first described the use of levosimendan in this patients' cohort.

While previous literature describing hemodynamic management during surgery is available,[20–22] especially for treating patients with pulmonary arterial hypertension,[23,24] data regarding the postoperative period is limited.[25] To date, high-grade guidelines for the postoperative management of LUTX patients are unavailable, and treatment is mainly guided by institutional experience.[26] Usually, at ICU admission, a judicious balance between careful fluid management and vasopressor use is necessary to achieve end-organ perfusion while avoiding

the risks of lung edema induced by reperfusion injury.[7] While a targeted protocol for hemodynamic management has been associated with reduced risk of PGD,[27] a lack of knowledge persists. In that single-center prospective interventional study, vasoactive support was guided by a standardized protocol. As compared to our data, similar dosages of norepinephrine were employed. Unfortunately, data regarding the dosages and proportion of use of other vasopressors and inodilators is not available in that analysis.

With our report, in a large cohort of patients treated with LUTX for mixed indications, we documented that at ICU admission, a significant portion (i.e., 25%) of patients had reduced cardiac index (<2.5 L/min/m^2) while the overall filling and pulmonary pressures were in the normal range, despite the continuation of vasopressor and inotropic support in the postoperative period. Vasopressors, such as norepinephrine, dopamine and epinephrine, were usually weaned in the first 48 h after ICU admission, possibly due to the progressive resolution of the vasoplegia subsequent to ischemia-reperfusion[28] and volemic optimization. Interestingly, a consistent part of the LUTX recipients was treated with inodilator support (i.e., dobutamine) to be continued and, eventually, as salvage therapy, with levosimendan. Of note, dobutamine and eventually levodimendan were never employed as first line agents, only after hypovolemia was corrected, and avoided in patients with ongoing or impending arrhythmias or high risk for rhythm disturbances. Moreover, inodilators are introduced always at minimal dosages, and no initial bolus is provided for levosimendan.

There may be several reasons for this particular pattern in hemodynamics after LUTX. Again, literature on the topic is scarce and mainly limited to managing patients with primary pulmonary hypertension.[24,29,30] In our cohort, we documented two cases of postoperative septic shock and hemorrhage requiring surgical revision,

and no case of anaphylactic shock. Since vasopressor support in these patients commenced prior to occurrence of the aforementioned complications, we did not exclude them from the analysis. Overall, we can exclude that anaphylaxis, septic shock, and hemorrhage could be the leading cause of postoperative hemodynamic impairment, at least in our cohort. Moreover, we did not document any postoperative coronary ischemic events; thus, we may exclude coronary disease as the pathophysiological cause of postoperative cardiac dysfunction. Regarding possible arrhythmic complications after surgery, we observed atrial fibrillation less frequently (i.e., 14%) than previously documented (i.e., 20%).[31] Thus, we exclude arrhythmias as possible causative agents of postoperative cardiac dysfunction after LUTX. We observed that LUTX indications different from cystic fibrosis (i.e., idiopathic pulmonary fibrosis, chronic obstructive pulmonary disease) were associated with an increased risk of postoperative vasoactive support, independently of enlistment age. This may be due to the increased incidence of pulmonary hypertension in those patients cohorts. Nevertheless, we did not find any association between preoperative pulmonary artery catheterization parameters and postoperative vasopressor need. Of note, a single patient in our cohort was enlisted for primary pulmonary hypertension. Thus, such observation cannot be applied to our cohort. Contrarily, we observed that several *graft* characteristics were independently associated with an increased risk of postoperative vasoactive support. Indeed, we documented that patients receiving a graft from a higher-risk donor (i.e., with a higher Oto score) or a graft suffering a longer cold ischemia time have an increased vasoactive need in ICU independently of pre-operative invasive catheterization parameters. Such observation suggests that ischemia-reperfusion injury may be at least in part causative of postoperative hemodynamic failure, leading to increased vasopressor use in the immediate postoperative period and subsequent inotropic support. This data are consistent with a large literature describing the inflammatory alterations occurring after LUTX,[32] and with a previous well-conducted study that documented the pathophysiological pathway through ischemia-reperfusion, proinflammatory cytokines storm, hemodynamic failure, and graft dysfunction.[33] Specifically, ischemia-reperfusion injury following lung transplant is associated with increased release of proinflammatory cytokines (i.e., interleukin 1β, tumor necrosis factor α, intercellular adhesion molecule 1), which have known detrimental cardiovascular effects, such as vasodilation and depression of myocardial contractility. Our work adds to this by describing an association between pre-implantation graft dysfunction and subsequent hemodynamic alterations. The observation that VASO+ patients had worse graft performance, increased need for invasive ventilation and ECMO, and earlier mortality further supports this hypothesis.

To assess the impact on these outcomes of the need for vasoactive support (as a proxy of postoperative hemodynamic failure), we chose an advanced propensity score matching the patient's cohorts. Of note, the cohorts were matched based on a set of covariates in which previous literature has documented impact outcomes after LUTX,[12–19] which we further screened out based on clinical meaningfulness and collinearity. From these data and previous literature, we thus hypothe-

size that ischemia/reperfusion injury might be the *primum movens* of a systemic inflammatory response leading to primary graft dysfunction, vasodilation, myocardial contractility impairment, and endothelial dysfunction. Nevertheless, the data from our study cannot confirm such a hypothesis, and further studies targeting the biological phenotyping of lung transplant recipients are necessary. While this is surely a compelling pathophysiological theory, several other more trivial reasons for the hemodynamic derangements we observed can be postulated. Indeed, increased ventilatory needs due to PGD may per se determine right ventricle dysfunction. Similarly, myocardial dysfunction may be subsequent to PGD owing to hypoxia and hypercapnia. Again, further studies are necessary to assess the causal relationships between hemodynamics and PGD.

A further interesting result of this report is the first extensive documentation of levosimendan use in the postoperative period. Previously, just a single-case report[34] depicted the use of levosimendan in this clinical scenario. Unfortunately, the limited number of patients did not allow us to conduct a propensity match analysis of the outcomes of patients treated with levosimendan. Thus, with our retrospective analysis, we cannot confirm or reject levosimendan's usefulness in treating postoperative cardiac failure. Further prospective interventional studies are necessary to assess the impact of levosimendan in the postoperative period of LUTX recipients. Still, this preliminary data are supportive of such an endeavor.

Our study has several limitations. First, with a retrospective cohort design, several potential confounding factors may not have been available during data analysis. Specifically, in our dataset, most of the intraoperative hemodynamic data (e.g., intraoperative need for vasopressors) were not suitable or adequately reported to be used as covariates. Moreover, with a retrospective study was not possible to discern the possible cause-effect relationship between PGD and inodilator use, and just an association could be observed. While on the one hand, we hypothesize that hemodynamic failure is concomitant with PGD and is part of the same physiopathological continuum, on the other hand, it cannot be excluded that PGD may be subsequent to the vasopressor and inodilator support. Further, prospective interventional studies are necessary to ascertain this association. Second, while echocardiographic analyses—which might have been of great use in determining the nature of postoperative cardiac dysfunction—were carried out in most of these patients, these analyses were carried out by different operators at variable time points, with diverse reporting. Thus, echocardiographic studies were not suited for this study. Further, prospective observational studies comprising a comprehensive echocardiographic evaluation are necessary to better describe the hemodynamic patterns of these patients' cohorts. Third, in our center, no fixed protocol is utilized for the hemodynamic management of patients who have undergone LUTX, and thus our observation may not apply to centers with different approaches.

In conclusion, vasoactive support frequently occurs after lung transplantation, especially in patients enlisted for LUTX for a diagnosis different from cystic fibrosis and receivers of grafts suffering longer cold ischemia time and from higher-risk donors. The need for vasoactive support is associated with a more complicated postoperative course.

Levosimendan may be a suitable option in these cases. Further prospective observational studies are necessary to elucidate if the association between indexes of ischemia/reperfusion and hemodynamic failure represent a possible treatable trait.

AUTHOR CONTRIBUTIONS

Vittorio Scaravilli and Amedeo Guzzardella contributed equally to the study and should be considered first co-authors. Vittorio Scaravilli and Amedeo Guzzardella conceived the study, led the study efforts, interpreted the data, and drafted the manuscript. Fabiana Madotto carried out statistical analyses and participated in data interpretation. Marco Bosone, Claudia Bonetti, and Valeria Musso carried out data acquisition and participated in data interpretation. Letizia Corinna Morlacchi, Valeria Rossetti, and Filippo Maria Russo participated in data acquisition and interpretation. Lorenzo Del Sorbo, Francesco Blasi, Mario Nosotti, Alberto Zanella, and Giacomo Grasselli interpreted the data. All authors drafted the manuscript, provided critical revision of the intellectual content, approved the final version of the paper, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

ORCID

Vittorio Scaravilli https://orcid.org/0000-0003-0877-7626

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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