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Posted Date: 5 August 2025

doi: 10.20944/preprints202508.0141.v1

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Article

# Effect of Creatinine on Various Clinical Outcomes in Patients with Severe Traumatic Brain Injury (TBI)

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## Abstract

**Background:** Traumatic brain injury (TBI) is a major public health concern. Creatinine (Cr) has been well studied as a marker of renal function, specifically the development of acute kidney injury (AKI) in TBI patients. We aimed to evaluate the effect of Cr on various clinical outcomes in patients with severe TBI. **Methods:** We investigated the relationship between Cr levels at various time points and a range of clinical variables, using parametric (ANOVA, two-tailed t-test, and linear regression modeling) statistical testing. **Results:** 1,000 patients were included in our study. We found a significant association between sex and Cr level at intensive care unit (ICU) admission ( $p=0.001$ ) and ICU discharge ( $p=0.005$ ). Degree of creatinemia had a significant effect on both mean ISS ( $p=0.0003$ ) and GCS ( $p=0.004$ ) scores at ICU admission as well as ISS ( $p=0.017$ ) and GCS ( $p=0.001$ ) scores at patient death timepoints. Change in Cr from Hospital to ICU admission was significantly correlated with vent days ( $p=0.045$ ). Change in Cr from ICU admission to ICU discharge was significantly correlated with hospital length of stay (LOS;  $p=0.001$ ), ICU LOS ( $p=0.000$ ), and vent days ( $p=0.011$ ). Overall, there were significant correlations between Cr at admission and ICU LOS ( $p=0.043$ ), Cr at ICU admission and ICU LOS ( $p=0.001$ ), and Cr at ICU admission and vent days ( $p=0.031$ ). **Conclusion:** Our findings support existing literature that demonstrates a positive relationship between Cr levels, ICU LOS, and vent days amongst patients with severe TBI.

**Keywords:** creatinine; traumatic brain injury; clinical outcomes; demographics; injury severity; length of stay

## 1. Introduction

Creatinine (Cr) is chemically known as  $\alpha$ -methyl guanidinoacetic acid, and is the final breakdown product of creatine phosphate in skeletal muscle, produced at a relatively constant rate proportional to muscle mass. Serum creatinine is formed through a spontaneous non-enzymatic anhydration of creatine in muscle cells. Levels are influenced by muscle mass, age, sex, and certain medications. As creatinine is freely filtered by the glomerulus and minimally secreted by renal tubules, it is the most widely used endogenous marker for estimating glomerular filtration rate (GFR) in clinical practice [1]. As such, a rise in creatinine is central to the diagnosis and staging of acute kidney injury (AKI). However, serum creatinine levels may lag behind acute changes in GFR, particularly in the early phase of AKI or after trauma, where rapid shifts in renal function and muscle metabolism occur [2].

In the context of traumatic brain injury (TBI) and major trauma, serum creatinine is often used to diagnose and stage acute kidney injury (AKI). AKI is a frequent and early complication after TBI, occurring in approximately 10–19% of patients, and is independently associated with increased mortality and worse neurological outcomes [3–5]. A 2021 study investigating occurrence rate, risk factors, timing, and association with outcome of acute kidney injury in a large cohort of TBI patients

across sixty-five ICUs in Europe reported that patients with AKI had a significantly increased ICU length of stay compared to patients without AKI, and that AKI occurrence was associated with increased ICU and overall mortality [3].

Hemodynamic instability, the use of nephrotoxic agents such as mannitol or vancomycin, rhabdomyolysis, and systemic inflammatory responses are all factors that can contribute to AKI and altered creatinine levels in TBI [5]. Additionally, serum creatinine at admission is an independent risk factor for subsequent AKI in TBI patients [5,6]. Some studies have also noted augmented renal clearance following TBI, especially in younger patients, leading to deceptively low serum creatinine despite increased glomerular filtration [7,8]. Thus, close monitoring of renal function and creatinine trends is essential in the management of TBI.

TBI is defined as an alteration in brain function, or other evidence of brain pathology, caused by an external mechanical force such as a blow, jolt, or penetration to the head. TBIs are classified by severity—mild, moderate, or severe—based on clinical criteria such as the Glasgow Coma Scale (GCS), duration of loss of consciousness, and presence of amnesia or focal neurological deficits [9–11]. GCS is the most widely used clinical scale to measure the severity of TBI, assessing eye, verbal, and motor responses to categorize TBI as mild (GCS 13–15), moderate (GCS 9–12), or severe (GCS  $\leq$ 8) [12]. TBI severity can also be measured using the Abbreviated Injury Scale (AIS), an anatomical scoring system that uses clinical and imaging findings to rate injury severity in six body regions (head/neck, face, thorax, abdomen, extremities, external) on a scale from 1 (minor) to 6 (maximal/fatal) [13]. The Injury Severity Score (ISS) is a widely used composite score derived from AIS scores. It is calculated by summing the squares of the three highest AIS scores from different body regions. An ISS  $>15$  is commonly used to define major trauma [14].

Mild TBI, or concussion, accounts for the majority of TBI cases and is characterized by transient neurological dysfunction, typically with GCS 13–15, brief or no loss of consciousness, and no abnormalities on standard neuroimaging. Most patients with mild TBI recover within weeks, though a small percentage may experience persistent symptoms (post-concussive syndrome), including headache, dizziness, cognitive impairment, and mood disturbances [9,15,16]. Moderate and severe TBIs are associated with more pronounced and prolonged impairment, including risk of permanent disability or death. The primary injury, or mechanical disruption of brain tissue at the moment of trauma, is followed by secondary injury, such as delayed cellular and molecular cascades (i.e., inflammation, oxidative stress, and neurovascular dysfunction) [9,17].

Based on the most recent CDC data, there were approximately 214,110 TBI-related hospitalizations in 2020 and 69,473 TBI-related deaths in 2021. People aged 75 years and older account for about 32% of TBI-related hospitalizations and 28% of TBI-related deaths. Additionally, males are nearly two times more likely to be hospitalized and three times more likely to die from a TBI than females [18]. TBI is a major public health concern, with millions of cases occurring annually worldwide. Management is tailored to severity, with acute stabilization, prevention of secondary injury, and multidisciplinary rehabilitation as key components for moderate-to-severe cases [10,11].

Creatinine is a well-studied endogenous marker of GFR and is frequently used to stage AKI in the setting of trauma. Our study aimed to analyze the relationship of creatinine to several clinical outcomes and timeframes amongst patients admitted with severe TBI.

## 2. Methods

We performed a single-center, retrospective review at Elmhurst Hospital, a Level 1 trauma center in Queens, New York City. All patients who presented to the hospital with a severe traumatic brain injury, defined as an AIS score of 3 or higher, between January 1, 2020, and December 31, 2023, were included in the study. Patients who tested positive for COVID-19 at the time of admission, those who died or were discharged within 24 hours of their original injury, and those who had non-severe and minor injuries were excluded. Patient data were obtained from the National Trauma Registry of the American College of Surgeons (NTRACS) database at our institution. Data extracted and organized in Excel included demographics (sex, age), injury type (blunt vs. penetrating), mechanism

of injury (e.g., fall, motor vehicle collision, assault), diagnosis (e.g., concussion, subdural hematoma, subarachnoid hemorrhage), and number of injuries (one to four or more). After data review, a final cohort of 1,000 patients was included in the analysis.

We conducted several levels of analysis:

- Analysis 1: Creatinine levels were compared at five time points against demographic and clinical factors using two-tailed t-test for 2-category analyses (sex, injury type) and ANOVA one-way test, with Welch's transformation when Bartlett's assumptions of equal variance were violated, for analyses of more than 2-categories (age range, injury mechanism, diagnosis, number of injuries).
- Analysis 2: Degree of creatinemia was related to mean GCS and ISS scores across various time points using a one-way ANOVA test, with Welch's transformation when Bartlett's assumptions of equal variance were violated.
- Analysis 3: Linear regression modeling was used to assess correlations between the continuous independent variable (change in creatinine level) and continuous (hospital length of stay, Intensive Care Unit length of stay, ventilator days) and categorical (mortality) dependent variables.
- Analysis 4: Linear regression modeling was used to assess correlations between the continuous independent variable (creatinine levels across admission) and continuous (hospital length of stay, Intensive Care Unit length of stay, ventilator days) and categorical (mortality) dependent variables.

### 3. Results

This study consisted of a cohort of 1,000 patients (Table 1; 23% female, N=232). Most patients (N=793, 64.26%) received the diagnosis of intraparenchymal hemorrhage (IPH). This was followed by subarachnoid hemorrhage (SAH; N=424, 34.36%), and concussion (N=15, 1.22%).

**Table 1.** Demographics.

	Male	Female
N (%)	768 (77%)	232 (23%)
Age (mean $\pm$ SD)	52.95 $\pm$ 9.83 years	72.4 $\pm$ 4.26 years
Creatinine at Hospital Admission (mean $\pm$ SD)	0.87 $\pm$ 0.07 mg/dL	0.755 $\pm$ 0.08 mg/dL
Creatinine at ICU Admission (mean $\pm$ SD)	0.75 $\pm$ 0.17 mg/dL	0.66 $\pm$ 0.055 mg/dL
Creatinine at ICU Discharge (mean $\pm$ SD)	0.625 $\pm$ 0.005 mg/dL	0.635 $\pm$ 0.065 mg/dL
Creatinine at Hospital Discharge (mean $\pm$ SD)	0.76 $\pm$ 0.04 mg/dL	0.325 $\pm$ 0.325 mg/dL
Creatinine at Death (mean $\pm$ SD)	0.00 $\pm$ 0.00 mg/dL	0.00 $\pm$ 0.00 mg/dL
Race (n, %)		
White	128 (17%)	53 (23%)
Black	61 (8%)	16 (7%)
Asian	92 (12%)	55 (23%)
Native Hawaiian or Other Pacific Islander	2 (0.25%)	2 (1%)
Other	469 (61%)	102 (44%)
Unknown	14 (2%)	4 (2%)
Ethnicity (n, %)		
Hispanic	384 (50%)	80 (34%)
Non-Hispanic	352 (46%)	142 (61%)

Unknown	31 (4%)	10 (5%)
Trauma Type (n, %)		
Blunt	749 (98%)	230 (99%)
Penetrating	19 (2%)	2 (1%)
Patient Weight (mean $\pm$ SD)	66.5 $\pm$ 8.5 kg	93 $\pm$ 39 kg
Glasgow Coma Score (mean $\pm$ SD)	9 $\pm$ 6	15 $\pm$ 0
Injury Severity Score (mean $\pm$ SD)	19.5 $\pm$ 1.5	20 $\pm$ 2
Hospital Length of Stay (mean $\pm$ SD)	13.5 $\pm$ 12.5	8.5 $\pm$ 2.5
ICU Length of Stay (mean $\pm$ SD)	4.92 $\pm$ 4.92	1.165 $\pm$ 1.165
Ventilator Days (mean $\pm$ SD)	0 $\pm$ 0	0.38 $\pm$ 0.38
Injury Pattern (n, %)		
EDH	0 (0%)	1 (0%)
SDH	1 (0%)	0 (0%)
SAH	338 (28%)	86 (26%)
IPH	603 (50%)	190 (57%)
Concussion	11 (1%)	4 (1%)
Other	248 (21%)	55 (16%)
Mortality (n, %)	83 (11%)	25 (11%)

Table 1: Demographic characteristics of the 1,000 patients included in the analysis. The cohort was predominantly male (n=768), identified as "other" race (n=571), non-Hispanic (n=494), sustained blunt injuries (n=979), and received a diagnosis of intraparenchymal hemorrhage (n=793). Abbreviations: ICU = Intensive Care Unit; EDH = epidural hematoma; SDH = subdural hematoma; SAH = subarachnoid hemorrhage; IPH = intraparenchymal hemorrhage.

Analysis 1 (Table 2) revealed a significant association between sex and Cr level at intensive care unit (ICU) admission ( $p=0.001$ ) and ICU discharge ( $p=0.005$ ). No significant associations were found between other demographic or clinical factors and creatinine levels at any of the measured time points.

**Table 2.** Comparison of Creatinine Levels at Five Time Points Against Demographic and Clinical Factors.

		Admission Cr	ICU Admission Cr	ICU Discharge Cr	Hospital Discharge Cr	Death Cr
Sex	Female	0.894	0.454	0.373	0.821	0.063
	Male	0.963	0.603	0.577	0.740	1.475
	<i>p</i> -value	0.241	0.001	0.005	0.770	0.303
Age Range	Under 18	0.696	0.530	0.434	0.440	0.000
	18-45	0.903	0.552	0.608	0.548	0.077
	46-74	0.973	0.593	0.494	0.800	2.866
	75+	0.974	0.563	0.455	1.08	0.151
	<i>p</i> -value	0.283	0.947	0.806	0.443	0.804
Injury Type	Blunt	0.9455	0.569	0.532	0.760	1.168
	Penetrating	0.978	0.519	0.416	0.6901	0.138
	<i>p</i> -value	0.754	0.657	0.309	0.617	0.339
Injury Mechanism	Fall	0.981	0.555	0.520	0.880	1.781
	Blunt Assault	0.909	0.634	0.578	0.636	0.071
	MVC	0.886	0.554	0.600	0.464	0.171

	Pedestrian Struck	0.871	0.616	0.530	0.532	0.158
	Micro MVC	0.846	0.564	0.501	0.534	0.026
	Penetrating Assault	0.996	0.545	0.437	0.696	0.145
	Other	0.843	0.302	0.209	0.672	0.000
	<i>p</i> -value	0.693	0.802	0.992	0.888	0.997
Diagnosis	Subdural	1.550	0.000	0.000	0.000	0.000
	Subarachnoid	0.942	0.605	0.628	0.600	0.129
	Epidural	0.640	0.460	0.530	0.610	0.000
	Intraparenchymal	0.962	0.577	0.556	0.809	1.433
	Concussion	1.160	0.786	0.707	0.489	0.293
	Other	0.884	0.560	0.486	0.560	0.097
	<i>p</i> -value	>0.05	>0.05	>0.05	>0.05	>0.05
Number of Injuries	One	0.979	0.550	0.457	0.936	2.140
	Two	0.886	0.546	0.595	0.548	0.119
	Three	1.040	0.734	0.700	0.689	0.165
	Four+	0.844	0.732	0.498	0.465	0.104
	<i>p</i> -value	0.217	0.124	0.469	0.399	0.831

Table 2: Cr at five time points (admission, ICU admission, ICU discharge, hospital discharge, and death) against demographics (sex, age range), and clinical factors (injury type, injury mechanism, diagnosis, number of injuries). Abbreviations: Cr = Creatinine; ICU = Intensive Care Unit; MVC = Motor Vehicle Collision.

Analysis 2 (Table 3) examined the effects of five different categories of creatinemia on mean ISS and GCS scores over five time points. For the Cr level at ICU admission, the creatinemia category had a significant effect on both mean ISS ( $p=0.0003$ ) and GCS ( $p=0.004$ ) scores. Likewise, at the Cr at patient death time point, creatinemia category had a significant effect on both mean ISS ( $p=0.017$ ) and GCS ( $p=0.001$ ) scores. No significant effect was seen on mean ISS or GCS scores at hospital admission, ICU discharge, or hospital discharge Cr.

**Table 3.** Effect of Creatinine Category on ISS and GCS Scores Across All Time Points.

		Extreme Hyper-creatinemia	Hyper-creatinemia	Normo-creatinemia	Hypo-creatinemia	Extreme Hypo-creatinemia	<i>p</i> -Value
Cr at Hospital Admission	ISS	19.78	21.75	18.17	17.34	18.05	0.056
	GCS	12.05	12.28	12.74	13.32	13.00	0.230
Cr at ICU Admission	ISS	20.81	22.16	19.89	18.90	17.29	0.0003
	GCS	11.79	12.61	12.16	13.48	13.10	0.004
Cr at ICU Discharge	ISS	19.95	17.64	19.21	18.44	18.20	0.607
	GCS	11.84	14.64	12.75	12.53	12.74	0.326
Cr at Hospital Discharge	ISS	20.32	19.18	17.83	17.79	18.91	0.448
	GCS	12.26	14.47	13.07	12.86	12.43	0.055
Cr at Death	ISS	21.00	26.25	19.10	38.50	18.36	0.017
	GCS	10.33	11.75	11.14	6.50	12.84	0.001

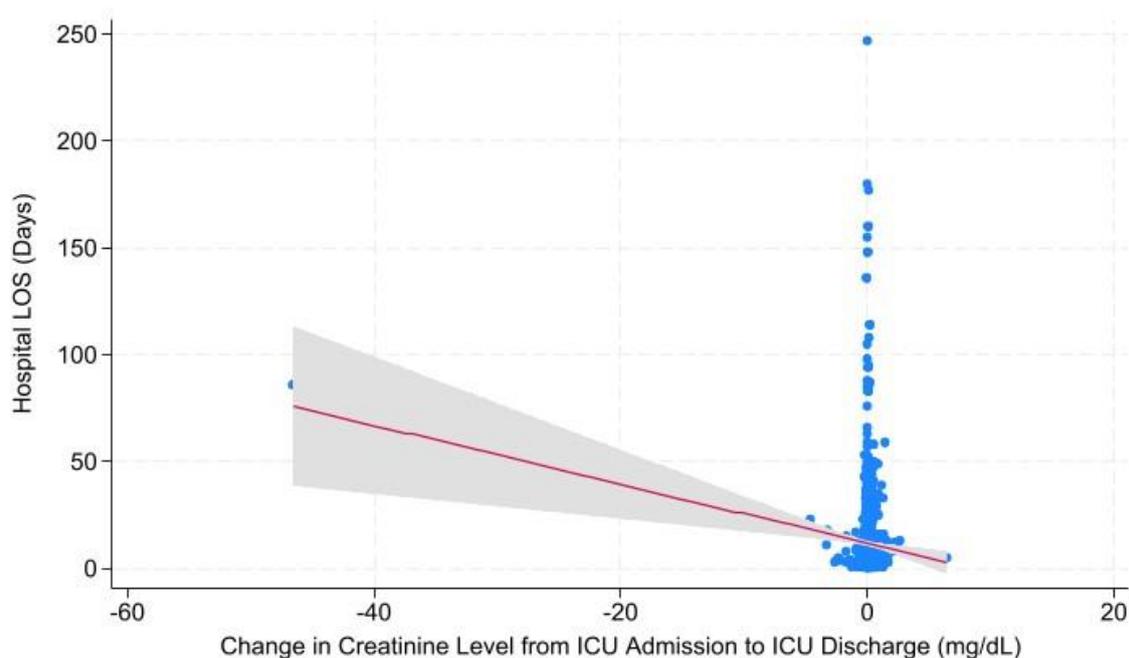
Table 3: The effect of various levels of creatinemia (extreme hyper-creatinemia, hyper-creatinemia, normo-creatinemia, hypo-creatinemia, and extreme hypo-creatinemia) on ISS and GCS severity rating scores across all five measured time points (hospital admission, ICU admission, ICU discharge, hospital discharge, and death). Abbreviations: Creatinine; ICU = Intensive Care Unit; ISS = Injury Severity Score; GCS = Glasgow Coma Scale.

The third level of analysis (Table 4) assessed correlations between change in creatinine level and continuous (hospital length of stay, ICU length of stay, ventilator days) and categorical (mortality) dependent variables. Change in Cr from Hospital to ICU admission was significantly correlated with ventilator days ( $p=0.045$ ; Coefficient  $\pm$  95% CI=  $-0.500 \pm -0.989 - -0.011$ ). Change in Cr from ICU admission to ICU discharge was significantly correlated with hospital length of stay (Figure 1;  $p=0.001$ ; Coefficient  $\pm$  95% CI=  $-1.380 \pm -2.180 - -0.580$ ), ICU length of stay ( $p=0.000$ ; Coefficient  $\pm$  95% CI=  $-0.542 \pm -0.827 - -0.257$ ), and ventilator days ( $p=0.011$ ; Coefficient  $\pm$  95% CI=  $-0.322 \pm -0.569 - -0.074$ ).

**Table 4.** Correlation Between Hospital LOS, ICU LOS, Ventilator Days, and Mortality in Changes in Creatinine Level.

Timeframe	Outcome	P-value	Coefficient $\pm$ 95% CI
Change in Cr Level from Hospital Admission to ICU Admission	Hospital LOS	0.497	$-0.550 \pm -2.14 - 1.04$
	ICU LOS	0.265	$0.321 \pm -0.887 - 0.244$
Change in Cr Level from ICU Admission to ICU Discharge	Ventilator Days	0.045	$-0.500 \pm -0.989 - -0.011$
	Mortality	0.139	$-0.019 \pm -0.043 - 0.006$
Change in Cr Level from Hospital Admission to ICU Discharge	Hospital LOS	0.001	$-1.380 \pm -2.180 - -0.580$
	ICU LOS	0.000	$-0.542 \pm -0.827 - -0.257$
	Ventilator Days	0.011	$-0.322 \pm -0.569 - -0.074$
	Mortality	0.148	$0.009 \pm -0.003 - 0.022$

Table 4: The relationship between changes in creatinine level during two time frames (hospital admission to ICU admission, and ICU admission to ICU discharge) and various outcomes (hospital length of stay, ICU length of stay, ventilator days, and mortality). Abbreviations: Creatinine; ICU = Intensive Care Unit; LOS = Length of Stay.



**Figure 1.** Change in ICU Admission to ICU Discharge Creatinine vs. Hospital Length of Stay. The relationship between hospital length of stay in days and change in creatinine level from ICU admission to ICU discharge,

which was a statistically significant finding ( $p=0.001$ ). Abbreviations: LOS = Length of Stay; ICU = Intensive Care Unit.

Analysis 4 (Table 5) assessed correlations between creatinine level across admission and continuous (hospital length of stay, ICU length of stay, ventilator days) and categorical (mortality) dependent variables. Overall, there were significant correlations between Cr at admission and ICU length of stay ( $p=0.043$ ; Coefficient  $\pm$  95% CI=  $0.586 \pm 0.019 - 1.152$ ), Cr at ICU Admission and ICU length of stay ( $p=0.001$ ; Coefficient  $\pm$  95% CI=  $1.029 \pm 0.429 - 1.630$ ) and Cr ICU Admission and vent days ( $p=0.031$ ; Coefficient  $\pm$  95% CI=  $0.576 \pm 0.054 - 1.098$ ). For patients with 1 injury ( $N=508$ ), there were significant correlations between Cr at ICU admission and hospital length of stay ( $p=0.024$ ; Coefficient  $\pm$  95% CI=  $1.238 \pm 0.162 - 2.315$ ), ICU length of stay ( $p=0.003$ ; Coefficient  $\pm$  95% CI=  $0.766 \pm 0.255 - 1.276$ ), and vent days ( $p=0.002$ ; Coefficient  $\pm$  95% CI=  $0.508 \pm 0.186 - 0.831$ ). For patients with 2 injuries ( $N=367$ ), there were significant correlations between Cr at admission and ICU length of stay (Figure 2;  $p=0.029$ ; Coefficient  $\pm$  95% CI=  $2.629 \pm 0.277 - 4.980$ ) and between Cr at ICU admission and ICU length of stay (Figure 3;  $p=0.010$ ; Coefficient  $\pm$  95% CI=  $2.399 \pm 0.572 - 4.227$ ).

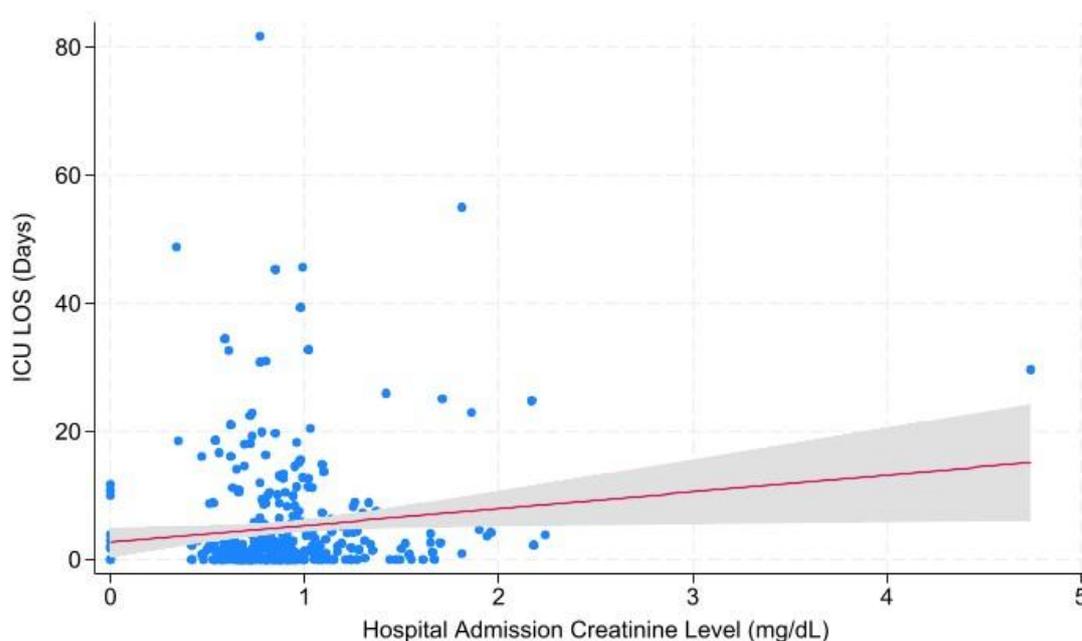
No significant associations were noted amongst patients who sustained 3 or more injuries. However, this subset comprised a relatively small cohort ( $N=89$  for 3 injuries and  $N=19$  for 4 or more injuries). Thus, these findings may represent a Type II error.

**Table 5.** Comparison of Cr Levels at Various Time Points to Clinical Outcomes, Stratified by Number of Sustained Patient Injuries.

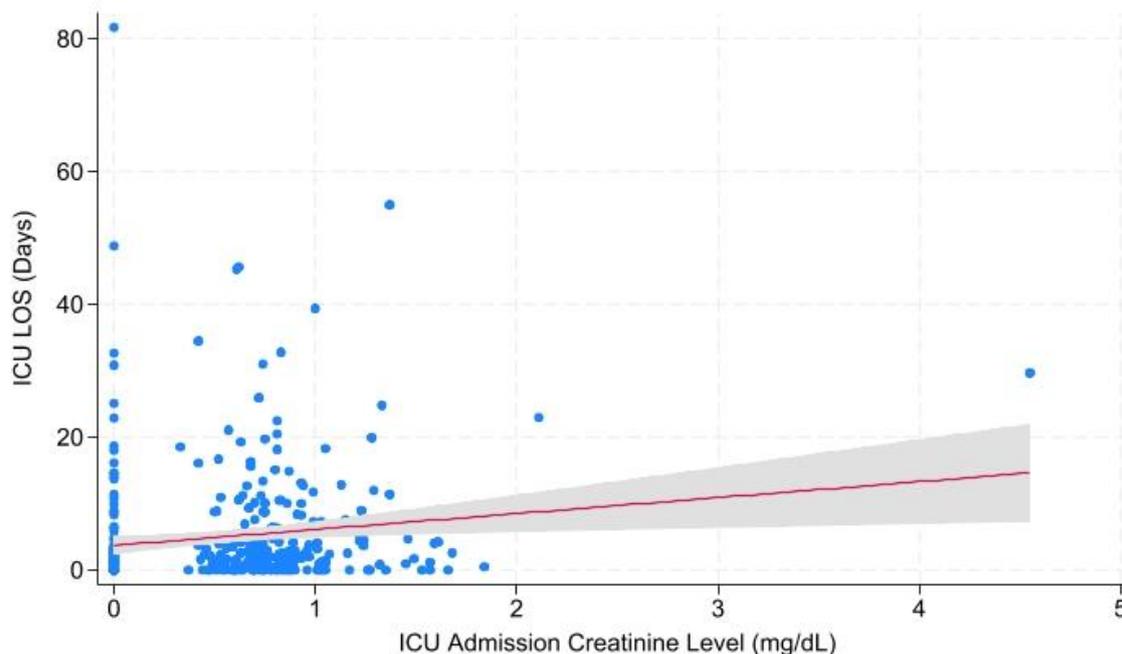
	Timeframe	Outcome	P-value	Coefficient $\pm$ 95% CI
Overall	Cr at Admission	Hospital LOS	0.472	$0.584 \pm -1.008 - 2.175$
		ICU LOS	0.043	$0.586 \pm 0.019 - 1.152$
		Ventilator Days	0.981	$0.006 \pm -0.486 - 0.497$
		Mortality	0.755	$-0.004 \pm -0.029 - 0.021$
	Cr at ICU Admission	Hospital LOS	0.135	$1.289 \pm -0.404 - 2.982$
		ICU LOS	0.001	$1.029 \pm 0.429 - 1.630$
		Ventilator Days	0.031	$0.576 \pm 0.054 - 1.098$
		Mortality	0.211	$0.017 \pm -0.010 - 0.043$
Cr at ICU Discharge	Mortality	0.417	$-0.005 \pm -0.017 - 0.007$	
1 Injury	Cr at Admission	Hospital LOS	0.174	$0.617 \pm -0.272 - 1.506$
		ICU LOS	0.061	$0.404 \pm -0.019 - 0.826$
		Ventilator Days	0.408	$0.113 \pm -0.155 - 0.391$
		Mortality	0.948	$0.001 \pm -0.022 - 0.023$
	Cr at ICU Admission	Hospital LOS	0.024	$1.238 \pm 0.162 - 2.315$
		ICU LOS	0.003	$0.766 \pm 0.255 - 1.276$
		Ventilator Days	0.002	$0.508 \pm 0.186 - 0.831$
		Mortality	0.197	$0.018 \pm -0.009 - 0.045$
Cr at ICU Discharge	Mortality	0.274	$-0.017 \pm -0.049 - 0.014$	
2 Injuries	Cr at Admission	Hospital LOS	0.927	$0.314 \pm -6.437 - 7.065$
		ICU LOS	0.029	$2.629 \pm 0.277 - 4.980$
		Ventilator Days	0.516	$0.562 \pm -1.139 - 2.263$
		Mortality	0.613	$0.024 \pm -0.070 - 0.119$
	Cr at ICU Admission	Hospital LOS	0.420	$2.151 \pm -3.083 - 7.385$
		ICU LOS	0.010	$2.399 \pm 0.572 - 4.227$
		Ventilator Days	0.154	$0.960 \pm -0.362 - 2.285$
		Mortality	0.602	$0.019 \pm -0.053 - 0.093$

3 Injuries	Cr at ICU Discharge	Mortality	0.577	-0.004 ± -0.019 – 0.011
		Hospital LOS	0.824	0.802 ± -6.337 – 7.942
	Cr at Admission	ICU LOS	0.699	0.365 ± -1.504 – 2.234
		Ventilator Days	0.478	-1.111 ± -4.209 – 1.988
		Mortality	0.420	-0.028 ± -0.098 – 0.041
	Cr at ICU Admission	Hospital LOS	0.747	-0.938 ± -6.691 – 4.816
		ICU LOS	0.936	0.061 ± -1.443 – 1.566
		Ventilator Days	0.956	-0.070 ± -2.569 – 2.429
	Cr at ICU Discharge	Mortality	0.958	-0.001 ± -0.058 – 0.055
		Mortality	0.943	-0.002 ± -0.058 – 0.054
		Hospital LOS	0.469	10.642 ± -20.387 – 41.671
	4+ Injuries	Cr at Admission	ICU LOS	0.159
Ventilator Days			0.406	3.980 ± -6.090 – 14.050
Mortality			0.203	-0.478 ± -1.251 – 0.296
Cr at ICU Admission		Hospital LOS	0.549	-7.523 ± -34.124 – 19.078
		ICU LOS	0.863	0.832 ± -9.435 – 11.098
		Ventilator Days	0.924	0.397 ± -8.432 – 9.225
Cr at ICU Discharge		Mortality	0.198	0.411 ± -0.246 – 1.068
		Mortality	0.133	-0.547 ± -1.285 – 0.192
		Hospital LOS	0.133	-0.547 ± -1.285 – 0.192

Table 5: The correlations between Cr Levels at various time frames (Cr at admission, Cr at ICU admission, Cr at ICU discharge) and clinical outcomes of interest (hospital length of stay, ICU length of stay, ventilator days, mortality), stratified by number of injuries sustained by the patient (overall, one, two, three, or four or more). Abbreviations: Creatinine; ICU = Intensive Care Unit; LOS = Length of Stay.



**Figure 2.** Hospital Admission Creatinine Level vs. ICU Length of Stay for Patients with Two Injuries. The significant relationship between creatinine level at the time of hospital admission and ICU length of stay in days among patients who sustained two injuries. Abbreviations: ICU = Intensive Care Unit; LOS = Length of Stay.



**Figure 3.** ICU Admission Creatinine Level vs. ICU Length of Stay for Patients with Two Injuries. The significant relationship between creatinine level at the time of ICU admission and ICU length of stay in days among patients who sustained two injuries. Abbreviations: ICU = Intensive Care Unit; LOS = Length of Stay.

#### 4. Discussion

The impact of creatinine levels among patients suffering severe TBI has been well studied, but mostly in the context of AKI, often defined by changes in serum creatinine, and its association with ICU outcomes in TBI populations [3–8,19,20]. Large multicenter cohort studies have demonstrated that AKI is associated with increased ICU length of stay and worse neurological outcomes in TBI patients. The Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI) study found that AKI (using KDIGO [21] creatinine criteria) was associated with longer ICU stays and higher mortality at 6 months [3]. Similarly, severe AKI (stage 3 or greater, based on creatinine) has been linked to increased hospital length of stay and greater need for tracheostomy and gastrostomy, which are indirect markers of prolonged ventilator dependence [19]. While our study did not examine AKI as a composite endpoint in examining TBI outcomes, we did consider the direct relationship between creatinine levels and a number of important clinical outcomes.

When comparing creatinine levels at different time points to demographic factors, we found a significant difference among sexes for creatinine at ICU admission and ICU discharge, with males presenting with higher creatinine levels at these time points. One 2021 study found sex-based differences in serum creatinine response after TBI [22]. In the acute phase, both male and female TBI patients showed changes in creatinine. However, elevated creatinine is associated with improved short-term neurological recovery in males, but not in females [22].

While we did not note any other significant relationships between demographics and creatinine in our study, existing literature suggests age is a strong predictor of both renal outcomes and overall prognosis after TBI, with patients < 65 years old having a higher risk of developing chronic kidney disease (CKD) post-injury [23,24]. One 2023 case-control study aimed to investigate the clinical outcomes of TBI patients with or without CKD comorbidity at the time of injury and found that ICU length of stay and hospitalization expenses were higher in the CKD group than the non-CKD group, although not statistically significant, and advanced age, low admission GCS score, elevated blood urea, and creatinine levels were significantly associated with a poor neurological prognosis [24].

There is no evidence in the medical literature that injury type (i.e., blunt vs. penetrating), injury mechanism, or specific type of intracranial injury (i.e., subarachnoid hemorrhage, epidural hematoma, etc.) has a significant independent impact on creatinine levels or the risk of AKI in patients with TBI. However, the number of injuries, and specifically whether a patient has isolated TBI or polytrauma, is associated with an increased risk of AKI and higher creatinine levels [3,5,25].

In this study, we did not note significant associations between the number of injuries and measured creatinine at any particular time point. We did, however, find significant relationships between baseline creatinine levels at certain timepoints and specific outcomes such as ICU length of stay and vent days when stratified by number of injuries. Specifically, patients with one or two injuries had a significant relationship between creatinine level at the time of ICU admission and ICU length of stay. This is in keeping with robust research that demonstrates higher creatinine levels and the development of AKI are associated with increased ICU length of stay in patients with TBI [26,27]. Overall, and for patients with 1 injury, creatinine level at ICU admission was significantly associated with ventilator days. As with increased ICU length of stay, previous multicenter studies and meta-analyses have shown that the number of vent days is positively correlated with AKI, as defined by creatinine levels [25,28,29].

Lastly, we found that the range of creatinemia was significantly associated with ISS and GCS scores at ICU admission and patient death timepoints. While the range of creatinemia has not been related to injury severity scoring in previous studies, several existing studies have shown that lower GCS and higher ISS are associated with higher creatinine levels and increased risk of AKI in severe TBI patients [5,20]. *Zhang et al. (2025)* conducted a systematic review and meta-analysis and reported that lower GCS at admission and  $GCS \leq 8$  were significantly associated with increased risk of AKI, as defined by elevated creatinine. Higher admission serum creatinine was also identified as a risk factor for AKI in TBI patients [5]. *De Cássia et al. (2024)* conducted a retrospective cohort study of severe TBI and showed that higher New Injury Severity Score (NISS) and lower GCS were independently associated with both the occurrence and severity of AKI, as well as with an increase in in-hospital mortality [20].

An important limitation of this study is the lack of demographic variables assessed in our analysis of the relationship between creatinine levels and severe TBI. While age and sex-based differences have been reported in serum creatinine levels following TBI [22–24], other demographic factors such as race and ethnicity have also been shown to influence creatinine levels [25]. In addition, pre-existing comorbidities such as diabetes mellitus, hypertension, chronic kidney disease, congestive heart failure, and higher body mass index (BMI) have all been shown to be associated with increased risk of increased creatinine levels and AKI in patients with severe TBI [25,30,31]. Secondly, most studies evaluated creatinine in the context of AKI, not as a standalone endpoint. There was little literature on creatinine as it relates to TBI alone, as it is so commonly used to assess GFR and AKI. As a result, the relationship between creatinine and our measured outcomes of interest may have low external validity as it pertains to the measurement of renal function.

## 5. Conclusion

Our analysis corroborates existing literature that demonstrates a positive relationship between creatinine levels, ICU length of stay, and ventilator days amongst patients with severe traumatic brain injury. Future research should focus on expanding clinical and demographic factors in the assessment of creatinine changes associated with severe TBI, as well as potentially including measurement of renal function and other clinical endpoints related to creatinine levels.

**Author Contributions:** **Conceptualization**—B.S.; **Resources**- B.S., and G.A.; **Methodology**- B.S. and Z.S., **Formal analysis**- B.S. and S.R., **Investigation**- B.S., K.T. and N.D.B., **writing—original draft preparation**—B.S. and S.D.M.; **writing—review and editing**—B.S. and J.W., **supervision**—B.S.; **project administration**—B.S. All authors have read and agreed to the published version of the manuscript.

**Funding:** There is no grant support or financial relationship for this manuscript.

**Institutional Review Board Statement:** This retrospective study was approved by the IRB at Elmhurst Facility on 5 July 2024, with IRB number 24-12-092-05G.

**Informed Consent Statement:** Retrospective analysis was performed on anonymized data, and informed consent was not applicable.

**Data Availability Statement:** The data was requested from the Elmhurst Trauma registry and extracted using electronic medical records after receiving approval from the Institutional Review Board at our facility (Elmhurst Hospital Center).

**Conflicts of Interest:** The authors have no competing interests to declare.

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