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Urine abnormalities predict acute kidney injury in COVID-19 patients: An analysis of 110 cases in Chennai, South India

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ABSTRACT

Background and aims: Renal involvement in Covid-19 infection is varied and can affect glomeruli, tubules, interstitium and can cause acute kidney injury (AKI). AKI is a strong predictor of mortality. Routine urinalysis gives an insight into the renal pathology of the patient. We studied the incidence of urinary abnormalities in hospitalised Covid-19 patients and analysed their impact on development of AKI and mortality.

Methods: Information on 110 hospitalised patients with confirmed Covid-19 was retrospectively collected and analysed. The demographic data such as age, gender, comorbid conditions such as diabetes mellitus, the need for dialysis and laboratory data such as urine for albumin, glucose, RBC and WBC, and serum creatinine were collected. The diagnosis of AKI was based on the KDIGO criteria. The outcomes studied were development of AKI and hospital mortality.

Results: Urine abnormalities were seen in 71% of the patients. Proteinuria in 58.2%, haematuria in 17.3%, pyuria in 8.2% of patients and concurrent proteinuria and haematuria was seen in 13.6% of patients. AKI was seen in 28.2% of patients and hospital mortality was 24.5%. AKI was strongly associated with mortality. Proteinuria and haematuria were good predictors of development of AKI, more strongly when they occurred concurrently ($p < 0.01$).

Conclusion: Our results suggest that urine analysis is a simple test, which can be used to predict development of AKI and mortality and may be used for risk stratification of Covid-19 patients, especially in low resource settings.

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1. Introduction

Covid-19 is caused by severe acute respiratory syndrome corona virus 2 (SARS-COV-2), a novel corona virus, which was first detected in the month of December 2019 from Wuhan province of China [1,2]. The disease has since then spread globally across and has been declared a pandemic by WHO in March 11, 2020 [3]. Clinical presentation in COVID 19 infection is varied ranging from no symptoms to severe respiratory illnesses, multisystem dysfunction, multiorgan failure, sepsis, shock and death [1,4]. Clinical presentation in patients with comorbidities especially diabetes is more severe with a higher mortality rate as these patients are predominantly older and have higher incidence of cardiometabolic risk factors like hypertension and obesity [5]. Presence

of these risk factors is responsible for mediating an adverse outcome in these patients [5].

Acute kidney injury (AKI) results from abrupt loss of renal function and its occurrence among Covid-19 infected patients is common and is strongly associated with increased morbidity and mortality [6,7]. The aetiology of renal involvement in Covid-19 infection is multifactorial and several mechanisms are proposed to be involved in kidney injury, including the direct invasion of SARS-CoV-2 into the renal parenchyma, an imbalanced Renin Angiotensin Activating System (RAAS), microthrombosis and indirect effects secondary to systemic inflammatory response. The SARS-CoV-2 upregulates the angiotensin converting enzyme 2 (ACE2) receptors which play a significant role in the cellular entry of the virus via a strong interaction with the receptor binding domain of 2019-nCoV with the S-protein [8]. The secondary causes of AKI in Covid-19 infection are predominantly presence of inflammatory cytokines and adverse hemodynamic response [8]. Therapeutic interventions used in critically sick patients like drugs

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which can be nephrotoxic, use of diuretics and mechanical ventilation also contribute to AKI [8]. Elderly patients and patients with comorbidities such as hypertension or diabetes developed AKI more frequently [8]. Several studies have found a significant association between AKI and death among Covid-19 infected patients [8–11]. An early detection of AKI would be beneficial to identify the patients at higher risk of poor outcome and an early intervention with specific therapies aimed at renal perfusion, ensuring optimum hemodynamic support and restriction of drugs causing nephrotoxicity, may help to improve the clinical status of Covid-19 patients [8]. We hypothesized that a simple test such as urine analysis predicts the development of AKI in Covid-19 infection and thereby may be useful in risk stratification of Covid-19 patients.

We aimed to determine: 1) the incidence of abnormality in urine parameters in Covid-19 infected patients and correlating it with the development of AKI. 2) incidence of AKI and its impact on hospital mortality.

2. Materials and methods

2.1. Study design and participants

We retrospectively studied the urinalysis data of patients admitted in our hospital during April 2020 to July 2020, which included all patients, diagnosed with COVID-19 infection in our hospital by real time fluorescence (RT-PCR) for the detection of nucleic acid of SARS-CoV-2 in respiratory samples, as per WHO protocols. Patients diagnosed with Covid-19 infection elsewhere referred to our hospital for further management, known patients of chronic kidney disease, renal transplant recipients and patients without a definite outcome i.e. patients still on admission and those discharged against medical advice were excluded from the study. The demographic data such as age, gender, comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease and malignancy, need for dialysis and duration of hospital stay were collected.

2.2. Laboratory investigations

The urine samples were collected in containers, transported and analysed within 2 h of collection. Samples were analysed by automated urine analyser UC-3500 (Sysmex, Europe GmbH) for chemical analysis and UF-5000 (Sysmex, Europe GmbH) for analysing the urine sediment. A further microscopic analysis of sediments was performed, if required. Urine sediments were prepared by centrifuging 5 ml of urine for 5 min at 1500 rotations per minute. After discarding the supernatant, a drop of the sediment was placed on the slide covered using cover slip and examined under microscope. Presence of 0–3 RBC's/high power field and 0–5 pus cells/high power field were considered normal and counts above these levels were reported as positive for microscopic haematuria and pyuria respectively. Trace proteinuria was considered as negative. The baseline and peak serum creatinine was recorded. The AKI was diagnosed based on the KDIGO criteria [12]. The outcome studied was hospital mortality. The study was approved by the institutional Ethical Committee.

2.3. Statistical analysis

Continuous variables were expressed as mean \pm SD and the categorical variables were expressed as proportions. The categorical variables were analysed by Fishers exact test and Chi square test as appropriate and the continuous variables were compared using the student *t*-test. Pearson's correlation test was used to determine significant correlation between variables. Kaplan-Meier survival

curve analysis was done to determine the correlation between AKI, abnormal urine parameters and in-hospital mortality and Log rank test was used for survival analysis. The sensitivity and specificity analysis was done to determine the significance of urine parameters in predicting the development of AKI. A *p* value of <0.05 was considered as statistically significant. The data was analysed using SPSS software (version 23).

3. Results

3.1. Baseline characteristics of the patients

The mean age of our study population was 61 ± 14.6 years and 70% were male. The baseline demographic parameter between survivors and non-survivors is shown in Table 1. Comorbid conditions were seen in 83(75.5%) patients, of which diabetes mellitus was the major contributor 58 (52.7%). The incidence of the abnormal urine parameters was glycosuria in 35(31.8%), haematuria in 19(17.3%), ketonuria in 14(12.7%), pyuria in 9(8.2%), and proteinuria in 64(58.2%). The concurrent proteinuria and haematuria was seen in 15(13.6%). The hospital mortality was 27(24.5%) and AKI was seen in 31(28.2%) patients (Table 1).

3.2. Comparison of abnormal urine parameters between patients with and without comorbidities

The incidence of abnormal urine parameters amongst patients with and without comorbidities was not found to be significant. Among the 27 patients without any comorbidity the incidence was found to be 66.7%, while the incidence among 83 patients with comorbidity the incidence was 72.3%. The incidence of abnormal urine parameters detected among patients with comorbidities vs. patients without comorbidities were the following, glycosuria (37.3% vs. 14.8%), ketonuria (14.5% vs. 7.4%), pyuria (6.02% vs. 14.8%), proteinuria (39.8% vs. 48.1%), haematuria (16.9% vs. 18.5%).

3.3. Incidence of acute kidney injury and its correlation with urine parameters

AKI was diagnosed in 31 (28.2%) patients based on KDIGO criteria. AKI was found to have a strong correlation with the hospital mortality (Pearson's correlation, $p < 0.01$) (Table 1 and Fig. 1). Proteinuria and haematuria were found to be significantly associated with AKI with high specificity (Table 2 and Table 3). Renal replacement therapy was initiated in 7 (6.4%) of patients and the incidence was higher in non-survivors compared to survivors (18.5% vs. 2.4%, $p = 0.005$) (Table 1). Proteinuria and haematuria independently did not significantly correlate with hospital mortality. However, the concurrent occurrence of proteinuria and haematuria was associated with significantly higher mortality (Pearson's correlation, $p = 0.015$) (Fig. 2).

4. Discussion

Urine studies are simple yet effectively aid in the diagnosis of renal diseases. Our retrospective study on 110 Covid-19 positive patients admitted in our hospital detected abnormal urine parameters among 71% of the patients. A larger proportion of patients presented with comorbidities of which diabetes mellitus was found to be most prevalent. Studies have revealed that diabetes is associated with increased incidence of Covid-19 infection and is associated with higher risk of complications [13,14] but to the best of our knowledge, studies on urine abnormalities in COVID 19 associated with comorbidities are not found in literature. In our study, no significant association of urine abnormalities with Covid-19

Table 1
Basic information of all COVID positive patients.

VARIABLES	TOTAL n = 110	SURVIVORS n = 83	NON-SURVIVORS n = 27	P VALUE ^a
GENERAL CHARACTERISTICS				
AGE	61.2 ± 14.6	59.9 ± 15.4	65.0 ± 12.9	0.122
SEX				
•MALES	77(70%)	57(68.7%)	20(74.1%)	
•FEMALES	33(30%)	26(31.3%)	7(25.9%)	0.595
ASSOCIATED COMORBIDITIES				
•DIABETES MELLITUS	58(52.7%)	44(53%)	14(51.9%)	0.916
•HYPERTENSION	52(47.3%)	42(50.6%)	10(37%)	0.220
•CORONARY ARTERY DISEASE	25(22.7%)	19(22.9%)	6(22.2%)	0.943
•MALIGNANCY	7(6.4%)	4(4.8%)	3(11.1%)	0.359
NIL COMORBIDITIES	27(24.5%)	19(22.9%)	8(29.6%)	0.752
BASELINE CREATININE	1.08 ± 0.7698	1.0159 ± 0.7629	1.3037 ± 0.7638	0.092
PEAK CREATININE	1.3 ± 1.2577	1.0988 ± 0.91245	2.0074 ± 1.8328	0.001
DURATION OF STAY	13.1 ± 9.79	12.695 ± 10.25	14.0 ± 8.85	0.544
URINE FINDINGS				
GLYCOSURIA	35(31.8%)	27(32.5%)	8(29.6%)	0.016
HAEMATURIA	19(17.3%)	12(14.5%)	7(25.9%)	0.171
KETONURIA	14(12.7%)	10(12.0%)	4(14.8%)	0.164
PYURIA	9(8.2%)	6(7.2%)	3(11.1%)	0.686
PROTEINURIA	64(58.2%)	52(62.7%)	12(44.4%)	0.096
PH	6.123 ± 0.7109	6.157 ± 0.7527	6.019 ± 0.5630	0.383
SPECIFIC GRAVITY	1.019 ± 0.0188	1.017 ± 0.007	1.024 ± 0.0358	0.084
INCIDENCE OF ACUTE KIDNEY INJURY(AKI)	31(28.2%)	13(15.7%)	18(66.7%)	0.000
CRRT INITIATED	7(6.36%)	2(2.4%)	5(18.5%)	0.005

CRRT-Continuous renal replacement therapy.

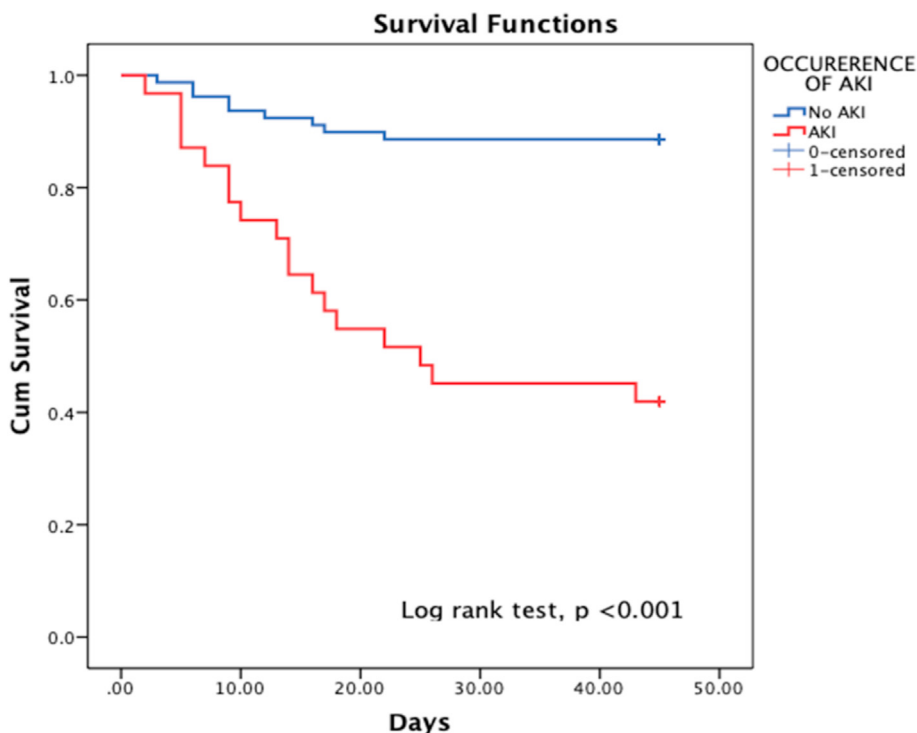


Fig. 1. Kaplan-Meier survival curves for patients with and without AKI with log rank test.

Table 2
Comparison of haematuria, proteinuria and pyuria among AKI and NON AKI patients.

URINE FINDINGS	AKI n = 31	NON-AKI n = 79	P-VALUE ^a
HAEMATURIA n (%)	10(32.3%)	9(11.4%)	0.009
PYURIA n (%)	3(9.7%)	6(7.6%)	0.720
PROTEINURIA n (%)	18(58.1%)	28(35.4%)	0.03
PROTEINURIA AND HAEMATURIA n (%)	10(32.3%)	5(6.3%)	0.000

associated with comorbidities was detected.

Studies have reported proteinuria and haematuria to be frequently observed among infected Covid-19 patients with evidences of urinary SARS-Co-V-2 excretion, suggesting the presence of renal reservoir for the virus [8]. Our study detected an incidence of proteinuria of 58.2% and haematuria of 17.3% among the hospitalised patients while a study on Chinese cohort reported an incidence of 43.9% and 26.7% of proteinuria and haematuria

Table 3
Sensitivity and specificity of urine findings in predicting AKI.

URINE FINDINGS	SENSITIVITY	SPECIFICITY	POSITIVE PREDICTIVE VALUE	NEGATIVE PREDICTIVE VALUE
PROTEINURIA	58.1%	64.6%	39.1%	79.7%
HAEMATURIA	32.3%	88.6%	52.6%	76.9%
PYURIA	9.7%	92.4%	33.3%	72.3%
COMBINED PROTEINURIA AND HAEMATURIA	32.3%	93.7%	66.7%	77.9%

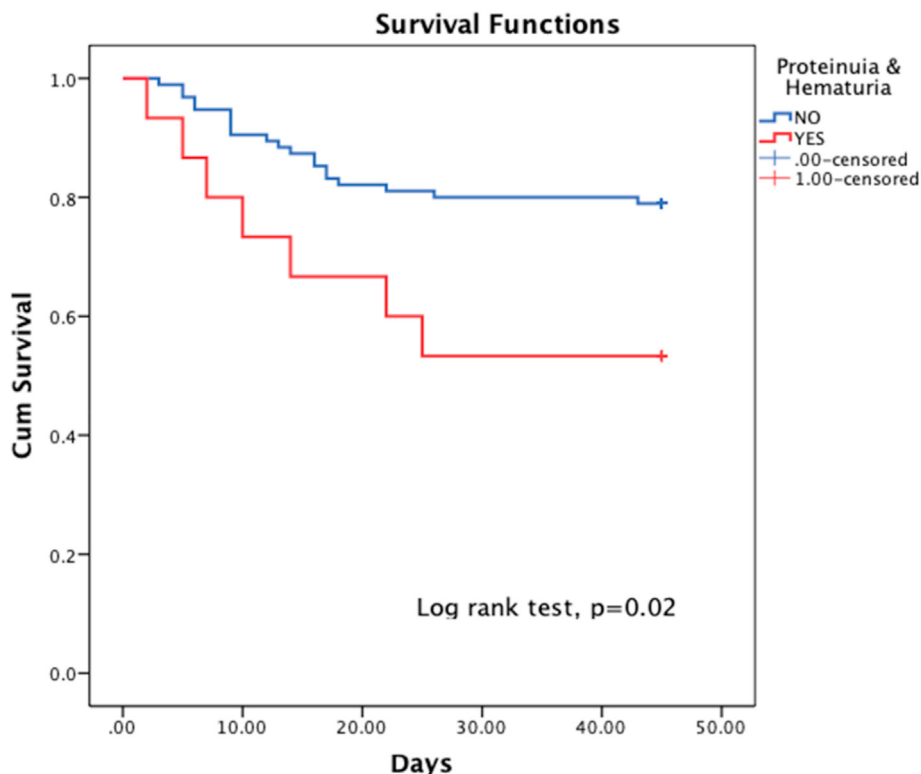


Fig. 2. Kaplan-Meier survival curves for patients with and without concurrent proteinuria and haematuria with log-rank test.

respectively [6].Urine parameters proteinuria and haematuria in isolation were not found to be associated with mortality unlike other studies which reported proteinuria and haematuria as isolated indicators of increased in-hospital morbidity and mortality [6]. However, the concurrence presence of haematuria and proteinuria significantly predicted hospital mortality in our study.

The incidence of AKI has been well documented among Covid-19 infected patients [6,8].The risk factors and causes of AKI in Covid-19 are diverse and multifactorial. We detected AKI among 28.2% of our patients which was higher than detected by Cheng et al. [6] where AKI was reported in 5.1% of their patients. The incidence of AKI reported by Hirsch et al. [15] was 36.6% which was higher than detected by our studies. As reported in other studies [6,15], development of AKI in our patients also conferred a poor prognosis. Initiation of continuous renal replacement therapy also was found as a significant poor prognostic factor among patients who developed AKI.

Covid-19 infection induces early development of proteinuria and impairs renal tubular function which has been proven by isolating the virus from the urine sample of infected patients and by demonstrating the expression of ACE2 receptors in the podocytes and proximal straight tubule cells [16].In our study, the incidence of proteinuria and haematuria among patients who developed AKI was detected to be 58.1% and 32.3% respectively while studies by

Pei et al. [17]reported an incidence of proteinuria and haematuria in 88.6% and 60% respectively. We found that proteinuria and haematuria were strongly associated with AKI with high specificity thus validating their clinical significance as strong indicators for identifying patients likely to develop AKI. Hence a close and continuous monitoring of patients presenting with proteinuria and haematuria would assist in early detection of patients with impending renal injury and resulting mortality, especially in low resource settings.

5. Limitations

We acknowledge some limitations in this study. This was a single-centre, retrospective study and thus might have a selection bias. The study findings need to be corroborated with a larger, multicentric study. Dynamic status of urine parameters was not available for majority of patients. Since there was no follow up, long term post-discharge clinical status is not available.

6. Conclusion

We conclude from our study that a simple, economical and commonly available test like urinalysis can aid in early diagnosis of renal impairment in Covid-19 patients. This would be useful,

especially in low resources settings as it would prompt early intervention which may improve the survival outcome of patients. Hence, we recommend urine routine analysis to be included in the investigation and surveillance protocol of all Covid-19 patients.

Declaration of competing interest

The authors have no conflict of interest.

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Nil.

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