Characteristics of and Outcomes After Dialysis-Treated Acute Kidney Injury 2009-2018: A Taiwanese Multicenter Study

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Characteristics of and Outcomes After Dialysis-Requiring AKI

Method and Cohort

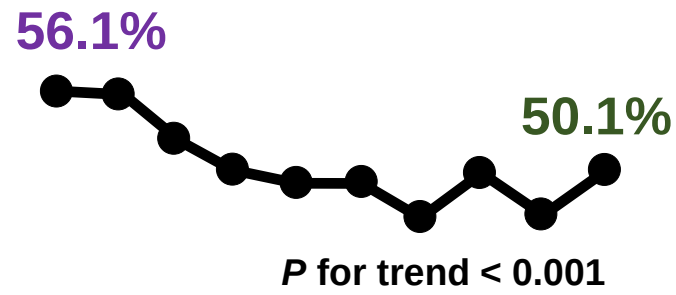
- Retrospective cohort study
- Six centers in Taiwan
- 2009-2018
- N = 9,535
  - ICU patients with D-AKI
  - Mean age: 66.5 years

Baseline Characteristics

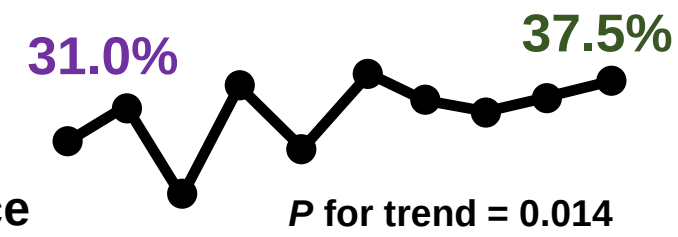
	2009	2018
Diabetes	40.6%	47.2%
CKD	60.5%	64.5%
Charlson comorbidity index (CCI) ≥ 8	20.0%	25.5%
SOFA score at dialysis initiation	14.0	13.6

Outcomes

ICU Mortality



Dialysis Dependence



CONCLUSION: We showed temporal reductions in mortality over time among ICU patients developing dialysis-requiring AKI, even taking the baseline comorbidities and disease severity into consideration.

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Characteristics of and Outcomes After Dialysis-Treated Acute Kidney Injury 2009-2018: A Taiwanese Multicenter Study

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Abstract

Rationale and objective: Dialysis-requiring acute kidney injury (AKI) is increasingly common in intensive care units (ICUs) and is associated with poor outcomes. Few studies have explored the temporal trends in severity of acute illness at dialysis initiation, indications for dialysis, and their association with patient outcomes.

Study Design: Multicenter retrospective cohort study.

Setting and participants: 9,535 adult patients admitted to the ICU and received their first dialysis treatment from Chang Gung Memorial Hospital system in Taiwan between 2009 and 2018.

Exposure: Calendar year.

Outcomes: ICU mortality and dialysis dependence among hospital survivors.

Analytical approach: The temporal trends over the study period were investigated using test statistics suited for continuous or categorical data. The association between the study year and the risk of mortality was analyzed using multivariable Cox regression with adjustment for relevant clinical variables, including the severity of acute illness, defined by the Sequential Organ Failure Assessment (SOFA) score.

Main Results: The mean SOFA score at dialysis initiation declined slightly from 14.0 in 2009 to 13.6 in 2018. There was no significant trend in the number of dialysis criteria that were fulfilled over time. Observed ICU mortality declined over time and appeared to be reverse J-shaped, with a substantial decline from 56.1% in 2009 to 46.3% in 2015 and a slight increase afterward. The

risk of mortality was significantly reduced from 2013 to 2018 compared with 2009 in adjusted models. The declining trend in ICU mortality over time remained significant. Dialysis dependence among survivors increased, mainly in patients with CKD, from 36.8% in 2009 to 43.9% in 2018.

Limitation: residual confounding from unmeasured factors over time such as severity of comorbidities, detailed medication interventions, and delivered dialysis dose.

Conclusion: We observed reductions in mortality among ICU patients with dialysis-requiring AKI between 2009 and 2018, even after adjusting for dialysis indication and severity of illness at dialysis initiation. However, dialysis dependence among survivors has increased over time, mainly in patients with pre-existing CKD.

Index words: Acute kidney injury, Renal replacement therapy, Intensive Care Units, Epidemiology, Disease severity, Mortality, Dialysis dependence

Plain Language Summary:

The current medical management of severe acute kidney injury (AKI) is primarily limited to supportive care and kidney replacement therapy if indicated, leading to perceptions that outcomes among intensive care unit (ICU) patients with dialysis-requiring AKI have not improved. In this multicenter retrospective study of ICU patients developing dialysis-requiring AKI between 2009 and 2018 in Taiwan, patient mortality declined over time despite increasing comorbidities. Moreover, the declining linear trends remain significant even when considering severity of acute illness at dialysis initiation, which was based on physiologic and laboratory measurements seldom evaluated in the prior studies. Further research should explore the basis for these improvements.

Introduction

Acute kidney injury (AKI) is a common complication in intensive care units (ICUs) and significantly affects morbidity and mortality.[1-4] For example, the mortality rate in critically ill patients with severe dialysis-requiring AKI reported is 50–70%.[2, 4, 5] Moreover, accumulating evidence shows that the incidence of dialysis-requiring AKI among critically ill patients is increasing, mainly due to the rising burden of the aging population and chronic comorbidities.[6]

The current medical management of severe AKI is primarily limited to supportive care and renal replacement therapy (RRT) if indicated, leading to perceptions that outcomes among patients with dialysis-requiring AKI have not improved. However, some studies have reported temporal reductions in mortality among hospitalized patients with dialysis-requiring AKI.[7, 8] Recently published analyses of two studies demonstrated improved survival among critically ill ICU patients over time.[9, 10] Although these two important population-based studies have endeavored to clarify the contribution of baseline characteristics, RRT modality, or varied admission diagnosis of ICU patients to improved outcomes over time, the lack of patients severity based on physiologic or laboratory measurements into consideration makes their findings somewhat inconclusive. Thus, it remains unclear whether the findings of mortality decline in critically ill patients with dialysis-requiring AKI over time are related to or independent of the severity or the timing of dialysis indication of enrolled patients.

Therefore, this multicenter study aimed to examine the recent trends in the characteristics and outcomes of critically ill patients developing dialysis-requiring AKI from 2009 to 2018. Furthermore, we aimed to clarify the contribution of changing comorbidities, the severity of acute

illness on ICU admission day and RRT initiation day, and dialysis indication on the changes in patient mortality over time.

Methods

Data source

This retrospective cohort study was performed using the Chang Gung Research Database (CGRD). The CGRD contains anonymized multicenter electronic medical records collected prospectively from six branches of Chang Gung Memorial Hospital (CGMH) (two tertiary medical centers and four district hospitals located from northern to southern Taiwan), the largest medical care system representing 10.2% of annual hospitalizations in Taiwan.[11, 12] The CGRD can offer researchers comprehensive medical records, including patient's date of birth, sex, inpatient orders, date and dosage of prescriptions, procedure charge code, vital signs, laboratory data, and examination reports. Comorbidities were identified based on the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic code. This study was approved by the institutional review board of CGMH (IRB 201900835B0), and the need for individual informed consent was waived because of the lack of identifiable personal information.

Study population

We used the data from CGRD to identify adult patients admitted to an ICU and received their first RRT, either acute intermittent hemodialysis or continuous RRT (CRRT), while in the ICU from 2009 to 2018. The first episode of ICU admission receiving RRT for one patient during the study period was defined as the index hospitalization. Time zero was defined as the day initiating

RRT during their ICU stay. The process for the inclusion and exclusion of the study cohort is shown in **Figure 1**. We excluded patients who had received renal transplantation or chronic dialysis before hospitalization. Patients who had received RRT before the ICU admission during the index hospitalization were also excluded. Of the 17,336 patients screened, 9,535 were included in our analysis.

Exposure and Covariate Ascertainment

The primary exposure of interest was the index year. Eligible patients were assigned to each calendar year group based on when they received their first RRT during their ICU stay. No patients were counted twice if their hospitalization period were across the 2 calendar years.

The covariates we examined were age, sex, body mass index (BMI), nine pre-existing comorbidities, Charlson comorbidity index (CCI), baseline estimated glomerular filtration rates (eGFRs), initial diagnosis, source of initial ICU admission, mechanical ventilation, mechanical circulatory support (MCS), including intra-aortic balloon pump (IABP), extracorporeal membrane oxygenation (ECMO), and the vasopressor type and dose. Comorbidities included diabetes, hypertension, coronary artery disease, heart failure hospitalization, stroke, chronic obstructive pulmonary disease, liver cirrhosis, malignancy, and chronic kidney disease (CKD). Heart failure hospitalization and stroke were defined from hospitalization records prior to the index hospitalization. Except for CKD, other comorbidities were defined as having at least two outpatient visits or one inpatient stay before the index hospitalization. Baseline eGFRs were based on serum creatinine (Cr) levels measured 7–365 days before admission and calculated using the Chronic Kidney Disease Epidemiology Collaboration creatinine equation.[13] The lowest serum Cr level was used if multiple measurements were available. We defined CKD as a baseline eGFR <60

mL/min/1.73 m^2. We examined the severity of acute illness using the total sequential organ failure assessment (SOFA) score (on ICU admission day and RRT initiation day) and lactate concentrations. The SOFA score was calculated as a composite point across six organ systems (0–4 each organ), based on the ratio of partial arterial pressure of oxygen to fraction of inspired oxygen, mean arterial pressure and vasopressor dose, platelet count, Glasgow Coma Scale score, bilirubin, and Cr level. The SOFA score ranges from 0 to 24 points, with higher scores indicating more severe organ dysfunction. Laboratory values (blood urea nitrogen (BUN), Cr, potassium (K), arterial blood pH, and bicarbonate concentrations) were extracted from the database on the RRT initiation date to examine the number of criteria fulfilled. In addition, dates were obtained to calculate the duration from ICU admission to RRT initiation.

Outcomes

The primary outcomes were patient mortality in ICU, in-hospital, and 90-day mortality. All three primary outcomes started the follow up duration from the day of initiation of RRT during the ICU stay. For mortality in ICU, the follow up duration ended the day of death during ICU, or discharge from ICU, whichever came first. For in-hospital mortality, the follow up duration ended the day of death during hospitalization, or discharge from hospital, whichever came first. For 90-day mortality, the follow up duration ended the day of death, or 90 days after the day of initiation of RRT, whichever came first. Other outcome measures included length of stay in ICU and hospital and dialysis dependence among hospital survivors.

Statistical Analysis

The demographics results were summarized using descriptive statistics and presented by each index year. Continuous data were expressed as the mean ± standard deviation or median with interquartile ranges for the obviously skewed data. Categorical data were expressed as numbers with percentages (%) of each item. The temporal trends over the study period for continuous variables (i.e., age, CCI score), skewed continuous variables (i.e., lactate level, length of stay) and categorical variables with 2 categories (i.e., sex, mortality and the dummy variables for main cause of admission), categorical variables with more than 2 ordinal categories (number of fulfilled indications and CCI score grouping) were investigated using the linear contrast in the analysis of variance, Jonckheere-Terpstra test, Cochran–Armitage test, and Mantel-Haenszel test, respectively. The association between the study year (using year 2009 as the reference category) and the risks of mortality was analyzed using multivariable Cox proportional hazard model with adjustment of branch, age, sex, BMI, CCI score, baseline eGFR, main admission diagnosis, duration from ICU admission to RRT initiation, modality of RRT, the status of MCS and any vasopressor use, and SOFA scores at RRT initiation. The temporal trend across years on the mortality rate was also assessed using the linear contrast in the multivariable Cox model. A two-sided *P* value of <0.05 was considered statistically significant. Data analyses were conducted using SAS software version 9.4 (SAS Institute, Cary, NC).

Results

The trend in the baseline characteristics of ICU patients with dialysis-requiring AKI

Table 1 shows the baseline characteristics of the study population by year. During the 10-year study period, 9,535 patients experienced dialysis-requiring AKI in the ICU. The mean age

was 66.5 ± 15.4 years, and 62.4% of patients were males. The most common comorbidities were diabetes (42.2%), hypertension (57.0%), and CKD (63.3%). There were several significant changes in the baseline characteristics over the study year. Compared with patients in the early years, patients in more recent years had a higher BMI and a higher prevalence of comorbidities such as diabetes (40.6% in 2009 to 47.2% in 2018, annual change 0.81%, P <0.001), hypertension, and CKD (Figure S1). Further, the CCI score increased significantly over this period (P for trend = 0.003), with the proportion of CCI score >8 increasing from 20.0% in 2009 to 25.5% in 2018 (Figure S2).

ECMO use increased over the study period (3.6% in 2009 to 8.0% in 2018), while the mechanical ventilation and vasopressors both decreased (**Table 2**). Furthermore, substantial shifts in vasopressor use during the decade wherein recent years have seen a significant decline in the use of dopamine (53.3% in 2009 to 11.4% in 2018, annual change -4.29%, P <0.001) but a notable increase in norepinephrine (42.1% in 2009 to 55.8% in 2018, annual change 1.59%, P <0.001).

The trend in the severity of acute illness and dialysis indications

The severity of acute illness at ICU admission and at the time of RRT and laboratory data, including lactate and C-reactive protein concentrations, are summarized by year in **Table 2**. The median time between ICU admission and RRT initiation was consistently 3 days. The proportion of patients using CRRT as the initial modality continued to rise during the study period from 24.4% in 2010 to 30.2% in 2018. The severity of acute illness at ICU admission assessed by total SOFA scores did not show a significant change over the study year (approximately 12.2, P = 0.679). However, SOFA scores at RRT initiation declined slightly from 14.0 in 2009 to 13.6 in 2018 (annual change -0.03, P = 0.027). The median lactate level, another marker of illness severity,

significantly decreased over time (55.4 mg/dl in 2009 to 42.2 mg/dl in 2018, annual change -1.64 mg/dl, *P* <0.001, **Figure S3**).

Table 2 also provides the dialysis indications of the patients at the time of RRT during the 10-year study period. There were modest but significantly increased levels of BUN and Cr at the time of RRT over this period (annual change 0.66 mg/dl and 0.07 mg/dl, *P* =0.004 and <0.001, respectively). The proportion of severe hyperkalemia (K>6.5 mmol/L) and acute pulmonary edema did not significantly change over time. Only the proportion of severe acidemia (pH <7.2) significantly declined from 34.7% in 2009 to 19.2% in 2018 (annual change -2.04%, *P* <0.001). However, there was no significant trend in the number of dialysis criteria fulfilled over time (*P* = 0.059).

Changes in patient mortality and dialysis dependence

As shown in **Table 3**, the median ICU and hospital stay lengths were similar over time at approximately 13 and 27 days, respectively. The observed ICU mortality declined over time (annual change -0.81%, *P* for linear trend <0.001). However, it appeared to be reverse J-shaped (*P* for quadratic term = 0.001), with a substantial decline from 56.1% in 2009 to 46.3% in 2015 and a slight increase in the following 3 years. A similar trend was observed for in-hospital mortality and 90-day mortality. After adjusting for baseline characteristics, interventions, and SOFA scores at RRT initiation, the risk of mortalities was significantly reduced from 2013 to 2018 compared with 2009. The declining trend of ICU mortality over time remained significant (*P* for linear trend <0.001, **Table 4**), with the most significant reduction in 2015 (adjusted hazard ratio, 0.81; 95% confidence interval, 0.70–0.92). However, the decline did not persist in the recent 3 years (2016–

2018). Similar declining trends of in-hospital mortality and 90-day mortality were observed in the adjusted models (*P* for linear trend = 0.001 and 0.004, respectively).

There was an increasing trend in the proportion of dialysis dependence among survivors at hospital discharge, from 31% in 2009 to 37.5% in 2018 (annual change 0.67%, *P* = 0.014). However, when stratified by baseline CKD status, the rise in dialysis dependence among survivors over time was only observed in patients with CKD (from 36.8% in 2009 to 43.9% in 2018, *P* = 0.045) but not in patients without CKD (at approximately 18.5%, *P* = 0.561) (**Table 3**).

Discussion

In this multicenter study of ICU patients developing dialysis-requiring AKI treated in a universal health care system, we observed declining patient mortality over the past decade despite the increasing comorbidities of these patients. Furthermore, we observed a modest decrease in the severity of acute illness at RRT initiation and a similar threshold of RRT initiation over the study year, as demonstrated by lower total SOFA scores, lower median lactate levels, and less severe academia. The adjusted model of decreasing linear trends in mortality remained significant, although the decline did not persist in the recent 3 years. Additionally, our study showed an increasing trend in dialysis dependence among hospital survivors, particularly in patients with CKD.

The present study results were consistent with previous studies regarding a reduction in mortality over time following dialysis-requiring AKI but had several unique aspects.[8-10] First, our patients represent a group of ICU patients with high comorbidities, which complement the previous two large-scale studies. In a nationwide cohort study in Japan from 2007 to 2016,

Miyamoto et al. found an increasing trend in the CCI score of ICU patients developing dialysis-requiring AKI, and their crude in-hospital mortality declined from 44.9% to 36.1%.[10] The proportion of CCI scores of more than four in Miyamoto's study is approximately 15%, representing a low to moderate comorbid population. However, our study showed that approximately 60% of patients had CCI scores of more than four. In a Canadian cohort of 21234 ICU patients with dialysis-requiring AKI, 90-day mortality declined from 50% in 1996 to 2000 to 45% in 2006 to 2010.[9] They reported that 60% of patients had a CCI score of <2. Second, in addition to the information about the proportion of mechanical ventilation or vasopressor use, the use of severity of illness score, such as SOFA scores, and laboratory data, including lactate level, allowed us to quantify better the severity of patients' condition at initiating RRT in the ICU. We still observed a significant decreasing mortality trend despite a slightly declining total SOFA score at RRT initiation over time. Finally, few studies have tried to look at the effect of the threshold of dialysis indications on patient outcomes over time, although the issue of optimal criteria for initiating RRT in critically ill patients remains controversial.[14-17] One may hypothesize that lower thresholds to start RRT over time may potentially enroll more "less severe" patients who are more likely to survive.[9] Our analysis did not conclude that dialysis criteria were the main contributor to the declining mortality. The proportion of severe hyperkalemia and acute pulmonary edema did not change over time except for the significant decline in the proportion of severe academia. Our study revealed a modest increase in the levels of BUN and Cr at the time of RRT over this period, even limiting the patients without CKD, suggesting that more liberal RRT initiation is less likely in the study period.

In our study, the total SOFA score at ICU admission did not change over time. Although the significance of the decline in mortality gradually attenuated after the inclusion of several

critical interventions and the severity at RRT initiation, they remained statistically significant. The explanation for better patient mortality is likely multifactorial, and we completely agree with Wald et al.,[9] who suggested that advances in critical care management contribute to improved outcomes. Population-based or nationwide cohorts have found improved mortality over the past decades for critically ill patients with acute myocardial infarction or heart failure,[18] severe sepsis and septic shock,[19, 20] and those who undergo cardiac surgery.[6, 21] This finding is valuable if these medical advances and improved ICU care may also bring survival benefits to those patients with dialysis-requiring AKI. For example, our study showed a substantial shift in vasopressor use over the study period. This could be the result of increasing awareness of the adverse effects of dopamine from several critical studies of vasopressors in 2010, and the concept of optimal vasopressor management has been effectively disseminated.[22, 23]

Although several trials of RRT-related intervention have not been shown to improve outcomes, they still convey some critical knowledge that help us provide better care for critically ill patients with dialysis-requiring AKI. To this point, various evidence-based guidance has emerged regarding dialysis catheter and anticoagulation management, selection of RRT modality, optimal RRT timing, and dose intensity, and they are sometimes required to adapt to the changing clinical needs of critically ill patients.[24-26] Thus, it is likely that increased awareness of potential drawbacks with intensive RRT, such as hypophosphatemia[27, 28] and subtherapeutic levels of antibiotics[28], more timely RRT intervention based on patient's potential demand and renal capacity[29, 30], or more skillful management of RRT-induced hemodynamic instability[31], may additively reduce the complication of RRT and possibly increase the chances of survival in our study population.

Although patient mortality declined over the study period, there was an increasing trend of dialysis dependence among hospital survivors from 31.0% in 2009 to 37.5% in 2018. This higher rate of dialysis dependence, compared with around 26% in Wald et al.'s study[9] and approximately 18%–19% in Miyamoto et al.'s study[10], may reflect a higher proportion of CKD and higher severity of acute illness in our study population. Contrary to the results of Miyamoto et al.'s study, we did not observe an increasing trend in dialysis dependence in patients without CKD, which is consistently around 18%. The discrepancy is unclear, but raises the possibility that dialysis dependence and death represent two competitive risks. Thus, the likelihood of becoming dialysis-dependent is decreased in the population with relatively high mortality. Further studies are required to explore this issue.

Our data showed that the declining mortality trends did not continue and even slightly reversed in 2016–2018, especially in-hospital and 90-day mortality. This might be explained by potentially including more patients with more devastating conditions that could not reflect by single SOFA scores. Another possibility is whether the improvement in survival is harder to achieve in dialysis-requiring critically ill patients with more complex comorbidities or extremely high comorbidities, e.g., underlying malignancy or CCI score >8. The cumulative effect of multiple comorbidities on an individual may vary with the combination and severity of the disorder.[32] In the future, investigations among ICU patients with dialysis-requiring AKI should be undertaken to identify certain combinations of comorbidities associated with a heightened mortality risk. Further studies incorporating serial measurements of SOFA scores are also needed to better characterize the severity of illness in this population. These data will allow us to better understand the basis for the observed declining mortality through contemporary treatment strategies.

The strengths of this study are the large, multicenter study and complete data collection at ICU admission and RRT initiation. Another strength of this study is that it is from a universal electronic medical records system, which provided data that are more consistent, and accuracy could be checked immediately compared with a nationwide registry database. However, this study has some limitations. First, our data comes from six centers in one country, potentially limiting external generalizability. Moreover, only patients with first-episode dialysis-requiring AKI after ICU admission were enrolled, and the results may not be extrapolated to all ICU patients undergoing dialysis. Potential heterogeneity of patients and regular care among different branches does exist. However, we have adjusted for the "branch" effect, and the results did not change. Second, comorbidity data were only collected from the CGMH system; this may have resulted in some miscoding. We also had no access to the mortality data of the patients who had survived until hospital discharge but possibly later died at other hospitals, which could have underestimated the 90-day mortality. However, any such misclassification would be a random effect and was likely to be nondifferential among each index year. Third, we used diagnostic codes rather than validated clinical criteria to ascertain comorbidities other than CKD. Fourth, trends in mortality might vary according to the etiologies of critically ill patients. The relatively small number of individual causes of admission prevented adequate subgroup analysis, and thus, the applicability of our data to a specific type of disease with dialysis-requiring AKI is limited. Finally, we cannot exclude the possibility of residual confounding in the analysis, such as severity of baseline comorbidities, detailed medication intervention, delivered dose of RRT, or strategy of fluid management.

In conclusion, this multicenter study demonstrated a decline in patient mortality among critically ill patients with dialysis-requiring AKI from 2009 to 2018. In addition, after adjustment for baseline characteristics and physiologic measurements of the severity of illness, the adjusted

mortality remained significant. Although these findings are encouraging, the burden of mortality and dialysis dependence remains high, especially in patients with CKD. Future work should focus on strategies to mitigate the risk of kidney injury and enhance renal recovery.

Supplementary material

Figure S1: The prevalence of selected comorbidities, including diabetes, hypertension, chronic kidney disease and malignancy across the study year.

Figure S2: The mean CCI total score and the proportion of CCI ≥8 across the study years.

CCI, Charlson's Comorbidity Index.

Figure S3: The mean SOFA score and median lactate level across the study years.

SOFA score, Sequential Organ Failure Assessment score

Authors' Contributions

Conceptualization: CCL, GK, CHC; Methodology: MJC, PCF, JJC, CLY; Formal Analysis: CCL, JJC, TYT; Investigation: CCL, GK, MJC; Supervision: YCC, YCT, CHC. Each author contributed important intellectual content during manuscript drafting or revision and agrees to be personally accountable for the individual's own contributions and to ensure that questions pertaining to the accuracy or integrity of any portion of the work, even one in which the author was not directly involved, are appropriately investigated and resolved, including with documentation in the literature if appropriate

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The authors declare that they have no relevant financial interests.

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Table 1. Baseline characteristics of the study population by year

Variable	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P trend[a]	Δ /y[b]
Number of patients	779	898	997	969	978	968	1022	946	990	988	-	
Age, years	65.7 ± 16.0	67.1 ± 15.5	65.7 ± 16.2	67.7 ± 14.9	67.0 ± 15.4	66.7 ± 15.4	65.6 ± 15.3	65.8 ± 15.2	67.7 ± 14.8	66.2 ± 14.8	0.953	0.003
Male	475 (61.0)	561 (62.5)	640 (64.2)	589 (60.8)	597 (61.0)	626 (64.7)	649 (63.5)	601 (63.5)	606 (61.2)	604 (61.1)	0.943	-0.01
Body mass index, kg/m^2	25.1 ± 4.9	25.1 ± 5.3	24.6 ± 5.1	24.9 ± 5.1	25.4 ± 5.1	25.3 ± 5.2	25.9 ± 5.3	25.7 ± 5.1	25.5 ± 5.4	26.0 ± 5.5	<0.001	0.12
Comorbidity												
Diabetes	316 (40.6)	340 (37.9)	388 (38.9)	397 (41.0)	421 (43.0)	406 (41.9)	444 (43.4)	409 (43.2)	436 (44.0)	466 (47.2)	<0.001	0.81
Hypertension	414 (53.1)	471 (52.4)	536 (53.8)	545 (56.2)	571 (58.4)	569 (58.8)	587 (57.4)	533 (56.3)	606 (61.2)	605 (61.2)	<0.001	0.92
Coronary artery disease	202 (25.9)	258 (28.7)	267 (26.8)	301 (31.1)	320 (32.7)	296 (30.6)	296 (29.0)	236 (24.9)	238 (24.0)	272 (27.5)	0.120	-0.25
Heart failure hospitalization	181 (23.2)	210 (23.4)	232 (23.3)	237 (24.5)	279 (28.5)	239 (24.7)	231 (22.6)	213 (22.5)	242 (24.4)	240 (24.3)	0.941	0.01
Stroke	106 (13.6)	145 (16.1)	136 (13.6)	137 (14.1)	132 (13.5)	116 (12.0)	140 (13.7)	123 (13.0)	119 (12.0)	128 (13.0)	0.042	-0.25
COPD	137 (17.6)	154 (17.1)	150 (15.0)	180 (18.6)	164 (16.8)	171 (17.7)	149 (14.6)	154 (16.3)	136 (13.7)	152 (15.4)	0.027	-0.30
Liver cirrhosis	157 (20.2)	172 (19.2)	175 (17.6)	150 (15.5)	152 (15.5)	156 (16.1)	156 (15.3)	139 (14.7)	134 (13.5)	127 (12.9)	<0.001	-0.72
Malignancy	283 (36.3)	295 (32.9)	309 (31.0)	332 (34.3)	316 (32.3)	353 (36.5)	383 (37.5)	318 (33.6)	349 (35.3)	379 (38.4)	0.015	0.42
CKD[c]	471 (60.5)	545 (60.7)	617 (61.9)	589 (60.8)	628 (64.2)	610 (63.0)	648 (63.4)	628 (66.4)	666 (67.3)	637 (64.5)	0.004	0.67
eGFR, ml/min/1.73m^2	52.8 ± 39.1	53.9 ± 38.7	51.0 ± 38.9	52.1 ± 38.7	49.3 ± 37.2	49.2 ± 38.0	49.6 ± 37.0	47.3 ± 37.4	46.1 ± 36.7	48.1 ± 36.5	<0.001	-0.74
CCI score	4.9 ± 3.4	4.6 ± 3.3	4.6 ± 3.4	4.6 ± 3.2	5.0 ± 3.5	4.8 ± 3.4	4.8 ± 3.5	4.7 ± 3.5	4.9 ± 3.5	5.2 ± 3.7	0.003	0.04
CCI score grouping											0.017	
0-1	133 (17.1)	161 (17.9)	196 (19.7)	183 (18.9)	160 (16.4)	166 (17.1)	189 (18.5)	187 (19.8)	177 (17.9)	172 (17.4)		0.003
2-3	153 (19.6)	217 (24.2)	237 (23.8)	209 (21.6)	211 (21.6)	194 (20.0)	228 (22.3)	211 (22.3)	220 (22.2)	191 (19.3)		-0.17

Variable	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	P trend[a]	Δ /y[b]
4-5	191 (24.5)	207 (23.1)	231 (23.2)	220 (22.7)	227 (23.2)	254 (26.2)	209 (20.5)	217 (22.9)	219 (22.1)	190 (19.2)		-0.36
6-7	146 (18.7)	137 (15.3)	126 (12.6)	173 (17.9)	168 (17.2)	157 (16.2)	167 (16.3)	126 (13.3)	150 (15.2)	183 (18.5)		0.004
≥8	156 (20.0)	176 (19.6)	207 (20.8)	184 (19.0)	212 (21.7)	197 (20.4)	229 (22.4)	205 (21.7)	224 (22.6)	252 (25.5)		0.52
Main cause of admission												
Coronary artery disease	42 (5.4)	50 (5.6)	55 (5.5)	75 (7.7)	80 (8.2)	69 (7.1)	71 (6.9)	72 (7.6)	69 (7.0)	81 (8.2)	0.007	0.25
Infection	183 (23.5)	211 (23.5)	255 (25.6)	248 (25.6)	255 (26.1)	260 (26.9)	278 (27.2)	249 (26.3)	271 (27.4)	217 (22.0)	0.465	0.12
Neurologic disorders	24 (3.1)	32 (3.6)	37 (3.7)	31 (3.2)	22 (2.2)	31 (3.2)	34 (3.3)	30 (3.2)	35 (3.5)	26 (2.6)	0.571	-0.04
Cardiovascular surgeries	44 (5.6)	58 (6.5)	74 (7.4)	61 (6.3)	57 (5.8)	54 (5.6)	55 (5.4)	52 (5.5)	64 (6.5)	62 (6.3)	0.572	-0.05
Other non-CVS surgeries	127 (16.3)	139 (15.5)	147 (14.7)	163 (16.8)	140 (14.3)	149 (15.4)	155 (15.2)	156 (16.5)	143 (14.4)	164 (16.6)	0.885	0.01
Trauma and burn	36 (4.6)	29 (3.2)	47 (4.7)	39 (4.0)	49 (5.0)	29 (3.0)	36 (3.5)	36 (3.8)	42 (4.2)	48 (4.9)	0.941	0.01
Others	323 (41.5)	379 (42.2)	382 (38.3)	352 (36.3)	375 (38.3)	376 (38.8)	393 (38.5)	351 (37.1)	366 (37.0)	390 (39.5)	0.09	-0.30

Abbreviations: Δ/y, annual change; CKD, chronic kidney disease; eGFR, estimated Glomerular filtration rate; CCI, Charlson's Comorbidity Index; CVS, cardiovascular surgery.

Data were presented as mean ± standard deviation or frequency (percentage).

[a]The linear contrast in the analysis of variance for continuous variable, Cochran–Armitage test for categorical variables with 2 categories, and Mantel-Haenszel test on the variable with more than 2 ordinal categories (CCI score grouping), respectively.

[b]the slope estimate of a simple linear regression of the proportion (or the mean) of each category per 1 calendar year.

[c]defined as eGFR <60 ml/min/1.73 m^2.

Table 2. Treatment, severity of acute illness and laboratory data of the study population by year

Variable	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	*P* trend[a]	Δ/y[b]
Treatment during ICU												
Mechanical ventilation	678 (87.0)	794 (88.4)	838 (84.1)	796 (82.1)	821 (83.9)	780 (80.6)	840 (82.2)	780 (82.5)	793 (80.1)	815 (82.5)	<0.001	-0.65
ECMO	28 (3.6)	45 (5.0)	56 (5.6)	60 (6.2)	55 (5.6)	55 (5.7)	53 (5.2)	74 (7.8)	69 (7.0)	79 (8.0)	<0.001	0.36
IABP	12 (1.5)	15 (1.7)	30 (3.0)	33 (3.4)	39 (4.0)	30 (3.1)	28 (2.7)	32 (3.4)	24 (2.4)	30 (3.0)	0.123	0.09
Vasopressor at RRT												
Any vasopressor	535 (68.7)	585 (65.1)	639 (64.1)	615 (63.5)	634 (64.8)	621 (64.2)	658 (64.4)	607 (64.2)	607 (61.3)	613 (62.0)	0.005	-0.49
Dopamine	415 (53.3)	407 (45.3)	425 (42.6)	366 (37.8)	329 (33.6)	288 (29.8)	247 (24.2)	221 (23.4)	177 (17.9)	113 (11.4)	<0.001	-4.29
Norepinephrine	328 (42.1)	402 (44.8)	446 (44.7)	451 (46.5)	509 (52.0)	528 (54.5)	560 (54.8)	529 (55.9)	527 (53.2)	551 (55.8)	<0.001	1.59
Epinephrine	234 (30.0)	246 (27.4)	251 (25.2)	223 (23.0)	218 (22.3)	219 (22.6)	231 (22.6)	210 (22.2)	207 (20.9)	217 (22.0)	<0.001	-0.78
Dobutamine	58 (7.4)	69 (7.7)	73 (7.3)	75 (7.7)	69 (7.1)	64 (6.6)	69 (6.8)	66 (7.0)	60 (6.1)	70 (7.1)	0.193	-0.12
Duration between ICU admission to RRT initiation, day	3 [2, 9]	4 [2, 9]	3 [2, 7]	3 [2, 8]	3 [2, 6]	3 [2, 7]	3 [2, 7]	3 [2, 8]	3 [2, 7]	3 [2, 7]	0.078	-0.13
CRRT as initial RRT modality	209 (26.8)	219 (24.4)	250 (25.1)	203 (20.9)	275 (28.1)	284 (29.3)	295 (28.9)	274 (29.0)	292 (29.5)	298 (30.2)	<0.001	0.70
SOFA score												
at ICU admission	12.4 ± 3.3	12.0 ± 3.4	12.0 ± 3.4	11.7 ± 3.4	12.2 ± 3.3	12.2 ± 3.2	12.3 ± 3.3	12.2 ± 3.1	12.1 ± 3.1	12.1 ± 3.1	0.679	0.01
at dialysis date	14.0 ± 3.4	13.8 ± 3.2	13.7 ± 3.2	13.5 ± 3.3	13.7 ± 3.2	13.6 ± 3.1	13.6 ± 3.3	13.8 ± 3.2	13.4 ± 3.1	13.6 ± 3.2	0.027	-0.03
Dialysis indication												
BUN >100 mg/dL	253 (32.5)	274 (30.5)	292 (29.3)	287 (29.6)	296 (30.3)	306 (31.6)	327 (32.0)	326 (34.5)	334 (33.7)	333 (33.7)	0.009	0.44
Creatinine >4 mg/dL	455 (58.4)	476 (53.0)	525 (52.7)	513 (52.9)	540 (55.2)	547 (56.5)	591 (57.8)	584 (61.7)	593 (59.9)	590 (59.7)	<0.001	0.79
Hyperkalemia (K ≥6.5)	42 (5.4)	52 (5.8)	79 (7.9)	75 (7.7)	70 (7.2)	100 (10.3)	77 (7.5)	66 (7.0)	93 (9.4)	56 (5.7)	0.159	0.13
Severe acidemia (pH ≤7.2)	270 (34.7)	287 (32.0)	356 (35.7)	308 (31.8)	241 (24.6)	239 (24.7)	224 (21.9)	178 (18.8)	201 (20.3)	190 (19.2)	<0.001	-2.04
Acute pulmonary edema	40 (5.1)	30 (3.3)	45 (4.5)	33 (3.4)	38 (3.9)	28 (2.9)	46 (4.5)	33 (3.5)	48 (4.8)	40 (4.0)	0.988	-0.001
Number of dialysis indication fulfilled											0.059	

Variable	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	*P* trend[a]	Δ/y[b]
1	307 (39.4)	341 (38.0)	337 (33.8)	352 (36.3)	378 (38.7)	347 (35.8)	401 (39.2)	368 (38.9)	370 (37.4)	358 (36.2)		0.02
2	216 (27.7)	235 (26.2)	291 (29.2)	269 (27.8)	266 (27.2)	287 (29.6)	288 (28.2)	301 (31.8)	298 (30.1)	299 (30.3)		0.41
≥3	102 (13.1)	100 (11.1)	121 (12.1)	101 (10.4)	89 (9.1)	94 (9.7)	93 (9.1)	70 (7.4)	94 (9.5)	81 (8.2)		-0.49
Laboratory data												
BUN, mg/dL	64.2 ± 46.0	59.7 ± 41.5	61.4 ± 42.6	61.4 ± 42.7	64.3 ± 42.4	66.9 ± 46.8	62.3 ± 43.7	65.7 ± 44.2	66.3 ± 42.2	64.4 ± 43.4	0.004	0.66
Creatinine, mg/dL	4.0 ± 3.0	3.8 ± 3.0	4.0 ± 3.2	4.0 ± 3.4	4.2 ± 3.1	4.3 ± 3.3	4.2 ± 3.3	4.5 ± 3.7	4.4 ± 3.4	4.3 ± 3.5	<0.001	0.07
Lactate, mg/dL	55.4 [22.3,114.3]	48.4 [20.5,102.0]	45.5 [19.5,118.9]	51.3 [20.4,109.7]	39.6 [17.8,99.9]	43.9 [19.8,103.0]	35.6 [17.3, 94.7]	35.5 [14.5, 84.6]	33.9 [15.2, 91.4]	42.2 [17.1, 99.5]	<0.001	-1.64
Peak CRP within 7 days, mg/dL	12.1 [4.8, 21.1]	12.2 [5.0, 21.6]	12.6 [5.4, 21.6]	13.0 [6.0, 21.6]	12.4 [5.8, 20.7]	13.0 [5.9, 22.4]	12.5 [5.7, 21.4]	12.5 [6.1, 22.8]	13.0 [6.1, 21.2]	12.9 [5.7, 23.4]	0.043	0.61

Abbreviations: Δ/y,annual change; ICU, intensive care unit; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; RRT, renal replacement therapy; IHD, intermittent hemodialysis; CRRT, continuous renal replacement therapy; SOFA, Sequential Organ Failure Assessment; BUN, blood urea nitrogen; CRP, C-Reactive protein.

Data were presented as mean ± standard deviation, median [interquartile range] or frequency (percentage).

[a]The linear contrast in the analysis of variance for continuous variables, Jonckheere-Terpstra test for skewed continuous variables, Cochran–Armitage test for categorical variables with 2 categories, and Mantel-Haenszel test on the variable with more than 2 ordinal categories (number of dialysis indication fulfilled), respectively.

[b]the slope estimate of a simple linear regression of the proportion (or the mean) of each category per 1 calendar year.

Table 3. Length of ICU, hospital stay and mortality data of the study population by year

Variable	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	*P* trend[a]	Δ/y[b]
Length of stay, day												
ICU	13 [6, 26]	13 [6, 28]	12 [5, 26]	13 [6, 27]	12 [6, 25]	12 [6, 26]	13 [6, 26]	13 [6, 29]	12 [6, 26]	13 [6, 28]	0.166	-0.06
Hospital	24 [13, 50]	27 [13, 52]	28 [13, 55]	28 [13, 53]	26 [13, 53]	27 [13, 50]	27 [14, 52]	28 [13, 52]	26 [14, 48]	26 [13, 50]	0.993	-0.39
Mortality												
ICU mortality	437 (56.1)	504 (56.1)	514 (51.6)	479 (49.4)	475 (48.6)	472 (48.8)	473 (46.3)	473 (50.0)	460 (46.5)	495 (50.1)	<0.001	-0.81
In-hospital mortality	489 (62.8)	579 (64.5)	611 (61.3)	563 (58.1)	553 (56.5)	545 (56.3)	555 (54.3)	546 (57.7)	559 (56.5)	575 (58.2)	<0.001	-0.75
Day 90 mortality	515 (66.1)	613 (68.3)	640 (64.2)	593 (61.2)	581 (59.4)	594 (61.4)	608 (59.5)	591 (62.5)	599 (60.5)	610 (61.7)	<0.001	-0.62
Dialysis dependence among hospital survivors												
Total	90 (31.0)	111 (34.8)	102 (26.4)	152 (37.4)	127 (29.9)	160 (37.8)	167 (35.8)	137 (34.3)	154 (35.7)	155 (37.5)	0.014	0.67
Non-CKD	16 (18.0)	19 (20.9)	16 (15.8)	22 (19.5)	14 (11.7)	22 (18.2)	27 (20.0)	23 (24.2)	24 (21.2)	15 (16.0)	0.561	0.25
CKD	74 (36.8)	92 (40.4)	86 (30.2)	130 (44.4)	113 (37.0)	138 (45.7)	140 (42.2)	114 (37.4)	130 (40.9)	140 (43.9)	0.045	0.66

Abbreviations: Δ/y, annual change; ICU, intensive care unit; CKD, chronic kidney disease.
Data were presented as median [interquartile range] or frequency (percentage).
[a]Jonckheere-Terpstra test for skewed continuous variables and Cochran–Armitage test for categorical variables, respectively.
[b]the slope estimate of a simple linear regression of the proportion (or the mean) of each category per 1 calendar year.

Table 4. Mortality data across the study period (using year 2009 as the reference) with adjustment of covariates*

Mortality / Statistics	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	*P* trend
ICU											
Crude HR	Reference	1.002	0.94	0.87	0.84	0.86	0.81	0.82	0.82	0.85	<0.001
(95% CI)		(0.88–1.14)	(0.83–1.07)	(0.77–0.99)	(0.73–0.95)	(0.76–0.98)	(0.71–0.92)	(0.72–0.94)	(0.72–0.93)	(0.74–0.96)	
Adjusted HR	Reference	1.10	0.997	0.94	0.84	0.85	0.81	0.82	0.84	0.82	<0.001
(95% CI)		(0.96–1.25)	(0.87–1.14)	(0.82–1.08)	(0.74–0.96)	(0.74–0.97)	(0.70–0.92)	(0.71–0.94)	(0.73–0.96)	(0.72–0.94)	
In-hospital											
Crude HR	Reference	1.000	0.91	0.85	0.82	0.83	0.80	0.85	0.85	0.87	<0.001
(95% CI)		(0.89–1.13)	(0.80–1.02)	(0.75–0.96)	(0.72–0.92)	(0.74–0.94)	(0.71–0.91)	(0.76–0.96)	(0.75–0.95)	(0.77–0.98)	
Adjusted HR	Reference	1.07	0.94	0.92	0.81	0.83	0.79	0.86	0.86	0.86	0.001
(95% CI)		(0.94–1.21)	(0.83–1.07)	(0.81–1.04)	(0.71–0.92)	(0.73–0.95)	(0.70–0.90)	(0.75–0.97)	(0.76–0.98)	(0.76–0.98)	
90-day											
Crude HR (95% CI)	Reference	1.01 (0.89–1.13)	0.89 (0.79–1.002)	0.82 (0.73–0.93)	0.79 (0.70–0.88)	0.84 (0.74–0.94)	0.78 (0.69–0.87)	0.84 (0.75–0.95)	0.79 (0.71–0.89)	0.82 (0.73–0.92)	
Adjusted HR	Reference	1.07	0.94	0.89	0.79	0.84	0.79	0.86	0.83	0.84	0.004
(95% CI)		(0.95–1.20)	(0.83–1.06)	(0.79–1.01)	(0.70–0.89)	(0.75–0.96)	(0.70–0.89)	(0.76–0.97)	(0.74–0.94)	(0.75–0.95)	

Abbreviations: ICU, intensive care unit; HR, hazard ratio; CI, confidence interval.

* Adjusted for branch, age, sex, BMI, main diagnosis category, CCI's total score, eGFR, duration from ICU admission to renal replacement therapy initiation, renal replacement therapy modality (IHD or CRRT), SOFA scores at RRT, IABP, ECMO and use of any vasopressor.

Figure Legends

Figure 1. The flowchart for illustrating the inclusion and exclusion of the study patients.