HHS Public Access

Author manuscript

J Trauma Acute Care Surg. Author manuscript; available in PMC 2021 October 01.

Published in final edited form as:

J Trauma Acute Care Surg. 2020 October ; 89(4): 761–767. doi:10.1097/TA.0000000000002864.

Urinary Cell Cycle Arrest Proteins TIMP-2 and IGFBP-7 Predict Acute Kidney Injury after Severe Trauma: A Prospective, Observational Study

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Abstract

Background: Recognition and clinical diagnosis of acute kidney injury (AKI) after trauma is difficult. The majority of trauma patients do not have a known true baseline creatinine, which makes application of the guidelines set forth by the international guidelines difficult to apply. Use of alternative biomarkers of renal dysfunction in trauma patients may be beneficial. We hypothesized that Urinary TIMP-2*IGFBP-7 would accurately predict AKI development in severely injured trauma patients.

Methods: A prospective observational study of adult (≥16 years) trauma ICU patients was performed between 9/2018–3/2019. Urine was collected on ICU admission and was measured for TIMP-2*IGFBP-7. Univariate, multivariable, and receiver operating characteristic (ROC) curve analyses were performed utilizing the optimal threshold generated by a Youden index.

Main Results: Of 88 included patients, 75% were male, with a median injury severity score was 27 (IQR 17–34), and age of 40 (IQR 28–54). Early AKI developed in 39 (44%) patients and of those, 7 (8%) required dialysis within 48 hours. Patients without early AKI had a TIMP-2*IGFBP-7 of 0.17 units (IQR 0.1–0.3) while patients with early AKI had a TIMP-2*IGFBP-7 of 0.46 units (IQR 0.17–1.29, p<0.001). On multivariable analyses,

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Conflicts of Interest: The authors have no conflicts of interest

TIMP-2*IGFBP-7 was associated with AKI development (p=0.02) and need for dialysis (p=0.03). Using the optimal threshold 0.33 units to predict AKI, the area under the ROC curve was 0.731, with an accuracy of 0.75, sensitivity of 0.72, and specificity of 0.78.

Conclusion: Urinary TIMP-2*IGFBP-7 measured on ICU admission accurately predicted 48-hour AKI and was independently associated with AKI and dialysis requirement after trauma and is a promising screening tool for treatment.

Keywords

Acute Kidney Stress; Severe Trauma; Acute Kidney Injury

Introduction

Acute kidney injury (AKI) following trauma is associated with increased mortality, cost, and prolonged length of stay. [1–4] AKI encompasses a spectrum of kidney dysfunction from asymptomatic renal insufficiency to severe AKI requiring dialysis. Currently, clinical practice depends on serum creatinine and physiologic indicators such as urine output to identify renal dysfunction. However, these may not become abnormal for 24 hours. [5] Furthermore, early treatment of renal dysfunction is imperative in trauma patients who suffer multiple renal insults in the acute post-traumatic period, including administration of nephrotoxins such as non-steroidal anti-inflammatory agents for pain or for anti-platelet activity, antibiotics for wound or surgical infection prophylaxis, high-osmolar contrast agent loads during vascular diagnostic or repair procedures, and large swings in fluid balance during resuscitation. [6]

In addition to the high risk of AKI after severe trauma, recognition and clinical diagnosis of AKI after trauma is difficult. Trauma patients frequently present with an elevated creatinine, which may be particularly difficult to interpret. The majority of trauma patients do not have a known true baseline creatinine, which makes application of the guidelines set forth by the international Kidney Disease Improving Global Outcomes (KDIGO) group difficult to apply. [6, 7] There is a need for an early and accurate biomarker of renal dysfunction in trauma patients. Two cell-cycle arrest proteins, tissue inhibitor of metalloprotease 2 (TIMP-2) and insulin-like growth factor binding protein 7 (IGFBP-7) are released during periods of cellular stress or injury. They are easily measured in the urine and are specific for a pre-injury phase that leads to AKI, known as acute kidney stress. [8] A series of experimental studies points to two mechanisms for this finding. First, proximal tubule injury leads to both TIMP-2 and IGFBP-7 release and failed reabsorption. [9] Second, decreased glomerular permselectivity increases the filtration of TIMP-2 and IGFBP-7. [9] Both of these mechanisms result in large increases of TIMP-2 and IGFBP-7 urinary excretion. The combination of these two markers, denoted TIMP-2*IGFBP-7, has been validated as a predictor of AKI and need for dialysis in numerous patient populations. [10–13] Treatment protocols triggered by acute kidney stress detected by TIMP-2*IGFBP-7 have shown to improve outcomes in surgical patients, suggesting that early detection and treatment of acute kidney stress may be beneficial to other high-risk populations, such as the severely injured. However, the correlation between acute kidney stress and outcomes after trauma is unknown. In a recent analysis of traumatically injured military patients, these biomarkers

only had modest accuracy (AUC 0.65) to predict a composite outcome of dialysis or mortality. [14] The hypothesis evaluated in this study was that urinary TIMP-2*IGFBP-7 accurately predicts 48-hour AKI in severely injured trauma patients.

Methods

This prospective observational study was conducted under an approved Institutional Review Board (IRB) (Universal Study, HSC-GEN-12–0059), which included all adult trauma patients (≥18 years) with a Foley catheter at the highest level of activation at Memorial Hermann Hospital Texas Medical Center (MHH-TMC) between September 2018 and March 2019. The criteria for highest activation include Glasgow Coma Scale score of 10 or less, heart rate greater than 120 beats per minute, systolic blood pressure of 90 mm Hg or less, respiratory rate less than 10 or greater than 29 breaths per minute, intubation, penetrating injury to torso, groin, head or neck, amputation proximal to ankle or wrist, paraplegia, quadriplegia, uncontrolled external hemorrhage, fracture to pelvis or two or more long bone fractures, and receipt of blood en route. The IRB approval was obtained for delayed consent, obtained from the patient or their legally authorized representative within 72 hours of admission, or as soon as possible. For patients who were discharged or died within 24 hours of admission, a waiver of consent was obtained. If consent could not be obtained, the patient was excluded from the study, and their samples destroyed. The study excluded pregnant women and prisoners. This was an opportunistic prospective study that ran parallel to other clinical studies at MHH-TMC; samples were collected when research staff was not directly involved in the other studies and available to process the samples.

Urine was collected from patients meeting inclusion criteria after arrival to the ICU. The median time from hospital arrival to ICU admission was 6 hours at the study institution. Upon collection, urine was stored at −80°C until analysis. Urine TIMP-2*IGFBP-7 in $(ng/mL)^2/1000$ was measured using the commercially available and FDA-approved NephroCheck® meter according to manufacturer instructions (Astute Medical). The results were not made available to clinicians.

Patient demographics, vital signs, mechanism and severity of injury, laboratory results, hourly urine output, and outcomes were collected from patient records. AKI was defined according to the KDIGO guidelines and assigned a stage. Serum creatinine, urine output, and need for dialysis are used to stage the severity of AKI which ranges from 1, indicating mild disease, to 3, indicating severe disease. [7] The baseline creatinine utilized for all AKI diagnoses was imputed by the Modification of Diet in Renal Diseases equation using an assumed baseline glomerular filtration rate of 75 ml/min. [4, 15] The primary outcome was development of AKI stage 1 or higher within 48 hours from arrival. Secondary outcomes included 7-day AKI incidence, need for dialysis, AKI stage 2 or 3, and in-hospital mortality.

Statistical Analysis

Descriptive analyses were performed to compare baseline demographic and clinical data between groups: No AKI versus AKI followed by No Acute Kidney Stress versus Acute Kidney Stress. Median values with interquartile range were used to describe continuous data and discrete data were reported as a total and frequency. Variables of interest were compared

using the Chi-squared test or a Wilcoxon rank-sum test for categorical and continuous variables, respectively.

The sample size was calculated based on the ability of TIMP-2*IGFBP-7 to predict AKI in trauma patients. A receiver operating characteristic (ROC) curve analysis with an area under the curve of ≥0.70, which correlates with previous reports, was applied with an expected power of 0.80 and a significance level of 0.05. [12] With an AKI incidence of 40%, 26 cases and 38 controls were required with a total sample size of 64 patients. To increase the expected power to 0.90, the necessary sample size was 85 patients. The package “pROC” was used to calculate sample size. [16]

An optimal threshold of TIMP-2*IGFBP-7 for AKI prediction was generated by a Youden index. Analyses were performed utilizing this threshold. Multivariable logistic regression models were utilized to assess the relationship between TIMP-2*IGFBP-7 or acute kidney stress, defined by the optimal threshold, and the primary outcome, AKI development within 48 hours. Model variables were selected a-priori by the investigators due to known or suspected confounding with AKI or mortality. These included age, arrival systolic blood pressure, arrival Glasgow Coma Scale motor score, and injury severity score. Similar models were fit for the secondary outcomes 48-hour dialysis requirement, 7-day AKI, 7-day dialysis requirement, and in-hospital mortality. Poisson models were built to evaluate the relationship between TIMP-2*IGFBP-7 or acute kidney stress, defined by the TIMP-2*IGFBP-7 optimal threshold, and ICU length-of-stay. Sensitivity analyses were performed using the threshold suggested by the test manufacturer for defining acute kidney stress: TIMP-2*IGFBP-7 of 0.3 units. [17] Associations were reported as odds ratios with confidence intervals and the Poisson models are reported as incident rate ratios. All data analyses were completed using R version 3.53 (R Core Team. 2013. *R: A language and environment for statistical computing*. R Foundation for Statistical Computing, Vienna, Austria).

Results

During the study period, 190 highest-level trauma activations were admitted to the ICU. Of those, 88 patients met inclusion criteria and consent was obtained. There were no missing data. Included patients were primarily male (75%) who had been injured by blunt mechanism (91%), with a median age of 40 years (IQR 28–54). Patients were severely injured with a median injury severity score of 27 (IQR 17–34). (Table 1)

Forty-two (48%) patients developed AKI within 7 days after trauma and 8 (9%) required dialysis. AKI developed in 39 (44%) patients within 48 hours from arrival. Patients who developed AKI were older, but the remaining demographics were similar between groups. (Table 1) The majority (93%) of post-traumatic AKI developed within 48 hours from arrival. Similarly, the majority of patients who required dialysis were first dialyzed within 48 hours from arrival (88%). While limited by sample size, there was a higher rate of mortality in patients who suffered AKI than who did not.

Optimal Threshold for Acute Kidney Stress after Trauma

Urine TIMP-2*IGFBP-7 was higher in patients who developed AKI than those who did not ($p<0.001$). On receiver operating characteristic analysis with the Youden index (J), TIMP-2*IGFBP-7 was associated with the maximum sum of the sensitivity and specificity in predicting 48-hour AKI at a threshold of 0.33 units (J=0.50, sensitivity at threshold = 0.72, specificity at threshold = 0.78, AUC = 0.73, 95% CI 0.65–0.84), which was associated with adequate discrimination. [18] (Figure 1) This process was repeated to identify the optimal threshold to predict 7-day AKI and similar findings were revealed (J=0.50, sensitivity at threshold = 0.71, specificity at threshold = 0.78, AUC = 0.74).

Patients were then stratified by the optimal threshold for acute kidney stress that predicts 48-hour AKI after severe trauma, defined as TIMP-2*IGFBP-7 ≥ 0.33 units. Acute kidney stress was present in 44% of patients. (Table 2) Patients with acute kidney stress were older and arrived with a lower systolic blood pressure than those without acute kidney stress. Patients with acute kidney stress were more likely to develop AKI at either 48 hours or by 7 days and were more likely to require dialysis or die.

Relationship between TIMP-2*IGFBP-7 and Outcomes

After adjustment for age, arrival systolic blood pressure, and arrival motor score, TIMP-2*IGFBP-7 was associated with 48-hour AKI development (aOR 5.87, 95% CI 1.88–31.83), 48-hour dialysis requirement (aOR 1.71, 95% CI 1.06–2.97), and increased ICU length of stay (aOR 1.06 days per unit, 95% CI 1.01–1.11). (Supplemental Table 1) Acute kidney stress, defined by TIMP-2*IGFBP-7 ≥ 0.33 was associated with 48-hour AKI development (aOR 6.94, 95% CI 2.56–20.12). (Supplemental Table 2)

Sensitivity Analysis Using Pre-Defined Acute Kidney Stress Threshold

The threshold for acute kidney stress as identified by other studies is 0.30. [16] On sensitivity analysis using the TIMP-2*IGFBP-7 threshold for acute kidney stress 0.3, similar results were found to the internally identified threshold value. The sensitivity was 0.71, specificity 0.71, and AUC 0.72 (95% CI 0.62–0.81).

Discussion:

Acute kidney stress, defined as urinary TIMP-2*IGFBP-7 ≥0.33 units on ICU admission for severe trauma, was common with an incidence of 44%. Acute kidney stress predicted 48-hour AKI development and 48-hour dialysis requirement with adequate discrimination after severe trauma. After adjustment, TIMP-2*IGFBP-7 was independently associated with AKI development, dialysis requirement, and longer ICU stay.

There is a need for an accurate indicator of renal dysfunction that is not limited by the shortcomings of creatinine. Early, mild elevations of creatinine may go unnoticed by the clinical team due to uncertainty regarding the baseline creatinine. Urinary kidney injury molecule 1 (KIM-1), plasma cystatin C, and urinary and plasma neutrophil gelatinase-associated lipocalin (NGAL) have been evaluated in various clinical settings to predict the development of AKI, but these have been outperformed by urinary TIMP-2*IGFBP-7 in

critically ill patients. [12, 19, 20] In a recent meta-analysis of biomarkers that predict AKI requiring dialysis, TIMP-2*IGFBP-7 outperformed creatinine, which is currently the most frequently utilized biomarker of kidney dysfunction in clinical care. [12] The study by Klein, et al. reported urinary TIMP-2*IGFBP-7 had a pooled AUC of 0.857 [95% CI 0.789–0.925] while creatinine had a pooled AUC of 0.764 [95% CI 0.732–0.796] in the prediction of AKI requiring dialysis. Similar to other studies in critically ill patients, the present study demonstrates that urinary TIMP-2*IGFBP-7 predicts renal dysfunction after severe trauma as well, with an AUC of 0.73. A recent study by Beyer, et al. similarly looked at the utility of urinary TIMP-2*IGFBP-7 in the combat setting and found a lower AUC in the detection of dialysis or death (0.65, 95% CI 0.44–0.86). [14] The authors concluded that TIMP-2*IGFBP-7 would not be beneficial in triaging individuals injured in combat. The time point at which their end point was measured was the duration of the initial hospitalization, which may have been too long to expect a single time point biomarker to measure. Other studies have found that beyond 24–48 hours from measurement, the detection power for AKI or AKI requiring dialysis declines. [12, 21] This may have contributed to the dampened predictive power in their study. The present study demonstrated moderately superior predictive power of the biomarkers also among injured patients compared to the study by Beyer et al., although patients in the present study were more severely injured and with higher dialysis and mortality event rates. Even so, our findings reveal a lower discrimination than the pooled AUC of 0.86 by Klein, et al. The importance of the discriminatory power of the biomarkers will depend on the threshold chosen for treatment and whether the treatment itself has significant risks that may outweigh benefits in patients who may not go on to develop AKI.

The threshold that should be utilized to maximize diagnostic accuracy of urinary TIMP-2*IGFBP-7 for the prediction of AKI has been previously evaluated in other clinical settings. [17, 22, 23]. The optimal threshold identified in this study was 0.33 units, remarkably similar to the threshold of 0.30 units, which is supported by other studies. [24–26] However, this threshold does not evaluate the optimal threshold level of treatment. Thresholds for treatment should be chosen with consideration to the benefits and harms. If treatments are generally inexpensive and with few harms, clinicians may be willing to treat acute kidney stress at a lower threshold. On the other hand, if there are significant costs or harms associated with treatment, they would be more inclined to choose a higher threshold. The results of the present study suggest that clinical application of urinary TIMP-2*IGFBP-7 measurements using acute kidney stress thresholds of either 0.33 units or 0.3 units are both appropriate and are likely to yield similar results in severely injured patients. Nonetheless, the optimal threshold for treatment should be re-examined upon integration into clinical care.

While the accuracy of TIMP-2*IGFBP-7 has been demonstrated, and reinforced in this study, the looming question remains: How should these markers be used in clinical care? There have been few advancements in the treatment of AKI, and treatment remains centered on prevention of further insults and supportive care. A recent modified Delphi panel report showed that physicians who currently utilize the TIMP-2*IGFBP-7 in clinical care agree on protocols regarding who to test and how to use the results. [27] First, the panel agreed that patients with severe trauma are a target population for urinary TIMP-2*IGFBP-7 testing,

especially those who have hemodynamic instability. Second, their consensus statement for potential interventions for patients with positive results (≥0.30 units) included medication modifications, instituting goal-directed volume management, and avoidance of high-chloride fluids. Patients with negative results, on the other hand, should be fast-tracked and continued on potentially nephrotoxic medications that are otherwise indicated. Two randomized trials of care bundles including goal-directed volume management in patients scoring positive for acute kidney stress showed an improvement in patient outcomes. [28, 29] In the first study of cardiac surgery patients, the care bundle resulted in a lower incidence of AKI of any stage and a lower incidence of stage 2 and 3 AKI. [28] The second study of major surgical patients demonstrated that the bundle was associated with a lower incidence of stage 2 and 3 AKI, decreased ICU length-of-stay, and decreased hospital length-of-stay. [29] Similar bundles may be beneficial for the severely injured patient population, who suffer a large AKI burden, with a 47.5% 7-day incidence reported in the present study.

While optimization of volume status and minimization of nephrotoxic exposure has improved outcomes to a certain extent, there is a lot of work to be done in the treatment of AKI of all etiologies. [30] Innate immune dysregulation may be an important and unaddressed renal insult leading to AKI. Trauma patients suffer multiple organ dysfunction syndrome, which is closely linked to AKI, and the consequence of a genomic storm leading to up-regulation of inflammatory pathways and down-regulation of adaptive pathways. [30–32] It may be appropriate to incorporate assessments of acute kidney stress into screening for patients who may benefit from novel therapies targeting the innate immune response to trauma, such as mesenchymal stem cells. [33]

Finally, there may be barriers to implementation of urine evaluation of TIMP-2*IGFBP-7. The results can be reported in an hour or less, making the results comparable with other routine laboratory evaluations. However, urine TIMP-2*IGFBP-7 measurement has potential economic consequences, given the high cost of the test, which is estimated to be over $200 for each measurement. Given the potential benefits of decreased severity of AKI and decreased ICU and hospital length-of-stay, as noted in the prior randomized trials, a cost trade-off is likely to favor use of the biomarker. An independent, non-industry funded, economic cost evaluation of the biomarker use is needed.

There are limitations to the reported study. First, urine was not evaluated for specific gravity, which may result in false-negatives if a diluted sample was collected. There were five samples that registered a TIMP-2*IGFBP-7 value of ≤0.04, which is the minimum value reportable by the meter. Two of these patients were AKI positive at 48 hours. Clinical application of the urinary TIMP-2*IGFBP-7 test would allow for resampling and retesting if these results are found. The effect of this limitation may be an underestimate of the predictive accuracy of the test, when re-sampling was not possible in this study. Second, we did not evaluate the trend of TIMP-2*IGFBP-7 over time. The scope was limited to evaluation for its utility as an ICU arrival screening test for acute kidney stress, but further work regarding its ability to detect renal recovery or persistent kidney insult in this population is warranted.

Conclusion:

Acute kidney stress, defined as urinary TIMP-2*IGFBP-7 ≥0.33 units on ICU admission for severe trauma, was common with an incidence of 44%. Furthermore, urinary TIMP-2*IGFBP-7 accurately predicted AKI and was independently associated with AKI and dialysis requirement after severe trauma. Early detection of acute kidney stress may result in earlier treatment and better renal outcomes for severely injured patients. Application of a treatment bundle that includes minimization of nephrotoxic exposures and optimization of volume based on the ICU admission urinary TIMP-2*IGFBP-7 may improve outcomes for severely injured trauma patients.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

The authors thank Kandice Motley for her assistance with data collection.

Disclosures: GH is supported by a T32 fellowship (grant no. 5T32GM008792) from National Institute of General Medical Studies of the National Institutes of Health. The authors have no conflicts of interest.

Meeting Presentation: 15th Academic Surgical Congress of the Association for Academic Surgery, February 6th, 2020 in Orlando, FL

Funding: GH is supported by a T32 fellowship (grant no. 5T32GM008792) from National Institute of General medical Studies of the National Institute of Health.

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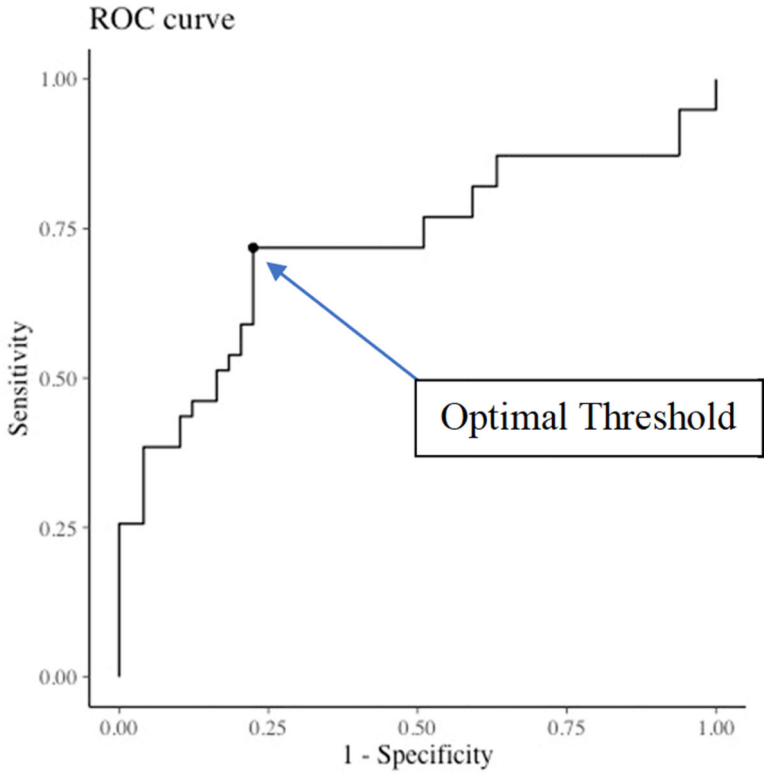

Figure 1:
Optimal Threshold to Predict 48-hour AKI

Table 1:

Demographic Data and Outcomes, by 48-hour AKI Status

Demographic or Outcome	All (n=88)	No AKI (n=49, 56%)	AKI (n=39, 44%)	p Value
Age, years	40 (28–54)	35 (22–47)	48 (37–66)	0.002
Male Sex	66 (75%)	36 (74%)	30 (77%)	0.90
Race/Ethnicity				
White	36 (41%)	15 (31%)	21 (54%)	
Black	11 (13%)	8 (16%)	3 (8%)	0.20
Hispanic	3 (3%)	2 (4%)	1 (3%)	
Asian	1 (1%)	1 (2%)	0	
Blunt Mechanism of Injury	70 (91%)	46 (93%)	34 (87%)	0.40
Transferred from Another Hospital	25 (28%)	14 (28%)	11 (28%)	1
Injury Severity Score	27 (17–34)	27 (17–34)	26 (16–32)	0.6
Arrival Systolic Blood Pressure, mmHG	122 (104–142)	122 (108–142)	122 (99–144)	0.5
Arrival Heart Rate, beats per minute	102 (81–118)	102 (81–119)	95 (81–116)	0.8
Arrival Glasgow Coma Scale	8 (3–15)	8 (3–15)	8 (3–15)	0.4
Transfusion in 24 hours, units[1]				
Total	1.5 (0–6.5)	1 (0–5)	4 (0–10.5)	0.05
Whole Blood	0 (0–0)	0 (0–0)	0 (0–0)	0.51
Packed Red Blood Cells	0 (0–4)	0 (0–2)	1 (0–4.5)	0.06
Fresh Frozen Plasma	1 (0–3)	0 (0–2)	2 (0–4.5)	0.02
Platelets	0 (0–0)	0 (0–0)	0 (0–1)	0.06
Urine TIMP-2*IGFBP-7	0.27 (0.13–0.55)	0.17 (0.10–0.30)	0.46 (0.17–1.29)	<0.001
Acute Kidney Stress (TIMP-2*IGFBP-7 ≥ *0.33 units*)	39	11	28	<0.001
Dialysis, 48 hours	7 (8%)	N/A	7 (18%)	N/A
AKI, 7 days	42 (48%)	3 (6%)	N/A	N/A
Dialysis, 7 days	8 (9%)	1 (2%)	7 (18%)	0.03
ICU Days	5 (3–12)	5 (3–12)	5 (3–13)	0.90
In-Hospital Mortality	11 (13%)	3 (6%)	8 (21%)	0.09

Continuous data presented as: median (IQR) AKI – Acute Kidney Injury, N/A – Not Applicable

Patients grouped by AKI development by 48 hours

[1]Includes pre-hospital transfusions

Table 2:

Demographic Data and Outcomes, By Acute Kidney Stress Diagnosis

Demographic or Outcome	All (n=88)	No Acute Kidney Stress (n=49, 56%)	Acute Kidney Stress (n=39, 44%)	p
Age, years	40 (28–54)	38 (25–45)	49 (32–66)	0.004
Male Sex	66 (75%)	34 (69%)	32 (82%)	0.30
Race/Ethnicity				
White	36 (41%)	17 (35%)	19 (49%)	
Black	11 (13%)	7 (14%)	4 (10%)	0.50
Hispanic	3 (3%)	1 (2%)	2 (5%)	
Asian	1 (1%)	1 (2%)	0	
Blunt Mechanism of Injury	70 (91%)	46 (92%)	34 (87%)	0.40
Transferred from Another Hospital	25 (28%)	14 (29%)	11 (28%)	1
Injury Severity Score	27 (17–34)	25 (17–29)	29 (16–34)	0.4
Arrival Systolic Blood Pressure, mmHG	122 (104–142)	126 (110–143)	114 (93–136)	0.07
Arrival Heart Rate, beats per minute	102 (81–118)	105 (83–117)	95 (76–122)	0.60
Arrival Glasgow Coma Scale	8 (3–15)	7 (3–15)	11 (3–15)	0.4
Transfusion in 24 hours, units[1]				
Total	1.5 (0–6.5)	1 (0–5)	4 (0–10.5)	0.04
Whole Blood	0 (0–0)	0 (0–0)	0 (0–0.5)	0.22
Packed Red Blood Cells	0 (0–4)	0 (0–2)	2 (0–5)	0.02
Fresh Frozen Plasma	1 (0–3)	0 (0–2)	2 (0–5)	0.02
Platelets	0 (0–0)	0 (0–0)	0 (0–1)	0.02
Urine TIMP-2*IGFBP-7	0.27 (0.13–0.55)	0.15 (0.07–0.18)	0.61 (0.44–1.47)	<0.001
AKI, 48 hours	39 (44%)	11 (22%)	28 (72%)	<0.001
Highest AKI Stage, 48 hours				
1	27 (31%)	8 (16%)	19 (49%)	<0.001
2	5 (6%)	2 (4%)	3 (8%)	
3	7 (8%)	1 (2%)	6 (15%)	
Dialysis, 48 hours	7 (8%)	1 (2%)	6 (15%)	0.06
AKI, 7 days	42 (48%)	13 (27%)	29 (74%)	<0.001
Dialysis, 7 days	8 (9%)	2 (4%)	6 (15%)	0.1
ICU Days	5 (3–12)	5 (3–12)	5 (3–12)	0.90

Demographic or Outcome	All (n=88)	No Acute Kidney Stress (n=49, 56%)	Acute Kidney Stress (n=39, 44%)	p
In-Hospital Mortality	11 (13%)	3 (6%)	8 (21%)	0.09

Continuous data presented as: median (IQR) AKI – Acute Kidney Injury

Acute Kidney Stress Defined by TIMP-2*IGFBP-7 ≥ 0.33 units

[1] Includes pre-hospital transfusions