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Association between pulmonary artery pulsatility and mortality after implantation of left ventricular assist device

Ali Akamkam ¹, Vincent Galand ², Marie Jungling ³, Clément Delmas ⁴, Camille Dambrin ⁵, Mathieu Pernot ⁶, Michel Kindo ⁷, Philippe Gaudard ⁸, Philippe Rouviere ⁹, Thomas Senage ¹⁰, Olivier Chavanon ¹¹, Marylou Para ¹², Vlad Gariboldi ¹³, Matteo Pozzi ¹⁴, Pierre-Yves Litzler ¹⁵, Gerard Babatasi ¹⁶, Olivier Bouchot ¹⁷, Costin Radu ¹⁸, Thierry Bourguignon ¹⁹, Nicolas D'Ostrevy ²⁰, Ramzi Abi Akar ²¹, Fabrice Vanhuysse ²², Maïra Gaillard ¹, Gilles Chatelier ²³, Audrey Fels ²³, Erwan Flecher ²⁴, Julien Guihaire ^{1 25 26}

¹ Department of Cardiovascular Surgery, Marie Lannelongue Hospital, Groupe Hospitalier Paris Saint Joseph, Le Plessis-Robinson, France.

² Department of Cardiology, University of Rennes, CHU Rennes, Rennes, France.

³ Department of Cardiac Surgery, Lille University Hospital, Heart-Lung Institute, Lille, France.

⁴ Department of Cardiology, University Hospital of Toulouse, Toulouse, France.

⁵ Department of Cardiovascular Surgery, University Hospital of Toulouse, Toulouse, France.

⁶ Haut-Lévêque Cardiological Hospital, Bordeaux II University, Bordeaux, France.

⁷ Department of Cardiovascular Surgery, University Hospitals of Strasbourg, Strasbourg, France.

⁸ Department of Anesthesiology and Critical Care Medicine, PhyMedExp, University of Montpellier, INSERM, CNRS, CHU Montpellier, Montpellier, France.

⁹ Department of Cardiac Surgery, University of Montpellier, CHU Montpellier, Montpellier, France.

¹⁰ Department of Cardiology and Heart Transplantation Unit, CHU Nantes, Nantes, France.

¹¹ Department of Cardiology and Cardiovascular Surgery, CHU Michallon, Grenoble, France.

¹² Department of Cardiology and Cardiac Surgery, Bichat-Claude Bernard Hospital, Paris, France.

¹³ Department of Cardiac Surgery, La Timone Hospital, Marseille, France.

¹⁴ Department of Cardiac Surgery, 'Louis Pradel' Cardiologic Hospital, Lyon, France.

¹⁵ Department of Cardiology and Cardiovascular Surgery, Hospital Charles Nicolle, Rouen, France.

¹⁶ Department of Cardiology and Cardiac Surgery, University of Caen and University Hospital of Caen, Caen, France.

¹⁷ Department of Cardiology and Cardiac Surgery, University Hospital François Mitterrand, Dijon, France.

¹⁸ Department of Cardiology and Cardiac Surgery, AP-HP CHU Henri Mondor, Créteil, France.

¹⁹ Department of Cardiac Surgery, Tours University Hospital, Tours, France.

²⁰ Department of Cardiac Surgery and Cardiology, CHU Clermont-Ferrand, Clermont-Ferrand, France.

²¹ Department of Cardiovascular Surgery, European Georges Pompidou Hospital, Paris, France.

²² Department of Cardiology and Cardiac Surgery, CHU de Nancy, Hôpitaux de Brabois, Nancy, France.

²³ Department of Clinical Research, Hôpital Paris Saint-Joseph, Groupe Hospitalier Paris Saint Joseph, Paris, France.

²⁴ Department of Thoracic and Cardiovascular Surgery, University of Rennes, CHU Rennes, Rennes, France.

²⁵ School of Medicine, University of Paris Saclay, Le Kremlin-Bicêtre, France.

²⁶ Inserm U999, Marie Lannelongue Hospital, Le Plessis-Robinson, France.

Keywords:

Circulatory assist devices; Database; Haemodynamics; Heart failure; Left ventricular assist device; Ventricle, right.

Abstract

Aims:

Right ventricular failure after left ventricular assist device (LVAD) implantation is a major concern that remains challenging to predict. We sought to investigate the relationship between preoperative pulmonary artery pulsatility index (PAPi) and mortality after LVAD implantation.

Methods and results:

A retrospective analysis of the ASSIST-ICD multicentre registry allowed the assessment of PAPi before LVAD according to the formula [(systolic pulmonary artery pressure - diastolic pulmonary artery pressure)/central venous pressure]. The primary endpoint was survival at 3 months, according to the threshold value of PAPi determined by the receiver operating characteristic (ROC) curve. A multivariate analysis including demographic, echographic, haemodynamic, and biological variables was performed to identify predictive factors for 2 year mortality. One hundred seventeen patients were included from 2007 to 2021. The mean age was 58.45 years (± 13.16), with 15.4% of women (sex ratio 5.5). A total of 53.4% were implanted as bridge to transplant and 43.1% as destination therapy. Post-operative right ventricular failure was observed in 57 patients (48.7%), with no significant difference between survivors and non-survivors at 1 month (odds ratio 1.59, $P = 0.30$). The median PAPi for the whole study population was 2.83 [interquartile range 1.63-4.69]. The threshold value of PAPi determined by the ROC curve was 2.84. Patients with $\text{PAPi} \geq 2.84$ had a higher survival rate at 3 months [$\text{PAPi} < 2.84$: 58.1% [46.3-72.8%] vs. $\text{PAPi} \geq 2.84$: 89.1% [81.1-97.7%], hazard ratio (HR) 0.08 [0.02-0.28], $P < 0.01$], with no significant difference after 3 months (HR 0.67 [0.17-2.67], $P = 0.57$). Other predictors of 2 year mortality were systemic hypertension (HR 4.22 [1.49-11.97], $P < 0.01$) and diabetes mellitus (HR 4.90 [1.83-13.14], $P < 0.01$). LVAD implantation as bridge to transplant (HR 0.18 [0.04-0.74], $P = 0.02$) and heart transplantation (HR 0.02 [0.00-0.18], $P < 0.01$) were associated with a higher survival rate at 2 years.

Conclusions:

Preoperative $\text{PAPi} < 2.84$ was associated with a higher risk of early mortality after LVAD implantation without impacting 2 year outcomes among survivors.

Introduction

Long-term mechanical left ventricular assist devices (LVADs) are implanted in selected patients with advanced heart failure refractory to optimal medical therapy.^{1–3} This procedure remains associated with high post-operative morbidity and mortality⁴ despite technological advances over the past two decades including the last generation of intra-corporeal centrifugal pumps. The 1 year survival rate after LVAD implantation currently ranges between 65% and 83%, according to recent clinical series and registries.^{5–8}

Right ventricular failure (RVF) occurs in 10–40% of cases during the early post-operative course after LVAD implantation.^{9–14} The definition and severity of post-LVAD RVF were standardized by the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry in 2016.¹⁵ This classification is based on clinical, biological, and haemodynamic (HD) variables and allows for ranging RVF as mild, moderate, severe, or severe acute. The physio-pathology of post-LVAD RVF is complex and multifactorial. The initiation of LVAD rapidly improves systemic venous re-turn, thus increasing right ventricular (RV) preload. That may unmask pre-existing RV dysfunction and worsen tricuspid regurgitation due to annulus dilatation. The leftward shift of the interventricular septum at LVAD initiation further leads to impaired RV contraction. Pericardial opening, volumic expansion, and associated valvular procedures with prolonged aortic cross-clamping during LVAD implantation also have a negative impact on RV function.^{16–18}

RVF markedly impairs LVAD preload and may therefore result in cardiogenic shock and death in the most severe cases.¹⁹ Identification of patients at risk of post-LVAD RVF is therefore of major interest. RV function is usually assessed by echographic and HD parameters, such as tricuspid annular plane systolic excursion (TAPSE), fractional area change (FAC), right ventricular stroke work index (RVSWI), pulse wave, pulmonary artery pressure (PAP), or central venous pressure.^{20–22} All these variables depend on loading conditions and may not accurately predict the post-LVAD RVF. The pulmonary artery pulsatility index (PAPi) has recently emerged as a robust parameter to assess RV function independently from left ventricular (LV) function.^{22–26} PAPi has already been evaluated preoperatively in patients requiring LVAD. Several studies have shown the correlation between a decreased PAPi and the occurrence of post-LVAD RVF.^{22–24, 27} The primary endpoint of the published studies was the occurrence of RVF or the need for right ventricular mechanical circulatory support (RV-MCS). To our knowledge, no study has reported the relationship between PAPi and mortality after LVAD implantation.

The ASSIST-ICD registry was initially established to investigate risk factors for ventricular arrhythmia after LVAD implantation. This is a real-life national registry considering the early outcomes of LVAD implantation in France between 2007 and 2016.⁶ In the present study, we investigated the relationship between preoperative PAPi and mortality after LVAD implantation. We aimed to define a threshold value of PAPi that could discriminate patients at high risk of early mortality within 3 months after LVAD implantation.

Material and methods

Design and population of the study

We performed a retrospective study combining data from a national multicentre registry (ASSIST-ICD) and our institutional database. The ASSIST-ICD registry included 671 patients implanted with an LVAD between 2007 and 2016 in 18 cardiac surgery centres in France. Moreover, 29 patients were implanted with an LVAD between 2017 and 2021 in our institution (Marie Lannelongue Hospital, Paris Saclay University, France). Five hundred sixty-one patients did not have preoperative pulmonary HD measurements and were not included in our study. Furthermore, 22 patients did not meet inclusion criteria and were not considered for study analysis (see below). A total of 117 patients implanted with an LVAD between 2007 and 2021 in 18 cardiac surgery centres were included for analysis (Figure 1).

Inclusion and exclusion criteria

The inclusion criteria were as follows: age ≥ 18 years; patients referred for LVAD implantation; known survival status; and pulmonary HD measurements performed prior to LVAD implantation.

The exclusion criteria were as follows: patients referred for LVAD implantation under short-term mechanical circulatory support (MCS) such as extracorporeal membrane oxygenation (ECMO) without previous pulmonary HD measurements; a missing preoperative ECMO implantation date; and pulmonary HD measurements performed more than 6 months before LVAD implantation.

Data collection

Demographic data were collected, including age, gender, body mass index, cardiovascular risk factors (smoking, high blood pressure, dyslipidaemia, and diabetes mellitus), past history of cardiac surgery, and the need for short-term MCS before LVAD implantation such as ECMO, Impella, and intra-aortic balloon pump (IABP).

Preoperative echographic data were collected, including left ventricular ejection fraction (LVEF), right ventricular ejection fraction (RVEF), TAPSE, S' wave, pre-existing mitral regurgitation, tricuspid regurgitation, aortic stenosis, and aortic regurgitation.

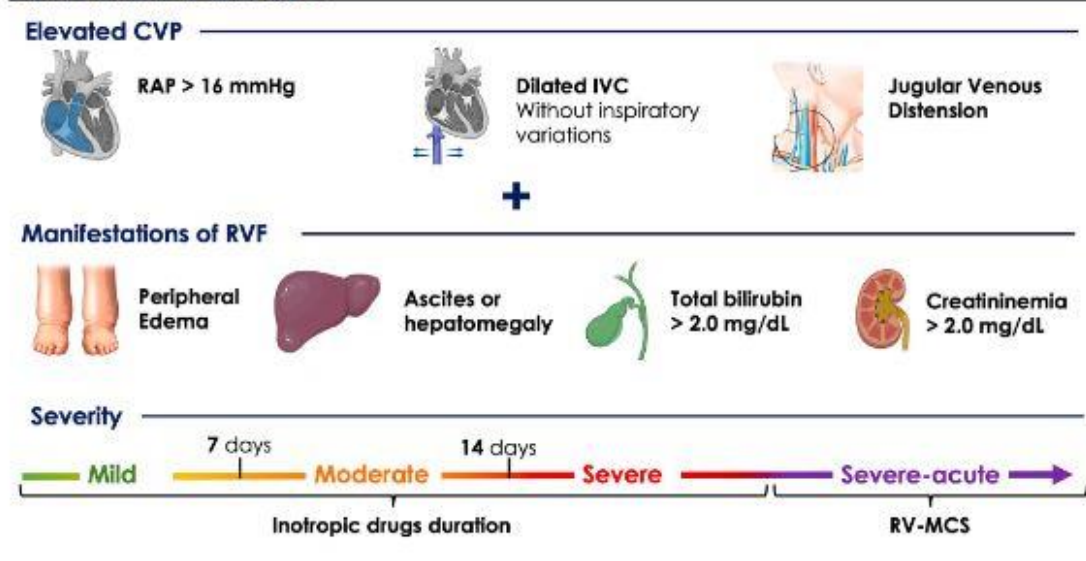
Assessment of pulmonary HD before LVAD implantation was investigated to collect right atrial pressure (RAP), systolic right ventricular pressure (sRVP), diastolic right ventricular pressure (dRVP), tele-diastolic right ventricular pressure (tdRVP), systolic pulmonary artery pressure (sPAP), diastolic pulmonary artery pressure (dPAP), mean pulmonary artery pressure (mPAP), pulmonary capillary wedge pressure (PCWP), cardiac output and cardiac index, and pulmonary vascular resistance (PVR). PAPI was defined as the ratio between pulmonary artery pulsatility and RAP as follows: $PAPi = (sPAP - dPAP) / RAP$.

Preoperative biological data were collected, including brain natriuretic peptide (BNP), N-terminal pro-brain natriuretic peptide, creatininaemia, total bilirubin, and natraemia.

The incidence of post-LVAD RVF was reported. We used the 2016 INTERMACS classification to define post-LVADR VF.¹⁵ The diagnosis was based on elevated RAP (RAP > 16 mmHg, dilated inferior vena cava, or jugular venous distension) associated with clinical (peripheral oedema, ascites, and hepatomegaly) or biological (bilirubin > 2.0 mg/dL and creatinine > 2.0 mg/dL) features of venous congestion and low cardiac output. This condition required the initiation of therapeutics to improve both myocardial contractility and RV loading conditions. RVF was considered mild if the duration of inotropic drugs was < 7 days, moderate between 7 and 14 days, and severe beyond 14 days. The use of short-term RV-MCS classified RVF as severe acute (Figure 2).

The occurrence of post-operative events was compared between survivors and non-survivors: incidence of renal re-placement therapy (RRT), need for ECMO support after LVAD implantation, incidence of long-term complications (drive line infection, LVAD infection, LVAD dysfunction, pump thrombo-sis, stroke, and bleeding), and intensive care unit (ICU) length of stay and hospital length of stay.

Figure 2 Definition and severity of post-left ventricular assist device right ventricular failure (RVF) according to the Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) registry. CVP, central venous pressure; IVC, inferior vena cava; RAP, right atrial pressure; RV-MCS, right ventricular mechanical circulatory support.



Statistical analysis

Quantitative variables were described as means \pm standard deviations or medians and interquartile ranges [Q1–Q3], depending on the distribution of the variables, and compared using Student's *t*-test or Wilcoxon's test. Qualitative variables were described as numbers (proportions) and compared using χ^2 test or Fisher's test, depending on the conditions of application. A receiver operating characteristic (ROC) curve with an assessment of the area under the curve (AUC) was performed to determine the threshold value of PAPI for predicting 3 month mortality. Univariate and multivariate analyses of demographic, biological, echographic, and HD data were performed to assess additional predictive factors for mortality. Predictive factors of mortality were evaluated using logistic regression. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated with univariate and multivariate models. For multivariate analysis, variables of interest were selected according to their statistical significance in the univariate analysis (critical P-value to enter the model:0.10). Post-operative survival was analysed by the Kaplan–Meier approach. A comparative analysis of survival curves was performed using the log-rank test. Statistical analyses were performed with R software [R Core Team (2021). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL:<https://www.R-project.org/>]. All tests were two-tailed, and a P-value<0.05 was considered statistically significant.

The primary endpoint was the 3 month survival rate according to the threshold value of PAPI determined by the ROC curve. We first performed an ROC curve evaluating the PAPI as a predictor of 3 month mortality. We then selected the value of PAPI with the best Youden index as the threshold value to compare the survival curves.

Ethics statement

The investigation conforms with the principles outlined in the Declaration of Helsinki. The ASSIST-ICD registry received approval from the Commission Nationale de l'Informatique et des Libertés (CNIL No. 915649). The study was also registered in the ClinicalTrials.gov database (NCT02873169). The study protocol was reviewed and approved by our institutional re-view board (registered as IRB-00012157). All living patients received a letter of non-opposition at their personal address with a 1 month deadline for response. No objections from patients were reported.

Results

Patient characteristics

The demographic characteristics of the study population are listed in Table 1.

The mean age at diagnosis was 58.4 ± 13.2 years, with a sex ratio of 5.5 men to 1 woman. Systemic hypertension (53.8% vs. 26.1%, $P < 0.01$) and diabetes mellitus (40.4% vs. 16.9%, $P < 0.01$) were more frequently observed among non-survivors. The proportion of smokers was 58.1% in our population, without difference between groups.

Seven patients in the registry had a past history of cardiac surgery before LVAD implantation, including four coronary artery bypass graftings, one coronary artery bypass grafting associated with mitral annuloplasty, one mechanical aortic valve replacement, and one systemic to pulmonary bypass using the Blalock–Taussig technique.

The median time from diagnosis of heart failure to LVAD implantation was six times longer in non-survivors compared with survivors ($P= 0.01$).

Most of the patients in our study were implanted with an LVAD either as a bridge to transplant (53.4%) or as a destination therapy (43.1%). Destination therapy was the main pre-operative project among non-survivors (52.9%), while it was considered in 35.4% of cases among survivors.

Thirty-two patients (27.3%) received short-term MCS before surgery, including 11 Impella, 5 IABP, and 16 veno-arterial ECMO, with no difference between groups.

Preoperative ventricular arrhythmias were more frequently observed in non-survivors. Preoperative use of inotropes was required in 88% of cases. Among these patients, 88.3% required dobutamine.

There was no significant difference between groups considering preoperative ultrasound variables for LV and RV functions. Similarly, preoperative pulmonary HDs were not different between groups.

Considering preoperative biological features, the median BNP level ($P= 0.02$) and the mean creatinine level ($P= 0.01$) were significantly higher in non-survivors, with a mean creatinine level of 147.9 μ mol/L (SD: 78.7) and a median BNP of 220 ng/mL [73–282].

Analysis of pulmonary artery pulsatility index and threshold value to predict 3 month mortality

The PAPI value was known in 111 out of 117 patients. The median value of preoperative PAPI in the overall cohort was 2.83 [1.63–4.69]. Preoperative PAPI was higher in survivors than in non-survivors (2.90 [2.03–4.94] vs. 2.42 [1.57–4.20], $P= 0.23$). ROC curve analysis of PAPI as a predictor of 3 month mortality showed an AUC of 0.68 [0.57–0.80]. The value with the best Youden index was 2.84, with a sensitivity of 78.2%, a specificity of 56.8%, a positive predictive value of 46.8%, and a negative predictive value of 84.2% (Figure 3).

Post-operative outcomes

The median follow-up for the study population was 9.23 months [2.76–18.07]. The median length of stay in the ICU was 20 days [11.0–35.0] for non-survivors and 16 days [9.00–27.50] for survivors ($P= 0.23$). The median length of hospital stay was 53 days [30.2–75.2] for non-survivors without a significant difference with survivors (53 days [41.5–70.5], $P= 0.44$).

RVF following LVAD implantation was observed in 57 patients (48.7%), with no significant difference between survivors and non-survivors (OR 1.59, $P= 0.30$). Considering the severity of RVF in these patients, 24.6% were mild, 15.8% were moderate, 17.5% were severe, and 42.1% were severe acute. The median duration of inotrope use was 6 days [3.00–14.00]. Nine patients (8.1%) required post-operative veno-arterial ECMO support with a mean duration of

5 days [2.0–11.0]. Overall survival rates were 84.6% [78.2–91.6%] and 63.3% [54.5–73.5%] at 1 month and 1 year, respectively.

The 1, 2, 3, and 12 month post-operative survival rates were 73.1% [78.2–91.6%] vs. 96.4% [91.5–100%], 62.1% [50.5–73.3%] vs. 90.9% [83.6–98.8%], 58.1% [46.3–72.8%] vs. 89.1% [81.1–97.7%], and 54.8% [42.6–70.6%] vs. 69.0% [56.9–83.7%], respectively, for patients with preoperative PAPI < 2.84 compared with those with PAPI ≥ 2.84 (log-rank test, P = 0.048). Survival at 3 months was significantly better when the PAPI was ≥ 2.84 in multivariate analysis [hazard ratio (HR) 0.08 [95% CI 0.02–0.28], P < 0.001] (Table 2). However, beyond 3 months, this difference was no longer statistically significant (HR 2.32 [0.76–7.14], P = 0.14).

Comparative survival according to the PAPI threshold value of 2.84 is presented in Figure 4.

Preoperative and post-operative determinants of 2 year survival

Univariate analyses of preoperative and post-operative predictive factors of 2 year survival are presented in Figures 5 and 6.

Among preoperative patients' characteristics, female gender (OR 0.34 [0.12–0.98], P = 0.04), high blood pressure (OR 0.30 [0.14–0.66], P < 0.01), obesity (OR 0.32 [0.10–1.00], P = 0.04), and diabetes mellitus (OR 0.30 [0.13–0.71], P < 0.01) were associated with an increased risk of mortality at 24 months after LVAD implantation. Similarly, preoperative ventricular arrhythmias (OR 0.38 [0.15–1.00], P = 0.04), pre-operative amiodarone therapy (OR 0.41 [0.19–0.88], P = 0.02), and LVAD implantation as destination therapy (OR 0.44 [0.20–0.94], P = 0.04) were found to be predictors of mortality.

Considering preoperative biomarkers, only a BNP level higher than 145 ng/mL was predictive of 2 year mortality (OR 0.74 [0.34–1.59], P < 0.01). Creatininaemia > 112 μmol/L (OR 0.56 [0.26–1.18], P = 0.12) and total bilirubin > 16.5 mg/dL (OR 0.74 [0.34–1.59], P = 0.44) were not associated with an increased risk of mortality at 24 months.

Preoperative variables of pulmonary HD such as RAP (OR 0.70 [0.33–1.47], P = 0.35), mPAP (OR 1.11 [0.53–2.31], P = 0.79), PCWP (OR 1.46 [0.69–3.07], P = 0.32), and PVR (OR 0.62 [0.29–1.32], P = 0.21) were not associated with mortality after LVAD implantation.

Even PAPI > 2.84 (OR 1.49 [0.70–3.16], P = 0.30) was not predictive of 2 year survival.

Among post-operative characteristics, RRT (OR 0.27 [0.11–0.61], P < 0.01), veno-arterial ECMO (OR 0.19 [0.04–0.93], P = 0.04), and epinephrine (OR 0.38 [0.17–0.83], P = 0.01) requirements were predictive of 2 year mortality

Heart transplantation after LVAD implantation was associated with better survival at 2 years (OR 24.24 [5.44–108.07], P < 0.001).

Table 1 Patients' characteristics

	N	Total (N = 117)	Non-survivors (N = 52)	Survivors (N = 65)	P**
Age	111	58.4 (13.2)	62.3 (9.6)	55.2 (14.8)	<0.01
Sex ^a					0.04
Men	117	99 (84.6%)	40 (76.9%)	59 (90.8%)	
Women	117	18 (15.4%)	12 (23.1%)	6 (9.3%)	
Cardiovascular risk factor ^d					
High blood pressure	117	45 (38.5%)	28 (53.8%)	17 (26.2%)	<0.01
Diabetes	117	32 (27.3%)	21 (40.4%)	11 (16.9%)	<0.01
Dyslipidaemia	117	49 (41.9%)	18 (34.6%)	31 (47.7%)	0.15
Smoker	117	68 (58.1%)	28 (53.8%)	40 (61.5%)	0.40
BMI (kg/m ²) ^a					
Mean (SD)	117	25.4 (4.4)	26.4 (4.9)	24.7 (3.8)	0.04
Normal (18.5–24.9)	117	58 (49.6%)	20 (38.5%)	38 (58.5%)	0.07
Obesity (>30.0)	117	16 (13.7%)	10 (19.2%)	6 (9.2%)	
Overweight (25.0–29.9)	117	43 (36.7%)	22 (42.3%)	21 (32.3%)	
Prior cardiac surgery ^a	117	7 (60%)	4 (7.7%)	3 (4.6%)	0.70
Aetiology ^{a,b}					0.50
DCM	63	33 (52.4%)	14 (50.0%)	19 (54.2%)	
ICM	63	15 (23.8%)	8 (28.5%)	7 (20.0%)	
HCM	63	4 (6.3%)	0 (0.0%)	4 (11.4%)	
Others	63	8 (12.7%)	4 (14.2%)	4 (11.4%)	
INTERMACS profile ^a					0.75
INTERMACS 1	117	16 (13.7%)	7 (13.5%)	9 (13.9%)	
INTERMACS 2	117	12 (10.3%)	8 (15.4%)	4 (3.4%)	
INTERMACS 3	117	75 (64.1%)	30 (57.7%)	45 (69.2%)	
INTERMACS 4–7	117	14 (12.0%)	7 (13.5%)	7 (13.5%)	
Preoperative MCS ^a					
Impella	117	11 (9.4%)	6 (11.5%)	5 (7.7%)	0.54
IABP	117	5 (4.27%)	3 (5.8%)	2 (3.1%)	0.65
ECMO	117	16 (13.7%)	7 (13.5%)	9 (13.9%)	0.95
Preoperative arrhythmia ^a					
AF	117	65 (55.6%)	33 (63.5%)	32 (49.2%)	0.12
VA < 30 days	117	22 (18.8%)	14 (26.9%)	8 (12.3%)	0.04
Preoperative medication use ^a					
CRT	117	34 (29.1%)	17 (32.7%)	17 (26.1%)	0.44
Beta-blockers	116	83 (71.5%)	38 (73.1%)	45 (70.3%)	0.74
Cardarone	116	60 (52.6%)	33 (64.7%)	27 (42.9%)	0.02
ARBs	116	19 (16.4%)	9 (17.3%)	10 (15.6%)	0.81
ACE inhibitors	116	64 (55.2%)	31 (59.6%)	33 (51.6%)	0.39
MRAs	116	76 (65.5%)	31 (59.6%)	45 (70.3%)	0.23
Diuretics	116	107 (92.2%)	47 (90.4%)	60 (93.7%)	0.51
Preoperative inotropic drugs ^a					
Requirement	117	103 (88.0%)	45 (86.5%)	58 (89.2%)	0.66
Dobutamine	117	91 (77.8%)	38 (73.1%)	53 (81.5%)	0.27
Levosimendan	117	24 (20.5%)	12 (23.1%)	12 (18.5%)	0.54
Norepinephrine	117	13 (11.1%)	6 (11.5%)	7 (10.8%)	0.90
Epinephrine	117	4 (3.4%)	2 (3.8%)	2 (3.1%)	>0.99
LVAD implantation					
Age ^c	111	57.9 (13.1)	61.6 (9.6)	54.7 (14.8)	0.01
Delay diagnosis to surgery ^c	117	1447 [124–4531]	2952 [1085–5126]	491 [54–3445]	<0.01
Combined surgery ^a	116	14 (12.1%)	5 (9.8%)	9 (13.8%)	0.51
Therapeutic project ^c					0.04
BTT	116	62 (53.4%)	21 (41.2%)	41 (63.1%)	
DT	116	50 (43.1%)	27 (52.9%)	23 (35.4%)	
BTR	116	1 (0.9%)	1 (2.0%)	0 (0.0%)	
BTD	116	3 (2.6%)	2 (3.9%)	1 (1.5%)	
Preoperative echography					
LVEF (%) ^c	114	20.2 (6.8)	19.7 (7.2)	20.5 (6.4)	0.69
RVEF (%) ^c	91	68.8 (10.1)	70.3 (11.0)	67.6 (9.4)	0.21
TAPSE (mm) ^c	82	15.7 (4.7)	16.0 (5.0)	15.6 (4.6)	0.82
S' wave (mm) ^d	85	10.0 [8.0–12.0]	11.0 [8.1–13.0]	10.0 [8.0–11.0]	0.22
sPAP (mmHg) ^c	100	52.3 (14.7)	54.1 (15.0)	51.0 (14.5)	0.56
Tricuspid regurgitation ≥ 2 ^a	96	41 (42.7%)	18 (43.9%)	23 (41.8%)	0.84
Mitral regurgitation ≥ 2 ^a	109	77 (70.6%)	32 (66.7%)	45 (73.8%)	0.42
Aortic stenosis ^a	111	3 (2.7%)	2 (4.1%)	1 (1.6%)	0.58
Aortic regurgitation ^a	108	22 (20.4%)	11 (23.4%)	11 (18.0%)	0.49

Table 1 (continued)

	N	Total (N = 117)	Non-survivors (N = 52)	Survivors (N = 65)	P**
Preoperative haemodynamics					
RAP (mmHg) ^d	114	9.5 [6.0–14.7]	10.0 [6.5–17.5]	9.0 [6.0–14.0]	0.16
sRVP (mmHg) ^c	90	52.7 (16.0)	52.0 (17.7)	53.2 (14.8)	0.73
dRVP (mmHg) ^d	72	5.0 [1.0–9.0]	5.0 [1.0–10.0]	4.0 [1.0–8.5]	0.65
tdRVP (mmHg) ^d	80	13.0 [8.0–18.2]	16.0 [9.0–19.0]	12.0 [8.0–18.0]	0.12
sPAP (mmHg) ^c	114	51.7 (16.5)	51.8 (17.1)	51.7 (16.2)	0.97
dPAP (mmHg) ^c	115	24.6 (8.9)	24.4 (9.1)	24.7 (8.8)	0.87
mPAP (mmHg) ^c	115	35.0 (11.2)	34.3 (11.0)	35.5 (11.5)	0.57
PCWP (mmHg) ^c	113	23.6 (8.8)	21.4 (8.6)	25.4 (8.6)	0.02
CO (L/min) ^c	113	4.0 (1.2)	4.0 (1.4)	3.9 (1.1)	0.86
CI (L/min/m ²) ^c	104	2.2 (0.6)	2.2 (0.6)	2.2 (0.6)	0.80
PVR (UW) ^d	113	3.0 [2.0–4.0]	3.2 [2.3–5.0]	2.9 [1.6–3.7]	0.13
Biological values					
NT-proBNP (ng/mL) ^d	50	738 [307–1497]	890 [173–1739]	717 [382–1339]	0.81
BNP (ng/mL) ^d	33	145 [73–282]	220 [141–318]	95 [54–176]	0.02
Creatininaemia (μmol/L) ^c	112	128.2 (62.4)	147.9 (78.7)	111.8 (37.8)	0.01
Natraemia (mmol/L) ^c	109	134.0 (6.2)	133.5 (5.8)	134.5 (6.4)	0.24
Bilirubinaemia (mg/L) ^d	106	16.5 [10.0–26.0]	18.5 [10.0–28.3]	16.0 [10.0–22.7]	0.20

Bold values indicate statistical significance.

ACE, angiotensin-converting enzyme; AF, atrial fibrillation; ARBs, angiotensin receptor blockers; BMI, body mass index; BNP, brain natriuretic peptide; BTD, bridge to decision; BTR, bridge to recovery; BTT, bridge to transplant; CI, cardiac index; CO, cardiac output; CRT, cardiac resynchronization therapy; DCM, dilated cardiomyopathy; dPAP, diastolic pulmonary artery pressure; dRVP, diastolic right ventricular pressure; DT, destination therapy; ECMO, extracorporeal membrane oxygenation; HCM, hypertrophic cardiomyopathy; IABP, intra-aortic balloon pump; ICM, ischaemic cardiomyopathy; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVAD, left ventricular assist device; LVEF, left ventricular ejection fraction; MCS, mechanical circulatory support; mPAP, mean pulmonary artery pressure; MRAs, mineralocorticoid receptor antagonists; N, total number of patients with the variable; NT-proBNP, N-terminal pro-brain natriuretic peptide; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RVEF, right ventricular ejection fraction; SD, standard deviation; sPAP, systolic pulmonary artery pressure; sRVP, systolic right ventricular pressure; TAPSE, tricuspid annular plane systolic excursion; tdRVP, tele-diastolic right ventricular pressure; VA < 30 days, ventricular arrhythmia in the 30 days before implantation.

^aData are presented as numbers (with percentages among the total, non-survivors, and survivors).

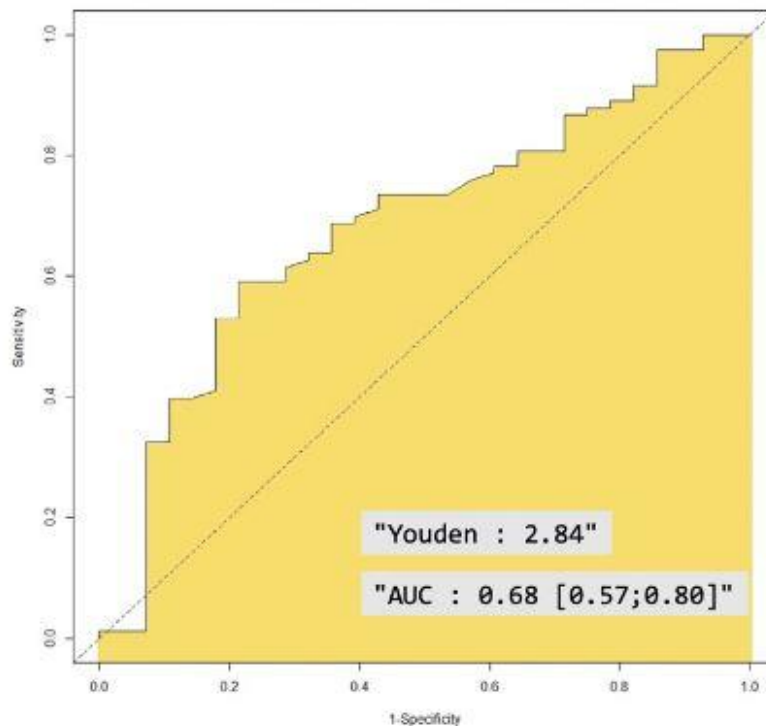
^bOther aetiologies included metabolic (amyloidosis and hemochromatosis), congenital (left ventricular non-compaction and single ventricle), and muscular (Duchenne myopathy, laminopathy, and myocarditis) diseases. Aetiologies can be associated.

^cQualitative data are presented as means (with standard deviations).

^dData are presented as medians [with interquartile ranges].

**Statistical test was considered statistically significant if $P < 0.05$.

Figure 3 Receiver operating characteristic curve of pulmonary artery pulsatility index as a predictor of 3 month mortality. AUC, area under the curve [95% confidence interval].



Multivariate analysis including preoperative and post-operative risk factors of mortality

Analysis of risk factors to predict 2 year mortality identified high blood pressure (HR 4.22 [95% CI 1.49–11.97], $P<0.01$) and diabetes mellitus (HR 4.90 [1.83–13.14], $P<0.01$). Implantation of LVAD as bridge to transplant (HR0.18 [0.04–0.74], $P= 0.02$) and heart transplantation (HR0.02 [0.00–0.18], $P<0.001$) were associated with increased survival at 2 years.

Discussion

RVF is known to be associated with adverse outcomes after LVAD implantation. Preoperative assessment of RV function is therefore a major challenge to characterize the surgical risk. In the present multicentric study, we investigated the relationship between the ratio of pulmonary artery pulsatility to RAP (PAPi), a marker of RV performance, and early mortality after LVAD implantation. We found that $\text{PAPi}<2.84$ was predictive of 3 month mortality in this population. The survival curves comparing patients with preoperative $\text{PAPi}<2.84$ and those with preoperative $\text{PAPi}\geq 2.84$ tend to reach 3 months after surgery. This was consistent with the lack of a significant difference in mortality between groups at 2 years.

The first description of the PAPi by Korabathina et al.²⁵ was in a patient presenting with RV myocardial infarction and requiring RV-MCS for refractory cardiogenic shock. As RVEF could not be measured in this setting, PAPi was applied to assess RV function. This variable was subsequently considered for the management of cardiogenic shock, as proposed by Tehrani et al.²⁸ The calculation of PAPi is easy and reproducible. However, the interpretation of this variable is subtle, as PAPi reflects both systolic and diastolic features of RV function. Moreover, determinants of RV afterload including pulmonary artery capacitance (PAC), PCWP, and PVR are not considered, whereas their impact on RV performance has been clearly demonstrated.²⁹ The relationship between PAPi and right ventricular stroke volume (RVSV) has also been established in previous studies.³⁰ However, the strength of this correlation is influenced by RV afterload, particularly by the PAC. Higher PAC values are associated with reduced variations in PAPi in response to changes in RVSV. This underscores the strong relationship between PAPi, RVSV, and afterload determinants. In advanced heart failure, PAC usually decreases; therefore, PAPi is associated with changes in RVSV and reflects RV performance.³¹ After LVAD implantation, PAC improves as a result of LV unloading, and PAPi becomes less sensitive to RVSV variations.³²

The threshold value of PAPi to predict severe or severe acute RVF after LVAD implantation remains a matter of de-bate. In other cardiovascular diseases that may lead to RVF such as acute myocardial infarction, open heart surgery, or chronic pulmonary hypertension, the critical threshold value for PAPi ranges from 0.9 to 3.5.^{25, 26, 33–36} The measurement of PAPi before LVAD implantation was first reported by Kang et al.²⁴ in 2015 in a single-centre retrospective study including 85 patients. We herein report for the first time that $\text{PAPi}<2.84$ was associated with an increased risk of post-operative mortality during the first 3 months after LVAD implantation. This cut-off value is higher than reported by other groups, as PAPi values ranging from 1.2 to 2.17 are usually considered critical thresholds associated with the occurrence of RVF after LVAD implantation.^{22–24} These former studies did not consider PAPi as a predictor of early mortality but as a predictive marker of severe RVF after LVAD

implantation. Though RVF refractory to optimal medical therapy is the leading cause of early mortality after LVAD implantation, we sought to investigate the relationship between preoperative PAPI and post-operative mortality in this population. Our findings underscore that $PAPi < 2.84$ may be considered a significant predictor of early death after LVAD implantation. As severe RVF can be successfully managed after LVAD implantation, we hypothesize that the incidence of RVF is higher than the mortality rate in this population. The threshold value of PAPI with the best sensitivity and specificity to predict early death after LVAD implantation in our study (2.84) is therefore higher than the value commonly considered to predict post-operative RVF (2.0), whatever the severity of RVF.

Table 2 Multivariate analysis of mortality factors using a Cox model

	HR [95% CI]	p**
Cardiovascular risk factor		
Age (>62 vs. <62 years)	0.92 [0.23–3.72]	0.91
Sex (female vs. male)	0.66 [0.24–1.81]	0.42
BMI (obesity vs. normal)	1.15 [0.33–3.94]	0.83
BMI (overweight vs. normal)	0.52 [0.18–1.49]	0.23
Hypertension (yes vs. no)	4.22 [1.49–11.97]	0.007
Diabetes (yes vs. no)	4.90 [1.83–13.14]	0.002
Preoperative data		
VA < 30 days (yes vs. no)	1.94 [0.76–5.00]	0.17
Cordarone (yes vs. no)	1.49 [0.61–3.66]	0.38
Creatinine (>112.0 vs. <112.0)	1.58 [0.70–3.57]	0.27
Delay from diagnosis to surgery (≥ 1447 vs. <1447)	1.16 [0.48–2.83]	0.74
Therapeutic project		
DT–BTR–BTD vs. BTT	0.18 [0.04–0.74]	0.018
Post-operative outcomes		
VA ECMO (yes vs. no)	2.15 [0.57–8.16]	0.26
Epinephrine (yes vs. no)	1.62 [0.72–3.67]	0.25
Bleeding (yes vs. no)	0.65 [0.23–1.77]	0.40
Transplantation (yes vs. no)	0.02 [0.00–0.18]	<0.001
PAPI		
≥ 2.84 vs. <2.84 survival prior to 3 months	0.08 [0.02–0.28]	<0.001
≥ 2.84 vs. <2.84 survival after 3 months	0.67 [0.17–2.67]	0.57

Bold values indicate statistical significance.

BMI, body mass index (kg/m^2); BTD, bridge to decision; BTR, bridge to recovery; BTT, bridge to transplant; CI, confidence interval; DT, destination therapy; HR, hazard ratio; PAPI, pulmonary artery pulsatility index; VA, ventricular arrhythmia; VA-ECMO, veno-arterial extracorporeal membrane oxygenation.

**Statistical test was considered statistically significant if $P < 0.05$.

Figure 4 Comparative survival according to the pulmonary artery pulsatility index (PAPI) threshold value of 2.84.

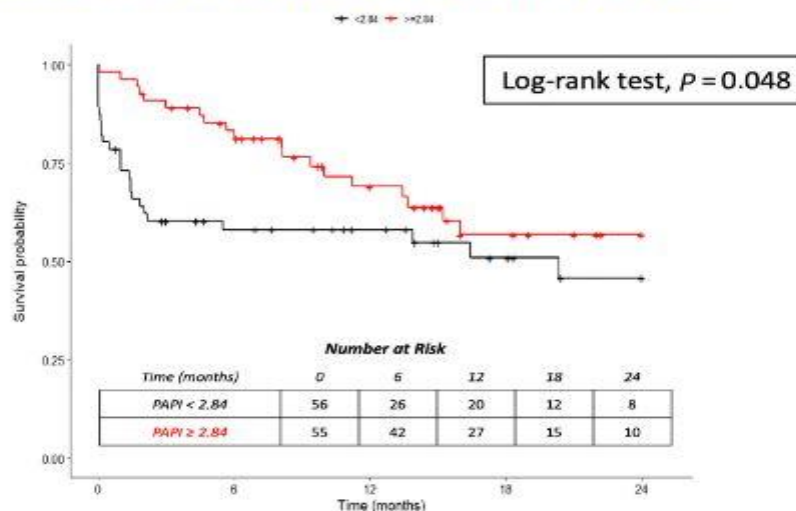


Figure 5 Univariate analysis including preoperative risk factors of mortality (univariate analysis). ACE, angiotensin-converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; CI, confidence interval; CRT, cardiac resynchronization therapy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; MRA, mineralocorticoid receptor antagonist; OR, odds ratio; VA < 30 days, early ventricular arrhythmia at 1 month. **Statistical test was considered statistically significant if $P < 0.05$.

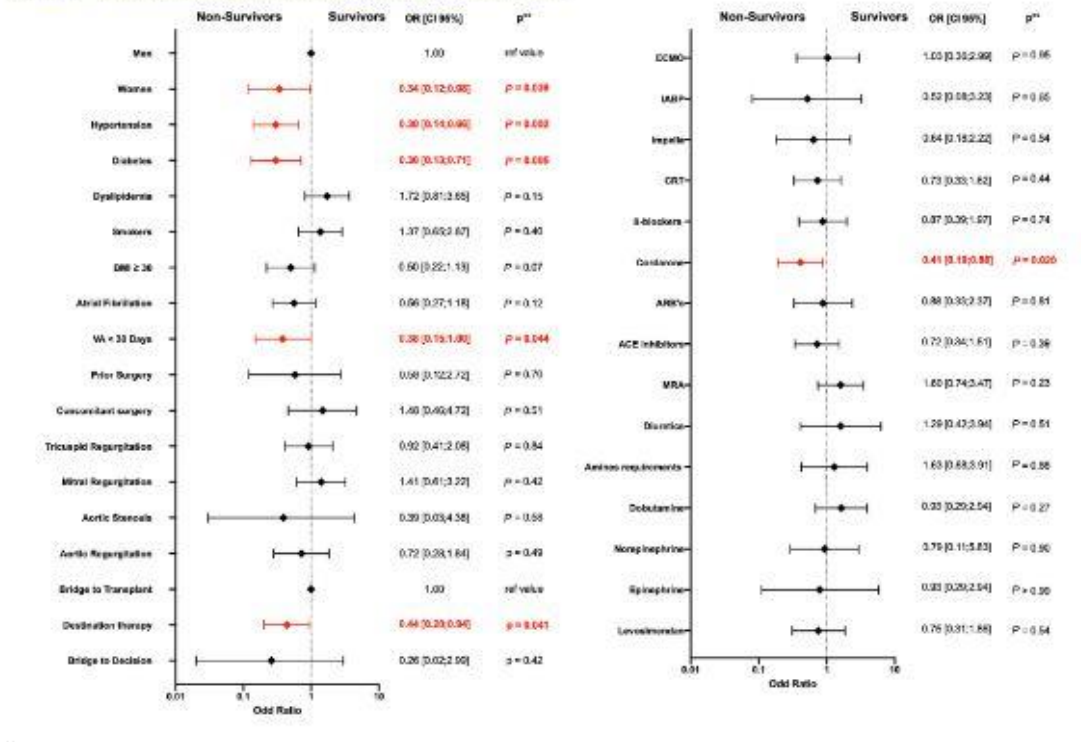
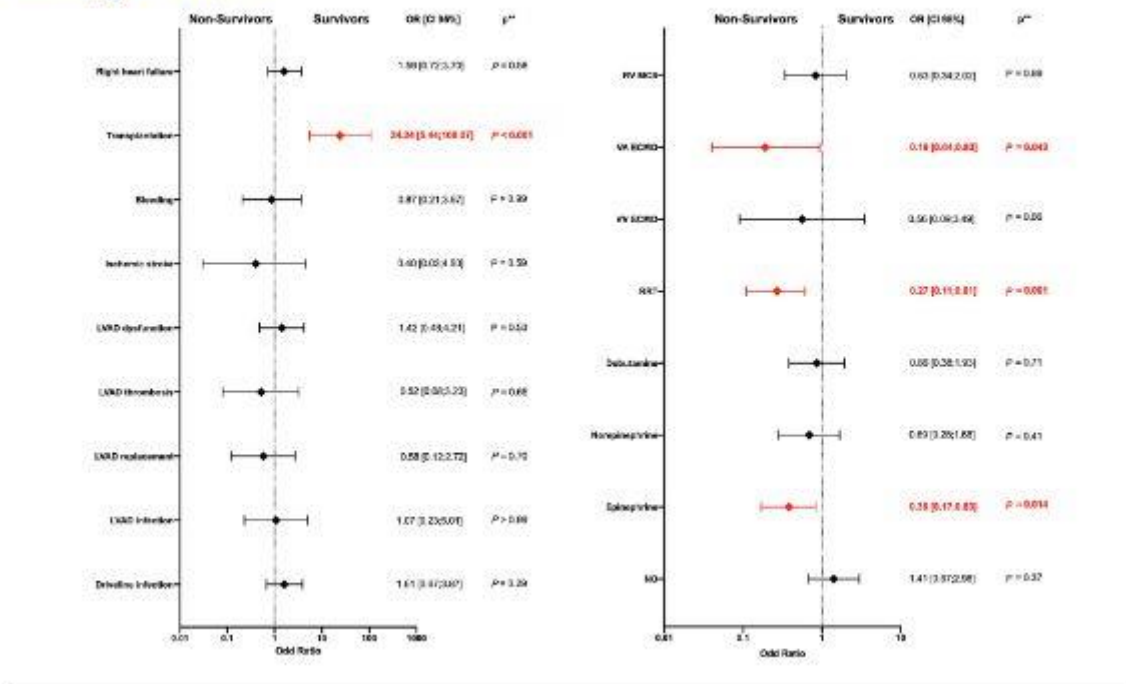


Figure 6 Univariate analysis including post-operative risk factors of mortality (univariate analysis). CI, confidence interval; LVAD, left ventricular assist device; NO, nitrous oxide; OR, odds ratio; RRT, renal replacement therapy; RV-MCS, right ventricular mechanical circulatory support; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VV-ECMO, veno-venous extracorporeal membrane oxygenation. **Statistical test was considered statistically significant if $P < 0.05$.



In the present study, the incidence of post-operative RVF(48.7%) was not significantly different between survivors and non-survivors but was higher than reported in the literature

(10–40%).^{11–13}As a consequence, we observed a 1 year survival rate (63%) lower than previously reported by other groups. In a multicentric analysis from the INTERMACS registry, Hariri et al. reported a 1 year survival rate of 82%.^{7,37}Similarly, Brescia et al. also reported 74.7% of 1 year survival in a prospective study involving 14 679 patients.⁸We defined RVF according to the INTERMACS classification to categorize the severity of post-LVAD RVF based on the duration of inotropic use and the requirement for RV-MCS.¹⁵However, we included patients with mild and moderate RVF, while previous studies did not consider post-LVAD RVF in cases of inotropic support for <14 days. The limited survival at 1 year in our study may be explained by the critical preoperative clinical condition, as 88% of patients were under pharmacological inotropic support before LVAD implantation. Moreover, 27.3% were supported by transient MCS (IABP, Impella, or ECMO) before LVAD implantation. The majority of our study population had, therefore, an INTERMACS profile ranging from I to III, a condition at high risk of post-operative morbidity and mortality.^{38, 39}

We found a threshold value of PAPI at 2.84 to predict the risk of early death within 3 months after surgery. This was the median value of PAPI in our study population. It is not feasible to rule out all patients with $PAPi < 2.84$ because nearly half of patients would be contraindicated for LVAD implantation. We suggest that risk stratification for RVF may rather consider the range of PAPI than a threshold value alone. In-deed, we consider in our practice that patients with $PAPi < 2$ may not be referred for LVAD implantation due to the major risk of refractory RVF and early post-operative death. On the other hand, $PAPi \geq 3$ is more favourable and would be associated with a low risk of post-operative death. In between ($2 < PAPi < 3$), LVAD implantation is feasible as post-operative RVF is usually reversible within a week after LVAD implantation. Isaza et al. showed that RV speckle tracking can be a valuable clinical tool to better predict RVF occurrence for this range of values.⁴⁰PAPI would therefore be beneficial for clinicians to both predict the risk of RVF and optimize preoperative and perioperative management to protect or assist the failing right ventricle.⁴¹

Limitations

Our study is limited by its retrospective design, which includes two different generations of LVAD (axial and centrifugal pumps). Further prospective studies are needed to validate our findings in larger prospective cohorts. We had to exclude patients with either incomplete or too-old preoperative measurements of pulmonary HD. Similarly, patients under ECMO support without a recent (<3 months) assessment of pulmonary HD could not be included; as RAP and PAP are artificially reduced by active venous drainage (RV unloading). The measurement of PAPI in this population is not relevant in clinical practice. We therefore consider that the exclusion of these patients does not affect the external validity of our results. The cause of death in the ASSIST-ICD registry was not collected, so we could not perform an analysis of mortality related to RVF.

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Conflict of interest

Ali Akamkam, Vincent Galand, Marie Jungling, Clément Delmas, Camille Dambrin, Mathieu Pernot, Michel Kindo, Philippe Rouviere, Thomas Senage, Olivier Chavanon, Marylou Para, Vlad Gariboldi, Matteo Pozzi, Pierre-Yves Litzler, Gerard Babatasi, Olivier Bouchot, Costin Radu, Thierry Bourguignon, Nicolas D'Ostrevy, Ramzi Abi Akar, Fabrice Vanhuyse, Maïra Gaillard, Gilles Chatelier, Audrey Fels, Erwan Flecher, and Julien Guihaire declare that they have no conflict of interest. Philippe Gaudard received a consultant fee from Abbott, Abiomed, and Air Liquide.

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