Acute kidney injury following severe trauma: Risk factors and long-term outcome

Mikael Eriksson, MD, Olof Brattström, MD, PhD, Johan Mårtensson, MD, PhD, Emma Larsson, MD, PhD, *and* **Anders Oldner, MD, PhD,** *Stockholm, Sweden*

BACKGROUND:	The trauma patient sustains numerous potentially harmful insults that may contribute to a notable risk of acute kidney injury (AKI). The aim of this study was to investigate the incidence of and to identify risk factors for AKI in severely injured trauma patients admitted to the intensive care unit (ICU). The patients were followed up for 1 year with respect to survival and end-stage renal disease.
METHODS:	Trauma patients admitted to the ICU for more than 24 hours at a Level I trauma center were included. The outcome measure was AKI diagnosed Days 2 to 7 of ICU treatment. Regression analysis was performed to identify factors associated with AKI development.
RESULTS:	A quarter of the patients (103 of 413) developed AKI within the first week of ICU admission. AKI was associated with increased 30-day (17.5% vs. 5.8%) and 1-year (26.2% vs. 7.1%) mortality. Risk factors for AKI were male sex, age, nondiabetic comorbidity, diabetes mellitus, Injury Severity Score (ISS) greater than 40, massive transfusion, and volume loading with hydroxyethyl starch (HES) within the first 24 hours. Unexpectedly, sepsis before AKI onset, admission hypotension, and extensive contrast loading (>150 mL) were not associated with AKI development. None of the surviving AKI patients had developed end-stage renal disease 1 year after injury.
CONCLUSION:	AKI in ICU-admitted trauma patients is a common complication with substantial mortality. Diabetes, male sex, and severe injury were strong risk factors, but age, nondiabetic comorbidity, massive transfusion, and resuscitation with HES were also associated with postinjury AKI. Based on the results of the current study, volume resuscitation with HES cannot be recommended in trauma patients. (*J Trauma Acute Care Surg*. 2015;79: 407–412. Copyright © 2015 Wolters Kluwer Health, Inc. All rights reserved.)
LEVEL OF EVIDENCE:	Prognostic study, level III; therapeutic study, level IV.
KEY WORDS:	Trauma; acute kidney injury; risk factors; epidemiology; long-term outcome.

Trauma is a global health concern with more than five million deaths annually attributed to injury.[1] For trauma patients surviving the initial phase, a number of complications may challenge further recovery. Acute kidney injury (AKI) is common in critically ill patients and strongly associated with poor outcome in general.[2,3] The trauma patient sustaining numerous potentially harmful insults has a notable risk of AKI. Direct lesions to the kidneys, shock, ischemia-reperfusion, rhabdomyolysis, exposure to nephrotoxic substances, abdominal compartment syndrome, and sepsis are all common findings in the severely injured. To what extent AKI contributes to postinjury morbidity and mortality is not fully elucidated. Considering the frequent occurrence of this complication and the number of severe trauma cases annually, it is reasonable to assume that postinjury AKI constitutes a significant health problem. Thus, further insight into factors associated with postinjury AKI is important and may facilitate future preventive strategies tailored to specific risk groups.

Until recently, the lack of a uniformly accepted definition of AKI has complicated research and comparison of studies. A new consensus definition merging the Risk, Injury, Failure, Loss, End stage (RIFLE) criteria and the Acute Kidney Injury Network (AKIN) definition, presented by the Kidney Disease Improving Global Outcomes (KDIGO) group, is now widely accepted (Table 1).[4]

The aim of this study was to identify risk factors for postinjury AKI in intensive care unit (ICU)–treated trauma patients. We used the new AKI definition in accordance with the consensus criteria. In the analysis, we included known and suspected risk factors also comprising exposure to hydroxyethyl starch (HES), radio contrast media, and pre-AKI sepsis. The patients were followed up for 1 year with respect to survival and end-stage renal disease.

PATIENTS AND METHODS

Setting

This retrospective cohort study of severely injured trauma patients was conducted at a mixed 13-bed ICU in a Level I trauma center at the Karolinska University Hospital, Solna, Sweden, which is the referral center for severe trauma

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From the Department of Anaesthesiology, Surgical Services and Intensive Care (M.E., O.B., E.L., A.O.), Karolinska University Hospital, Solna; and Section of Anaesthesiology and Intensive Care Medicine (M.E., O.B., J.M., E.L., A.O.), Department of Physiology and Pharmacology, Karolinska Institutet, Stockholm, Sweden; and Department of Intensive Care (J.M.), Austin Hospital, Melbourne, Victoria, Australia.

Address for reprints: Mikael Eriksson, MD, Department of Anaesthesiology, Surgical Services and Intensive Care Medicine, Karolinska University Hospital, Solna, SE-171 76 Stockholm, Sweden; email: mikael.eriksson@karolinska.se.

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cases for the entire Stockholm area, covering approximately two million inhabitants.

Data Collection and Study Population

The study cohort consisted of trauma patients admitted to the ICU following initial resuscitation and, where indicated, interventional surgery in the trauma unit. Patients 15 years or older with an expected ICU length of stay of more than 24 hours were included between February 2007 and September 2012. Patients with a known history of chronic kidney disease according to patient records or those deceased before Day 2 were not included. Prehospital and baseline data from the trauma unit were collected retrospectively from the trauma registry and patient records. To ensure quality, all data were verified twice. Data were collected until ICU discharge or death, which ever occurred first.

Comorbidity was defined by the presence of at least one International Classification of Diseases, 10th Revision, code included in the Charlson comorbidity index as adapted by Gabbe et al.[5] Diagnoses were retrieved from patient records. Injury severity was defined using the Injury Severity Score (ISS); data were taken from the hospital trauma registry using the Abbreviated Injury Scale (AIS) version 2005. Massive transfusion was defined as administration of 10 or more units of packed red blood cells in the first 24 hours. Shock upon arrival was defined as systolic arterial blood pressure (SAP) of less than 90 mm Hg. Sepsis was defined as probable or documented infection together with at least three systemic inflammatory response syndrome criteria.[6] Sepsis was defined as onset of sepsis up to the day of AKI diagnosis in the AKI group or sepsis within the first week in the non-AKI group. Organ failure was defined according to the Sequential Organ Failure Assessment (SOFA). A score of 3 or greater for any domain in 1 day or more during the ICU stay was considered organ failure. Multiple-organ failure (MOF) was defined as organ failure in two or more organs simultaneously during at least 1 day of ICU stay.

Outcome Measures

The outcome measure was AKI using the KDIGO creatinine or urine output criteria diagnosed between Day 2 and 7 of ICU treatment (Table 1). For baseline serum creatinine (sCr), we used the lowest value of either the measured sCr in the first 24 hours or estimated sCr calculated using the Modification of Diet in Renal Disease (MDRD) equation, as recommended by the Acute Dialysis Quality Initiative (ADQI) Group (assuming a lower normal glomerular filtration rate of 75 mL/min/1.73 m^2),[7] a concept in line with several previous studies.[3,8–10] The calendar day of arrival to the trauma unit was considered arrival day, and Day 1 the succeeding calendar day. Thus, Day 2 starts between 24 hours and 48 hours after admittance to the trauma unit. Long-term follow-up regarding survival and end-stage renal disease was retrieved from national health registries and patient charts by means of the Swedish personal identification number.[11]

TABLE 1. Staging of AKI According to KDIGO

Stage	sCr	Urine Output
1	1.5–1.9 times baseline	<0.5 mL/kg/h for 6–12 h
	OR	
	≥0.3 mg/dL (≥26.5 μmol/L) increase	
2	2.0–2.9 times baseline	<0.5 mL/kg/h for ≥12 h
3	3.0 times baseline	<0.3 mL/kg/h for ≥24 h
	OR	OR
	Increase in sCr to ≥4.0 mg/dL (≥353.6 μmol/L)	Anuria for ≥12 h
	OR	
	Initiation of renal replacement therapy	

Ethical Approval

The regional ethical review board in Stockholm approved the study. No patient consent was needed for a retrospective register and journal study according to the ethical approval

Statistical Analysis

Comparisons of continuous variables were performed using the Mann-Whitney U-test or Kruskal-Wallis test where appropriate; data were presented as median with interquartile ranges (IQRs). Categorical variables were compared using the Pearson χ^2 test. Analyses of potential risk factors for AKI were performed using univariate logistic regression. A priori selected variables in the model included sex, age, history of somatic comorbidity, presence of diabetes mellitus, ISS, massive transfusion, shock on arrival, resuscitation with HES 130/0.4 and other fluids, administration of iodinated radio contrast media, and sepsis during the time at risk. ISS, administration of HES, other fluids, and radio contrast media were categorized as depicted in tables. Statistically significant variables were carried forward to the multivariable model. Data are presented as odds ratios with corresponding 95% confidence intervals. A $p < 0.05$ was considered statistically significant. We also performed an interaction analysis of the effect of ISS and massive transfusion, admission SAP of less than 90 mm Hg, and administration of HES, respectively, as well as admission SAP of less than 90 mm Hg and massive transfusion; these interactions were tested by a likelihood ratio test. The performance of the logistic regression model was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Kaplan-Meier survival curves were plotted for 1-year postinjury survival for AKI and non-AKI patients. The log-rank test was used to examine the difference of survival curves between the groups. All data analysis was performed using IBM SPSS Statistics 21.0 (SPSS Statistics IBM, Armonk, NY).

RESULTS

Four-hundred twenty-two patients admitted to the ICU for more than 24 hours after trauma were included in the database. Four patients with a known history of chronic kidney disease and five patients who died before Day 2 were excluded, yielding 413 subjects in the final analysis. Baseline characteristics are shown in Table 2. The median age was 40 years, 78% were male, and the median ISS was 25. A vast majority, 89%, presented with blunt trauma and road traffic accidents were the most common mechanism of injury.

One hundred three patients (24.9%) developed AKI during the first week in the ICU. A majority (94%) was

TABLE 2. General Characteristics of the Patient Cohort

Age, median (IQR), y	40 (27–57)
Female/male, n (%)	91 (22.0)/322 (78.0)
History of somatic comorbidity, n (%)	75 (18.2)
Mechanism of injury, n (%)	
Traffic related	182 (44.1)
Fall	77 (18.6)
Assault	46 (11.1)
Self inflicted	65 (15.7)
Others	43 (10.4)
Blunt trauma, n (%)	368 (89.1)
Admission SAP < 90 mm Hg, n (%)	67 (16.2)
Admission GCS score, median (IQR)	13 (8–15)
Blood transfusions 24 h, median (IQR), U	2 (0–6.0)
Massive transfusion, n (%)	75 (18.2)
Fluid load 24 h, median (IQR), L	6.4 (4.5–9.7)
ISS, median (IQR)	25 (17–34)
Invasive mechanical ventilation, n (%)	295 (71.4)
ICU length of stay, median (IQR), d	4 (2–9)
Hospital length of stay, median (IQR), d	17 (10–33)
30-d postinjury mortality, n (%)	36 (8.7)
1-y postinjury mortality, n (%)	49 (11.9)

Continuous parameters are presented as median (IQR), and categorical parameters are presented as n (%). Admission refers to the admission to the trauma unit.
GCS, Glasgow Coma Scale.

diagnosed by increased creatinine and not oliguria only. Stages 1, 2, and 3 according to the KDIGO definition developed in 59%, 13%, and 28% respectively. Twenty-seven patients were treated with continuous renal replacement therapy; six of these were treated with occasional intermittent hemodialysis at the end of ICU stay. None of the survivors in the AKI group eligible (n = 76) were dialysis dependent 3 months or 1 year after trauma. Six patients were treated with intermittent hemodialysis for a short period after discharge from the ICU.

Characteristics of patients with and without AKI are shown in Table 3. Patients who developed AKI were more likely to be male, were older, and had more comorbidity. They were more severely injured and exhibited signs of physiologic derangement on admission to a greater extent. Patients with AKI had a higher 30-day and 1-year postinjury mortality compared with the non-AKI cohort (17.5% vs. 5.8% and 26.2% vs. 7.1%, respectively; Table 3, Fig. 1). All deceased Swedish residents are recorded in the cause-of-death register. The register includes data for cause and time of death and is updated yearly and linked to the patient charts. Thus, no patients were lost to follow-up.

In univariate logistic regression analysis, male sex, age, diabetes mellitus, nondiabetic somatic comorbidity, ISS greater than 40, massive transfusion, administration of HES, sepsis, and shock on arrival were all associated with AKI. In the multivariable regression analysis, all variables except sepsis and shock remained independent risk factors for AKI (Table 4, Fig. 2). Diabetes mellitus, male sex, and severe injury were strongly associated with AKI development. None of the interactions tested were statistically significant.

DISCUSSION

This is the first study to explore the incidence of AKI, as defined by the recently proposed KDIGO criteria, and its long-term consequences following severe trauma. In addition, our high-resolution database allowed us to identify a number of independent risk factors of AKI development in such trauma patients. A quarter of the patients developed AKI within the first week; 26% of these patients received continuous renal replacement therapy. The AKI group had a threefold increase in 30-day mortality, a difference that was slightly enhanced by 1 year. None of the surviving AKI patients had developed end-stage renal disease 1 year after injury. Diabetes mellitus and nondiabetic comorbidities, male sex, age, ISS greater than 40, massive transfusion, and fluid resuscitation with HES were independently associated with the development of postinjury AKI in the ICU, whereas sepsis was not. To our knowledge, this study is the first to show potential harm from administration of low-molecular HES in the trauma setting.

The baseline characteristics of the study cohort were consistent with numerous previous reports with a high incidence of blunt trauma, road traffic accidents, and a fairly young study cohort predominantly of male sex.[8–10,12–14] Although the incidence of AKI in our material is in line with several other studies, the incidence of postinjury AKI as defined by the KDIGO or RIFLE/AKIN criteria in the literature differs

TABLE 3. Baseline Characteristics and Clinical Outcome for Patients With and Without AKI

Group	Non-AKI	AKI	*p*
n (%)	310 (75.1)	103 (24.9)	
Age, median (IQR), y	36 (25–51)	54 (36–69)	0.000
Male, n (%)	233 (75.2)	89 (86.4)	0.017
Nondiabetic comorbidity, n (%)	31 (10.0)	24 (23.3)	0.001
Diabetes mellitus, n (%)	9 (2.9)	11 (10.7)	0.001
ISS, median (IQR)	24 (17–33)	29 (19–43)	0.000
ISS of 16–24, n (%)	107 (34.5)	22 (21.4)	
ISS of 25–40, n (%)	100 (32.3)	32 (31.1)	0.000
ISS > 40, n (%)	42 (13.5)	34 (33.0)	
Blunt trauma, n (%)	273 (88.1)	95 (92.2)	0.239
Admission SAP < 90 mm Hg, n (%)	40 (12.9)	27 (26.2)	0.002
Admission GCS score, median (IQR)	14 (8–15)	11 (7–15)	0.005
Massive transfusion, n (%)	39 (12.6)	36 (35.0)	0.000
Fluid load 24 h, median (IQR), L	5.8 (4.0–8.5)	8.6 (5.3–13.9)	0.005
HES, median (IQR), L	0.5 (0–1.0)	1.0 (0–1.5)	0.000
HES administered, n (%)	177 (57.1)	74 (71.8)	0.008
Intravenous contrast < Day 2, median (IQR), mL	100 (90–161)	120 (90–194)	0.029
Sepsis, n (%)	75 (24.2)	47 (45.6)	0.000
Renal replacement therapy, n (%)	0 (0.0)	27 (26.2)	0.000
MOF Day 2–7, n (%)	59 (19.0)	58 (56.3)	0.000
ICU length of stay, median (IQR), d	3.0 (2.0–6.0)	10.0 (4.3–17.0)	0.000
30-d postinjury mortality, n (%)	18 (5.8)	18 (17.5)	0.000
1-y postinjury mortality, n (%)	22 (7.1)	27 (26.2)	0.000

Continuous parameters are presented as median (IQR), and categorical parameters are presented n (%). Admission refers to the admission to the trauma unit.
GCS, Glasgow Coma Scale.

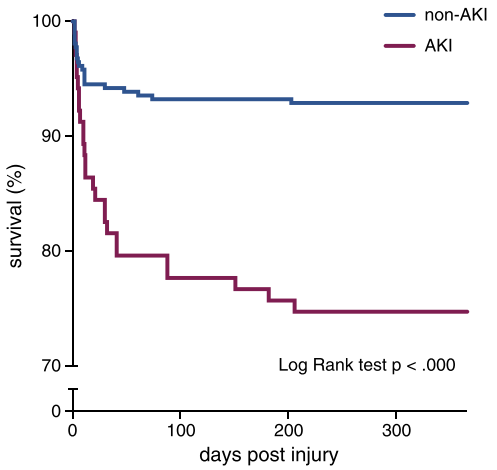

Figure 1. One-year postinjury survival. Kaplan-Meier curves displaying 1-year postinjury survival for AKI (n = 103, *red line*) and non-AKI patients (n = 310, *blue line*).

between 6% and 50%.[8–10,12–18] This wide range may to some extent be explained by variations in injury severity, age, mechanisms of injury, and other factors. Another important difference between studies is the timing of the AKI diagnosis. Some authors advocate that an early diagnose of AKI, up to 24 hours or 72 hours after admission, is preferable to avoid confounders such as sepsis, MOF, or nephrotoxic injury that might not be directly attributed to trauma.[8,14] In contrast, a very early AKI diagnosis may be hampered by creatinine release from muscle injury as suggested by Moore et al.[19] In contrast, several other studies classify AKI up to 28 days or anytime during the ICU stay.[9,10,12] The outcome measure used in the current study was AKI diagnosed between Days 2 and 7 of ICU treatment to reduce potential effects of muscle injury and possible underresuscitation. We also adjusted our model for sepsis as a potential confounder for later onset of AKI.

Age is a well-known risk factor for AKI, whereas less clear evidence exists regarding the influence of sex. Diverging results can be found in the literature. A large study from Australia and New Zealand showed that female sex was associated with higher odds of postinjury AKI within the first 24 hours of admission. In contrast and in analogy with the current study, Plurad et al. found male sex to be an independent risk factor.[8,20] In our study, the association between male sex and AKI was further strengthened in the multivariable analysis, (Table 4) an effect partly explained by the older age noted in the female cohort. One may speculate in methodological factors that promote male AKI diagnoses over female. Such factors could be that the MDRD equation renders a relatively lower sCr in men or that men increase their subsequent sCr for nonrenal reasons, such as rhabdomyolysis, to a larger extent than women. The difference between men and women concerning the use of Cr_{MDRD} as baseline sCr was modest (21% vs. 15%, respectively). Moreover, the MDRD-based method for assessment of baseline creatinine has been used in several studies including those focused on postinjury AKI. Male sex as a risk factor is not a systematic finding in these studies.[9,10,19] In fact, Bagshaw et al. noted the opposite: female sex was an independent risk factor for early postinjury AKI in their study using only MDRD-based baseline sCr, suggesting that the methodology used is a limited confounder in this regard.[8] Thus, it seems that male sex may be a risk factor when studying AKI in the period used in the current study as opposed to AKI during the first 24 hours as noted in the study mentioned earlier.

Comorbidities such as diabetes mellitus, cardiovascular disease, chronic liver disease, and cancer are known risk factors for the development of AKI in trauma as well as nontrauma patients, well in agreement with the current study.[8,13,21] We chose to classify the presence of somatic comorbidity by the Charlson index as adopted by Gabbe et al. Diabetes mellitus, a diagnosis frequently associated with trauma-related AKI, was analyzed as a separate entity.[5,13] A diagnosis of diabetes might indicate the presence of diabetic nephropathy, but there were no differences in first measured sCr between subjects with and without diabetes. Although old and not updated, the Charlson index of comorbidity includes the known risk factors stated earlier. We also performed an alternate

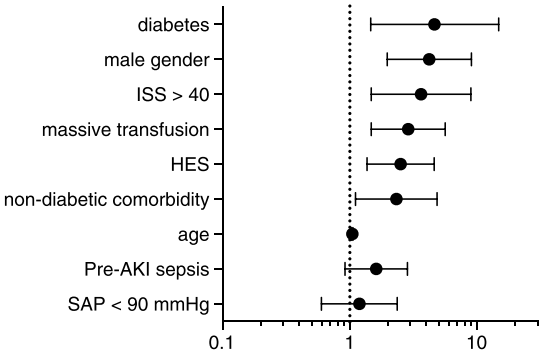

Figure 2. Multivariable model for AKI risk. Odds ratio and 95% confidence interval. Admission refers to the admission to the trauma unit.

TABLE 4. Univariate and Multivariable Model for AKI Risk

	Univariate	Multivariable	*p*
Male sex	2.10 (1.13–3.90)	4.23 (1.97–9.08)	0.000
Age	1.04 (1.02–1.05)	1.05 (1.03–1.06)	0.000
Nondiabetic comorbidity	2.73 (1.52–4.93)	2.33 (1.11–4.86)	0.025
Diabetes mellitus	4.00 (1.61–9.95)	4.65 (1.46–14.8)	0.009
ISS of 16–24	0.84 (0.40–1.73)	0.76 (0.32–1.77)	0.519
ISS of 25–40	1.30 (0.65–2.60)	1.15 (0.51–2.60)	0.737
ISS > 40	3.29 (1.60–6.79)	3.64 (1.48–8.99)	0.005
Massive transfusion	3.73 (2.21–6.32)	2.89 (1.48–5.65)	0.002
Admission SAP < 90 mm Hg	2.40 (1.38–4.16)	1.19 (0.60–2.37)	0.613
Received HES	1.92 (1.18–3.11)	2.52 (1.37–4.63)	0.003
>5-L intravenous fluids*	1.26 (0.80–1.98)		
Radio contrast > 150 mL intravenous	1.10 (0.68–1.80)		
Sepsis	2.63 (1.65–4.19)	1.62 (0.92–2.85)	0.092

*Transfused blood product and HES excluded.

Univariate and multivariable model for AKI risk, odds ratio and 95% confidence interval. Admission refers to the admission to the trauma unit.

multivariable model including all comorbidities noted in patient records as a variable without altered results.

Several studies have found an association between AKI and trauma severity, expressed as either ISS or physiologic derangements, for example, base excess or elevated lactate levels.[9,10,18,19] In our cohort, this effect was statistically significant only in the most severely injured subgroup with an ISS greater than 40. Less severe injury was not associated with AKI in the multivariable logistic regression.

Iodinated radio contrast has a well-known nephrotoxic potential and was thus included in the model.[10,18,22–24] Since 89% of all contrast doses were administered before Day 2 (94% of doses in the AKI group), this was the time frame chosen for the variable in the logistic regression analysis. Almost all patients received radio contrast, by dichotomizing into two categories (more or less than 150 mL); all patients given more than a single standard dose of contrast for enhanced computed tomography were included in the high-exposure group. There was no association between high exposure and postinjury AKI development, a finding in line with several recent reports.[18,23]

The association of blood transfusions and AKI in our cohort has also been noted elsewhere.[9,13] The need for massive transfusion of blood products might be a surrogate for increased injury severity and illness beyond that measured in scoring systems but may also have a causal relation. Stored blood products increase their free hemoglobin content over time with subsequent nitric oxide scavenging effects that may contribute to reduced renal blood flow and hemoglobin-induced tubular injury.[25] In this context, the release of free iron seems an important pathway catalyzing the production of free radicals, resulting in tubular stress.[26]

Hetastarches have been in the focus of several recent studies. It has been convincingly shown that these products are associated with AKI and adverse outcome in septic patients.[27–30] Recently, the US Food and Drug Administration recommended health professionals not to use HES in critically ill adults patients.[31] In perioperative and trauma settings, this association has been more difficult to demonstrate. A recent meta-analysis could not show any harmful effects from HES administration in surgical patients, and in a South-African single-center study, HES 130/0.4 was superior to saline in patients with penetrating trauma in terms of reducing AKI.[17,32] In contrast, older higher-molecular starches with higher-molar substitutions have been associated with postinjury AKI. Allen et al. recently showed that HES 450/0.7 was associated with AKI after blunt trauma, and this is consistent with previous findings.[33,34] In the current study, synthetic colloids were used as part of a resuscitation algorithm where clear fluids, crystalloid, or colloids, at the discretion of the physician, were administered before the start of blood transfusions. HES was used only in the trauma unit and not in the ICU during the study period. Sixty percent of the patients received HES; this treatment was independently associated with AKI development. These patients were slightly more injured and more commonly in shock, sepsis was more frequent, and they received more transfusions but had a lower proportion of comorbidity (data not shown). All these covariates were included in the final regression model, indicating that HES administration has a harmful effect on the kidney in this setting. To our knowledge, HES 130/0.4 has previously not been shown to be associated with AKI in trauma patients.

A very low rate of missing data and no loss to long-term follow-up strengthen the study. All Swedish citizens have a unique 12-digit personal identification number that facilitate identification on a patient-specific level in national registries. The Swedish registry of total population provides data on survival with a minimal loss to follow-up. Moreover, the study uses the latest AKI definition and a regression model adjusted for highly relevant confounders. Variables were retrieved with high resolution and a minimal data loss. Possible limitations are associated with the registry-based study design. Our study is a single-center study that can be considered to reduce the generalizability; nevertheless, the trauma cohort in this study is largely similar to those described in other studies. There was a dominance of male sex and a majority of younger patients, with a mean age of approximately 40 years and one third of the patients exhibiting some preexisting medical condition. Thus, the demography is much in line with several other trauma studies.[35–38]

CONCLUSION

AKI in ICU-treated trauma patients is a common complication with significant mortality. In the present study, a quarter of the AKI patients received renal replacement therapy in the ICU, whereas none of the survivors of AKI developed end-stage renal disease 1 year after injury. Diabetes, male sex, and severe injury were strong risk factors, but age, nondiabetic comorbidity, massive transfusion, and resuscitation with HES were also independently associated with postinjury AKI. This was not noted for pre-AKI sepsis, shock on admission, or radio contrast. Based on the current findings, volume resuscitation with HES should be avoided in trauma patients.

AUTHORSHIP

M.E. contributed to study design, collected and verified data, and performed the statistical analysis. O.B. created the registry, contributed to the study design, and collected and verified data. J.M. contributed to the study design and interpretation of data. E.L. was involved in the interpretation of data and performed the statistical analysis. A.O. contributed to the study design and interpretation of data and created the registry. All authors were involved in drafting and critically revising the manuscript. All authors read and approved the final manuscript.

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DISCLOSURE

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