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*Research Article*

***Long-Term Clinical Outcomes of Acute Kidney Disease in Patients Receiving Extracorporeal Membrane Oxygenation***

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Short Title: Outcomes of Acute Kidney Disease in Extracorporeal Membrane Oxygenation Patients

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Keywords: acute kidney disease, critically ill, extracorporeal membrane oxygenation, major adverse kidney event, readmission.

**Abstract**

**Introduction:** Extracorporeal membrane oxygenation (ECMO) is widely used; however, studies on the long-term outcomes of ECMO are scarce. We investigated the long-term clinical outcomes of acute kidney disease (AKD) in patients receiving ECMO.

**Methods:** Electronic data (2009–2018) were retrospectively collected from a multicenter database. Patients were divided into two groups (AKD and non-AKD) according to their AKD status 8–90 days after the initiation of ECMO. Inverse probability of treatment weighting (IPTW) was used to balance baseline covariates between the two groups. The primary outcomes were major adverse kidney events (MAKEs) and major adverse cardiovascular events (MACEs), and the secondary outcomes were all-cause readmission, sepsis-related readmission, infection-related readmission, and dementia.

**Results:** Total 395 patients were eligible for analysis; of them, 160 patients (40.5%) developed AKD. The AKD group had a higher risk of MAKEs (hazard ratio [HR]: 2.06; 95% confidence interval [CI]: 1.68–2.53) than did the non-AKD group. Subgroup analysis revealed that the observed unfavorable effect of AKD on the risk of MAKEs was more pronounced in patients receiving venovenous ECMO than in those receiving venoarterial ECMO (HR: 5.69 vs. 1.85, respectively; P for interaction = 0.004). AKD group had a higher risk of MACE during the initial 3-year post- ECMO in comparison to those without (HR: 1.68; 95% CI: 1.22–2.30). Moreover, the risks of all-cause, sepsis-related, and infection-related readmissions were high in AKD survivors.

**Conclusions:** AKD is associated with an increased risk of long-term MAKEs and initial 3-year MACE in ECMO recipients. In addition, AKD is associated with increased risks of all-cause, infection-related, and sepsis-related readmissions.

## Introduction

The use of extracorporeal membrane oxygenation (ECMO) has been growing worldwide [1], providing life support to critically ill patients with survival rates ranging from 29% to 58% [2]. As more patients survive the acute phase of ECMO, understanding its long-term outcomes is crucial. However, few studies have explored this area. ECMO recipients have higher risks of all-cause mortality, increased readmissions, reduced quality of life, and higher medical costs compared to non-recipients [3-6]. Furthermore, ECMO survivors experience poor general health, impaired social functioning, and reduced physical capacity [3]. These long-term issues extend beyond the acute phase and impact not only patients but also their families. Optimizing care for ECMO survivors is essential.

ECMO recipients commonly develop various kidney dysfunctions, such as acute kidney injury (AKI), acute kidney disease (AKD), chronic kidney disease (CKD), and end-stage kidney disease (ESKD), all of which indicate worse outcomes for these individuals [7, 3, 8-10]. AKD serves as the transitional state (8–90 days after the initial kidney insult) between AKI and CKD [11]. Currently, few studies have focused on the outcome of AKD in the context of ECMO recipients. A recent retrospective study conducted by Hsu and colleagues, involving 168 ECMO patients, identified AKD as an independent predictor of ECMO recipients' survival [10]. However, It's currently unclear whether AKD increases the risk of other vital organ dysfunctions, such as recurrent kidney injuries, major cardiovascular adverse events, and dementia, similar to the effects observed with AKI or CKD. Studies have shown that AKI and CKD can have detrimental consequences on future vital organ health, leading to a higher risk of ESKD, cardiovascular and dementia, and readmission [12-18]. These are all serious conditions that require thorough investigation in ECMO patients. However, there is a lack of information available regarding the long-term complications specifically related to ECMO survivors. Notably, literature concerning cognitive function in ECMO survivors remains scarce. [19]

Therefore, this study was conducted to investigate the outcomes of AKD in patients receiving ECMO. We hypothesized that AKD would increase the risks of long-term major adverse kidney events (MAKEs), major adverse cardiovascular events (MACEs), dementia, and readmission in ECMO survivors.

## Methods

### Data Source

We retrospectively collected electronic data from the Chang Gung Research Database (CGRD). The CGRD is the electronic medical records database of the Chang Gung Medical Foundation and contains detailed clinical information, laboratory data, and hemodynamic profiles of patients. This foundation is the largest medical facility in Taiwan, comprising seven hospitals with a total of 9000 beds. The database covers overall and disease-specific information of patients in Taiwan and can be used for medical studies [20, 21]. To assess disease diagnosis in the present study, we used the diagnostic codes outlined by the *International Classification of Diseases*, *Ninth Revision*, *Clinical Modification* for records before 2015 and those outlined by the *International Classification of Diseases*, *Tenth Revision*, *Clinical Modification* for records after 2016. The diagnostic codes used in this study are listed in Supplemental Table 1. The data structure of the CGRD has been validated in several studies [22, 21]. This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 202100124B0; Jan 03, 2021). The requirement for informed consent was waived because the CGRD does not store specific personal identification data.

### Study Population

The unique reimbursement (Taiwan National Health Insurance) code for ECMO (first time for extracorporeal circulation: 68036B) has been used in CGRD since September 1, 2009. Therefore, we identified patients who received ECMO between September 1, 2009, and December 31, 2018. Patients were excluded if they had unknown demographic data (age or sex), were aged <20 years, had been receiving dialysis before ECMO insertion (either between admission and ECMO insertion or before admission), and had been previously diagnosed as having dementia. Patients who survived <90 days or were followed up for <90 days were also excluded. Moreover, patients without sufficient data on serum creatinine level, which is required to determine the status of AKI and AKD, were excluded (Fig. 1).

**AKI and AKD**

In this study, the initiation of ECMO was designated as day 0. To define AKI, we utilized the Kidney Disease: Improving Global Outcomes AKI criteria. We compared patients' baseline creatinine levels with their highest creatinine levels during the first 7 days after ECMO initiation during index admission [23]. The baseline creatinine level was determined by using the lowest creatinine level in the 3 months preceding the index admission. Alternatively, if such data were unavailable, we alternatively used the creatinine data first recorded on the first day of the index admission.

For defining AKD, we employed criteria based on the Kidney Disease Improving Global Guidelines [24, 11]. AKD was defined as >50% increase in serum creatinine, or a decrease of at least 35% in estimated glomerular filtration rate (eGFR) from baseline, or a newly developed eGFR <60 ml/min/1.73 $m^2$ between 8 and 90 days after ECMO initiation. It is important to note that in case of subacute damage to the kidney, AKI may not be observed during AKD diagnosis [11]. When multiple creatinine values were available within 8–90 period, the presence of AKD was determined using the creatinine level recorded on the day closest to Day 90 after ECMO initiation.

**Covariates**

We collected data on the clinical characteristics, AKI susceptibility and renal nonrecovery factors for ECMO or critical illness population according to previous studies or availability in our data set [7, 3, 25, 9, 4, 26, 27, 15, 28]. The clinical characteristics included demographics, eGFR, vital signs at ECMO insertion, ECMO modes, comorbidities, and first recorded laboratory results at baseline and before ECMO initiation. We further assessed the overall health status of patients at baseline by using the Charlson Comorbidity Index (CCI) [29]. Finally, we assessed sequential organ failure on the day following ECMO insertion to evaluate the risk of short-term mortality.

**Outcomes**

We evaluated in-hospital and long-term (after 90 days) outcomes after ECMO insertion. The primary outcomes were MAKEs and MACEs during follow-up. MAKEs comprised newly diagnosed ESKD requiring chronic dialysis, new-onset CKD (defined as an eGFR of <60 mL/min per 1.73 $m^2$ according to the Modification of Diet in Renal Disease equation), and all-cause mortality. MACEs were defined as the composite outcomes of cardiovascular death, acute myocardial infarction (AMI), ischemic stroke, and heart failure–related hospitalization. Cardiovascular death was defined according to the Standardized Definitions for Cardiovascular and Stroke Endpoint Events in Clinical Trials by the United States Food and Drug Administration. The incidences of AMI and ischemic stroke were recorded in the inpatient setting. The secondary long-term outcomes were all-cause readmission, sepsis-related readmission, infection-related readmission, and new-onset dementia. To analyze each long-term outcome, patients were followed from Day 91 after ECMO insertion to the occurrence of the outcome, death, or last hospital visit (database end date: December 31, 2018), whichever came first.

**Statistical Analysis**

To balance the baseline covariates between the AKD and non-AKD groups, we used inverse probability of treatment weighting (IPTW) with average treatment effects based on propensity scores. Propensity scores were estimated using a multivariable logistic regression model, which included all covariates (Table 1) and the index date (date of ECMO insertion). The balance of covariates between the groups was confirmed using standardized difference (STD); absolute STD values of <0.1 and <0.2 indicated negligible and nonsubstantial between-group, respectively. The in-hospital outcomes were compared between the groups using the Mann–Whitney U test for continuous variables and the chi-square test for categorical variables. The risk of long-term outcomes was compared between the groups using the Cox proportional hazards model. Furthermore, subgroup analysis was performed including MAKE and MACE data stratified by several variables. Some missing values were noted in the laboratory data; therefore, the data were imputed using a single expectation–maximization algorithm before IPTW adjustment. Since we excluded a significant number of patients who did not survive for 90 days and those with missing creatinine data, we also conducted a sensitivity analysis to assess the potential impact of these exclusions on the outcomes of our analyses. All analyses were performed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA). A two-sided *P* value of <0.05 was considered statistically significant.

## Results

### AKD Incidence After ECMO

During the study period, 1501 patients received ECMO. Of them, 395 patients were eligible for analysis. Among them, 160 (40.5%) patients developed AKD during 8–90 days after ECMO initiation (Fig. 1). Of these 160 patients, 119 (74.3%) developed AKI during the first 7 days. Of the remaining 235 patients without AKD, 64 (27.2%) clinically recovered from AKI.

### Baseline Characteristics

The mean age of our cohort was 55.7 years, and 71% (n = 280) of all included patients were men. Patients with AKD were older than patients without it. In addition, the AKD group had higher dyslipidemia and CKD prevalence rates; baseline CCI scores; and pre-ECMO BUN, serum creatinine, and potassium levels than did the non-AKD group (Table 1). After IPTW adjustment, all baseline characteristics between the AKD and non-AKD groups were not substantially different, with all the absolute STD values <0.2. The incidence of AKI was higher in the AKD group compared to the non-AKD group (74.3% vs 27.2%). Clinical characteristics, in-hospital outcomes, and survival outcomes based on AKI status within 7 days after ECMO initiation are presented in Supplemental Table 2.

### In-Hospital Outcomes

The likelihood of poor in-hospital outcomes 8–90 days after ECMO was higher in the AKD group than in the non-AKD group. Specifically, the AKD group had shorter ECMO-to-dialysis duration, longer ECMO duration, longer ventilation duration, and longer intensive care unit and hospital stay than did the non-AKD group (Table 2).

### Long-Term Outcomes

The duration of follow-up was 20 (interquartile range: 8–56) and 34 (interquartile range: 15–68) months in the IPTW-adjusted AKD and non-AKD groups, respectively (Table 1). The long-term outcomes, categorized based on the patient's AKD status, are summarized in Table 3. The risk of MAKEs was significantly higher in the AKD group (hazard ratio [HR]: 2.06, 95% confidence interval [CI]: 1.68–2.53, $P < 0.001$; Fig. 2A) than in the non-AKD group. The risks of all components of MAKEs, such as all-cause mortality, new-onset CKD, and ESKD with chronic dialysis, were significantly higher in the AKD group than in the non-AKD group; among them, ESKD with chronic dialysis had the highest HR (HR: 2.88, 95% CI: 1.12–7.42, $P = 0.028$; Fig. 2B). The risk of MACEs did not differ significantly between the groups (HR: 1.29, 95% CI: 0.84–1.98, $P = 0.241$; Fig. 2C); however, the risk of cardiovascular death was significantly higher in the AKD group (HR: 2.35, 95% CI: 1.05–5.23) than in the non-AKD group. Regarding the secondary outcomes, the risks of all-cause, sepsis-related, and infection-related readmissions were higher in the AKD group (Fig. 2D and E) than in the non-AKD group. The risk of long-term dementia did not differ substantially between the groups.

Observed from Figure 2C, the two groups crossed at approximately 5 to 6 years of follow up which implied the proportionality assumption may not be held. Therefore, we conducted a piecewise analysis for MACE to investigate whether the impact of AKD diminishes over time, as depicted in Supplemental Figure 1. Individuals with AKD had higher risk for developing MACE within the initial 3 years of ECMO compared to those without AKD (HR: 1.68, 95% CI: 1.22–2.30). However, this effect was not observed beyond the 3-year landmark.

### Subgroup Analysis

Subgroup analysis revealed that the observed nonfavorable effect of AKD on the risk of MAKEs was more pronounced in patients receiving V-V ECMO than in those receiving V-A ECMO (HR: 5.69 vs. 1.85, respectively; $P$ for interaction = 0.004; Fig. 3). Regarding MACEs, no evidence of substantial between-group heterogeneity was found (Supplemental Table 3).

Since AKI has been known to be associated with future CV events, we performed a subgroup analysis by excluding individuals with AKI from the non-AKD group and another IPTW-adjusted cohort was created, as outlined in Supplemental Table 4. In this analysis, individuals with AKD had a significantly elevated risk of MACE compared to those without both AKD and AKI (HR 1.37, 95% CI 1.02–1.84). This increased MACE risk was primarily attributed to a higher likelihood of cardiovascular death (HR: 2.48, 95% CI 1.57–3.92).

### Sensitivity and Additional Analyses

In the main study, we excluded 584 patients who died within 90 days of follow-up and 103 patients with missing creatinine data to assess AKI or AKD. To evaluate the potential influence of these excluded patients on both in-hospital and long-term outcomes, we conducted a sensitivity analysis (supplemental tables 5 and 6). The HR of MAKE and cardiovascular death in the AKD group remained significantly higher than in the non-AKD group. Although the differences did not reach statistical significance, a higher risk for all-cause readmission, sepsis-related readmission, and infection-related readmission was observed in the AKD group compared to non-AKD group. Overall, the results of the sensitivity analyses were consistent to that of the main analyses which may confirm the robustness of the findings.

The long-term outcomes, classified according to the patient's AKI status (and another IPTW-adjusted cohort was created), are presented in Supplemental Table 7. Patients with AKI exhibited a higher incidence of new diagnosis CKD, ESKD with chronic dialysis, and a composite outcome of MAKE. Additionally, sepsis-related readmission and infection readmission rates were elevated in patients who experienced AKI compared to those without.

**Discussion**

To the best of our knowledge, this study is the first to explore the effects of AKD status on the risks of long-term MAKEs, MACEs, and readmissions in ECMO survivors. ECMO survivors with AKD had poorer long-term outcomes in terms of MAKEs and cardiovascular death than did those without AKD. Readmission rates also varied considerably when patients were stratified according to post-ECMO AKD status, including all-cause, sepsis-related, and infection-related readmissions.

Detrimental effects of AKI have been reported in ECMO survivors, and our findings further suggest that these effects are also relevant for AKD. AKI increases the risks of long-term mortality and MAKEs in critical ill patients and ECMO recipients [26, 30]. Mortality risk is higher in patients with AKI requiring dialysis than in those not requiring dialysis. Even after these patients recover from dialysis requiring AKI, their mortality risk is still higher than those without AKI [26]. As the transition from AKI to CKD, AKD has similar deleterious effect ECMO survivors. AKD has been reported to a predictor for mortality in ECMO recipients after multivariate analysis [10]. After IPTW adjustment in the present study, patients with AKD were found to have worse long-term survival than did those without AKD. Thus, AKD increases not only the overall mortality rate of ECMO survivors but also the likelihood of future kidney-related adverse events and cardiovascular death. Currently, kidney function surveillance has been proposed as standard of care in pediatric ECMO survivors [31]. The intensive monitoring of kidney and cardiovascular functions is recommended during the long-term follow-up of adult ECMO survivors with AKD.

In our study, the incidence of AKI is higher in the AKD group compared to the non-AKD group, which is expected considering AKD is an extension of AKI over time. The patients with AKI experience unfavorable in-hospital outcomes, including earlier initiation of dialysis after ECMO, longer duration of mechanical ventilation, and hospital days. These findings are consistent with previous studies [4, 17]. Another population-based study demonstrated that AKI patients requiring dialysis had a higher risk of in-hospital mortality, longer hospital and ICU stays [26]. Moreover, the study also found that non-recovery dialysis-requiring AKI patients had a higher long-term MAKE risk compared to those who recovered from dialysis-requiring or did not experience AKI. Our study also shows slightly a higher risk for long-term MAKE in those with AKI than those without, although the difference was not statistically significant. The lack of significance might be attributed to our smaller sample size, different exclusion criteria, and grouping methods compared to previous studies. AKD is considered an ongoing renal pathophysiological process following AKI without timely renal recovery within 7 days [11]. The more prominent detrimental effect of AKD on long-term complications, such as MAKE and readmission, compared to AKI, may be attributed to the persistent pathophysiological nature of AKD. More studies are required to determine whether AKD directly contributes to these long-term complications or serves as an intermediate factor for AKI. The pathophysiological interplay between AKI, AKD, and long-term complications requires further investigation to better understand their relationships and mechanisms.

Subgroup analysis performed in the present study indicated that the nonfavorable effect of AKD on the risk of MAKEs was more pronounced in patients receiving V-V ECMO than in those receiving V-A ECMO. From a pathophysiological perspective, V-A ECMO is associated with more kidney damage than V-V ECMO. The continuous blood flow from V-A ECMO results in a decrease in pulsatility, which can compromise renal blood flow due to periarteritis in the kidney and disruption of the renin-angiotensin system [32]. Additionally, V-A ECMO has more complications such as hemorrhage or thromboembolism than V-V ECMO [33]. Although some studies have reported higher incidences of AKI in patients receiving V-A ECMO than in those receiving V-V ECMO, others studies have indicated no substantial difference between the two modes of ECMO; this suggests that patients' baseline characteristics or AKI etiologies might be more important for ECMO-related AKI than are the ECMO modes [1, 34, 28]. Direct comparison of the two modes in terms of kidney insult is difficult because of the differences in clinical indications. Furthermore, higher rates of stage 3 AKI and KRT use have been reported in patients receiving V-V ECMO than in those receiving V-A ECMO; a higher severity of AKI is associated with a higher risk of MAKEs [35, 34]. In general, patients receiving V-V ECMO are more susceptible to sepsis and have more comorbidities than are those receiving V-A ECMO [36]. Whether patient characteristics and sepsis-related kidney injury contribute to the more pronounced negative effects of AKD on the risk of long-term MAKEs in patients receiving V-V ECMO remains unclear. Hence, further studies are required to clarify the associations between patient characteristics, kidney injury etiologies, ECMO modes, and long-term kidney outcomes.

Cardiovascular complications following AKI have been previously described in the literature, termed as cardiorenal syndrome type 3 [37]. However, the inconsistency in the reported adverse effects of AKI on cardiovascular health can be attributed to the observational nature of these studies [38]. Notably, insights from prospective studies such as Assessment, Serial Evaluation, and Subsequent Sequelae of Acute Kidney Injury (ASSESS-AKI) and AKI Risk in Derby (ARID) indicate that the risk of developing adverse cardiovascular outcomes diminishes after adjusting for kidney function three months post the index hospitalization [39, 40]. The findings from our study, indicating a connection between the presence of AKD in ECMO patients and cardiovascular death, are consistent with this concept. Furthermore, the detrimental impact of AKD on MACE is more pronounced in the initial 3 years following ECMO initiation but diminishes thereafter. The reasons behind the gradual attenuation of this adverse effect over time remain unclear. While additional research is necessary to explore the cardiovascular consequences of AKD, given the limited existing literature, it is recommended to closely monitor cardiovascular health in ECMO survivors, particularly within the first three years.

ECMO survivors with AKD are more likely to be rehospitalized during long-term follow-up than are those without AKD. Moreover, the AKD group exhibited higher risks of all-cause, sepsis-related, and infection-related readmissions than did the non-AKD group. After rigorous ITPW adjustment, the AKD group consistently had more sepsis-related readmissions during long-term follow-up than did the non-AKD group. Further studies are needed to elucidate the precise mechanisms underlying the observed association between AKD and increased readmission risks. A population-based retrospective study reported that patients with AKI had markedly higher risks of 30- and 90-day all-cause readmissions than did those without AKI, and this association remained significant after covariate adjustment [41]. Patients with AKI are likely to have subsequent infection, and sepsis-related readmission [42-45]. Significantly, individuals who developed sepsis following AKI were also more likely to undergo dialysis treatment and experienced extended hospitalization periods [42]. Even patients with complete recovery from AKI have higher risks of infection 1 year after the initial AKI incidence [46]. Doi et al. indicated the post-AKI impairment of patients' immune function is a possible reason for the higher risk of readmission in this population. Thus, future studies are warranted to explore the crosstalk between the immune system and kidneys. AKI may develop due to inflammatory insults, and AKI itself exerts profound immune-dysregulatory effects [47]. In the pathophysiologic context, AKI impairs neutrophil rolling and migration, subsequently hindering the neutrophil recruitment cascade [47]. Patients with AKI and sepsis have higher levels of resistin, which impedes neutrophil migration and bacterial killing, than do healthy population [48, 49, 47].

Presumably, ECMO creates routes for pathogen invasion from surgical sites or circuits, thus rendering recipients with kidney injury susceptible to subsequent infection [42]. AKD is the transition state between AKI and CKD and thus is expected to exert reasonably similar negative effects via immune system–kidney crosstalk. Our findings suggest that AKD may have a comparable impact on all-cause and infection-related readmissions as AKI does. Further well-controlled prospective studies are needed to confirm the influence of kidney–immune crosstalk.

**Conclusions**

Among ECMO survivors, patients with AKD had higher risks of MAKEs and cardiovascular death than did those without AKD. AKD patients also had a higher risk of MACE within the initial 3 years following the initiation of ECMO. In addition, the likelihoods of all-cause, sepsis-related, and infection-related readmissions were higher in patients with AKD than in those without AKD. The effect of AKD on the risk of MAKEs was more prominent in patients receiving V-V ECMO than in those receiving V-A ECMO. AKD should not be regarded as only a transient clinical status; rather, it should be deemed a predictor of long-term clinical outcomes. Clinicians should routinely monitor kidney and cardiovascular functions and check for infection during the long-term follow-up of ECMO survivors with AKD.

## Statements

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### Statement of Ethics

This study was approved by the Institutional Review Board of Chang Gung Memorial Hospital (approval number: 202100124B0; Jan 03, 2021). The requirement for informed consent was waived by the Institutional Review Board because the CGRD does not store specific personal identification data.

### Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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### Author Contributions

Ming-Jen Chan: Writing- Original draft preparation and Editing, Methodology, Software Shao-Wei Chen: Conceptualization, Methodology Pei-Chun Fan: Writing- Reviewing, Data curation Cheng-Chia Lee: Visualization, Data curation George Kuo: Visualization, Methodology, Software Jia-Jin Chen: Methodology, Software Yung-Chang Chen: Supervision, Conceptualization Chih-Hsiang Chang: Supervision, Conceptualization, Writing- Reviewing. All authors have read and agreed to the published version of the manuscript.

### Data Availability Statement

The data that support the findings of this study are not publicly available for protecting privacy of research patients but are available from corresponding author upon reasonable request.

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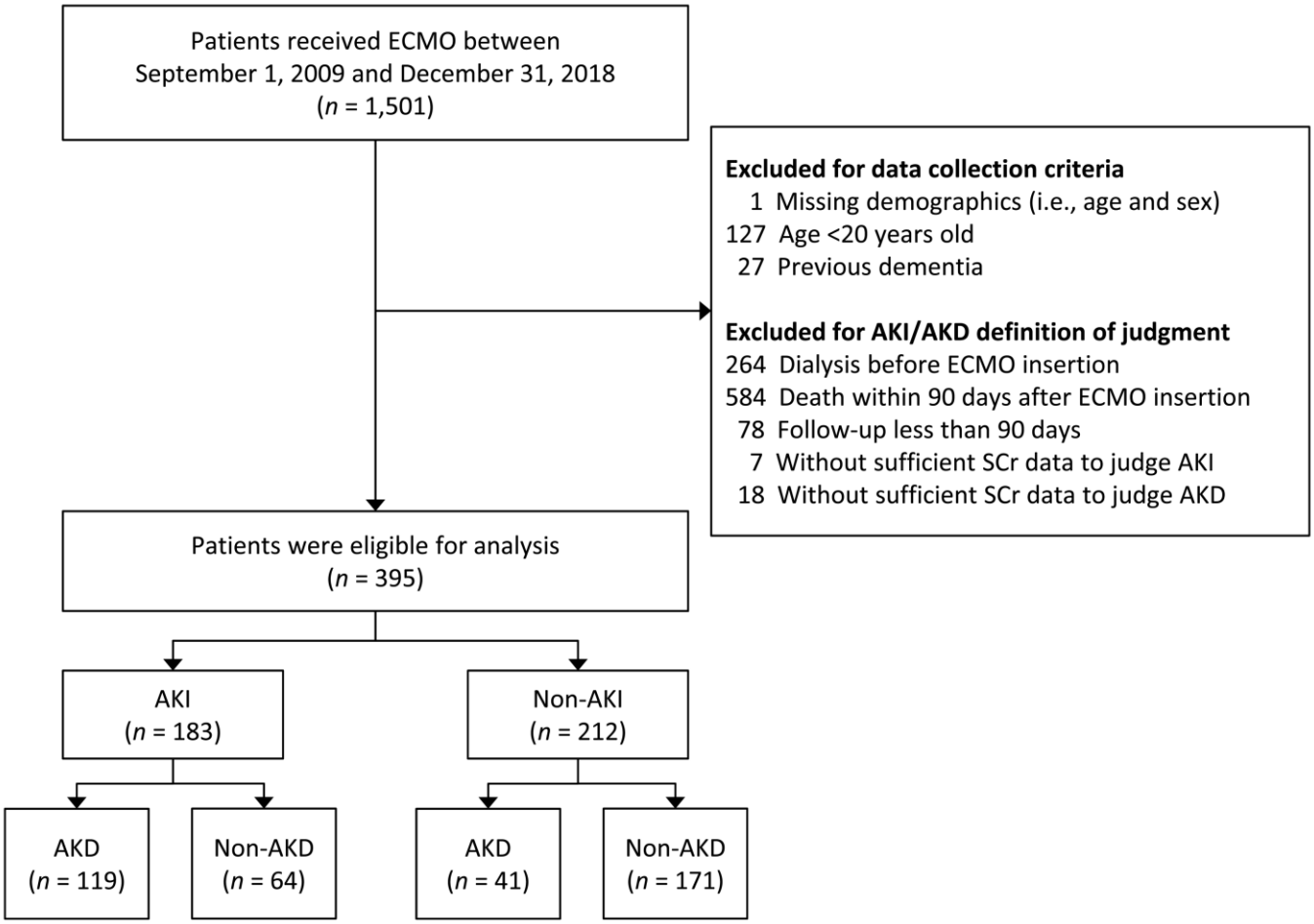
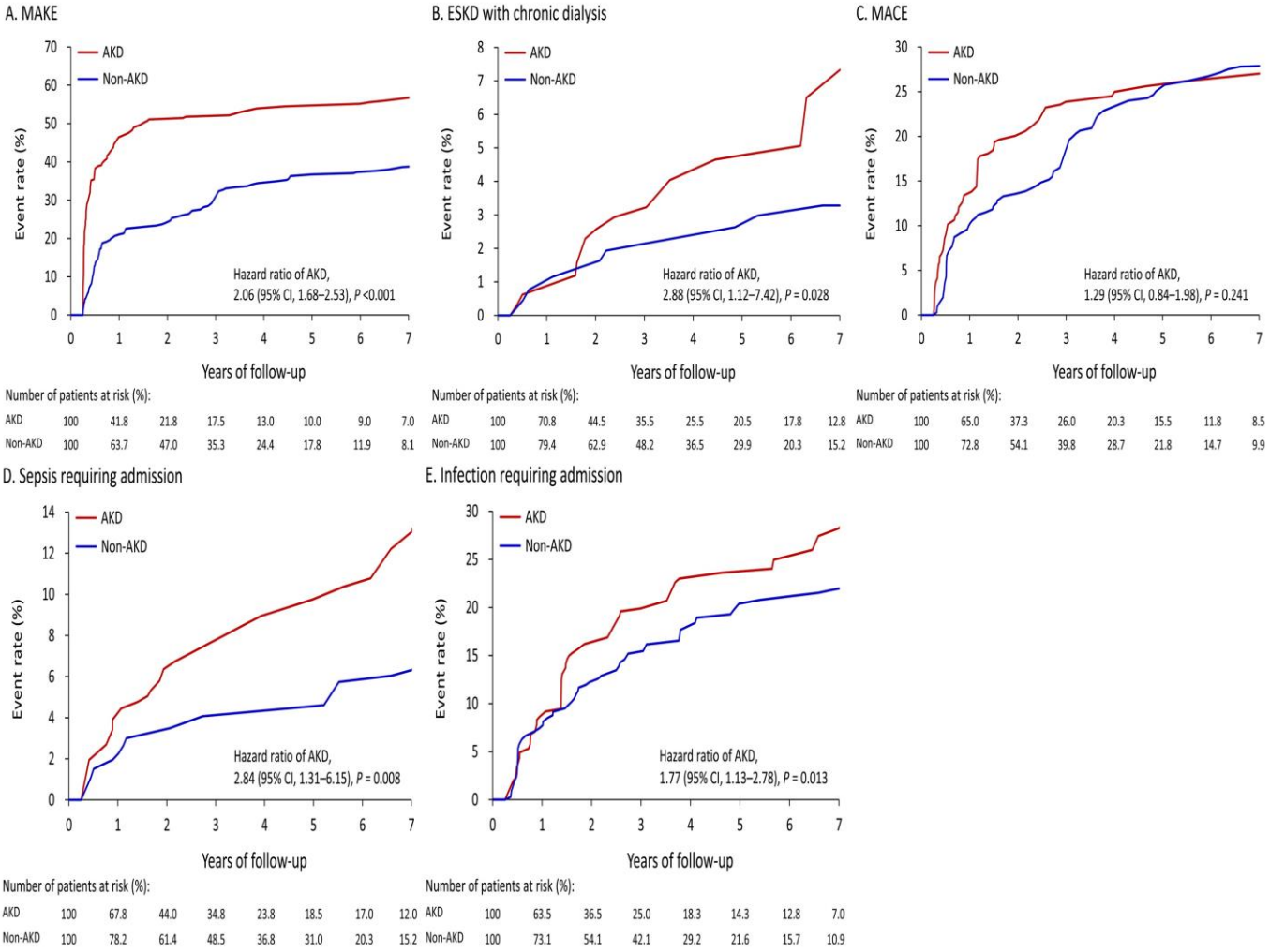
**Figure Legends**

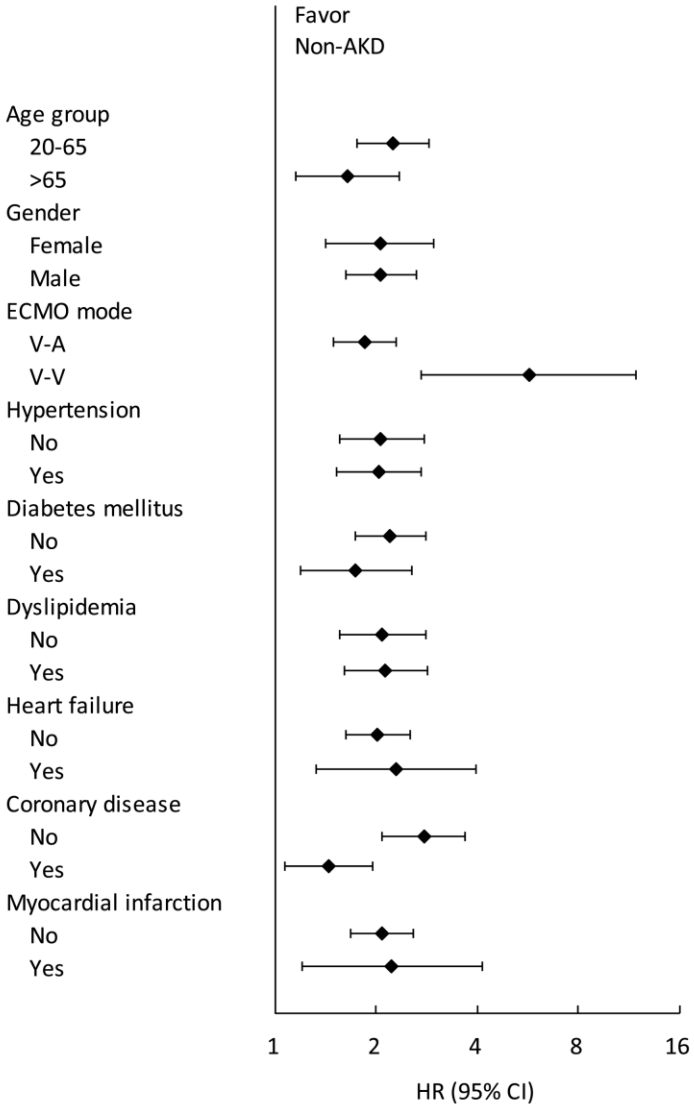
Fig. 1. Flowchart for patient selection
AKD, acute kidney disease; AKI, acute kidney injury; ECMO, extracorporeal membrane oxygenation; SCr, serum creatinine.

Fig. 2. IPTW-adjusted cumulative rate of MAKEs (A), ESKD with chronic dialysis (B), MACEs (C), sepsis-related readmission (D), and infection-related readmission (E) stratified by AKD status during follow-up.
AKD, acute kidney disease; CI, confidence interval; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiovascular event; MAKE, major adverse kidney event.

Fig. 3. Results of subgroup analyses performed to assess the risk of MAKEs in the IPTW-adjusted AKD and non-AKD groups.
AKD, acute kidney disease; ECMO, extracorporeal membrane oxygenation; IPTW, inverse probability of treatment weighting; MAKE, major adverse kidney event; V-A, venoarterial; V-V, venovenous.








| | Event rate after IPTW | | AKD *vs* . Non-AKD | |
|---|---|---|---|---|
| | AKD | Non-AKD | HR (95% CI) | *P* value for interaction |
| Age group | | | | 0.156 |
| 20-65 | 54.1% | 35.9% | 2.25 (1.75 - 2.88) | |
| >65 | 67.2% | 50.6% | 1.64 (1.15 - 2.34) | |
| Gender | | | | 0.970 |
| Female | 57.0% | 39.4% | 2.05 (1.42 - 2.96) | |
| Male | 58.0% | 39.9% | 2.07 (1.62 - 2.65) | |
| ECMO mode | | | | 0.004 |
| V-A | 59.6% | 46.6% | 1.85 (1.49 - 2.30) | |
| V-V | 49.8% | 11.2% | 5.69 (2.72 - 11.93) | |
| Hypertension | | | | 0.916 |
| No | 48.8% | 34.5% | 2.07 (1.55 - 2.77) | |
| Yes | 70.6% | 47.3% | 2.03 (1.52 - 2.71) | |
| Diabetes mellitus | | | | 0.300 |
| No | 55.3% | 36.5% | 2.20 (1.73 - 2.81) | |
| Yes | 65.6% | 49.7% | 1.74 (1.19 - 2.54) | |
| Dyslipidemia | | | | 0.932 |
| No | 48.4% | 31.8% | 2.09 (1.56 - 2.81) | |
| Yes | 72.7% | 50.8% | 2.13 (1.60 - 2.83) | |
| Heart failure | | | | 0.674 |
| No | 55.5% | 38.6% | 2.02 (1.62 - 2.52) | |
| Yes | 73.0% | 50.4% | 2.29 (1.33 - 3.95) | |
| Coronary disease | | | | 0.002 |
| No | 57.7% | 32.6% | 2.77 (2.09 - 3.67) | |
| Yes | 57.7% | 49.6% | 1.44 (1.07 - 1.95) | |
| Myocardial infarction | | | | 0.827 |
| No | 56.2% | 40.9% | 2.08 (1.67 - 2.58) | |
| Yes | 69.3% | 31.4% | 2.23 (1.20 - 4.16) | |

**Table 1**. Demographic and clinical characteristics of patients with or without AKD during 8-90 days after ECMO insertion

| | | | Before IPTW and EM imputation# | | | After IPTW and EM imputation$ | | |
|---|---|---|---|---|---|---|---|---|
| Variable | Available Numbers | Total (n = 395) | AKD (n = 160) | Non-AKD (n = 235) | STD | AKD | Non-AKD | STD |
| Age, years | 395 | 55.7±14.0 | 58.2±13.6 | 54.0±14.0 | 0.30 | 55.8±14.4 | 55.8±13.8 | <0.01 |
| Age group | 395 | | | | | | | |
| 20-65 years | | 291 (73.7) | 108 (67.5) | 183 (77.9) | -0.23 | 72.9% | 73.9% | -0.02 |
| >65 years | | 104 (26.3) | 52 (32.5) | 52 (22.1) | 0.23 | 27.1% | 26.1% | 0.02 |
| Male | 395 | 280 (70.9) | 112 (70.0) | 168 (71.5) | -0.03 | 67.3% | 69.3% | -0.04 |
| Baseline eGFR, mL/min/1.73m$^2$ | 395 | 62.5±31.8 | 59.6±33.0 | 64.4±30.9 | -0.15 | 63.1±30.7 | 63.0±31.7 | <0.01 |
| BMI, kg/m$^2$ | 391 | 26.6±12.8 | 25.6±3.8 | 27.3±16.2 | -0.14 | 25.9±3.6 | 26.6±13.0 | -0.07 |
| Vital sign at ECMO | | | | | | | | |
| SBP, mmHg | 394 | 120.0±27.1 | 120.9±28.6 | 119.4±26.0 | 0.06 | 121.7±29.0 | 120.6±27.0 | 0.04 |
| DBP, mmHg | 394 | 70.2±19.3 | 69.3±21.7 | 70.8±17.5 | -0.08 | 71.3±23.0 | 70.4±17.4 | 0.04 |
| Heart rate, beats/min | 395 | 92.8±20.9 | 93.3±21.5 | 92.4±20.6 | 0.04 | 92.0±21.1 | 93.4±21.0 | -0.07 |
| ECMO mode | 395 | | | | | | | |
| V-A | | 320 (81.0) | 129 (80.6) | 191 (81.3) | -0.02 | 80.2% | 80.6% | -0.01 |
| V-V | | 75 (19.0) | 31 (19.4) | 44 (18.7) | 0.02 | 19.8% | 19.4% | 0.01 |
| Comorbidity | | | | | | | | |
| Hypertension | 395 | 167 (42.3) | 66 (41.3) | 101 (43.0) | -0.04 | 40.7% | 41.3% | -0.01 |
| Diabetes mellitus | 395 | 100 (25.3) | 46 (28.8) | 54 (23.0) | 0.13 | 23.1% | 24.6% | -0.04 |
| Dyslipidemia | 395 | 174 (44.1) | 80 (50.0) | 94 (40.0) | 0.20 | 38.1% | 41.9% | -0.08 |
| Heart failure | 395 | 46 (11.6) | 21 (13.1) | 25 (10.6) | 0.08 | 12.5% | 10.1% | 0.07 |
| Coronary artery disease | 395 | 166 (42.0) | 65 (40.6) | 101 (43.0) | -0.05 | 37.8% | 42.1% | -0.09 |
| Myocardial infarction | 395 | 47 (11.9) | 18 (11.3) | 29 (12.3) | -0.03 | 11.3% | 11.9% | -0.02 |
| Chronic kidney disease | 395 | 78 (19.7) | 44 (27.5) | 34 (14.5) | 0.32 | 19.0% | 18.8% | 0.01 |
| COPD | 395 | 28 (7.1) | 13 (8.1) | 15 (6.4) | 0.07 | 6.5% | 7.0% | -0.02 |
| Liver cirrhosis | 395 | 14 (3.5) | 6 (3.8) | 8 (3.4) | 0.02 | 5.4% | 3.2% | 0.11 |
| Peripheral arterial disease | 395 | 38 (9.6) | 16 (10.0) | 22 (9.4) | 0.02 | 10.8% | 12.0% | -0.04 |
| Risk score | | | | | | | | |
| CCI at baseline | 395 | 2.2±2.3 | 2.5±2.7 | 2.0±2.0 | 0.22 | 2.1±2.4 | 2.2±2.3 | -0.03 |
| SOFA at the 2$^{nd}$ day after ECMO | 277 | 11.7±2.4 | 12.0±2.4 | 11.6±2.4 | 0.16 | 11.6±2.3 | 11.4±2.4 | 0.07 |
| Hospital level | 395 | | | | | | | |
| Medical center | | 343 (86.8) | 141 (88.1) | 202 (86.0) | 0.06 | 86.3% | 86.5% | -0.01 |
| District/regional hospital | | 52 (13.2) | 19 (11.9) | 33 (14.0) | -0.06 | 13.7% | 13.5% | 0.01 |
| Laboratory data at pre-ECMO | | | | | | | | |
| BUN, mg/dL | 216 | 26.3±20.0 | 30.6±23.7 | 22.9±15.9 | 0.38 | 24.9±18.9 | 25.0±17.1 | <0.01 |
| Creatinine, mg/dL | 243 | 1.3±0.9 | 1.5±1.1 | 1.2±0.8 | 0.33 | 1.29±0.88 | 1.32±0.93 | -0.03 |
| Sodium, mg/dL | 241 | 138.4±5.5 | 138.7±6.2 | 138.1±4.9 | 0.10 | 138.3±5.3 | 138.0±4.8 | 0.06 |
| Potassium, mg/dL | 385 | 3.86±0.71 | 3.95±0.73 | 3.80±0.69 | 0.21 | 3.8±0.7 | 3.9±0.7 | -0.04 |
| Calcium, mg/dL | 314 | 7.8±1.0 | 7.8±1.1 | 7.7±0.9 | 0.10 | 7.9±1.1 | 7.8±0.9 | 0.06 |
| Laboratory data at baseline | | | | | | | | |
| LDL, mg/dL | 250 | 70.5±46.6 | 73.6±52.0 | 68.2±42.2 | 0.11 | 71.6±44.9 | 67.5±42.0 | 0.09 |
| HDL, mg/dL | 248 | 35.2±12.6 | 34.8±13.1 | 35.5±12.3 | -0.05 | 34.9±13.1 | 35.1±12.0 | -0.01 |
| Triglyceride, mg/dL | 277 | 113 [79, 166] | 111 [71, 164] | 116 [82, 173] | 0.02 | 106 [66, 163] | 123 [84, 177] | -0.01 |

| Variable | Available Numbers | Total (n = 395) | Before IPTW and EM imputation# AKD (n = 160) | Non-AKD (n = 235) | STD | After IPTW and EM imputation$ AKD | Non-AKD | STD |
|---|---|---|---|---|---|---|---|---|
| Total cholesterol, mg/dL | 270 | 156.5±48.1 | 157.0±49.2 | 156.1±47.5 | 0.02 | 153.6±46.2 | 156.4±45.4 | -0.06 |
| HbA1C, % | 224 | 6.8±1.6 | 6.9±1.6 | 6.8±1.6 | 0.05 | 6.8±1.6 | 6.9±1.6 | -0.07 |
| Uric acid, mg/dL | 200 | 7.0±2.9 | 7.1±2.9 | 6.9±2.8 | 0.07 | 6.7±2.8 | 7.1±2.9 | -0.15 |
| Follow-up month | 395 | 29 [12, 66] | 19 [7, 51] | 38 [16, 70] | -0.40 | 20 [8, 56] | 34 [15, 68] | -0.25 |

Abbreviation: AKD, acute kidney disease; BMI, body mass index; BUN, blood urea nitrogen; CCI, Charlson Comorbidity Index; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; ECMO, extracorporeal membrane oxygenation; eGFR, estimated glomerular filtration rate; EM, expectation maximization; HbA1C, glycated hemoglobin; HDL, high-density lipoprotein; IPTW, inverse probability of treatment weighting; LDL, low-density lipoprotein; SBP, systolic blood pressure; SOFA, sequential organ failure assessment; STD, standardized difference; V-A; venoarterial; V-V, venovenous;

# Data were presented as frequency (percentage), mean ± standard deviation or median [25$^{th}$, 75$^{th}$ percentiles];

$ Data were presented as percentage, mean ± standard deviation or median [25$^{th}$, 75$^{th}$ percentiles];

**Table 2**. In-hospital outcomes of patients with or without AKD during 8-90 days after ECMO insertion

| | | Before IPTW# | | | After IPTW$ | | |
|---|---|---|---|---|---|---|---|
| Outcome | Total (n = 395) | AKD (n = 160) | Non-AKD (n = 235) | *P* value | AKD | Non-AKD | *P* value |
| Days from ECMO to dialysis initiation* | 5 [2, 60] | 5 [2, 38] | 209 [2, 1291] | 0.189 | 5 [2, 38] | 2 [2, 406] | <0.001 |
| Duration of ECMO, day | 5 [3, 8] | 7 [4, 10] | 4 [2, 6] | <0.001 | 7 [4, 9] | 4 [2, 7] | <0.001 |
| Ventilator days | 11 [6, 27] | 21 [10, 56] | 9 [5, 15] | <0.001 | 16 [9, 42] | 9 [5, 17] | <0.001 |
| ICU days | 15 [9, 27] | 25 [14, 51] | 11 [7, 19] | <0.001 | 21 [13, 42] | 12 [7, 20] | <0.001 |
| Admission days | 39 [25, 66] | 61 [34, 100] | 33 [22, 46] | <0.001 | 52 [30, 84] | 36 [22, 50] | <0.001 |
| Tracheotomy | 141 (35.7) | 80 (50.0) | 61 (26.0) | <0.001 | 36.2% | 37.4% | 0.757 |
| Long-term use of urethral catheters | 27 (6.8) | 14 (8.8) | 13 (5.5) | 0.213 | 8.4% | 6.8% | 0.384 |

Abbreviation: AKD, acute kidney disease; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; IPTW, inverse probability of treatment weighting;

# Data were presented as frequency (percentage) or median [25$^{th}$, 75$^{th}$ percentiles];

$ Data were presented as percentage or median [25$^{th}$, 75$^{th}$ percentiles];

* Available number of patients = 102.

**Table 3**. Long-term outcomes (> 90 days after ECMO insertion) of patients with or without AKD during 8-90 days after ECMO insertion

| | Before IPTW# | | After IPTW$ | | | |
|---|---|---|---|---|---|---|
| Outcome | AKD (n = 160) | Non-AKD (n = 235) | AKD | Non-AKD | HR (95% CI) for AKD | *P* value |
| MAKE | | | | | | |
| All-cause death | 40 (25.0) | 22 (9.4) | 19.9% | 13.2% | 1.95 (1.04 - 3.65) | 0.036 |
| New diagnosis of CKD* | 73 (45.6) | 80 (34.0) | 46.8% | 32.7% | 1.93 (1.33 - 2.80) | <0.001 |
| ESKD with chronic dialysis | 13 (8.1) | 8 (3.4) | 7.3% | 3.3% | 2.88 (1.12 - 7.42) | 0.028 |
| Composite outcome | 96 (60.0) | 89 (37.9) | 57.7% | 39.8% | 2.06 (1.68 - 2.53) | <0.001 |
| MACE | | | | | | |
| Cardiovascular death | 33 (20.6) | 15 (6.4) | 16.2% | 9.0% | 2.35 (1.05 - 5.23) | 0.037 |
| Acute myocardial infarction | 9 (5.6) | 14 (6.0) | 5.1% | 5.6% | 1.08 (0.43 - 2.74) | 0.873 |
| Ischemic stroke | 9 (5.6) | 8 (3.4) | 3.7% | 3.1% | 1.40 (0.51 - 3.89) | 0.515 |
| Heart failure hospitalization | 25 (15.6) | 43 (18.3) | 15.7% | 17.7% | 1.09 (0.61 - 1.97) | 0.770 |
| Composite outcome | 52 (32.5) | 62 (26.4) | 28.8% | 28.1% | 1.29 (0.84 - 1.98) | 0.241 |
| Secondary outcome | | | | | | |
| All-cause readmission | 93 (58.1) | 134 (57.0) | 64.5% | 57.6% | 1.41 (1.04 - 1.91) | 0.027 |
| Sepsis-related readmission | 21 (13.1) | 13 (5.5) | 14.9% | 7.2% | 2.84 (1.31 - 6.15) | 0.008 |
| Infection-related readmission | 43 (26.9) | 49 (20.9) | 30.0% | 22.7% | 1.77 (1.13 - 2.78) | 0.013 |
| Dementia | 4 (2.5) | 7 (3.0) | 1.9% | 2.5% | 0.95 (0.25 - 3.56) | 0.942 |

Abbreviation: AKD, acute kidney disease; CI, confidence interval; ESKD, end stage kidney disease; HR, hazard ratio; IPTW, inverse probability of treatment weighting; MACE, major adverse cardiac events; MAKE, major adverse kidney disease;

# Data were presented as frequency (percentage);

$ Data were presented as percentage;

* Defined as eGFR <60 mL/min/1.73m$^2$