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ORIGINAL RESEARCH

Long-Term Changes in Estimated Glomerular Filtration Rate in Left Ventricular Assist Device Recipients: A Longitudinal Joint Model Analysis

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BACKGROUND: Advanced kidney disease is often a relative contraindication to left ventricular assist device (LVAD) implantation because of concerns for poor outcomes including worsening kidney disease. Data are lacking on long-term changes and sex-based differences in estimated glomerular filtration rate (eGFR), with published data limited by potential bias introduced by the competing risks of death and heart transplantation.

METHODS AND RESULTS: We conducted a longitudinal analysis of 288 adults receiving durable continuous-flow LVADs from January 2010 to December 2017 at a single center. A joint model was constructed to evaluate change in eGFR over 2 years, the prespecified primary outcome, adjusted for the competing risks of death and heart transplantation. Median baseline eGFR was 60 mL/min per 1.73 m^2 (interquartile range 42–78). At 2 years, 74 patients died and 104 received a heart transplant. In unadjusted analysis, LVAD recipients had a modest initial increase in eGFR of ≈2 mL/min per 1.73 m^2 within the first 6 months after implantation, followed by a decrease in eGFR below baseline values at 1 and 2 years. Men experienced an eGFR decline of 5 to 10 mL/min per 1.73 m^2 over the first year which then stabilized, while women had an ≈5 mL/min per 1.73 m^2 increase in eGFR within the first 6 months followed by decline towards baseline eGFR levels (interaction P=0.005).

CONCLUSIONS: Estimated GFR remains relatively stable in most patients following LVAD implantation. Larger studies are needed to investigate sex-based differences in eGFR and to evaluate eGFR trajectory and mortality in LVAD recipients with lower eGFR.

Key Words: competing risk ■ eGFR ■ joint model ■ LVAD ■ ventricular assist device

See Editorial by Nair and Lamba.

Implantation of left ventricular assist devices (LVADs) can be life-saving medical therapy for individuals with advanced heart failure.[1,2] Since 2006, >33 000 patients have received LVADs in the United States, with ≈70% of newly implanted LVADs intended for life-long use (destination therapy).[3,4] Chronic kidney disease (CKD) is a common comorbid condition among individuals with advanced heart failure. Advanced CKD is a relative contraindication to LVAD implantation because of concerns for poor outcomes accompanying chronically low glomerular filtration rate (GFR). These include poor survival, poor quality of life, and potential worsening of kidney disease necessitating dialysis.[5–8] With the increased proportion of patients receiving LVADs as destination therapy, management of CKD in these patients will be of increasing clinical focus.

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CLINICAL PERSPECTIVE

What Is New?

- Estimated glomerular filtration rate (eGFR) is stable in most patients after left ventricular assist device implantation after controlling for the competing events of death and heart transplantation, though there may be sex-based differences in eGFR trajectory after left ventricular assist device implantation.
- There was no association between baseline eGFR and mortality in this single-center population.

What Are the Clinical Implications?

- Larger studies are needed to investigate mortality, risk of kidney failure, and sex-based differences in change in eGFR after left ventricular assist device, particularly among left ventricular assist device recipients with baseline eGFR <30 mL/min per 1.73 m^2, to identify patients with low baseline eGFR but at low risk for kidney disease progression.

Nonstandard Abbreviations and Acronyms

INTERMACS	Interagency Registry for Mechanically Assisted Circulatory Support

Prior literature mostly focuses on the presence of CKD before LVAD implantation as a risk factor for adverse kidney events in the initial weeks to months after LVAD implantation. There are less published data about longer-term risk. Several studies have shown an initial improvement in estimated glomerular filtration rate (eGFR) after LVAD implantation followed by a subsequent decline over the next several months.[9–13] There are only limited data on long-term changes in eGFR, need for kidney replacement therapy, and survival,[14–16] which are critical elements to patients and programs for making allocation decisions. To our knowledge, no studies to date have accounted for the competing risks of death and heart transplantation when describing changes in GFR over time, a limitation that may bias results.

The objective of this study was to investigate the longitudinal changes in eGFR over the first 2 years following LVAD implantation while accounting for the competing risks of death and heart transplantation. These results will have important implications for understanding prognosis and patient selection for LVAD placement. Findings also have the potential to inform decisions surrounding heart versus combined heart and kidney transplantation by providing a better understanding of the trajectory of eGFR after restoration of cardiorenal hemodynamics.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Population and Design

We conducted a longitudinal analysis of a cohort of all patients who received a durable continuous-flow LVAD from January 2010 to December 2017 at Tufts Medical Center, Boston, MA, an advanced heart failure referral center. Patients were identified using the electronic health records and followed until June 30, 2018, or until transfer to another center. LVADs implanted during this time period included HeartMate II (Abbott) or HeartWare LVAD (Medtronic).

Patients with a left ventricular ejection fraction <25% and New York Heart Association class IV functional capacity refractory to optimal medical therapies were considered for LVAD at Tufts, consistent with contemporary Centers for Medicare and Medicaid Services coverage criteria. Absolute and relative contraindications to LVAD at Tufts Medical Center during the study time-period are summarized in Table S1.

Patients were excluded from the study cohort if they were <18 years of age, were receiving maintenance dialysis at the time of LVAD implantation, or had previously received an LVAD. This study was approved and the requirement for informed consent was waived by the Tufts Health Sciences Institutional Review Board.

Clinical Characteristics

Estimated GFR was determined using the Chronic Kidney Disease Epidemiology Collaboration 2009 creatinine equation.[17] Baseline eGFR was defined as the median of all eGFR values obtained in the 30 days before LVAD implantation.[18] For descriptive purposes, patients were stratified into 3 groups according to their baseline eGFR: baseline eGFR ≥60 mL/min per 1.73 m^2, 30–59 mL/min per 1.73 m^2, and <30 mL/min perp 1.73 m^2. Baseline values for all other clinical characteristics and laboratory measurements were defined as the closest measurement before LVAD implantation. Baseline characteristics included age, sex, race, history of diabetes, heart failure cause, LVAD indication as a bridge to transplant versus destination therapy, type of LVAD, INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)[19] profile

(Table S2), hemoglobin, blood urea nitrogen, total bilirubin, and serum sodium concentration. Measures of urine protein and urine albumin were not included because these were not routinely collected during the study period.

Outcomes

The prespecified primary outcome was change in eGFR over time. Secondary outcomes were a 30% increase or decrease from baseline in eGFR, all-cause death, or heart transplantation during the 2-year follow-up period. Estimated GFR was defined as stable if the percent change in eGFR at follow-up compared with baseline fell in between the range of a 30% increase or decrease. Outcomes were reported for the entire cohort and in subgroups stratified by baseline eGFR.[20] A 30% change in eGFR was chosen because this level of decrease in eGFR is predictive of future kidney failure.[21] We also conducted sensitivity analyses using a 40% increase or decrease in eGFR and a 57% increase or decrease in eGFR (approximately equivalent to a doubling of serum creatinine), which have been used as alternate definitions of clinically significant changes in eGFR in the literature.[21] Patients were followed for up to 2 years after LVAD implantation, with eGFR data available monthly during this time. Instances of death and heart transplantation were ascertained from review of the electronic health records. For the descriptive outcome measure of a 30% change in eGFR, patients were censored at time of death, heart transplantation, or at the end of the follow-up period after initial LVAD surgery implantation if the patient was alive and had not received transplantation. End of follow-up was defined as the earlier of 2 years or the end of the study period.

Statistical Analysis

Descriptive summary statistics are presented as n (%), mean±SD, or median (interquartile range) as appropriate and compared across pre-LVAD implantation eGFR strata, using χ^2 test for categorical variables and ANOVA for continuous variables, as appropriate. For non-normal distributions, the Kruskal–Wallis test was used for continuous variables. Hypothesis tests were 2-tailed with an α of 0.05.

Survival was estimated using Kaplan–Meier analysis. Multivariable Cox proportional hazards regression models were used to evaluate the association between baseline eGFR, treated as a continuous variable, and time to death censored at 2 years. Model covariates were selected a priori based on clinically relevant associations and availability in the database. These included age, sex, bridge to transplantation versus destination therapy, history of diabetes, and history of ischemic cardiomyopathy. Proportional hazards assumption was assessed using Schoenfeld residuals (Figure S1).

One challenge in modeling GFR is that people who die or are transplanted cannot contribute to assessment of GFR decline.[22,23] A joint model was therefore constructed to examine changes in eGFR over time while simultaneously accounting for informative censoring related to the competing risks of death and heart transplantation. The first part of the joint model includes a linear mixed effects model to model eGFR. Follow-up time was modeled using the natural cubic spline function and 2 internal knots, 3 and 13.8 months, with individual subjects set as the random effects and age and sex as fixed effects. Age and sex were included as covariates in the joint models because of significant univariate associations with change in eGFR in preliminary analyses (Figure S2). For the 30 individuals who required dialysis shortly after LVAD implantation, eGFR measurements were considered missing for the duration of their time on dialysis. The second part of the joint model includes a Cox proportional hazards regression model to evaluate the association between baseline eGFR and the outcomes of death or heart transplant treated as separate outcomes in the Cox model and censored at 2 years. A joint model was then fitted using a Weibull distribution to predict eGFR over time.

All analyses were performed using R version 3.5.3 (R Foundation for Statistical Computing, Vienna, Austria). The JM package was used for the joint model analysis.

RESULTS

A total of 288 patients received a durable LVAD during the specified time period and met inclusion criteria. One hundred forty-four patients (50%) had a baseline eGFR ≥60 mL/min per 1.73 m^2, 122 (42%) had a baseline eGFR 30–59 mL/min per 1.73 m^2, and 22 (8%) had a baseline eGFR <303 mL/min per 1.73 m^2. Thirty-three patients were censored because of end of follow-up on June 30, 2018, before the 2-year threshold, of whom 13 were censored before having 1 year of follow-up data. There were no patients with missing measurements of eGFR at 6 months, while 5 patients had missing measurements at 1 and 2 years. Missing data at 1 and 2 years generally reflected transfer of care to other local institutions.

Baseline Patient Characteristics

Baseline characteristics are presented in Table. LVAD recipients were predominantly men (79%) and White (81%), with a median baseline eGFR of 60 (interquartile range, 42–78) mL/min per 1.73 m^2. Patients with a baseline eGFR ≥60 mL/min per 1.73 m^2 were slightly younger and were more often implanted with a bridge

Table 1. Baseline Characteristics by Baseline Estimated Glomerular Filtration Rate

Characteristic	Overall N=288	eGFR ≥60 n=144 (50%)	eGFR 30–59 n=122 (42%)	eGFR <30 n=22 (8%)	*P* value
Male	228 (79%)	111 (77%)	101 (83%)	16 (73%)	0.39
Age (y)*	56 (12)	53 (12)	60 (10)	60 (14)	<0.001
Race and ethnicity					0.89
Asian	8 (3%)	4 (3%)	4 (3%)	0 (0%)	
White	232 (81%)	115 (80%)	100 (82%)	17 (77%)	
Hispanic	25 (9%)	14 (10%)	8 (7%)	3 (14%)	
Black	23 (8%)	11 (8%)	10 (8%)	2 (9%)	
Device type					0.53
HeartMate 2	125 (43%)	58 (40%)	66 (54%)	11 (50%)	
HeartWare	163 (57%)	86 (60%)	56 (46%)	11 (50%)	
Bridge to transplant	170 (59%)	93 (65%)	67 (55%)	10 (46%)	0.11
Baseline eGFR†, mL/min per 1.73 m^2	60 [42–78]	78 [68–94]	45 [38–53]	25 [24–27]	<0.001
Serum creatinine†, mg/dL	1.3 [1.0–1.7]	1.0 [0.9–1.2]	1.6 [1.4–1.8]	2.5 [2.4–2.7]	<0.001
Diabetes	122 (42%)	52 (36%)	56 (46%)	14 (64%)	0.03
Ischemic cardiomyopathy	113 (39%)	54 (38%)	45 (37%)	14 (64%)	0.05
INTERMACS profile					0.42
Profile 1	21 (7%)	10 (7%)	11 (9%)	0 (0%)	0.67
Profile 2	103 (36%)	51 (35%)	41 (34%)	11 (50%)	0.16
Profile 3	79 (27%)	42 (29%)	33 (27%)	4 (18%)	
Profile 4	16 (6%)	7 (5%)	9 (7%)	0 (0%)	
Profile 5–7	1 (<1%)	0 (0%)	1 (<1%)	0 (0%)	
Temporary circulatory support	102 (35%)	48 (33%)	43 (35%)	11 (50%)	0.09
Serum sodium, mEq/L*	134 (5)	134 (5)	134 (5)	134 (4)	0.67
Total bilirubin, mg/dL,†	1.0 [0.7–1.5]	1.0 [0.6–1.5]	1.1 [0.7–1.5]	1.1 [0.7–1.3]	0.58
Blood urea nitrogen, mg/dL†	25 [17–38]	19 [15–27]	30 [23–45]	48 [37–68]	<0.001
Hemoglobin, g/dL†	10.9 [9.4–12.5]	10.9 [9.8–12.5]	11.0 [9.2–12.7]	10.0 [9.3–11.5]	0.16

eGFR indicates estimated glomerular filtration rate; and INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.
*Mean (SD).
†Median [interquartile range].

to transplant strategy than patients in other eGFR strata. A higher proportion of patients with lower baseline eGFR had diabetes and ischemic cardiomyopathy as compared with those with higher baseline eGFR. Baseline characteristics stratified by sex are shown in Table S3. Compared with women, men were older with a lower proportion receiving LVADs as bridge to transplant and a higher proportion with ischemic cardiomyopathy.

Descriptive Outcome Measures Following LVAD Implantation

By 6 months, 55 (19%) patients who received an LVAD had a 30% or greater increase in eGFR from baseline, 16 (6%) had a 30% or greater decrease in eGFR, 136 (47%) had stable eGFR, 48 (17%) died, and 33 (11%) received a heart transplant (Figure 1). Across eGFR groups, most patients had either stable or improved eGFR, while few patients had a decrease in eGFR. No patient with baseline eGFR <30 mL/min per 1.73 m^2 had a 30% decrease in eGFR, while 11 (50%) had a 30% increase in eGFR. Similar trends were seen at 1 and 2 years, with a higher proportion of LVAD recipients dying or receiving heart transplant. Thirty patients (10.4%) required kidney replacement therapy postoperatively, of whom 17 (56.7%) had died by 6 months. One additional patient with a baseline eGFR 30 to 59 mL/min per 1.73 m^2 was still receiving dialysis by the 6-month follow-up and had died by 1 year. In sensitivity analyses, use of a 40% or 57% change in eGFR threshold to define outcome groups yielded similar results, albeit with more patients defined as having stable eGFR (Figures S3 and S4).

Baseline eGFR and Survival

There was no statistically significant difference in survival by baseline eGFR strata (*P*=0.2) (Figure 2). Among those with baseline eGFR <30 mL/min perp 1.73 m^2

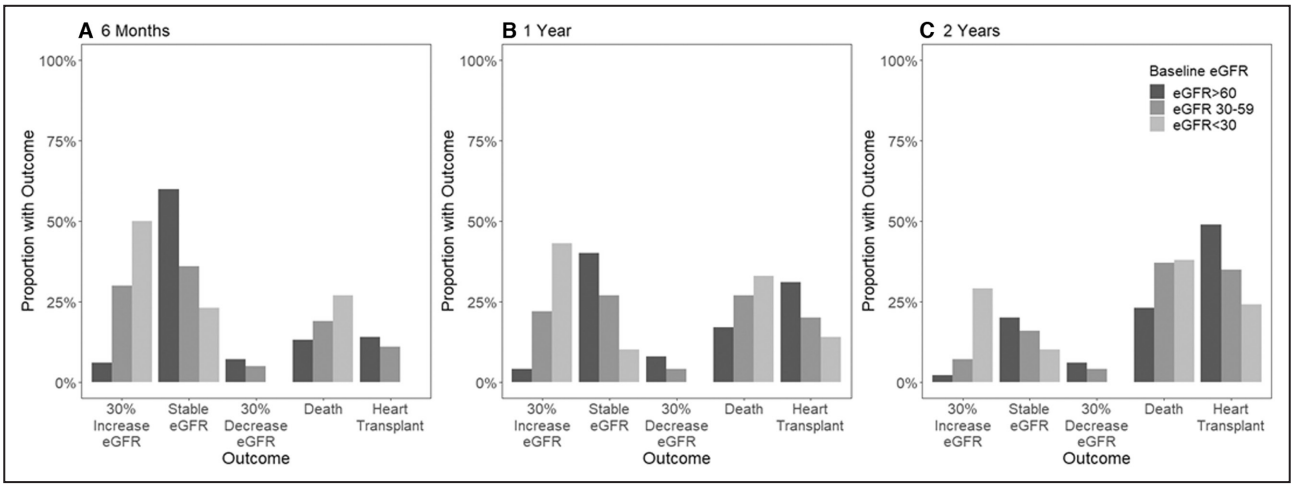

Figure 1. Outcomes of patients at 6 months and 1- and 2-year follow-up.
Outcomes include 30% increase in eGFR, stable eGFR, 30% decrease in eGFR, death, or heart transplant at (**A**) 6 months, (**B**) 1 year, and (**C**) 2 years after LVAD implantation. eGFR indicates estimated glomerular filtration rate; and LVAD, left ventricular assist device.

who died within 30 days, all deaths (n=4) occurred within the first 8 days following implantation. Causes of death included postoperative vasogenic shock with multi-organ system failure, shock attributed to right ventricular failure, and sepsis. One-year survival was 83% among those with baseline eGFR ≥60 mL/min per 1.73 m^2, 73% among those with baseline eGFR 30 to 59 mL/min per 1.73 m^2, and 67% among those with

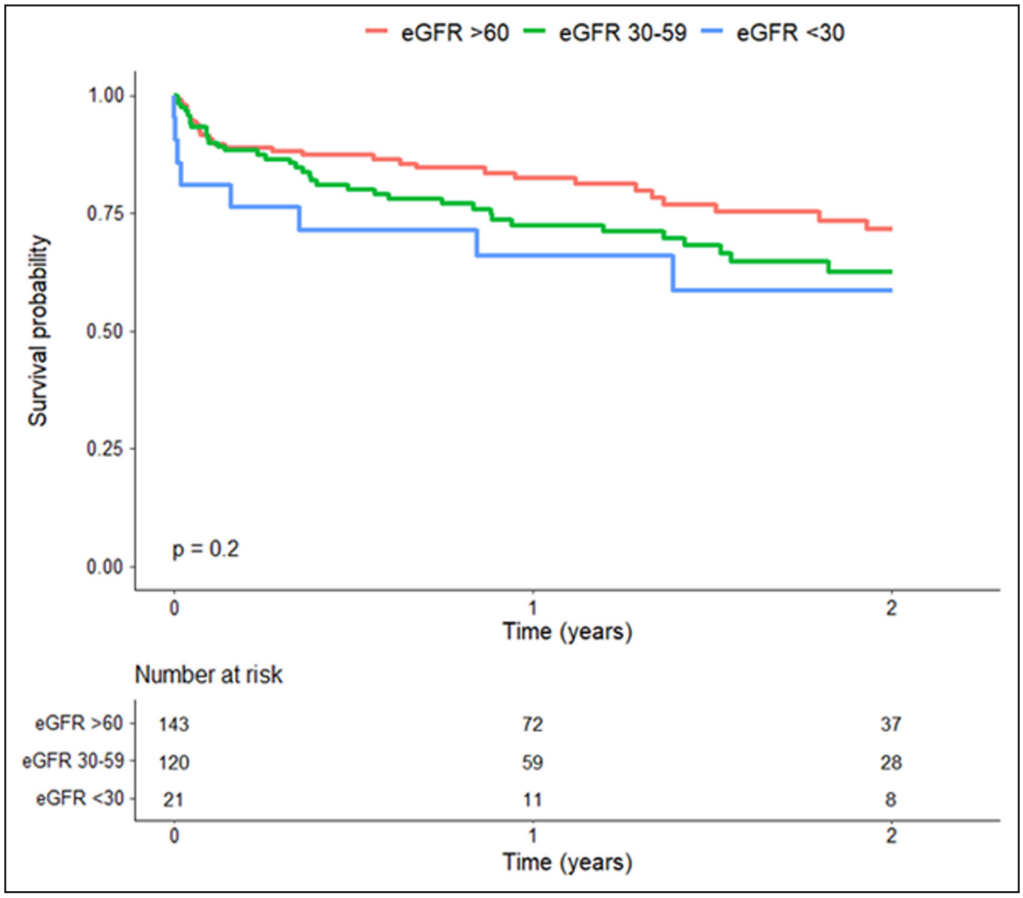

Figure 2. Postsurgery survival according to baseline eGFR.
Kaplan–Meier survival analysis of patients from time of LVAD implantation to 2 years. eGFR indicates estimated glomerular filtration rate; and LVAD, left ventricular assist device.

baseline eGFR <303 mL/min perp1.73 m^2 (P=0.13). In an unadjusted Cox proportional hazards model, higher eGFR was associated with a lower risk of death (hazard ratio [HR] 0.95 [95% CI, 0.90–0.99], P=0.03, per each 5 mL/min per 1.73 m^2 higher baseline eGFR), but this association was attenuated in the fully adjusted model (HR 0.96 [95% CI, 0.91–1.02], P=0.21) (Figure 3).

Competing Risk Analysis of Changes in eGFR

Unadjusted joint model analysis revealed that individuals had a small initial increase in eGFR (≈2 mL/min per 1.73 m^2) within the first 6 months following LVAD implantation followed by a decline to below baseline eGFR values at 1 and 2 years (Figure 4A, Table S4). Joint model analysis adjusted for age, sex, and baseline eGFR showed that men did not have an increase in eGFR after LVAD implantation and experienced a decline of ≈5 to 10 mL/min per 1.73 m^2 over the first year, with eGFR remaining fairly stable over the following year (Figure 4B, Table S3). Women had an increase in eGFR within the first 6 months of ≈5 mL/min per 1.73 m^2 that then declined towards baseline levels (interaction P=0.005) (Figure 4C). On aggregate, older patients had lower baseline eGFR, but eGFR remained relatively stable over 2 years regardless of age (Figure S2).

DISCUSSION

In this single-center clinical population of LVAD recipients, we found that most recipients have stable eGFR for the first 2 years after LVAD implantation, even after consideration of competing events. Subtle differences in eGFR trajectory existed between men and women. For men, eGFR declined in the first year after LVAD implantation without any initial postoperative improvement in eGFR. Conversely, women experienced an initial increase in eGFR after LVAD implantation followed by a decline to near baseline eGFR. There was no association between baseline eGFR and death in the overall cohort.

Several prior studies have examined changes in GFR after LVAD implantation and generally showed a modest increase in GFR after LVAD implantation followed by a decline towards baseline level.[10,11,14,16] Limitations of most prior studies were small sample sizes for most studies, short duration of follow-up, and highly variable definitions of kidney function using either creatinine or eGFR. Moreover, all of these studies only described changes in eGFR among those LVAD recipients who did not die or have a heart transplant. Few studies have presented data extending to 2 years, and, among those that have, eGFR at 1 to 2 years was similar to baseline, and may even improve among patients with an eGFR <60 mL/min perp1.73 m^2.[14–16] For example,

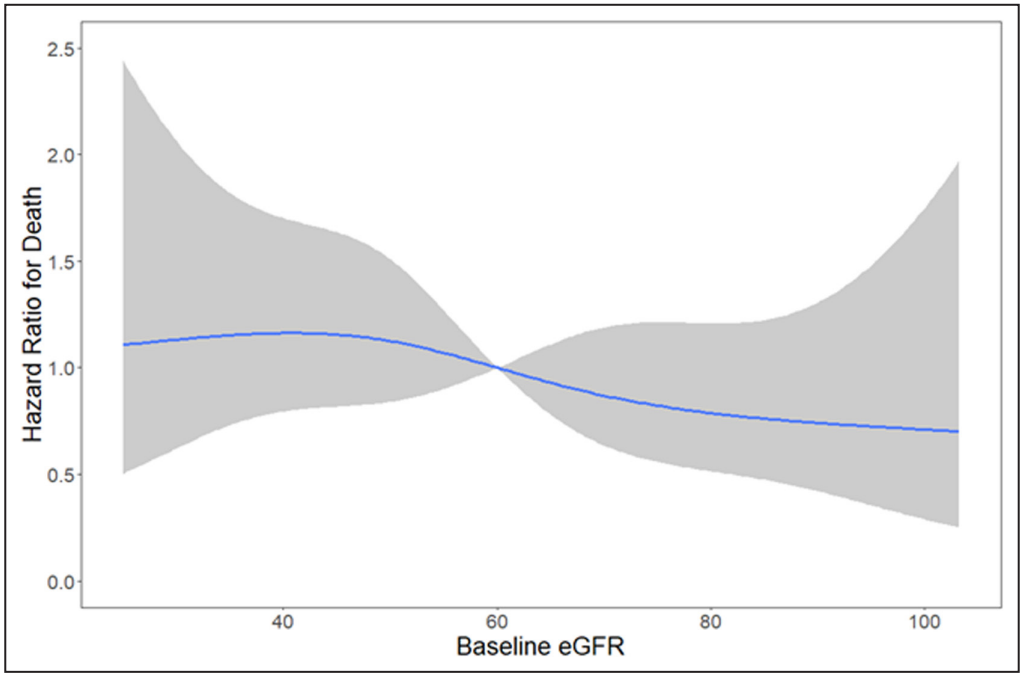

Figure 3. Risk association of baseline eGFR and mortality.
Time to death at 2 years after LVAD implantation. The hazard ratio was estimated using multivariable Cox proportional hazards model adjusted for sex, age, diabetes, bridge to transplant, and ischemic cardiomyopathy. eGFR indicates estimated glomerular filtration rate; and LVAD, left ventricular assist device.

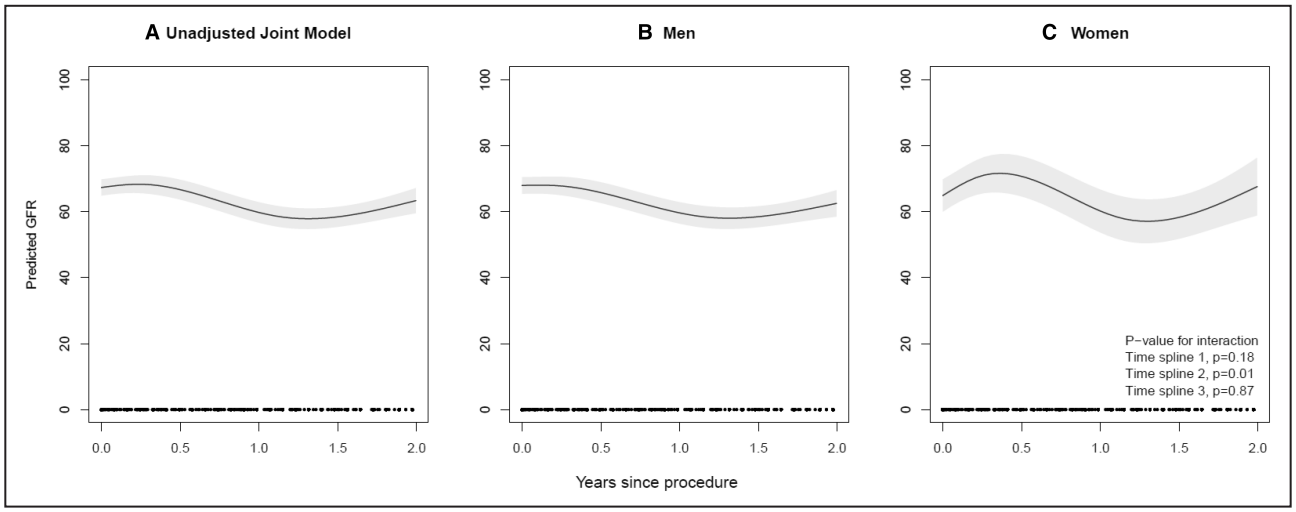

Figure 4. Competing risk analysis of changes in eGFR after LVAD.
Prediction curves were generated based upon a joint model fitted for linear mixed-effects model of monthly eGFR measurements and Cox proportional hazards model of death and heart transplant. **A**, Shows the unadjusted joint model. **B** and **C**, Show prediction curves for men and women for mean age and baseline eGFR. **B**, Shows prediction curve of eGFR over time for the joint model for men. **C**, Shows the prediction curve of eGFR over time for the joint model for women. eGFR indicates estimated glomerular filtration rate; GFR, glomerular filtration rate; and LVAD, left ventricular assist device.

an analysis of 3363 patients from INTERMACS found that at 1 month, median eGFR was 22 mL/min per 1.73 m^2 higher compared with baseline but similar to baseline measures at 1 year.[10] Our patient population overall is similar to INTERMACS with respect to age, sex, GFR, and proportion of LVADs implemented as destination therapy over the same time period as our study. In contrast, 80% of LVAD recipients at our institution were White compared with 66% of LVAD recipients in INTERMACS.[4]

A multicenter longitudinal analysis of change in eGFR after LVAD implantation in 400 LVAD recipients showed similar findings with peak eGFR levels at ≈3 months.[14] These authors describe a triphasic change in eGFR after LVAD implantation: eGFR increases in the first phase, has an opportunity to maintain in the second phase, and declines in the third phase. While we observed a similar pattern in unadjusted analysis, we did not observe this triphasic change in eGFR in men in our study. It may be that this triphasic change in eGFR would not have been observed in either a sex-stratified analysis or in a competing risks model. These differences aside, our study supports the findings of these prior studies and extends them by demonstrating that, even after accounting for informative censoring because of death or heart transplantation, trajectory of eGFR is relatively stable for most patients after LVAD implantation. Currently most programs include low eGFR as a relative contraindication to LVAD because of concerns for future deterioration in GFR, whether because of an acute insult from the LVAD surgery itself or a more chronic decline in GFR, and potential need for kidney replacement therapy. Our findings suggest that less stringent eGFR criteria may be appropriate in select patients.

Although in aggregate, eGFR is stable for most patients after LVAD implantation, at the individual level some patients will have significant improvement or worsening of eGFR over time. There are several reasons for variable changes in eGFR following LVAD implantation. First, improvement in eGFR among individuals with lower baseline eGFR may reflect the amelioration of cardiorenal syndrome following LVAD implantation. Second, patients with end-stage heart failure may have considerable sarcopenia. This loss of skeletal muscle mass results in lower than expected serum creatinine generation and consequently incorrectly high estimates of GFR. Muscle mass may increase after LVAD implantation, especially for patients who are sarcopenic at implantation, leading to increased creatinine generation. This could appear as decrease in eGFR whereas the true GFR has not changed.[24–26] This highlights the need for muscle-mass independent measures of GFR in this medically complex patient population. Third, LVAD implantation itself may have effects on the kidney, including acute kidney injury related to the surgery itself. The currently used continuous flow LVADs may also have long-term effects on kidney vasculature, which could cause declines in GFR.[27] Fourth, changes in eGFR after LVAD implantation may merely reflect regression to the mean. We attempted to address this problem by utilizing the median of multiple eGFR measurements before LVAD implantation. The current study cannot

differentiate among these effects, and further research is required to determine (1) whether and to what extent these mechanisms affect GFR in LVAD recipients and (2) whether they can be predicted in order to optimize LVAD utilization decision making.

In contrast to our study, previous studies have not evaluated differences in eGFR trajectory between women and men. One potential explanation for the observed differences in our study could be an observed higher proportion of men with ischemic cardiomyopathy as compared with women. Ischemic disease might indicate a greater amount of intrinsic atherosclerotic vascular-related kidney disease that would not be reversed effectively by improving heart failure physiology via LVAD implantation. Women were also slightly younger than men, suggesting women may have had less opportunity for decline secondary to these or other causes of CKD.[28] A higher proportion of women in this study received LVADs as a bridge to transplant rather than destination therapy, suggesting that women may have been slightly healthier than men with presumably healthier kidneys. Alternatively, observed sex-based differences in eGFR in our cohort may be less reflective of degree of intrinsic kidney disease and more reflective of sex-based differences in body composition after LVAD implantation. Muscle composition and strength improve after LVAD surgery. With this improvement in muscle mass, creatinine would be expected to also increase independent of GFR.[29] It is unknown whether there are sex-based differences in changes in body composition after LVAD implantation. If men had a greater increase in muscle mass than women, this could also explain the differential change in eGFR between men and women after LVAD implantation. If confirmed, this might lead to sex-specific criteria for decisions regarding LVAD implantation.

Our study did not demonstrate a robust association between baseline eGFR and mortality. This may reflect the small number of patients with baseline eGFR <303 mL/min perp1.73 m^2 and the resultant lack of power to detect a statistically significant difference. Selection bias likely also plays a role. In the earliest, randomized trials of LVADs, 1-year survival was only 25% among those participants not receiving an LVAD.[30] While heart failure management has certainly improved over the past decades, in our study, LVAD patients with an eGFR <303 mL/min perp1.73 m^2 had a 1-year survival of 67%, potentially consistent with a relative mortality benefit despite the presence of advanced kidney disease. Prior studies examining the association between pre-LVAD eGFR and mortality have yielded mixed results. A retrospective study of 220 patients who were enrolled in LVAD clinical trials from 1996 to 2003 showed that those in the lowest quintile of baseline creatinine clearance had worse survival compared with those in the highest quintile.[31] However, a retrospective study of 86 LVAD patients did not demonstrate an association after adjustment for demographic and other comorbid factors.[12] Despite these contrasting findings, low baseline eGFR does impact the selection process for LVAD implantation, with potential exclusion of patients with advanced kidney disease from receiving an LVAD. Given the high mortality rate among patients with end-stage heart failure not treated with LVAD or heart transplantation, it is possible that many individuals with low baseline GFR may derive a mortality benefit from LVAD implantation.

Strengths of this study include the following. First, we used a rigorous method for determining baseline eGFR to minimize bias by using the median eGFR of all the measurements in the 30 days before LVAD implantation. Thus, our results are less likely to reflect regression to the mean. Also, our study is the only study to date to utilize a competing risk approach to longitudinal analysis of change in eGFR over time. It is important to account for competing risks when analyzing eGFR trajectory in LVAD patients because patients who died may have had lower eGFR that was not captured in such analyses. This would result in trends in eGFR appearing better overall, given the focus on survivors only.

Limitations of this study include the lack of a control group with which to compare our LVAD patients. Therefore, we do not know kidney outcomes or survival outcomes in those patients who never received an LVAD and must make assumptions from prior LVAD clinical trials. Second, all LVAD programs have a selection process to determine which patients receive an LVAD, introducing a selection bias. It may be that only patients who are expected to have favorable kidney outcomes would be offered a LVAD implant. Although our sample size is large compared with prior studies, we were limited by power for subgroup analyses. Data were analyzed at a single center whose patient population comprised predominantly White men, which may limit generalizability. There may be factors such as social determinants of health, which could have long-term impacts on GFR not captured in this single-center analysis. GFR was estimated by creatinine, which is heavily influenced by muscle mass. Measured GFR or GFR estimated by biomarkers less affected by muscle mass could yield different results, as could controlling for surrogates of muscle mass in the statistical analysis, but these data were not available. Other markers of kidney damage, such as albuminuria and kidney size, were not consistently measured at our center, so we were unable to report these values. Finally, our population comprises predominantly HeartMate 2 and HeartWare LVAD recipients, because these were the devices implanted at the time of data collection. Since most patients now receive HeartMate 3 devices, this may also affect generalizability of our results.

CONCLUSIONS

In summary, eGFR remains relatively stable in most patients after LVAD implantation in competing risk analysis, and there was no observed association between baseline eGFR and mortality in a selected population. There is need to better identify patients with low baseline eGFR but at low risk for progression of kidney disease. Our finding that women may have a different eGFR trajectory than men needs to be corroborated in larger sample sizes to confirm whether there are in fact sex-based differences in the natural history of kidney disease in LVAD recipients. Finally, there is still equipoise concerning the association between baseline eGFR and mortality. To address this, larger studies are needed to investigate hard outcomes such as death and kidney failure among LVAD recipients with an eGFR <303 mL/min per 1.73 m^2.

ARTICLE INFORMATION

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Disclosures

None.

Supplemental Material

Table S1–S4
Figure S1–S4

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Supplemental Material

Table S1. Absolute and Relative Contraindications to LVAD Implantation at Tufts Medical Center at the Time of Study.

Absolute Contraindications	Relative Contraindications
• Cardiogenic shock with multiorgan failure • Severe right ventricular failure • Life expectancy <2 years (not due to cardiac disease) • Recent stroke • Active cancer, infection, or bleeding • Cirrhosis • Contraindication to long-term anticoagulation • Irreversible severe pulmonary disease • Severe cachexia or extreme frailty • Pregnancy • Active substance abuse • Inability to comply with medication adherence and ambulatory follow-up • Inadequate home support or coping skills • Chronic hemodialysis	• eGFR <40 ml/min/1.73m^2 or serum creatinine >2-2.5 mg/dL not expected to improve after LVAD • Bilirubin >4-5 mg/dL • Transaminases >3 times the upper limit of normal • Uncontrolled diabetes with end organ damage • BMI >40 kg/m^2 or Stage III obesity

BMI, body mass index; *eGFR*, estimated glomerular filtration rate; *LVAD*, left ventricular assist device.

Table S2. INTERMACS Clinical Profiles.

Profile	Description
1	Critical cardiogenic shock
2	Progressive decline despite inotropes
3	Stable on inotropes
4	Heart failure symptoms at rest despite optimal oral medical therapy
5	Comfortable at rest on oral medications but intolerant of physical exertion
6	Comfortable at rest and able to mild, but not heavy, physical exertion
7	Stable at rest and with exertion

INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support.

Table S3. Baseline Characteristics by Sex.

Characteristic	Women (n=60)	Men (n=228)	p-value
Age (years) *	52 ± 13	57 ± 11	0.001
Baseline eGFR † (ml/min/1.73m^2)	65 [45, 80]	60 [41, 77]	0.32
Bridge to transplant	43 (72%)	127 (56%)	0.04
Diabetes	22 (37%)	100 (44%)	0.39
Ischemic cardiomyopathy	7 (12%)	106 (47%)	<0.001
Intermacs Profile			0.71
Profile 1	6 (13%)	15 (9%)	
Profile 2	23 (51%)	80 (46%)	
Profile 3	13 (20%)	66 (38%)	
Profile 4-7	3 (7%)	14 (8%)	
Temporary Circulatory Support	23 (51%)	79 (45%)	0.58

* Mean (SD). † Median [IQR]. *eGFR*, estimated glomerular filtration rate; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support.

Table S4. Point Estimates of Longitudinal Process of Joint Model.

Unadjusted Joint Model

Spline	**β-coefficient**	**Standard Error**	**P-value**
Intercept	0.37	0.06	<0.001
Time Spline 1	-0.76	0.09	<0.001
Time Spline 2	-0.25	0.11	0.02
Time Spline 3	-0.28	0.07	<0.001

Joint Model Adjusted for Baseline eGFR, Age, and Sex

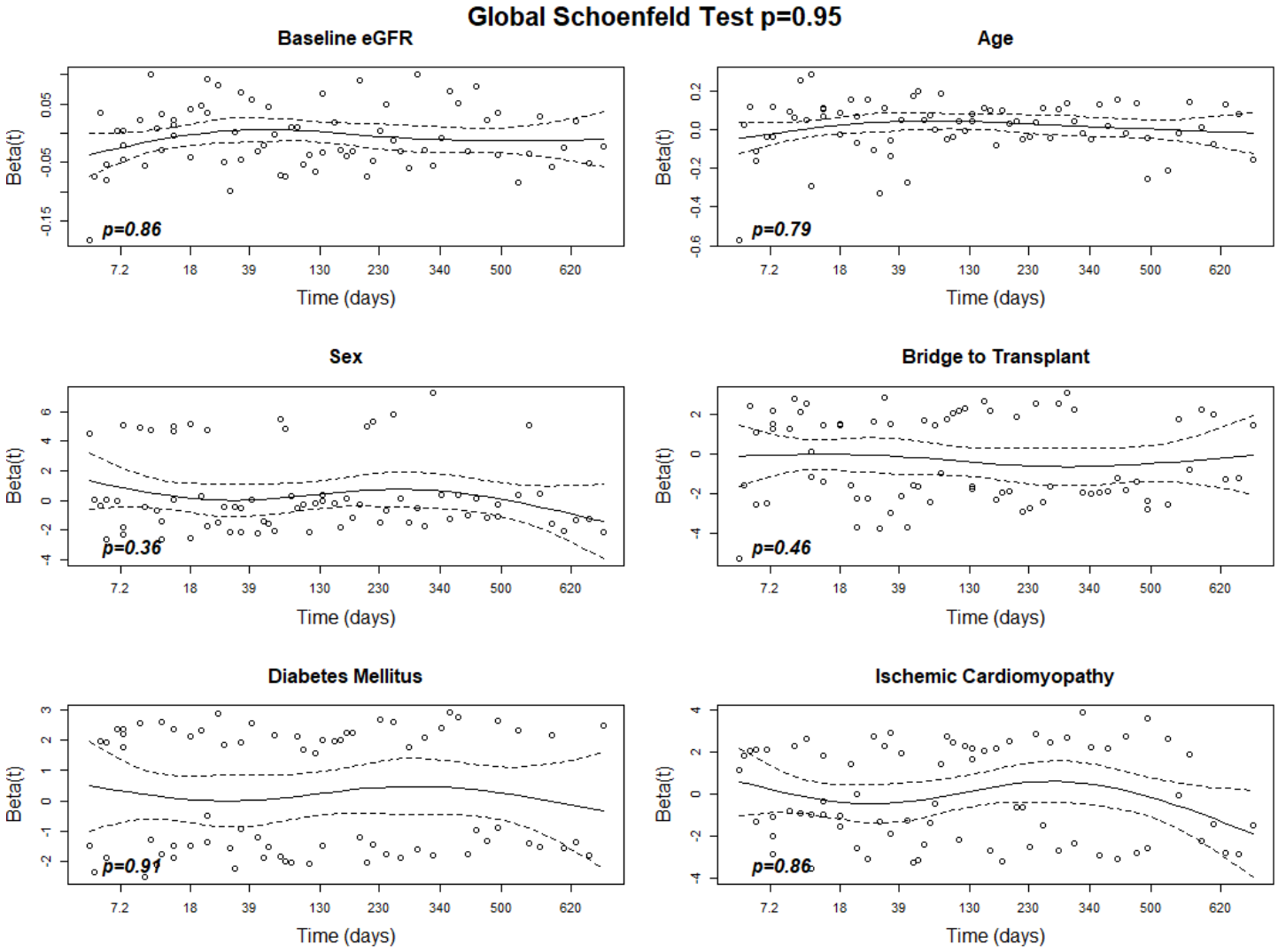
Spline	**β-coefficient**	**Standard Error**	**P-value**
Intercept	0.4	0.06	<0.001
Time Spline 1	-0.71	0.10	<0.001
Time Spline 2	-0.39	0.12	<0.001
Time Spline 3	-0.29	0.08	<0.001
Age	-0.47	0.06	<0.001
Sex	-0.15	0.14	0.28

Point Estimates for Women Demonstrating Interaction With Sex

Spline	**β-coefficient for Interaction**	**Adjusted β-coefficient**	**Standard Error for Interaction**	**P for Interaction**
Intercept	-0.15	0.25	0.14	0.28
Spline 1	-0.32	-1.03	0.24	0.18
Spline 2	0.77	0.38	0.27	0.005
Spline 3	0.04	-0.25	0.20	0.85

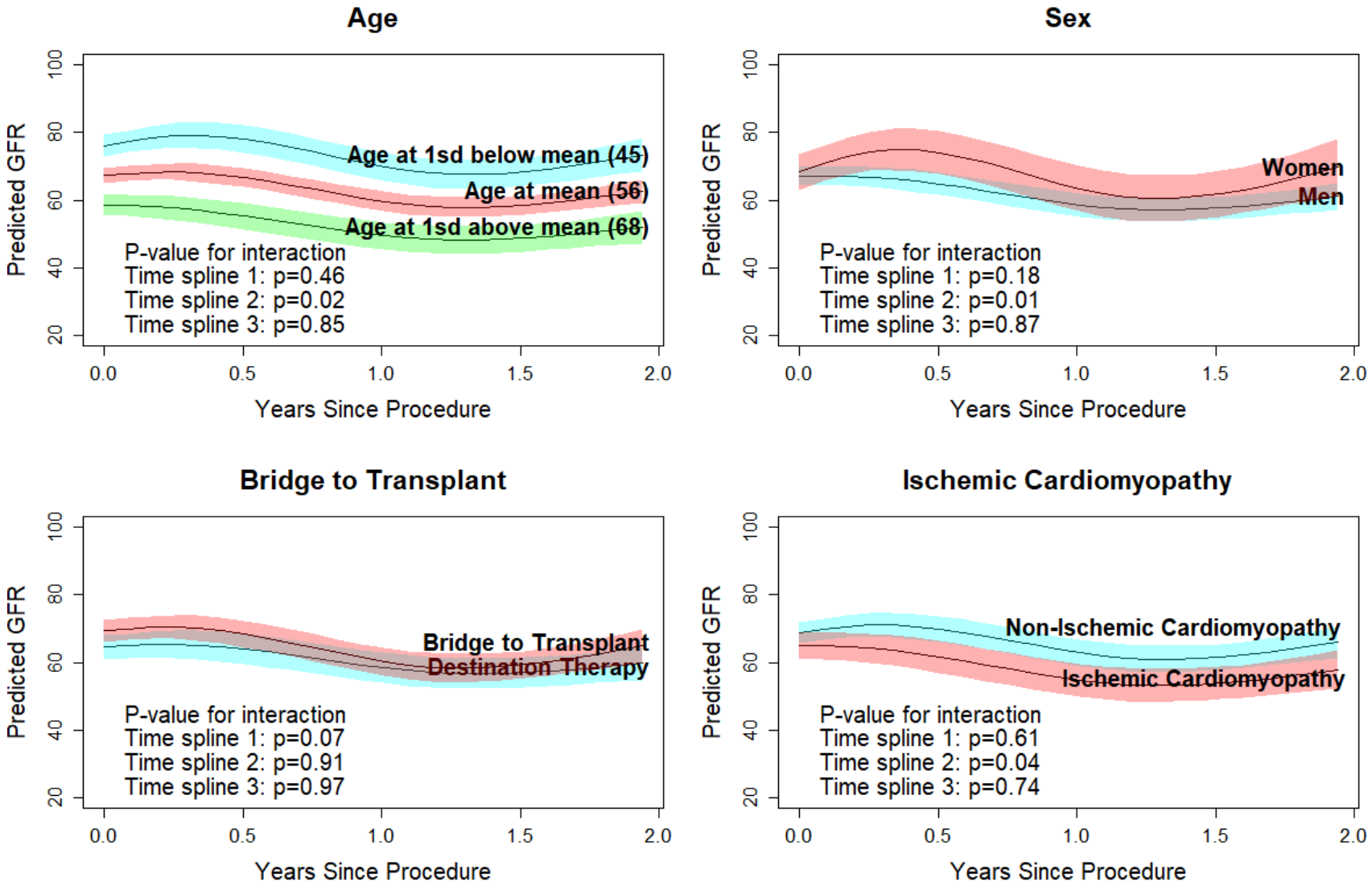
eGFR, estimated glomerular filtration rate.

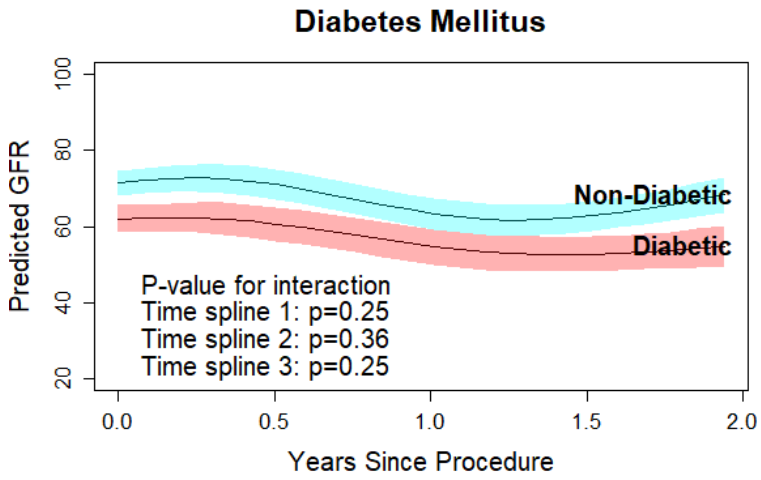
Figure S1. Schoenfeld Residuals for Multivariable Cox Proportional Hazards Model Indicating Proportional Hazards Assumption Was Met.

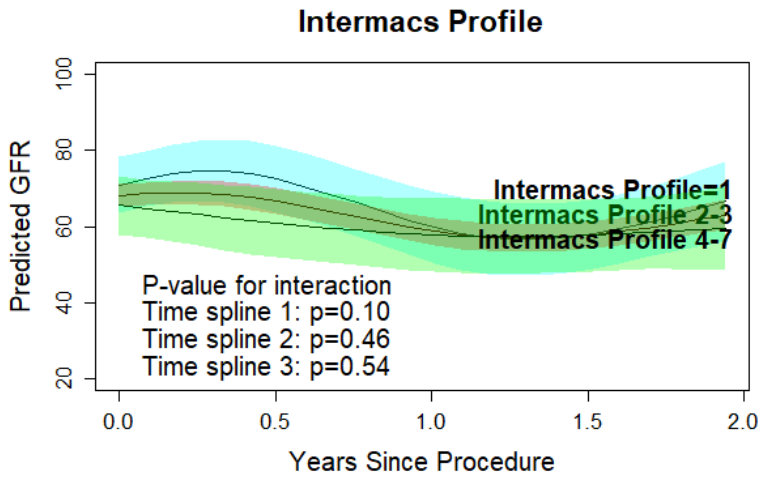


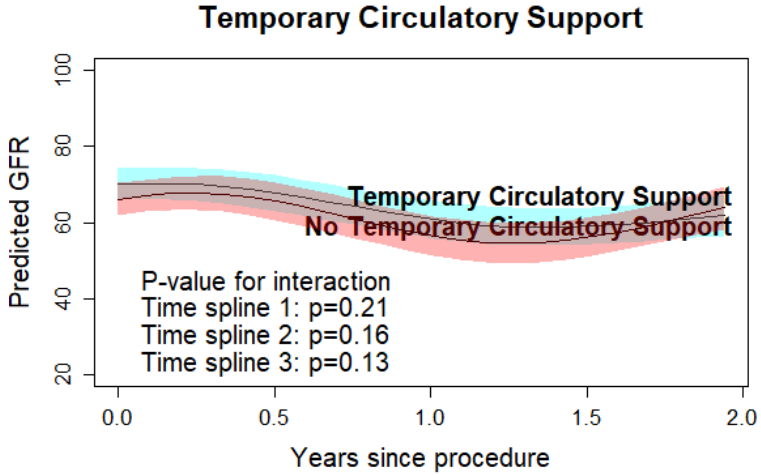
eGFR, estimated glomerular filtration rate.

Figure S2. Association of Covariates with Change in eGFR on Joint Model Analysis.



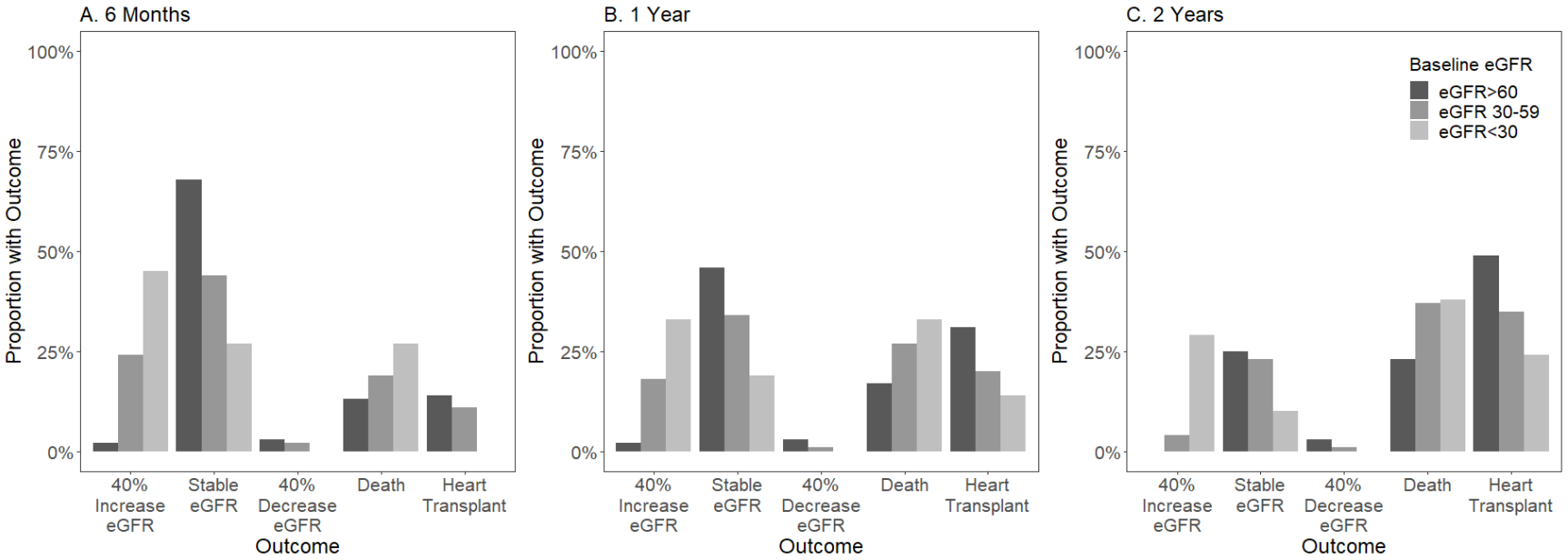

Diabetes Mellitus
Predicted GFR
Years Since Procedure
Non-Diabetic
Diabetic
P-value for interaction
Time spline 1: p=0.25
Time spline 2: p=0.36
Time spline 3: p=0.25


Intermacs Profile
Predicted GFR
Years Since Procedure
Intermacs Profile=1
Intermacs Profile 2-3
Intermacs Profile 4-7
P-value for interaction
Time spline 1: p=0.10
Time spline 2: p=0.46
Time spline 3: p=0.54


Temporary Circulatory Support
Predicted GFR
Years since procedure
Temporary Circulatory Support
No Temporary Circulatory Support
P-value for interaction
Time spline 1: p=0.21
Time spline 2: p=0.16
Time spline 3: p=0.13

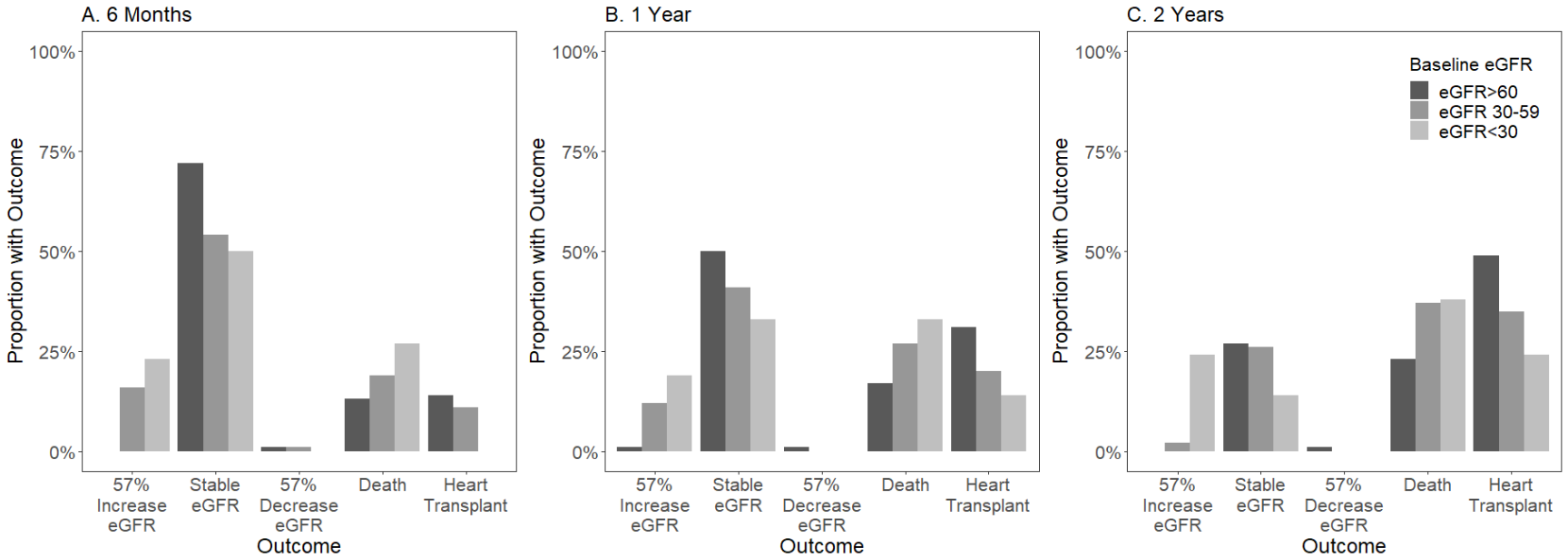
eGFR, estimated glomerular filtration rate; *GFR*, glomerular filtration rate; *INTERMACS*, Interagency Registry for Mechanically Assisted Circulatory Support.

Figure S3. Clinical Outcomes of Patients at Follow-up for 40% Change in eGFR.



Increase refers to a 40% increase in eGFR, decrease refers to a 40% decrease in eGFR, and stable refers to no significant change in eGFR at follow-up. Outcomes include 40% increase in eGFR, stable eGFR, 40% decrease in eGFR, death, or heart transplant at (A) 6 months, (B) 1 year, and (C) 2 years after LVAD implantation. *eGFR*, estimated glomerular filtration rate.

Figure S4. Clinical Outcomes of Patients at Follow-up for 57% Change in eGFR.



Increase refers to a 57% increase in eGFR, decrease refers to a 57% decrease in eGFR, and stable refers to no significant change in eGFR at follow-up. Outcomes include 57% increase in eGFR, stable eGFR, 57% decrease in eGFR, death, or heart transplant at (A) 6 months, (B) 1 year, and (C) 2 years after LVAD implantation. *eGFR*, estimated glomerular filtration rate.