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Original Article

Incidence and risk factors of acute kidney injury in severely burned patients in Mulago Hospital, Uganda - a prospective cohort

Joel Wandabwa[1], Robert Kalyesubula[2], Irene Najjingo[3], Joanitah Nalunjogi[3], Badru Ssekitooleko[1], Ronald Mbiine[1], Rose Alenyo[1]

[1]Department of Surgery, Makerere University, College of Health Sciences, Kampala, Uganda; [2]Department of Internal Medicine and Department of Physiology, Makerere University, College of Health Sciences, Kampala, Uganda; [3]Makerere University Lung Institute, Kampala, Uganda

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Abstract: Background: Acute Kidney Injury (AKI) is associated with increased mortality among severely burned patients. According to World Health Organization (WHO) 11 million people suffer from burns worldwide and burns contribute to 180,000 deaths yearly. Majority of these burns occur in the Low and Middle-Income Countries. Currently there is no published data on the incidence, risk factors and outcomes of AKI among patients with severe burns in Uganda. Early screening and treatment of patients at risk of developing AKI has been shown to improve survival. We therefore carried out a study to determine the incidence and risk factors of AKI in Uganda. Methods: This was a prospective cohort study that consecutively included patients with severe burns admitted in Mulago National Referral Hospital burns unit between February and May 2018. Patients were followed up for 14 days and AKI was assessed according to the KIDGO criteria. The incidence of AKI was expressed as a proportion. Kaplan Meier graph was used to estimate the median survival of patients with or without AKI. The risk factors for AKI were assessed using cox proportion hazard regression analysis. Results: Of the 147 patients screened, 92 met the inclusion criteria but 2 declined to participate in the study. Of the study participants, 48 (53.3%) were male, 47 (52.2%) were aged 3 years and below, the median TBSA was 17 (IQR; 13-23), 58 (69.9%) had low albumin levels and 16 (18.6%) had inhalation burns. The incidence of AKI was found to be 34.4% (95% CI; 25.9-45.9) with a mortality of 11.76% (95% CI; 6.37-20.73). Total burn surface area HR=3.10 (95% CI; 1.39 to 6.94 P=0.003) was the only independent risk factor for AKI. Conclusion: The incidence and mortality rate of AKI in patients with severe burns was found to be high. Having burns greater than 18% TBSA was an independent risk factor for AKI. Therefore, patients with burns greater than 18% should be assessed regularly for AKI so that treatment is instituted early should it occur.

Keywords: AKI, incidence, risk factors, Uganda

Introduction

According to the World Health Organization (WHO), 11 million people sustain burns worldwide and this results in approximately 180,000 deaths annually. About 95% of these burns and burn-related mortality occur in the Low and Middle-Income Countries according to the 2015 global health estimates [1]. Acute kidney injury (AKI) is a well-known complication of severe burns and contributes to the increased mortality in this group. Patients with severe burns have a high incidence of AKI of 30% and a mortality rate of more than 80% [2]. Other studies have shown the incidence of AKI to range from 26% to 49% depending on the method used to measure AKI [3].

Acute kidney injury can be classified as early or late depending on the time of onset. Early AKI develops within 0-2 days after injury and late AKI develops 2-14 days following the injury [4]. One of the risk factors of early AKI is inadequate fluid resuscitation resulting in hypovolemia and poor renal perfusion, direct cardiac suppression from TNF-Alpha and precipitation of denatured proteins in the renal tubules [5]. Late AKI is often a result of sepsis, multiple organ dysfunction, respiratory failure and use of nephrotoxic drugs [6].

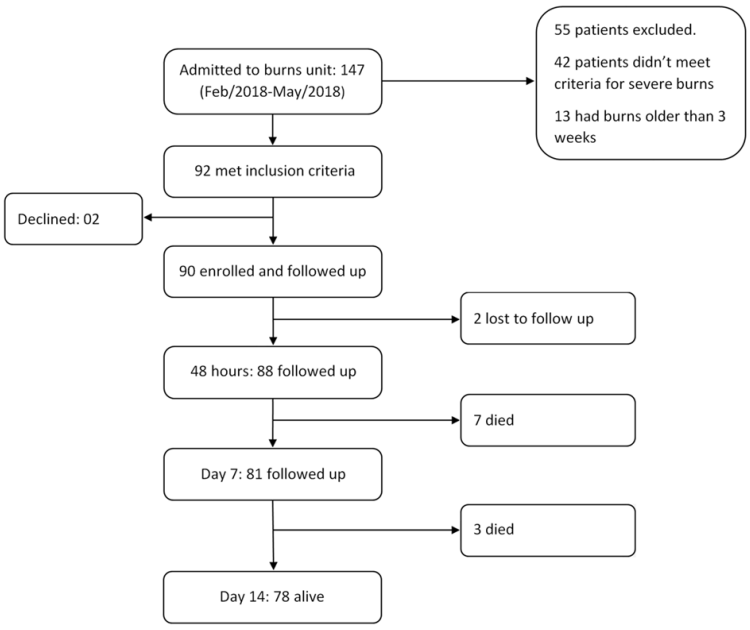

Figure 1. Flow chart of patients with severe burns at Mulago National Referral Hospital between February 2018 and May 2018. A total of 147 patients presented with burns at the Burn Unit, 42 had mild to moderate burns while 13 had burns older than two weeks and were not eligible to participate. In this study, 92 patients met the inclusion criteria but 2 declined to participate and were excluded.

There are several risk factors for AKI among patients with burns. Studies have shown age to be a risk factor for AKI. In particular, children under 10 years with severe burns have been found to develop AKI with subsequent death [7]. Another risk factor for development of AKI is depth and total surface area of burns as this causes excess fluid loss through the damaged skin. This results in hypotension with shock. Physical characteristics such as extremes of age, female sex, obesity, respiratory failure, low blood pressure, high white blood cell counts and proteinuria are other established risk factors of AKI in patients with severe burns [8].

Mulago hospital receives about 40 patients with severe burns monthly who are at a risk of developing AKI according to literature. Proper management of AKI requires special consideration and a high index of suspicion often guided by incidence and risk factors. Early identification through screening of high risk patients as well as early treatment has been shown to improve survival. For patients who are diagnosed with AKI, management should be initiated as soon as possible including access to dialysis and renal replacement therapy [9]. There is scanty information on incidence and risk factors of AKI among patients with severe buns in Uganda. We therefore determined the incidence and risk factors of AKI in severely burned patients in Mulago National Referral Hospital burns unit.

Materials and methods

Study design and setting

This was a prospective cohort carried out in the Burns Unit of Mulago National Referral Hospital between February 2018 and May 2018. Mulago is a national referral hospital which receives patients from several regions of Uganda. It has the largest burns Unit in the country comprising of the Burns Intensive Care Unit (ICU) and a general ward. The unit has a 50-bed capacity on the general ward, as well as a 9 bed capacity ICU. From a review of ward records, the burns unit attends to close to a monthly admission of 40 patients.

Adult patients with severe burns of partial thickness greater or equal to 20% Total Burn Surface Area (TBSA) or full thickness burns equal or greater than 10% TBSA were recruited in the study. Children were enrolled if they presented with partial thickness burns equal to or greater than 10% TBSA and full thickness burns equal to or greater than 5% TBSA or with inhalation burns and high voltage electrical burns presenting to the emergency unit within 14 days after the burn injury. However patients on Renal Replacement Therapy or dialysis, and those with a diagnosis of End Stage Renal Disease (ESRD) or AKI prior to injury were excluded from the study.

A total of 147 patients presented with burns at the Burn Unit, 42 had mild to moderate burns while 13 had burns older than two weeks and were not eligible to participate. In this study, 92 patients met the inclusion criteria but 2 declined to participate and were excluded (see **Figure 1**).

Diagnosis of AKI

Acute kidney injury was diagnosed by using serum creatinine measured at admission, 48 hours, 7 days and 14 days of follow up according to the Kidney Disease (KDIGO) criteria [10]. Patients with an increase in serum creatinine by 0.3 mg/dl or more than or equal to 26.5 micromoles/L within 48 hrs or increase in serum creatinine to more than or equal to 1.5 times the baseline were presumed to have AKI.

Data collection and measurements

Patient demographics, clinical characteristics and history of any chronic illness were collected on a semi structured questionnaire. The basic demographics included age, sex, weight, height, education level while clinical characteristics included; time from injury to admission, sepsis (existence of infection by clinical response to antibiotics, fever >39°C, hypothermia <36.5°C, progressive tachycardia >110 beats/min, progressive tachypnoea >25/min and inability to continue enteral feedings for >24 hrs), inhalation burns (burns to the pharynx and inhalation of toxic gases from combustion), degree of burns (depth of burns), nature of burns (cause of burns) and amount of fluid administered to the patient during resuscitation. These were collected on the questionnaire by a trained nurse. Patient creatinine, urea, albumin and protein levels were measured at admission, 48 hours, 7 days and 14 days during follow up. Creatinine, urea, albumin and protein levels were measured using the COBAS INTEGRA 400_Plus machine. Five milliliters of blood were collected and taken in the laboratory for processing. The blood was centrifuged at 800 rpm to obtain serum. For Albumin, two microliters of serum were aliquoted and mixed with twenty microliters of the diluent. One hundred microliters of the reagent were equally diluted with twenty microliters of the diluent. A total volume of one hundred forty-two microliters of the mixture were placed in the sample cup and placed in the sample well. For Creatinine, two microliters of serum were mixed with five microliters of the diluent. Seventy-seven microliters of the reagent were equally diluted with thirty-two microliters of the diluent. A total volume of one hundred twenty-two microliters of the mixture were placed in the sample cup and placed in the sample well. For urea, two microliters of serum were mixed with forty-three microliters of the diluent. Fifty microliters of the reagent were diluted with one fifty microliters of the diluent. A total volume of two hundred forty-five microliters of the mixture were placed in the sample cup and placed in the sample well. For total protein, two microliters of serum were mixed with twenty-eight microliters of the diluent. Ninety microliters of the reagent were diluted with thirty-two microliters of the diluent. A total volume of one hundred fifty-two microliters of the mixture were placed in the sample cup and placed in the sample well. The test was run for twenty minutes in the COBAS machine and the results printed. Albumin and total protein were recorded in grams per deciliter, creatinine was recorded in micromoles per liter while Urea in millimoles per liter.

Data analysis

Data was captured into the computer using EPI DATA version 3.1 and exported into Stata 13.0 for analysis. Patient sex, nature of burns, degree of burns, chronic illness, blood pressure and inhalation burns were summarize as proportions while age, burn surface area, albumin, protein and urea levels were summarized as means and standard deviation or median and inter-quartile range depending on the distribution. Incidence of AKI was calculated as the number of new cases of AKI over the total number of patients followed up. Kaplan Meier graph was used to estimate the median survival of patients with and without AKI. Cox proportion hazard regression analysis was used to analyze the risk factors of AKI among patients with severe burns. First the proportional hazard assumptions were assessed, and none was violated. The cox proportion hazard model was run with each of the predictors to assess for independent association of the predictors with the outcome. Having inhalation burns, burns surface area and albumin had *P*-values less than 0.2 and were considered for multivariate analysis. At multivariate, interaction was assessed using the chunk test while confounders were retained only if the hazard ratios changed by greater than or equal to 10%. Confidence intervals were presented at 95% level of significance along with the *P*-values and hazard ratios. Statistical significance of

Table 1. Socio demographic and clinical characteristics of study participants with severe burns at Mulago National Referral Hospital

Variable	Number (n=90)	Percentage (%)
Age categorized at median		
0-3 years	47	52.2
4-75 years	43	47.8
Sex		
Males	48	53.3
Females	42	46.7
Burn surface area (categorized at median)		
7-17	46	51.1
18-71	44	48.9
Nature of burns		
Flame burns	23	25.6
Scalds	67	74.4
Urea (categorized at median)		
1.20-2.20	46/81	56.8
2.21-6.10	35/81	43.2
Albumin (categorized at normal ranges)		
15.2-34.9	58/83	69.9
35.0-44.2	25/83	30.1
Blood pressure		
Normal	26/32	81.2
Abnormal	6/32	18.8
Inhalation burns		
No	70/86	81.4
Yes	16/86	18.6
Protein (categorized at median)		
38.90-53.90	41/80	51.3
53.91-70.40	39/80	48.8

factors was considered at a *P*-value less than 0.05.

Ethical considerations

Ethical Approval was obtained from Mulago Hospital Ethics Committee and Makerere University School of Medicine Ethics and Research Committee (REC REF # 2018-026). Informed consent was obtained for patients above 18 years while assent was obtained from study participants aged between 8 to 17 years and confidentiality was observed.

Results

A total of 147 patients were screened for severe burns at Mulago National Referral Hospital burns unit. Of the 147 patients screened, 92 met the inclusion criteria, 2 declined to participate and 90 were enrolled in the study as demonstrated by the flow chart (**Figure 1**).

Patient characteristics

Of the 90 participants, 47 (52.2%) were 3 years and below, 48 (53.3%) were male, 44 (48.9%) had a total burn surface area of greater than 18. Clinically, 67 (74.7%) had scalds, 24 (26.7%) 46 (56.8%) had low urea levels, 58 (69.9%) had hypoalbuminemia, 6 (18.8%) of the 32 adults had high blood pressure and 16 (18.6) of the participants had inhalation burns as demonstrated in **Table 1**.

Incidence of AKI

Of the 90 study participants enrolled in the study, 31 developed AKI resulting in an incidence of 34.4% (95% CI; 25.9-45.9) by the KDIGO criteria. Of the 31 participants with AKI, 11 (35.5%) died within 14 days of follow up. With the Kaplan Meier survival graph, the median survival of the participants with AKI was above 50%. At the beginning of the follow up, the survival of the participants drops on day one but later becomes constant up to day 6 from where it becomes poor up to day 10. From this point, it becomes constant up to day 14. From the graph, the survival of patients without AKI is constant throughout the follow up period as shown in **Figure 2**.

Risk factors for AKI

The development of AKI was similar regardless of sex, age of the patient, nature of burns, urea, protein and blood pressure. Total burn surface area, inhalation burns and albumin had *P*-values less than 0.2 and were included for multivariate analysis as shown in **Table 2**. From the multivariate analysis none of the factors was found to have interaction with the predictor variables. Total burn surface area HR=3.10 (95% CI; 1.39 to 6.94 P=0.003) was found to be an independent risk factor for AKI after con-

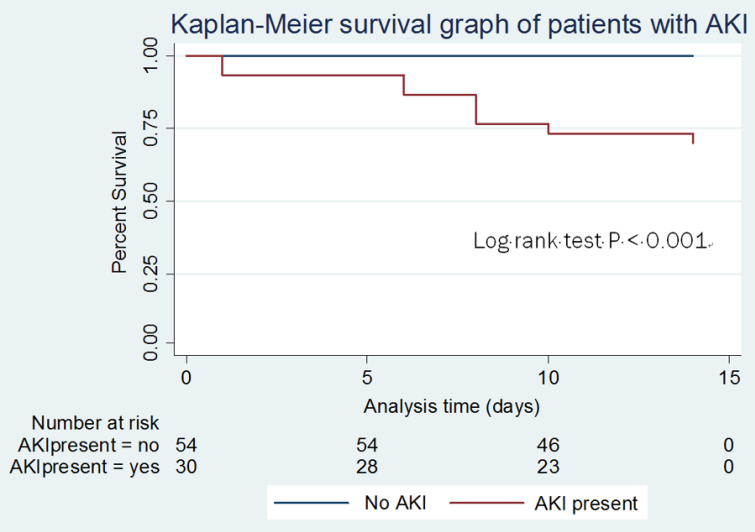

Figure 2. Kaplan Meier curves showing survival of patients with and without AKI at Mulago National Referral Hospital. From the Kaplan Meier survival graph, the median survival of patients with AKI was above 50%. At the beginning of the follow up, the survival of the patients drops on day one, but later becomes constant up to day 6 where it becomes poor up to day 10 and after becomes constant up to day 14. However, the survival of patients without AKI is constant throughout the follow up period. The difference in survival of patients with and without AKI is statistically significant.

trolling for possible confounders. Risk factors for AKI are summarized in **Table 3**.

Discussion

The incidence of acute kidney injury (AKI) among patients with severe burns in Mulago National Referral Hospital was found to be 34.4% (95% CI; 25.9 to 45.9). This incidence is similar to that of 34.9% got from a systematic review carried out in 2010 that looked at AKI among patients with severe burns [11]. In 2013, a meta-analysis that looked at the world incidence of AKI in both children and adults found the incidence of AKI to be 33.7 in children and in the current study, 68% of the study participants were children [12]. Another study carried out in Chicago found the incidence of AKI to vary between 26 to 49% depending on a number of factors and in the current study, the incidence of AKI is within this range [3]. A study in Tanzania found the incidence of AKI to be 10% among children. This study also reported a 7 fold mortality among patients with AKI as compared to those without AKI [13]. This is similar to what we observed in our study, there was a significant mortality among patients with AKI as shown on the Kaplan Meier curve. However in the developed countries, the incidence of AKI was estimated to be 21.6% in adults and up to 33.7% among children [12]. This study observed a slightly higher incidence compared to what has been observed in developed countries, diarrheal disease, malaria, nephrontoxins, sepsis, late presentation of patients to health care facilities, surgical complications and the lack of resources to support patients with established AKI are major challenges in developing countries that predispose them to AKI [14].

Risk factors for AKI

Total burn surface area was the only significant risk factor for AKI. Those with total burn surface area greater than 18% were 3 times more likely to develop AKI than those with a burn surface area of 17% and below. These results are consistent with findings of other studies that showed burn surface area as an independent predictor of AKI [8]. A systematic review also showed evidence that burn surface area is a significant factor for development of AKI [15]. Hypoalbuminemia was not found to be a risk factor for development of AKI in our study. Those with low albumin levels were at greater risk of developing AKI than those with normal albumin levels. Findings from a retrospective study reported a high risk of AKI and associated mortality among patients with greater burn surface area and sepsis. This study however didn't find inhalation burns to be associated with AKI nor risk of death among burn patients [16]. Our study did not also find inhalation burns to be a risk factor for AKI, however results from a systematic review reported inhalation burns to be a risk factor for AKI [15]. This could be explained the few patients who had in halation burns rendering our study less powered to detect a statistically significant difference.

Elevated blood pressure was not found to be a risk factor for AKI in our study. Other studies have found elevated blood pressure (BP) to be

Table 2. Bivariate analysis of association between patient characteristics and AKI in Mulago National Referral Hospital

Variable	Hazard ratio (HR)	95% CI	*P*-Value
Age in years			
0-75 years	1.01	0.99 to 1.03	0.317
Sex			
Males (48)	1.00		
Females (42)	0.85	0.42 to 1.72	0.643
Burn surface area (categorized at median)			
7-17 (46)	1.00		
18-71 (44)	3.10	1.39 to 6.94	0.003
Nature of burns			
Flame burns (23)	1.00		
Scalds (67)	0.68	0.32 to 1.44	0.311
Urea (categorized at median)			
1.20-2.20 (46)	1.00		
2.21-6.10 (35)	1.32	0.65 to 2.67	0.443
Protein (categorized at median)			
38.90-53.90 (41)	1.00		
53.91-70.40 (39)	0.75	0.36 to 1.54	0.425
Albumin (categorized at normal ranges)			
15.2-34.9 (58)	1.00		
35.0-44.2 (25)	0.50	0.21 to 1.22	0.129
Blood pressure			
Abnormal (6)	1.00		
Normal (26)	0.55	0.17 to 1.78	0.316
Inhalation burns			
No (70)	1.00		
Yes (16)	1.93	0.86 to 4.33	0.113

Table 3. Multivariate analysis of significant risk factors for AKI in Mulago National Referral Hospital, February 2018 to May 2018

Variable	Hazard ratio (HR)	95% CI	*P*-Value
Burn surface area (categorized at median)			
7-17	1.00		
18-71	3.10	1.39 to 6.94	0.003

a risk factor for AKI [17]. However, our findings were that only 6 adults had elevated blood pressure. Majority of the participants were below 18 years of age and so we didn't have enough numbers to assess this factor.

Age was not found to be a risk factor for AKI in our study yet other studies have found it to be a risk factor for AKI [8]. This could be because patients with extremes of age; particularly those above 60 years were at greatest risk of AKI. In this study only 2 of the patients were above the age of 60 years and patients were enrolled consecutively as they came to the hospital during the study period of February to May 2018.

Sepsis has also been known to be associated with AKI however in our study, we didn't find it to be an independent predictor of AKI. This is consistent with other studies that have found sepsis as a late complication of AKI but not a risk factor to development of AKI [2]. Studies that have found sepsis to be associated with AKI have reported sepsis to be confounded by older age and having pre-existing chronic kidney disease and in our study patients with chronic kidney disease were excluded so that it doesn't confound the relationship [18].

Female sex, obesity and proteinuria have also been found to be risk factors for AKI [17]. In our study these were not found to be significant risk factor probably because majority of our participants were male and only 5 of them were obese. Since majority of the participants had BMI within normal range, we did not find obesity to be a risk factor for AKI.

Elevated urea level has been found to be a risk factor for AKI [19] yet in our study we did not find this to be a risk factor. This could be explained by the fact that none of the participants had urea values above the normal range. Duration from injury to admission in hospital was not a risk factor for development of AKI. This is consistent with other studies that did

not find this as a risk factor. A meta-analysis and systematic review showed that time of stay in ICU was rather a risk factor for AKI and subsequent mortality [15].

Strength of the study

The study was conducted at Mulago National Referral Hospital which gets patients from all over Uganda therefore this study can be generalizable. This being a prospective design we were able to determine the incidence and risk factors of AKI. The study was done in a clinical setting which represents the true outcomes of the testing.

Limitations

First, serum Creatinine can be elevated in absence of AKI there for this creates a measurement bias in the outcome however the obtained incidence was within the range of the known incidence by other studies and the minimum change in serum Creatinine required to make diagnosis of AKI was considered too large.

Second, serum creatinine and Urine output can be normal in presence of significant AKI. Over 60-75% of nephrons must be lost before decline in renal function is manifested. This also created a measurement bias.

Conclusion

The incidence of AKI was found to be high among patients with severe burns as assessed by the KDIGO criteria. Total burn surface area was the only independent risk factor for AKI. With the high incidence of AKI, clinicians should actively look out for the development of AKI in severely burned patients especially those with inhalation burns, burn surface area greater than 18% and low albumin levels so that treatment is instituted early. Also since the incidence is within what other studies have found, serum creatinine levels alone can be used to make diagnosis of AKI. Uganda being a resource limited setting, this method is affordable and less tedious than monitoring of hourly urine output. However, we recommend another study using both creatinine and hourly urine output in the diagnosis of AKI since the KDIGO criteria uses both parameters for comparison with our findings. We also recommend further studies assessing for risk factors of AKI while controlling for hypertension as a potential confounder.

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Disclosure of conflict of interest

None.

Address correspondence to: Joel Wandabwa, Department of Surgery, Makerere University, College of Health Sciences, Kampala, Uganda. E-mail: wandkitjoel@gmail.com

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