Urinary tract trauma as a predictor of acute kidney injury in severely injured patients: A retrospective analysis of observational studies

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Aim. The main objective of this study was to determine whether urinary trauma increases the risk of acute kidney injury (AKI) in patients with severe trauma. As a secondary objective, we assessed the reliability of neutrophil gelatinase-associated lipocalin (NGAL) in the early prediction of AKI in this patient population.
Methods. Retrospective analysis of two prospective observational studies involving 179 adult patients with severe trauma (Injury Severity Score >16). NGAL levels were measured by taking a blood sample 24 h after admission. AKI was diagnosed according to the Kidney Disease Improving Global Outcomes (KDIGO) classification.
Results. The overall incidence of AKI was 29%. Kidney or vascular injury was an independent risk factor for AKI (risk ratio [RR] = 3.1, 95% confidence interval [CI] 1.93–4.90). Trauma to urinary passages was also associated with an increased risk of AKI (RR = 4.2, 95% CI 2.70–6.46). Among patients without urinary tract injury, serum NGAL levels were significantly higher in trauma patients who developed AKI during the first 5 days in the intensive care unit (ICU) compared to patients without this organ dysfunction (214.6 µg/L [IQR 167.3] vs. 90.6 µg/L [IQR 58.4]; $P<0.001$). In patients with urinary tract trauma, there was no difference in the NGAL levels between the two groups (184.6 µg/L [IQR 139.9] vs. 118.3 µg/L [IQR 118.1]; $P=0.216$). NGAL was not a reliable predictor of AKI in patients with urinary trauma (AUC 0.660).
Conclusion. Urinary tract injury is associated with a significant increase in AKI in patients with severe trauma during the first 5 days of hospitalization in the intensive care unit. In these patients, NGAL is not a reliable predictor of the development of AKI.

Key words: acute kindey injury, severe trauma, NGAL

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INTRODUCTION

Trauma remains the leading cause of morbidity and mortality worldwide, despite significant improvements in the care of critically injured patients[1]. Urinary tract injuries are less common, accounting for only 10% of all serious injuries[2]. Despite its location in the well-protected retroperitoneal space, the kidney is the most commonly injured organ, accounting for approximately 65–90% of all urotraumas[2,3]. Injuries to the ureter, bladder, and urethra are rare[2]. The most common mechanism of renal injury is blunt trauma associated with high-velocity deceleration (80–95%), whereas penetrating trauma (gunshot and stab wounds) occurs only in 1.4–3.3% of cases. However, the predominant type of injury varies by geographical location, with penetrating injuries being more common in the USA and South America than in Europe[2,4].

Organ dysfunction is the third most frequent cause of death in patients with serious injuries, after fatal bleeding and traumatic brain injury[5]. Acute kidney injury (AKI) is common among patients with organ failure after trauma, with a reported incidence between 24 and 50% (ref.[5,6]). Trauma-related AKI (TRAKI) usually develops very early, and 96% of all cases are diagnosed within 5 days of intensive care unit (ICU) stay[7].

Patients with multiple traumas are exposed to several AKI risk factors, including hemorrhage, systemic inflammation, rhabdomyolysis, and second hits due to emergency surgery and infections[5,7]. Because the development of AKI is associated with many adverse outcomes, such as increased length of hospital stay, mortality, and total cost of healthcare, it is essential to identify all risk factors early and, in indicated cases, initiate preventive measures with the aim of reducing the incidence of AKI and subsequent complications[6,7]. For this reason, risk-prediction models have been developed for AKI based on analysis of the demographic, clinical, and biochemical data at the time of admission to the ICU (ref.[8]), and on prehospital variables, the Injury Severity Score (ISS), and the presence of hemorrhagic shock[5]. The possibility of predicting TRAKI by detecting biomarkers of renal impairment at hospital admission was described recently[9]. Neutrophil-gelatinase associated lipocalin (NGAL) is a very promising biomarker for early detection of AKI, especially if the

time of renal insult is known, such as post-cardiac surgery or exposure to a radiocontrast agent[10]. However, the ability of NGAL to predict TRAKI in patients with urinary tract injuries has not yet been investigated.

Although it seems intuitive that direct damage to the urinary tract will affect its function, very little is known about the risk of developing AKI in this context. Therefore, we aimed to assess whether urinary tract injury is an independent risk factor for AKI. We also tested the ability of NGAL to predict the development of AKI early in this specific patient population.

METHODS

Study design

We conducted a retrospective analysis of two prospective observational clinical trials that enrolled a total of 192 consecutive patients with severe trauma (ISS>16) aged >18 years and directly admitted from the scene to the Emergency Room of the University Hospital Ostrava (Level I trauma center) during the period from June 2013 to December 2016 or July 2019 to April 2022. The exclusion criteria were injuries incompatible with life (expected death within 24 h), cardiac arrest at the scene or during transport to the hospital, history of significant kidney disease, and pregnancy. Both prospective studies were approved by the Ethics Committee (reference numbers: 219/b/2013 and 424/2019) and fulfilled the principles of the Declaration of Helsinki.

Management of patients and data collection

All seriously injured patients were provided with comprehensive care according to the principles of damage control resuscitation (DCR) and Advanced Trauma Life Support (ATLS) (ref.[11,12]). After completion of the primary survey and stabilization of vital functions, all patients underwent whole-body computed tomography (CT) with contrast agent to determine injuries, including in the urinary tract. The severity of trauma was assessed using the ISS (ref.[13]). Urinary tract injuries were divided into two groups: injuries to the kidney and its vascular supply, or injuries to the ureter, bladder, and urethra. We recorded basic demographic data, including age, gender, and mechanism of injury, and the ISS using a case report form. In addition to standard laboratory examinations according to the practices in our workplace, blood samples were taken 24 hours after admission to determine NGAL, myoglobin, IL-6, and creatinine levels. Serum creatinine was measured every morning for 5 days from admission to the ICU. All laboratory parameter measurements were performed in accordance with the manufacturers' instructions.

Renal function assessment

AKI was diagnosed by the peak serum creatinine levels according to the Kidney Disease Improving Global Outcomes (KDIGO) classification, which defines AKI as an increase in the serum creatinine ≥ 26.5 μmol/L within 48 h or ≥ 1.5 times from baseline within the preceding 7 days (ref.[14]). Due to the baseline value of serum creatinine being unknown in patients with severe trauma, we calculated it according to the Modification of Diet in Renal Disease (MDRD) formula using a glomerular filtration rate of 75 mL/min/1.73 m^2. We set the admission creatinine level and lowest creatine level in the first 5 days of the ICU stay as baseline values according to the methodology of previous studies[5,15].

Statistical analysis

Continuous data were expressed as means and standard deviations (SDs) or medians with interquartile ranges (IQRs) according to their distribution (analyzed by Shapiro-Wilk test of normality), and categorical variables were presented as counts with percentages. Comparisons of two Gaussian variables were performed with a two-sample t-test, and the Mann-Whitney test was used for non-normally distributed data. A simple linear regression model was used to assess the correlation between urinary tract trauma and AKI. The relative risk of developing AKI was presented as a risk ratio (RR) and 95% confidence interval (CI). Receiver operating characteristics (ROC) curves were created for different NGAL thresholds for the prediction of AKI. The best threshold was defined as the NGAL value maximizing the Youden index (sensitivity + specificity-1). All data were analyzed using IBM SPSS V26 software. Significance was defined as $P<0.05$.

RESULTS

The combined database included a total of 192 patients. A total of 179 patients were analyzed because 13 died before completion of the study protocol and were excluded. Patients were predominantly male, with an average age of 43.7 years (±15.7) and mean ISS of 32.5 (±9.7). Fifty-one patients (28.5%) experienced AKI (any stage): 27 (53%) were classified as KDIGO 1, 12 (23.5%) as KDIGO 2, and 12 (23.5%) patients were classified as AKI KDIGO 3, 9 of which required renal replacement therapy (RRT). Characteristics of the patients and injuries are presented in Table 1.

Injury of the urinary system is an independent predictor of AKI development, with an RR of 3.4 (95% CI 2.25–5.06), whereas injury to the kidney or its vascular supply led to a 3-fold increase in the risk of AKI (RR = 3.1, 95% CI 1.93–4.90) and injury to the urinary passages had an RR of 4.2 (95% CI 2.70–6.46). The risk of developing AKI was not significantly different for both types of injury (RR=1.4, 95% CI 0.86–2.14).

In patients without injury to the urinary system, the NGAL level 24 h after admission was significantly higher in patients who developed AKI in the following 5 days in the ICU compared to patients who did not develop this organ dysfunction (214.6 μg/L [IQR 167.3] vs. 90.6 μg/L [IQR 58.4]; $P<0.001$). In patients with urinary system injury, the NGAL level did not differ in both groups (184.6 μg/L [IQR 139.9] vs. 118.3 μg/L [IQR 118.1]; $P=0.216$, Fig. 1).

Table 1. General characteristics of patients and injuries according to AKI status.

Characteristic	Non-AKI n=128 (71.5%)	AKI n=51 (28.5%)	*P*
Gender, male	99 (77.3%)	40 (78.4%)	0.359
Age, years	40.5 (23)	45.0 (28)	0.150
ISS	29.0 (8)	34.0 (18)	<0.001
SOFA 24h	8 (3)	10 (4)	<0.0005
RRT	0	9	
Blunt trauma	128 (71.5%)	48 (26.8%)	
MVA	42 (32.8%)	15 (31.3.%)	
Motorbike	7 (5.5.%)	6 (12.5%)	
Fall	36 (28.1%)	14 (29.2%)	
Pedestrian, bicycle	36 (28.1%)	8 (16.7%)	
Other	7 (5.5%)	5 (10.4%)	
Penetrating trauma	0 (0%)	3 (1.7%)	
Gunshot wound	0 (0%)	1 (33.3%)	
Stab wound	0 (0%)	2 (66.7%)	
Urinary system trauma	8	18	
Kidney and renal vessels	7	12	
Extrarenal UT	1	6	
NGAL (µg/L)	91.0 (63.1)	198.1 (165.1)	<0.001
Interleukin-6 (ng/L)	206.4 (340.4)	373.0 (469.0)	<0.001
Lactate (mmol/L)	1.3 (0.5)	1.9 (1.4)	0.042
Procalcitonin (µg/L)	0.4 (1.1)	3.9 (6.9)	<0.001
Creatinine (µmol/L) Day 1	79.5 (30)	144.0 (50)	<0.0005
Creatinine (µmol/L) Day 2	67.0 (25.0)	127.0 (38.0)	<0.0005
Creatinine (µmol/L) Day 3	64.0 (20.0)	109.0 (49.0)	<0.0005
Creatinine (µmol/L) Day 4	62.0 (18.0)	96.0 (32.0)	<0.0005
Creatinine (µmol/L) Day 5	61.0 (19.0)	88.0 (39.0)	<0.0005

Data are presented as n (%) or median (IQR).
ISS, Injury Severity Score; SOFA, Sequential Organ Failure Assessment; MVA, motor vehicle accident; NGAL, neutrophil gelatinase-associated lipocalin.

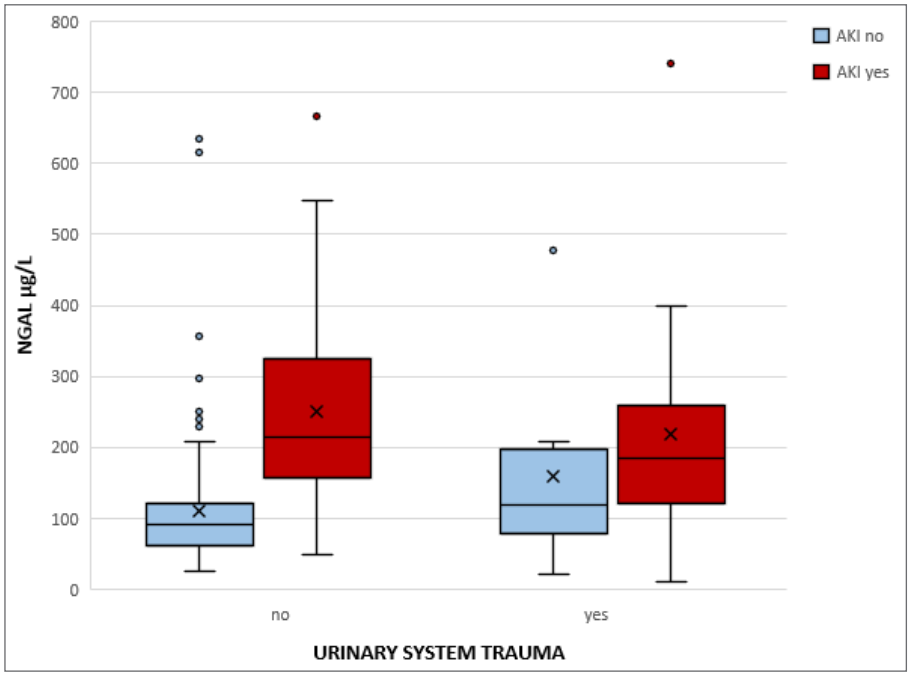

Fig. 1. Neutrophil gelatinase-associated lipocalin (NGAL) levels in patients with and without urinary tract injury.
The lower edge of the box represents the 25th percentile, the line inside of the box indicates the median, and the upper edge of the box is the 75th percentile. X indicates the mean value. AKI, acute kidney injury.

Table 2. Performance of NGAL in predicting acute kidney injury.

NGAL	AUC-ROC	Standard error AUC-ROC	P	95% CI	Cut-off value	Sensitivity (%)	Specificity (%)
No urinary system trauma	0.851	0.041	<0.001	0.773–0.930	138.3 µg/L	76	82
Urinary system trauma	0.660	0.124	0.196	0.418–0.902	172 µg/L	56	75

NGAL, neutrophil gelatinase-associated lipocalin.

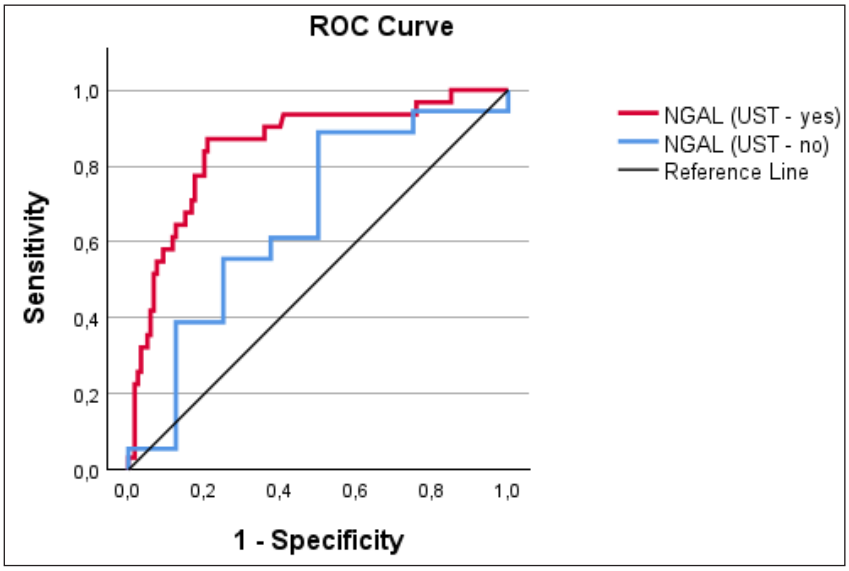

Fig. 2. ROC curves for the prediction of acute kidney injury in patients with or without urinary system trauma (UST).
NGAL, neutrophil gelatinase-associated lipocalin.

Based on the area under the ROC curve (AUC), NGAL was a reliable predictor of AKI in patients without urinary system injury (AUC 0.851, 95% CI 0.773–0.930). In a subgroup of patients with urinary trauma, NGAL had poor predictive value for AKI (AUC 0.660, 95% CI 0.418–0.902; Table 2 and Fig. 2).

DISCUSSION

In this nearly 6-year study, we found that AKI occurs in 29% of patients with severe trauma who were admitted to the ICU. In these patients, AKI occurs as a result of a number of renal aggressions, of which massive bleeding, an uncontrolled systemic inflammatory response, tissue hypoperfusion, and rhabdomyolysis are key factors in the development of renal impairment. Early identification of patients at increased risk of AKI is essential, as this organ dysfunction has been shown to be associated with increased morbidity and mortality in ICUs (ref.[5,6,8]). For this reason, AKI risk prediction models have been developed that assess patient risk factors, the type of injury and its physiological consequences, and a number of other factors. However, little is known about the risk of AKI in patients with urinary trauma.

In our study, 14.5% of patients suffered trauma to the urinary system, among other injuries. These injuries include both relatively common direct injuries to the kidney or its blood supply and rare injuries to the urinary passages. Regardless of the type of injury, these patients have approximately 3-fold higher risk of developing AKI in the first 5 days after trauma.

These findings suggest that damage to the kidney or its vascular supply leads to nephron loss with a subsequent reduction in the glomerular filtration rate (GFR) (ref.[5]). Moreover, the injured kidney is more prone to failure due to the other insults caused by trauma. Interestingly, we found that injury of the urinary passages is associated with approximately the same risk of AKI as renal trauma. Urinary tract obstruction with blood is probably the most common cause of postrenal TRAKI, with increasing intraluminal hydrostatic pressure leading to impaired renal blood flow and GFR. In addition, bladder and urethral injuries are often associated with unstable pelvic fractures, and AKI occurs as a result of the massive blood loss that is common in these injuries[16].

Our results are consistent with Harrois' study, in which only severe renal injury with AIS ≥3 increased the risk of AKI (OR 2.3, 95% CI 0.8–6.4) (ref.[5]). In our study, all patients with urinary trauma, regardless of severity, were at an increased risk of developing AKI. One possible explanation is that the patients in our study had more severe trauma (ISS = 29 [IQR 12] vs. ISS = 14 [IQR 16]). Being exposed to greater renal insult (e.g., bleeding, rhabdomyolysis), these patients are more prone to develop AKI even with less severe urinary tract injuries.

The first prospective study investigating the development of AKI in patients with renal injury was conducted by Chávez-Iñiguez et al., who found a 4-fold higher probability of developing AKI in patients with a high-grade

renal injury[7]. However, these results cannot be generalized, as 70% of AKI cases involved penetrating injury to the kidney caused by a firearm or knife, which is not a typical mechanism of renal injury in Europe, where blunt trauma predominates[2]. Surprisingly, the authors did not demonstrate a higher risk of AKI in patients who had undergone nephrectomy[7]. We could not confirm this finding in our study because nephrectomy was performed in only two patients, as non-operative management (NOMA) is the preferred approach to patients with renal injury (especially blunt injury) (ref.[4]).

As multiple factors are involved in the development of TRAKI, no single risk factor would satisfactorily predict the development of renal failure in all patients. The accuracy of AKI prediction can be improved with the use of biomarkers[5]. NGAL is a 25 kDa protein with multiple functions in the immune response and iron metabolism. It is also a growth factor involved in kidney development[17]. Recently, several studies have shown that NGAL is a reliable and early predictor of AKI in the heterogeneous ICU population[9,10].

In our study, the serum concentration of NGAL was an excellent early biomarker for TRAKI, with an AUC of 0.9, which is in line with the results of previous studies[18]. However, in patients with a urinary tract injury, the reliability of NGAL in predicting AKI is significantly reduced. A possible explanation is the increased addition of NGAL from the damaged urinary tract to the systemic pool, which is normally formed in the lungs and liver[19]. This may have an impact on the reliability of NGAL levels in the prediction of AKI.

The main strength of our study is the use of the KDIGO classification, which is more sensitive for the diagnosis of AKI in ICU patients than the RIFLE criteria[5]. However, we must acknowledge several limitations of this study. First, this was a retrospective study, though the data were collected prospectively. Second, we used only creatinine levels, not urine output, to diagnose AKI, which may have underestimated the prevalence of AKI. Finally, this study has shown an association between urinary tract trauma and AKI, but cannot prove causality.

CONCLUSION

Urinary tract injury in severely injured patients is associated with a significant increase in the risk of TRAKI during the first 5 days in the ICU. NGAL is not a reliable biomarker for early detection of AKI in these patients.

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