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Improved outcomes of renal injury following burn trauma☆

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ABSTRACT

Background: Acute kidney injury (AKI) is common in major burn injuries and associated with increased mortality. With advances in surgical and critical care it is unclear if mortality in this population remains this high. This study aims to describe incidence and outcomes of patients admitted to intensive care (ICU) with a burn injury who develop AKI. We additionally sought to determine risk factors for developing AKI.

Methods: A historical cohort study of patients admitted to ICU from 2010 to 2016 with major burn injury was conducted. Demographic, laboratory, and clinical information was collected. AKI was defined by Acute Kidney Injury Network (AKIN) classification. Multivariable logistic regression was used to model association between baseline risk factors and risk of AKI.

Results: Of the 151 patients included, 64 people developed AKI (42%) defined by stages 1–3 of AKIN criteria. The median TBSA was 20% (IQR 9–41). Renal replacement therapy was required in 18/64 (28%) who developed AKI. Multivariable logistic regression demonstrated association between AKI and the following variables: APACHE II score (OR 1.2, 95%CI 1.1–1.3, P = 0.001), age (OR 1.8 per 10-year increase, 95%CI: 1.2–2.5, P = 0.002) and log(TBSA). Fractional polynomial regression analysis demonstrates that the best functional form of TBSA was in the natural logarithm (OR 2.7, 95%CI: 1.5–4.7, p = 0.001). Compared to those without AKI, patients with AKI had longer duration of mechanical ventilation, (median 11 [IQR 6–19] vs. 4 [IQR 2–9] days), ICU stay (15 [IQR 9–22] vs. 6 [IQR 3–10] days), and increased mortality (14 of 64(22%) vs. 4 of 87(5%).

Conclusions: AKI is common in patients with a major burn injury. However, mortality is lower than described in the literature, particularly for those who required renal replacement therapy.

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1. Background

Acute kidney injury (AKI) is a significant consequence of burn injury, and may require treatment with renal replacement therapy (RRT) [1]. The overall incidence of AKI in patients admitted to hospital for burn injury has been reported at 39.6% [2]. Despite this, there continues to be ongoing variability in the literature regarding the attributable mortality in patients who have sustained AKI in the setting of major burn injury [as defined by the American Burn Association classification] with various studies reporting between 21 and 72% [2]. This likely reflects differing patient populations, changing definitions of AKI, and variable time periods in which the studies were conducted [3,4]. It could also reflect improving outcomes due to advances in burn patient care.

AKI in burn patients will typically follow one of two patterns. A patient may present with renal failure early in the first few days of hospitalization, potentially due to pre-renal failure secondary to hypovolemia or myocardial suppression [5]. Alternatively, a patient may experience delayed onset AKI after a period of weeks, potentially associated with sepsis and circulating inflammatory mediators [6]. Burn patients with renal failure who survive their burn generally recover their renal function, however they may be at a higher risk of developing chronic kidney disease later in life [7].

Severity of disease in adult patients being admitted to the ICU can be quantified using the Acute Physiology and Chronic Health Evaluation II (APACHE II) score, which is helpful in describing study populations [8]. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [9] is an accepted guidelines to standardize the conduct and reporting of observational studies.

Incidence of AKI in intensive care unit (ICU) patients overall ranges between 20-50%, with a mortality that can exceed 50% in certain patient populations [10]. In general, outcomes for ICU patients have improved over the last three decades [11]. However, despite significant improved outcomes in patients who have sustained major burn injuries in recent decades [12], mortality of patients with major burns with AKI has not significantly improved [13–19].

To address this perceived discrepancy, we performed an historical cohort study of patients admitted to the intensive care unit with a major burn injury to determine the contemporary incidence and independent risk factors for the development of AKI in this population. We additionally sought to determine outcomes of patients who develop AKI, compared to those who do not.

2. Methods

We performed an historical cohort study and report the results in accordance with the STROBE statement [9]. The study was approved by the Clinical Research Ethics Board of Vancouver General Hospital and the University of British Columbia (H16-01959) who waived the requirement for written informed consent.

2.1. Study population & hospital characteristics

We used the Regional Critical Care Database to identify all patients admitted to the ICU at Vancouver General Hospital with 'major burn' as the primary diagnosis between January 2010 and June 2016 [20]. We excluded patients who had a pre-existing diagnosis of chronic renal failure, based on review of admission histories by data abstraction nurses. The ICU at Vancouver General Hospital is an adult closed, 34 bed mixed medical-surgical unit that operates on an approximate 1:1.2 nurse-to-patient ratio. It is staffed by fellowship trained subspecialty critical care medicine physicians and is affiliated with the University of British Columbia. The indication for admission of a burned patient to the ICU is the need for mechanical ventilation. The Plastic Surgery service follows all patients with burns admitted to the ICU as a consulting service, providing surgical treatment for burn injury and guidance on wound care.

2.2. Data collection

Data were abstracted from both the Regional Critical Care Database and from the clinical record into a standardized case-report form in Microsoft Excel (Redmond, Washington, USA). In addition to demographic information. We collected data related to the burn injury, baseline patient characteristics, treatment variables and patient outcomes.

With regards to burn injury, we abstracted the following information: burn mechanism (*explosion, chemical, electrical, flame, scald, and contact burn*), total body surface area (TBSA) percentage, and the presence of inhalation injury on bronchoscopy (yes/no). The patients were considered to have any of the following medical and social variables (yes/no) if they were documented on the physician admission history: hypertension, coronary artery disease, diabetes mellitus, chronic kidney disease, liver disease, illicit drug abuse, smoking, and alcohol abuse. Furthermore, the patients were considered to have a diagnosis of either hypertension or diabetes mellitus if anti-hypertensive or hyperglycemic medications were prescribed on the provincial formulary (PharmaNet). The current prescriptions (outpatient) for the following medications were documented: angiotensin converting enzyme (ACE) inhibitors, nonsteroidal anti-inflammatory drugs (NSAIDs), and angiotensin receptor blockers (ARBs). The baseline creatinine for each patient was estimated using the Modification of Diet in Renal Disease (MDRD) equation (back-estimation) [21]. We assumed the estimated glomerular filtration rate (eGFR) to be 75 ml/min/1.73 m^2.

The following data was abstracted daily for the first 7 days of intensive care: fluids (administered/lost/balance), use of vasopressors (yes/no), synthetic colloids administered (yes/no, volume ml), albumin administered (yes/no, volume ml), documented mean arterial pressure goal, 6:00 am hemoglobin concentration, transfusion of red blood cells (yes/no, number of units). The 06:00 am serum creatinine concentration and daily maximum serum creatinine concentration were collected for the first 21 days in hospital.

The following treatment and outcome variables were collected from the chart: days from burn injury to first surgical excision, tracheostomy performed (yes/no), and any hospital

prescription of nephrotoxic medications (*aminoglycoside antibiotics, NSAIDs, ACE-inhibitors, and ARBs*). The following data were obtained from the Regional Critical Care Database: use of renal replacement therapy, days of intensive care and hospitalization, days of mechanical ventilation, Acute Physiology and Chronic Health Evaluation (APACHE) II score, and mortality.

2.3. Definition of acute kidney injury

There are two accepted classification systems for renal injury — the Acute Kidney Injury Network (AKIN) classification and the Risk, Injury, Failure, Loss, End-stage (RIFLE) criteria [22]. AKIN has been shown to be more predictive of mortality in burn patients than the RIFLE criteria [23]. The AKIN classification system stages renal injury into three categories — AKIN Stage 1 (increase in serum creatinine by >0.3 mg/dl [1.5 fold] or decrease in urine output by 0.5 ml/kg/h over 6 h), AKIN Stage 2 (creatinine increase by 2 fold from baseline), and AKIN Stage 3 (creatinine increases by 3 fold from baseline, or urine output of less than 0.3 ml/kg/h in 24 h). We defined RRT as the need for either continuous venovenous hemodiafiltration (CVVHDF) or intermitted hemodialysis.

2.4. Sample size & statistical analysis

The sample size was designed to ensure stability around our point estimates of a multivariable model. Assuming an expected risk of AKI of 40% (based on initial sampling of the Regional Critical Care Database), and allowing for approximately 7–8 events per covariate [24], a sample size of approximately 150 patients would be required. All analyses were performed using Stata 15.0 (StataCorp, Texas, USA). All hypothesis tests were two-sided and we considered a p-value of less than 0.05 to be statistically significant. Normally distributed, non-normally distributed, and categorical data were described with mean (standard deviation (SD)), median (interquartile range (IQR)), and proportion (percent), respectively. Univariable comparisons of continuous variables were performed using independent t-tests for normally distributed data and Wilcoxon rank-sum test for non-normally distributed data. Missing data is presented where applicable. A complete-case analysis was performed.

We sought to model the association between baseline covariates and the risk of developing AKI as a dichotomous outcome variable (defined by AKIN 1–3). The following predictor variables were chosen *a priori* because of their likely

Table 1 – Baseline cohort characteristics.

	Total cohort (n = 151)	AKI (n = 64)	No-AKI (n = 87)	p-Value
Age in years, mean (SD)	48 (16)	52 (15)	45 (16)	0.0069
Male gender, n(%)	117 (77)	49 (77)	68 (78)	0.85
Body mass index, mean (SD)	27 (5)	28 (6)	26 (5)	0.033
Missing BMI, n(%)	17 (11)	10 (16)	7 (8)	0.19
Medical comorbidities, n(%)				0.23
Hypertension, n(%)	24 (17)	14 (23)	10 (12)	
Coronary artery disease, n(%)	17 (12)	12 (20)	5 (6)	
Chronic kidney disease, n(%)	3 (2)	3 (5)	0	
Diabetes mellitus, n(%)	11 (8)	7 (11)	4 (5)	
Liver disease, (%)	13 (9)	10 (17)	3 (4)	
Missing comorbidity data, n(%)	8 (5)	3 (5)	5 (6)	
Drug use, n(%)	36 (37)	15 (36)	21 (38)	0.85
Missing, n(%)	54 (36)	22 (34)	32 (37)	0.86
Current or past smoking, n(%)	84 (76)	34 (72)	50 (78)	0.51
Missing, n(%)	60 (26)	17 (27)	23 (26)	1.0
Alcohol use, n(%)	48 (48)	20 (47)	28 (50)	0.84
Missing, n(%)	52 (34)	21 (33)	31 (36)	0.73
Home medications, n(%)				
Non-steroidal anti-inflmmatory drugs, n(%)	6 (4)	4 (7)	2 (2)	0.23
ARB or ACEI, n(%)	4 (3)	3 (5)	1 (1)	0.31
Missing home medication use data, n(%)	6 (4)	6 (9)	0	0.0050
APACHE II score, mean (SD)	16 (6)	19 (5)	13 (5)	<0.0001
Total body surface area, median (IQR)	20 (9–41)	34 (18-50)	15 (7–30)	<0.0001
Baux score, median (IQR)	90 (76–105)	103 (90–114)	81 (70-94)	<0.0001
Mechanism of injury, n(%)				0.23
Flame	79 (52)	38 (59)	41 (47)	
Explosion	53 (35)	18 (28)	35 (40)	
Scald	9 (6)	2 (3)	7 (8)	
Electrical	7 (5)	4 (6)	3 (3)	
Contact	3 (2)	2 (3)	1 (1)	

AKI = acute kidney injury (defined by Acute Kidney Injury Network (AKIN) score of 1–3; SD = standard deviation; IQR = interquartile range; ARB = angiotensin II receptor blocker; ACEI = angiotensin converting enzyme inhibitor; APACHE = Acute Physiology and Chronic Health Evaluation.

association with the risk of AKI: age, APACHE II score, cumulative fluid balance in the first 24 h, inhalational injury (yes/no), pre-existing hypertension (yes/no), use of vasoactive agents in the first 24 h and TBSA. In order to assess the best functional form of continuous covariates (age, APACHE II, cumulative fluid balance, TBSA), we initially performed fractional polynomial logistic regression. Fractional polynomial regression allows the fitting of non-linear continuous variables. This demonstrated that all of these covariates, except for TBSA, could be included as linear covariates in the final multivariable logistic model. The best functional form for TBSA was the natural logarithm, which was included in the final multivariable logistic regression model. Finally, we assessed for multicolinearity by calculating the variance inflation factor for all predictor variables in the final multivariable model. The variance inflation factor for all variables was under 1.6 indicating an absence of multicolinearity.

3. Results

Database search revealed 152 patients. We excluded one patient who died within 4 h of ICU admission following the decision to withdrawal life-sustaining therapy. Baseline characteristics of the cohort are presented in Table 1. Overall, the cohort had a mean age of 48 (SD 16) years and 117 of 151 (77%) were male. The median TBSA was 20% (IQR 9–41) and inhalational injury occurred in 67 patients (44%). The population of the catchment area was 4.59 million persons in 2013, leading to an incidence of 5.64 major burns/1,000,000 people per year. 72.4% of patients underwent surgery for their burn injury.

During the first 21 days of admission, 64 of 151 (42%) of patients developed AKI by AKIN criteria with the following stages: AKIN stage 1 (33 of 151 (22%)), AKIN stage 2 (11 of 151 (7%)) and AKIN stage 3 (20 of 151 (13%)). Daily serum creatinine concentrations for patients who developed AKI, developed AKI and required RRT and who did not develop AKI are presented in Fig. 1. Overall, CVVHDF was used in 18 of 64 (28%) of patients who developed AKI. CVVHDF was used for a median of 9 (IQR 4–15]) days. Of these 18 patients who required CVVHDF, 9 (50%) subsequently required intermittent hemodialysis for a median number of sessions of 3 (IQR 1–6). There were no patients who were on intermitted hemodialysis at hospital discharge. The creatinine levels over time for the AKI, AKI with RRT, and non-AKI groups are shown in Fig. 1.

Clinical outcomes are presented in Table 2. Patients who developed AKI had more days of mechanical ventilation, intensive care and hospitalization when compared to those patients who did not develop AKI. Mortality was higher in patients with AKI (14 of 64 (22%)) compared to those who did not develop AKI (4 of 87 (5%)). Mortality in patients with AKI who required RRT was 39% (7 of 18) vs 15% (7 of 46) in those with AKI who did not require RRT.

Univariable and multivariable logistic regression models are presented in Table 3. On the final multivariable logistic regression, Age (OR 1.8 per 10-year increase (95%CI: 1.2–2.5, p = 0.002), and APACHE II score (OR 1.2 per 1 unit increase (95% CI: 1.1–1.3, p = 0.001), independently associated with the risk of developing AKI. Although both the use of vasoactive agents and cumulative fluid balance in the first 24 h were significant

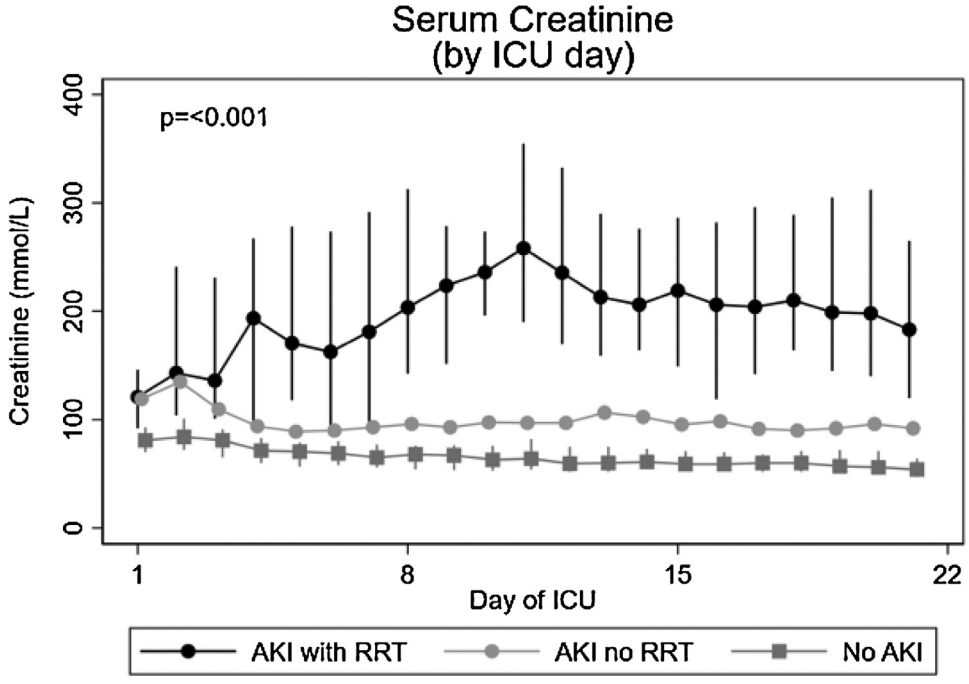

Fig. 1 – Serum creatinine concentration by day of ICU stratified by acute kidney injury [AKI] with renal replacement therapy [RRT], AKI without RRT and no AKI. Point estimates are medians and lines are interquartile ranges. Generalized linear regression demonstrated that at least one of the stratum of serum creatinine concentrations differeed from the others [$p < 0.0001$].

Table 2 – Clinical interventions and outcomes stratified by AKI.

	Total cohort (N = 151)	AKI (N = 64)	No-AKI (N = 87)	P value
Administration of vasopressors, n(%)	81 (54)	44 (69)	37 (43)	0.0020
Days of vasopressors, median (IQR)	2 (0-6)	6 (2-12)	0 (0-3)	<0.0001
Days to first burn surgery, median (IQR)	5 (3-8)	6 (3 – 8)	5 (3-8)	0.95
Mechanical ventilation, n(%)	146 (97)	63 (98)	83 (95)	0.40
Days of mechanical ventilation, median (IQR)	6 (3-13)	11 (6-19)	4 (2-9)	<0.0001
Days of intensive care, median (IQR)	8 (4-17)	15 (9-22)	6 (3-10)	<0.0001
Days of hospitalization, median (IQR)	25 (12-45)	43 (22-63)	19 (9-34)	<0.0001
Death in intensive care, n(%)	16 (11)	13 (20)	3 (3)	0.0010
Death in hospital, n(%)	18 (12)	14 (22)	4 (5)	0.0020

AKI = acute kidney injury, AKIN = Acute Kidney Injury Network; SD = standard deviation; IQR = interquartile range.

Table 3 – Univariable and multivariable logistic regression for the development of AKI as defined by AKIN stage 1-3. Note that multiple fractional polynomial regression modeling was used to ensure that continuous variables were expressed in the best functional form which was as a linear in the log-dds for age, APACHE and cumulative fluid balance in the first 24 h. TBSA was best expressed as a ln(tbsa) (i.e. fractional polynomial of 0). However, to best interpret the effect of TBSA on the risk of AKI, we also inserted TBSA in quartiles as an indicator variable in the final model.

$$log\frac{p_x}{1-p_x}) = \beta_0 + \beta_1 age10 + \beta_2 apache2 + \beta_3 \ln(tbsa) + \beta_4 fluid\,balance + \beta_5 inhalational + \beta_6 vasopressor + \beta_7 htn$$

Predictor variable	Unadjusted			Adjusted		
	OR	95% CI	P-value	OR	95% CI	P-value
Age per 10 year increase	1.3	1.1–1.7	0.008	1.8	1.2–2.5	0.002
APACHE II score per 1 unit increase	1.2	1.1–1.3	<0.0001	1.2	1.1–1.3	0.001
Cumulative fluid balance in first 24 hours per 1 l increase	1.1	1.0–1.2	0.007	1.1	0.97–1.1	0.22
Inhalational injury (yes/no)	1.5	0.78–2.9	0.22	1.8	0.75–4.4	0.19
Preexisting hypertension (yes/no)	2.1	0.88–5.2	0.093	1.1	0.32–3.7	0.91
Vasoactive agents (yes/no)	3.0	1.5–5.9	0.002	0.87	0.33–2.3	0.78
Log(TBSA)	1.03	1.01–1.05	<0.0001	2.7	1.5–4.7	0.001

OR = odds ratio; CI = 95% confidence interval.

on univariable analysis, the significant effects did not persist in the final multivariable model. Fractional polynomial regression demonstrates that the best functional form of TBSA was in the natural logarithm. Log(TBSA) was significant in both the univariable and multivariable model (OR 2.7, 95%CI: 1.5–4.7, p = 0.001). The probability of AKI by TBSA is presented in Fig. 2.

4. Discussion

In this historical cohort study of patients admitted to the ICU with a major burn, a significant number of patients developed AKI as defined by AKIN criteria. Increasing age, higher APACHE II score, and a greater TBSA were all associated with a greater likelihood of developing AKI. This is logical in that patients with more co-morbidity, less physiologic reserve, or a larger magnitude of injury are more likely to develop organ failure. Patients who developed AKI had a longer duration of mechanical ventilation, intensive care and hospitalizations. Patients who developed AKI had a higher risk of mortality compared to those who did not. The risk of mortality was highest in those patients who required RRT — again a logical finding that patients who experience significant enough renal

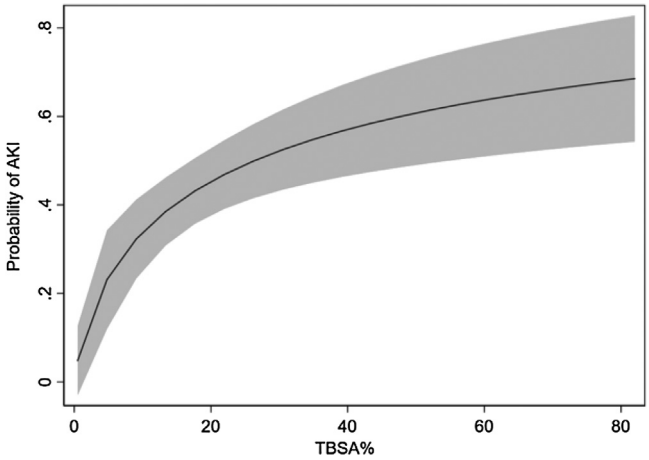

Fig. 2 – Margins plot of the probability of acute kidney injury [AKI] by total body surface area [TBSA]. The line represents the predicted probabilities for AKI by TBSA using the final multiariable model where TBSA was inserted following log-transformation. The shaded area is the 95% confidence interval of the prediction.

damage to require RRT are at a higher likelihood of succumbing to multi-organ failure.

Previous observational studies and meta-analysis have attempted to identify the risk factors for developing AKI in patients admitted with a major burn injury [3,4,14,18]. A recent meta-analysis showed that the overall risk of AKI for burn patients in the 18 studies included in their meta-analysis was 40% [2], remarkably similar to the 42% demonstrated in our study. They found similar risk factors for the development of AKI as seen in our study, including: age, TBSA, and APACHE II score. Although not consistent across all studies included in their meta-analysis, they reported both inhalational injury and etiology of burn as risk factors for development of AKI. These two factors were not associated with AKI in our study. Overall, in the 11 studies included in the meta-analysis examined mortality, death occurred in 341 of 1116 (31%) of patients with AKI (range 21–72%). Mortality in our cohort was 22%. There were a small number of patients in our cohort with TBSA $<$ 10%, who were intubated and admitted to ICU because of significant inhalational injury.

Coca et al. attempted to identify demographic and clinical risk factors associated with both the development of AKI and the risk of mortality [18]. In their study, 81 of 304 (27%) of patients developed AKI as defined by RIFLE. In contrast to our study, TBSA was not associated with AKI in their final multivariable model. In addition, they demonstrated that inhalational injury, catheter infection, and sepsis were all associated with an increased risk of developing AKI. However, catheter infections and sepsis are downstream variables to the initial burn injury, inferring that the burn injury readily leads to AKI through sepsis. Including these intermediate variables (e.g. sepsis) in a regression model does not allow for correct estimates of predictor variables [25]. Therefore, by including sepsis and catheter infection, any possible effect of TBSA may have been mitigated. Concordant with our results, those patients who developed AKI in the study by Coca were at higher risk of mortality. Although the risk of AKI was higher in our cohort (42% vs. 27%), the risk of mortality was lower in those in patients with AKI requiring RRT (39% vs 73%). Our model additionally demonstrated that APACHE II score, cumulative fluid balance and use of vasoactive agents in first 24 h were significant predictors of mortality.

Palmieri and colleagues performed a historical cohort study of 60 adult patients admitted to a burn ICU with a TBSA $>$ 20% [26]. Using RIFLE criteria, 32 of 60 (53%) of patients developed AKI. In their cohort, 11 of 32 patients with AKI died compared to none without AKI. They performed a multivariable regression model attempting to identify predictor of mortality. However, with only 11 outcome events (deaths), their multivariable model is grossly over fitted. It is a generally accepted number of events per covariate to ensure stability around the final point estimates is 10 [27]. Thus, rather than the 7 covariates included, they should have included only one regression parameter. This instability is apparent with the wide confidence intervals around the regression parameters. As such, any inference with their multivariable results is problematic. The population in our study differs from Palmieri in that our patients had approximately 10% lower TBSA, but were older and sicker ay initial presentation by APACHE II score. Although our population had fewer overall days of mechanical ventilation and ICU, this may reflect differences in practice. In contrast, our mortality was lower in those patients who developed AKI (22 vs. 34%), although direct comparison in outcomes is challenging due to differences in patient cohort.

As with all historical cohort studies, there are several limitations that need to be addressed. First, as the baseline creatinine was not available for many of the patients we estimated patient's serum creatinine from an assumed eGFR using the MDRD equation (back-estimation). In general critical care patients, this formula may lead to an over-estimate of AKI, particularly in patients with chronic kidney disease [28]. Given the age distribution of patients and relative lack of co-morbidities, it is likely that the majority of patients did not have chronic kidney disease. Second, as with many ICU studies examining AKI, we only used the change in serum creatinine criteria for AKIN, rather than the urine output criteria. Using the serum creatinine criteria alone may miss some cases of AKI [29]. Third, we only have 67 patients who developed AKI which limits our ability to adjust for additional potential confounders. As with all historical cohort studies, unmeasured or residual confounding may be an alternate explanation for our results. Fourth, initiation of RRT was at the discretion of the attending physician and not based on prespecified criteria. As such, the use of RRT is subject to confounding by severity whereby RRT may have been used in less severely ill patients when compared to previous studies. Finally, generalizability is limited to ICUs with similar patient and care profiles.

In conclusion, AKI in major burn patients continues to be a major complication, contributing to prolonged hospital stays and increasing morbidity and mortality. Although the number of patients requiring RRT was small, the mortality in this group is not as high as previously reported.

Conflict of interest statement

No conflict of interests.

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REFERENCES

[1] Brusselaers N, Monstrey S, Colpaert K, Decruyenaere J, Blot SI, Hoste EA. Outcome of acute kidney injury in severe burns: a

systematic review and meta-analysis. Intensive Care Med 2010;36(June (6)):915–25.
[2] Wu G, Xiao Y, Wang C, Hong X, Sun Y, Ma B, et al. Risk factors for acute kidney injury in patients with burn injury: a meta-analysis and systematic review. J Burn Care 2017;38(October (5)):271–82.
[3] Stewart IJ, Sosnov JA, Howard JT, Chung KK. Acute kidney injury in critically injured combat veterans: a retrospective cohort study. Am J Kidney Dis 2016;68(October (4)):564–70.
[4] Heegard KD, Stewart IJ, Cap AP, Sosnov JA, Kwan HK, Glass KR, et al. Early acute kidney injury in military casualties. J Trauma Acute Care Surg 2015;78(May (5)):988–93.
[5] Colpaert K, Hoste EA. Acute kidney injury in burns: a story of volume and inflammation. Crit Care 2008;12(6):1.
[6] Ibrahim AE, Sarhane KA, Fagan SP, Goverman J. Renal dysfunction in burns: a review. Ann Burns Fire Disasters 2013;26(1):16–25.
[7] Helanterä I, Koljonen V, Finne P, Tukiainen E, Gissler M. The risk for end-stage renal disease is increased after burn. Burns 2016;42(March (2)):316–21.
[8] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13(October (10)):818–29.
[9] Vandenbroucke JP, von Elm E, Altman DG, Gøtzsche PC, Mulrow CD, Pocock SJ, et al. STROBE initiative. Strengthening the reporting of observational studies in epidemiology [STROBE]: explanation and elaboration. Epidemiol Camb Mass 2007;18(November (6)):805–35.
[10] Case J, Khan S, Khalid R, Khan A. Epidemiology of acute kidney injury in the intensive care unit. Crit Care Res Pract 2013;2013:479730.
[11] Zimmerman JE, Kramer AA, Knaus WA. Changes in hospital mortality for United States intensive care unit admissions from 1988 to 2012. Crit Care 2013;17(2):R81.
[12] Kamolz L-P. Burns: learning from the past in order to be fit for the future. Crit Care Lond Engl 2010;14(1):106.
[13] Mustonen K-M, Vuola J. Acute renal failure in intensive care burn patients [ARF in burn patients]. J Burn Care Res 2008;29 (February (1)):227–37.
[14] Stewart IJ, Tilley MA, Cotant CL, Aden JK, Gisler C, Kwan HK, et al. Association of AKI with adverse outcomes in burned military casualties. Clin J Am Soc Nephrol 2012;7(February (2)):199–206.
[15] Soltani A, Karsidag S, Garner W. A ten-year experience with hemodialysis in burn patients at Los Angeles County + USC Medical Center. J Burn Care Res 2009;30(September (5)):832–5.
[16] Chung KK, Juncos LA, Wolf SE, Mann EE, Renz EM, White CE, et al. Continuous renal replacement therapy improves survival in severely burned military casualties with acute kidney injury. J Trauma Inj Infect Crit Care 2008;64(February (Supplement)):S179–87.
[17] Chung KK, Lundy JB, Matson JR, Renz EM, White CE, King BT, et al. Continuous venovenous hemofiltration in severely burned patients with acute kidney injury: a cohort study. Crit Care 2009;13(3):1.
[18] Coca SG, Bauling P, Schifftner T, Howard CS, Teitelbaum I, Parikh CR. Contribution of acute kidney injury toward morbidity and mortality in burns: a contemporary analysis. Am J Kidney Dis 2007;49(April (4)):517–23.
[19] Mosier MJ, Pham TN, Klein MB, Gibran NS, Arnoldo BD, Gamelli RL, et al. Early acute kidney injury predicts progressive renal dysfunction and higher mortality in severely burned adults. J Burn Care Res 2010;31(January (1)):83–92.
[20] Wenner JB, Norena M, Khan N, Palepu A, Ayas NT, Wong H, et al. Reliability of intensive care unit admitting and comorbid diagnoses, race, elements of Acute Physiology and Chronic Health Evaluation II score, and predicted probability of mortality in an electronic intensive care unit database. J Crit Care 2009;24(September (3)):401–7.
[21] Bellomo R, Ronco C, Kellum JA, Mehta RL, Palevsky P. Acute Dialysis Quality Initiative workgroup. Acute renal failure — definition, outcome measures, animal models, fluid therapy and information technology needs: the Second International Consensus Conference of the Acute Dialysis quality Initiative [ADQI] Group. Crit Care Lond Engl 2004;8(August (4)):R204–12.
[22] Lopes JA, Jorge S. The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review. Clin Kidney J 2013;6(February (1)):8–14.
[23] Chung KK, Stewart IJ, Gisler C, Simmons JW, Aden JK, Tilley MA, et al. The acute kidney injury network [AKIN] criteria applied in burns. J Burn Care Res 2012;33(4):483–90.
[24] Vittinghoff E, McCulloch CE. Relaxing the rule of ten events per variable in logistic and Cox regression. Am J Epidemiol 2007;165(March (6)):710–8.
[25] Schisterman EF, Cole SR, Platt RW. Over adjustment bias and unnecessary adjustment in epidemiologic studies. Epidemiol Camb Mass 2009;20(July (4)):488–95.
[26] Palmieri T, Lavrentieva A, Greenhalgh DG. Acute kidney injury in critically ill burn patients. Risk factors, progression and impact on mortality. Burns 2010;36(March (2)):205–11.
[27] Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. J Clin Epidemiol 1996;49 (December (12)):1373–9.
[28] Pickering JW, Endre ZH. Back-calculating baseline creatinine with MDRD misclassifies acute kidney injury in the intensive care unit. Clin J Am Soc Nephrol 2010;5(July (7):1165–73.
[29] Macedo E, Malhotra R, Claure-Del Granado R, Fedullo P, Mehta RL. Defining urine output criterion for acute kidney injury in critically ill patients. Nephrol Dial Transplant 2011;26 (February (2)):509–15.