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Serum Uric Acid as An Early Marker of Injury Severity in Trauma Patients: A Cross-Sectional Study at a Ugandan Tertiary Hospital

Okwi Nick
School of Medicine, Makerere University College of Health Sciences, Kampala
drnickokwi@gmail.com

Galukande Moses
School of Medicine, Makerere University College of Health Sciences, Kampala
mosesg@img.co.ug

Rukundo Gideon
Mulago National Referral and Teaching Hospital, Kampala
grugali@yahoo.com

Abstract:
Background: Trauma is still the leading cause of death in many regions of the world. Several severity scores have been developed to assist in the management of trauma victims. The Injury Control Centre in Uganda developed the Kampala Trauma Score (KTS II) for use in resource-limited settings. With the limitations of the existing trauma scoring systems, there is a need to explore new, affordable, easy to use accurate diagnostics. Some studies in high income countries have shown that Serum Uric Acid (SUA) has been previously shown to be elevated in trauma and serves as an Alarmin. The aim of this study, therefore, was to determine the correlation between SUA levels and injury severity in trauma patients in a resource limited setting.

Methods: An analytical, single center, cross-sectional study carried out at a tertiary hospital AE unit in Kampala. Trauma patients aged ≥18 years presenting within 24 hours after injury were recruited consecutively after obtaining a written informed consent.
Injury severity was determined using the KTS II scoring system and venous blood was drawn for SUA assay. Data were analyzed and the correlation of SUA levels with severity of trauma as defined by KTS II was made.

Results: A total of 154 patients was recruited with a male to female ratio of 5.4: 1. Road traffic crashes (RTC) were the commonest (64%) cause of injury; pedestrians were involved in 30% of the cases. The correlation between SUA levels and severity between injury was depicted by the area under the receiver operator characteristics curve = 0.6015.

Conclusion: Serum uric acid was a poor prediction of severity of injury among trauma patients in this low resource environment.

Keywords: Trauma, Serum Uric acid, injury severity, KTS II Score, Biomarker, Alarmin.

INTRODUCTION

Globally, trauma is among the leading causes of mortality especially in the productive age groups and has since gained public health significance(1). Traumatic injury results in a vast immune response that may culminate in MODS and/or death(2). Severity of response corresponds to severity of injury and outcome on the host(3, 4). This response has been widely studied by measuring blood levels of proinflammatory cytokines such as Interleukin 6 (4,5-13) but this is unaffordable, not easily available, requires high technology and skilled personnel yet in a setting of resource limited countries. The search for newer, affordable and better diagnostic biomarkers would potentially have great impact on workup and its use for diagnostic accuracy and hence predict outcome of trauma in a resource limited countries.(6)

In 2010, in Uganda study, Mutooro et al (7) found that 80% of polytrauma patients were within the productive age bracket of 18 – 45 years whereas 37% of injuries were due to road traffic crashes. In another Uganda study at the national referral hospital, trauma was the single most common reason for admission to the surgical wards, with a mean age of 25 years involving mostly male patients. (8)
Injury severity scoring helps in triage and prediction of outcome. Many severity scores have since been developed: all based on either anatomical or physiological parameters or both. Their complexities have seen them undergo many revisions, (9, 10, 11). One of those revised is the Kampala Trauma Score which was designed for use in resource limited settings (12). However, there is mounting confusion as to which scoring systems can be used to adequately control for the trauma case mix. (13)

Traumatic injury results in a vast immune response that may culminate in death(2). Severity of response corresponds to severity of injury and outcome on the host(3, 4). This response has been widely studied by measuring blood levels of proinflammatory cytokines such as Interleukin 6 (4, 5, 14) but this is unaffordable, not easily available, requires high technology and highly skilled personnel. Therefore the need to search for newer, affordable and better diagnostic biomarkers suitable for a resource limited countries.(6)

SUA has emerged as a crucial, very early mediator of damage response to injury (15). The discovery and recognition of SUA as an Alarmin with pro-inflammatory role in trauma may provide a molecular link between cell injury and immunity and thus have important implications for inflammation, vaccines and autoimmunity (16, 17).
This study, therefore describes the correlation between SUA and injury severity in a low resource setting.

Methods

Study Design and Setting

This was an analytical, single-center, cross-sectional study carried out at Mulago National Referral Hospital (MNRH) in the Accident and Emergency unit (A&E). MNRH with a 1500 bed capacity serves as Makerere University's teaching hospital in Uganda. The A&E department handles both medical and surgical emergencies in separate wings. It also has an operating room, an X-ray and ultrasound facility, and 4 bedded resuscitation rooms. Also closer to it are; a blood bank, haematology, microbiology and chemistry laboratories.

This A&E unit is open 24 hours and is headed by a consultant Surgeon who leads a team of anaesthesiologist, surgical residents (trainees), medical officers, paramedics, nurses and other support staff.

Study Participants Recruitment

On arrival in the A&E unit, patients were triaged and transferred to the assessment rooms where they were immediately attended to by doctors. Following admission, patients were sent to the resuscitation rooms where they were managed according to the ATLS protocol. Patients requiring surgery were resuscitated and immediately sent to the operating rooms. Other patients were either treated and discharged or sent to the holding emergency ward where they were reviewed within 24 hours before being transferred to the admitting firm or specialized units.

Sampling and Data Collection

All trauma patients who presented to the A&E unit within 24 hours of injury during the study period and aged 18 years and above between 1st March and 31st April 2015 were eligible for the Study after consent/proxy consent was obtained. Individuals with history, physical examination or previous investigations/medical documents who were known to have gout and renal disease were excluded. Using the Fishers Arctanh transformation formula for correlation studies, sample size of 150 was estimated inclusive of 10% for unforeseen errors.

A non-probability sampling technique specifically consecutive sampling was used, at least 3 participants (154 respondents) were enrolled every day. From a list, study participants were identified in A&E by the Doctors in that department using patient files and where necessary inpatient registers, they were confirmed and recruited.

All patients were assessed using the ATLS principles of triage, primary and secondary survey.
Using a pre-determined data sheet the following variables were documented; age, sex, occupation, mechanism of injury, type of injury, body region injured, time of admission, duration of the injury and KTS II scores.

Four to five milliliters of venous blood were withdrawn from a convenient peripheral vein and sent to the clinical chemistry laboratory Mulago (Certified Laboratory) on the same day (within 1 hour) of which the reader of the index test (Laboratory technician) was blinded to the patients KTS II SCORE. The clear and non-haemolysed specimen was allowed to clot for at least 30 minutes before centrifuging at 1,000 x. The serum layer was then removed and assayed immediately or stored at 2-8^{o} Celsius.
All biochemical parameters were measured by automated standard enzymatic Roche method on analyzer Cobas C systems (Roche Diagnostics, Mannheim, Germany) at the clinical chemistry lab located on the 3rd floor, Mulago hospital.

This clinical chemistry analyzer Cobas 6000 that employs the Roche assay method is a slight modification of the colorimetric method developed by Town et al. It is an enzymatic colorimetric test. In this reaction, uricase cleaves uric acid to form allantoin and hydrogen peroxide. In the presence of peroxidase, 4-aminophenazone is oxidized by hydrogen peroxide to form a quinine-diimine dye. The intensity of the red color formed is proportional to the uric acid concentration and it is determined photometrically by measuring the increase in absorbance.

Data Handling
Prospective data were captured on paper case report forms and then double entered into EPIDATA, cleaned and validated.
A backup copy was created, frozen and transferred to STATA version 11 for analysis.
The categorical variables were summarized using frequencies and proportions, mean and standard deviation or median and inter-quartile range for skewed data. Using the KTS II as the reference standard, patients were divided into mild (non-severe) group with scores >8 and severe group with scores of ≤8.
A Receiver Operator Characteristic (ROC) curve was plotted for SUA level as a predictor of injury severity using the KTS II score and the area under the curve determined for the specificity and sensitivity.
The database was reviewed for consistency and completeness and updated using a standardized approach.

Ethical Consideration
Ethical clearance was obtained from the Makerere University School of Medicine Research and Ethics Committee (SOMREC). Informed consent was obtained from participants or Next of Kin prior to inclusion into the study. Patients were free to opt out of the study and they were nott denied any treatment.
For patients with altered mentation, unconscious and/or unknown, proxy consent was obtained from the SOMREC. However, informed consent was obtained when they recovered their conscience. Severely injured patients were resuscitated while maintaining confidentiality and privacy.

Results
A total of 154 trauma patients was seen in the study period between March and April 2015. Eighty seven sustained mild trauma (KTS II >8) while sixty seven sustained severe trauma (KTS II ≤8).

KTS II Scores
The mean (standard deviation) score was 7.72 (1.75).

Characteristics of the Study population are shown in tables 1, 2 and 3
Age: The injured patients were mainly young adults of productive age category 18 to 29 years representing eighty seven (56.49%) of the study participants of which forty six (52.87%) and forty one (47.12%) sustained severe and mild trauma respectively.
Injured patients in the category of 30 to 44 years were fifty (33.76%) of the study participants.

Gender: More males, one hundred and thirty (84.41%) than females, twenty eight (18.12%) sustained injuries during the study period. The p-value was 0.086.
Considering males alone, seventy nine (60.76%) was severely injured as compared to ten (35.7%) of females alone who sustained severe injury too.

Education Level: Sixty three (40.90%) study participants had studied up to primary school level, only forty seven (30.51%) up to secondary level while only fifteen (9.74%) participants studied up to tertiary school level. Twenty nine (18.83%) had no formal education.

Occupation: Majority of the trauma patients, sixty (38.96%), where businessmen and women, whereas thirty (19.48%) were peasants. Only twenty six (16.88%) were salaried workers.

Mode of Transport: Fifty two (33.77%) study participants arrived at the Accident and Emergency unit in a Police pickup of which thirty two (80%) was severely injured.
Similarly, only forty one (26.62%) injured patients were brought in an Ambulance of which thirty one (75.61%) were severely injured.
In total, sixty three (70.78%) of the severely injured patients arrived in an ambulance (34.83%) and police pick (35.95%).

Body Region Injured: The most commonly injured body regions was headed, face and neck with seventy one (46.10%) patients affected. The second most affected body region was abdomen/visceral pelvis accounting for forty (25.97%) patients.
Sixty one (39.61%) patients had more than one body region injured and the least body region injured was the external/skin accounting for only eight (5.19%) of the study participants.

Mechanism of Injury: Ninety nine (64.29%) study participants were involved in road traffic crashes and only thirty nine (25.32%) were assaulted. Of those involved in a road traffic crash, 42.27% were passengers and 29.90% pedestrians.
Sixteen (10.39%) study participants sustained a fall, gunshot wounds, Burns and bomb blast injuries combined.

Type of Injury: The most common type of injury was blunt trauma, accounting for sixty five (42.21%) and followed closely by penetrating trauma (38.31%) of the study participants.

Therapy Prior to Admission: One hundred and thirty five (90.60%) of study participants had received a combination of therapy (intravenous fluids, NSAIDS and antibiotics) prior to admission.

Duration of Injury: The median duration of injury among study participants was 3.0 (1.-14) hours and the mean (standard deviation) duration of injury was 4.56 (3.62) hours.

Serum Uric Acid: One hundred and twelve (72.72%) had normal SUA levels (3.0 to 7.0 mg/dl). Of the forty two (27.27%) with abnormal values, 28 (66.67%) were study participants who sustained severe injuries.

SUA and dUration of Injury (Figure 3): From linear regression, every unit increase in time of injury (i.e for every hourly increase in time of injury), SUA increased by 0.04 (-0.05-0.13) with a p-value = 0.392.

An Association of Sua Levels With Severity of Injury As Defined By The KTS II (Table 4, Figure 1 & 2): The association between SUA levels in trauma patients in this study population and severity of injury was not significant. This was shown by an insignificant distribution of SUA levels among the severely and mildly injured groups of patients. Only forty two (27.27%) of injured patients had abnormal levels of SUA (P=0.174)
When SUA levels were varied by 1 mg/dl starting from 2 mg/dl (Table 4), a receiver operator characteristic (ROC) curve was generated (Figure 2) and the area under the curve was 0.6015.

DISCUSSION

The purpose of this study was to determine the correlation of SUA and the severity of injury as defined by KTS II. This is the first study to describe this relationship over the environment. We found that SUA did not correlate with the severity of injury.

The area under the ROC curve was 0.6015, scores ranging from 0.50 to 0.69 are considered poor as a predictor of severity of disease. At a cut off level of 5mg/dl, serum uric acids levels were not able to differentiate between severe and non-severe injury with a sensitivity of 61% but a low specificity of 48%, positive and negative predictive values of 62% and 48% respectively.

These findings are contrary to studies by Zhu et al and Moor et al who noted a significant elevation of SUA in patients with trauma and Closed head injury induced in mammal studies. (18,19). This difference could be due to the fact that Zhu et al analyzed SUA levels of trauma patients in intensive care unit and was a retrospective study whereas Moor et al studied SUA rise in closed head injury in mammals as opposed to humans.

In this study, the median duration of injury among study participants was 3.0 (1.-14) hours and the mean duration of injury was 4.56 (SD 3.62) hours. This exceeded the recommended 'golden hour' in trauma management. Mujuni et al found a mean duration of injury of 4 hours(21) while Kalanda et al found a duration of 3.5 hours(22). In Germany, Steinsballe et al found a median (IQR) duration of 40(32-49) minutes(4). This high difference could be due to a poor Ambulance system in Uganda.
For the correlation of SUA levels with duration of injury in hours, every unit increase in time of injury (i.e. for every hourly increase in time of injury), SUA increased by 0.04 (-0.05-0.13) with a p-value = 0.392. Implying a non-significant relationship between SUA and time of injury.

This is comparable to a study by Dubick et al, found that SUA levels remained within the normal ranges up to four days post trauma and there was no variation between the burns and the non-burn (control) patients (20).

Characteristics of the Study Population
The age ranged from 18 – 64 years with a mean of 30.28 (9.01) years. Most affected age category was 18 to 44 years accounting for 90.23% of the study population. This finding is comparable to findings in other studies. Mutooro et al found 80.3% of trauma patients to be within the age bracket 18 – 45 years (7). Mujuni et al in Mulago Hospital found the mean age to be 29.5 years.(21)

Males constituted 130 (84.41%) of the injured patients, giving a male to female ratio of 5.4:1 with p=0.086. This is comparable to other studies done in Mulago. Mujuni et al found a ratio of 4.5:1 (21), Kalanda et al found a ratio of 4.7 : 1(22) and Birabwa Male found a ratio of 5:1(23). The male predominance could be because of the male gender being more involved various outdoor economic and social activities making them more prone to injuries/accidents.

Sixty three (40.90%) of the study participants had studied only upto primary school whereas up to 29 (18.80%) of the participants had no formal education at all (p=0.006). Other studies in trauma done within Mulago(21, 23) all found a low education level in the study populations. This could be because of poor understanding of road safety rules.

Most of the study participants, 60 (38.96%), were involved in some form of business activity (p=0.007) whereas 30 (19.48%) were peasants. Kalanda et al in a prospective study found 38.36% were involved in business activity(22). Renee et al while reviewing trauma registries in Mulago Hospital found the most frequently injured population were students – 20% and casual laborers – 17%(8). However, Mujuni et al in a prospective cohort study found that 38.46% of the trauma patients they studied were involved in boda boda business and this is comparable to this study's finding(21).

Only 41 (26.62%) of the injured patients were brought to Hospital in an Ambulance. 52 (33.77%) of the victims were brought in Police pickup. Note that Sixty three (40.90%) of the severely injured patients arrived in an ambulance or police pickup. Renee et al reported that <5% of trauma victims came in an Ambulance compared to 22% brought in police vehicles. This difference could be attributed to an improving Ambulance system and policing in Uganda.

The most frequently injured body region was the head, face and neck with 71 (46.10%) patients affected. The second most injured body region was abdomen/viscera accounting for 40(25.97%) of the study population. Kobusingye et al found the most frequently injured body region to be head and neck – 44% followed by bony pelvis/extremities at 39%(24). Similar findings were reported by Mutooro et al(7) and Demyttenaere(25).

The commonest cause of injury was road traffic crashes (RTC) accounting for 99 (64.29%) followed by assault, thirty nine (25%) of the study population. Other studies reported similar findings. Mujuni et al found RTC to contribute 64.3% followed by assaults at 25% While Chalya et al in Tanzania found 64%(21, 26).

Passengers were the most vulnerable group of people. They constituted 42%, followed by passengers at 29.90% and drivers at 28%. Mutooro et al found passengers, especially those on motorcycles as the most vulnerable accounting for 69%(7). The above findings show a persistently high contribution of RTC to morbidity. This could be attributed to motorized development and rural-urban migration leading to unemployment of young youth. These youth commonly resort to driving motorized two-wheelers, boda-bodas, which according to a WHO finding is a high cause for road injuries and deaths(27).

42% patients sustained blunt trauma and 38% sustained penetrating trauma. Similarly, Mutooro et al found the commonest type of injury was penetrating trauma at 58% and 42% were blunt trauma (7). However, Chalya et al found blunt trauma to be responsible for 89.8% of injuries (21).

LIMITATIONS

We used a cross-sectional study design which cannot be relied on to make strong conclusions and we could not fully ascertain the history of chronic illnesses or chronic medication use that some patients had been on, especially those unknown and those brought in by Police

CONCLUSION

SUA levels, neither correlated with severity of injury as defined by the KTS II nor showed a significant variation with the duration of the injury. Road traffic crashes are still the most causes of injury and the most injured body regions are the head, face and neck. Another study needs to be done to further evaluate various biomarkers to accurately define the severity of injury.

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CONFLICT OF INTEREST

The authors declare no competing interest in this work.

AUTHOR CONTRIBUTION

ON and GM originated the concept. ON collected data, performed data analysis and wrote the first draft. All authors performed critical reviews of the manuscript for intellectual content. All authors performed intellectual reviews and approved the final manuscript.

ABBREVIATIONS

- A& E Accident & Emergency
- KTS Kampala Trauma Score
- ROC Receiver operator characteristic
- RTC Road traffic crashes
- SUA Serum Uric Acid
- WHO World Health Organization

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Legend of Figures

Figure 1: Receiver operator characteristic (ROC) for serum uric acid levels

Figure 2: Linear regression analysis showing variation of serum uric levels with duration of injury in hours among trauma patients attending Mulago Hospital

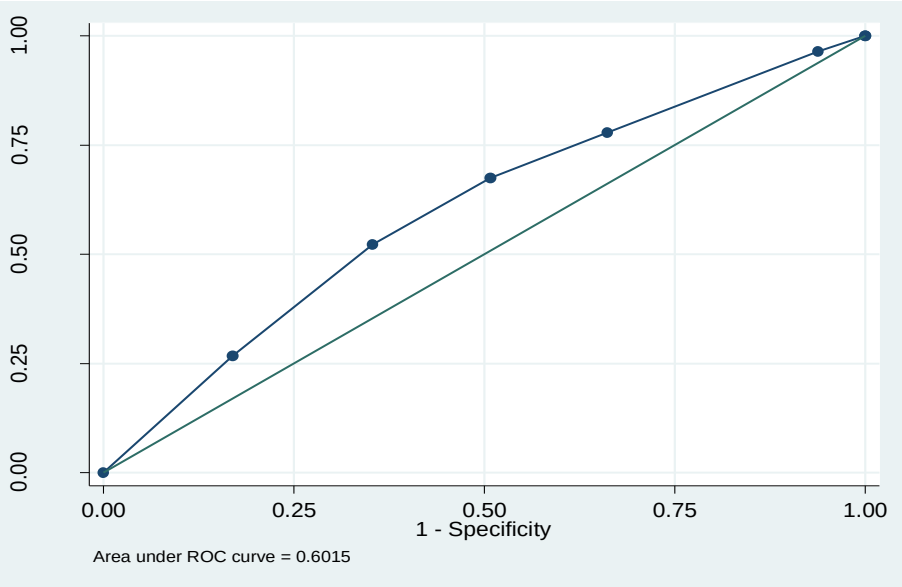

Figure 1: Receiver operator characteristic (ROC) for serum uric acid levels

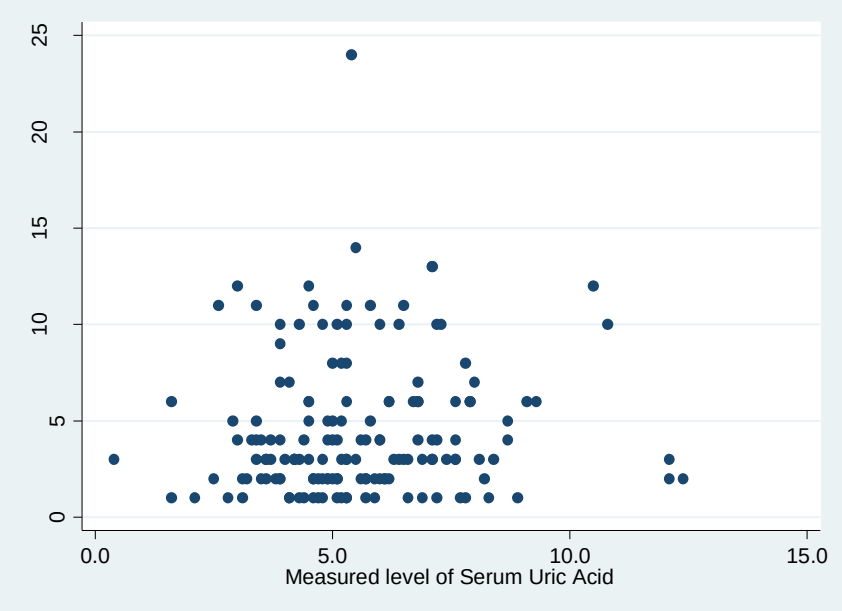

Figure 2: Linear regression analysis showing variation of serum uric levels with duration of injury in hours among trauma patients attending Mulago Hospital

Table 1: Socio-demographic characteristics of the study population by Severity of Trauma among trauma patients attending Mulago Hospital

Variable	Severity of disease			
	Mild	Severe		
	N (%)	N (%)	OR(95%CI)	p-value
Age categories (years)				
18 to 29	41(63.08)	46(52.27)	Reference	
30 to 44	19(29.23)	33(37.50)	1.55(0.77-3.13)	0.224
45 to 60	5(7.69)	9(10.23)	1.60(0.50-5.18)	0.429
Sex				
Male	51(78.46)	79(88.76)		
Female	14(21.54)	10(11.24)	0.46(0.19-1.12)	0.086
Occupation				
Peasant	8(12.31)	22(24.72)	Reference	
Business	24(36.92)	36(40.45)	0.55(0.21-1.42)	0.216
Salaried	15(23.08)	11(12.36)	0.27(0.09-0.82)	0.021
Student	8(12.31)	1(1.12)	0.05(0.01-0.42)	0.007
Other	10(15.38)	19(21.35)	0.69(0.23-2.10)	0.515
Level of education				
No formal education	7(10.77)	22(242.72)	Reference	
Primary education	24(36.92)	39(43.82)	0.52(0.19-1.39)	0.192
Secondary education	27(41.54)	20(22.47)	0.24(0.08-0.66)	0.006
Tertiary education	7(10.77)	8(8.99)	0.36(0.10-1.37)	0.134
Mode of transport				
Ambulance	10(15.38)	31(3.83)	Reference	
Police pick up	20(30.77)	32(35.96)	0.52(0.21-1.27)	0.152
Boda boda*	16(24.62)	10(11.24)	0.20(0.07-0.58)	0.003
Ordinary car	16(24.62)	16(17.98)	0.32(0.12-0.87)	0.026
Other	3(4.62)	0	-	-

*These are commuter motorcycles

Table 2: Injury characteristics of the study population by Severity of Trauma among trauma patients attending Mulago Hospital

Variable	Severity of disease			
	Non-Severe	Severe		
	N (%)	N (%)	OR(95%CI)	p-value
Body region injured				
Head, Face and Neck	22(33.85)	49(55.06)	Reference	
Thorax	4(6.15)	2(2.25)	0.22(0.04-1.32)	0.098
Abdominal/visceral pelvis	24(36.92)	16(17.98)	0.30(0.13-0.67)	0.003
External (Skin)	7(10.77)	1(1.12)	0.06(0.01-0.55)	0.012
≥ 2 regions involved	8(12.31)	21(23.60)	1.18(0.45-3.07)	0.737
Mechanism of injury				
Road traffic crush	33(50.77)	66(74.16)	Reference	
Assault	18(27.69)	21(23.60)	0.58(0.27-1.24)	0.162
Fall	4(6.15)	0	-	-
Gunshot	3(4.62)	1(1.12)	0.17(0.02-1.67)	0.127
Burn	6(9.23)	1(1.12)	0.08(0.01-0.72)	0.024
Bomb blast	1(1.54)	0	-	-
Type of injury				
Penetrating	20(30.77)	39(43.82)	Reference	
Blunt force	33(50.77)	32(35.96)	0.50(0.24-1.03)	0.059
Burn	6(9.23)	1(1.12)	0.09(0.01-0.76)	0.027
≥ 2 injury types	6(9.23)	17(19.10)	1.45(0.50-4.26)	0.496
Serum uric acid				
Normal	51(78.46)	61(68.54)		
Abnormal	14(21.54)	28(31.46)	1.67(0.80-3.51)	0.174

Table 3: Clinical characteristic of the study population by Severity of Trauma among trauma patients attending Mulago Hospital

Parameter	Kampala Trauma scores	
	Score	**Number (%)**
Age	1 = 5 – 55 years	154(100)
Systolic blood pressure(mmHg)	2: More than 89	144(93.51)
	1 : Between 89 – 50	9(5.84)
	0 : Equal or below 49	1(0.65)
Respiratory rate(breaths/min)	2: 0-29	112(72.73)
	1: 30+	39(25.32)
	0: ≤ 9	3(1.95)
Neurological status	3:Alert	83(53.90)
	2:Responds to verbal stimuli	35(22.73)
	1:Responds to painful stimuli	28(18.18)
	0:Unresponsive	8(5.19)
Score for serious injuries	2: None	31(20.13)
	1:One injury	62(40.26)
	0: More than one	61(39.61)

Table 4: Serum uric acid Sensitivity, Specificity, positive predictive and negative predictive values at different cutoff levels using KTS II as the reference standard

Selected Serum uric acid cut offs	**Kampala Trauma Score**					
	Severe N (%)	**Non-severe N (%)**	**Sensitivity (95%CI)**	**Specificity (95%CI)**	**PPV (%)**	**NPV (%)**
At 2						
Severe	86(96.63)	65(100)	96.62			
Mild	3(3.37)	0	(90.46-99.30)	-	56.95	-
At 3						
Severe	83(93.26)	61(93.85)	93.26	5.97		
Mild	6(6.74)	4(6.15)	(85.90-97.49)	(1.65-14.59)	57.64	15.49
At 4						
Severe	70(78.65)	51(78.46)	78.65	20.90		
Mild	19(21.35)	14(21.54)	(68.69-86.63)	(11.92-32.57)	57.85	42.42
At 5						
Severe	54(60.67)	33(50.77)	60.67	47.76		
Mild	35(39.33)	32(49.23)	(49.75-70.87)	(35.40-60.32)	62.07	47.76
At 6						
Severe	32(35.96)	21(32.31)	35.96	65.67		
Mild	57(64.04)	44(67.69)	(26.05-46.82)	(53.06-76.85)	60.38	43.56
≥7						
Severe	23(25.84)	11(16.92)	23.84	80.60		
Mild	66(74.16)	54(83.08)	(17.14-36.21)	(69.11-89.24)	67.65	45.00

