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Determinants of Major Adverse Kidney Events in Extracorporeal Membrane Oxygenation Survivors

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OBJECTIVES: The majority of extracorporeal membrane oxygenation patients develop acute kidney injury, and 40–60% require renal replacement therapy. This study aimed to examine determinants of major adverse kidney events in extracorporeal membrane oxygenation survivors.

DESIGN: Retrospective cohort study.

SETTING: Barnes Jewish Hospital, St. Louis, MO.

PATIENTS: Patients admitted at Barnes Jewish hospital between 2008 and 2017 and requiring extracorporeal membrane oxygenation. Patients 18 years old and older who survived to hospital discharge were considered for the study.

INTERVENTIONS: None.

MEASURES AND MAIN RESULTS: Patients who were admitted to a single center between 2008 and 2017, were on extracorporeal membrane oxygenation for more than 24 hours and survived hospital discharge were included. Major adverse kidney event was defined as either doubling serum creatinine, incident end-stage renal disease, or death. Acute kidney injury was defined as Kidney Disease: Improving Global Outcomes stages 2–3. Complete acute kidney injury recovery was defined as a return to 50% of baseline serum creatinine and partial recovery as an improvement in acute kidney injury stage without a return to 50% of baseline serum creatinine. Survival analysis plots and Cox regression models were fitted to examine the associations of acute kidney injury status, acute kidney injury recovery, and other factors with major adverse kidney event. Among 188 extracorporeal membrane oxygenation patients who survived until hospital discharge, 63% had acute kidney injury and 41% required renal replacement therapy. The mean follow-up time was 3.4 years. Kaplan-Meier survival curves showed that patients with no/partial recovery from acute kidney injury had a higher rate of major adverse kidney event compared with those with no acute kidney injury. Multivariate analysis showed that acute kidney injury (adjusted hazard ratio =1.79 [95% CI = 1.00–3.21]), no/partial recovery from acute kidney injury (adjusted hazard ratio = 2.94 [95% CI = 1.46–5.92]), and initiation of renal replacement therapy on the day or after extracorporeal membrane oxygenation (adjusted hazard ratio = 5.4 [95% CI = 1.14–25.6]) were significant determinants of major adverse kidney event after adjustment for potential confounders.

CONCLUSIONS: Acute kidney injury, acute kidney injury recovery status, and timing of initiation of renal replacement therapy are determinants of major adverse kidney events in patients who received extracorporeal membrane oxygenation.

KEY WORDS: acute kidney injury; end-stage renal disease; extracorporeal membrane oxygenation; major adverse kidney event; renal replacement therapy; serum creatinine

The use of extracorporeal membrane oxygenation (ECMO) for adults with severe cardiac or respiratory failure has increased exponentially over the last decade (1). Although a potentially lifesaving procedure, ECMO

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carries a high risk of mortality (2) and is associated with bleeding, thromboembolic events, and end-organ damage, including kidney injury (3). Acute kidney injury (AKI) is the norm rather than the exception in patients who require ECMO support: 80% develop AKI (4), and 40–60% require renal replacement therapy (RRT) (5). Patients with severe underlying illnesses such as acute respiratory distress syndrome (ARDS) and cardiogenic shock are at high risk for sepsis and are commonly exposed to nephrotoxic agents, all of which predispose them to develop AKI. ECMO may contribute to kidney injury due to the nonpulsatile flow and prolonged contact of blood with the extracorporeal circuit leading to intravascular hemolysis and systemic inflammation (4). The association between AKI and short-term outcomes is well established. ECMO patients who require RRT have a 3.7-fold increase in-hospital mortality (5) and increased length of hospital stay (6). On the other hand, the impact of AKI and RRT on long-term renal and cardiovascular outcomes is less well understood. Determining which subset of patients is at higher risk of developing long-term adverse kidney events is essential. First, it may help guide patient selection for ECMO. Second, it may help advise which patients will benefit the most from posthospitalization specialized renal care. Therefore, the objective of this study was to examine long-term renal outcomes in an ECMO cohort and determine factors associated with major adverse kidney events (MAKEs) in patients who survived their hospitalization.

MATERIALS AND METHODS

Study Design and Data Sources

This retrospective cohort study used records of patients from Barnes Jewish hospital admitted between 2008 and 2017 and requiring ECMO (flowchart 1). *International Classification of Diseases,* 9th Edition and *International Classification of Diseases*, 10th Edition (ICD-10) codes were used to identify all patients who required ECMO during that period. Patients 18 years old and older who survived hospital discharge were included, whereas those with ECMO duration of fewer than 24 hours, history of end-stage renal disease (ESRD), or in-hospital death were excluded. Baseline demographics and comorbidities, as well as details about ECMO (indication, type, timing, duration) and AKI (onset, severity, need for RRT—including timing, type, and duration), were collected through a detailed review of electronic health records (by A.B., F.A.T.). The study was approved, and the need for individual informed consent was waived from the institutional review board (IRB) of Washington University in St. Louis and Barnes Jewish Hospital (IRB ID number 201903180).

Definitions of Exposure and Covariables

AKI, the primary exposure variable, was determined using both serum creatinine (Scr) and urine output criteria (9). AKI Kidney Disease: Improving Global Outcomes (KDIGO) stages 2 and 3 were considered to constitute AKI in accordance with many contemporary AKI epidemiologic studies (10–12), whereas AKI KDIGO stage 1 and no AKI encompassed those without AKI. AKI recovery status was determined at hospital discharge or at 90 days, whichever came first. Complete AKI recovery was defined as a return to 50% of baseline Scr and partial recovery as an improvement in the AKI stage without returning to 50% of baseline Scr. Baseline Scr was defined as the lowest Scr available up to 12 months before the index hospitalization. If no prior Scr was available, we used the lowest between hospital Scr during ECMO admission and Scr corresponding to an estimated glomerular filtration rate (eGFR) of 75 mL/min/1.73 m^2 back-calculated through the Modification of Diet in Renal Disease equation. Pre-existing CKD was defined as sustained eGFR of less than 60 mL/min/1.73 m^2 present at least for 3 months before the ECMO admission. Incident ESRD was defined as requiring hemodialysis, peritoneal dialysis, or kidney transplantation 3 months after RRT initiation. ECMO indications and types were determined by chart review, and definitions were based on Extracorporeal Life Support Organization registry (1) and ICD-10 codes. Definitions of comorbid conditions (**Table 1**) were based on definitions used to develop the Charlson Comorbid Index (13). Also, we obtained data on smoking status and hypertension based on the patient's medical history by chart review.

Outcomes

Our primary outcome was the development of MAKEs, defined as either persistent doubling of Scr, incident ESRD, or death from any cause. Data on long-term survival, Scr after discharge, and incident ESRD were collected from patient charts, if available.

TABLE 1.
Clinical Characteristics of the Study Sample by Acute Kidney Injury Status

Variables	AKI[a] (*N* = 119), *n* (%)	No AKI (*N* = 69), *n* (%)	*p*
Age (yr), mean ± SD	45 ± 15	46 ± 15	0.77
Gender (female)	43 (36)	33 (48)	0.12
Race (White)	85 (71)	53 (77)	0.53
Body mass index (kg/m^2), mean ± SD	31 ± 8	29 ± 8	0.21
Smoking status (ever)	61 (51)	37 (54)	0.88
Hypertension	42 (35)	25 (36)	0.90
Diabetes mellitus	24 (20)	9 (13)	0.27
Coronary vascular disease	30 (25)	9 (13)	0.05
Congestive heart failure	43 (36)	20 (29)	0.32
Chronic kidney disease	20 (17)	9 (13)	0.50
Baseline estimated glomerular filtration rate, mean ± SD	90 ± 30	87 ± 32	0.58
Chronic obstructive pulmonary disease	9 (8)	8 (12)	0.35
Charlson Comorbidity Index score			0.59
0–2	84 (71)	55 (80)	
≥ 3	35 (29)	14 (20)	

AKI = acute kidney injury.
[a]Denotes stages 2–3 of AKI.

Persistent doubling of Scr was ascertained based on discharge Scr. Patients who were lost to follow-up before January 1, 2019, were linked with the U.S. Renal Data system (USRDS) (7) and the National Death Index (NDI) (8) to ascertain incident ESRD and mortality status, respectively. Data linkage was performed using social security numbers, first and last name, sex, and date of birth. For patients with no further laboratories in the chart after discharge from the ECMO admission, the last follow-up date was interpolated to be on December 31, 2018, the date of the last available data from USRDS and NDI at the time of study end.

Statistical Analysis

Descriptive statistics expressed as a number of cases and percentages by AKI status were calculated using a chi-square test. Survival analysis was performed to compare the risk of MAKE between the AKI and non-AKI groups and between nonrecovered versus recovered AKI subgroups. Cox proportional hazard regression was used to estimate the unadjusted and adjusted hazard ratios (HRs) and their 95% CIs for associations between AKI status, AKI recovery, and MAKE while on ECMO in separate models. The model covariates were selected based on biological plausibility and previously published models in the literature. Since the time between RRT and ECMO is dependent on AKI status, the adjusted model, including time between RRT and ECMO, was limited to the AKI group. Stratification by AKI recovery was not possible, given the small sample size of subgroups. Statistical significance was determined by a p value of less than 0.05. Interactions with age, gender, race, and other conditions were tested. Log-log plots and Schoenfeld residuals tested the proportional hazards assumption; there were no violations of the proportionality of hazards assumption. Data analysis was performed using STATA Version 13.0 (StataCorp LP, Station, TX).

RESULTS

Among 578 patients who required ECMO between 2008 and 2017, 188 patients met the eligibility criteria and were included in the analysis (**Fig. 1**). Baseline characteristics of our sample by AKI status are shown in **Tables 1** and **2**. One hundred nineteen of 188 (63%) had AKI, and 78 of 188 (41%) required RRT. Among patients with AKI, 75 of 119 (63%) had full AKI recovery, 16 of 119 (13%) had partial AKI recovery, and 28 of 119 (24%) had no recovery

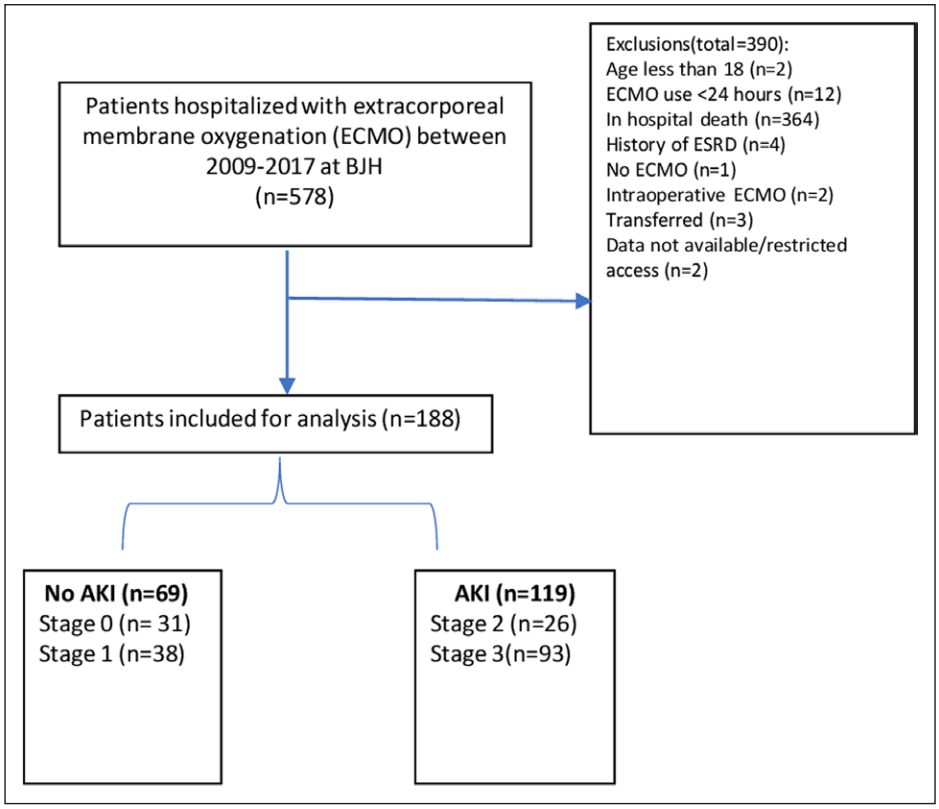

Figure 1. Study flow chart. AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, ESRD = end-stage renal disease.

from AKI. The mean age of the study population was 46, 40% were females, and 73% were White. Seventy percent of patients were on ECMO for a primary cardiac indication. The average duration of ECMO support was 11 days. Among the 78 patients who required RRT, 11 of 78 (14%) started RRT a day or more before ECMO initiation, 16 of 78 (21%) began RRT on the same day of ECMO initiation, and 51 of 78 (65%) started ECMO a day or more after ECMO initiation. Patients with AKI were significantly more likely to be on ECMO for a cardiac rather than a respiratory indication. They had a longer length of stay (LOS) compared with patients with no AKI. The mean follow-up time was 3.4 years. Kaplan-Meier survival plots showed that the rate of MAKE was significantly higher in patients with AKI compared with those without AKI (p log-rank < 0.001). Patients with no/partial recovery from AKI also had a higher rate of MAKE compared with those with complete recovery or no AKI (p log-rank < 0.001) (**Fig. 2**) (**Fig. 1**, Supplemental Digital Content, http://links.lww.com/CCX/A911; **Fig. 2**, Supplemental Digital Content, http://links.lww.com/

TABLE 2.
Extracorporeal Membrane Oxygenation and Other Characteristics of the Study Sample by Acute Kidney Injury Status

Variables	AKI[a] (*N* = 119), *n* (%)	No AKI (*N* = 69), *n* (%)	*p*
ECMO indication (cardiovascular)	91 (77)	40 (58)	**0.008**
Type of ECMO (venoarterial/central)	95 (80)	48 (70)	0.06
Duration of ECMO (d), mean ± SD	11 ± 10	11 ± 16	0.87
Length of stay (d), mean ± SD	56 ± 32	44 ± 29	**0.01**
Follow- up years, mean ± SD	3 ± 2	3 ± 2	0.82
Timing of RRT in relation to ECMO			
RRT before ECMO	11 (9)	–	
RRT same day or after ECMO	67 (56)	–	
Time between RRT and ECMO (d), mean ± SD	3 ± 8	–	
Duration of RRT in hospital (d), mean ± SD	31 ± 20	–	

AKI = acute kidney injury, ECMO = extracorporeal membrane oxygenation, RRT = renal replacement therapy.
[a]Denotes stages 2–3 of AKI.
Boldface values are highlighting the p values that were significant (i.e., $p < 0.05$). Dashes indicate not applicable.

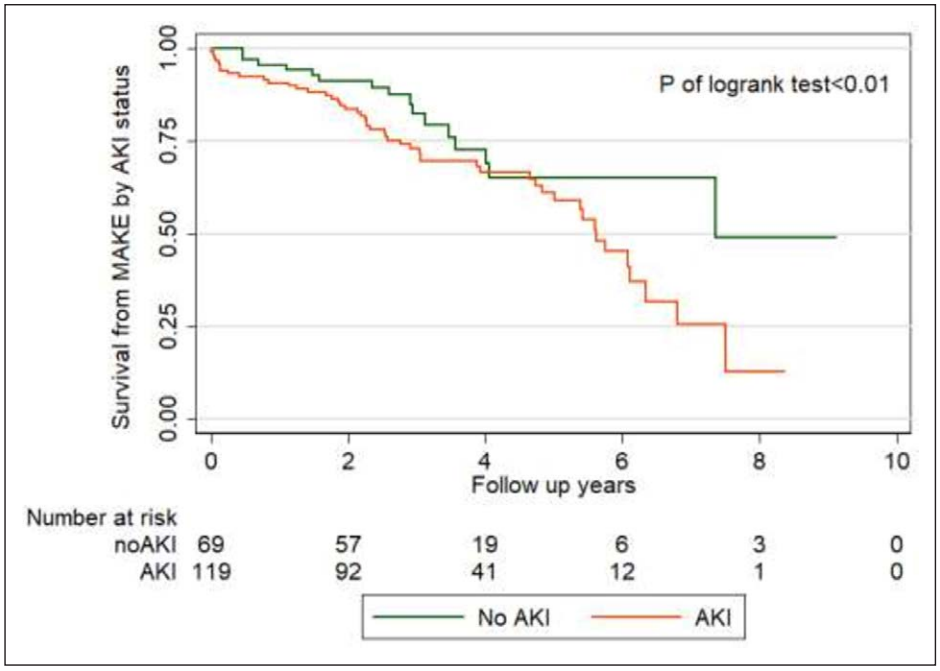

Figure 2. Kaplan-Meier survival plots show survival rates from major adverse kidney event (MAKE) according to presence of acute kidney injury (AKI) versus no AKI.

CCX/A911). The unadjusted Cox regression analysis showed that age, Charlson Comorbidity Index, baseline eGFR, AKI status, AKI recovery status, the timing of initiation of RRT, and ECMO type were all associated with MAKE (**Table 3**). Multivariate analysis showed that patients with AKI had a 1.79-fold greater MAKE hazard than those without AKI while on ECMO (95% CI for adjusted HR [aHR] = 1.00–3.21). Patients with no/partial recovery from AKI had a 2.94-fold higher MAKE hazard compared with those with no AKI (95% CI for aHR = 1.46–5.92). Initiation of RRT the same day or after ECMO conferred a 5.4-fold increase in MAKE risk compared with initiation of RRT before ECMO (95% CI for aHR = 1.14–25.6) (Table 3).

Long-term mortality was 33 of 119 (28%) in the AKI group and 12 of 69 (17%) in the no AKI group. Incident ESRD was 15 of 119 (13%) in the AKI group and three of 69 (4%) in the no AKI group. Doubling of Scr was 20 of 119 (17%) in the AKI group and five of 69 (7%) in the no AKI group (**Fig. 3**, Supplemental Digital Content, http://links.lww.com/CCX/A911).

DISCUSSION

This study of 188 consecutive patients who survived their ECMO hospitalization at an ECMO referral center shows that AKI confers an increased risk of long-term MAKE. Over a mean follow-up time of 3.4 years, patients with AKI had a 79% increase in MAKE risk compared with those without AKI. Patients with no or partial recovery from AKI at hospital discharge also had a significant increase in MAKE risk compared with those with no AKI or with full AKI recovery. The timing of RRT initiation was another significant determinant of MAKE. Patients who were started on RRT the same day or after the index ECMO initiation day had a 5.4-fold increase in MAKE risk than those who started on RRT a day or more before ECMO initiation.

Our study findings that AKI and AKI nonrecovery are associated with long-term MAKE are concurrent with two recent studies examining long-term renal outcomes after ECMO. Chen et al (14) found that dialysis-requiring AKI (D-AKI) in adult ECMO patients conferred a 2.08 (95% CI [1.76–2.45]) increase in the hazard of MAKE than non D-AKI. They also found that D-AKI nonrecovery was associated with higher long-term mortality compared with D-AKI recovery or no AKI. Findings from that study were based on the national health insurance research database in Taiwan, which did not allow them to capture nondialysis requiring stages of AKI and limited their assessment of renal recovery. Besides, the database did not include information about when RRT was initiated during the index hospitalization. Despite these major differences in study design, the Taiwanese study results seem consistent with our findings. In a single-center study from France, Vinclair et al (15) examined factors associated with MAKE in a cohort of patients requiring venoarterial ECMO (VA-ECMO). Interestingly, this study found that baseline eGFR, KDIGO AKI stage at ECMO cannulation, and the number of RBC packs received while on ECMO were associated with MAKE at 1 year. Almost 40% of ECMO survivors had a 30% decline in eGFR or more at 1 year. Unfortunately, this study did not report MAKE outcomes beyond 1 year.

TABLE 3.

Unadjusted and Adjusted Hazard Ratios of the Association Between Acute Kidney Injury Status, Extracorporeal Membrane Oxygenation and Other Clinical Characteristics and Major Adverse Kidney Event

Variables	Unadjusted HR	95% CI	Adjusted[a] HR	95% CI
Acute kidney injury	**1.75**	1.00–3.10	**1.79**	1.00–3.21
Age (yr)	**1.03**	1.01–1.04	1.01	0.98–1.04
Ever smoker	1.43	0.88–2.35	–	
Charlson Comorbidity Index score	**1.28**	1.15–1.44	1.20	0.94–1.54
Congestive heart failure	**1.81**	1.11–2.95	1.35	0.71–2.59
Diabetes mellitus	**2.00**	1.12–3.53	1.12	0.54–2.29
ECMO for cardiovascular indication	**2.08**	1.12–3.87	–	
Venoarterial/central ECMO	**2.75**	1.33–5.67	2.02	0.91-4.47
RRT same day or after ECMO	**5.40**	1.14–25.6	–	
Baseline estimated glomerular filtration rate level	**0.98**	0.97–0.99	0.99	0.98-1.01
Duration of ECMO support (d)	1.01	0.98–1.03	1.01	0.99-1.03
Duration of RRT in hospital (d)	1.01	0.99–1.03	–	
Duration of RRT total (d)	1.01	0.99–1.02	–	
Length of stay (d)	1.00	0.99–1.01	–	
Time Between RRT and ECMO			Adjusted[b] HR	
RRT before ECMO			1.00	
RRT same day or after ECMO			5.37	1.10–25.6 ($p = 0.04$)

ECMO = extracorporeal membrane oxygenation, HR = hazard ratio, RRT = renal replacement therapy.

[a]Adjusted for the following variables including AKI status that are clinically relevant: age, sex, race, baseline estimated glomerular filtration rate (eGFR) level, diabetes mellitus, hypertension, congestive heart failure (CHF), Charlson Comorbidity Index score, duration of ECMO support, and ECMO type.

[b]Adjusted for the following variables that are clinically relevant: age, sex, race, baseline eGFR level, time between RRT and ECMO imitation, diabetes mellitus, hypertension, CHF, Charlson Comorbidity Index score, duration of ECMO support, and ECMO type.

Boldface values signify the hazard ratios with 95% CI that do-not cross 1. Dashes indicate analysis for adjusted HR was not done for these variables.

Our finding that patients who initiated RRT a day or more before ECMO initiation had a lower MAKE risk is a novel finding and warrants further exploration. It is possible that AKI for which RRT is initiated prior to ECMO is essentially driven by the illness that led to ECMO, namely cardiogenic shock or ARDS. In these cases, the benefits of ECMO, through improvements in kidney perfusion and oxygen tissue delivery, may outweigh any potentially harmful effects of hemolysis and inflammation caused by the extracorporeal circuit on the kidneys and therefore lead to favorable long-term renal outcomes. On the other hand, AKI patients with RRT initiation after ECMO could well represent a different population phenotype, in which intravascular hemolysis secondary to the extracorporeal circuit plays a more central role in the pathophysiology of AKI. Findings from the French study of an association between MAKE at 1 year and the number of RBC packs received while on ECMO align with this theory (15). The other possibility is that early initiation of RRT in patients with severe cardiac or respiratory failure who require ECMO is associated with favorable long-term renal outcomes. Although evidence from recent large randomized controlled studies does not favor "prophylactic" or early initiation of RRT (12, 16), one can argue that the epidemiology and pathophysiology of AKI in ECMO patients are different than in other critically ill patients, such as AKI in patients with septic shock or following major surgery (17).

It is worthwhile noting that patients who developed AKI on ECMO had a significantly longer hospital LOS compared with patients without AKI (56 vs 44 d;

$p = 0.01$) as shown in Table 2. This aligns with previous studies linking AKI with increased in-hospital mortality and LOS (18). Patients on VA-ECMO had a trend toward higher rates of AKI (80% in the VA-ECMO/central ECMO vs 70% in the venovenous ECMO [VV-ECMO] group) (Table 2), although type of ECMO (venoarterial/central vs venovenous) did not appear to be significantly associated with long-term MAKE in the multivariate analysis (aHR 2.02 [0.91–4.47] (Table 3).

Several limitations of this study should be mentioned. First, the large number of patients excluded from our initial sample risks selection bias. There are also unmeasured covariates that could confound the observed associations, including concurrent medications. Our sample was relatively small to detect a true association among the different renal conditions and adverse outcomes, as evident by the nonsignificance of some associations and wide CIs. Last, data are based on a single-center's experience, which prevents the generalizability of our findings.

The study's strengths include that it is one of the first studies to look at long-term renal outcomes in the ECMO population. It has a longer follow-up time (3.4 yr) compared with those mentioned above Taiwanese (2.4 yr) and French (1 yr) studies and, in contrast to these two studies, did not exclude patients with pure respiratory failure requiring VV-ECMO. Important information such as AKI stage and timing of initiation of RRT and AKI recovery were accurately recorded. Data were linked with the U.S. Renal Data System dataset and the NDI. Therefore, death status and need for long-term dialysis in this cohort were accurately captured. In addition, the main exposure and covariates were objectively measured using ICD-10 codes. Last, we employed cause-specific hazards models that allow time to event analysis, which accounts for multiple outcomes, including death.

CONCLUSIONS

Our study showed that in patients with severe cardiac or respiratory failure who require ECMO and survive to hospital discharge, AKI KDIGO stages 2–3 and partial or nonrecovery from AKI were associated with long-term MAKE. These findings can help inform any future guidelines or recommendations for post ECMO specialized renal care. Our finding of an association between timing of initiation of RRT and MAKE indicates the need for future studies that focus on the role of prophylactic or early RRT initiation in this population.

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