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The value of urinalysis in predicting acute kidney injury and mortality in COVID-19 patients

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Abstract. *Kidney involvement is frequent among patients with coronavirus disease 2019 (COVID-19). However, kidney involvement is varied and mild kidney injury can easily go unnoticed. We aimed to investigate the urinalysis data of COVID-19 patients on admission and to explore the value of urinalysis in the prediction of acute kidney injury (AKI) and in-hospital mortality in patients with COVID-19.*

Methods. The demographic, clinical and laboratory data of patients with confirmed COVID-19 were retrospectively collected from the electronic health records of the hospital. The outcomes were the development of AKI and in-hospital mortality.

Results. 244 patients were included in the analysis. The mean age was 59.6 ± 13.7 and 65.2% of patients were male. Serum creatinine on admission was 0.86 (0.72-1.05) mg/dL. Glucosuria, proteinuria and hematuria were found in 36.1%, 22.9% and 22.1% of patients, respectively. AKI was detected in 63 patients (25.8%) at any time of hospitalization. According to multivariate analysis, AKI development was associated with higher WBC and decreased eGFR as well as with proteinuria on admission. During median 8 (IQR, 5-12) days of follow-up, 33 patients (13.5%) died. Older age, higher C-reactive protein levels and proteinuria on admission were also independent predictors of in-hospital mortality.

Conclusion. Proteinuria on admission was associated with the development of AKI and in-hospital mortality in patients with COVID-19. Urinalysis can be useful for early diagnosis of kidney damage before serum creatinine rise and mortality prediction in COVID-19 patients.

Key words: *acute kidney injury, COVID-19, proteinuria, urinalysis.*

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Діагностична цінність аналізу сечі для прогнозування гострого пошкодження нирок і смертності у пацієнтів з COVID-19

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Резюме. *Ураження нирок часто діагностується у пацієнтів з коронавірусною хворобою 2019 року (COVID-19). Однак воно може може не проявлятись клінічно і легко залишитись непоміченим. Це дослідження мало на меті дослідити дані аналізу сечі пацієнтів з COVID-19 під час надходження до стаціонару та визначити значення аналізу сечі для прогнозування гострого пошкодження нирок (ГПН) та госпітальної смертності у пацієнтів з COVID-19.*

Методи. У цьому досліджені ми ретроспективно аналізували демографічні, клінічні та лабораторні дані пацієнтів з підтвердженим COVID-19, які були отримані з електронних медичних пацієнтів. Наслідками, які підлягали аналізу були розвиток гострого пошкодження нирок (ГПН) та внутрішньолікарняна смертність.

Результати. До аналізу було включено 244 пацієнти, серед яких було 65,2% чоловіків. Середній вік становив 59,6 ± 13,7 , медіана креатиніну сироватки на момент надходження становила 0,86 (0,72-1,05) мг/дл. Глюкозурія, протеїнурія та гематурія виявлені у 36,1%, 22,9% та 22,1% пацієнтів відповідно. ГПН було діагностовано у 63 пацієнтів (25,8%). За даними багатофакторного аналізу, розвиток ГПН був асоційований з підвищенням лейкоцитів і зниженням ШКФ, а також з рівнем протеїнурії під час госпіталізації. Протягом 8 (5-12) днів спостереження 33 пацієнти (13,5%) померли. Старший вік, більш високий рівень С-реактивного білку та протеїнурія на час госпіталізації були незалежними предикторами внутрішньолікарняної смертності.

Висновок. Протеїнурія була асоційована з розвитком ГПН та внутрішньолікарняною смертністю у пацієнтів з COVID-19. Аналіз сечі може бути корисним для ранньої діагностики ураження нирок до підвищення креатиніна сироватки і прогнозування смертності у пацієнтів з COVID-19.

Ключові слова: *гостре ураження нирок, COVID-19, протеїнурія, аналіз сечі.*

Introduction. In December 2019, a new strain of coronavirus was identified and officially named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. Clinical presentations of coronavirus disease 2019 (COVID-19) can range from asymptomatic infection, influenza-like symptoms, and acute pneumonia to severe respiratory failure. Besides lungs, kidney involvement is also well defined [2].

Kidney involvement, defined both as urinary abnormalities and changes in kidney function, might be present in up to 75% of cases [3]. Because of the expression of the membrane-bound peptidase angiotensin-converting enzyme 2 (ACE2) in tubular epithelia and podocytes and the known property of ACE2 as a facilitator of cell entry for SARS-CoV-2, it has been proposed that direct viral infection into the kidneys may account for some of the acute kidney injury (AKI) pathogenesis for patients with COVID-19 [4]. However, kidney involvement during COVID-19 disease may have a broad clinical spectrum, and mild kidney injury can easily go unnoticed. Several studies have found a significant association between AKI and death among COVID-19 infected patients. Early detection of AKI would be beneficial to identify the patients to improve the clinical status of COVID-19 patients [4, 5].

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Urine analysis may be useful to predict the development of AKI and mortality in COVID-19 patients. Multiple observational studies have reported the presence of proteinuria and hematuria in COVID-19 patients [6, 7, 8, 9, 10, 11, 12]. However, at present, there have been relatively few studies focusing on urinalysis parameters except hematuria and proteinuria in COVID-19 patients [6, 9, 11].

In this study, we aimed to investigate the urinalysis data of COVID-19 patients on admission and to explore the value of urinalysis in the prediction of AKI and in-hospital mortality in patients with COVID-19.

Materials And Methods. Patients hospitalized with a diagnosis of COVID-19 between October 2 and December 25, 2020, were enrolled in this retrospective observational study. The diagnosis of COVID-19 was confirmed with at least one positive real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test result in cases admitted with symptoms, signs and findings (laboratory/radiological) suggestive of COVID-19, according to the national guidelines [13]. We excluded

the following patients; patients who were on regular hemodialysis, pregnant, who were transferred from the intensive care unit (ICU), who had urinary tract infection, or who had urethral catheters. For patients who had multiple qualifying hospital admissions, we included only the first hospitalization however outcomes were recorded according to the last hospitalization.

The source of medical records was OCTOMED (Kartal Dr.Lutfi Kirdar City Hospital Automation Program) electronic database system. The National Public Health Data Management System database was also used as an external data source, particularly to track the RT-PCR test results and to obtain data on previous creatinine values. We collected data for patient demographics, comorbidities, vital signs and laboratory test results on admission. Laboratory data consisted of measurements of white blood cell (WBC), lymphocyte, hemoglobin (Hb), platelet count (PLT), serum glucose, urea, creatinine (SCr), albumin, sodium, potassium, chloride, calcium, aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), C-reactive protein (CRP), ferritin, fibrinogen, D-dimer and creatinine kinase (CK) levels. The first value of laboratory data within 48 hours of hospital admission was taken. Additionally, peak and discharge creatinine values were also collected. IL-6 was taken once as the highest value during hospitalization. Furthermore, medications used for the treatment of COVID-19 were also recorded.

We additionally collected urinalysis with automated microscopy that was obtained within 48 hours after admission. The urine samples were collected in containers, transported and analyzed within 2 h of collection. The analyses were carried out on H-800 and FUS-200 automatic modular urine analyzers (Dirui Industry, Changchun, China). Further microscopic analysis of sediments was performed, if required.

Outcomes data were retrieved until January 10, 2020. By the time of this analysis, all patients had either died or had been discharged from the hospital. The primary outcome was the development of AKI and the secondary outcome was in-hospital mortality.

Study definitions. The date of hospital admission was accepted as the first day. Patients using antihypertensive drugs were accepted as hypertensive, while those using antidiabetic drugs were accepted as diabetic.

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [**14**]. Decreased eGFR was defined as < 60 mL/min/1.73 m^2.

AKI on admission or during hospital stay was defined according to Kidney Disease: Improving Global Outcomes (KDIGO) criteria as follows: stage 1, as an increase in SCr level by 0.3 mg/dL within 48 hours or 1.5 to 1.9 times increase in SCr from baseline within 7 days; stage 2, as 2 to 2.9 times increase in SCr within 7 days; stage 3, as 3 or more times increase in SCr within 7 days of initiation of renal replacement therapy (RRT) [**15**]. Patients were stratified according to the highest AKI stage attained during their hospital stay. Available baseline value for each patient was taken as the mean outpatient value 7-365 days prior to admission [**16**]. If the baseline value of SCr was not available, the lowest value during hospitalization was taken [**15**]. We did not use the urine output criteria to define AKI as the documentation of urine output in the electronic health record was unavailable.

Renal glycosuria was defined in a person if blood glucose level rises higher than 170–200 mg/dL who doesn't have diabetes or if blood glucose level rises higher than 200–250 mg/dL who has type 2 diabetes mellitus and the filtered glucose load exceeds the capacity for tubular glucose reabsorption [**17**].

Proteinuria was defined as the presence of ≥1+ on dipstick urinalysis. Trace proteinuria was considered negative. Microscopic hematuria was accepted as the presence of three or more erythrocytes per high-power field. Pyuria was also accepted as the presence of five or more leukocytes per high-power field.

The follow-up period started from the date of hospitalization and ended the day of discharge or in-hospital mortality.

Statistical analysis. Continuous data are presented as mean with standard deviation (SD) or as median and interquartile range (IQR) in case of non-normal distribution. Categorical data are presented as percentages. For multiple group comparisons of categorical variables, the Chi-square test was used. Continuous variables were first analyzed for normality using the Kolmogorov-Smirnov test and then were compared using the independent sample t-test or the Mann-Whitney U test, when appropriate. To explore the risk factors associated with AKI we performed logistic regression models, with adjustment for risk factors that differed between subjects who developed AKI and those who did not. Also, multivariate logistic regression analyses were used to estimate the risk factors associated with in-hospital mortality. We did not include associates of decreased eGFR (urea, creatinine, eGFR) and Hburia in our prediction models. Kaplan-Meier survival curve analysis was done to determine the correlation between proteinuria and in-hospital mortality and log-rank test was used for survival analysis. All tests were performed using SPSS for Windows, version 17.0 software (SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

Ethics. The study protocol was approved by the Clinical Research Ethics Committee of Kartal Dr. Lutfi Kirdar City Hospital (approval date: 14.10.2020, approval number: 2020/514/187/15) and the Scientific Committee of the Ministry of Health (approval no: 2020-10-08T16_20_20). The study was conducted in accordance with the 1975 Declaration of Helsinki, as revised in 2013.

Results. 695 patients have been hospitalized in infectious clinics with COVID-19 diagnosis in study time. Of these 695 patients, 244 patients were included in the analysis. The flow chart of the study is shown in Figure 1.

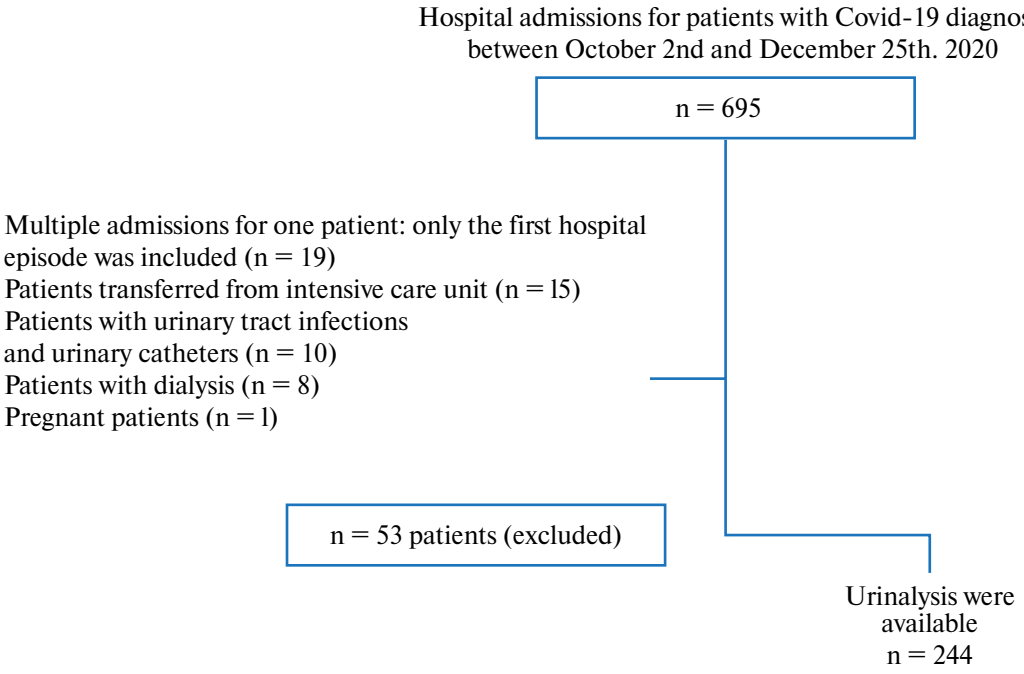

Fig. 1. Flow chart of the study cohort.

The mean age was 59.6 ± 13.7 and 65.2% of patients were male. The median time from diagnosis to hospital admission was 5.5 (IQR, 1-8) days. 130 patients (53.3%) had hypertension and 91 patients (37.3%) had diabetes mellitus. Thirty-seven (15.7%) patients were admitted with fever and 164 (67.2%) patients were admitted with oxygen saturation (SaO2)≤ 93% in a resting state.

On admission of the 244 patients, median serum urea and SCr were 34 (IQR, 26.8-48) and 0.86 (0.72-1.05) mg/dL, respectively. eGFR<60 mL/min per 1.73 m2 was reported in 44 (18%) of patients. During hospitalization, the median peak SCr was 0.95 (IQR, 0.80-1.25) mg/dL. The mean HbA1c of diabetic patients was 7.91 ± 1.99%. Most of the patients (98.8%) had elevated CRP values at admission. IL-6 was available in 96 patients with a median value of 28.3 (IQR, 7.03-113.6) pg/mL.

Thirty-three patients (13.5%) were admitted with AKI. AKI was detected in 63 patients (25.8%) at any time of hospitalization including stage 1 in 41/63 (65.1%) patients, stage 2 in 7/63 (11.1%) patients, and stage 3 in 15/63 (23.8%) patients. Table 1 shows the baseline demographic and clinical characteristics and laboratory values of all patients and a comparison of the patients grouped according to the presence of AKI.

Table 1

The demographic, clinical and laboratory characteristics of the patients stratified according to the presence of AKI

Variables	All patients (n=244)	No AKI (n=181)	AKI (n=63)	P
Age (years)	59.6 ± 13.7	57.1 ± 13.3	66.9 ± 12.2	0.000
Gender (male,%)	65.2	62.9	71.4	0.276
HT (%)	53.3	53.6	73	0.000
DM (%)	37.3	32.6	50.8	0.010
Time diagnosis to admission (day)	5.5 (1-8)	6 (2-9)	3 (1-7)	0.012
Fever on admission (%)	15.2	14.4	17.5	0.566
sBP (mmHg)	120 (110-130)	120 (110-130)	110 (110-130)	0.776
dBP (mmHg)	70 (70-80)	70 (70-80)	70 (70-80)	0.226
SaO2 (%)	91 (89-94)	92 (89-94)	91 (88-63)	0.542
WBC (x10^3/µL)	6.6 (4.8-9.3)	6.3 (4.7-8.6)	7.4 (5.0-11.6)	0.046

Continuation of Table 1

Variables	All patients (n=244)	No AKI (n=181)	AKI (n=63)	P
Lymphocyte (x10³/μL)	1.0 (0.62-1.3)	1.0 (0.7-1.4)	0.8 (0.6-1.3)	0.472
Hemoglobin (g/dL)	13.1 (12.0-14.1)	13.1 (12.4-14)	12.6(11.4-14.3)	0.089
Platelet (x10³/μL)	207.0 (161.0-278.8)	208 (165-277.5)	200 (150-296)	0.806
Glucose (mg/dL)	133 (110-192.5)	128 (110-184)	136 (115-200)	0.284
Urea (mg/dL)	34 (26.8-48)	31 (25-40)	50 (33-78.5)	0.000
Creatinine (mg/dL)	0.86 (0.72-1.05)	0.8 (0.67-0.95)	1.14 (0.91-1.45)	0.000
eGFR (ml/min/1.73 m²)	89.4 (68.7-102.7)	95.6 (82-105.7)	61 (42.7-84.7)	0.000
Decreased eGFR (%)	16.8	7.2	44.4	0.000
Albumin (g/L)	3.5 (3.3-3.7)	3.5 (3.3-3.7)	3.5 (3.1-3.6)	0.260
Sodium (mEq/L)	137 (133-139)	137 (134-139)	135 (132-140)	0.058
Potassium (mEq/L)	4.3 (4-4.6)	4.3 (4-4.63)	4.1 (3.9-4.6)	0.081
Chloride (mEq/L)	98.8 ± 4.9	99.5 ± 4.5	97.5 ± 5.6	0.070
Calcium (mg/dL)	8.97 (8.75-9.27)	8.93 (8.72-9.29)	9.03 (8.81-9.24)	0.320
AST (U/L)	36 (26-55)	36.5 (27-55)	33 (25-59)	0.544
ALT (U/L)	30 (18-47.8)	31 (18-51)	22 (17-44)	0.113
LDH (U/L)	349 (276-448)	352 (277-444)	334.5 (255-463.8)	0.861
CRP (mg/L)	81.8 (44.3-137.6)	73 (39.6-128.6)	104 (60.4-178)	0.002
Ferritin (ng/mL)	493.3 (254.1-817.7)	489.3 (234.4-788.3)	502.1 (320.2-888.8)	0.219
Fibrinogen (mg/dL)	590.8 ± 155.9	580.4 ± 152.7	617.5 ± 162.1	0.302
D-Dimer (μg/L)	825 (537.5-1395)	780 (502.5-1277.5)	935 (637.5-2117.5)	0.023
CK (U/L)	99 (57-201)	94.5 (52.3-199)	108 (61-226)	0.382

Abbreviations. *ALT: alanine aminotransferase; AST: aspartate aminotransferase; CK: creatinine kinase; CRP: C-reactive protein; dBp: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HT: hypertension; LDH: lactate dehydrogenase; SaO2: oxygen saturation; sBP: systolic blood pressure; WBC: white blood cell.*

Compared with patients without AKI, patients who developed AKI were significantly older, had more comorbidities; hypertension and diabetes mellitus and were admitted to emergency in a shorter time after COVID-19 diagnosis. Moreover, patients with AKI had higher leukocytes, CRP and D-dimer values than patients without AKI. The median value of serum urea, SCr, eGFR and percentage of decreased eGFR on admission were significantly higher in patients who developed AKI than patients who did not.

Urinalysis data of study patients are shown in Table 2.

Table 2

Urinalysis data obtained within 48 hours in patients with COVID-19

Variables	All patients n=244	No AKI n=181	AKI n=63	P
pH, median (IQR)	6 (5.5-6)	6 (6-6.5)	5.8 (5.5-6)	0.000
Specific gravity, median (IQR)	1019.5 (1012-1028)	1020 (1011-1028)	1018 (1013-1027)	0.977
Protein, n (%)				
0, negative or trace	188 (77.1)	150 (82.9)	38 (60.3)	
1+	29 (11.9)	16 (8.8)	13 (20.6)	0.000
2+~3+	27 (11)	15 (8.3)	12 (19.1)	
Blood, n (%)				
0, negative or trace	189 (77.5)	153 (84.5)	36 (57.1)	
1+	26 (10.7)	17 (9.4)	9 (14.3)	0.000
2+~3+	29 (11.8)	11 (6.1)	18 (28.6)	

Continuation of Table 2

Variables	All patients n=244	No AKI n=181	AKI n=63	P
Glucosuria, n (%)	88 (36.1)	64 (35.4)	24 (38.1)	0.697
Ketonuria, n (%)	38 (15.6)	28 (15.5)	10 (15.9)	0.939
Urine microscopy automated, n (%)				
White blood cells ≥ 5/hpf	22 (9)	12 (6.6)	10 (15.9)	0.027
Red blood cells ≥ 3/hpf	54 (22.1)	27 (14.9)	27 (42.9)	0.000
Epithelial cells*	39 (15.9)	31 (17.1)	9 (14.3)	0.600
Yeast cells*	9 (3.7)	8 (4.6)	3 (4.8)	0.783

Abbreviations. *AKI: acute kidney injury; hpf: high power field. *if ≥ 1 element/hpf is present.*

The median pH value was 6 (IQR, 5.5-6) and the median urine-specific gravity was 1019.5 (IQR, 1012-1028). After excluding glycosuric patients, the median urine-specific gravity was 1017 (IQR, 1010-1023) in 156 patients. Glycosuria was found in 88 (36.1%) patients and the median blood glucose level at the time of urinalysis was 268 (IQR, 210.5-321.5) (data regarding blood glucose at the time of urinalysis in glucosuric patients were available in 48 patients). Only six patients of glucosuric patients (6/48, 12.5%) had a blood glucose value under the renal threshold defined. By urine dipstick, 189 patients (77.5%) had no heme and 188 patients (77.1%) had no proteinuria. The percentage of patients with proteinuria, hematuria and pyuria was significantly higher in patients with AKI. In contrast, urine pH was significantly lower in patients with AKI than in patients without AKI.

Most patients received antiviral therapy (favipiravir, 93.4%; remdesivir, 5.3%), low-molecular-weight heparin (LMWH) (93.4%) and corticosteroid therapy (dexamethasone, 82.4%, pulse methylprednisolone, 33.6%). Patients with AKI received hydroxychloroquine treatment less frequently than those without AKI. However, the patients with AKI received more antibacterial therapies than patients without AKI. The treatments of the study patients; all patients and patients grouped according to the presence of AKI are shown in Table 3.

Table 3

The treatments of the patients stratified according to the presence of AKI

Variables	All patients n=244	No AKI n=181	AKI n=63	P
Treatment				
Antiviral, %	98.4	98.3	98.4	0.998
LMWH, %	93.4	95	88.9	0.091
Corticosteroid, %	91.4	90.6	93.7	0.605
O2, %	74.2	72.9	77.8	0.449
Colchicine, %	34.8	33.7	38.1	0.528
Antibacterial, %	29.1	24.9	41.3	0.014
Hydroxychloroquine, %	27.5	30.9	17.5	0.039

Abbreviaions. *LMWH: low-molecular-weight heparin.*

According to multivariate logistic regression analysis of risk factors on admission associated with the development of AKI in patients with COVID-19 are shown in Table 4.

Table 4

Multivariate logistic regression analysis of risk factors on admission associated with AKI development in patients with COVID-19

Variables	Multivariate		
	OR	95% CI	P
Age, years	1.026	0.995-1.059	0.105
Hypertension	1.562	0.669-3.651	0.303
Diabetes	1.159	0.527-2.546	0.714
Time diagnosis to admission, day	0.958	0.873-1.051	0.367

Continuation of Table 4

Variables	Multivariate		
	OR	95% CI	P
WBC (x103/μL)	1.000	1.000-1.000	0.028
Decreased eGFR	4.771	1.969-11.558	0.001
CRP (mg/dL)	1.003	0.999-1.008	0.188
D-Dimer (μg/L)	1.000	1.000-1.000	0.901
Urine pH	0.468	0.215-1.019	0.056
Proteinuria	2.470	1.104-5.528	0.028
Hematuria	2.001	0.820-4.882	0.127
Pyuria	0.920	0.259-3.264	0.897

Abbreviations. *CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; WBC: white blood cell.*

AKI development was associated with higher WBC and decreased eGFR as well as with proteinuria on admission.

During median 8 (IQR, 5-12) days of follow-up, thirty-five patients (14.3%) were admitted to the ICU and 33 patients (13.5%) died. Patients with AKI had significantly higher ICU admission and in-hospital mortality rates than patients without AKI (39.5% vs. 5.5%, P=0.000; 38.1% vs. 5%, P=0.000). Five patients (7.9% of patients with AKI) required continuous renal replacement therapy (CRRT).

Comparison of the demographic, clinical, and laboratory characteristics on admission between patients who survived and who died were shown in Table 5.

Table 5

Comparison of the demographic, clinical and laboratory characteristics on admission between patients who survived and who died

Variables	Patients who survived (n=211)	Patients who died (n=33)	P
Age (years)	58.2 ± 13.6	68.5 ± 10.4	0.000
Gender (male,%)	63	78.8	0.077
HT (%)	51.2	66.7	0.097
DM (%)	35.5	48.5	0.153
sBP (mmHg)	120 (110-130)	120 (110-130)	0.476
dBP (mmHg)	70 (70-80)	120 (110-130)	0.529
SaO2 (%)	92 (89-94)	90 (87-92)	0.006
Lymphocyte (x103/μL)	1.0 (0.7-1.4)	0.6 (0.5-1.1)	0.001
Hemoglobin (g/dL)	13.1 (12.3-14.1)	12.1 (11.1-13.9)	0.065
Platelet (x103/μL)	216 (161-278)	191 (144-289)	0.304
Creatinine (mg/dL)	0.83 (0.69-1.0)	1.09 (0.91-1.35)	0.000
eGFR < 60 mL/min/1.73m2	13.7	36.4	0.001
AKI	11.8	27.3	0.017
Albumin (g/L)	3.5 (3.3-3.7)	3.3 (2.9-3.6)	0.053
Sodium (mEq/L)	137 (134-139)	135 (132-140.5)	0.397
Potassium (mEq/L)	4.3 (3.9-4.6)	4.4 (4-4.7)	0.333
CRP (mg/L)	74.6 (38.8-129)	115 (77.4-204.5)	0.000
Ferritin (ng/mL)	489.3 (256.7-804.6)	520.3 (182.5-878.6)	0.828
D-Dimer (μg/L)	750 (505-1250)	1410 (845-3250)	0.000
Urine ph	6 (5.5-6)	5.5 (5.5-6)	0.003
Urine specific gravity	1020 (1012-1028)	1018 (1014-1029)	0.858
Proteinuria (%)	18.9	48.5	0.000

Continuation of Table 5

Variables	Patients who survived (n=211)	Patients who died (n=33)	P
Glucosuria (%)	36.9	30.3	0.458
Ketonuria (%)	14.7	21.2	0.337
Urine microscopy automated, n (%) White blood cells ≥ 5/hpf Red blood cells ≥ 3/hpf	 9.5 18	 6 42.4	 0.524 0.000

Abbreviations. *AKI: acute kidney injury; CRP: C-reactive protein; dBP: diastolic blood pressure; DM: diabetes mellitus; eGFR: estimated glomerular filtration rate; HT: hypertension; SaO2: oxygen saturation; sBP: systolic blood pressure.*

Compared to the patients who survived, deceased patients were older and they had significantly higher SCr, CRP, ferritin, D-dimer and lower SaO2, lymphocyte and urine pH levels. Moreover, patients who died had significantly higher percentages of AKI, decreased eGFR, proteinuria and hematuria than patients who survived. According to multivariate analysis, patients with older age, higher CRP level, and proteinuria were at a higher risk of death than were patients without those findings (Table 6).

Table 6

Risk factors on admission associated with mortality in-hospital of COVID-19 patients

Variables	Multivariate		
	OR	95% CI	P
Age, years	1.049	1.008-1.091	0.017
SaO2 (%)	0.943	0.861-1.033	0.205
Lymphocyte (x103/μL)	0.999	0.998-1.000	0.274
Decreased eGFR	1.322	0.406-4.305	0.643
AKI	1.027	0.297-3.552	0.966
CRP (mg/L)	1.006	1.001-1.011	0.025
D-Dimer (μg/L)	1.000	1.000-1.000	0.272
Urine pH	0.503	0.184-1.377	0.181
Proteinuria	2.709	1.030-7.128	0.043
Hematuria	1.495	0.551-4.058	0.429

Abbreviations. *AKI: acute kidney injury; CRP: C-reactive protein; eGFR: estimated glomerular filtration rate; SaO2: oxygen saturation.*

Kaplan-Meier analysis revealed a significantly higher in-hospital mortality rate for patients with proteinuria (P=0.013) (Fig. 2).

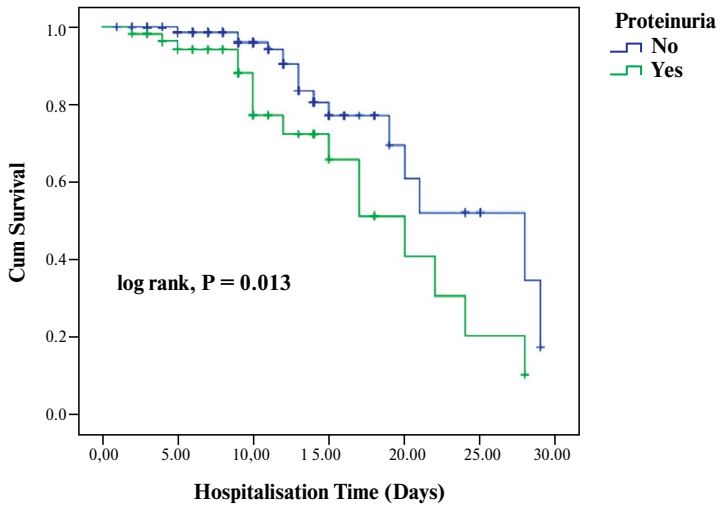

Fig. 2. Kaplan-Meier survival analysis of COVID-19 patients subgrouped by proteinuria.

Discussion. In this retrospective analysis, we investigated the urinalysis data of COVID-19 patients, incidence and risk factors of AKI development, and mortality in-hospital in patients with COVID-19.

The importance of urine to show the severity of COVID-19 was firstly reported by Liu et al. In this study they found significantly higher positive rates of hematuria, and proteinuria and higher urine pH in COVID-19 patients compared to healthy controls [41.2% vs. 22.2%, 28.6% vs. 11.1%, 6.27 ± 0.6 vs. 5.94 ±0.7, respectively]. However, in contrast, urine-specific gravity was found significantly lower in COVID-19 patients than healthy controls (1020 ± 0.007 vs. 1023 ± 0.007) [6]. Hirsch et al. found the median value of urine-specific gravity as 1020 (IQR, 1010-1020) [8]. We found urine-specific gravity lower than previous reports especially in patients without glucosuria. Urine ph value was similar to the values reported previously [8, 10].

Notably, glucosuria was found in 36.1% of patients similar to a previous report [12]. In our study most of the patients received corticosteroids. However; in only six patients (12.5%), renal glucosuria was found without serum glucose level not exceeding the renal threshold for glucose similar to a previous report [18]. It may be a result of proximal tubule injury in patients with COVID-19.

The rates of other urine parameters such as ketonuria and pyuria were found in our study as 15.6% and 9%, respectively. These changes had not been focussed in previous reports mostly. We found lower rates of pyuria than other studies [6, 9]. Hirch et al. had found the frequency of pyuria more than our study in COVID-19 patients with AKI (36.5% vs. 15.9%) [8].

The high frequency of renal abnormalities including proteinuria and hematuria were reported in previous reports ranging between 20.3-89.8% and 6-81%, respectively [3, 6, 7-12, 19]. Our study detected an incidence of proteinuria of 22.9% and hematuria of 22.1% on admission among the hospitalized patients with COVID-19.

The quantification and characterization of proteinuria were begun to be investigated in recent studies. Huart et al. found proteinuria over 500 mg/g in 68 patients (44%) and they also found urine α1-microglobulin (a marker of tubular injury) concentration higher than 15 mg/g in 89% of patients suggesting tubular proteinuria [20]. In a recent analysis, Karras et al. found urine protein-creatinine ratio at admission ≥ 1g/g in 84 patients (42%) with a urine albumin-protein ratio <50% in 92% of patients. They also found urine retinol-binding protein concentrations as ≥ 0.03 mg/mmol in 62% of patients suggesting that COVID-19 associated proteinuria reflected low-molecular-weight proteins, which cannot be reabsorbed by the proximal kidney tubule due to acute tubular damage [21].

Among our study population, we observed an incidence of AKI of 25.8% similar to other reports [11, 22-24]. The reported rates of AKI are extremely variable; however, available evidence suggests that it likely affects >20% of hospitalized patients and >50% of patients in the ICU [25]. In a recent meta-analysis; the incidence of AKI was reported as 13.28% (162/1220) in all included studies [26]. Differences may have resulted from definitions of AKI and the populations studied. The pathogenesis of AKI in patients with COVID-19 is likely multifactorial, involving both the direct effects of the SARS-CoV-2 virus on the kidney such as collapsing glomerulopathy, endothelial damage, coagulopathy, complement activation, and inflammation and the indirect mechanisms resulting from systemic consequences of viral infection or effects of the virus on distant organs including the lung, in addition to mechanisms relating to the management of COVID-19 [27]. Some studies reported the presence of viral particles within both the tubular epithelium and podocytes on electron microscopy, implying the direct infection of the kidney [28, 29], others failed to demonstrate the presence of virus in the kidney [30-32]. In addition to direct pathophysiological mechanisms, renal dysfunction in the context of COVID-19 may also arise through the systemic effects of SARS-CoV-2 infection and critical illness. Volume depletion, exposure to nephrotoxins, increase in renal ven pressure and reduced filtration due to positive end-expiratory pressure (PEEP), the release of cytokines, vasoactive substances and damage-associated molecular patterns (DAMPs) from lung injury are also other mechanisms for kidney injury [27].

Risk factors of AKI in COVID-19 are diverse and multifactorial. A number of previous studies have suggested that the development of AKI in COVID-19 patients may be affected by multiple risk factors, such as older age, male sex, black race, comorbidities, increased CRP, proteinuria at admission, the need for ventilator support, use of vasopressor drug treatment [3, 8, 20, 23, 25]. On the basis of our multivariate logistic regression analysis; higher leukocytes, decreased eGFR and presence of proteinuria were independent predictors of AKI. As reported previously, we observed a high prevalence of hematuria and proteinuria in COVID-19 patients with AKI [3, 12, 19, 21, 22]. However, in a recent study, they found no significant differences in proteinuria, hematuria and leukocyturia among patients with AKI compared with non-AKI patients [24].

Several mortality risk scores have been proposed to predict mortality in COVID-19 patients [33, 34, 35], most of which did not include an evaluation of kidney status. However, kidney indicators seem to be the main predictors of mortality. We found the highest mortality frequencies in patients with AKI compared to patients without AKI (38.1% vs. 5%, P=0.000) consistent with previous reports [19, 23, 36]. In a recent meta-analysis, COVID-19 patients with AKI had a significantly increased risk of death compared to patients without AKI (OR 30.46, 95% CI 9.29-15.19) [26]. We also found that proteinuria on admission was independently associated with in-hospital mortality and had a 2.7 times higher risk of death similar to previous reports [11, 12, 37]. Pei et al. showed higher overall mortal-

ity in the patients with renal involvement, including hematuria, proteinuria, and AKI, compared with that of patients without renal involvement (11.2% vs 1.2%, P=0.006) [3]. Cheng et al. reported the incidence of mortality in-hospital in the patients with elevated baseline serum creatinine on admission was 33.7%. They also found that proteinuria of any degree, hematuria of any degree, elevated baseline BUN, elevated baseline SCr, peak SCr > 133 mmol/l, and AKI over stage 2 were independently associated with mortality [7]. In another study, Portoles et al. confirmed that elevated baseline SCr, previous chronic kidney disease, hematuria, and in-hospital AKI were independent risk factors for mortality in-hospital after adjusting for age, sex and comorbidity [9]. However; in a recent study, Ouahmi et al. reported that proteinuria was not found as an independent predictor for in-hospital mortality [24].

This study has several limitations. The number of patients included in this study is limited, and there were some missing data. Second, an accurate baseline serum creatinine and urine output was not available, which may have led to an under or overestimation of AKI or erroneous associations. We also were unable to distinguish patients who had preexisting proteinuria and hematuria prior to the presentation from those who had it new-onset on admission due to lack of previous urinalysis in most patients. Third, disease severity was not defined because of missing data. Finally, the quantification of proteinuria could not be investigated.

In conclusion, proteinuria on admission is associated with the development of AKI and in-hospital mortality in patients with COVID-19. We hence reinforce the suggestion that urinalysis may be useful for the evaluation of COVID-19 progression and early diagnosis of kidney damage before SCr rise. Early detection and effective intervention of kidney involvement may help to reduce the development of AKI and to improve the vital prognosis of COVID-19.

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Data availability statment. The data that support the findings in this study are available from the corresponding author, [M.O.], upon reasonable request.

Authors contributions.

Meric Oruc: conception and design, data acquisition, analysis and interpretation of data, drafting the article, providing intellectual content of critical importance to the work described

Ayse Batirel: conception and design, analysis, providing intellectual content of critical importance to the work described

Sinan Trabulus: conception and design, analysis, drafting the article, providing intellectual content of critical importance to the work described, final approval of the version to be published.

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