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Significance level of uric acid in serum to predict mortality in patients with acute kidney injury

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ABSTRACT. Acute kidney injury is widely recognized in acute urate nephropathy, but hyperuricemia is now considered as a threat for acute kidney injury and its mortality. The objective of the study was to observe the effect of uric acid levels in patients with acute kidney injury as a predictor of mortality. A cross-sectional study was conducted at inpatients nephrology department of Pakistan Institute of Medical Sciences, Islamabad from May 2019 to May 2020. The outcome of the study was measured in terms of normal and elevated uric acid levels in acute kidney injury patients. 196 patients with acute kidney injury, who were followed up through history, examination and serum markers included in this study. The association of the outcome with serum uric acid levels was analyzed using the chi-square test.The mean age of the patients was 46.54 ± 19.06 years. It included 115 (58.7%) males and 81 (41.3%) females. The average level of uric acid was 7.29 ± 2.35 mg/dL. 158 (80.6%) patients were discharged and 38 (19.4%) expired. Serum uric acid is positively interrelated with renal function test levels. The correlation was significant with a p-value ⩽ 0.05. The mean uric acid of individuals who expired was significantly more than the mean uric acid of discharged patients (p = 0.0001). Out of 158 discharged patients 56 (35.44%) had hyperuricemia and out of 38 expired patients 32 (84.2%) had hyperuricemia. As a result, it was seen that among the patients who had expired increased levels of uric acid were seen (p>0.0001). The study concluded that high uric acid is a predictor of the outcome of patients with acute kidney injury.

Keywords: Acute kidney injury; mortality; patients; prognosis; uric acid.

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Introduction

Acute kidney injury (AKI) is an event of acute or subacute loss of kidney function for a period ranging from 7 to 90 days (Gameiro et al., 2020). It is a condition with multiple underlying causes and risk factors, mostly seen in ICU and less commonly observed in community settings (Louzada & Ferreira, 2021). The causes include hyperuricemia, radiographic contrast agents, hemolysis, rhabdomyolysis, hypercalcemia, and poisonous substances, among other pre-renal, renal and post-renal causes (Alscher et al., 2019). The classification criteria of AKI is RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) (Koza, 2016).

Uric acid is the end product of purine metabolism (Muiesan et al., 2016). The kidneys excrete two-thirds of the uric acid while the rest of one-third is eliminated via GI tract. Increase in production or impaired excretion of uric acid can cause hyperuricemia (Maiuolo et al., 2016). Uric acid is broken down by urine excreted oxidase (urease) to allantoin. Raised uric acid levels are defined as UA levels ⩾ 6.5 mg/dl or 7 mg/dl in men and ⩾ 6 mg/dl in women. A number of studies suggested that serum uric acid was an independent risk factor for renal and cardiovascular disease and could predict a high mortality in patients with hypertension, heart failure and diabetes. It has been identified as a marker of renal diseases (Romi et al., 2017).

Many researchers have concluded that raised serum uric acid levels are a risk factor for the development of systemic diseases like hypertension, chronic kidney disease and cardiovascular disease (Srivastava et al., 2019).

Role of uric acid in the acute kidney injury is widely recognized in acute urate nephropathy but the hyperuricemia is now also considered among one of the independent risk factors for AKI mortality (Maruhashi et al., 2018). It's levels in the serum rise to peak in 18-24 hours and level more than 15 $mgdL^{-1}$ is associated with significant mortality in patients who develop AKI with previously normal uric acid levels (Goldstein

et al., 2016). Serum uric acid has a significant role in pathogenesis of renal vasoconstriction, endothelial dysfunction, pro-inflammatory, pro-oxidative, antiangiogenic properties and disturbances in autoregulation causing acute kidney injury (Tanaka et al., 2018). It is seen that although uric acid has an antioxidant effect but the net effect leads towards AKI (Sánchez-Lozada, 2018). Elevated serum uric acid is associated with the risk of gout and uric acid stones which may lead to acute kidney injury (Nigam & Bhatnagar, 2018). However, the objective of this study was to observe the effect of uric acid levels in acute kidney injury patients as a predictor of their mortality.

Methodology

The present research was a cross-sectional study and conducted at inpatients nephrology department of Pakistan Institute of Medical Sciences, Islamabad from May 2019 to May 2020. A sample of 196 patients with acute kidney injury participated in the study by consecutive non-probability sampling. Patients with no previously known renal disease, acute kidney injury caused by acute glomerulonephritis, drug use, toxin-mediated, acute ischemia, acute infections, and idiopathic causes were included in the study. Those with acute on chronic renal failure, chronic kidney diseases, chronic glomerulonephritis, diabetes mellitus, hypertension, chronic heart failure, chronic liver failure, chronic infectious disease, organ transplant, autoimmune diseases, and immuno-compromised states were excluded from the study.

After approval from the ethical committee (10/PIMS/IRB-2019) of the hospital, study participants were informed about the purpose, procedures, and importance of the study. Written consent was taken from each participant/close relative. Relevant medical history was taken from the patient or the attendant regarding etiology. Blood samples for serum uric acid, urea and creatinine were taken at admission and sent to the hospital pathology laboratory. Serum uric acid levels were measured with an autoanalyzer that used a phosphotungstic acid reagent.

At the end of the hospital stay, the outcome of the patient in terms of discharged or expired was documented from a valid patient medical record. All data were stored on specially designed proforma separately for each case along with the photocopies of the original lab reports to minimize bias. Each case was verified and then entered on Excel sheet.

SPSS version 23 was used to record and analyze the gathered data. For quantitative variables (serum urea, age, creatinine, and levels of uric acid), mean and standard deviations were calculated. Calculation of frequencies was done for qualitative variables like gender, etiology, and outcome. Association of outcome with serum uric acid levels was analyzed using the chi-square test, keeping a 95% confidence interval with the significant level of $\leqslant 0.05$.

Results

The study included a total of 196 subjects with their ages ranging from between 16-82 years (mean age = 46.59 ± 19.06 years). It included 115 (58.7%) males and 81 (41.3%) females. The frequency and percentage of causes of AKI like dehydration secondary to fluid loss, hypotension secondary to blood loss (antepartum hemorrhage and postpartum hemorrhage and post-operative), septicemia, drug induced acute interstitial nephritis, glomerulonephritis and tumor lysis syndrome (malignancies) were recorded (Table 1).

Table 1. Causes of acute kidney injury in patients, n = 196.

Causes of AKI	Frequency	Percentage
Dehydration	79	40.3%
Hypotension	59	30.1%
Septicemia	40	20.4%
Drug induced	11	5.6%
Glomerulonephritis	5	2.5%
Tumor lysis syndrome	2	1%
Total	196	100%

Out of the total 158 (80.6%) patients were discharged and 38 (19.4%) expired. In all patients, uric acid levels ranged from 3.7 to 15.8 mg dL^{-1} with a mean of 7.29 ± 2.35 mg dL^{-1} was recorded. The urea levels ranged from 48 to 735 mg dL^{-1} with a mean of 212.2 ± 109.8 mg dL^{-1} and the creatinine levels ranged from 1.3 to 34

mg dL^{-1} with a mean of 7.2 ± 4.7 mg dL^{-1} was recorded. There was significant association of uric acid levels between discharged patients and expired patient of acute kidney injury observed (Table 2). There was direct relation between serum uric acid, serum urea levels and creatinine observed (Table 3).

Table 2. Association of uric acid levels in AKI patients, n = 196.

Outcome		Mean	SD	χ^2 value*	p-value
Uric acid levels	Discharged	6.84	2.12	114.254	.0001
	Expired	9.18	2.38		

*: Chi square test.

Table 3. Correlation between uric acid, urea and creatinine levels in AKI patients, n = 196.

		Uric acid levels	Urea levels	Creatinine level
Uric acid levels	Correlation coefficient	.226	1.00	1.00
	Sig. (2-tailed)	.001	-	-
Urea levels	Correlation coefficient	1.00	.226	1.00
	Sig. (2-tailed)	-	.001	-
Creatinine levels	Correlation coefficient	1.00	1.00	.150
	Sig. (2-tailed)	-	-	.036

Pearson test for correlation coefficient and p-value showed the strength of the relationship between uric acid, urea and creatinine levels (p = 0.001, 0.001 & 0.036) respectively.

The outcome of normal uric acid level and hyperuricemia (elevated uric acid level) was measured in discharged patients and expired patients (Table 4).

Table 4. Statistics of normal and elevated uric acid levels in AKI patients, n = 196.

Outcome; uric acid levels		Frequency	Percentage
Discharged patients	Normal	102	64.55
	Elevated	56	35.44
	Total	158	100
Expired patients	Normal	6	15.8
	Elevated	32	84.2
	Total	38	100
Chi square value	46.752	p-value	.0001

The results showed that the group who expired had a higher proportion of individuals with hyperuricemia. Out of 38 expired patients; 25 had septicemia, 2 had drug induced acute interstitial nephritis, 1 had glomerulonephritis, 1 had tumor lysis syndrome, and 9 had hypotension secondary to dehydration or blood loss.

Discussion

To compare the outcomes in normal and elevated uric acid groups, this study included 196 patients with acute kidney injury. The average uric acid level found was 7.29 ± 2.35 mg/dL. 158 (80.6%) patients were discharged and 38 (19.4%) expired. Serum uric acid had a direct relation with urea and creatinine levels; $p \leqslant 0.05$. The mean uric acid of expired individuals was significantly more than the mean uric acid of discharged patients (p = 0.0001). The discharged patients had 35.44% hyperuricemia and the expired patients had 84.2% hyperuricemia. Hence, proven that uric acid levels in patients who expired were significantly raised (p = 0.0001).

Similar studies on the subject are lacking in our setup. A study done by Haq et al., (2010) and in their study, the relationship between serum uric acid, serum urea & creatinine was observed. Patients more than 40 years with blood urea $\geqslant$ 40 mgdL^{-1} & serum creatinine $\geqslant$ 1.3 mgdL^{-1}. Majority patients were males and with normal RFTs (urea & creatinine). Some patients were found to have increased serum uric acid. Patients with deranged RFTs had raised serum uric acid levels ($p \leqslant 0.05$). Serum uric acid levels didn't show a high percentage of association with cause of renal disease.

Hyperuricemia has an adverse effect on various diseases such as hypertension, heart failure and renal failure (Srivastava et al., 2019). Wasserman et al., (2010) studied the trend of serum uric acid through epidemiological, clinical & lab data. The range of serum uric acid, mean at admission were 1.2 to 24 mgdL^{-1}, 6.1 ± 2.7 mg dL^{-1}. It was noted that uric acid was directly proportional to mortality (p = 0.025) and was a prognostic factor for mortality in

variable regression analysis (CI:95%, range 1.00-1.22; p = 0.04; odds ratio: 1.11). In patients having a normal uric acid, the rate of mortality was 5%, whereas, in those with raised uric acid levels the rate went up to 27%. It was therefore, proven that serum uric acid is an important mortality predictor in patients.

A similar study was also done on children by Hooman et al., (2010). Patients with serum uric acid (SUA) ⩾ 8 mg dL^{-1}were taken as subjects. Expired patients showed the relation between mortality and SUA ($p \leqslant 0.05$), a relative risk was 1.88. The relative risk of death calculated in patients who required vasopressor and had serum uric acid ⩾ 8 mg $dL^{-1}$was 1.04 and 1.33 in those who needed mechanical ventilation. It was noticed that there was poor prognosis (p = 0.001) in patient that needed to be put on mechanical ventilation (p = 0.001) and vasopressor. In pediatric cases, SUA is not independently associated with mortality. Instead, use of mechanical ventilation and inotropic agents has a much more significant prognostic value and the only place where we do take the role of SUA in to account is in sepsis (Lidén, 2018).

Uric acid also plays a role in chronic kidney disease. A study carried out in Thailand on the workers of electric generation authority of Thailand showed that a low GFR (⩽ 60) increased from 1.7 to 6.8% and raised creatinine was 6.8% which increased to 16.9%. The odds ratio for decreased kidney function was 1.82 (1.12 to 2.98), for hyperuricemia 2.57 (1.0 to 6.81), for systolic hypertension 1.68 (1.02 to 2.77) (Thawornchaisit et al., 2015).

The mechanism by which raised SUA leads to renal vasoconstriction and hypertension causing hypertension and kidney disease (Barkas et al., 2018). To study the relation between decreased kidney function and uric acid, a study was carried on data of cardiovascular and patients from a group with atherosclerosis. Mean GFR was 90.4 ± 19.4 mL $min^{-1}1.73\ m^{-2}$, mean creatinine was 0.9 ± 0.2 mgdL^{-1}, and uric acid was 5.9 ± 1.5 mgdL^{-1} at baseline. 2.3% individuals had kidney disease by creatinine increase, while 5.6% had kidney disease by GFR decrease at follow-up period. In creatinine-based and GFR, baseline uric acid level was associated with increased risk of kidney disease (CI;95%, range 1.01 to 1.14 [odds ratio 1.07] and CI;95%, range 1.02 to 1.21 [odds ratio 1.11], respectively) (Rincon-Choles et al., 2017).

Therefore, elevated uric acid levels affect the renal functions in many ways; i) a direct relation of general population getting affected with incident kidney disease. ii) Can predict progression of renal disease. iii) Are linked to pathogenesis and progression of hypertension and hypertension associated ESRD. iv) Can predict mortality in acutely sick patients including patients with acute kidney injury (Kamei et al., 2014).

No local study has directly studied the prognostic significance of uric acid in acute kidney injury. Testing uric acid is a simple test and easy test and can help categorize those acute kidney injury patients with poor prognosis and requiring aggressive and intensive therapy and ICU care. More studies on a larger scale with a prospective study design and control of confounding factors can provide more robust evidence in this regard.

Conclusion

This study concluded that as proven uric acid has a good predictor cause of mortality among patients with AKI and can therefore, be used as a tool to predict mortality at admission that help us in categorizing patients for aggressive therapy and ICU admissions.

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