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ORIGINAL ARTICLE

Major adverse kidney events predict reduced survival in ventricular assist device supported patients

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Abstract

Aims There is limited data describing major adverse kidney events (MAKE) in patients supported with ventricular assist devices (VAD). We aim to describe the association between MAKE and survival, risk factors for MAKE, and renal trajectory in VAD supported patients.

Methods and results We conducted a single-centre retrospective analysis of consecutive VAD implants between 2010 and 2019. Baseline demographics, biochemistry, and adverse events were collected for the duration of VAD support. MAKE was defined as the first event to occur of sustained drop (>50%) in estimated glomerular filtration rate (eGFR), progression to stage V chronic kidney disease, initiation or continuation of renal replacement therapy beyond implant admission or death on renal replacement therapy at any time. One-hundred and seventy-three patients were included, median age 56.8 years, 18.5% female, INTERMACS profile 1 or 2 in 75.1%. Thirty-seven patients experienced MAKE. On multivariate analysis, post-implant clinical right ventricular failure and the presence of chronic haemolysis, defined by the presence of schistocytes on blood film analysis, were significantly associated with increased risk of MAKE (adjusted odds ratio 9.88, $P < 0.001$ and adjusted odds ratio 3.33, $P = 0.006$, respectively). MAKE was associated with reduced survival (hazard ratio 4.80, $P < 0.001$). Patients who died or experienced MAKE did not demonstrate the expected transient 3-month improvement in eGFR, seen in other cohorts.

Conclusions MAKE significantly impacts survival. In our cohort, MAKE was predicted by post-implant right ventricular failure and chronic haemolysis. The lack of early eGFR improvement on VAD support may indicate higher risk for MAKE.

Keywords Major adverse kidney events; Survival; Ventricular assist device

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Introduction

Impaired renal function negatively impacts prognosis of heart failure patients at all stages of their management. In patients requiring durable mechanical circulatory support with implantation of a ventricular assist device (VAD), several adverse kidney events have been associated with lower survival. Historically, the focus has been on the impact of peri-operative acute kidney injury (AKI) and renal replacement therapy (RRT) as an adverse prognosticator. With destination therapy constituting the majority of VAD implants globally, it is important to consider the impact of adverse kidney events throughout the duration of VAD support on morbidity, mortality, and quality of life.[1]

Initially developed as a tool to evaluate risk of AKI progression, major adverse kidney events (MAKE) have been increasingly used as a measure of clinical effectiveness, both in AKI, and more recently, heart failure trials.[2–4] We sought to define the impact of MAKE throughout VAD support on survival.

The typical trajectory of renal function following VAD support is an early improvement within the first few months followed by a gradual decline back to pre-implant baseline.[5] Multiple theories including progressive right ventricular (RV) dysfunction, chronic haemolysis, and lack of pulsatility have

been postulated in contributing to this late decline from peak renal function; however, these have not been fully explored in clinical studies.[6] Chronic haemolysis has not been uniformly defined in the context of VAD supported patients.

We looked to establish the relationship between MAKE and survival on VAD support, to determine predictors of MAKE, and to analyse differences in estimated glomerular function rate (eGFR) trend based on survival and MAKE status.

Methods

Study design

The study protocol was approved by the local hospital's human research ethics committee (2020/ETH00410). Consecutive patients supported with VAD between January 2010 and December 2019 inclusive at a single heart transplant referral centre were included for retrospective analysis.

The primary objective of this study was to (i) identify risk factors for developing MAKE on VAD support, (ii) evaluate the time-to-event relationship between MAKE and survival to transplantation, and (iii) identify renal trajectory in the VAD supported cohort, and whether this trajectory differed in patients dying on VAD support or those who experienced MAKE.

Data collection

All data were obtained from patients' electronic and paper based medical records. Baseline demographics, heart failure aetiology, medical history, INTERMACS profile, VAD configuration, peri-implant support, pre-implant transthoracic echocardiography, pre-implant right heart catheterization, and stable medical therapy at 3-month's support were collected. Biochemistry results were obtained from the local hospital's pathology service. Creatinine values closest to pre-specified time points (pre-implant, day 7, 1 month, 3 months, 6 months, 9 months, and 12 months) were obtained and transformed into eGFR using the 2021 CKD-EPI eGFR equation.[7] All lactate dehydrogenase (LDH) values available on the local hospital pathology electronic system for the first 12-month support were averaged to calculate the average LDH. Chronic haemolysis was defined as the presence of schistocytes on blood film, in the absence of significant LDH or plasma-free haemoglobin elevation/haemoglobin drop or need for blood transfusion. Clinical RV failure on VAD support was defined in accordance with the Mechanical Circulatory Support Academic Research Consortium Consensus Statement.[8]

MAKE were defined as the first event to occur of

1. sustained drop in eGFR $>$ 50% of the pre-implant value as measured during stable outpatient clinic visits, with two readings collected at least 1 month apart;
2. progression to stage V chronic kidney disease (CKD) with eGFR $<$15 mL/min/1.73 m^2 at any time beyond the index implant admission;
3. RRT initiation or continuation beyond the index implant admission, or death while on RRT at any time.

Statistical analysis

Descriptive statistics were summarized as mean ± standard deviations or median with interquartile range for continuous variables based on normality and counts with percentages for categorical data. All statistical tests were two sided, and *P*-values $<$0.05 were considered significant. All data analysis was conducted using R studio version 1.4, with packages lme4, survival, survminer, and sjPlot (R Foundation for Statistical Computing, Vienna, Austria).

Predictors of major adverse kidney events

Univariate analysis for predictors of MAKE was performed using Student's *t*-test or Mann–Whitney *U* test for continuous variables and χ^2 or Fisher's exact test for categorical variables. Any parameter with significant *P*-value was tested with univariate logistic regression. Significant univariate predictors were included in a multivariable logistic regression models. Model 1 included all parameters significant on univariate logistic regression, and model 2 was restricted to parameters significant within model 1.

Time to event analysis for major adverse kidney events and survival to transplant

Time to event analysis was performed for MAKE events using Kaplan–Meier censoring for transplant or death, with Cox regression analysis performed to evaluate the risk of death on VAD support in patients experiencing MAKE.

Modelling of renal trajectory over the first 12 months of ventricular assist devices support

Linear mixed models with random patient intercepts were used to evaluate eGFR. Pre-specified time points were used as categorical fixed effects variables. Differences in eGFR at each pre-specified time point were compared with pre-implant eGFR (intercept) in the entire cohort. MAKE and death on VAD support were analysed in separate models as a fixed interacting factor with time.

Results

One hundred and seventy three consecutive VAD supported patients were studied. The median age was 56.8 (45.9–63.1) years, with 32 (18.5%) being female. Devices used include the Medtronic HeartWare HVAD (n = 164) and Abbott HeartMate 3 (HM3, n = 7), with two patients being implanted with the Heartware MVAD. Nineteen patients (11.0%) had a biventricular assist device (dual HVAD) configuration. The majority were INTERMACS profile 1 or 2 at the time of their implant (75.1%). Seven patients (4.0%) were on RRT at implant. Twenty-nine patients (17.3%) required RRT in the immediate post-operative period. All patients were bridge-to-transplant at the time of implant.

One hundred and twenty-five patients survived to transplant, 2 patients remain on VAD support, and 46 patients died on VAD support. MAKE could not be assessed in the two patients remaining on VAD support, nor five patients who completed their treatment at other transplant centres. Of the remaining patients, 37 (22.3%) experienced MAKE, occurring at a median 72 (interquartile range 8–260) days. *Table 1* summarizes differences in baseline demographics, co-morbidities, pre-implant renal function, right heart catheterization, RV function on echocardiography, peri-implant organ support, and stable medical therapy in patients experiencing MAKE on VAD support. Pre-implant eGFR, INTERMACS profile 1 or 2, RRT prior to implant, pre-implant right atrial pressure (RAP), pulmonary artery pulsatility index, and BiVAD configuration were significantly different between the MAKE and no MAKE groups. While on VAD support, patients with MAKE had higher average LDH, more frequently had schistocytes present suggestive of chronic haemolysis, and were more likely to have clinical RV failure. For those surviving and not transplanted prior to 3 months, the use of renin-angiotensin system (RAS) blockers (including angiotensin converting enzyme inhibitors or angiotensin receptor blockers) appeared protective.

Univariate logistic regression was performed on all parameters that differed significantly between the MAKE and no MAKE groups, except for pulmonary artery pulsatility index, which correlated significantly with RAP. All parameters that remained significant were included in a multivariate logistic regression model, model 1, for the prediction of MAKE, as shown in *Table 2*. Model 2 was optimized to include only parameters found to be significant in model 1. Clinical RV failure significantly increased the risk of MAKE (adjusted odds ratio 9.88 with $P < 0.001$), as did the presence of schistocytes on blood film as a marker of chronic haemolysis (adjusted odds ratio 3.33, $P = 0.006$).

Due to small numbers, we did not assess for statistically significant differences between the predominant devices used (HVAD and HM3). Numerically, MAKE occurred in 2 (22.2%) HM3 supported patients and 122 (22.3%) HVAD supported patients, with no appreciable difference in rates of RV failure (42.8% in HM3 vs. 52.9% in HVAD) nor chronic haemolysis (42.8% in HM3 vs. 27.8% in HVAD).

Time-to-event analysis was performed to examine the relationship between MAKE and survival to transplantation, as shown in the Kaplan–Meier survival curve in *Figure 1*. *Figure 2* shows Kaplan–Meier survival curves for the individual components of MAKE: drop in eGFR >50%, progression to stage V CKD, and need for RRT beyond the index admission respectively. On Cox regression analysis, MAKE was associated with a hazard ratio for death on VAD support of 4.80 (95% confidence interval 2.66–8.66, $P < 0.001$).

Linear mixed models with random patient intercepts were used to describe the relationship between eGFR and time at pre-specified points within the first 12 months of VAD support, as well as to evaluate how MAKE and survival status interacted with this relationship. The point estimates of eGFR at each time point according to MAKE and survival status are shown in *Figure 3*. The model output is shown in *Table*s S1–S3, with the intercept defined as pre-implant eGFR in the reference group. In the first model looking at eGFR and time, eGFR increased significantly from pre-implant values at all time points in the first 3 months, shown in *Table* S1. This is consistent with the known typical trajectory of improvement in renal function in the first few months of VAD support. Table S2 shows the second model using survival status as an interacting factor. While those surviving to transplant had significantly higher eGFRs at all time points within the first 3 months, those dying on VAD support had a flat eGFR trajectory, with no significant difference in eGFR from pre-implant values seen at any time point. In Table S3, patients without MAKE show a similar increase in eGFR from pre-implant levels extending out to the first 9 months of VAD support. Although patients with MAKE did not have a significantly lower pre-implant eGFR, compared with the pre-implant eGFR in the no MAKE group, they had significantly lower eGFR at all time points except at 1 month.

Discussion

This study represents the first description of MAKE in patients supported with VAD. We have shown their detrimental impact upon survival, identified potential predictors of MAKE as well as demonstrated differences in renal trajectories in patients dying on VAD support and those experiencing MAKE.

Current literature on renal events in VAD supported patients is limited to the impact of pre-existing chronic kidney disease, and adverse kidney events occurring around the time of implant. Reassuringly, a recent analysis of the STS INTERMACS database suggested patients who required pre-implant RRT but have renal recovery within the first month of support had similar survival to those who never required RRT.[9] However, overall survival was lower in

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Table 1 Predictors of major adverse kidney events

	No MAKE (n = 129)	MAKE (n = 37)	P-value
Baseline demographics			
Age (years)	56.8 [47.9–62.7]	57.4 [44.3–63.1]	0.445
Gender			
Male, n (%)	104 (77.6)	30 (22.4)	ref
Female, n (%)	25 (78.1)	7 (21.9)	0.950
Aetiology			
Dilated, n (%)	70 (75.3)	23 (24.7)	ref
Ischaemic, n (%)	50 (83.3)	10 (16.7)	0.237
Other, n (%)	9 (68.2)	4 (30.8)	0.639
Co-morbidities			
Diabetes mellitus, n (%)	28 (22.2)	13 (36.1)	0.091
Hypertension, n (%)	47 (37.3)	8 (22.2)	0.097
Atrial fibrillation, n (%)	51 (40.5)	19 (52.8)	0.189
Chronic kidney disease, n (%)	61 (47.2)	24 (64.9)	0.059
Prior stroke, n (%)	19 (15.1)	5 (14.2)	0.907
INTERMACS profile			
Profile 3 or 4, n (%)	35 (89.7)	4 (10.3)	ref
Profile 1 or 2, n (%)	94 (74.0)	33 (26.0)	0.039*
Pre-implant biochemistry			
eGFR (mL/min/1.73 m^2)	63 [50–82]	53 [40–77]	0.025*
Pre-implant right ventricular function			
Normal, n (%)	41 (75.9)	13 (24.1)	ref
Mildly impaired, n (%)	36 (85.7)	6 (14.3)	0.232
Moderately impaired, n (%)	29 (80.6)	7 (19.4)	0.605
Severely impaired, n (%)	11 (55.0)	9 (45.0)	0.080
Pre-implant right heart catheterization			
RAP (mmHg)	14 [10–18]	22 [17–25]	<0.001*
mPAP (mmHg)	41 [36–47]	42 [37–50]	0.506
PCWP (mmHg)	28 [24–30]	30 [26–33]	0.128
Cardiac output (L/min)	3.0 [2.5–3.9]	2.8 [2.5–3.9]	0.658
Cardiac index (L/min/m^2)	1.6 [1.4–1.9]	1.5 [1.4–2.0]	0.552
PVR (dynes/s/cm^5)	327 [236–462]	296 [204–480]	0.813
PAPi	2.1 [1.5–2.8]	1.3 [0.9–1.9]	0.007*
Peri-implant support			
IABP, n (%)	46 (35.7)	16 (43.2)	0.401
VA-ECMO, n (%)	18 (14.0)	8 (21.6)	0.258
Ventilation, n (%)	14 (10.9)	7 (18.9)	0.193
Pre-implant RRT, n (%)	2 (1.6)	5 (13.9)	0.001*
VPa-ECMO post implant, n (%)	20 (15.5)	8 (21.6)	0.381
Post-implant RRT, n (%)	7 (5.4)	22 (59.5)	<0.001*
Configuration			
LVAD, n (%)	118 (80.3)	29 (19.7)	ref
BiVAD, n (%)	11 (57.9)	8 (42.1)	0.039*
Stable medical therapy (at 3 months)			
Beta-blocker, n (%)	73 (58.9)	10 (41.7)	0.120
RAS blockers, n (%)	70 (56.5)	4 (16.7)	<0.001*
MRA, n (%)	65 (52.4)	8 (33.3)	0.087
Loop/thiazide diuretic, n (%)	106 (85.5)	22 (91.7)	0.532
Calcium channel blocker, n (%)	27 (21.8)	8 (33.3)	0.223
Vasodilator, n (%)	49 (39.5)	11 (45.8)	0.563
Average LDH on support (U/L)	491 [427–551]	559 [485–661]	0.004*
Schistocytes present, n (%)	28 (21.9)	19 (52.8)	<0.001*
Clinical RV failure, n (%)	50 (40.3)	32 (88.9)	<0.001*

Values expressed as mean ± SD, median [IQR], count (%).
*P-value <0.05.
BiVAD, biventricular assist device; eGFR, estimated glomerular filtration rate; IABP, intra-aortic balloon pump; LDH, lactate dehydrogenase; LVAD, left ventricular assist device; MAKE, major adverse kidney events; mPAP, mean pulmonary artery pressure; MRA, mineralocorticoid receptor antagonist; PAPi, pulmonary artery pulsatility index; PVR, pulmonary vascular resistance; RAP, right atrial pressure; RAS, renin-angiotensin system; RRT, renal replacement therapy; RV, right ventricle; VA-ECMO, veno-arterial extracorporeal membrane oxygenation; VPa-ECMO, veno-pulmonary artery extracorporeal membrane oxygenation.

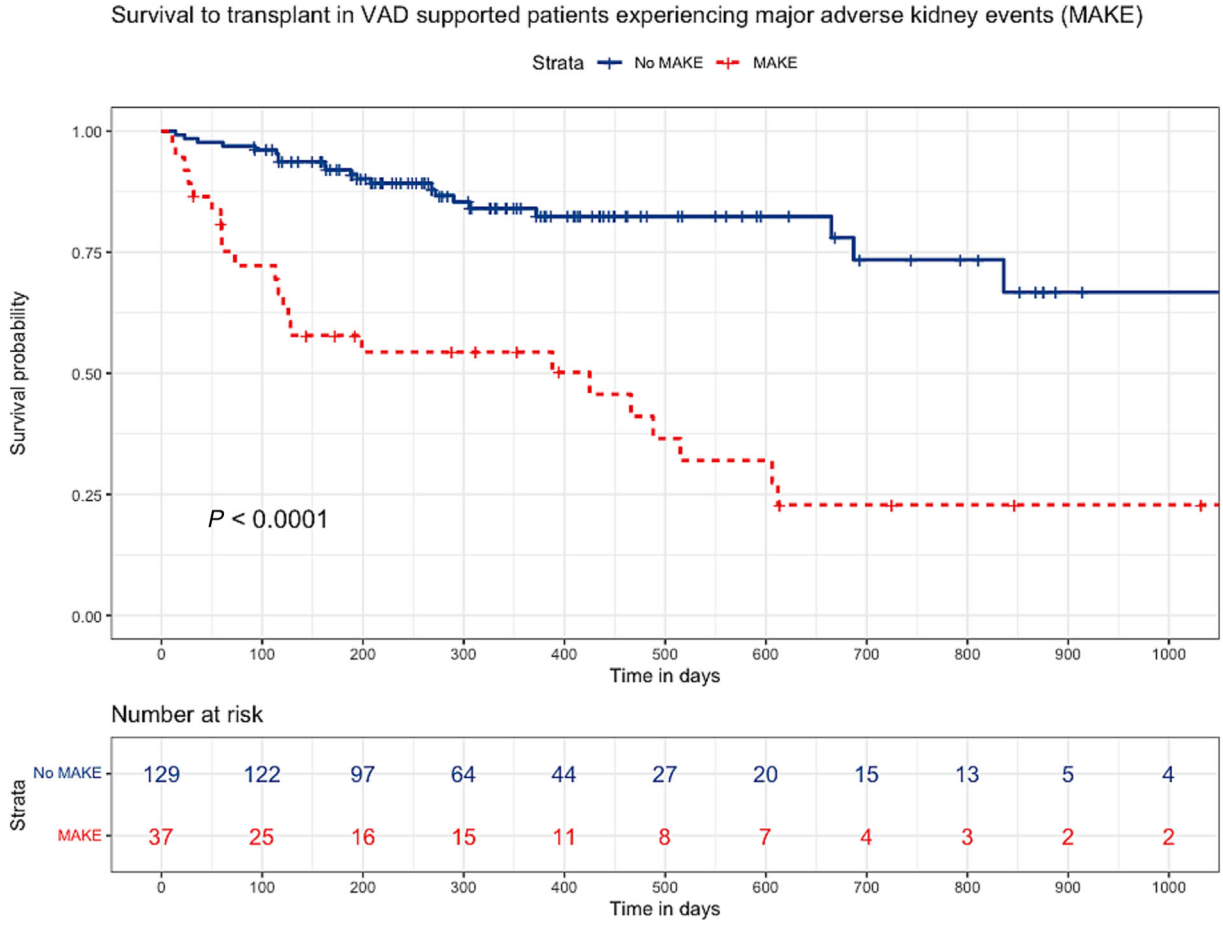
pre-implant RRT patients who continued to require RRT at 1 month after implant, and in those newly commenced on RRT post-operatively.[9] Negative predictors of renal recovery included BiVAD support, inotrope requirement at 1 week and various biochemical parameters.[9] Post-implant AKI, particularly with RRT requirement, has been shown to increase the risk of in-hospital mortality, 30-day rehospitalization and 30-day mortality.[10–12] Multiple, and often contradictory, predictors of post-implant RRT requirement have been described, including both older and younger age, intra-aortic

Table 2 Multivariate regression analysis for predictors of MAKE

	Univariate analysis		Model 1		Model 2	
	Unadjusted odds ratio (uOR)	*P*-value	Adjusted odds ratio (aOR)	*P*-value	Adjusted odds ratio (aOR)	*P*-value
Pre-implant eGFR[†]	0.98 (0.97–1.00)	0.040	1.00 (0.97–1.04)	0.866	-	-
INTERMACS 1 or 2	3.07 (1.12–10.85)	0.047	0.85 (0.14–5.74)	0.859	-	-
Pre-implant RRT	10.24 (2.10–73.90)	0.007	5.86 (0.16–315.65)	0.315	-	-
Pre-implant RAP[‡]	1.08 (1.02–1.16)	0.030	1.04 (0.97–1.12)	0.160	-	-
RAS blockers	0.15 (0.04–0.44)	0.001	0.30 (0.05–1.38)	0.138	-	-
Clinical RV failure	11.84 (4.37–41.60)	<0.001	5.27 (1.10–32.74)	0.049	9.88 (3.55–35.23)	<0.001
Schistocytes present	3.99 (1.84–8.78)	<0.001	7.52 (1.99–34.16)	0.004	3.32 (1.41–7.98)	0.006
BiVAD configuration	2.96 (1.06–7.99)	0.033	0.56 (0.05–4.54)	0.605	-	-

Model 1: All parameters significant on univariate analysis with $P < 0.05$. Model 2: All parameters significant in Model 1.
[†]per mL/min/1.73 m^2 change in eGFR.
[‡]per 1 mmHg change in RAP.
BiVAD, biventricular assist device; eGFR, estimated glomerular filtration rate; MAKE, major adverse kidney events; RAP, right atrial pressure; RAS, renin-angiotensin-system; RRT, renal replacement therapy; RV, right ventricular.

Figure 1 Kaplan–Meier curve of survival to transplant in VAD supported patients experiencing MAKE. MAKE, major adverse kidney events; VAD, ventricular assist devices.



balloon pump use, higher pre-implant creatinine and RAP, and longer cardiopulmonary bypass time.[13–15] The risk of persisting or new RRT requirement beyond this initial implant period has scarcely been described; however, pre-operative RRT in patients listed for heart transplant is well described risk factor for post-transplant mortality.[16]

Figure 2 Kaplan–Meier curves of survival to transplant in VAD supported patients by individual components of major adverse kidney events. (A) Survival to transplant in VAD supported patients with eGFR drop >50%. (B) Survival to transplant in VAD supported patients progressing to stage V CKD. (C) Survival to transplant in VAD supported patients requiring RRT beyond index admission, or death on RRT. CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; RRT, renal replacement therapy; VAD, ventricular assist devices.

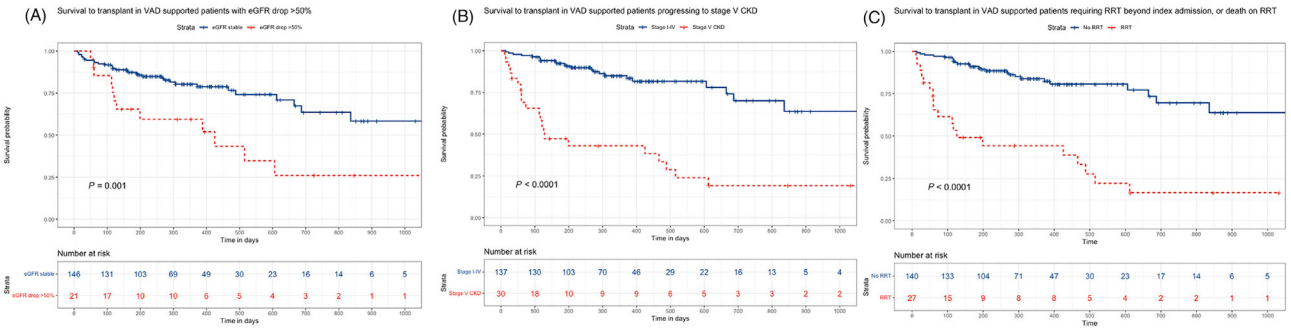
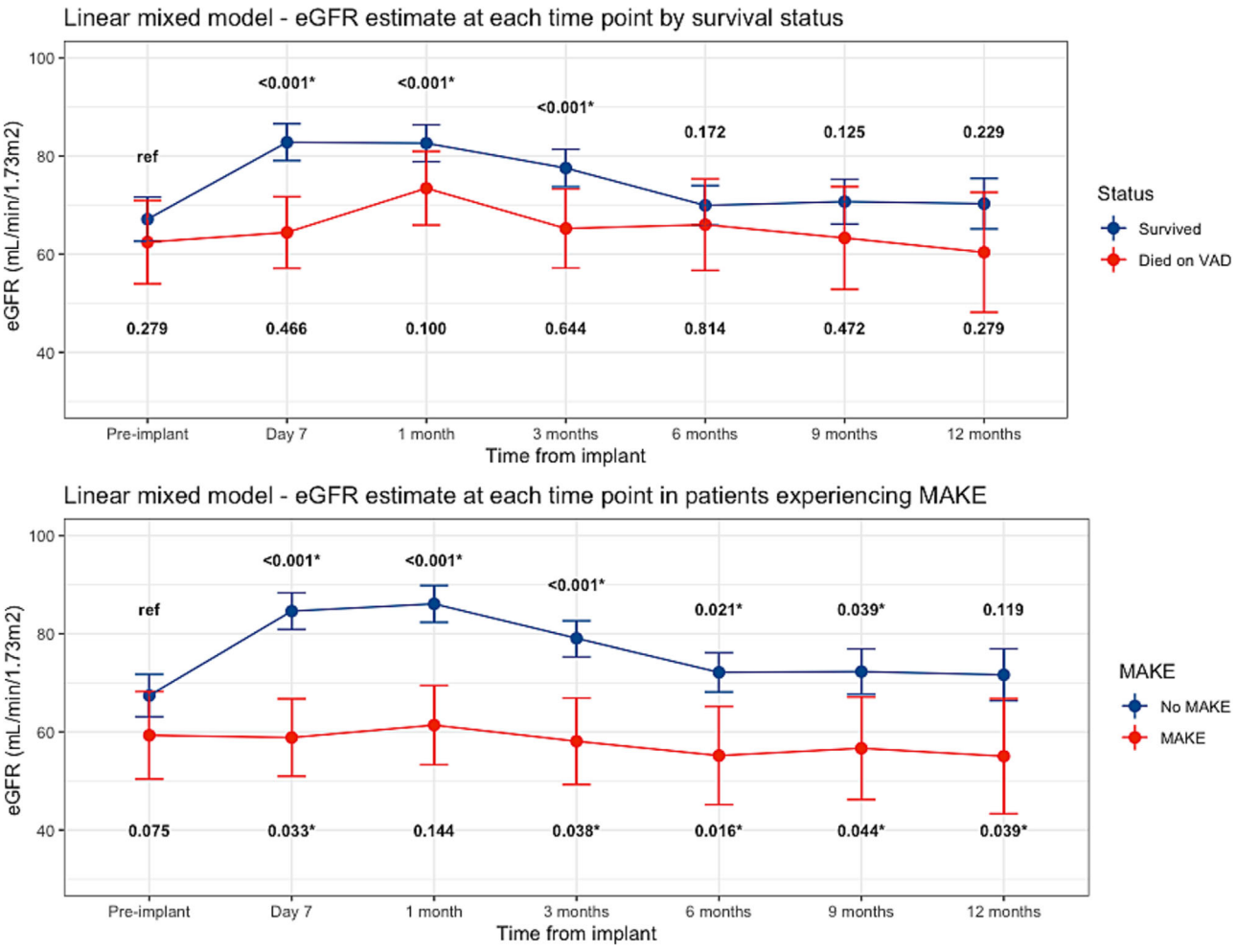


Figure 3 Linear mixed model point estimates for eGFR at each time point according to survival and MAKE status. eGFR, estimated glomerular filtration rate; MAKE, major adverse kidney events; VAD, ventricular assist devices.



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We looked at a time-to-event analysis of MAKE at any time during the VAD support period. We specifically did not include short-term RRT immediately post-implant unless the patient did not have renal recovery, or died while on RRT, to address the paucity of data in this area. Unsurprisingly, MAKE was associated with reduced survival. Univariate predictors of MAKE were characterized by a sicker pre-implant cohort, with more severe INTERMACS profile, higher pre-implant RAP, more frequent requirement for BiVAD configuration, and more frequent requirement for pre-implant RRT. The use of RAS blockers at 3 months post-implant appeared protective on univariate analysis, although this is likely confounded by the fact that patients with significant renal impairment are less likely to be treated with these agents.

On multivariate analysis, clinical RV failure during VAD support, a postulated mechanism for late renal dysfunction, significantly increased the risk of MAKE. Similarly, the presence of schistocytes on blood film, a marker of chronic haemolysis, also increased the risk of MAKE. These additional findings are important as they support previous postulated mechanisms for late renal decline in patients supported with VAD. Renal venous hypertension resulting from right heart failure not only drives ischaemic acute tubular necrosis, but also results in over-activation of RAS, which both worsens renal function and exacerbates right heart failure.[6] Furthermore, the lack of pulsatile flow is thought to result in periarteritis, which also mediates RAS activation.[6] Through these mechanisms, RAS blockers may confer protection by reducing RAS activation mediated renal decline resulting from both right heart failure and lack of pulsatility, although this did not remain significant on multivariate regression analysis in our cohort. Pigment nephropathy from haemolysis has been documented, however chronic haemolysis in VAD cohorts have not been defined.[6] Traditionally, haemolysis in the context of VAD support is defined by significant elevation in LDH; however, moderate elevations arise in the context of RV dysfunction, pulmonary, and hepatic injury.[8] Schistocytes are the hallmark of microangiopathic haemolytic anaemia, arising from mechanical disruption of the red blood cell membrane in circulation, an acquired condition in the setting of intravascular mechanical devices. Their presence on peripheral blood film thus may indicate the presence of haemolysis in the absence of other causes such as disseminated intravascular coagulation.[17] We defined chronic haemolysis by the presence of schistocytes on blood film in the absence of a discrete acute thrombosis, haemolysis or bleeding event and found this to be significantly associated with MAKE.

Multiple single centre and registry data analyses have demonstrated a typical renal trajectory of improvement in eGFR over the first few months of VAD support, followed by a decline towards baseline.[5,18] Previous studies have described improvement in renal function in the first month of VAD support being associated with increased survival, likely with a U-shaped distribution at the extremes of renal function change.[5,18] Predictors of renal improvement include younger age, lower pre-implant eGFR and pre-operative intra-aortic balloon pump support.[19]

Recently, Walther at al used latent mixed models to identify 5 distinct kidney function trajectories, describing differences in clinical characteristics and outcomes in patients belonging to the different groups.[20] The eGFR trajectories from this publication are included for comparison in *Figure* S1.[20] Group 1 appeared most consistent with our cohort of patients who did not experience MAKE, with an initial improvement seen peaking between 7 days and 3 months, with a gradual decline towards baseline by 12 months. Conversely, while none of the trajectories exactly matched our MAKE cohort, the closest would be trajectory group 3. In Walther's study, group 3 patients had an initial drop in their eGFR to 1-month post implant, with improvement back towards baseline over the 12-month period, compared with our cohort, where patients experiencing MAKE had lower eGFR at all time points except pre-implant and 1 month. Compared with group 1, group 3 patients had more pre-implant RRT and CKD. Comparing the outcomes of the five groups, group 3 patients had both the lowest probability of survival and the lowest probability of transplant.[20]

There are several key limitations to this study. Firstly, this was a retrospective study; thus, we were limited by the availability of data. While survival status was known for all patients, MAKE events could only be identified if they occurred during treatment at our centre. Our study cohort comes from a single centre and all included patients were 'bridge-to-transplant'; thus, our data may not be generalizable to the larger destination therapy VAD cohort. Furthermore, the majority of our patients were managed with the Medtronic Heartware HVAD device over the study period, which has subsequently been discontinued. Globally, lower hemocompatibility adverse events have been reported with the HM3 device; however, we still saw MAKE and chronic haemolysis events in our small cohort of HM3 patients, suggesting further research is needed in these patients. We did not look at pulsatility as a determinant of MAKE due to lack of standard algorithms for defining pulsatility across different devices. We adopted a novel method of defining chronic haemolysis but were limited to specimens analysed in our laboratory and may have misclassified patients based on missing data. We looked at clinical right RV failure as a predictor of MAKE, however did not stratify between early and late RV failure due to small numbers. In our linear mixed model, we did not include other interacting factors due to small numbers.

In our cohort, we see a strong association between MAKE and reduced survival. Furthermore, we evaluate in a clinical setting the role of previously postulated mechanisms of renal function decline such as RV failure and chronic haemolysis in predicting MAKE. Our study raises the importance of MAKE on survival and the need to identify

and address any risk factors for the development of MAKE, particularly if a similar finding is seen in the destination therapy cohort. It also highlights the differences in renal trajectory in patients dying on pump and experiencing MAKE; given that the trajectories diverge early, careful attention to eGFR trajectory in patients may provide an opportunity to optimize patient and pump factors to reduce the incidence of these events. The role of RAS blockers in protecting against MAKE events will need to be further evaluated, as there is likely a bidirectional relationship between the ability to use these agents due to severe renal impairment and the risk of MAKE. Similarly, the role of drugs such as sodium-glucose cotransporter-2 inhibitors, which have been established as renoprotective in chronic heart failure patients, will need to be evaluated for safety, tolerability, and efficacy in reducing kidney events and renal function decline. As device technology continues to improve, it is important to uniformly define chronic haemolysis and pulsatility and their impact on events such as survival, MAKE, renal decline, and other adverse haemocompability events.

Conclusions

MAKE are associated with reduced survival in bridge-to-transplant VAD supported patients. Post-operative clinical RV failure and chronic haemolysis appear to increase the risk of MAKE. Future studies should look at destination therapy patients, particularly those supported with the HM3 device, and look at defining whether non-pulsatile flow also plays a role in risk of MAKE. Patients with MAKE and death on pump differ in their renal trajectory; if these results are replicated in future studies, this early divergence may provide early insight into the risk of these events, particularly in patients where renal function fails to improve in the first few months of VAD support.

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Conflict of interest

The authors have no financial conflicts of interest relevant to this manuscript to disclose.

Supporting information

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

Table S1: Linear mixed model of eGFR trajectory.
Table S2: Estimated glomerular filtration rate trajectory by survival status.
Table S3: Estimated glomerular filtration rate trajectory in patients experiencing major adverse kidney events (MAKE).
Figure S1: Estimated glomerular filtration (eGFR) plots for the 5 trajectory groups in (A) primary sample and (B) internal validation sample, derived using latent class mixed models in publication by Walther et al.

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