Kidney Medicine

Epidemiology and Outcomes of AKI Treated With Continuous Kidney Replacement Therapy: The Multicenter CRRTnet Study

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Rationale & Objective: Continuous kidney replacement therapy (CKRT) is the predominant form of acute kidney replacement therapy used for critically ill adult patients with acute kidney injury (AKI). Given the variability in CKRT practice, a contemporary understanding of its epidemiology is necessary to improve care delivery.

Study Design: Multicenter, prospective living registry.

Setting & Population: 1,106 critically ill adults with AKI requiring CKRT from December 2013 to January 2021 across 5 academic centers and 6 intensive care units. Patients with pre-existing kidney failure and those with coronavirus 2 infection were excluded.

Exposure: CKRT for more than 24 hours.

Outcomes: Hospital mortality, kidney recovery, and health care resource utilization.

Analytical Approach: Data were collected according to preselected timepoints at intensive care unit admission and CKRT initiation and analyzed descriptively.

Results: Patients' characteristics, contributors to AKI, and CKRT indications differed among centers. Mean (standard deviation) age was 59.3 (13.9) years, 39.7% of patients were women, and median [IQR] APACHE-II (acute physiologic assessment and chronic health evaluation) score was 30 [25-34]. Overall, 41.1% of patients survived to hospital discharge. Patients that died were older (mean age 61 vs. 56.8, $P < 0.001$), had greater comorbidity (median Charlson score 3 [1-4] vs. 2 [1-3], $P < 0.001$), and higher acuity of illness (median APACHE-II score 30 [25-35] vs. 29 [24-33], $P = 0.003$). The most common condition predisposing to AKI was sepsis (42.6%), and the most common CKRT indications were oliguria/anuria (56.2%) and fluid overload (53.9%). Standardized mortality ratios were similar among centers.

Limitations: The generalizability of these results to CKRT practices in nonacademic centers or low- and middle-income countries is limited.

Conclusions: In this registry, sepsis was the major contributor to AKI and fluid management was collectively the most common CKRT indication. Significant heterogeneity in patient- and CKRT-specific characteristics was found in current practice. These data highlight the need for establishing benchmarks of CKRT delivery, performance, and patient outcomes. Data from this registry could assist with the design of such studies.

Visual Abstract included

Complete author and article information provided before references.

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Acute kidney injury (AKI) occurs in approximately 50-60% of patients admitted to the intensive care unit (ICU).[1,2] About 10%-15% of these patients receive acute kidney replacement therapy (KRT). As the population ages and becomes medically more complex with a higher burden of comorbidity, the incidence of AKI receiving KRT in inpatient settings—particularly in the ICU—is expected to increase.[3,4] When acute KRT is prescribed, it may occur in 2 forms: continuous kidney replacement therapy (CKRT) or intermittent kidney replacement therapy.[5] Although each form may have specific benefits and limitations and offer the ability to deliver a targeted therapy most suited to a given patient in a specific context, CKRT is the therapy of choice for hemodynamically unstable patients and is the mainstay of multiorgan support in critically ill patients, being the modality chosen in over 75% of acute initiations of KRT in the ICU in developed countries.[6] Despite the frequent use of CKRT in the ICU, there is considerable variation in how CKRT is prescribed and delivered. Because of this, there is a growing call for better evidence to guide best practices and to monitor CKRT performance and delivery.[7-9] A robust understanding of CKRT practice patterns is necessary to ensure the optimal prescription and delivery of best evidence-based practices for the growing and vulnerable critically ill patient population.[10,11]

Mortality in patients with AKI on CKRT remains high (ie, 50%-75%) and there is a paucity of clinical trials testing interventions that can affect delivery of care and relevant outcomes in these patients.[12,13] Although mortality rates are mostly related to specific patient factors, improved and more efficient resource use may be achieved, resulting in improved value of health care resources. In this context, CRRTnet—a multicenter data registry of adult patients undergoing CKRT—was created to assess epidemiology and variations in patient characteristics and

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PLAIN LANGUAGE SUMMARY

Continuous kidney replacement therapy (CKRT) is frequently utilized in intensive care units. However, what type of patients are usually started on CKRT, how CKRT is prescribed, or what usually happens to patients who have CKRT is unknown. The CRRTnet registry has created a database of such patients that outlines these characteristics. The database has revealed that critically ill patients with acute kidney injury who need CKRT typically have sepsis and require CKRT for fluid management, but there are significant variations in practice across different intensive care units. Information derived from this registry can assist with future work of establishing targets for CKRT delivery, performance, and outcomes to improve the quality of care received by these vulnerable patients.

prescription and delivery of therapy.[14] Specific objectives of this study were to evaluate and assess the case mix, acuity diagnosis, clinical course and outcomes of adult patients undergoing CKRT while also to establish a large, comprehensive registry of critically ill adult patients receiving this therapy. This is the first report of a comprehensive program suited to develop a large multimodal data repository of CKRT patients with detailed information regarding clinical data, CKRT programmatic and therapy data, as well as processes of care and outcomes. This project will deliver an important resource for designing of clinical trials and benchmarking CKRT Key Process Indicators and clinical outcomes. Herein, we report the epidemiological findings of the initial phase of the CRRTnet program.

METHODS

Study Design

CRRTnet is a prospective, multinational, and multicenter observational study of adult patients undergoing CKRT. It is ongoing, and this article reports on data collected across 5 academic medical centers and 6 ICUs in Canada and the United States from December 2013-February 2021 (University of Alberta Hospital, Edmonton, Canada; London Health Sciences Centre, London, Canada; University of Mississippi, Jackson, Mississippi; University of Michigan, Ann Arbor, Michigan; and University of Kentucky, Lexington, Kentucky). The study is registered on ClinicalTrials.gov (identifier NCT02034448), and details of the study protocol were previously published.[14] Each of the participating centers received local institutional review board approval for CRRTnet study procedures with a waiver for informed consent given the deidentified and observational nature of the data.

Inclusion criteria included adult patients aged 18 to 89 years old who received CKRT for greater than 1 day during an index hospitalization. Exclusion criteria included patients who had CKRT initiated at an outside hospital before transfer. For patients that received multiple courses of CKRT during admission, only the data from the first CKRT course were considered. Patients with pre-existing kidney failure treated by maintenance KRT were excluded. We also excluded patients with coronavirus 2 infection as these patients will be evaluated separately.

Clinical Data

Data were collected according to preselected timepoints at ICU admission and CKRT initiation (Table S1). Aggregated data throughout the period of CKRT (up to day 14) were also collected. Data included demographics (age, sex), comorbidity including the Charlson Index, hospitalization characteristics of acuity of illness including the APACHE-II (acute physiologic assessment and chronic health evaluation)score, admission source, primary admission diagnoses, contributing factors to AKI, laboratory parameters, and CKRT indications. Fluid overload was defined as (total amount of fluid input − total amount of fluid output) × 100/(weight at CKRT initiation). Data on non-kidney organ support such as mechanical ventilation, vasoactive medications, and extracorporeal membrane oxygenation were also collected. Data related to CKRT prescription, including catheter position/type, dose, modality, and anticoagulation were also collected. All data were harmonized and manually validated by 10% review of charts by the investigative team. Continuous data were evaluated for outliers, and systematic exclusion of data <1 and >99 percentiles was applied.

Study Outcomes

The primary outcome was survival at hospital discharge. Secondary outcomes included resource utilization and organ recovery outcomes, including length of stay in the ICU/hospital, receipt and duration of intermittent hemodialysis after CKRT, receipt of intermittent hemodialysis at ICU discharge, receipt of tracheostomy, and status of hemodialysis dependence at hospital discharge.

Statistical Analysis

Clinical parameters of included patients were evaluated and analyzed descriptively. Categorical data are presented as frequency and percentages. Continuous data are summarized with their median and interquartile ranges (IQRs) or mean and standard deviation according to data distribution. Two-group comparisons of clinical characteristics according to hospital mortality were done using the χ^2 test for categorical independent variables, and a t test or Mann-Whitney *U* test for continuous variables as appropriate. A multivariable logistic regression model based on all clinical parameters that were different in patients that died versus survived as reported in Table 1 was developed to generate a mortality probability that was used to calculate a standardized mortality ratio for each study site. The standardized mortality ratio was calculated by the ratio of the

Table 1. Patient Characteristics in the CRRTnet Cohort Stratified According to Hospital Mortality

	All Cohort n=1,106	Survivors n=455	Nonsurvivors n=651	*P*
Demographics				
Age, y, mean ± SD	59.3 ± 13.9	56.8 ± 14.1	61.0 ± 13.4	<0.001
Women, n (%)	439 (39.7%)	191 (42%)	248 (38.1%)	0.22
BMI, kg/m^2, median [IQR]	30.2 [25.7-36.2]	30.1 [25.9-36.5]	30.2 [25.6-35.9]	0.70
Comorbidities				
Charlson Score, median [IQR]	2 [1-4]	2 [1-3]	3 [1-4]	<0.001
Diabetes, n (%)	474 (42.9%)	195 (42.9%)	279 (42.9%)	0.99
Cardiovascular disease[a], n (%)	486 (43.9%)	182 (40%)	304 (46.7%)	0.006
Chronic pulmonary disease, n (%)	192 (17.4%)	62 (13.6%)	130 (20%)	0.02
Moderate or severe kidney disease, n (%)	277 (25.1%)	120 (26.4%)	157 (24.1%)	0.08
Moderate or severe liver disease, n (%)	176 (15.9%)	54 (11.9%)	112 (17.2%)	0.005
Cancer[b], n (%)	202 (18.3%)	63 (13.9%)	139 (21.4%)	0.001
Hospitalization characteristics				
Hospital LOS, d, median [IQR]	17 [6-39]	32.5 [18-57.8]	9 [4-23]	<0.001
ICU LOS, d, median [IQR]	10 [4-21]	15 [8-28]	6 [3-15]	<0.001
APACHE-II score, median [IQR]	30 [25-34]	29 [24-33]	30 [25-35]	0.003
SOFA score, median [IQR]	15 [13-17]	14 [12-16]	15 [13-18]	0.02
Admission Source, n (%)				<0.001
Emergency	230 (20.8%)	112 (24.6%)	118 (18.1%)	
Floor/Ward	273 (24.7%)	90 (19.8%)	183 (28.1%)	
ICU	182 (16.5%)	92 (20.2%)	90 (13.8%)	
Other	421 (38.1%)	161 (35.4%)	260 (39.9%)	
ICU type, n (%)				<0.001
Cardiovascular	212 (19.2%)	84 (18.5%)	128 (19.7%)	
Medical	281 (25.4%)	60 (13.2%)	221 (34%)	
Combined Medical/Surgical	536 (48.5%)	270 (59.3%)	266 (40.9%)	
Other	77 (7%)	41 (9%)	36 (5.5%)	
Primary admission diagnosis, n (%)				<0.001
AKI	56 (5%)	36 (7.9%)	20 (3.1%)	
Sepsis	202 (18.3%)	64 (14%)	138 (21.2%)	
Acute/decompensated liver failure	67 (6.1%)	20 (4.4%)	47 (7.2%)	
Cardiovascular emergency	164 (14.8%)	58 (12.8%)	106 (16.3%)	
Respiratory failure	285 (25.8%)	109 (24%)	176 (27%)	
Post-surgery	120 (10.8%)	62 (13.6%)	58 (8.9%)	
Other	212 (19.2%)	106 (23.3%)	106 (16.3%)	
Emergency surgery on admission, n (%)	151 (13.7%)	67 (14.7%)	84 (12.9%)	0.44
Hours from ICU admission to CKRT initiation, median [IQR]	26 [10.5-70.9]	26.5 [9.9-72.1]	26 [11-68.2]	0.34
Contributing factors to AKI, n (%)				
Sepsis	471 (42.6%)	156 (34.3%)	315 (48.4%)	<0.001
Cardiogenic	189 (17.1%)	56 (12.3%)	133 (20.4%)	<0.001
Hepatorenal	121 (10.9%)	34 (7.5%)	87 (13.4%)	0.03
Major surgery	184 (16.6%)	83 (18.2%)	101 (15.5%)	0.28
Other	487 (44%)	146 (32.1%)	341 (52.4%)	<0.001
CKRT indications, n (%)				
Extravascular fluid overload	379 (34.3%)	132 (29%)	247 (37.9%)	0.003
Pulmonary edema	217 (19.6%)	72 (15.8%)	145 (22.3%)	0.009
Oliguria/anuria	622 (56.2%)	219 (48.1%)	403 (61.9%)	<0.001
Hyperkalemia	297 (26.9%)	84 (18.5%)	213 (32.7%)	<0.001
Acidosis	449 (40.6%)	132 (29%)	217 (33.3%)	<0.001
Uremia	451 (40.8%)	149 (32.8%)	302 (46.4%)	<0.001
Other	187 (16.9%)	63 (13.9%)	124 (19.1%)	0.001

Abbreviations: AKI, acute kidney injury; APACHE, acute physiologic assessment and chronic health evaluation; BMI, body mass index; CKRT, continuous kidney replacement therapy; ICU, intensive care unit; IQR, interquartile range; LOS, length of stay; SD, standard deviation.
[a]Includes myocardial infarction, congestive heart failure, and peripheral vascular disease.
[b]Includes leukemia, lymphoma, solid tumors, and metastasis.

observed mortality by the predicted mortality of the global model and was compared by χ^2 test across sites. The study conforms to the Strengthening the Reporting of Observational Studies in Epidemiology checklist for observational studies.[15] R version 4.0 was used for statistical analyses.

RESULTS

Study Participants

A total of 1,541 patients were available in the CRRTnet registry across 5 academic centers and 6 ICUs in North America, and 1,106 patients were included in this study (Fig 1, Fig S1, and Table 1). Mean (standard deviation) age was 59.3 (13.9) years, 39.7% of patients were female, and median APACHE-II was 30 (IQR, 25-34). Patients had significant comorbidities with a median Charlson score of 2 (IQR, 1-4). Most frequent comorbid conditions included cardiovascular disease (43.9%), diabetes (42.9%), chronic kidney disease (25.1%), chronic pulmonary disease (17.4%), cancer (18.3%), and moderate to severe liver disease (15.9%). The most common reason for ICU admission was for respiratory failure (25.8%), followed by sepsis (18.3%) and cardiovascular emergency (14.8%). Of the patients, 10.9% were post-surgery. An admission diagnosis of AKI was the primary indication for admission in 5.1% of patients. Patients were most commonly admitted from the hospital ward (24.7%), the emergency department (20.8%), or transferred from another ICU (16.5%). The overall lengths of ICU and hospital stay were 10 (IQR, 4-21) and 17 (IQR, 6-39) days, respectively (Table 1).

Mortality Outcome

The all-cause hospital mortality rate was 58.9% (651 of 1,106) encompassing 613 patients who died in the ICU and 38 after ICU discharge. Patients who died were older (61 ± 13.4 vs. 56.8 ± 14.1; $P < 0.001$), more comorbid (Charlson score 3 [IQR, 1-4] vs. 2 [IQR, 1-3], $P < 0.001$), had higher acuity of illness (APACHE-II score 30 [IQR, 25-35] vs. 29 [IQR, 24-33], $P = 0.003$; SOFA score 15 [IQR, 13-18] vs. 14 [IQR, 12-16], $P = 0.021$), and had shorter hospital (9.0 [IQR, 4.0-23.0] vs. 32.5 [IQR, 18.0-57.8], $P < 0.001$ and ICU (6.0 [IQR, 3.0-15.0] vs. 15.0 [IQR, 8.0-28.0], $P < 0.001$) lengths of stay (Table 1). Standardized mortality ratios for each study site are reported in Fig 2. There was no statistically significant difference in standardized mortality ratios across sites ($P = 0.224$). Observed mortality rates according to strata of APACHE-II and SOFA versus Charlson scores are represented in Fig S2. Patient characteristics according to study site are presented in Table S2.

Contributing Factors to AKI and CKRT Indications

CKRT was initiated at a median of 26 [IQR, 10.5-70.9] hours from ICU admission for the cohort, and this time did not differ significantly between patients who survived or died (26.5 [IQR, 9.9-72.1] vs. 26.0 [IQR, 11.0-68.2],

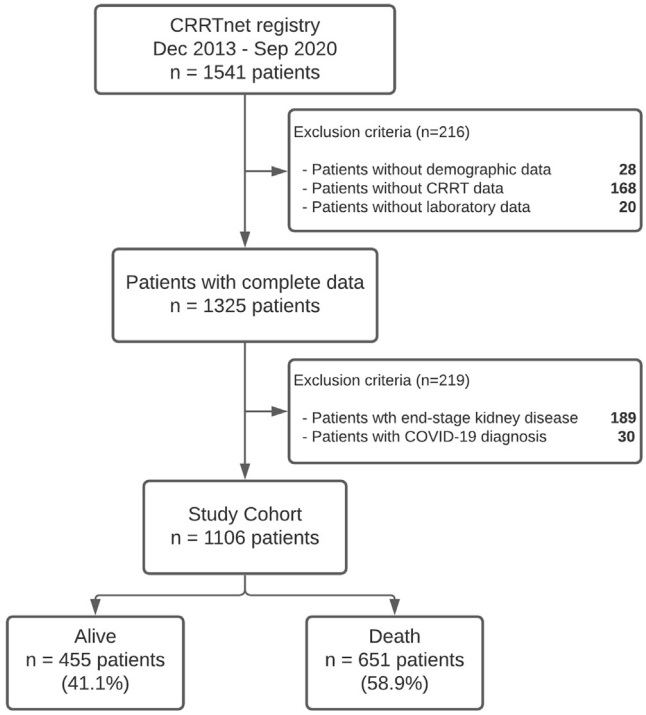

Figure 1. Study cohort derivation.

$P = 0.34$, respectively) (Table 1). The most common indications for CKRT initiation were oliguria/anuria (56.2%, range across sites 20.2%-76.3%), followed by fluid overload encompassing pulmonary edema and extravascular fluid overload (overall, 53.9% [range 13.2%-77.9%]) (Table 1 and Table S2). Extravascular fluid overload accounted for 63% of these cases whereas pulmonary edema accounted for 37% of cases. Other common causes of CKRT initiation included uremia (40.8%), metabolic acidosis (40.6%), and hyperkalemia (26.9%) (Table 1, Table S2, and Fig 3). These indications were not mutually exclusive, and the presence of more than one of these indications was associated with increased mortality (46.2% for 1 indication [n=357], 57.4% for 2 indications [n=216], and 67.9% for ≥3 indications [n=533], P-trend < 0.001) (Fig S3). The most common contributing factors to AKI were sepsis (42.6%, range across sites 16.2%-69.2%), cardiogenic (17.1%, range 5.5%-25.2%), major surgery (16.6%, range 2.7%-38.6%) and liver disease (10.9%, range 2.4%-17.1%) (Table 1 and Table S2). Patients that died were more likely to have either sepsis, cardiac, or liver disease as contributing factors to their AKI compared with survivors (48.4% vs. 34.3%, $P < 0.001$; 20.4% vs. 12.3%, $P < 0.001$; and 13.4% vs. 7.5%, $P = 0.03$, respectively) (Table 1).

Characteristics of Patients at CKRT Initiation

There was heterogeneity in clinical characteristics and laboratory data at the time of CKRT initiation across study sites (Table S3). Clinical data at the time of CKRT initiation differed significantly between survivors and nonsurvivors

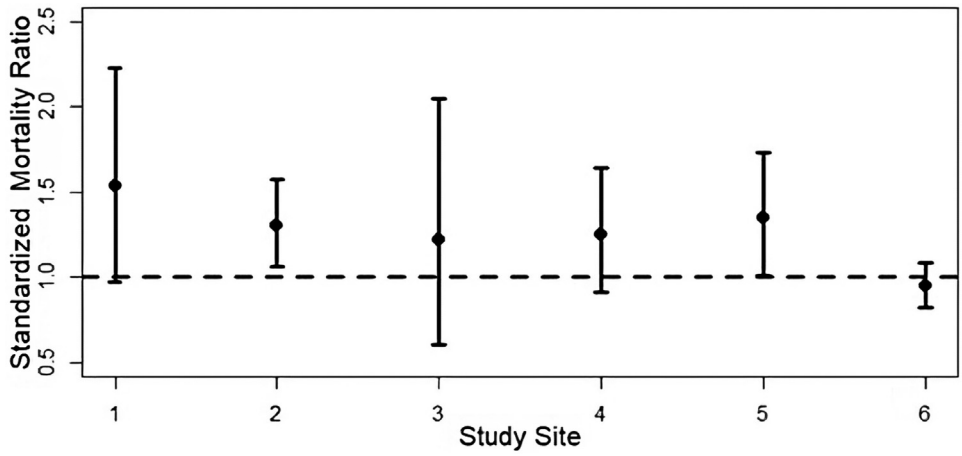

Figure 2. Standardized mortality ratios across CRRTnet study sites. Error bars denote 95% confidence intervals. Between-site comparison of standardized mortality ratios, $P = 0.224$.

(Table 2). Nonsurvivors had higher SOFA scores (14.2 [IQR, 12.0-17.0] vs. 12.6 [IQR, 10-15], $P < 0.001$), were more frequently mechanically ventilated (86.5% vs. 80.4%, $P = 0.01$), were more often receiving vasoactive medications (85.3% vs. 73.6%, $P < 0.001$), and were more commonly receiving extracorporeal membrane oxygenation support (7.1% vs. 3.1%, $P = 0.006$). The degree of fluid overload from ICU admission to CKRT initiation was not different between nonsurvivors and survivors (median 5.2% [IQR, 1.5-12.2] vs. 5.2% [IQR, 1.1-11.9], $P = 0.60$) (Table 2). When the cohort was restricted to patients with fluid management indications for CKRT such as extravascular fluid overload, pulmonary edema, and/or oliguria/anuria (n=758), the degree of fluid overload from ICU admission to CKRT initiation was also not different between nonsurvivors and survivors (median 5% [IQR, 1.3-12.4] vs. 6.2% [IQR, 1.3-13.6], $P = 0.29$) (Table 2).

Characteristics of CKRT Prescription

The majority of patients had right internal jugular catheters inserted (50.2%, range 32.9%-75.9%), followed by left internal jugular (27.2%, range 11.0%-44.2%) and femoral catheters (15.3%, range 10.4%-52.1%). The most common prescribed modality of CKRT was continuous veno-venous hemodiafiltration (80.5%, range 1.9%-97.7%), followed by continuous veno-venous hemofiltration (16.5%, range 0%-88.7%). Continuous veno-venous hemodialysis was used in only 2.2% (range, 0%-7%) of instances, and slow continuous ultrafiltration in 0.9% (range, 0%-5.7%) of instances (Table 3 and Fig 4). Median prescription dose was 31.3 (IQR, 25.6-40) mL/kg/h across the entire cohort, with a range from 25.3-36.8 mL/kg/h across sites, and it was significantly higher in those patients who died versus survived (32.4 [IQR, 26.4-41.1] vs. 30.0 [IQR, 24.8-38.1] mL/kg/h, $P < 0.001$). Anticoagulation strategies differed between sites. The most common type of anticoagulation was regional citrate (45.8%, range 0.7%-95.5%) and its use was more frequent in survivors than in nonsurvivors (55.8% vs. 38.7%, $P < 0.001$). Unfractionated heparin anticoagulation was used in only 5.7% (range 0%-26.6%) of instances, with other or no anticoagulation being used in 48.6% (range 4.5%-75.2%) of instances (Table 3 and Fig 4).

Resource Utilization

Intermittent hemodialysis after CKRT was used in 7.1% of patients who ultimately died and in 62.9% of those who survived. Further, 24% of survivors received tracheostomy, and in those patients discharged alive from the hospital, 53.2% were still hemodialysis-dependent at ICU discharge, and 31.4% remained hemodialysis-dependent at hospital discharge (Table 4). CKRT program logistics available at CRRTnet participating institutions during the study period are reported in Table S4.

DISCUSSION

The CRRTnet is an ongoing multicenter, prospective registry of critically ill adult patients undergoing CKRT. To date, we have recruited 1,541 patients across 5 academic institutions and 6 ICUs, of which 1,106 participants with AKI requiring CKRT were included in this study. Included patients had a high severity of acute illness with a mortality rate of 58.9%, and the most common reason for admission to the ICU was respiratory failure followed by sepsis. The primary indications for CKRT initiation were oliguria/anuria followed by fluid overload. The most common modality of CKRT was continuous veno-venous hemodiafiltration with regional citrate being the anticoagulation chosen most often.

There have been other published reports of patients undergoing CKRT.[16-20] The CRRTnet registry expands upon prior reports as it provides detailed and granular information of the epidemiology of critically ill adult patients with AKI undergoing CKRT, the etiology of AKI, and the prescription and provision of CKRT across distinct

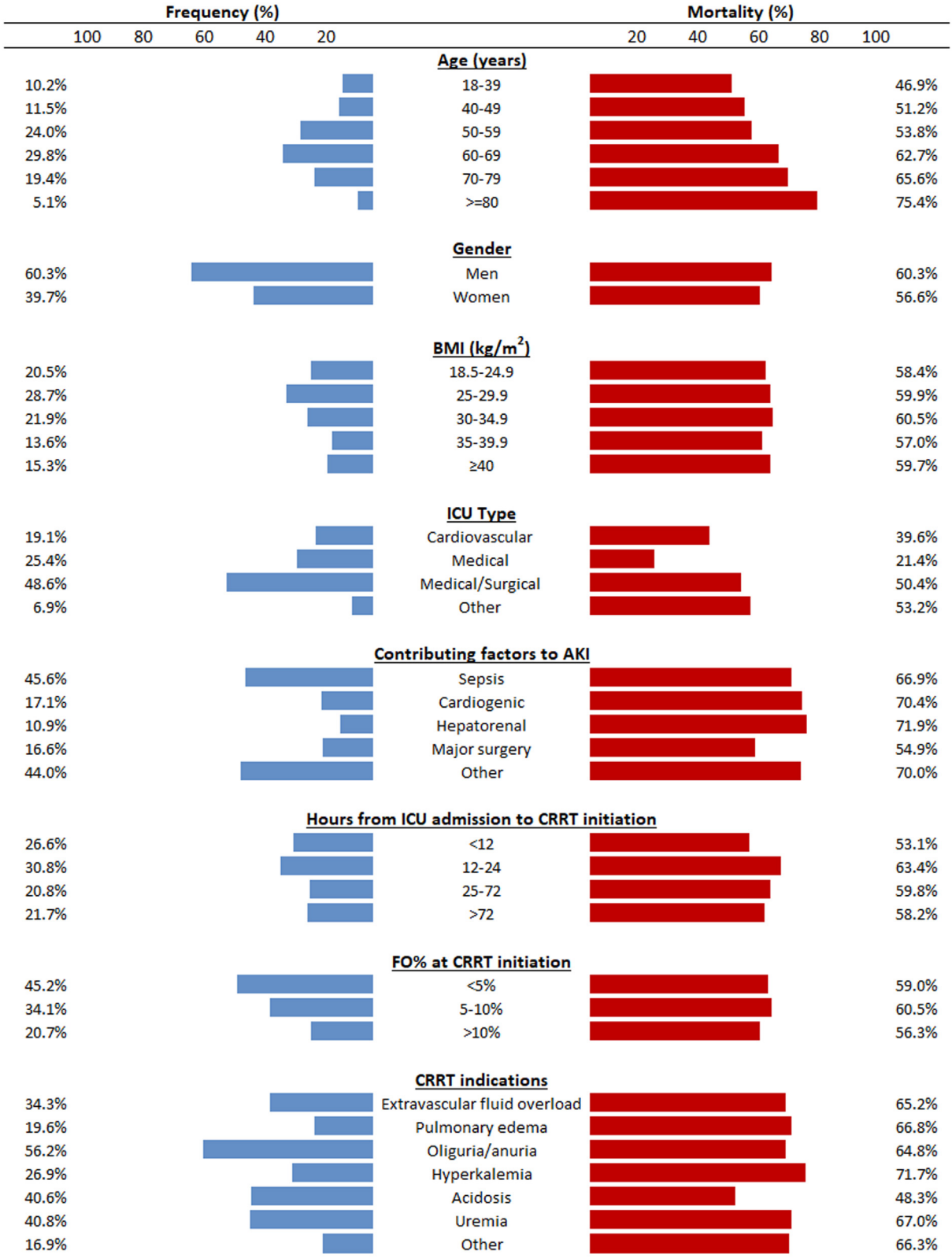

Figure 3. Frequency distribution of selected clinical characteristics. Frequencies are displayed in blue and hospital mortality rates are displayed in red. Abbreviations: BMI, body mass index; CRRT, continuous renal replacement therapy; FO, fluid overload; ICU, intensive care unit.

Table 2. Clinical Data at the Time of CKRT Initiation Stratified According to Hospital Mortality

	All Cohort n=1,106	Survivors n=455	Nonsurvivors n=651	*P*
Clinical characteristics				
SOFA score	13.6 [11-16]	12.6 [10-15]	14.2 [12-17]	<0.001
Glasgow coma scale	7 [3-10]	8 [3-11]	6 [3-10]	<0.001
Central venous pressure, mm Hg	14 [10-18]	14 [10-18]	14 [10-18.8]	0.51
Vasoactive drug use[a], n (%)	890 (80.5%)	335 (73.6%)	555 (85.3%)	<0.001
Mechanical ventilation, n (%)	929 (84.0%)	366 (80.4%)	563 (86.5%)	0.01
ECMO, n (%)	60 (5.4%)	14 (3.1%)	46 (7.1%)	0.006
%FO from ICU admission to CKRT initiation	5.2 [1.3-12.1]	5.2 [1.1-11.9]	5.2 [1.5-12.2]	0.60
%FO from ICU admission to CKRT initiation[b] (n=758 with fluid management indications for CKRT)	5.4 [1.3-13.1]	6.2 [1.3, 13.6]	5 [1.3, 12.4]	0.29
Laboratory data				
WBC, 10^3/μL	14.7 [9.8-21.4]	14.5 [9.5-19.9]	14.8 [9.9-21.9]	0.31
Hemoglobin, g/dL	8.5 [7.7-9.6]	8.4 [7.7-9.5]	8.5 [7.8-9.6]	0.61
Hematocrit, %	25.6 [23.0-29.1]	25.0 [23.0-28.8]	26.0 [23.3-29.3]	0.04
Platelet, 10^3/μL	102.0 [60.0-172.0]	118.0 [66.0-186.5]	94.0 [54.0-158.8]	0.002
INR	1.6 [1.2-2.1]	1.3 [1.2-1.8]	1.7 [1.4-2.4]	<0.001
PTT, s	38.0 [30.1-50.0]	35.0 [29.0-45.0]	41.0 [32.2-53.0]	<0.001
Sodium, mmol/L	138.0 [135.0-142.0]	138.0 [135.0-142.0]	138.0 [135.0-142.0]	0.31
Potassium, mmol/L	4.3 [3.9-4.8]	4.2 [3.8-4.7]	4.4 [3.9-4.9]	<0.001
Chloride, mmol/L	102.0 [98.0-106.0]	102.0 [99.0-106.0]	102.0 [98.0-105.0]	0.20
Bicarbonate, mmol/L	21.0 [18.0-23.0]	21.0 [19.0-24.0]	20.0 [17.0-23.0]	<0.001
Creatinine, mg/dL	3.6 [2.2-8.1]	4.1 [2.4-10.0]	3.2 [2.0-6.1]	<0.001
BUN, mg/dL	45.1 [29.4-64.0]	46.4 [31.4-65.0]	44.0 [27.7-63.1]	0.12
Magnesium, mg/dL	2.1 [1.9-2.3]	2.1 [1.9-2.3]	2.1 [1.9-2.3]	0.05
Calcium, mg/dL	8.3 [7.7-9.0]	8.3 [7.8-9.0]	8.2 [7.6-8.9]	0.03
Ionized calcium, mg/dL	4.4 [4.0-4.7]	4.4 [4.1-4.7]	4.3 [4.0-4.6]	0.60
Phosphate, mg/dL	4.7 [3.6-5.8]	4.5 [3.4-5.5]	4.8 [3.7-6.1]	<0.001
Bilirubin, mg/dL	2.3 [0.9-6.0]	1.8 [0.8-4.5]	3.0 [1.1-6.8]	<0.001
Albumin, g/dL	2.2 [1.8-2.7]	2.2 [1.8-2.7]	2.2 [1.8-2.7]	0.65
pH	7.34 [7.27-7.40]	7.35 [7.30-7.41]	7.33 [7.25-7.39]	<0.001
Lactate, mg/dL	10.8 [6.2-15.3]	10.8 [7.2-15.3]	10.3 [5.1-15.5]	0.01
FiO_2, %	50.0 [40.0-60.0]	40.0 [35.0-60.0]	50.0 [40.0-70.0]	0.001
PaO_2, mm Hg	94.0 [77.0-116.0]	94.0 [78.0-114.3]	94.0 [77.0-119.0]	0.68
$PaCO_2$, mm Hg	39.0 [33.0-45.0]	39.0 [34.0-45.0]	38.0 [33.0-45.0]	0.53
Oxygen saturation, %	97.0 [94.9-99.0]	96.8 [95.0-98.1]	97.0 [94.2-99.0]	0.34

Note: All continuous data are reported as median and interquartile range (25th-75th percentiles).
Abbreviations: BUN, blood urea nitrogen; CKRT, continuous kidney replacement therapy; ECMO, extracorporeal membrane oxygenation; FiO_2, fraction of inspired oxygen; FO, fluid overload; ICU, intensive care unit; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; PTT, partial thromboplastin time; SOFA, sequential organ failure assessment; WBC, white blood cell.
[a]Includes: norepinephrine, vasopressin, epinephrine, phenylephrine, milrinone, dobutamine, and dopamine.
[b]Determined only for patients in which CKRT was indicated for fluid management due to extravascular fluid overload, pulmonary edema, and/or oliguria/anuria.

centers. Data from the CRRTnet registry could be used to improve the quality of care delivery to critically ill patients undergoing CKRT. The CRRTnet registry could also provide a standards-based verification program designed to help sites to improve quality across CKRT programs using their own data and establish the infrastructure to determine benchmarks both internally to programs as well as to other analogous sites.[21,22] Ultimately, this will create the framework to establish, measure, and improve each program quality infrastructure and improve care for critically ill patients requiring CKRT.

The CRRTnet registry collects specific data on the provision, prescription, and delivery of CKRT. The ability to compare prescription patterns across distinct ICUs and report on these data will allow us to evaluate benchmarks and provide targets for the optimal provision of CKRT. For example, most of the CRRTnet centers adhered to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommendations related to dialysis catheter location being in either the right internal jugular or in femoral veins.[23] However, this practice varied and carried a frequency of 44.5%-86.4%. Interestingly, left internal jugular catheter location was utilized in up to 44.2% of instances, highlighting that significant local practice variation exists and perhaps culture-specific practice patterns. Although median prescribed CKRT dose across CRRTnet

Table 3. CKRT Prescription Characteristics in the CRRTnet Cohort and Stratified by Study Site

Characteristic	All Cohort n=1,106	Site 1 n=73	Site 2 n=308	Site 3 n=53	Site 4 n=247	Site 5 n=139	Site 6 n=286
Catheter position, n (%)							
Right IJ	555 (50.2%)	24 (32.9%)	105 (34.1%)	33 (62.3%)	118 (47.8%)	58 (41.7%)	217 (75.9%)
Left IJ	301 (27.2%)	8 (11.%)	136 (44.2%)	6 (11.3%)	60 (24.3)	59 (42.4)	32 (11.2)
Femoral	169 (15.3%)	38 (52.1%)	32 (10.4%)	12 (22.6%)	38 (15.4)	19 (13.7)	30 (10.5%)
Subclavian	26 (2.4%)	3 (4.1%)	6 (1.9%)	1 (1.9%)	14 (5.7)	2 (1.4)	—
No catheter[a]	55 (5%)	—	29 (9.4%)	1 (1.9%)	17 (6.9)	1 (0.7)	7 (2.4%)
Catheter type, n (%)							
Tunneled	60 (5.4%)	—	32 (10.4%)	1 (1.9%)	18 (7.3%)	8 (5.8%)	1 (0.3%)
Acute	1,046 (94.6%)	73 (100%)	276 (89.6%)	52 (98.1%)	229 (92.7%)	131 (94.2%)	285 (99.7%)
Prescription dose, mL/kg/h	31.3 [25.6-40]	34.3 [28.1-40.3]	36.8 [30-43.3]	25.9 [23.8-27.5]	25.3 [22.9-28.3]	26.8 [21.5-31.7]	36.8 [31.2-45.7]
Prescription dose[b], n (%)							
<25 mL/kg/h	240 (21.7%)	11 (15.1%)	36 (11.7%)	15 (28.3%)	116 (47%)	55 (39.6%)	7 (2.4%)
25-30 mL/kg/h	233 (21.1%)	12 (16.4%)	38 (12.3%)	19 (35.8%)	85 (34.4%)	38 (27.3%)	41 (14.3%)
>30 mL/kg/h	592 (53.5%)	49 (67.1%)	226 (73.4%)	9 (17%)	42 (17%)	41 (29.5%)	225 (78.7%)
CKRT modality, n (%)							
CVVHDF	890 (80.5%)	27 (37%)	301 (97.7%)	1 (1.9%)	247 (100%)	64 (46.1%)	250 (87.4%)
CVVHD	24 (2.1%)	—	—	2 (3.8%)	—	2 (1.4%)	20 (7%)
CVVH	182 (16.5%)	46 (63%)	6 (2%)	47 (88.7%)	—	73 (52.5%)	10 (3.5%)
SCUF	10 (0.9%)	—	1 (0.3%)	3 (5.6%)	—	—	6 (2.1%)
Anticoagulation, n (%)							
Citrate	506 (45.8%)	24 (32.9%)	134 (43.5%)	40 (75.5%)	236 (95.5%)	1 (0.7%)	71 (24.8%)
Heparin	63 (5.7%)	14 (19.2%)	11 (3.6%)	1 (1.9%)	—	37 (26.6%)	—
Other	9 (0.8%)	—	9 (2.9%)	—	—	—	—
None	528 (47.7%)	35 (47.9%)	154 (50.0%)	12 (22.6%)	11 (4.5%)	101 (72.7%)	215 (75.2%)
CKRT duration, d	5 [3-8]	4 [2-6]	7 [4-13.2]	4 [2-6]	8 [5-10]	6 [4-11]	3 [2-4]
CKRT duration, n (%)							
<2 d	58 (5.2%)	8 (11%)	1 (0.3%)	5 (9.4%)	1 (0.4%)	1 (0.7%)	42 (14.7%)
≥2 d	1048 (94.8%)	65 (89%)	307 (99.7%)	48 (90.6%)	246 (99.6%)	138 (99.3%)	244 (85.3%)

Note: All continuous data are reported as median and interquartile range (25th-75th percentiles).
Abbreviations: CKRT, continuous kidney replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodialfiltration; ECMO, extracorporeal membrane oxygenation; IJ, internal jugular; SCUF, slow continuous ultrafiltration.
[a]CKRT was connected in tandem with ECMO circuits without a catheter.
[b]Percentages do not add to 100% because of missing data.

centers was adherent to clinical practice guidelines, variations were also observed. This may be related to disease severity and temporary higher needs of solute clearance, as sites caring for patients with higher severity of illness on presentation had higher CKRT prescription doses. Anticoagulation practices also largely differed between sites. When used, the most frequent anticoagulation type remained regional citrate, with unfractionated heparin being utilized in a minority of instances. This is in keeping with recommended clinical practice guidelines.[23] Finally, the modality of CKRT differed across sites, with most centers providing continuous veno-venous hemodiafiltration followed by continuous veno-venous hemofiltration. Only a minority of CKRT was performed by continuous veno-venous hemodialysis. As there exists no current evidence for an optimal CKRT modality, these practices may reflect institutional preferences and local culture.[24]

Interestingly, although the precise CKRT prescription and delivery differed among sites, this did not translate to statistically significant different standardized mortality ratios. This may reflect the fact that outcomes of patients undergoing CKRT may be in part related to having CKRT performed at experienced high-volume centers with extensive expertise and available logistics for the provision of CKRT, rather than specific factors associated with the CKRT prescription. Importantly, additional data will be needed to compare provision of CKRT and patient outcomes between large academic centers and smaller, lower-volume community centers. However, registries like CRRTnet can assess concordance (or lack thereof) with current guidelines and identify discordant practices and opportunities for continuous improvement.

Although other previous evaluations of critically ill patients undergoing CKRT have included large patient populations, these were retrospective in nature and were not able to include granular data on the provision of CKRT.[16-19] The inclusion of detailed patient characteristics, contributing factors to AKI, and indications for the initiation of CKRT in the CRRTnet registry provides further insights into the epidemiology of this growing patient population. For

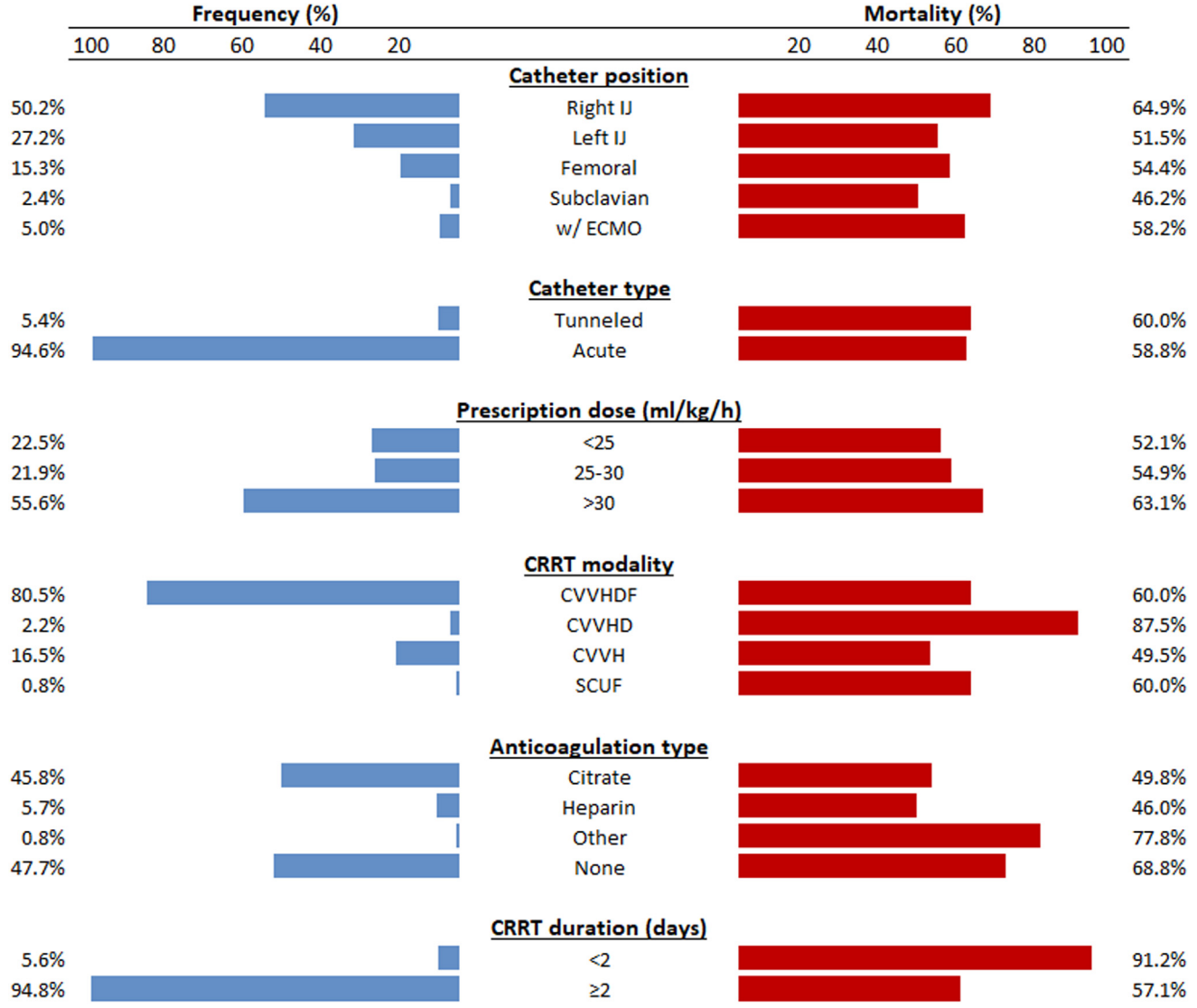

Figure 4. Frequency distribution of selected CKRT prescription characteristics. Frequencies are displayed in blue and hospital mortality rates are displayed in red. Prescription dose is based on total effluent prescribed dose in mL per kg per hour (mL/kg/h). Abbreviations: CRRT, continuous renal replacement therapy; CVVH, continuous veno-venous hemofiltration; CVVHD, continuous veno-venous hemodialysis; CVVHDF, continuous veno-venous hemodiafiltration; ECMO, extracorporeal membrane oxygenation; IJ, internal jugular; SCUF, slow continuous ultrafiltration.

example, the CRRTnet registry highlights the fact that although sepsis was the most common contributing factor for AKI requiring CKRT, fluid management was the most common indication. Importantly, fluid management encompasses indications such as extravascular fluid overload, pulmonary edema, and oliguria/anuria, which are specifically collected in the CRRTnet registry. The overall degree of fluid overload quantified from ICU admission to CKRT initiation was moderate in the CRRTnet registry (median 5.2%, IQR, 1.3%-12.1%), which could be related to preemptive fluid management practice patterns at participating institutions (median of 26 hours from ICU admission to CKRT initiation). One should note that the CRRTnet registry included a majority of patients recruited before the publication of the STARRT-AKI trial, which indicated that an accelerated KRT strategy was not associated with a lower risk of death and that it was associated with additional adverse events such as increased risk of dependence on KRT.[25] This has led to a decrease in accelerated initiations of acute KRT for critically ill patients. With future evaluations of the CRRTnet living registry, it may be possible to evaluate changes in temporal practice and initiation parameters for CKRT according to evolving evidence.

Although the CRRTnet registry has several strengths (ie, multicenter, heterogeneous ICU case mix, prospective evaluation), some important limitations exist and require discussion. First, this was an evaluation of 5 academic CKRT practices and may not be generalizable to CKRT practices in nonacademic centers. Future registry work will need to recruit from both metropolitan and rural sites as

Table 4. Clinical Outcomes and Healthcare Resource Utilization in the CRRTnet cohort

Outcomes	N (%) or median [IQR]
A. All cohort	**(All cohort=1,106)**
ICU mortality	613 (55.4%)
Hospital mortality (after ICU)	38 (3.5%)
B. Nonsurvivors	**(Nonsurvivors=651)**
Time to death (d), median [IQR]	13.8 [7.5-25]
HD utilization after CKRT	46 (7.1%)
Need of tracheostomy	9 (1.4%)
ICU (d), median [IQR]	6 [3-15]
Hospital (d), median [IQR]	9 [4-23]
C. Survivors	**(Survivors=455)**
HD utilization after CKRT	286 (62.9%)
HD-dependence at ICU discharge	242 (53.2%)
Need of tracheostomy	109 (24%)
HD-dependence at hospital discharge	143 (31.4%)
Last serum creatinine[a], median [IQR]	2.3 [1.5-6.1]
ICU (d), median [IQR]	15 [8-28]
Hospital (d), median [IQR]	33 [18-58]

Abbreviations: CKRT, continuous kidney replacement therapy; HD, hemodialysis; ICU, intensive care unit; IQR, interquartile range.
[a]Determined only for patients that were not HD dependent at hospital discharge.

well as nonacademic sites. However, the registry did include a broad case mix of ICUs (ie, mixed, medical, surgical, and cardiovascular) to be able to best capture a broad representation of critically ill adult patients with AKI requiring CKRT in the ICU. Second, although we do report on prescribed CKRT dose, we do not have data to report on delivered dose. However, most patients in our cohort had prescribed doses greater than 25 mL/kg/h, which would imply that a sufficient minimal dose was likely achieved in most instances. Although outside the scope of this epidemiological manuscript, future analysis of our cohort may include the association of dynamic prescribed CKRT dose and clinical outcomes. Finally, this study reports only on patients with AKI (not kidney failure) receiving CKRT and did not characterize those requiring intermittent KRT as the initial KRT modality. As such, the results may not be generalizable to the population of patients in the ICU receiving intermittent modalities of KRT, or those with pre-existing kidney failure becoming critically ill. Future studies will be necessary to best characterize the general ICU population receiving any modality of acute KRT.

In summary, the CRRTnet living registry represents the largest, prospective data of adult critically ill patients with AKI receiving CKRT in the ICU. This report provides detailed information regarding the epidemiology of these patients as well as detailed descriptions of contributors to AKI, indications for CKRT initiation, and the CKRT prescriptions. We found that sepsis was the major contributor to AKI, and fluid management was collectively the most common indication for CKRT initiation. The latter finding should direct research initiatives toward evaluating best practices of fluid management during CKRT. Importantly, significant heterogeneity in patient- and CKRT-specific characteristics were found in current practice. The latter highlights the need for establishing benchmarks of CKRT performance and developing risk-classification/subphenotyping tools for adaptive trial design in future CKRT studies. Data from this registry could assist with the design of such needed studies.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Figure S1: Geographic distribution of CRRTnet study sites

Figure S2: Observed mortality according to Charlson Comorbidity Index and APACHE-II and SOFA scores

Figure S3: Relationship between the number of CKRT indications and hospital mortality.

Table S1: Definitions and Data Management Procedures of All Validated Data Collected in the CRRTnet Registry

Table S2: Patient Characteristics in the CRRTnet Cohort Stratified by Study Site

Table S3: Clinical Data at the Time of CKRT Initiation Stratified by Study Site

Table S4: Self-reported CKRT Logistics Available at CRRTnet Participating Institutions During the Study Period

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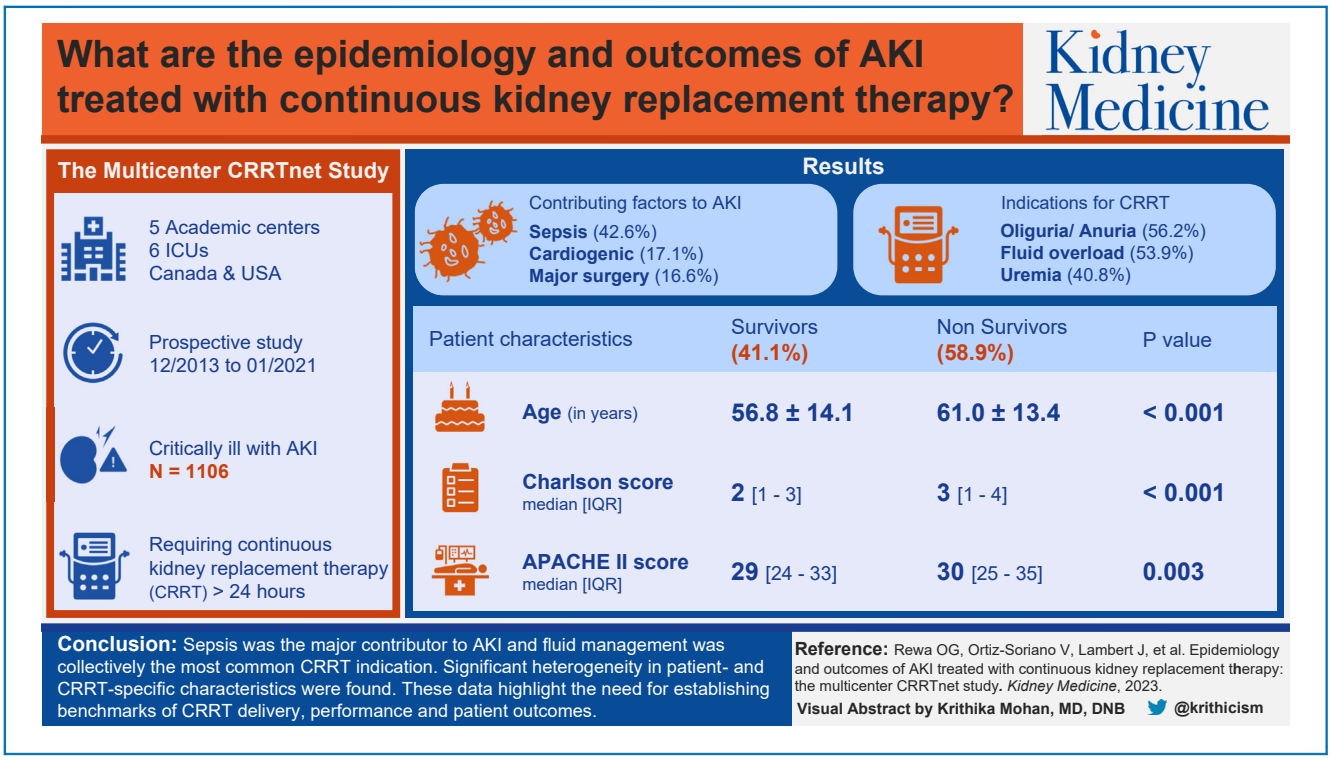
What are the epidemiology and outcomes of AKI treated with continuous kidney replacement therapy?
Kidney Medicine
The Multicenter CRRTnet Study
5 Academic centers
6 ICUs
Canada & USA
Prospective study
12/2013 to 01/2021
Critically ill with AKI
N = 1106
Requiring continuous kidney replacement therapy (CRRT) > 24 hours
Results
Contributing factors to AKI
Sepsis (42.6%)
Cardiogenic (17.1%)
Major surgery (16.6%)
Indications for CRRT
Oliguria/ Anuria (56.2%)
Fluid overload (53.9%)
Uremia (40.8%)
Patient characteristics
Survivors (41.1%)
Non Survivors (58.9%)
P value
Age (in years)
56.8 ± 14.1
61.0 ± 13.4
< 0.001
Charlson score median [IQR]
2 [1 - 3]
3 [1 - 4]
< 0.001
APACHE II score median [IQR]
29 [24 - 33]
30 [25 - 35]
0.003
Conclusion: Sepsis was the major contributor to AKI and fluid management was collectively the most common CRRT indication. Significant heterogeneity in patient- and CRRT-specific characteristics were found. These data highlight the need for establishing benchmarks of CRRT delivery, performance and patient outcomes.
Reference: Rewa OG, Ortiz-Soriano V, Lambert J, et al. Epidemiology and outcomes of AKI treated with continuous kidney replacement therapy: the multicenter CRRTnet study. Kidney Medicine, 2023.
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