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Failure to rescue: obesity increases the risk of mortality following early graft failure in heart transplantation in UNOS database patients

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Key question

In heart transplant patients who develop early graft failure, which recipient risk factors predict mortality at 90 days?

Key finding(s)

Obesity was found to have an OR of 3.32 (p<0.01) in predicting mortality after the development of early graft failure.

Take-home message

Careful discussion regarding transplant candidacy and risk is warranted in obese patients and if EGF develops consider aggressive rescue.

	Donor-Adjusted Backwards Stepwise Multivariable Regression		
Recipient Characteristics	OR	95% CI	p-value
Obesity, BMI > 30	3.32	1.41-7.82	<0.01
History of Any Cigarette Use	1.26	0.61-2.62	0.63
Total Days on the Waitlist	1.00	0.99-1.00	0.09
History of Diabetes	1.41	0.58-3.38	0.77
History of Recipient Defibrillator	1.75	0.87-3.49	0.11
Sizemismatch by BMI	2.49	0.71-8.82	0.16
History of Prior Cardiac Surgery	1.50	0.75-3.00	0.25

Abstract

OBJECTIVES: Early graft failure (EGF) is a devastating postoperative complication following heart transplant. Institutional studies have modelled donor and recipient risk factors predictive of graft failure. To date, no studies have assessed specific recipient profiles associated with mortality after recipients suffer from EGF. The objective of this study was to identify this recipient profile.

METHODS: We performed a retrospective review of patients in the United Network for Organ Sharing database undergoing heart transplant from August 2000 to September 2019. EGF was defined as graft dysfunction at 24 hours post-heart transplant. The primary outcome was 90-day mortality. To isolate recipient characteristics associated with mortality, we performed the univariate analysis on 24 recipient characteristics adjusted for high-risk donor characteristics (ischaemic time, donor age, race mismatch, BUN/creatinine ratio) predictive of 1-year mortality ($P < 0.2$). We then performed backward stepwise multivariable regression adjusted for identified donor characteristics to determine recipient characteristics associated with mortality after EGF ($P < 0.05$).

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RESULTS: We identified 302 patients diagnosed with post-transplant EGF. Among these patients, mortality was 82% within 90 days of transplantation. Adjusted univariate analysis identified 7 factors associated with mortality. Adjusted backward stepwise multivariable regression identified BMI > 30 as predictive of mortality at 90 days after EGF.

CONCLUSIONS: Patients who develop EGF after heart transplant are at high risk for mortality. Careful discussion regarding transplant candidacy and risk is warranted in obese patients. In addition, minimizing donor factors associated with graft dysfunction is critical during preoperative planning in these recipients.

ABBREVIATIONS

BMI	Body mass index
CI	Confidence interval
EGF	Early graft failure
ISHLT	International Society for the Heart & Lung Transplantation
OR	Odds ratio
PGD	Primary graft dysfunction
UNOS	United Network for Organ Sharing

INTRODUCTION

Heart failure affects an estimated 64.3 million patients worldwide. In the USA, the prevalence of heart failure has continued to increase due to the ageing population [1]. Orthotopic heart transplantation remains the definitive treatment for this condition. Patients who undergo heart transplantation benefit from a >90% survival at 1 year [2]. Despite the promising outcomes, primary graft dysfunction (PGD) remains a serious outcome following cardiac transplantation and contributes to a significant proportion of perioperative mortality [3]. PGD is identified by the development of single or biventricular failure without a secondary cause and occurs in the immediate postoperative period. Rapid diagnosis, prompt circulatory support and in severe cases emergent retransplantation may be necessary for the recipient's survival [4].

The devastating consequences of PGD have led to the careful consideration of donor and recipient factors that may predict the probability of cardiac allograft failure. Segovia *et al.* proposed a 6-item risk index that included recipient and donor factors for graft failure including right atrial pressure ≥10 mmHg, recipient age ≥60 years, diabetes mellitus, inotrope dependence, donor age ≥30 years and length of ischaemic time ≥240 min (RADIAL). A high RADIAL index predicted graft failure with a good correlation and maintained its predictive capabilities in a subsequent prospective analysis [5]. Subsequent studies have identified age, history of diabetes or history of prior sternotomy as other recipient factors that may contribute to the development of PGD. Two limitations of the RADIAL index and these studies are they reflect institutional-level experiences, and they do not identify recipient characteristics that predict worse outcomes once PGD has developed [6]. We undertook this study to aid cardiac surgeons in identifying patients that require emergent rescue after the development of graft failure and identify recipient characteristics that predict mortality after the development of early graft failure (EGF) using a large national transplant database.

PATIENTS AND METHODS

Ethics statement

The United Network for Organ Sharing (UNOS) data were acquired and approved for intended use. The study was approved by the University of Pennsylvania Institutional Review Board (protocol # 850952, confirmation number: dfhicebh) and the consent of patients was waived.

Study design and participants

A retrospective review of the (UNOS) database was performed from January 2000 to September 2019 to identify all incidences of graft dysfunction in heart transplant recipients. Recipient mortality was identified and patient characteristics were recorded for patients who survived and for those who did not survive. Dual organ transplant and paediatric cases were excluded from analysis. A diagram depicting patient inclusion and exclusion criteria is displayed in Fig. 1.

Variables and data sources

The UNOS database contains limited data on postoperative timing and use of mechanical circulatory support, cardiac catheterization and echocardiography. UNOS only contains details on the occurrence, time and cause of graft failure in a recipient's record, which limits the ability to determine the incidence of PGD and the rate of decline of cardiac function following transplantation. Therefore, the variable EGF was created and used as a surrogate for PGD with a similar time point at 24 h post-transplant. EGF was defined as 'primary graft failure' or 'PGD' by the transplant institution staff reporting patient information to UNOS. Twenty-five relevant recipient characteristics that could be associated with mortality following EGF were identified from the database and are shown in Fig. 2. To isolate these recipient characteristics from donor variables that may portend worse outcomes, the analysis was adjusted for donor variables (ischaemic time, donor age, race mismatch and BUN/creatinine ratio) that predict both short- and long-term mortality after heart transplantation [7]. The primary outcome of interest was mortality at 90 days.

Statistical analysis

Multivariable regression was performed separately on 24 recipient characteristics to identify recipient variables that may be associated with mortality at 90 days (Fig. 2). Recipient characteristics with a significance of $P < 0.2$ were entered into a backward stepwise multivariable regression. In this model, recipient characteristics that predicted 90-day mortality after EGF with a significance of $P < 0.05$ were included in the final recipient profile. The multivariable regressions were adjusted for donor variables associated with mortality as identified above. Following identification of recipient characteristics that may be predictive of mortality at 90 days, *post hoc* chi-square analysis was performed to determine if there was an unadjusted association between the recipient characteristic(s) and 90-day mortality. Missing data were excluded from analysis. Chi-squared and multivariable regressions were performed using Stata 17 [8].

RESULTS

A total of 63 046 adult single-organ cardiac transplants were identified from the UNOS database from 2000 to 2019. Of these, 302 patients developed EGF (0.5%) at 24 h post-transplant. Mortality at 90 days was 82% (249 patients). Of the surviving patients, 87% (46 patients) were re-transplanted while only 13% (7 patients) survived without re-transplant.

Basic characteristics of patients who developed EGF are shown in Table 1. Body mass index (BMI) was significantly different between the deceased and survival groups (28 vs 26, respectively, $P = 0.02$). There was a non-significant higher proportion of recipients with type 2 diabetes in the mortality group compared to the survival group (21% vs 9% respectively, $P = 0.054$).

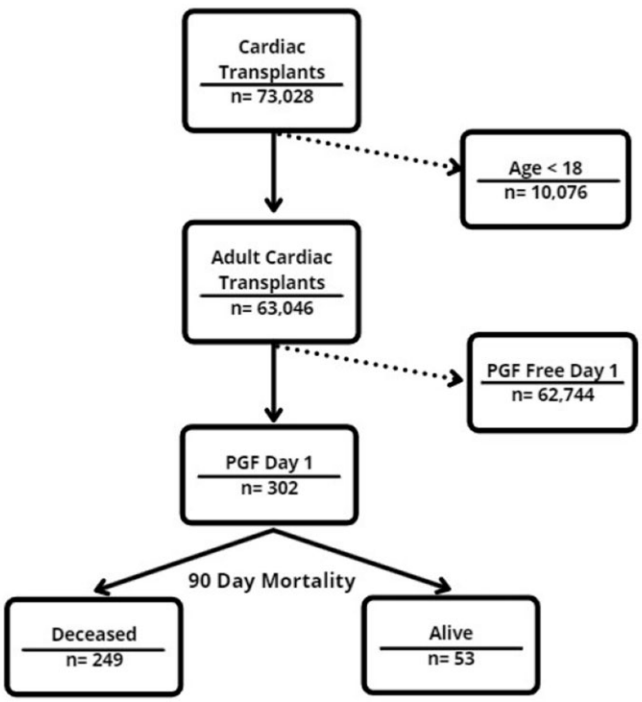

Figure 1: Schematic of inclusion and exclusion criteria. EGF: early graft failure.

On donor-adjusted multivariable analysis, 7 recipient characteristics were associated with 90-day mortality at a significance of $P < 0.2$ (Table 2). These variables included obesity with a BMI of >30 [odds ratio (OR) 3.32, 95% confidence interval (CI) 1.41–7.82], history of any cigarette use (OR 1.69, 95% CI 0.86–3.30), total days on the waitlist (OR 1.00, 95% CI 0.99–1.00), history of diabetes (OR 2.37, 95% CI 0.88–6.34), history of recipient defibrillator (OR 1.83, 95% CI 0.94–3.56), size mismatch by BMI (OR 3.34, 95% CI 0.99–11.31) and history of prior cardiac surgery (OR 1.6, 95% CI 0.83–3.08). Following donor-adjusted backward stepwise multivariable regression of these variables, obesity with a BMI of >30 (OR 3.32, 95% CI 1.41–7.82, pseudo R^2: 0.04, area under receiver operating characteristic curve 0.63) as identified as a predictor of 90-day mortality after the development of EGF. On *post hoc* unadjusted chi-squared analysis, obesity was significantly associated with 90-day mortality ($P = 0.02$).

DISCUSSION

The present study provides one of the first analysis of a large national transplant database to determine which recipient characteristics predict mortality after the development of EGF. The incidence of EGF in this cohort was low at 0.5% but carried a very high mortality at 82%. In general, survival was dependent upon retransplantation. Analysis of 24 recipient characteristics with backward stepwise multivariable regression revealed obesity with a BMI of >30 as an independent predictor of mortality at 90 days.

Obesity has been steadily rising among adults in America for decades and is expected to see continued growth in prevalence for the foreseeable future [9]. In heart failure patients, there has been a concurrent rise in the incidence of diseases associated obesity and metabolic syndrome such as diabetes and sleep apnoea [10]. These trends portend worse outcomes in cardiac surgery as obesity has been independently associated with a higher mortality caused by myocardial infarction, chronic rejection, infection and renal failure following cardiac transplant [11]. As a reflection of the risks obesity poses on transplant patients, the 2016 International Society for Heart & Lung Transplantation (ISHLT) consensus recommended against transplanting patients with a pretransplant BMI >35 kg/m^2 [12]. These recommendations when combined with the present study further demonstrate the risks obesity has on graft and recipient survival. Importantly, obese

Age	Total Days on the Waitlist	Infection Requiring Antibiotics Prior to Transplant
BMI	Any Diabetes Type	Inotropes at Transplant
Gender	Type 2 Diabetes	Implanted Defibrillator
Any History of Cigarette Use	ECMO	Any Mechanical Circulatory Support (IABP/VAD/ECMO)
Current Cigarette Use	Dialysis Use Prior to Transplantation	Prior Cardiac Surgery
Highest Level of Education at Waitlisting	Functional Status at Time of Transplant	IABP
Ethnicity	Sex Mismatch	VAD
BMI Size Mismatch	Height Size Mismatch	Weight Size Mismatch

Figure 2: Recipient characteristics selected for regression analysis. BMI: body mass index; ECMO: extra-corporeal membrane oxygenation; IABP: intra-aortic balloon pump; VAD: ventricular assist device.

patients with a of BMI >30 who develop EGF are at a considerable risk for short-term mortality. Ultimately, a consideration for transplant or more aggressive rescue is necessary when graft failure is suspected in this population.

Mitigating the detrimental effects of obesity on the heart by employing bariatric surgery has gained some traction in the previous few years. Several recent series have been published on laparoscopic sleeve gastrectomy in heart failure patients as a means to reduce BMI below 35 kg/m^2, allowing for transplant candidacy. Individuals with heart failure are able to tolerate bariatric surgery with few complications after careful perioperative planning and collaboration with cardiac anaesthesia [13–15]. Bariatric surgery has also led to a regression in New York Heart Association class in some and discontinuation of ventricular assist device in others, obviating the need for transplantation. Punchai et al. [16] described their experience with laparoscopic sleeve gastrectomy on obese ventricular assist device patients and found a reduction in New York Heart Association class from preoperative class 3 to preoperative class 2. In a case report of 2 patients with a BMI of >40 kg/m^2 and severe heart failure requiring left ventricular assist device (LVAD) implantation, Nathan et al. [17] described improvement in left ventricular ejection fraction to normal values and a significant decrease in BMI over 2 years. In both patients, the LVAD was explanted and heart transplantation was not necessary.

Table 1: Recipient characteristics of patients with early graft failure

Recipient characteristics	Patients with EGF (*n* = 302)
BMI (mean)	28
Obese, BMI >30 (%)	32
Age (mean)	52
Gender (male, %)	70
Life support (VAD/ECMO/IABP, %)	43
Type 2 diabetes (%)	19
Dialysis prior to transplant (%)	8
Any cigarette use (%)	40
Cigarette use >10 years (%)	4
Total days on the transplant waitlist (mean)	258
Infection requiring IV antibiotics prior to transplant (%)	11
BMI size mismatch (%)	17
Sex mismatch (%)	29
History of prior cardiac surgery (%)	61
Survived at 90 days (%)	82

BMI: body mass index; ECMO: extracorporeal membrane oxygenation; EGF: early graft failure; IABP: intra-aortic balloon pump; VAD: ventricular assist device.

Limitations

A limitation of the UNOS database is the paucity of clinical data that exists in the immediate post-operative period. This includes data such as pretransplant medications (including long-term immunosuppression), important labs such as preoperative glycosylated haemoglobin or insulin use in cardiac transplant patients. When graft failure occurs, no details are available to determine if the graft dysfunction is right ventricular, left ventricular or biventricular. Thus, clinical diseases with complex definitions must be inferred from the available patient records. The definition for PGD was formalized in 2014 by an ISHLT consensus as a response to the wide variance in incidence reported by single study institutions [18]. Similar to this study, PGD was defined as graft failure within 24 h of transplant. However, the definition included left and right failure as well as a severity scale of mild, moderate or severe for left ventricular PGD [18]. The efforts of ISHLT provide the cardiac transplant world with a common language with which to describe and measure the incidence deleterious effects of PGD. However, given the limitations of available data from UNOS, a surrogate definition of EGF was necessarily employed in this study. Despite these limitations, the high mortality of 82% found in the current study is similar to previous descriptions of severe PGD [6]. Given this, obese patients who develop severe PGD may be at a higher risk for mortality than non-obese recipients with severe PGD, which could prompt

Table 2: Recipient characteristics associated with 90-day mortality after early graft failure on donor-adjusted univariate and backward stepwise multivariable regression

Recipient characteristics	Donor-adjusted univariate analysis			Donor-adjusted backwards stepwise multivariable regression		
	OR	95% CI	*P*-Value	OR	95% CI	*P*-Value
Obesity, BMI >30	3.32	1.41–7.82	<0.01	3.32	1.41–7.82	<0.01
History of any cigarette use	1.69	0.86–3.30	0.13	1.26	0.61–2.62	0.63
Total Days on the waitlist	1.00	0.99–1.00	0.09	1.00	0.99–1.00	0.09
History of diabetes	2.37	0.88–6.34	0.09	1.41	0.58–3.38	0.77
History of recipient defibrillator	1.83	0.94–3.56	0.07	1.75	0.87–3.49	0.11
Size mismatch by BMI	3.34	0.99–11.31	0.05	2.49	0.71–8.82	0.16
History of prior cardiac surgery	1.60	0.83–3.08	0.16	1.50	0.75–3.00	0.25
History of recipient RVAD	0.47	0.12–1.88	0.28	–	–	–
History of dialysis	0.73	0.25–2.15	0.57	–	–	–
Male gender	1.32	0.67–2.61	0.42	–	–	–

Relevant recipient characteristics are shown. Recipient characteristics with a significance of $P < 0.2$ on univariate analysis were entered into a backward stepwise multivariable regression to determine recipient factors independently associated with 90-day mortality after EGF. Donor variables included in model adjustment: ischaemic time, age, donor-recipient race mismatch and BUN/Cr ratio. All mechanical support variables (VAD, ECMO, IABP) when entered into the regression model together did not change results.

BMI: body mass index; CI: confidence interval; Cr: creatinine; ECMO: extra-corporeal membrane oxygenation; EGF: early graft failure; IABP: intra-aortic balloon pump; OR: odds ratio; RVAD: right ventricular assist device; VAD: ventricular assist device.

consideration of urgent rescue therapies including extracorporeal membrane oxygenation.

A potential future direction includes repeating the analysis at an institutional level utilizing the ISHLT definition of PGD. Recipients can be stratified by side and severity of ventricular failure to determine how these factors impact mortality when paired with obesity and pulmonary resistance data can be included to analyse the relationship among BMI, pulmonary resistance and PGD. In addition, parameters that define treatment strategies such as the use of mechanical support for patients with PGD should be studied and an analysis of risk factors for EGF can be performed. Ultimately, updating the UNOS database to include post-operative ultrasound, cardiac catheterization, mechanical circulator support information and the timing of these interventions will allow for a more uniform analysis using the formal PGD definition. Finally, other measures of donor–recipient size mismatch such as height mismatch can be included in the analysis.

CONCLUSION

Careful discussion regarding transplant candidacy and risk is warranted in patients with obesity. In addition, minimizing donor factors associated with graft dysfunction and choosing healthier donors is reasonable during pre-operative planning in these recipients. With these modifications, organ and recipient selection can be carried out in a more thoughtful manner that will allow for transplantation in obese recipients with the greatest opportunity for survival.

Conflict of interest: none declared.

Data Availability Statement

The data underlying this article can be requested from the United Network for Organ Sharing database at www.unos.org/data. In addition, our tailored dataset and analysis can be requested and will be shared to the corresponding author.

Author contributions

David Alan Herbst: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Visualization; Writing—original draft. **Amit Iyengar:** Conceptualization; Writing—review & editing. **Noah Weingarten:** Conceptualization; Writing—review & editing. **Mark R. Helmers:** Conceptualization; Writing—review & editing. **Samuel T. Kim:** Writing—review & editing. **Pavan Atluri:** Conceptualization; Supervision; Writing - review & editing.

Reviewer information

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