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A model for acute kidney injury in severe burn patients

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ABSTRACT

Introduction: In patients with severe burns, morbidity and mortality are high. One factor related to poor prognosis is acute kidney injury. According to the AKIN criteria, acute kidney injury has 3 stages based on urine output, serum creatinine level, and renal replacement therapy. In this study, we aimed to create a decision tree for estimating risk of acute kidney injury in patients with severe burn injuries.

Methods: We retrospectively evaluated 437 adult patients with ≥20% total burn surface area injury who were treated at the Baskent University Ankara and Konya Burn Centers from January 2000 to March 2020. Patients who had high-voltage burn and previous history of kidney disease were excluded. Patient demographics, medical history, mechanism of injury, presence of inhalation injury, depth of burn, laboratory values, presence of oliguria, need for renal replacement therapy, central venous pressure, and prognosis were evaluated. These data were used in a "decision tree method" to create the Baskent University model to estimate risk of acute kidney injury in severe burn patients.

Results: Our model provided an accuracy of 71.09% for risk estimation. Of 172 patients, 78 (45%) had different degrees of acute kidney injury, with 26 of these (15.1%) receiving renal replacement therapy. Our model showed that total burn surface area was the most important factor for estimation of acute kidney injury occurrence. Other important factors included serum creatinine value, burn injury severity score, hemoglobin value, neutrophil-to-lymphocyte ratio, and platelet count.

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Conclusion: The Baskent University model for acute kidney injury may be helpful to determine risk of acute kidney injury in burn patients. This determination would allow appropriate treatment to be given to high-risk patients in the early period, reducing the incidence of acute kidney injury.

1. Introduction

The mortality rate in patients with severe burn injuries ranges from 1.4% to 18% [1,2]. Several scoring systems have been used to predict the severity of trauma. The injury severity score (ISS) is the most popular of these [3]. The burn injury severity score (BISS) is then obtained by multipling the ISS score with the burn patients' age and total burn surface area (TBSA) [1].

Acute kidney injury (AKI) is described as an abrupt impairment of kidney functions; AKI is a common major complication of severe burns and may benefit from renal replacement therapy (RRT) [4]. Studies have documented AKI development after burn injuries in 30% of patients and reported a mortality rate among AKI patients of between 50% and 80% [5,6].

In general, the clinical presentation of AKI after burn injuries has 2 different patterns. The first is characterized by prerenal insufficiency immediately (0–3 days) after burn, due to hypovolemia and myocardial suppression [7]. The second occurs at a later period (4–14 days) as a result of circulatory inflammatory mediators and sepsis [8]. Although the accumulation of data from previous studies has advanced our understanding of the pathobiology of AKI after burns, a proportional improvement could not be achieved in terms of its treatment [9–11]. Although most AKI patients recover from renal dysfunction over time, they bear an increased risk for development of chronic kidney disease during their remaining lifetime [12]. On the other hand, AKI mechanisms in patients with high-voltage burns (electrical and lightning) are different from patients with other burns [13–15]. In high-voltage burns, the depth of burn and myoglobinuria due to muscle damage are more important factors rather than TBSA, hypovolemia, and sepsis for development of AKI [16–18].

Determination of AKI risk is important so that effective prophylactic therapy can be administered and nephrotoxic agents can be avoided. More than 30 factors have been defined in the literature as contributors for AKI development [19,20]. The first criteria established for the purpose of predicting AKI is a combination of previous definitions, which resulted in coining of Risk, Injury, Failure; Loss, End-Stage Renal Disease (RIFLE) criteria [5]. Because of limitations with RIFLE criteria, the Acute Kidney Injury Network (AKIN) was established as further criteria and have been widely used (Table 1) [21]. Classification in both RIFLE and AKIN classification is made according to serum creatinine value and urine output. However, in the AKIN classification, different from the RIFLE classification, a better distinction is made between loss of kidney function and end-stage renal disease. For example, the increase in serum creatine value of less than 50% but at least 0.3 mg/dL is classified as "normal" according to the RIFLE classification, while it is classified as "stage 1" according to the AKIN classification [22]. In 2010, both sets of criteria were combined, which gave rise to The Kidney Disease: Improving Global Outcomes (KDIGO), setting new criteria; however, KDIGO has not yet been used for burn patients [23].

In the present study, our aim was to determine the factors that cause AKI in severe burn injury patients (≥20% TBSA) and to construct a decision tree from these factors to help identify patients at high risk for AKI.

2. Material and methods

2.1. Patient groups

In this retrospective clinical study of 437 patients who were hospitalized at the Baskent University Ankara and Konya Burn Centers from January 2000 to March 2020 (Figs. 1 and 2), 265 patients were excluded because of <20% TBSA, known chronic kidney disease prior to burn injury, high-voltage burn injury (electrical and lightning), and age of <18 years. The reason for

Table 1 – The Acute Kidney Injury Network (AKIN) classification system.

Stage	Serum creatinine	Urine output criteria
1	Creatinine × 1.5–2.0 (mg/dL) from baseline OR Creatinine increased by at least 26.4 μmol/L	u/o < 0.5 mL/kg/h × 6 h
2	Creatinine × 2.0–3.0 (mg/dL) (i.e., doubled or tripled creatinine)	u/o < 0.5 mL/kg/h × 12 h
3	Creatinine > 3.0 (mg/dL) OR Creatinine level over 354 μmol/L, with an acute increase of at least 44 μmol/L OR Initiation of RRT	u/o < 0.3 mL/kg/h × 24 h OR Anuria for 12 h

RRT: renal replacement therapy; u/o: urinary output.

Fig. 1 – Baskent University Ankara Hospital Burn Center (6th Floor).
A—front view, B—secretary desk, C—patient room for childs,D—patient room for adults.

including a rate of ≥20% TBSA in the present study is that systemic effects of burns other than electrical burns and especially the development of AKI are seen in burns with ≥20% TBSA [4,20]. Patients were divided into 2 groups according to development of AKI after 21 days (the "no AKI group"; n = 94) or development of AKI within 21 days (the "AKI group"; n = 78). We collected all stages of AKIN classifications under the AKI group (Fig. 3).

For all 172 patients included in our study, data were collected via the hospital automation medical record system. Data collected included demographic characteristics (age and sex), medical history, mechanism of burn injury, presence of inhalation injury, central venous pressure (CVP), TBSA, BISS, and laboratory values. From medical history, status of diabetes mellitus, coronary artery disease, and hypertension was queried. The decision as to whether patients had inhalation

Fig. 2 – Baskent University Ankara Hospital Burn Center.
A—training room, B—intensive care unit, C—wound care unit, D—operation room.

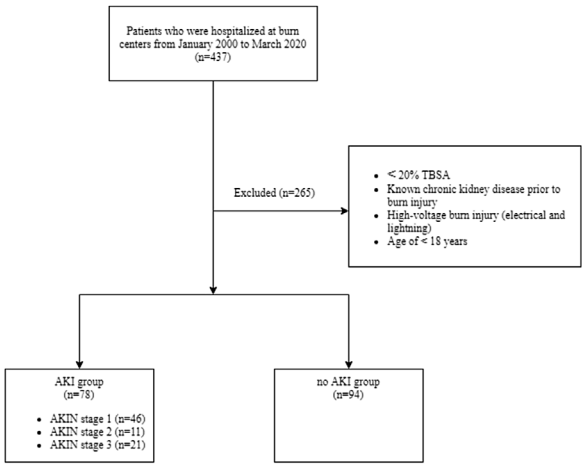

Fig. 3 – Consort diagram of entire study population.

burn was made based on bronchoscopy. Laboratory values were obtained within the first 24 h after burn injury occurrence and included hemoglobin level, platelet count, neutrophil-to-lymphocyte ratio (NLR), blood urea nitrogen, and serum creatinine level. Moreover, we recorded presence of oliguria (urinary output ≤500 mL/24 h), RRT administration, and fatal outcome during hospitalization. In this study, we determined the parameters based on the mechanism of the development of acute kidney injury and predisposing factors such as diabetes mellitus [24].

2.2. *Statistical analyses*

Statistical analyses were performed using SPSS 20.0 statistical software package. All values are shown as means ± SD quantitatively and as numbers and percentages qualitatively. Categorical data were analyzed using Pearson chi-square test. Kolmogorov-Smirnov tests were used to assess normalcy of quantitative variables. The results did not present a normal distribution. For this reason, quantitative variables were assessed by Mann-Whitney U tests.

3. Decision tree method for creating the Baskent University model for acute kidney injury

Decision trees are widely used in machine learning applications in the field of medicine with its easy interpretation and effective performance in the solution of nonlinear problems [25]. A decision tree model uses various statistical calculations in order to place the given attribute within the nodes of the tree structure [26]. These calculations are aimed to find the strongest parameter that can homogeneously classify the given dataset. Each available parameter is tested for the relevant node, and the strongest parameter is selected. The branches connecting the node to the subnodes express the test condition according to the values that the current node can take. In order to calculate the strongest attribute for a given node, entropy-based information gain ratio is used as in the study reported by Sancak et al. [27]. Suppose that:

Si: Samples of class Ci

Pi : Probability of data i belongs to class Ci

A: Attribute A = {a1, a2, . . . , av}

In this case, the information needed to classify the samples is calculated as:

$$IS_1, S_2, \ldots, S_m) = -\sum_{i=1}^{m} p_i \log_2 p_i$$

The entropy measure for attribute A that will divide the sample set into v subsets is calculated as follows:

$$EA) = \sum_{j=1}^{v} \frac{s_{1j} + s_{2j} + \ldots + s_{mj}}{s} I(s_{1j}, \ldots, s_{mj})$$

Sij indicates the samples in class Ci that belongs to subset Sj, the information for subset Sj is calculated as:

$$IS_{1j}, S_{2j}, \ldots, S_{mj}) = -\sum_{i=1}^{m} p_{ij} \log_2 (p_{ij})$$

In this case, information gain is the difference between information and entropy and calculated as given below:

$$GA) = IS_1, S_2, \ldots, S_m) - E(A)$$

In the present study, a decision tree application was implemented by using the data mining tool Rapid Miner Studio 9.3. Because the parameters in the data set are both numerical and categorical data, the C4.5 algorithm was preferred [28]. Information gain ratio was used for partitioning, and the largest tree depth was selected as 20. Minimal gain is

Table 2 – Demographics and medical history of patients.

	Total cohort, n = 172 (100%)	AKI, n = 78 (45.3%)	No AKI, n = 94 (54.7%)
Demographic			
Mean age ± SD, years	35 ± 15	36 ± 16	34 ± 11
Male sex, n (%)	126 (73.2%)	61 (78.2%)	65 (69.1%)
Medical history, n (%)			
Hypertension	11 (6.4%)	9 (5.2%)	2 (1.1%)
Coronary artery disease	1 (0.6%)	1 (0.6%)	0 (0%)
Diabetes mellitus	11 (6.4%)	7 (4%)	4 (2.3%)

AKI: acute kidney injury; SD: standard deviation.

set to 0.01, minimal leaf size is 2.0, minimal size for the split is taken as 4.0. A tenfold cross-validation test was used for training and testing of the established decision tree model. Samples were randomly selected for each layer. The original class distribution was kept in each fold. The model provided an accuracy of 71.09%, with the area under the curve calculated as 0.844.

Apart from the general performance metrics of the model, the AKIN score distribution was also calculated as a ratio of the sample size in each leaf (class node). This ratio was calculated as the number of data samples belonging to the specific class (indicated by the given leaf node) divided by the number of total data samples in the given leaf node. AKIN class ratios of each leaf node are shown in Fig. 1.

4. Results

4.1. *Patient characteristics*

Mean age of patients was 35.8 ± 15 years. There were 126 male patients (73.2%) and 46 female patients (26.8%) (Table 2). Within the first 21 days of hospitalization, 94 patients (54.7%) did not experienced AKI (no AKI group). AKI group consisted of AKIN stage 1, stage 2, and stage 3 patients. Thirty-eight (82.6%) of 46 patients with AKIN stage 1 were male and 8 (17.4%) were female. The mean age of AKIN stage 1 patients was 36.6 ± 17.8 years. Six (54.5%) of 11 patients with AKIN stage 2 were male and 5 (45.5%) were female. The mean age of AKIN stage 2 patients was 49 ± 21.7 years. Seventeen (80.9%) of 21 patients with AKIN stage 3 were male and 4 (19%) of them were female. The mean age of AKIN stage 3 patients was 42.6 ± 17.6 years.

Patient laboratory values are summarized in Table 3. Mean TBSA was 42.9% (interquartile range [IQR], 20–95). Causes of burns in patients were as follows: 124 (72%) with fire/flame burns, 31 (18%) with scald burns, 11 (6.4%) with explosion burns, and 6 (3.5%) with chemical burns (Table 4). Inhalation injury occurred in 29 patients (16.8%), and 18 patients (10.4%) developed oliguria after burn injury.

In no AKI group, mean TBSA was 29.06 (IQR, 21–35). In AKI group, mean TBSA of AKIN stage 1 patients was 39.07 (IQR, 26–47), mean TBSA of AKIN stage 2 patients was 58.33 (IQR, 42–79), and mean TBSA of AKIN stage 3 was 61.86 (IQR, 40–80).

Of 172 study patients, 26 received RRT (Table 4). Indications for RRT were fluid overload in 14 patients, metabolic disorders in 6 patients, acidosis in 3 patients, and oliguria/anuria in 3 patients. In the AKI group (n = 78), 46 patients were in AKIN stage 1, 11 were in AKIN stage 2, and 21 were in AKIN stage 3 (Table 5). During the course of treatment, 44 patients (25.6%) died.

Table 4 – Mechanism of injuries and clinical outcomes of patients.

Mechanism of injury	Total cohort	AKI	No AKI
Flame, n (%)	124 (72%)	62 (36%)	62 (36%)
Scald, n (%)	31 (18%)	4 (2.32%)	27 (15.7%)
Explosion, n (%)	11 (6.4%)	10 (5.8%)	1 (0.6%)
Chemical, n (%)	6 (3.5%)	2 (1.16%)	4 (2.32%)
TBSA, median ± SD	43 ± 20	47 ± 21.3	29 ± 9
BISS, median ± SD	11 ± 7.6	9 ± 7.3	15 ± 6.5
Mean CVP, mm Hg	4.77	4.77	4.77
Inhalation injury, n (%)	29 (16.8%)	25 (14.5%)	4 (2.3%)
Oliguria, n (%)	18 (10.4%)	18 (10.4%)	0 (0%)
RRT, n (%)	26 (15.1%)	26 (15.1%)	0 (0%)
Exitus, n (%)	44 (25.6%)	37 (21.5%)	7 (4%)

AKI: acute kidney injury; BISS: burn injury severity score; CVP: central venous pressure; RRT: renal replacement therapy; SD: standard deviation; TBSA: total burn surface area.

5. Baskent University model for acute kidney injury

According to the Baskent University model for AKI (BUMAKI), the most important factor for development of AKI was determined to be TBSA. If TBSA was >51%, the probability of developing AKI was 100%. If TBSA was ≤51%, the serum creatinine level should be evaluated. If the serum creatinine value was >0.8 mg/dL, BISS should be evaluated. In cases where BISS was ≤11.4, the risk for AKI development could be determined according to hemoglobin levels. When BISS was >11.4 and hemoglobin values were ≤15 g/dL, a low risk of AKI

Table 5 – Distribution of patients in the AKI group according to AKIN stage.

AKIN stage	Number of patients	%
1	46	59
2	11	14.1
3	21	26.9
Total	78	100

AKIN: Acute Kidney Injury Network.

Table 3 – Laboratory values of patients.

	Total cohort	AKI	No AKI
BUN, mg/dL	15 ± 6	15 ± 6	14 ± 3
Creatinine, mg/dL	0.8 ± 0.3	0.85 ± 0.4	0.86 ± 0.2
Hemoglobin, g/dL	14 ± 3	14 ± 3	14 ± 2
Platelet, /μL	251,000 ± 107,000	255,000 ± 112,000	239,000 ± 93,000
NLR	12 ± 9	12 ± 8	12 ± 11

AKI: acute kidney injury; BUN: blood urea nitrogen; NLR: neutrophil-to-lymphocyte ratio; SD: standard deviation.
Results are mean ± SD.

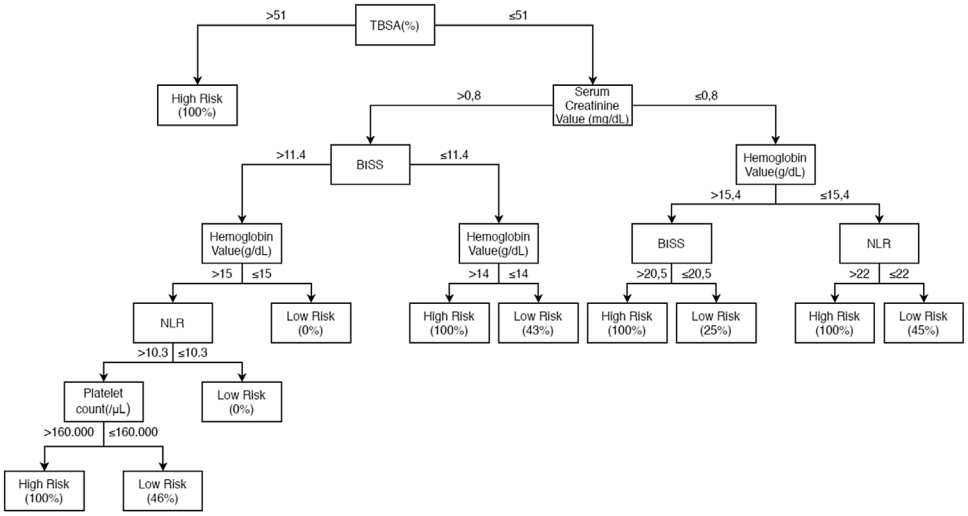

Fig. 4 – BUMAKI algorithm for patients with severe burns (TBSA ≥ 20%). Numbers in parentheses at the ends of the branches of the tree indicate the patient's risk of developing acute kidney injury. BISS: Burn injury severity score; NLR: neutrophil-to-lymphocyte ratio; TBSA: total burn surface area.

development was indicated. However, if hemoglobin values were >15 g/dL, then NLR and platelet count should be evaluated for risk of AKI development. If serum creatinine values were ≤0.8 mg/dL and TBSA was <51%, then BISS or NLR should be evaluated according to hemoglobin value to determine risk of AKI development (Fig. 4).

According to our statistical analyses, presence of sepsis, inhalation injury, oliguria, and hypertension were other significant factors for development of AKI in severe burn patients ($p < 0.05$). According to our statistical analysis, AKI developed in 22 patients (20%) without sepsis and in 56 patients (90.3%) with sepsis. Also, AKI developed in 53 patients (37.1%) without inhalation burn and in 25 patients (86.2%) with inhalation burn. AKI was observed in 60 (39%) of the patients without oliguria and in 18 (100%) of the patients with oliguria. AKI developed in 9 (81.8%) of the patients with hypertension and in 69 (42.9%) of the patients without hypertension.

6. Discussion

In the present study, we created a decision tree to estimate the risk of early development of AKI in severe burn patients. According to the decision tree method, the most important factor affecting the development of AKI was TBSA. In addition, serum creatinine levels, BISS, hemoglobin values, NLR, and platelet count were shown to be important factors in the estimation of early development of AKI in patients with severe burn injury. Other important factors included presence of sepsis, inhalation injury, oliguria, and hypertension.

In the early period after severe burns, AKI develops as a result of hypovolemia, increased inflammatory mediators, tissue destruction, release of denatured protein, and cardiac function. Cardiac output can also decrease because of hypovolemia and fluid loss to the interstitial space [29]. Together, these factors damage the tubular system, and this damage is relevant with burn size [5]. Within the BUMAKI criteria, if TBSA was >51%, the risk of development of AKI was high. Therefore, if TBSA is >51%, attention should be paid to the patient's intravenous fluid resuscitation and nephrotoxic agents should not be used in treatment [29–31].

Serum creatinine is an indicator of glomerular filtration rate, and serum creatinine levels are generally used as a marker to estimate AKI. In 2012, Chung at al. compared severe burn patients with AKI and without AKI. They found that the serum creatinine level was significantly higher in the AKI group [6]. Within the BUMAKI criteria, serum creatinine values are first evaluated if TBSA is ≤51%. In cases where TBSA ≤ 51% and serum creatinine levels are higher than 0.8 mg/dL, systemic hemodynamics should be optimized so that adequate renal perfusion and perfusion pressure are maintained [32].

In patients with severe burns, hemoglobin values may increase depending on the hypovolemia and depth of the burns [33]. Increased hemoglobin values and heme proteins can lead to acute kidney damage [34]. In the BUMAKI criteria, hemoglobin is considered a factor that affects development of AKI. In cases where hemoglobin levels do not decrease despite fluid resuscitation, phlebotomy may be applied to prevent acute kidney damage [35].

In the study from Prat et al. [36], platelet counts decreased in burn patients in the early period. In addition, microparticle formation at early time points after burn injury may obscure platelet numbers, leading to falsely elevated platelet counts by common complete blood count methods [36]. In the BUMAKI criteria, platelet counts of ≥160,000/μL were shown to be related to AKI development. High platelet counts may indicate hypovolemia. On the other hand, it is well known that increased platelet sequestration and increased expression levels of the markers have been reported in kidneys after AKI [37]. We suggest that, if increased platelet counts are detected in severe burn patients, antiplatelet therapies should be started to preserve renal function.

The ISS scoring system is used to estimate trauma-related mortality. BISS, which is the ISS version adapted to burn patients, combines age and TBSA as continuous variables to the ISS to give a more accurate estimate of mortality risk [1,38]. In our study, we first collected patient BISS scores as a parameter. When we created BUMAKI, we saw that BISS had an impact on AKI development. However, although TBSA and age are components of BISS, age was not included in any of the decision tree branches when we developed the BUMAKI criteria. Our opinion on this issue is that the components of BISS do not have the same effect on the development of AKI.

Increased NLR in acute phases of infection in burn patients is an indirect indicator of infection severity and features as a risk factor for AKI [39,40]. Because tissue destruction involves not only the skin but also the underlying structures, visceral injuries may occasionally occur, with infectious complications being common in patients with burn injuries [41]. In BUMAKI, burn patients with increased NLR had a higher incidence of AKI, which is attributable to the fact that concomitant infections in burn patients interfere with renal perfusion.

CVP is usually used as an indicator of fluid resuscitation. On the other hand, some studies have found that, in severe burns, CVP may not reflect the correct pressure value, as it may be affected by intraabdominal pressure [42,43]. Our results showed that CVP did not play an important role in the development of AKI in patients with severe burn injuries.

The relationship between inhalation injury and AKI in severe burn patients is not completely clear. In their study, Kim at al. found that inhalation injury contributed to the presence of AKI [44]. However, they could not clearly explain this mechanism. Our statistical analyses showed that the AKI group had a significantly higher rate of inhalation injury. However, our BUMAKI criteria found that inhalation injury was not a predictive factor for development of AKI.

Sepsis, oliguria, and hypertension are already known risk factors for development of AKI [32,44–46]. In creation of BUMAKI with the decision tree method, these 3 factors were not included. However, our statistical analyses showed that sepsis, oliguria, and hypertension were significantly dominant in the AKI group. Therefore, although these factors were not included in the BUMAKI criteria, these 3 factors should be considered as contributing to the development of AKI in burn patients.

From our study results, we suggest that the BUMAKI criteria could be applied on admission of burn patients. Accordingly, patients could undergo a preassessment in terms of TBSA, serum creatinine level, BISS, hemoglobin level, NLR, and platelet count in the first 24 h after burn injury. We propose that patients at higher risk of AKI be determined and then treated with fluid resuscitation, RRT, if chosen, and consultation with nephrologists, with a possible ultimate outcome of rapid and effective treatment of AKI.

Our treatment algorithm might be upgraded with larger prospective studies. If myoglobinuria can be added among the parameters, patients with high voltage burns can be included and the determining power of the study may increase. We did not include this parameter in our study because we could not reach the values of myoglobinuria in some of our patients. This situation can be shown as the limitation of our study.

7. Conclusions

According to our proposed algorithm (BUMAKI), risk of AKI development can be predicted in the first 24 h in patients with severe burns. According to BUMAKI prepared based on the data of our patient population, AKI developed at any stage of the AKIN classification from all high-risk patients. BUMAKI should be used to assist clinicians in predicting the development of AKI in patients rather than making a diagnosis. As already known, RRT treatment is generally not needed in AKIN stage 1 patients. Therefore, according to our decision tree model, some precautions such as providing effective fluid resuscitation in the early period and avoiding nephrotoxic agents should be taken to prevent AKI development instead of direct RRT treatment in patients with high risk for AKI development.

Authors' contributions

Conceiving and designing the study; or collecting the data; or analyzing and interpreting the data: EK, AA, CA, ET, CBS, EAS, SCY, OA, MH. Writing the manuscript or providing critical revisions that are important for the intellectual content: MH, EK. Approving the final version of the manuscript: MH.

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Conflicts of interest

There is no conflict of interest (None).

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