ORIGINAL ARTICLE

Risk Factors and Outcomes of Post-traumatic Acute Kidney Injury requiring Renal Replacement Therapy: A Case–Control Study

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Abstract

Background: Acute kidney injury (AKI) following severe trauma is common. However, the requirement of renal replacement therapy (RRT) in these patients is rare and is associated with high morbidity and mortality. The primary objective of this study was to the identify odds of risk factors, in particular, hypotension at presentation, for the requirement of RRT in patients with AKI following trauma.

Methods: We performed a case–control study involving patients who were admitted to the intensive care unit (ICU) at a level I trauma center for at least 24 hours. The primary outcome measure was a study of the odds of risk factors associated with the requirement of RRT in such patients. Univariate comparisons and multiple logistic regression analyses were done to identify other risk factors.

Results: The presence of crush injury, sepsis, and elevated serum creatinine (sCr) on arrival were identified to be independent risk factors for RRT requirement. Hypotension and exposure to radiocontrast or nephrotoxic antimicrobials were not found to be associated with the need for RRT. Acute kidney injury requiring RRT was associated with significantly increased ICU length of stay (15 days vs 5 days; $p < 0.001$) and higher mortality (83% vs 35%; $p < 0.001$).

Conclusion: The presence of crush injury, sepsis, and elevated sCr on presentation were identified to be independent risk factors while hypotension association was insignificant for AKI requiring RRT in our investigation.

Keywords: Acute kidney injury, Crush syndrome, Hemorrhagic shock, Renal replacement therapy, Trauma.

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Highlights

Acute kidney injury is common following severe trauma but not all patients with AKI require RRT. However, patients requiring it have high morbidity and mortality. Therefore, we did this study to identify risk factors, in particular, hypotension at presentation to the emergency department (ED) for the requirement of RRT and its effect on outcome following severe trauma.

Introduction

Trauma is one of the leading causes of mortality worldwide, accounting for 5 million deaths annually and its incidence continues to rise.[1] The three most common causes of death following trauma include uncontrolled hemorrhage, traumatic brain injury, and multiple organ failure.[2] Acute kidney injury following trauma is one of the most common organ dysfunctions with different studies reporting its incidence from 15% to 50%.[3]

Renal dysfunction in patients following severe trauma is a distinct disorder that differs from AKI in the general ICU population. In a recent multinational epidemiological study conducted in a mixed adult ICU population, the incidence of AKI according to Kidney Disease Improving Global Outcome (KDIGO) criteria was reported to be 57% with 13% of them requiring RRT and worse renal recovery among survivors.[4] In contrast, a pooled analysis of studies investigating post-traumatic AKI reported an average incidence of AKI at 24% with 2% needing RRT and most of the patients recovering well after AKI.[5] However, the initiation of RRT in patients following severe trauma markedly changes their course of illness, classifying them directly into class 3 of AKI Network (AKIN)[6] and KDIGO criteria[7] and is independently associated with markedly increased ICU length of stay and mortality.[3,5,8]

Multiple risk factors have been implicated in the development of AKI in patients following trauma that include age, hemorrhagic shock, rhabdomyolysis, presence of comorbidities, the severity of the injury, multiorgan failure, comorbidities such as diabetes as well as factors related to patient care such as exposure to radiocontrast agents, nephrotoxic drugs, and use of colloids.[3,8–16] However,

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contrary to common thought, hypotension on presentation to the ED has inconsistently shown to be a risk factor in previous studies.[3,8,16,17]

The objective of the study is to identify risk factors associated with the development of AKI requiring RRT in patients following trauma and evaluate the role of hypotension at presentation in the development of AKI needing RRT.

Methods

Setting and Participants

This retrospective case–control study was conducted at Jai Prakash Narayan Apex Trauma Center, All India Institute of Medical Sciences, New Delhi, India. The study population consisted of trauma patients in the hospital requiring admission in the Trauma ICU or step-down unit for at least 24 hours following initial presentation or via the operating rooms after interventional surgery. Inclusion criteria consisted of patients of age 18–65 years, admitted between January 2017 and December 2018. Information was retrieved from the electronic medical record database (VistA CPRS 1.0.26.76) of the concerned subjects. Data were collected until hospital discharge or death, whichever occurred first. To minimize selection bias, the study was done by two separate data collectors, one responsible for recruiting cases and controls and the other for retrieval of data from the ED.

Cases were defined as adult patients undergoing RRT following polytrauma and were recruited from the ICU registry maintained prospectively with the index date being the first date of RRT initiation. Patients with a known history of chronic kidney disease or prior RRT before admission to the ICU were excluded. Eligible controls were the post-trauma patients admitted to the ICU during the same time period who did not require RRT. Cases or controls were excluded from the analysis if their exposure status information was unavailable.

Variables

The main exposure variable was the occurrence of hypotension following trauma which was defined as the first episode of systolic blood pressure (SBP) less than 90 mm Hg, noted either on arrival to the ED or preceding RRT. Duration of hypotension was defined as the approximate time (minutes) the patient remained hypotensive with SBP less than 90 mm Hg with or without vasopressors, noted from the nursing vital chart. The severity of hypotension was defined as the nadir SBP recorded during the hypotensive episode (SBP0). Sepsis was defined as documented sepsis or septic shock in physician–patient notes along with microbiology culture evidence, preceding the initiation of RRT. Crush injury was defined as the presence of degloving injury, history of compartment syndrome, or partial or total amputation documented in the patient record. Other variables measured on a binary scale included administration of intravenous contrast for enhanced computed tomography or trans-catheter angioembolization procedure, and use of nephrotoxic antimicrobials such as colistin, aminoglycosides, or vancomycin. Variables measured on a continuous scale included injury severity score (ISS), acute physiology and chronic health evaluation (APACHE) II score at the time of ICU admission, the time duration from injury to arrival at the ED in hours, time duration from arrival to RRT initiation in days and baseline creatinine measured within six hours of presentation.

Statistical Analysis

The sample size calculation was derived from the hypothesized association of hypotension with AKI requiring RRT. With the assumptions of alpha error of 5%, power of 80%, case–control ratio 1:1, minimal detectable risk (odds ratio) of 3.0, and prevalence of hypotension in trauma patients to be around 25% based upon institutional trauma audit, a sample size of 60 patients in each group of cases and controls, respectively, was estimated. Data were presented as mean with standard deviation (SD) or median with interquartile range (IQR). Categorical variables were compared using Pearson χ^2 test and continuous variables were compared with the Student's test. Non-parametric data were compared using Mann–Whitney *U* test. Analyses of potential risk factors for AKI requiring RRT were performed using conditional multiple logistic regression and were adjusted for confounding and effect modification. Data are presented as odds ratios with corresponding 95% confidence intervals. All data analysis was performed in R v3.3.3 (R Foundation for Statistical Computing, Vienna, Austria) using RStudio v1.0.136 (RStudio Inc, Boston, MA, USA).

Ethical Approval

The institutional ethics committee approval was taken prior to the conduct of the study. Patient consent was not obtained since the study was retrospective and involved retrieval of data from ICU-based registry and electronic health records with no direct patient contact.

Results

After exclusions, 59 patients who underwent RRT during their ICU stay were included whereas, for the control group, 57 patients were included.

The median age of the patient population in both groups was 38 years and consisted mostly of men (92%) involved in road traffic accidents, predominantly sustaining blunt trauma injury. The median (IQR) time interval from ICU admission to RRT was 4 (2.5–8) days. On univariate analysis of patients in both groups; the number of patients with crush injury and sepsis was significantly higher in the RRT group. Baseline creatinine was found to be significantly higher in the RRT group. The median length of ICU stays (15 vs 5 days, $p < 0.001$) and mortality (49% vs 20%, $p < 0.001$) was significant in the RRT group compared to the control group (Table 1).

Multiple logistic regression analysis for independent risk factors for RRT requirement showed the presence of crush injury, elevated baseline creatinine, and sepsis to be associated with the need for RRT (Table 2). Hypotension and severity of hypotension denoted with SBP on arrival were not found to be associated with AKI requiring RRT.

Discussion

Main Findings

The median age of patients was 38 years consisting mostly of males in good health, involved in road traffic accidents, and sustaining predominantly blunt trauma. The baseline population characteristics correlated well with that of previous studies.[15–17] Presence of crush injury, elevated baseline creatinine, and sepsis were identified to be independent risk factors for the need of RRT. We did not find hypotension to be a risk factor for the RRT requirement. A possible explanation for our finding could be that

Table 1: Baseline characteristics and outcomes for patients requiring RRT vs no RRT

	RRT (n = 59)	*No RRT (n = 57)*	*p-value*
Age (years), median (IQR)	38 (27–48)	38 (28–49)	0.95
Gender: Male (%)	57 (96)	50 (88)	0.09
Mechanism of injury, *n* (%)			0.48
Traffic related	43 (73)	40 (70)	
Fall	12 (20)	9 (18)	
Assault	3 (5)	4 (7)	
Others	1 (2)	4 (7)	
Blunt trauma, *n* (%)	56 (95)	51 (90)	0.45
ISS, median (IQR)	25 (9–34)	16 (9–25)	0.39
APACHE II score, mean ± SD	20 ± 7.8	19 ± 6.2	0.57
Hypotension, *n* (%)	25 (42)	17 (30)	0.16
Duration of Hypotension (minutes)	60 (30–60)	45 (30–60)	0.28
Injury to ED arrival time (hours)	4 (1.1–5)	3 (2–3)	0.179
Baseline sCr median (IQR), mg dL^{-1}	1.5 (0.9–12.5)	0.8 (0.58–1.2)	<0.001
Crush injury, *n* (%)	19 (28%)	8 (8%)	0.021
Use of radiocontrast, *n* (%)	45 (76%)	40 (70%)	0.53
Nephrotoxic drugs, *n* (%)	19 (33%)	15 (26%)	0.525
Sepsis, *n* (%)	38 (64%)	24 (43%)	0.016
Mortality	49 (83%)	20 (35%)	<0.001

Categorical data are presented as number (%); Continuous data presented as median (interquartile range) or mean ± standard deviation. APACHE II, acute physiology and chronic health evaluation score; ED, emergency department; ICU, intensive care unit; ISS, injury severity score; LOS, length of stay; RRT, renal replacement therapy; sCr, serum creatinine

Table 2: Univariate and conditional multivariate logistic regression for risk of requiring RRT

	Univariate OR (95% CI)	*p-value*	*Multivariate OR (95% CI)*	*p-value*
Hypotension	1.73 (0.8–3.73)	0.16	2.26 (0.441–11.60)	0.32
SBP0	0.99 (0.97–1.01)	0.26	1.01 (0.97–1.04)	0.68
Sepsis	2.49 (1.18–5.26)	0.02	3.20 (1.13–9.10)	0.029
Crush injury	2.91 (1.15–7.34)	0.02	3.77 (1.26–11.30)	0.017
Baseline creatinine	2.66 (1.52–4.66)	<0.001	2.70 (1.53–4.76)	0.006
Nephrotoxic drugs	1.30 (0.58–2.90)	0.53	1.06 (0.34–3.27)	0.92

CI, confidence interval; OR, odds ratio; SBP0, systolic blood pressure during hypotension episode

after the presentation to ED, hypotension was rapidly corrected, thereby preventing renal ischemia and associated sequelae. Similarly, the severity or duration of hypotension was not found to be associated with the requirement of RRT, although restrictions apply to these findings since we lacked the pre-hospital data in our patients, which could have offered a better insight into their hemodynamic status before arrival to ED. The results from our study showed that an elevated sCr measured within 6 hours of the presentation was strongly associated with AKI requiring RRT, consistent with the findings of the previous studies[9,11,14,18] It has been argued that the sCr measured early (<24 hours after presentation) may lead to over-estimation of AKI because of ongoing catabolic stress and dehydration while a later measurement of sCr may lead to under-estimation of AKI secondary to the dilution effect from fluid resuscitation and could also be confounded with sepsis, radiocontrast and other nephrotoxic drugs coming into effect after ICU admission.[3] However, our findings suggest that an elevated sCr following trauma may be an early sign of severe kidney dysfunction progressing to require RRT and should not be ignored.

The current study also found the presence of crush injury to be an independent risk factor for the development of AKI requiring RRT, which, is consistent with findings of previous studies.[18–21] Although we could not ascertain the presence of rhabdomyolysis with laboratory evidence in our patients, definition criteria consisting of partial or total amputation, degloving injuries, and compartment syndrome served as surrogate marker for rhabdomyolysis. Sepsis has been found to be associated with post-traumatic AKI in multiple studies, well in agreement with the finding of our study.[5]

We did not find an association of RRT with the use of radiocontrast since almost all the patients in both groups underwent contrast-enhanced computed tomography. Nephrotoxic antimicrobials such as vancomycin, colistin, and aminoglycosides are commonly implicated in the development of AKI. However, they were not found to be risk factors associated with AKI requiring RRT, presumably because of the general protocol followed in the ICU to avoid nephrotoxic drugs whenever possible. The significance of the above findings is exploratory in nature and needs further robust research to establish causality.

Strengths and Limitations

The notable limitations of our study include limited sample size given the relative infrequency of RRT in trauma patients and single-center design limiting the generalizability of the study. Nevertheless, our study cohort was largely similar to those described in previous studies. Moreover, a complete dataset for studied exposure variables with minimal loss of data and a regression model adjusted for known confounders adds to the strength of this study. Indications for RRT mostly included fluid overload, rising blood urea and creatinine, decreased urine output, or refractory hyperkalemia and the patients were administered on instructions from critical care attending physicians and nephrologist. The sole RRT modality used in our ICU was sustained low-efficiency dialysis (Fresenius Kabi AG, Bad Homburg, Germany) with dosing individualized according to each patient's need. The decision for RRT was taken by the attending physicians which could have been variable in the terms of individual threshold and may have affected the timing for RRT in cases, which, however, is of limited significance since the timing of initiation of RRT does not seem to change the mortality outcome.[22–24] We could not retrieve other known exposure variables associated with AKI following trauma such as units of blood transfused, serum lactate, and serum phosphate in our patients.

The aim of the study was to evaluate specific associations between the presumed risk factors and AKI requiring RRT. We did not report discrimination and calibration of the model and other related statistics since our aim was not to develop a prediction model.

Conclusion

In conclusion, post-traumatic AKI is multifactorial. The presence of crush injury, elevated sCr at presentation and sepsis were identified to be independent risk factors for RRT requirement, while it did not hold true for hypotension on arrival, exposure to nephrotoxic agents, or radiocontrast exposure.

Strobe Statement

The manuscript has been prepared and revised according to the STROBE statement – a checklist of items.

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