Journal Pre-proof

MECHANICAL CIRCULATORY SUPPORT IN SEVERE PRIMARY GRAFT DYSFUNCTION: PERIPHERAL CANNULATION BUT NOT EARLIER IMPLANTATION IMPROVES SURVIVAL IN HEART TRANSPLANTATION

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PII: S1053-2498(23)01784-9
DOI: https://doi.org/10.1016/j.healun.2023.03.008
Reference: HEALUN 7884

To appear in: *Journal of Heart and Lung Transplantation*

Please cite this article as: Aleix Olivella MD , Luis Almenar-Bonet MD, PhD , Francisco González-Vilchez MD, PhD , Carles Díez-López MD , Beatriz Díaz-Molina MD, PhD , Zorba Blázquez-Bermejo MD , José Manuel Sobrino-Márquez MD, PhD , Manuel Gómez-Bueno MD , Iris P. Garrido-Bravo MD, PhD , Eduardo Barge-Caballero MD, PhD , Marta Farrero-Torres MD, PhD , Maria Dolores García-Cosio MD, PhD , Teresa Blasco-Peiró MD , Antonia Pomares-Varó MD , Javier Muñiz MD, PhD , José González-Costello MD, PhD , MECHANICAL CIRCULATORY SUPPORT IN SEVERE PRIMARY GRAFT DYSFUNCTION: PERIPHERAL CANNULATION BUT NOT EARLIER IMPLANTATION IMPROVES SURVIVAL IN HEART TRANSPLANTATION, *Journal of Heart and Lung Transplantation* (2023), doi: https://doi.org/10.1016/j.healun.2023.03.008

Original Clinical Science

MECHANICAL CIRCULATORY SUPPORT IN SEVERE PRIMARY GRAFT DYSFUNCTION: PERIPHERAL CANNULATION BUT NOT EARLIER IMPLANTATION IMPROVES SURVIVAL IN HEART TRANSPLANTATION

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ABSTRACT

Background: Primary graft dysfunction (PGD) still affects 2-28% of heart transplants (HT). Severe PGD requires mechanical circulatory support (MCS) and is the main cause of death early after HT. Earlier initiation has been suggested to improve prognosis but the best cannulation strategy is unknown.

Methods: Analysis of all HT in Spain between 2010 and 2020. Early (<3 hours after HT) vs late initiation (≥3 hours after HT) of MCS was compared. Special focus was placed on peripheral vs central cannulation strategy.

Results: 2376 HT were analyzed. 242 (10.2%) suffered severe PGD. 171 (70.7%) received early MCS and 71 (29.3%) late MCS. Baseline characteristics were similar. Patients with late MCS had higher inotropic scores and worse renal function at the moment of cannulation. Early MCS had longer cardiopulmonary bypass times and late MCS was associated with more peripheral vascular damage. No significant differences in survival were observed between early and late implant at 3 months (43.82% vs 48.26%; log-rank p=0.59) or at 1 year (39.29% vs 45.24%, log-rank p=0.49). Multivariate analysis did not show significant differences favoring early implant. Survival was higher in peripheral compared to central cannulation at 3 months (52.74% vs. 32.42%, log-rank p 0.001) and one year (48.56% vs. 28.19%, log-rank p 0.0007). In the multivariate analysis, peripheral cannulation remained a protective factor.

Conclusions: Earlier MCS initiation for PGD was not superior compared to a more conservative approach with deferred initiation. Peripheral compared to central cannulation showed superior 3-month and 1-year survival rates.

Keywords: Mechanical Circulatory Support, Primary graft dysfunction, heart transplantation, VA ECMO, Peripheral Cannulation.

Abbreviations: PGD, Primary graft dysfunction; HT, Heart Transplant; MCS, Mechanical circulatory support; VA ECMO, Venoarterial extracorporeal membrane oxygenator; VAD, Ventricular assist devices; LVAD, Left ventricular assist device

INTRODUCTION

Primary graft dysfunction (PGD) is a feared complication that affects between 2 and 28% of heart transplants (HT)[1], and remains the main cause of death early after HT, accounting for over 30% of deaths during the first month[2].

The 2014 ISHLT consensus[1] established a universal definition of PGD, and graded it in a severity scale. Use of mechanical circulatory support (MCS) to maintain end-organ perfusion has gained importance during the last decade in this scenario, with around 6% of HT receiving MCS after HT [3-4]. Several types of support have been reported, with a predominance of venoarterial extracorporeal membrane oxigenator (VA ECMO) compared to other ventricular assist devices (VAD). Some studies have suggested better outcomes with VA ECMO against other modalities [5]

The evidence regarding the benefit of MCS in PGD is limited to case series and retrospective observational studies [6-11], with discordant characteristics in donors and recipients, and until 2014, even the definition of PGD had not been properly addressed [1]. The high rate of complications derived from this aggressive modality of support remains a major concern for its use [12]. Some data suggests that an earlier MCS implantation in PGD might improve prognosis by reducing the time of insufficient end organ perfusion, but the largest cohort examining this issue included only 38 subjects [6].

VA ECMO can be cannulated both peripherally and centrally. Peripheral cannulation allows for primary chest closure, diminishing potential risks of chest infections and early respiratory weaning, at the expense of a higher risk of limb ischemia, impaired unloading of the heart and potential risk of harlequin syndrome. In postcardiotomy shock, evidence is conflicting [13-14], but generally no difference in survival between these two strategies has been clearly defined, and in PGD, evidence is very limited[15].

We performed a retrospective analysis of the Spanish Heart Transplant Network of all HT performed between 2010 and 2020 examining the benefit of earlier (<3 hours after HT) vs late (>3hours after HT) MCS in severe PGD. We also assessed differences between central vs peripheral ECMO cannulation.

MATERIAL AND METHODS

We performed an analysis on the Spanish Heart Transplant Registry, a national database registering all HT in Spain. All patients signed an informed consent to collect their anonymized data prospectively. Between January 1st 2010 and December 31th 2020, 2905 adult HT were performed in 17 Spanish centers, 2745 > 18 years old. Excluding 55 combined transplants, a total of 2690 single HT from 17 centers were eligible to be analyzed. 3 centers in Spain declined participating in the collection of additional data, therefore we were left with 14 centers and 2376 HT analyzed (see flowchart in **Figure 1**). The local ethics committee approved this study.

Current transplant procedure, MCS strategy and outcomes

Transplant surgery was performed following local protocols. The decision to initiate MCS, the type of device and cannulation strategy, management and weaning was performed according to each center preferences and experience. We considered graft

survival as the primary outcome in the survival analysis (death of the patient or retransplant).

PGD definition

PGD was defined according to the 2014 ISHLT consensus [1]. In summary, PGD excludes discernible causes such as hyperacute rejection, pulmonary hypertension, or known surgical complications. The diagnosis has to be made in the first 24 hours after surgery. PGD is divided in PGD-left ventricle that includes left and biventricular dysfunction and PGD-right ventricle that implies right ventricular dysfunction alone. Both were included in the analysis.

The severity scale includes mild, moderate or severe, according to hemodynamics, inotrope doses and MCS. Severe PGD requires dependence on left, right or biventricular MCS, excluding intraaortic balloon pump, such as venoarterial extracorporeal membrane oxygenator (VA ECMO), left ventricular assist device (LVAD), biventricular assist device, percutaneous LVAD or right ventricular assist device.

Early vs late MCS initiation

Given the absence of an accepted definition of “early” and “late” MCS in PGD, we considered early MCS implant as 3 hours or less after unclamping the aorta after HT or patients already on MCS preHT that remained supported after HT. Late MCS implant was defined as that initiated 3 hours after unclamping the aorta after HT.

Cannulation technique

Each center followed their local protocol. We considered central cannulation when the MCS cannulas were inserted directly into the great vessels through a sternotomy.

Peripheral cannulation was defined when the MCS cannulas were inserted through the peripheral vessels.

Data collection

The Spanish Transplant Registry systematically registers prospective data from all HTs performed in Spain. For the purpose of our study, some data relevant for the analysis was retrospectively added from medical records (**see Table S1**), including the Vasoactive Inotrope Score [16].

Statistical analysis

Quantitative and qualitative variables are described as mean ± standard deviation and percentages respectively.

Differences between early and late MCS are analyzed with Chi-squared test or Fisher-exact test when required for categorical variables and the U Mann Whitney test (two-sample Wilcoxon rank-sum) for quantitative variables.

Survival curves were obtained with the Kaplan-Meier function, analyzing differences between early and late MCS by Log-Rank test. For the multivariate Cox regression analysis, variables with a p value ≤ 0.15 in the univariate analysis related to exposure (time of implantation) were selected and were compared between the groups with and without graft survival at 3 months and 1 year, unless there was a high proportion of missing values (>15%). All variables with a p value ≤ 0.15 in the previous analysis were included in the initial model and the resulting model was simplified by a backward method procedure excluding non-significant variables (p > 0.05). We forced the inclusion of the variables “early MCS implant” and “peripheral cannulation” as they

were the exposures of interest and evaluated the proportional hazard assumption for all variables included in the models.

RESULTS

From 2376 HT included, 504 (21.21%) suffered PGD according to the ISHLT consensus definition, with the diagnosis being made in the first 24 hours after surgery 242 of them, received MCS (48.02%). According to our definition, 171 (70.66%) received early MCS and 71 (29.34%) late MCS. None of the 242 patients with severe PGD, who needed MCS, received a re-transplant during the first year of follow-up.

General characteristics of the cohort

Data on the characteristics of recipients and donors of all HT with severe PGD are presented in **Table 1**. Mean age was 52.3 years old, with a predominance of men. 47.5% were under ambulatory inotropic support prior to HT. Patients were frequently in critical condition, with 27.0% under mechanical ventilation prior to HT and 45.0% under MCS at the time of surgery. Median ischemic time was 210 min, CPB time was 157 min. Induction was used in 86.3% of the cohort, the majority with basiliximab (97.1%).

Baseline characteristics: early vs late MCS

Data about the characteristics of early vs late MCS are described in **Table 1 and 2**. Early MCS was initiated 0.73 ± 0.86 hours after unclamping, and 28.46 ± 33.3 hours in late-MCS. In early MCS, 11.70% maintained the same MCS used prior to HT, and 83.63% were implanted with a MCS during the HT surgery.

No significant differences were documented regarding recipient characteristics. An early implant has become more frecuent in recent years and preHT MCS was more frequent in early MCS. Early MCS was more frequent in patients with preHT impaired hepatic function, but no significant differences were seen immediately postHT. Donor characteristics did not significantly differ between early vs late MCS implant, except for higher noradrenaline doses in late MCS.

Patients with late MCS had higher vasoactive-inotropic scores at the time of cannulation and more severe renal failure, but lactate levels did not differ significantly.

Concerning the surgery, total ischemic time did not influence MCS implant timing, but early MCS was more likely with longer cardiopulmonary bypass (CPB) times. Immunosuppressive strategies did no differ significantly, although late MCS tended to receive induction therapy more frequently (83.53% vs 92.96%, p = 0.064), mostly with basiliximab.

Regarding implant modality, VA ECMO was more frequently used in early MCS, but no difference between central vs. peripheral cannulation was documented.

Follow up and complications

Complications postHT are presented in **Table 3**. Similar to other reports, mortality was high among severe PGD, with mortality at 3 months and 1 year of 54.1% and 57.9%, respectively. The main causes of death were PGD and infections. Patients with severe PGD required long periods of mechanical ventilation (median 10 days), and suffered a high burden of complications, mainly infections, most of them non-related to MCS, bleeding related and non-related to MCS, severe peripheral vascular complications and need for renal replacement therapy.

Time under MCS, intubation time and length of stay in Critical Care did not differ between early and late MCS. Rates of death under MCS were similar (early 27.98% vs late 31.43%, p 0.59). Total infections, rejection (**See Table S2**) and neurological complications did not differ significantly, although a worse renal function at one-month postHT was noted in late MCS (creatinine 1.08 ± 0.85 mg/dl vs 1.4 ± 1.06 mg/dl, p 0.035). Causes of death did not differ between the two groups.

Focusing on MCS complications, late MCS was associated with more peripheral vascular damage (7.60% vs 18.31%, p 0.014) but no differences were seen in MCS related infections, strokes, embolisms, bleeding, venous thrombosis or need of renal replacement therapy.

Survival in early vs late MCS

Survival curves at 3 months and 1 year are presented in **Figure 2**. No significant differences were observed at 3 months in early vs late MCS initiation after HT (43.82%, 95% CI 36.23%-51.14% vs 48.26%, 95% CI 36.11%-59.38%; Log-Rank p=0,5947) or at 1 year (39.29%, 95% CI 31.85%-46.63% vs 45.24%, 95% CI 33.25%-56.47%, Log-Rank p=0,4953).

In the univariate Cox regression analysis, early MCS implant was not associated with a reduction in mortality at 3 months (HR 1.11, 95% CI 0.76-1.63, p = 0.60) or 1 year (HR 1.14, 95% CI 0.78-1.65, p=0.501). A multivariate Cox regression analysis considering predictors of death differing between early and late MCS (see **Table 4 and 5**), did not show significant differences favoring an early implant at 3 months (HR 1.09, 95% CI 0.72–1.65, p= 0.960) or at 1 year (HR 1.01, 95% CI 0.67–1.52, p=0.952). In the multivariate analysis at one year, recipient BMI (HR 1.05, 1.01-1.10, p value 0.015),

bilirubin preHT ≥2 mg/dl (HR 1.62, 1.09–2.42, p 0.017), induction use (HR 0.37, 0.23–0.60, p<0.001), peripheral cannulation (HR 0.44, 0.31-0.64, p<0.001) and year of transplant (HR 0.92, 0.87-0.98, p 0.012) were significant predictors of outcome.

Differences between central and peripheral cannulation

Differences between central and peripheral cannulation are presented in **Table 6**. 104 patients received central cannulation and 132 peripheral cannulation. Patients with central access had higher vasoactive-inotropic scores and more renal dysfunction, without significant differences in lactate levels preMCS. As expected, VA ECMO was the main MCS in peripheral cannulation.

Peripheral cannulation was associated with more non-related MCS infections, but less MCS-related mayor bleeding. As expected, severe vascular complications were more frequent in peripheral MCS as well as lymphorrhagia at the access point and venous thrombosis. No significant differences in intubation time, stroke, embolisms or renal replacement therapy were recorded. When comparing central and peripheral cannulation complications stratified by early or late MCS, the results were similar, except for a higher use of renal replacement therapy in the central cannulation vs peripheral in the late MCS group (see **Table S4 and S5**).

Remarkably, survival was higher in peripheral compared to central cannulation (see **Figure 3**) at three months (32.42% vs 52.74%, log-rank p 0.001) and at one year (28.19% vs 48.56%, log-rank p 0.0007). Survival curves differed early in the course of these patients. In the multivariate analysis, peripheral cannulation remained as a protective factor at 3 months (HR 0.51, 95% CI 0.36-0.74, p< 0.001) and 1 year (HR 0.44, 95% CI 0.31-0.64, p<0.001), (**see Tables 4 and 5**).

Complications of VA ECMO vs other VADs

Comparing patients under VA ECMO (201) vs other-VADs (36) (see **Table S3**), no differences were seen in intubation time, infections, stroke, embolisms, vascular complications or thrombosis. VA ECMO patients exhibited higher rates of non-MCS related bleeding (49.25% vs 25.00%, p 0.01) and lymphorrhagia at the cannulation access (10.95% vs 0%, p 0.031). Survival curves were similar between VA ECMO and other VADs (See **Figure S1**).

DISCUSSION

To our knowledge, this is the largest cohort of patients with severe PGD reported in literature. In 242 patients with severe PGD, we report that early MCS, as the one initiated intraoperatively or <3h after HT, doesn't improve survival in severe PGD. Remarkably, peripheral cannulation in this setting offers significantly better outcomes after HT compared to central cannulation, which also challenges some evidence from postcardiotomy shock [13], and the scarce available reports in PGD [15]. Furthermore, this fact is not dependent on the usage of VA ECMO vs other VADs as previously described in a 44 patients cohort [5].

In a contemporary, prospective, nationwide Spanish cohort from 2010 to 2020, 21% of patients suffered PGD and 48% of them had severe PGD receiving MCS, of which 71% received early MCS and 29% late MCS. This group of patients exhibited similar features as previously reported in the literature, although most of these reports are small [6-11] and until 2014 the definition of PGD was not uniform.

The general PGD rates in our study are in line with previous data. In the metanalysis performed by Buchan et al [19], PGD rate was 20.5% (21.21% in our study). However,

severe PGD seems slightly higher in our cohort (10.5% compared to 7.7% in the previous article). These differences could be a consequence of the use of older donors in Spain [2], with a mean donor age of 42.2±14.9 years compared to 36 years (IQR 23-50 years) in the metanalysis.In our cohort, the majority of patients were in a very advanced situation prior to HT, reflected by 47.5% needing ambulatory inotropic support, 27.0% under mechanical ventilation and 45.0% under MCS at the time of surgery. Mortality was remarkably high, with a 54.13% mortality at 3 months and 57.85% at one year. Other authors have reported similar or better survival rates at one year [4-12,17-18], reflecting the complexity and diversity of this scenario. In the setting of PGD, an aggressive vs conservative strategy for MCS has only been explored by DeRoo et al. in a retrospective analysis of a single-center 38 patients cohort comparing two eras, with results favoring early initiation [6]. Our findings contrast with the strikingly high one-year survival rates reported by DeRoo et al. [6], ranging from 67% to 90% depending on a more aggressive or conservative strategy with MCS, considering that the general assumed mortality in PGD with or without MCS is around 30% [1] and in severe PGD around 40% [19]. Although the prevalence of severe PGD in DeRoo's cohort was 10.5%, very similar to ours, most of their patients were in a much more stable situation under long-term MCS prior to HT (no patients with ventilation and less than 20% prior inotrope use) and the vasoactive inotropic scores prior to MCS implant postHT were half the values seen in our series. Also, the mean donor age in their series was 30 years old compared to 47 years old in our series, resulting in a much shorter support time of 4 days compared to 8 days in our series. All these factors could explain the differences in survival seen between both series.

The importance of early MCS in cardiogenic shock has progressively been advocated in order to prevent end-organ damage and avoid the subsequent shock cascade [20]. In PGD, the early unload and avoidance of the toxic effects derived from lactic acidosis and high doses of inotropes and vasoactive drugs to the graft, that is already suffering from ischemic reperfusion injury, may help improve outcomes[21].

In our 242 patient cohort requiring MCS, no differences in mortality after multivariate analysis were documented when comparing an aggressive early vs late MCS initiation. In our cohort, the majority of early MCS left the operating room already under MCS (95.4%), possibly reflecting more severe cases, also illustrated by longer CPB times, although total ischemic times were similar. This could be counterbalanced by the higher vasoactive-inotropic scores and more severe renal failure in late MCS at the time of cannulation, reflecting longer times with poor end-organ perfusion until initiation of support, although lactate levels did not differ significantly. This point is important, given that even though PGD was diagnosed in the first 24 hours after the HT surgery in both early and late MCS implant groups, lactates at the time of implant were similar. Therefore, it makes sense that if patients at the time of MCS implant, both in the early and late implant group, were in a similar clinical situation, evaluated by the best marker of end-organ dysfunction (lactate), outcomes should be similar. It also emphasizes that it should be the clinical situation and not the timing related to the surgery that should guide MCS implant in patients with PGD, given the significant complications related to MCS.

PreHT MCS was more frequent in early MCS (specially VA-ECMO), and might have contributed to less significant differences in survival in this group. Nevertheless, it

could also be argued that this could reflect a tendency to maintain VA-ECMO after HT in patients that might no longer need it and, therefore, favor the early MCS group. Either way, preHT MCS was not a significant predictor of survival in our cohort. Time under MCS, intubation time and length of stay in Critical Care did not differ between early and late MCS, and rates of death under MCS were similar. A non-significant tendency towards more bacterial infections was documented in late MCS, but total infections and rejection were similar, although a worse renal function at one-month postHT was noted in late MCS. Regarding MCS complications, peripheral vascular complications were more frequent in late MCS. As cannulation type did not differ between early and late MCS, this might not explain the lack of benefit.

Interestingly, patients that received peripheral cannulation exhibited remarkably better survival. Central cannulation is frequently used in post-cardiotomy shock, as it employs cannulas already in place for cardiopulmonary bypass. It ensures adequate venous drainage and allows for greater cardiac decompression than peripheral cannulation[22]. In addition, there is less concern for retrograde flow and upper body hypoxemia. A key disadvantage of central cannulation is that it requires re-entering the chest for MCS discontinuation, conferring an increased risk of bleeding, surgical re‑exploration and mediastinitis, and most of them remain intubated. In contrast, peripheral cannulation allows for primary chest closure, extubation and patient mobilization, at the expense of the risk of upper body hypoxemia, aortic root thrombus formation, left ventricular distension, and lower extremity ischemia. However, as in most cases of PGD, the RV is more dysfunctional than the LV, peripheral VA-ECMO for PGD usually is not associated with poor unload of the LV and is therefore a theoretical good option for PGD. In postcardiotomy shock, retrospective analysis

have generally found no difference in outcomes between these two strategies [23-24], except for isolated reports of better survival with central cannulation[25]. A recent meta-analysis showed no difference in survival between central vs peripheral cannulation [13], but another meta-analysis focusing on post-cardiotomy shock suggested superior outcomes with peripheral cannulation [14], as central cannulation portended higher rates of major bleeding, chest reopening for bleeding/tamponade and need for more blood product transfusions. In the scenario of PGD, evidence is extremely limited [15]. In our cohort, peripheral cannulation was associated with more non-related MCS infections and vascular damage but less MCS-related mayor bleeding, without significant differences in intubation time, stroke, embolisms, thrombosis or renal replacement therapy. Survival curves separated early in the course of these patients and this difference remained after adjusting for other statistically significant variables in the multivariate analysis.

The chosen VAD might have influenced these results, as VA ECMO was more frequently used in early vs late MCS (89.22% vs 74.29%). Some studies have suggested better outcomes with VA ECMO against other VADs [5]. In our cohort, with 201 patients under VA ECMO and 36 with other VADs, no significant differences in survival were seen between these two groups, although numerically higher survival rates for VA ECMO compared to other VADs were noted. Nevertheless, VA ECMO patients exhibited higher rates of non-MCS related bleeding, vascular complications, venous thrombosis and lymphorrhagia of cannulation access point.

The improvement in survival over the years is probably related to improved medical management, with better outcomes for more recent transplants being statistically

significant in the multivariate analysis. An early implant has progressively been more frecuent as shown in the data, but this does not explain by itself the difference in survival.

Our study has several limitations. First, despite being the largest cohort of severe PGD, it still carries the same limitations as other observational studies. Although based on prospective data, some key information was acquired retrospectively from clinical records. Second, the definition of early vs late initiation of MCS was adopted according to investigators criteria but it is similar to De Roo's study [6] and it clearly selects a cohort of early implant (95% intraoperatively). Third, no data regarding blood product usage was obtained, and it might have influenced the results, for example, if more severe postsurgical hemorrhages might have caused deeper shock and need for MCS or triggered transfusion-related complications. Fourth, the lack of statistical significance of the tendency towards higher survival rates of VA ECMO compared to other VAD could be secondary to insufficient statistical power. Fifth, the results of this study come from Spain, and despite reflecting practice in a wide geographic area, results might not be applicable to other countries with different HT allocation policies.

In conclusion, in a cohort of HT patients with severe PGD, early MCS initiation was not superior to a more conservative approach with deferred initiation. However, peripheral compared to central cannulation showed superior 3-month and 1-year survival rates, apparently at the expense of less major MCS related bleeding. MCS modality, comparing VA ECMO with other VADs, did not influence outcomes.

Author contributions

All authors have contributed in the collection of data, analysis, manuscript elaboration and its critical review.

Declaration of Competing Interest

Dr. González-Vilchez has received support for attending meetings and/or travel expenses from Pfizer and Novartis; Dr. Farrero-Torres has received honoraria for lectures and presentations from Astra Zeneca, Boehringuer, Novartis and Vifor and is member of board of the Sociedad Española de Cardiologia and the International Society for Heart and Lung transplantation; Dr. Pomares-Varó has received support for attending meetings from Novartis and Bayer; Dr. González-Costello has received honoraria for lectures from Abbott, participation in advisory boards from Abbott and Chiesi and support for attending meetings from Abbott. None of the other authors has a financial relationship with a commercial entity that has an interest in the subject of the presented manuscript or other conflicts of interest to disclose.

Acknowledgements

Raquel López-Vilella, Víctor Donoso Trenado, José Antonio Vázquez de Prada, Elena García-Romero, Pablo Catalá-Ruíz, Vanesa Alonso Fernández, Cristina Fidalgo Muñiz, Antonio Adeba García, Virginia Martin Manzano, Carlos Ortiz-Bautista, Javier Castrodeza Calvo, Paula Navas Tejedor, Eduardo Zatarain Nicolas, Maria Jesus Valero, Adolfo Villa, Iago Sousa, Manuel Martinez-Selles, Antonio Grande Trillo, Diego Rangel Sousa, Sara Lozano Jiménez, Francisco Hernández Pérez, Cristina Mitroi, Mercedes Rivas Lasarte, José María Vieitez Flórez, Javier Segovia Cubero, Susana Villar García, Alberto Forteza Gil, Reyes Iranzo, Rubén Jara Rubio, Francisco Pastor Pérez, Domingo Pascual Figal, Sergio Canovas López, Maria G Crespo Leiro, José J Cuenca Castillo, David Couto Mallón, Gonzalo

Barge Caballero, Maria J Paniagua Martin, Joan Guzman-Bofarull, Juan Delgado-Jiménez, Juan Carlos López-Azor, Irene Marco Clement, Ana Portoles Ocampo, María Lasala Alastuey, Sonia Mirabet Pérez, Vicens Brossa Loidi, Marta de Antonio Ferrer, Laura López López, Alba Maestro Benedicto, Carles Moliner Abos.

Financial disclosure statement

The present study has not received any financial aid.

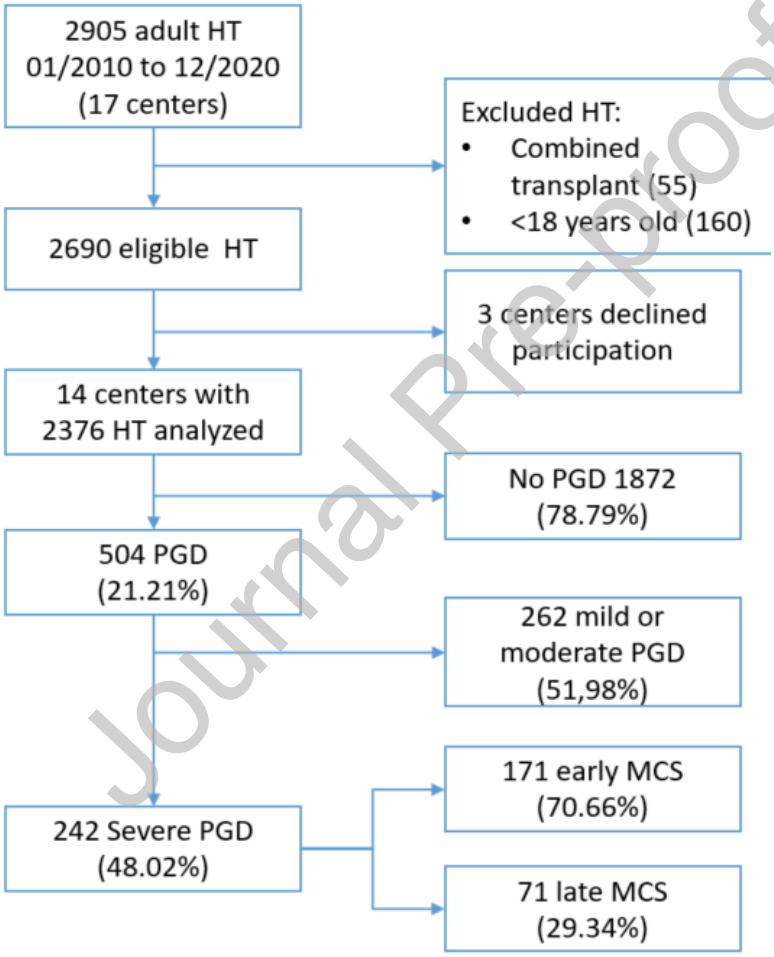

Figure 1: Flowchart of patients receiving a heart transplant in Spain between 2010 and 2020 and suffering primary graft dysfunction.
HT – Heart Transplant; PGD – Primary graft dysfunction; MCS – Mechanical circulatory support.

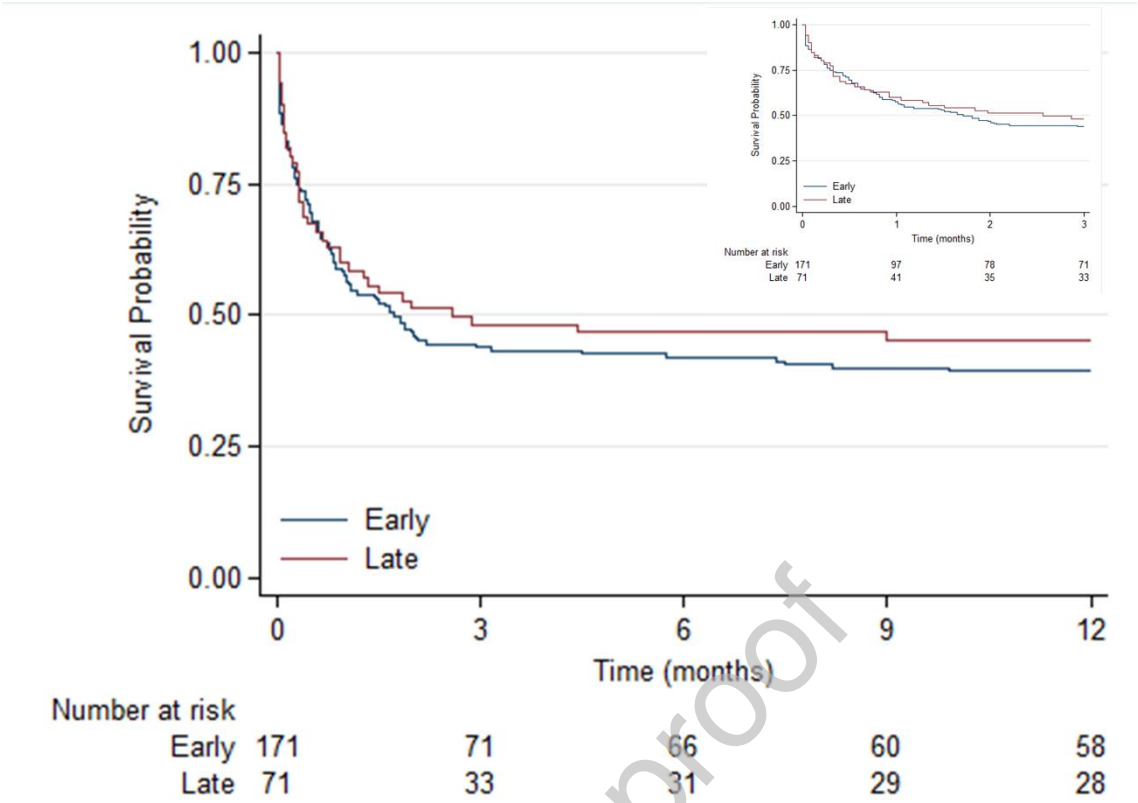

Figure 2: Survival curves according to early or late initiation of mechanical circulatory support. Log-Rank test 3 months: p=0.5947. Log-Rank test 1 year: p=0.4953.

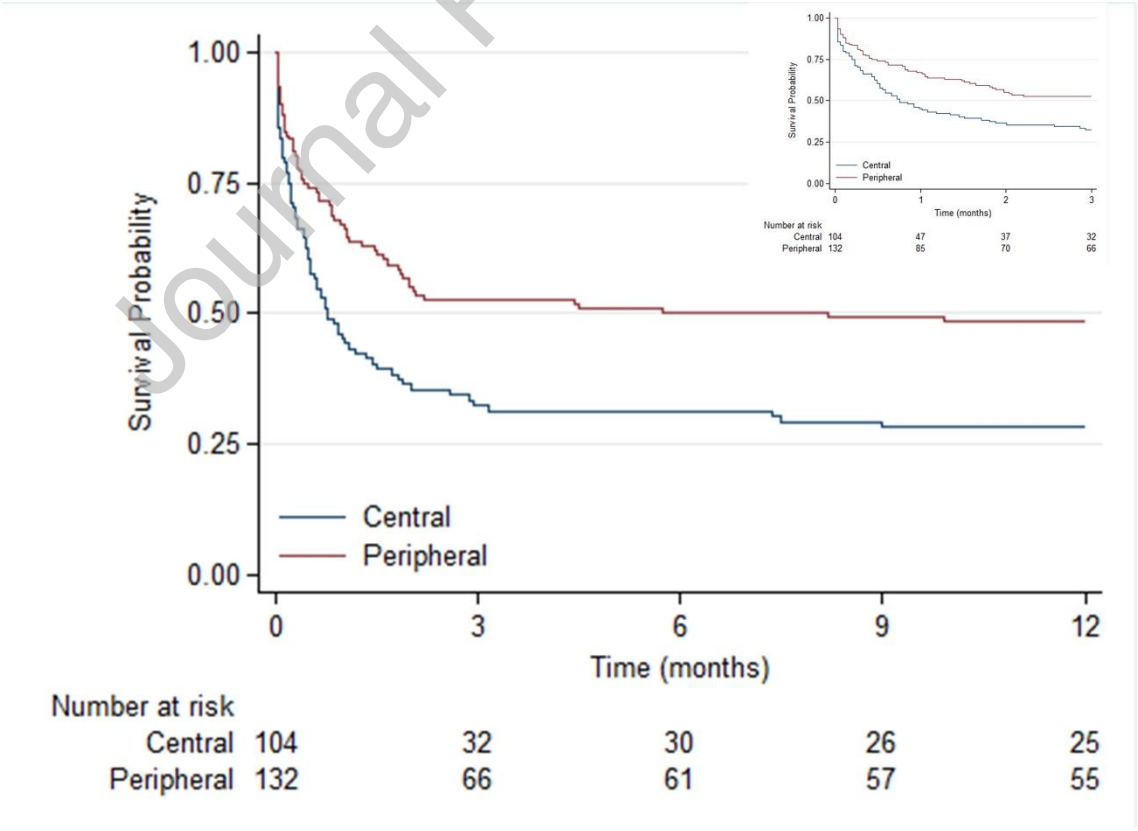

Figure 3: Survival curves according to central or peripheral cannulation of mechanical circulatory support. Log-Rank test 3 months: p=0.001. Log-Rank test 1 year: p=0.0007.

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Table 1: Baseline characteristics of early vs late mechanical circulatory support in severe PGD.

RECIPIENT DATA	**Total cohort**		**Early MCS**		**Late MCS**		**p-value**
	n		n		n		
Patients	242		171		71		
Year of transplant	242		171	2016 ± 3	71	2015 ± 3	0.014
Era of transplant							0.060
2010-2015	107	44.21%	69	40.35 %	38	53.52 %	
2016-2020	135	55.78%	102	59.65 %	33	46.48 %	
Age (years)	242	55 (45-63)	171	56 (45-63)	71	55 (43-62)	0.786
Sex (male)	177	73.14%	130	76.02 %	47	66.20 %	0.116
Weight (Kg)	242	70 (62-80)	171	70 (63-82)	71	70 (60-79)	0.166
Height (cm)	242	167.87 ± 8.68	171	167.92 ± 8.68	71	167.75 ± 8.74	0.956
BMI (kg/m^2)	242	25.2 (22.22-28.23)	171	25.71 (22.53-28.39)	71	23.63 (21.63-27.55)	0.056
Cardiac disease							0.943
Non-ischemic DCM	78	32.23%	56	32.75 %	22	30.99 %	
Ischemic DCM	95	39.26%	66	38.60 %	29	40.85 %	
Others	69	28.51%	49	28.65 %	20	28.17 %	

Ambulatory inotropic treatment	115	47.52%	87	50.88 %	28	39.44 %	0.105
Creatinine pre-HT (mg/dl)	241	1.1 (0.8-1.4)	170	1.1 (0.8-1.4)	71	1.11 (0.8-1.5)	0.825
Bilirubin (mg/dl)	211	1.1 (0.7-1.91)	151	1.17 (0.7-2.0)	60	1.0 (0.63 - 1.52)	0.290
AST (IU/L)	226	30 (23-41)	161	32 (24-47)	65	28 (20-36)	0.043
ALT (IU/L)	231	28 (19-47)	167	29 (19-50)	64	25 (17-36.5)	0.053
Diabetes mellitus	52/240	21.67%	35/169	20.71 %	17/71	23.94 %	0.579
Peripheral vasculopathy	14/239	5.86%	7/168	4.17 %	7/71	9.86 %	0.128
Pre-HT tobacco use	19	7.85%	14	8.19 %	5	7.04 %	0.132
Mechanical ventilation pre-HT	64/237	27.00%	50/167	29.94 %	14/70	20.00 %	0.116
MCS preHT	240		169		71		0.030
None	116	48.33%	75	44.38 %	41	57.75 %	
Intraaortic balloon pump	16	6.67%	9	5.33 %	7	9.86 %	
VA ECMO	50	20.83%	43	25.44 %	7	9.86 %	
VAD Continuous flow	50	20.83%	37	21.89 %	13	18.31 %	
VAD Pulsatile flow	8	3.33%	5	2.96 %	3	4.23 %	
PreHT MCS	124	51.24%	94/169	55.62 %	30/71	42.25 %	0.059
Patient situation	241		171		70		0.246
At home	109	45.23%	76	44.44 %	33	47.14 %	
Conventional hospitalization	11	4.56%	5	2.92 %	6	8.57 %	
Critical Care Unit	102	42.32%	76	44.44 %	26	37.14 %	
Surgical Critical Care	19	7.88%	14	8.19 %	5	7.14 %	

DONOR DATA							
Age (years)	242	47 (36-54)	171	47 (35-54)	71	48 (38-55)	0.524
Sex (male)	146/241	60.58%	106/170	62.35%	40/71	56.34%	0.384
Weigh (Kg)	242	75 (65-81)	171	75 (65-82)	71	72 (65-80)	0.315
Height (cm)	239	170 (165-175)	170	170 (165-175)	69	170 (162-175)	0.433
BMI (kg/m^2)	239	25.39 (23.37-27.77)	170	25.62 (23.44-27.76)	69	24.98 (22.86-27.97)	0.402
Days in critical care	215	2 (1-5)	152	2 (1-5)	63	3 (1-6)	0.692
Dobutamine use pre-HT	6/207	2.90%	5	3.40%	1	1.67%	0.675
Noradrenaline Pre-HT (µg/kg/min)	219		155		64		0.029
None	44	20.09%	29	18.71%	15	23.44%	
0-0.10	53	24.20%	37	23.87%	16	25.00%	
0.11-0.5	96	43.84%	75	48.39%	21	32.81%	
>0.5	26	11.87%	14	9.03%	12	18.75%	
Cause of death	241		170		71		0.093
Traumatism	54	22.41%	44	25.88%	10	14.08%	
Cerebrovascular	167	69.29%	111	65.29%	56	78.87%	
Other	20	8.30%	15	8.82%	5	7.04%	

BMI – Body mass index; DCM – Dilated cardiomyopathy; preHT – Preheart transplant; MCS – Mechanical circulatory support; AST - Aspartate aminotransferase; ALT - Alanine aminotransferase; VA ECMO – Venoarterial extracorporeal membrane oxygenator; VAD – Ventricular assist device; PGD – Primary graft dysfunction; BIV – Biventricular; RVAD – Right ventricular assist device

Table 2: Surgical and post-heart transplant data of early vs late mechanical circulatory support in severe PGD.

RECIPIENT DATA	Total cohort		Early MCS		Late MCS		p-value
	n		n		n		
Patients	242		171		71		
SURGICAL DATA							
Total ischemic time (min)	242	210 (150-250)	171	208 (145-250)	71	210 (170-241)	0.413
CPB time (min)	239	157 (120-215)	169	168 (125-233)	70	143 (116-189)	0.010
Surgical technique	239		169		70		0.630
Standard	90	37.66%	62	36.69 %	28	40.00 %	
Bicaval	149	62.34%	107	63.31 %	42	60.00 %	
Re-transplant	3	1.24%	2	1.17 %	1	1.41%	1.000
Induction use	208/241	86.31%	142/170	83.53 %	66/71	92.96 %	0.064
MCS DATA POST-HT							
Moment of implantation							
Prior to HT	20	8.26%	20	11.70 %	0	0.00%	<0.001
During HT	143	59.09%	143	83.63 %	0	0.00%	
After leaving operating room	79	32.64%	8	4.68 %	71	100.00%	
Time until initiation of MCS (hours)	242	9.6 ± 22.8	151	0.73 ± 0.86	71	28.46 ± 33.3	<0,001
Support type	241		170		71		<0.001
Biventricular	200	82.99%	149	87.65 %	51	71.83 %	
Left	15	6.22%	12	7.06 %	3	4.23%	
Right	26	10.79%	9	5.29 %	17	23.94 %	
Vasoactive-inotropic score	127	70.26 ± 60.97	81	56.2 ± 48.99	46	95.02 ± 71.81	<0.001
Lactate preMCS (mmol/L)	148	7.79 ± 5.06	87	7.75	61	7.84 ±	0.99

				± 5.02		5.15	4
Creatinine preMCS (mg/dL)	130	1.66 ± 0.85	63	1.55 ± 1.01	67	1.75 ± 0.66	0.007
ALT preMCS (U/L)	99	635.33 ± 1472.66	43	166.07 ± 331.52	56	995.66 ± 1864.4	0.175
MCS postHT	237		167		70		0.003
VA ECMO	201	84.81%	149	89.22 %	52	74.29 %	
Centrimag® BIV	4	1.69%	3	1.80 %	1	1.43%	
Centrimag® RVAD	13	5.49%	4	2.40 %	9	12.86 %	
ABIOMED® BIV	1	0.42%	1	0.60 %	0	0.00%	
ABIOMED® RVAD	2	0.84%	0	0.00 %	2	2.86%	
Other	16	6.75%	10	5.99 %	6	8.57%	
Cannulation	236		167		69		0.488
Central	104	44.07%	76	45.51 %	28	40.58 %	
Peripheral	132	55.93%	91	54.49 %	41	59.42 %	
Time under MCS (days)	232	7.89 ± 7.53		8.15 ± 8		7.28 ± 6.29	0.944
Death during MCS	69/238	28.99%	47/168	27.98 %	22/70	31.43 %	0.593

PGD – Primary graft dysfunction; CPB – Cardiopulmonary bypass; MCS – Mechanical circulatory support; VA ECMO – Venoarterial extracorporeal membrane oxygenator; VAD – Ventricular assist device; BIV – Biventricular; RVAD – Right ventricular assist device.

Table 3: Complications and follow up of patients with severe primary graft dysfunction with early or late initiation of mechanical circulatory support.

RECIPIENT DATA	**Total cohort**		**Early MCS**		**Late MCS**		**p-value**
	n		n		n		
Patients (n)	242		171		71		
Time under MCS (days)	232	7,89 ±	163	8,15 ± 8	69	7,28 ± 6,29	0.944

		7,53					
Length of stay in critical care (days)	220	17 (8-31)	154	17 (8-30)	66	17 (9-31)	0.981
Days under mechanical ventilation (days)	124	10 (4-20)	81	9 (3-18)	43	13 (6-24)	0.078
Mayor infection related to MCS	8/237	3.38 %	6/168	3.57%	2/69	2.90%	1.000
Mayor infection non-related to MCS	112/241	46.47 %	74/170	43.53 %	38/71	53.52%	0.156
Severe peripheral vascular complication	26	10.74 %	13	7.6%	13	18.31%	0.014
Ischemic stroke	14	5.79 %	8	4.68%	6	8.45%	0.363
Hemorrhagic stroke	8	3.31 %	5	2.92%	3	4.23%	0.696
Mayor bleeding related to MCS	75/239	31.38 %	55/169	32.54 %	20/70	28.57%	0.547
Mayor bleeding non-related to MCS	108	44.63 %	77	45.03 %	31	43.66%	0.846
Venous thrombosis	21	8.68 %	13	7.60%	8	11.27%	0.452
Renal replacement therapy	110/241	45.64 %	74/170	43.53 %	36/71	50.70%	0.308
Lymphorrhagia in access site	22	9.09 %	14	8.19%	8	11.27%	0.466
Death during MCS	69/238	28.99 %	47/168	27.98 %	22/70	31.43%	0.593
Mortality			171		71		
3 months	131	54.13 %	95	55.56 %	36	50.70%	0.490
1 year	140	57.85 %	102	59.65 %	38	53.52%	0.379
Cause of death at 3 months	130		94		36		0.614
PGD	74	56.92 %	53	56.38 %	21	58.33%	
Acute rejection	4	3.08 %	2	2.13%	2	5.56%	
Infection	23	17.69 %	19	20.21 %	4	11.11%	
Allograft vasculopathy	2	1.54 %	2	2.13%	0	0.00%	
Multiorgan failure	4	3.08 %	3	3.19%	1	2.78%	
Other	23	17.69 %	15	15.96 %	8	22.22%	

MCS – Mechanical circulatory support; PGD – Primary graft dysfunction.

Table 4. Multivariate Cox regression model for survival at 3 months according to time of implant of MCS in primary graft dysfunction.

	Initial model (n=211)				Final model (n=217)			
	HR	CI 95%		p-value	HR	CI 95%		p-value
Early MCS implant	1.04	0.68	1.60	0.863	1.09	0.72	1.65	0.694
Recipient BMI	1.06	1.01	1.11	0.010	1.06	1.02	1.11	0.006
Bilirubin≥2 mg/dl preHT	1.53	0.98	2.38	0.059	1.71	1.14	2.56	0.010
Mechanical Ventilation preHT	1.20	0.78	1.85	0.405				
Smoker pre-HT	0.61	0.34	1.09	0.097				
CPB time (min)	1.00	1.00	1.00	0.198				
Peripheral cannulation	0.53	0.37	0.78	0.001	0.51	0.36	0.74	<0.001
Year of HT	0.94	0.88	1.00	0.044	0.92	0.87	0.98	0.015

MCS – Mechanical circulatory support. BMI – Body mass index as kg/m2. HT – Heart Transplant. CPB – Cardiopulmonary bypass. The variable Mechanical Ventilation pre-HT included in the initial model violated the proportional hazard assumption. The final model complies with the proportional hazards assumption.

Table 5. Multivariate Cox regression model for survival at 12 months according to time of implant of MCS in primary graft dysfunction.

	Initial model (n=210)				Final model (n=216)			
	HR	CI 95%		p-value	HR	IC 95%		p-value
Early MCS implant	0.97	0.63	1.48	0.878	1.01	0.67	1.52	0.956
Recipient BMI (1 kg/m^2)	1.05	1.01	1.10	0.023	1.05	1.01	1.10	0.015
Bilirubin ≥2 mg/dl pre-HT	1.51	0.98	2.32	0.060	1.62	1.09	2.42	0.017
Mechanical Ventilation preHT	1.12	0.73	1.71	0.599				
Smoker preHT	0.63	0.35	1.14	0.127				
CPB time (min)	1.00	1.00	1.00	0.132				
Induction therapy	0.34	0.20	0.58	<0.001	0.37	0.23	0.60	<0.001
Year of HT	0.93	0.87	0.99	0.033	0.92	0.87	0.98	0.012
Peripheral cannulation	0.43	0.29	0.63	<0.001	0.44	0.31	0.64	<0.001

MCS – Mechanical circulatory support. BMI – Body mass index as kg/m2. HT – Heart Transplant. CPB – Cardiopulmonary bypass. The 2 models presented in this table comply with the proportional hazards assumption.

Table 6: Complications depending on central vs peripheral cannulation.

RECIPIENT DATA	**Central**		**Peripheral**		**p-value**
	n		n		
Patients (n)	104		132		
Age (years)	104	53.5 (42.5-62.5)	132	56 (45-62)	0.791
Gender (male)	71	68.27%	31	23.48%	0.157
BMI (kg/m^2)	104	25.06 (22.1-28.31)	132	25.49 (22.14-28.27)	0.773

MCS preHT	102		132		0.302
None	56	54.90%	57	43.18%	
Intraaortic balloon pump	7	6.86%	7	5.30%	
VA ECMO	18	17.65%	32	24.24%	
VAD Continuous flow	17	16.67%	32	24.24%	
VAD Pulsatile flow	4	3.92%	4	3.03%	
PreHT MCS	46/102	45.10%	75/132	56.82%	0.075
Time of implantation	104		132		<0.001
Prior to HT	0	0.00%	20	15.15%	
During HT	71	68.27%	69	52.27%	
After leaving operating room	33	31.73%	43	32.58%	
Time until initiation of MCS (hours)	104	10.08 ± 24.92	112	9.19 ± 21.03	0.361
Lactate preMCS (mmol/L)	68	8.54 ± 5.79	79	7.21 ± 4.27	0.295
Creatinine preMCS (mg/dL)	60	1.81 ± 1	67	1.52 ± 0.68	0.033
ALT preMCS (U/L)	95	58.34 ± 104.2	130	42.09 ± 48.82	0.408
Vasoactive-inotropic score	70	76.18 ± 56.75	57	62.99 ± 65.55	0.007
MCS postHT	103		132		<0.001
VA ECMO	72	69.90%	128	96.97%	
Centrimag® BIV	4	3.88%	0	0.00%	
Centrimag® RVAD	13	12.62%	0	0.00%	
ABIOMED® BIV	1	0.97%	0	0.00%	
ABIOMED® RVAD	2	1.94%	0	0.00%	
Other	11	10.68%	4	3.03%	
Time under MCS (days)	100	7.58 ± 7.01	130	8.21 ± 7.95	0.534
Length of stay in critical care (days)	92	18 (7-29)	122	17 (8-32)	0.729
Death under MCS	42/104	40.38%	27/131	20.61%	0.001
Extubated under MCS	12/100	12.00%	25/128	19.53%	0.126
Days under mechanical ventilation (days)	50	15.4 ± 13.65	70	14.47 ± 17.94	0.124
Mayor infection related to MCS	2/103	1.94%	6/132	4.55%	0.471
Mayor infection non-related to MCS	36	34.62%	75	56.82%	0.001
Severe peripheral vascular complication	2	1.92%	24	18.18%	<0.001
Ischemic stroke	8	7.69%	6	4.55%	0.407
Hemorrhagic stroke	5	4.81%	3	2.27%	0.306

Mayor bleeding related to MCS	45	43.27%	30	22.73%	0.001
Mayor bleeding non-related to MCS	43	41.35%	65	49.24%	0.227
Access point lymphorrhagia	2	1.92%	20	15.15%	<0.001
Venous thrombosis	4	3.85%	17	12.88%	0.020
Renal replacement therapy	53/104	50.96%	55/131	41.98%	0.170
Mortality	104		132		
3 months	70	67.31%	61	46.21%	0.001
1 year	74	71.15%	66	50.00%	0.001
Cause of death at 3 months	69		61		0.005
PGD	49	71.01%	25	40.98%	
Acute rejection	1	1.45%	3	4.92%	
Infection	9	13.04%	14	22.95%	
Allograft vasculopathy	1	1.45%	1	1.64%	
Multiorgan failure	0	0.00%	4	6.56%	
Other	9	13.04%	14	22.95%	

BMI – Body Mass Index; MCS – Mechanical circulatory support; HT – Heart Transplant; ALT – alanine aminotransferase; VA ECMO – Venoarterial extracorporeal membrane oxygenator; VAD – Ventricular assist device; BIV – Biventricular; RVAD – Right ventricular assist device