Earlier CRRT is Associated with Reduced Mortality in Rhabdomyolysis Patients

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Research Article

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Abstract

Background: Continue renal replacement therapy (CRRT) is commonly employed for rhabdomyolysis (RM) patients. However, the optimal initiation timing of CRRT and prognostic factors were not well evaluated for patients with RM. We aimed to investigate the efficacy of CRRT timing on mortality and the risk factors of death in RM patients who accepted CRRT.

Methods: RM patients who received CRRT between May 2010 and May 2021 in our center were retrospectively included. The primarily endpoint was 90-day mortality. Univariate and multivariate logistic analyses were performed to identify the risk factors of 90-day mortality.

Results: A total of 134 patients were included in our present study. The 90-day mortality rate was 38.06%. Most of the patients (88.81%) reached peak creatine kinase (CK) within 72 hours after admission, and 58 (43.28%) patients received CRRT before the peak CK occurrence (earlier CRRT) and 76 (56.72%) of patients had CRRT after the peak CK occurrence (later CRRT). Multivariate logistic regression analysis showed that CRRT initiation after the peak CK occurrence (OR = 3.74, 95%CI 1.17-11.95, p = 0.026), the elevated serum cTnI (OR = 1.23, 95%CI 1.02-1.49, p = 0.032), and the need of mechanical ventilation support (OR = 7.18, 95%CI 1.67-30.83, p = 0.008) were independent risk factors of 90-day mortality. Similar results were obtained in a subgroup analysis of patients with acute kidney injury (AKI).

Conclusions: Earlier CRRT initiation before the peak CK occurrence was associated with lower 90-day patient mortality.

Background

Rhabdomyolysis (RM) is a complex clinical syndrome characterized by the damage of skeletal muscle cell and the release of cellular contents such as myoglobin (MB), creatine kinase (CK), and electrolyte into the blood circulation. A variety of medical and surgical conditions can lead to the development of RM and is particularly common in patients with trauma and heat stroke, the morbidities were reported up to be 31% [1] and 32% [2], respectively. In addition to muscle damage, RM could induce a series of life-threatening complications. Acute kidney injury (AKI) is the most common and severe complication of RM, occurred in 20%-60% of patients with RM. And, for RM related AKI patients, the mortality rate was significantly increased and was reported to be as high as 60% [3, 4].

The elevated circulation myoglobin, which could accelerate kidney injury by promoting vasoconstriction, blocking renal tubules, causing oxidative stress lipid peroxidation, and inducing inflammation, is considered to be the most important pathogenesis of RM related AKI [5-7]. Traditional treatment for the prevention of RM related AKI included the blockade of causative factors and early rehydration to dilute serum and urine myoglobin concentration [5]. However, rehydration was limited in the RM patient who had AKI and electrolyte disturbances. Continuous renal replacement therapy (CRRT) is used as an important intervention in 8%-41% of patients with severe rhabdomyolysis [4, 8]. It was reported that CRRT was effective on the clearance of serum myoglobin, correction of electrolyte disturbance, removal of

inflammatory mediators, and stabilization of the internal environment [9-11]. Therefore, timely CRRT initiation is essential to improve prognosis.

Currently, the timing of CRRT initiation in patients with RM remained controversial [12]. For crush injury and heat stroke patients, the two common causes of RM, researchers suggested that CRRT should be more aggressively adopted due to the aforementioned advantages [13, 14]. However, in a systematic review of the potential benefits of CRRT in patients with RM, Zeng et al. found that although creatinine, myoglobin and electrolyte levels improved in patients with CRRT, mortality remained unchanged [15]. Therefore, other researchers suggested that initiation of CRRT should only be considered in the presence of severe AKI complications that do not respond to initial treatment [16]. These controversial opinions on the CRRT initiation timing confused the clinicians. And, to the best of our knowledge, there is no study directly investigated the CRRT initiation timing in RM patients.

Therefore, we conducted a retrospective study in RM patients who accepted CRRT, aimed to evaluate the timing of CRRT initiation on patient mortality and analyze the risk factors of patient mortality.

Methods

Population and setting:

From May 2010 to May 2021, patients who diagnosed rhabdomyolysis (CK >1000 IU/l) with a typical clinical presentation or etiology predisposing to RM were retrospectively included. Patients with any of the following criteria were excluded: 1. age <18 years; 2. chronic kidney disease (CKD) diagnosed before admission; 3. elevated CK caused by acute myocardial infarction (AMI); 4. patients who had CRRT before hospital admission to our center; 5. Missed patients. The ethics committee of the Xijing hospital was informed and approved this retrospective study (ethical number: KY20213020-1). Due to the present study was retrospectively noninterventional designed, the written informed consent for participation in this study was waived. All patient data were kept confidential.

Data collection:

Patient data was collected from the electronic medical record. Demographic data included age, gender, medical history (hypertension, diabetes, cardiovascular disease), and admission diagnosis. Laboratory data including leukocytes, hemoglobin, platelets, albumin, globulin, bilirubin, PT, cTnI, Nt-proBNP, calcium, potassium, and biomarkers of renal function (creatinine, eGFR) on hospital admission and before CRRT initiation were collected as well. AKI was diagnosed and graded according to the 2012 KDIGO AKI guideline [17]. The severity of disease was evaluated by APACHE Ⅱ score and SOFA score. To determine the time of peak CK, every measurement of CK during the hospital staying was recorded, if there were multiple peak CK, recorde the time when the first peak CK occurrence. The start and stop time, treatment duration, anticoagulation methods, dose of CRRT were recorded. The net ultrafiltration intensity (NUF) was calculated by the formula proposed by Naorungroj *et al* [18]. NUF was classified as low, medium, and high intensity according to the findings of Raghavan *et al* [19]. All of the CRRT mode was continue veno-

venous hemofiltration (CVVH) and performed by using Gambro instrument with AN 69 dialyzer (M100; Gambro Renal Products).

Outcome:

The primary outcome was 90-day mortality. Patients who survived at discharge were followed up by telephone. Patient long-term survival and renal outcome were asked and recorded.

Statistical analysis:

According to the time of peak CK and the time of CRRT initiation, patients were classified into CRRT before the peak CK occurrence (earlier CRRT) and CRRT after the peak CK time (later CRRT). Categorical variables were described as frequencies and percentages and tested using the Chi-square test or Fisher exact test. Normally distributed continuous variables were expressed as mean ± SD and tested using the Student's t-test. Continuous variables with non-normal distribution were expressed as IQR (the 25th to 75th percentile) and tested using the Mann-Whitney U test. Independent risk factors of 90-day mortality were identified using logistic regression analysis. Collinearity diagnosis was employed to eliminate highly related variables. For variables with extremely skewed distributions, logarithmic transformation is performed in the analysis. The Kaplan-Meier curve was used to describe patient accumulated survival proportion and intergroups comparison was performed using log-rank test. Subgroup analysis was performed according to the patient etiologies and occurrence of AKI. All statistics were calculated using SPSS 26.0. A two-side $p < 0.05$ was considered as statistic significance.

Results

After the selection, 134 patients were included in the final analysis (Figure 1). Patient characteristics were showed in (Table 1). The medial age of the included patients was 49 (IQR 33.75, 62.25) years and 112 (83.58%) patients were male. Trauma (n = 29, 21.64%), heat stroke (n = 28, 20.9%), and vascular ischemia (n = 19, 14.18%) were the most common causes of RM. Other causes included physical labor (n = 12, 9.0%), bee stings (n = 11, 8.21%), toxic substances (n = 8, 5.97%), infections (n = 8, 5.97%), endocrine diseases (n = 7, 5.22%), drugs (n = 6, 4.48%), surgery (n = 5, 3.73%), and stroke (n=1,0.75%). Of the included patients, 111 (82.84%) developed AKI before CRRT, and 44 (32.83%) developed advanced AKI (AKI 2 or 3 stage). Median eGFR before CRRT was 32.97 ml/min/1.73m^2 (IQR 16.89, 58.56). Medical history included diabetes mellitus (n = 20, 14.93%), hypertension (n = 33, 24.63%), and cardiovascular disease (n = 15, 11.19%). The median CK was 6703.5 IU/L (IQR 1070-25940.75) at the hospital admission and the median peak CK was 14293 IU/L (IQR 4974.75-42906) during the hospital staying. 119 (88.81%) patients reached peak CK within 72h after admission, and the remained patients had the peaking CK within 7 days after admission. CRRT was initiated within 72h after admission in 106 (79.1%) patients. 58 (43.28%) patients received CRRT before the occurrence of peak CK and 76 (56.72%) patients had CRRT after the peak CK time (Table 2).

The median follow-up time was 58.9 (33.8, 71.0) months. During the follow-up time, 40.3% (n = 54) patient deaths were observed. Almost all of the deaths occurred within 90 days after the hospital admission. The 90-day mortality rate was 38.06% (n = 51). In univariate analysis, higher APACHE Ⅱ score, SOFA score, Nt-proBNP, cTnI, lower albumin and globulin on hospital admission, higher APACHE Ⅱ score, SOFA score and Nt-proBNP, lower albumin and globulin before the CRRT, time from admission to CRRT, CRRT initiation later than the peak CK time, and the need of mechanical ventilation support were associated with 90-day mortality (Additional file 1: Table S1). The multivariate logistic regression analysis showed that CRRT initiation later than the peak CK (OR = 3.74, 95%CI 1.17-11.95, p = 0.026), the elevated serum cTnI at admission (OR = 1.23, 95%CI 1.02-1.49, p = 0.032), and the need of mechanical ventilation support (OR = 7.18, 95%CI 1.67-30.83, p = 0.008) were independent risk factors of 90-day mortality (Additional file 1: Table S1). These three factors were identified as independent risk factors of 90-day mortality in the subgroup analysis of RM patients with AKI as well (Additional file 1: Table S2).

The 90-day mortality rates were 27.59% (n = 16) and 46.05% (n = 35) in the patients received CRRT before the peak CK occurrence (earlier CRRT) and the patients received CRRT after the peak CK time (later CRRT), respectively. Kaplan-Meier survival curves showed that the later CRRT group had significantly increased mortality risk during the follow-up (log-rank test, p = 0.015, Figure 2). And, in the subgroup analysis of AKI patients and trauma-induced RM patients, the mortality risk was significantly higher in the later CRRT group as well（Additional file 3: Figure S1. Subgroup analysis).

Discussion

To the best of our knowledge, the present study is the first report explored the CRRT initiation timing on patient mortality and risk factors of patient mortality in RM patients who underwent CRRT. We have the following findings in our present study. Firstly, RM patients who received CRRT had high short-term mortality. Secondly, relatively earlier CRRT initiation (before the peak CK) was association with lower risk of 90-day mortality. Moreover, the requirement of mechanical ventilation and the elevated serum cTnI concentration were identified as independent risk factors of 90-day mortality as well.

RM is a common severe clinical presentation with complicated etiologies. The causes of RM were different among various studies [4, 8, 20]. In our present cohort, the common causes were trauma, heat stroke, and vascular ischemia. Trauma and vascular ischemia had been widely reported as major causes of RM as well [21, 22]. Compared with previous studies, a higher proportion of heat stroke was found in our cohort. Due to the inclusion of RM patients who received CRRT, the incidence of AKI (82.84%) of our cohort was dramatically higher than previous reports. Half of the patients need aggressive therapies such as mechanical ventilation (45.52%), vasoactive drugs (37.31%), and blood transfusion (60.3%). Most likely, the disease severity of the included patients mainly contributed to relatively high 90-day mortality rate (38.1%), which in the upper range of the previous reports (20.5%-40%) [8, 22].

CRRT is increasingly used in critically ill patients as a part of organ support. There are still no clear criteria for when to initiate CRRT in clinical practice. Premature CRRT may expose patients to the risk of

additional CRRT-related complications. Nevertheless, delayed initiation of CRRT might increase the risk of organ injury by fluid overload and acid-base and electrolyte disorder [23, 24].The timing of CRRT for AKI was evaluated by several high-quality RCT, but the conclusions were controversial. The ELAN trial, which included 93% of surgical patients, showed that the early CRRT group had a significantly lower mortality and 1-year renal function unrecovered rate than the delayed treatment group [25]. Similar findings were observed in the AKIKI2 trail, the timing of treatment in this trail was further delayed in the later CRRT group (treatment was initiated only after 72 hours of oliguria or a blood urea nitrogen concentration above 112 mg/dL and emergence of mandatory indications) [26]. However, the other studies didn't observe increased patient survival in the earlier CRRT group [27-29]. The inclusion of patients with different baseline disease was considered to be one of the causes of these controversial results, which suggested that the timing of RRT initiation should be evaluated in specialized patient group [30].

Compared to AKI patients with other etiologies, the patients with RM induced AKI are more likely to be benefited from CRRT by the continuous clearance of serum myoglobin and other toxic substances released from the damaged myocytes. Up to now, there is no study evaluated the timing of CRRT initiation for RM patients. However, the risk factors for patients who may developed AKI and required RRT have been extensively reported. It is believed that the increased serum myoglobin is the causative factor of AKI in RM patients. However, the short half-life (2-6 hours) limited the predictive validity of myoglobin on AKI development [31]. CK rises within 12 hours after the onset of muscle injury and peaks within 24-72 hours [31]. CK does not directly cause kidney damage, but it is considered to be a sensitive marker of muscle injury. Saskya Byerly et al. found out that patients with higher serum peak CK had more severe muscle injuries, greater Injury severity score, and increased risk of fracture [32]. Meanwhile, the longer half-life of CK makes it a relatively good marker for predicting patient prognosis. In a large cohort of 3111 trauma patients, Anatole Harrois et al. reported that the peak CK value was higher in patients with AKI stage R, I, and F than patients without AKI (2800IU/L vs. 977IU/L, $p < 0.001$) [33]. Additionally, CK level was reported to be associated with the need of CRRT as well. In a retrospective study of 2371 RM patients, McMahon et al. developed a prediction model of RRT or mortality with eight clinical variables, which included CK value [8]. However, the use of CK value to predict death and RRT in patients with RM is controversial because of the large variation in CK cutoff values.[15].

Our study further explored the predictive role of CK and found that CRRT initiation before peak CK time were associated with lower 90-day mortality risk. The appearance of peak CK can be localized the phase of 24-72 hours after myocytes damage, the CRRT initiation before the CK peak time could be considered as earlier CRRT, compared with the CRRT initiation after the CK peak time. Additionally, CK is a large molecule with a molecular weight of 87 KD and can not be cleared by CRRT [34, 35]. The appearance of peak CK is theoretically independent of CRRT. Therefore, the classification of earlier and later CRRT according to the CK peak is reliable in RM patients with CRRT. Furthermore, in the earlier phase of RM, the systemic inflammatory response was activated [36]. The increase of CK and MB were accompanied by a gradual rise in various inflammatory cytokines, including TNF-α, IL-1β, and IL-6 , as well [37]. And, it is reported that CRRT could reduce serum inflammation cytokines and facilitates immunomodulation [38,

39]. Therefore, earlier CRRT most likely could benefit RM patients by the clearance of MB and the alleviation of inflammatory response.

Moreover, the requirement of mechanical ventilation and serum cTnI concentration were identified as independent risk factors of 90-day mortality in our present study. Previous studies showed that the need of mechanical ventilation in patients underwent RRT is an independent risk factor of patient mortality [40]. In our cohort, the requirement of mechanical ventilation, which indicated severe physical condition and additional organ involvement, was understandable to be identified as one of the independent risk factors of 90-day mortality as well.

CTnI is a sensitive biomarker of myocardial injury, while elevated cTnI has been observed in RM patients in previous studies [41, 42], which indicated cardiac involvement and are associated with poor prognosis [43]. In a cohort study of 178 RM patients, a high accuracy of hs-cTnI was reported on the prediction of in-hospital death or prolonged hospital stay (AUC 0.74，95%CI 0.68-0.80) [44].The causes of RM, including sepsis, stroke, medications, and trauma, may lead to micro-injury to the myocardium, which is the major cause of elevated cTnI [45]. Moreover, massive release of cytokines, oxygen free radicals, and activation of systemic inflammatory response in RM patient could result in myocardial cell damage as well [42]. And in RM patients with CRRT, volume overload and ischemic-hypoxic injury to the myocardium could also be considered as the potential cause of elevated cTnI. These relationships most likely explain the identification of cTnI as one of the independent risk factor of 90-day mortality in our present study. The routinely monitoring of cardiac function would be helpful for RM patients with or without CRRT.

Our present study has several limitations. First, this is a single-center study. The disease spectrum might be different from other centers. Multi-center study should be performed to validate our findings. Second, although we reported a large cohort of RM patients with CRRT, the overall sample size is relatively small. The second type of error needs to be alerted on understanding our results. Third, the peak of CK cannot be judged prospectively, which may limit the direct use of our findings in clinical practice. However, our findings suggested that earlier CRRT may benefit RM patient survival. Further studies evaluate the timing of CRRT on RM patients are warranted and could consider the use of CK as one of the criteria for CRRT initiation.

Conclusions

RM patients who received CRRT commonly had more severe disease condition and higher mortality than those who did not have CRRT. Earlier CRRT initiation before the peak CK time is associated with reduced patient mortality. Further studies are warranted to identify the CRRT timing for RM patients.

List Of Abbreviations

CRRT: continue renal replacement therapy; RM: rhabdomyolysis; CK: creatine kinase; AKI: acute kidney injury; MB: myoglobin; CKD: chronic kidney disease; AMI: acute myocardial infarction; MAP: mean arterial

pressure; APACHE Ⅱ: acute physiology and chronic health evaluation Ⅱ; SOFA: sequential organ failure assessment score; WBC, white blood cell; eGFR: estimated glomerular filtration rate.

Declarations

Ethics approval and consent to participate

The ethics committee of the Xijing hospital was informed and approved this retrospective study (ethical number: KY20213020-1). Due to the present study was retrospectively noninterventional designed, the written informed consent for participation in this study was waived. All patient data were kept confidential.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

The study was designed by SRS, BM and XYL. BM, XYL collected, analysis, interpreted data, drafted, and revised the manuscript. YY, FM, LJZ, HW collected data. BM and SRS critically revised the manuscript, supervised the research group and ensured the integrity of the data.

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Tables

Table 1: Characteristics of patients at hospital admission

Variables	**All patients (n= 134)**
Age	49 (33.75, 62.25)
Male (n, %)	112 (83.58%)
MAP (mm/Hg)	92.28±17.75
Causes of rhabdomyolysis	
Trauma (n, %)	29 (21.64%)
Heat stroke (n, %)	28 (20.9%)
Vascular ischemia (n, %)	19 (14.18%)
Other (n, %)	58 (43.28%)
Comorbidity, n (%)	
Diabetes (n, %)	20 (14.93%)
Hypertension (n, %)	33 (24.63%)
Cardiovascular disease (n, %)	15 (11.19%)
Use of Mechanical ventilation (n, %)	61 (45.52%)
Use of Vasoactive drugs (n, %)	50 (37.31%)
Blood transfusion (n, %)	81 (60.45%)
Variables at admission to hospital	
APACHE	15.99±8.36
SOFA	7.02±3.44
eGFR (ml/min/1.73 m2)	41.34 (21.38, 68.99)
Serum creatinine (μmol/L)	166 (103, 261.5)
Albumin (g/L)	37.99±8.47
Globulin (g/L)	25.48±4.60
cTnI (ng/ml)	0.42 (0.06, 1.64)
Log (Nt-proBNP+1) (pg/ml)	3.26 (2.41, 3.67)
Hemoglobin (g/L)	138.68±30.41
WBC (10^9/L)	13.99 (9.21, 20.90)
Platelet (10^9/L)	147.50 (79.25, 210.75)

Calcium (mmol/L)	2.03±0.29
Potassium (mmol/L)	4.12 (3.66, 4.78)
Prothrombin time (s)	12.6 (11.40, 13.98)
Admission CK (IU/L)	6703.5 (1070, 25940.75)
Peak CK (IU/L)	14293 (4974.75, 42906)

MAP, mean arterial pressure; APACHEII, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CK, creatine kinase; WBC, white blood cell.

Table 2: Variables at initiation of CRRT and outcomes of patients	
Variables at initiation of CRRT	**All patients (n=134)**
APACHE□	16.51±8.16
SOFA	8.38±3.92
Time from ICU admission to RRT (h)	28 (21, 45.60)
Timing of RRT initiation	
Before the peak CK	58 (43.28%)
Later than the peak CK	76 (56.72%)
Net ultrafiltration intensity	
Low intensity (< 1.01mL/kg/hr)	72 (53.73%)
Moderate-intensity (1.01–1.75 mL/kg/hr)	26 (19.40%)
High intensity (> 1.75 mL/kg/hr)	36 (26.87%)
AKI stage at initiation of CRRT	
AKI 0 (n, %)	23 (17.16%)
AKI I (n, %)	67 (50%)
AKI □, □ (n, %)	44 (32.84%)
Serum creatinine (μmol/L)	188 (115, 306.75)
eGFR (ml/min/1.73 m2)	32.971 (16.89, 58.56)
Prothrombin time (s)	12.8 (11.7, 14.8)
Calcium (mmol/L)	1.94±0.27
Potassium (mmol/L)	4.21 (3.68, 5.04)
Hemoglobin (g/L)	134.46±30.68
Platelet (10^9/L)	125.5 (59.75, 205.5)
WBC (10^9/L)	14.80 (11.08, 21.04)
Albumin (g/L)	36.49±7.60
Globulin (g/L)	25.08±4.83
cTnI (ng/ml)	0.48 (0.1, 1.99)
Log (NtproBNP+1) (pg/ml)	3.33 (2.48, 3.87)
Outcomes	

Length of hospitalization (days)	10 (5, 18.25)
length of CRRT treatment (h)	48.5 (24, 104.75)
In hospital mortality (n, %)	20 (14.93%)
90-day mortality (days) (n, %)	51 (38.06%)
CRRT, continue renal replacement therapy; APACHEII, acute physiology and chronic health evaluation II; SOFA, sequential organ failure assessment; CK, creatine kinase; AKI, acute kidney injury; eGFR, estimated glomerular filtration rate; WBC, white blood cell.	

Figures

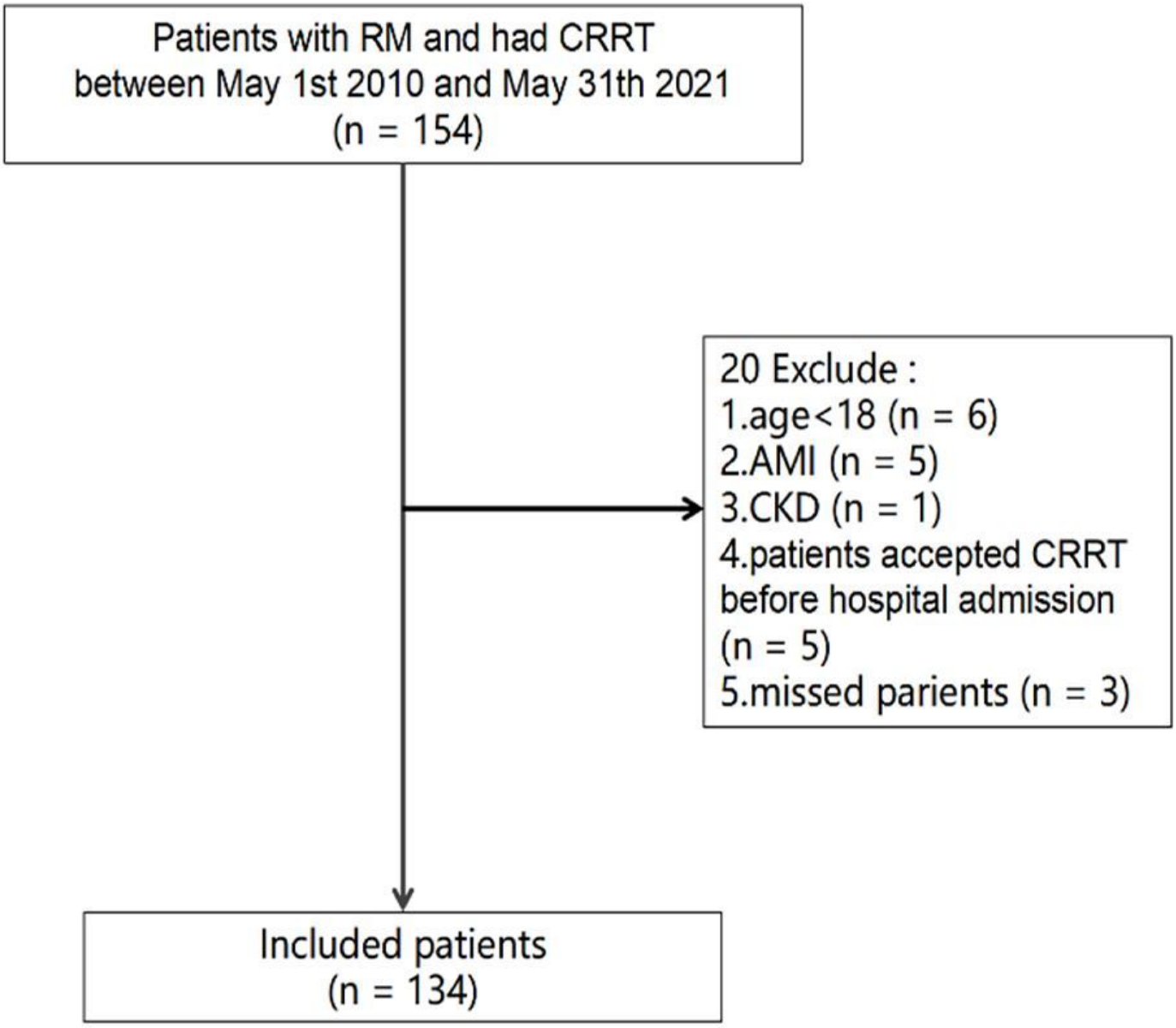

Figure 1

Flow chart of patient inclusion

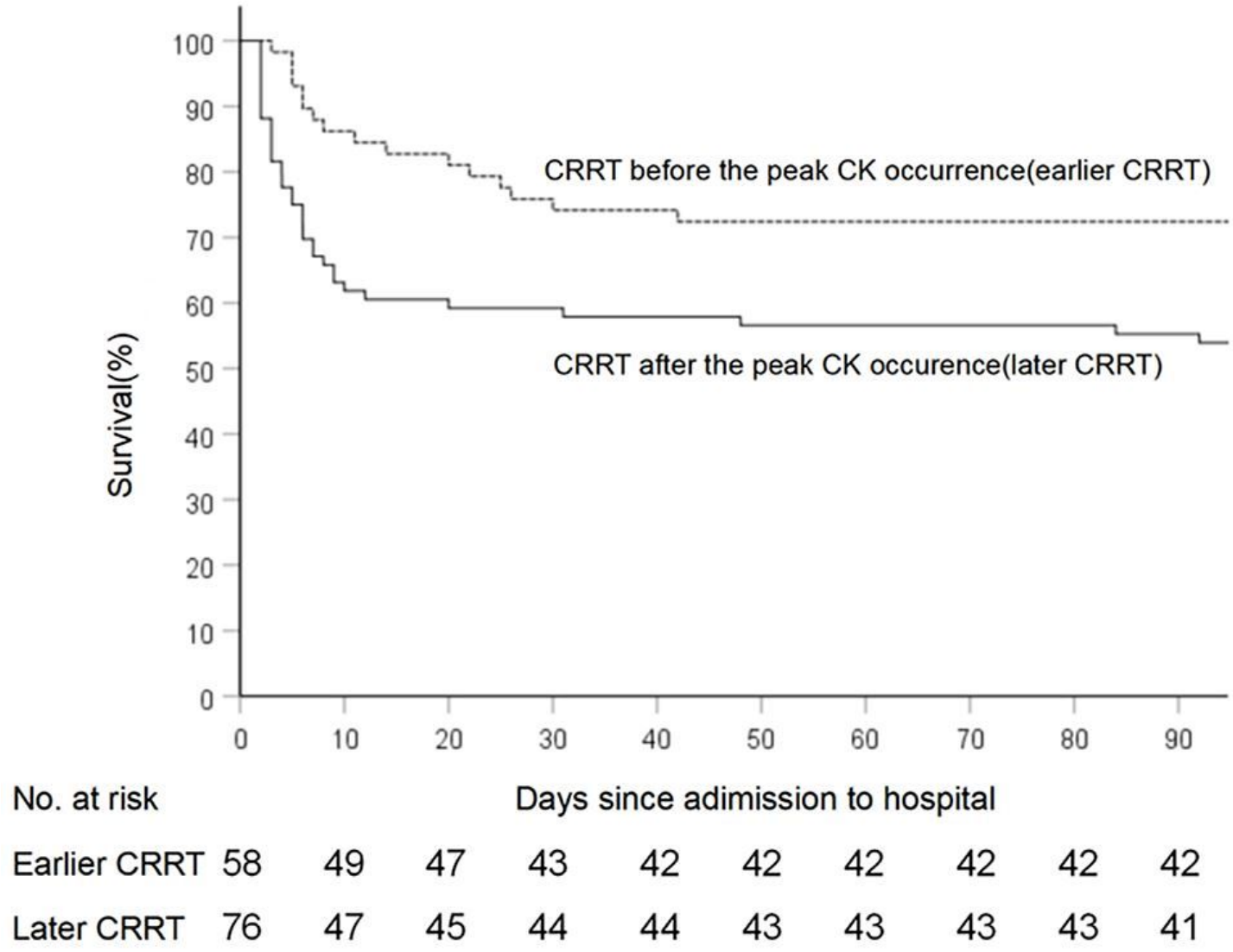

Figure 2

Kaplan-Meier Curves of patient survival

Supplementary Files

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- supplementaryfile.docx