Kidney function on admission predicts in-hospital mortality in COVID-19

Sinan Trabulus, MD
ORCID: 0000-0003-3843-5950
Department of Nephrology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

Cebrail Karaca, MD
ORCID: 0000-0003-0969-7708
Department of Nephrology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

İlker İnanç Balkan, MD
ORCID: 0000-0002-8977-5931
Department of Infectious Diseases and Clinical Microbiology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

Mevlüt Tamer Dincer, MD
ORCID: 0000-0002-5397-7697
Department of Nephrology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

Ahmet Murt, MD
ORCID: 0000-0002-1948-2914
Department of Nephrology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa
Fehmi Tabak, MD
ORCID: 0000-0001-8632-2825
Department of Infectious Diseases and Clinical Microbiology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

Nurhan Seyahi, MD
ORCID: 0000-0001-7427-618X
Department of Nephrology, Cerrahpasa Medical Faculty, Istanbul University - Cerrahpasa

Corresponding author:
Prof. Dr. Nurhan Seyahi
Istanbul Universitesi - Cerrahpasa
Cerrahpasa Medical Faculty, Department of Nephrology
Fatih, Istanbul, 34360 Turkey
Phone: (+90-212) 230 2996
E-mail: nseyahi@yahoo.com

Running Title: Mortality and Kidney Function in COVID-19
Abstract

Background

Recent data have reinforced the concept of a reciprocal relationship between COVID-19 and kidney function. However, most studies have focused on the effect of COVID-19 on kidney function, whereas data regarding kidney function on the COVID-19 prognosis is scarce. Therefore, in this study, we aimed to investigate the association between eGFR on admission and the mortality rate of COVID-19.

Methods

We recruited 336 adult consecutive patients (male 57.1%, mean age 55.0±15.9) that were hospitalized with the diagnosis of COVID-19 in the tertiary care university hospital. Data were collected from the electronic health records of the hospital. On admission, eGFR was calculated using the CKD-EPI formula. Acute kidney injury was defined according to the KDIGO criteria. Binary logistic regression and Cox regression analyses were used to assess the relationship between eGFR on admission and in-hospital mortality of COVID-19.

Results

Baseline eGFR was under 60 mL/min/1.73m² in 61 patients (18.2%). Acute kidney injury occurred in 29.1% of the patients. In-hospital mortality was calculated as 12.8%. Age-adjusted and multivariate logistic regression analysis (p:0.005, odds ratio:0.974, CI:0.956-0.992) showed that baseline eGFR was independently associated with mortality. Additionally, age-adjusted Cox regression analysis revealed a higher mortality rate in patients with an eGFR under 60 mL/min/1.73m².

Conclusions

On admission eGFR seems to be a prognostic marker for mortality in patients with COVID-19; We recommend to determine eGFR in all patients on admission and use it as an
additional tool for risk stratification. Close follow-up should be warranted in patients with reduced eGFR.

**Keywords:** Acute kidney injury; COVID-19; eGFR; mortality; SARS-CoV-2.
Introduction

An outbreak of a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) has emerged from Wuhan city, China [1]. In December 2019 and spread to over 214 countries and territories worldwide, within six months. The first case of COVID-19 in Turkey was confirmed on March 10, 2020, and the World Health Organization declared the disease a pandemic on March 11. In severe cases, acute respiratory failure due to diffuse alveolar damage constitutes the main clinical characteristics of COVID-19, whereas kidneys are among the most common extrapulmonary targets of the virus [1-3].

Chronic kidney disease (CKD) is associated with alterations of innate and adaptive immunity. The reasons for these alterations are accumulated pro-inflammatory cytokines due to decreased renal clearance, increased generation of inflammatory molecules by uremic toxins and impact of uremia on immunocompetent cells [4]. When compared to the general population, both the pneumonia risk and the mortality rate due to pneumonia are increased in patients with CKD [5,6]. In line with this information, to date, many studies have focused on the effect of COVID-19 on kidneys [7]. However, data regarding the reciprocal side of this relationship is scarce [8]. In this study, we primarily aimed to investigate the effects of kidney function on the prognosis of COVID-19, exclusively focusing on the estimated glomerular filtration rate (eGFR) on admission, and secondarily, to determine the rate of acute kidney injury (AKI) in those patients.

Materials and Methods

Setting

The study was conducted in a tertiary care university hospital in Istanbul, where approximately 60% of all cases in Turkey were reported [9]. Istanbul University - Cerrahpasa,
Cerrahpasa Medical Faculty hospital is among the largest university hospitals in Istanbul with a total of 897 hospital beds, 270 of which were allocated for the current pandemic.

**Patients**

Medical records of consecutive adult (>18 years) patients hospitalized between March 15 and May 1, 2020, were reviewed. Outcomes data until June 1, 2020, were retrieved.

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) suggesting COVID-19, according to the national guidelines [10].

Patients without any RT-PCR positivity and those considered as ‘possible’ or ‘probable’ cases according to the European Centres for Disease Control and Prevention (ecdc) criteria were not included in the study (Fig 1) [11].

**Diagnostic methodology**

Combined pharyngeal and nasopharyngeal swab samples were obtained for RT-PCR assay. In cases followed with invasive mechanical ventilation in ICU, lower respiratory tract specimens were also obtained.

RNAs were extracted by a commercial kit (Bio-Speedy nucleic acid extraction kit, Bioeksen, Turkey), following extraction a commercial RT-PCR kit (Bio-Speedy, COVID-19 RT-qPCR Kit, Bioeksen, Turkey) that targets RdRp gene of COVID-19 was used for detection of COVID-19 RNA in the samples. Both kits were used according to the manufacturer’s protocol. RT-PCR was performed with 20 µl final volume using the following protocol: 5 min RT-PCR at 52°C, 10-sec initial denaturation step at 95°C, followed by
40 cycles of 1 sec at 95 °C, and 30 sec at 60 °C. Rotor-Gene Q 5plex HRM platform was used for amplification and detection.

**Data collection and design**

Demographic, clinical and laboratory data were retrieved from the electronic database of the hospital by two different teams (from Nephrology and Infectious Diseases departments) first, cross-checked and then, were screened for duplicate records, missing, and erroneous data. The National Public Health Data Management System database was used as an external data source, particularly to track molecular test results. Data regarding medications were obtained from the medical records of the patients and via the National Health Insurance database when necessary.

Clinical data consisted of symptoms and vital findings including temperature (on admission) and oxygen saturation (lowest levels). Comorbidities were retrieved from medical records. Patients using antihypertensive drugs were accepted as hypertensive, and those using antidiabetic drugs were accepted as diabetic. Laboratory data consisted of serum urea, creatinine, uric acid, sodium, potassium, calcium, albumin, lactate dehydrogenase (LDH), liver function tests (AST, ALT), C-reactive protein (CRP), procalcitonin, ferritin, D-dimer, fibrinogen, creatine phospho-kinase (CPK), hematocrit (Htc), white blood cell (WBC), lymphocyte, platelet count (PLT) and urinalysis on admission. Additionally, discharge and peak creatinine values were also collected. For two patients there was more than one admission, only first admission values are recorded and mortality data were obtained from the last admission.

The data underlying this article will be shared on a reasonable request to the corresponding author.
Study definitions

The date of hospital admission was accepted as the first day. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula [12].

AKI was defined as an acute increase in the serum creatinine level of at least 0.3 mg/dl within 48 hours or a 50% increase in the serum creatinine level within 7 days from the baseline according to the KDIGO guideline. Staging of AKI was also performed according to the same guideline [13]. Complete renal recovery was defined as the regression of the discharge creatinine level to the baseline creatinine level and partial renal recovery was defined by a difference of less than 0.3 mg/dl between the baseline and discharge creatinine levels.

Body temperature was measured using non-contact infrared thermometers and the presence of fever was defined as a temperature of more than 37.8°C. Microscopic hematuria was accepted as the presence of ≥1+ (three or more erythrocytes per high-power field) on dipstick urine testing. Proteinuria was defined as the presence of ≥1+ (at least 30-100 mg/dL) on dipstick urinalysis.

The study protocol was approved by the local medical ethical committee (approval no: 2020-56318) and the Scientific Committee of the Ministry of Health (approval no: 2020-05-07T13_09_11). The study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Statistical analysis

Data were expressed as mean±standard deviation, if not stated otherwise. Categorical variables were compared using the chi-square test and two-tailed exact significances (Fisher’s exact test) were reported. Continuous variables were first analyzed for normality using the Kolmogorov-Smirnov test and then were compared using the paired samples t-test or the Mann-Whitney U test when appropriate. Age-adjusted odds ratios were
obtained with the use of logistic regression. Variables that were significantly associated with mortality in the age-adjusted analysis were used to construct a multivariate model. Binary logistic regression analysis with forward conditional selection was used to evaluate the determinants of in-hospital mortality. Age-adjusted survival was calculated using the Cox regression analysis.

All tests were performed using SPSS for Windows, version 22.0 software (SPSS Inc, Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

Results

Baseline demographic, clinical and laboratory parameters

We examined a total of 336 unique patients. The demographic and clinical characteristics of the patients stratified by baseline eGFR are shown in Table 1. Patients were usually middle to older age (median: 54; range 18-94) and male gender (57.1%) was more prominent. The most common symptoms at admission were as follows; cough in 156 (46.4%), fever in 119 (35.4%), dyspnea in 89 (26.5%), weakness in 58 (17.3%), diarrhoea in 29 (8.6%), nausea/vomiting in 26 (7.7%), myalgia in 26 (7.7%), headache in 14 (4.2%), expectorating in nine (2.7%), and smell and taste disorder in two (0.6%) patients.
Table 1. Demographic and clinical characteristics of all patients and patients with a baseline eGFR <60 and ≥60 mL/min/1.73 m².

| Characteristics          | All patients (n=336) | Patients with baseline eGFR <60 mL/min/1.73 m² (n=61) | Patients with baseline eGFR ≥60 mL/min/1.73 m² (n=275) | p       |
|--------------------------|----------------------|-----------------------------------------------------|-----------------------------------------------------|---------|
| Age (years)              | 55.0±16.0            | 69.9±12.9                                           | 51.7±14.7                                           | <0.001  |
| Gender, male             | 192 (57.1)           | 29 (47.5)                                           | 163 (59.3)                                          | 0.115   |
| Diabetes mellitus        | 63 (18.8)            | 23 (37.7)                                           | 40 (14.5)                                           | <0.001  |
| Hypertension             | 120 (35.7)           | 42 (68.9)                                           | 78 (28.4)                                           | <0.001  |
| Asthma bronchiale        | 20 (6.0)             | 1 (1.6)                                             | 19 (6.9)                                            | 0.142   |
| COPD                     | 19 (5.7)             | 12 (19.7)                                           | 7 (2.5)                                             | <0.001  |
| Heart failure            | 16 (4.8)             | 6 (9.8)                                             | 10 (3.6)                                            | 0.050   |
| Malignancy               | 31 (10.1)            | 5 (9.8)                                             | 26 (10.2)                                           | 1.000   |

Data are expressed as mean±SD for quantitative parameters and n (%) for nominal parameters. eGFR: estimated glomerular filtration rate, COPD: chronic obstructive pulmonary disease.

Hypertension was the most common comorbid disease, followed by diabetes mellitus (Table 1). Six patients were on chronic hemodialysis treatment and there was only one patient with kidney transplantation.
eGFR was <60 mL/min/1.73 m² in the minority of the patients (18.1%). These patients were older and comorbid conditions such as diabetes, hypertension and chronic obstructive pulmonary disease (COPD) were more common among them (Table 1). Laboratory data on the admission of the patients are shown in Table 2. Besides differences in the laboratory parameters that were related to our kidney function-based classification, patients with an eGFR <60mL/min/1.73 m² had higher uric acid, potassium, LDH, ALT, CRP, procalcitonin, ferritin, D-dimer, WBC, and lower calcium, albumin, hematocrit levels, when compared to patients with an eGFR ≥60 mL/min/1.73 m². Only the lowest oxygen saturation was recorded in all patients and in patients with an eGFR <60mL/min/1.73 m² oxygen saturation was lower compared to those of the patients with eGFR >60 mL/min/1.73 m² (89.3±8.3% vs 92.4±5.9%, respectively; p 0.01).

Table 2. Laboratory findings of all patients and patients with a baseline eGFR <60 and ≥60 mL/min/1.73 m².

| Parameters          | All patients (n=336) | Patients with baseline eGFR <60 mL/min/1.73 m² (n=61) | Patients with baseline eGFR ≥60 mL/min/1.73 m² (n=275) | p     |
|---------------------|----------------------|-------------------------------------------------------|-------------------------------------------------------|-------|
| Urea (mg/dL)        | 37.6±31.0            | 80.6±50.7                                             | 28.0±10.4                                             | <0.00 |
| Creatinine (mg/dL)  | 1.2±1.2              | 2.6±2.3                                               | 0.8±0.2                                               | <0.00 |
| Admission eGFR (mL/min/1.73 m²) | 83.1±28.7         | 34.7±17.6                                             | 93.8±17.5                                             | <0.00 |

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|                               | Group 1      | Group 2      | Group 3      | p-value |
|-------------------------------|--------------|--------------|--------------|---------|
| Peak creatinine (mg/dL)       | 1.5±1.7      | 3.5±3.3      | 1.1±0.5      | <0.00   |
| Time to peak creatinine (day) | 4.1±4.6      | 4.3±5.2      | 4.1±4.4      | 0.691   |
| eGFR calculated using peak creatinine (mL/min/1.73 m²) | 70.6±30.7 | 26.8±16.2 | 80.3±24.0 | <0.00   |
| Discharge creatinine¹ (mg/dL) | 1.1±1.1      | 2.4±2.2      | 0.9±0.4      | <0.00   |
| Discharge eGFR¹ (mL/min/1.73 m²) | 83.5±31.0   | 38.7±23.6   | 93.5±22.4   | <0.00   |
| Uric acid² (mg/dL)            | 5.1±2.0      | 7.4±2.7      | 4.6±1.4      | <0.00   |
| Sodium (mEq/L)                | 137.7±3.8    | 137.0±4.9    | 137.8±3.6    | 0.229   |
| Potassium (mEq/L)             | 4.3±0.5      | 4.5±0.8      | 4.3±0.5      | 0.029   |
| Calcium¹ (mg/dL)              | 8.7±0.6      | 8.5±0.6      | 8.8±0.6      | <0.00   |
| Albumin³ (g/dL)               | 3.9±0.5      | 3.5±0.5      | 4.0±0.5      | <0.00   |
| Test          | Mean ± SD | Mean ± SD | Mean ± SD | p-value |
|--------------|-----------|-----------|-----------|---------|
| LDH (U/L)    | 298.6±287.4 | 361.8±280.1 | 284.6±287.6 | 0.016   |
| AST (U/L)    | 38.6±73.7  | 67.3±163.6 | 32.2±23.5  | 0.614   |
| ALT (U/L)    | 35.2±89.5  | 50.7±181.9 | 31.8±49.8  | 0.003   |
| CRP (mg/dL)  | 57.9±72.6  | 97.5±88.1  | 49.1±65.7  | <0.00   |
| Procalcitonin³ (ng/mL) | 1.4±9.3  | 2.7±8.8  | 1.1±9.4  | <0.00   |
| Ferritin⁴ (ng/mL) | 506.8±889.6  | 892.0±1731.3  | 426.2±549.7  | 0.008   |
| D-dimer (ng/mL) | 1.6±3.1  | 3.2±4.3  | 1.2±2.6  | <0.00   |
| Fibrinogen⁵ (mg/dL) | 443.8±165.1  | 458.6±160.3  | 440.5±166.3  | 0.467   |
| CPK⁶ (U/L)   | 157.5±359.1 | 128.6±125.4 | 164.0±392.7 | 0.950   |
| Hematocrit¹ (%) | 38.0±5.7  | 34.5±6.4  | 38.8±5.2  | <0.00   |
| White blood cell (/mm³) | 6602.7±3491.1  | 7845.9±4414.9  | 6326.9±3195.7  | <0.00   |
| Lymphocyte (/mm³) | 1519.0±1595.1  | 1226.2±706.6  | 1583.9±1725.7  | 0.113   |
| Platelet (/mm³) | 215087.1±150039.8  | 211426.2±115593.9  | 215899.1±156825.1  | 0.834   |
Data are expressed as mean±SD. eGFR: estimated glomerular filtration rate, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, CPK: creatine phospho-kinase.

1There were missing data in less than three patients.
2Uric acid was measured in 325 patients.
3Procalcitonin was measured in 310 patients.
4Ferritin was measured in 318 patients.
5Fibrinogen was measured in 297 patients.
6CPK was measured in 301 patients.

Urinalysis was available in 67 patients; hematuria was detected in 23 and proteinuria in 17 patients.

Drugs used for the management of COVID-19 are summarised in Table 3. Favipiravir was more commonly used in patients with an eGFR <60 mL/min/1.73 m². There were no statistically significant differences between the two groups (eGFR <60mL vs ≥60 mL/min/1.73 m²) regarding other drugs (Table 3).

**Table 3. Drugs used in the treatments of all patients and patients with a baseline eGFR<60 and ≥60 mL/min/1.73 m².**

| Drug          | All patients (n=336) | Patients with baseline eGFR<60 mL/min/1.73 m² (n=61) | Patients with baseline eGFR≥60 mL/min/1.73 m² (n=275) | p     |
|---------------|----------------------|-----------------------------------------------------|------------------------------------------------------|-------|
| Hydroxychloroquine | 332 (98.8)         | 59 (96.7)                                           | 273 (99.3)                                           | 0.152 |
| Oseltamivir   | 285 (84.8)           | 48 (78.7)                                           | 237 (86.2)                                           | 0.166 |
### Data are expressed as n (%). eGFR: estimated glomerular filtration rate, LMWH: low-molecular-weight heparin.

**Prevalence of AKI, intensive care unit admission, and in-hospital mortality**

Patients stayed at the hospital on average nearly for 10 days. AKI was detected in 98 patients (29.1%) and most (68.3%) of the AKI cases were stage 1 (Table 4). Intensive care unit (ICU) admission was necessary for 17.6% of the patients. Twelve point eight per cent of the patients died during their hospitalization.

**Table 4. Incidence of acute kidney injury, intensive care unit admission and in-hospital mortality.**

| Characteristics    | All patients (n=336) | Patients with baseline eGFR <60 mL/min/1.73 m² (n=61) | Patients with baseline eGFR ≥60 mL/min/1.73 m² (n=275) | p  |
|--------------------|----------------------|------------------------------------------------------|------------------------------------------------------|----|
| Azithromycin       | 294 (87.5)           | 51 (83.6)                                            | 243 (88.4)                                           | 0.292 |
| Favipiravir        | 169 (50.2)           | 41 (67.2)                                            | 128 (46.5)                                           | 0.004 |
| Lopinavir/ritonavir| 27 (8.0)             | 6 (9.8)                                              | 21 (7.6)                                             | 0.421 |
| Tocilizumab        | 57(17.8)             | 9 (14.8)                                             | 48 (17.5)                                            | 0.708 |
| LWMH               | 192 (57.3)           | 40 (65.6)                                            | 152 (55.3)                                           | 0.115 |
| Glucocorticoid     | 21 (6.3)             | 2 (3.3)                                              | 19 (6.9)                                             | 0.390 |
Patients with an eGFR <60 mL/min/1.73 m² had longer hospital stays. AKI was more common in patients with a baseline eGFR <60 mL/min/1.73 m². All three stages of AKI were also more common in patients with a baseline eGFR <60 mL/min/1.73 m² (Table 4).

Continuous renal replacement therapy was performed in four cases due to stage 3 AKI, and in three of them, baseline eGFR was <60 mL/min/1.73 m². Thirty-four patients with AKI have died (34.6%), we observed complete renal recovery in 36 (36.7%) and partial renal recovery in 23 patients (23.4%) of the remaining 64 patients. Discharge creatinine remained 0.3 mg/dL above admission creatinine in five patients (5.1%). In-hospital mortality was significantly lower (3.7%, p<0.001) in patients without AKI compared to that of the patients with AKI.

The ICU admission and in-hospital death rates were significantly higher in patients with a baseline eGFR <60 mL/min/1.73 m² (Table 4). Specifically, three of the six patients
who were on chronic hemodialysis treatment have also died and the kidney transplantation recipient survived.

**Determinants of in-hospital mortality**

A total of 43 patients (12.8%) were dead during the hospital stay. Comparison of the demographic, clinical, and laboratory findings of the deceased and living patients is given in Table 5. Patients who died were older and commonly had comorbid conditions such as diabetes, hypertension, COPD, heart failure and malignancy. Laboratory parameters associated with kidney function were worse in the patients who died. Compared to the patients who survived, deceased patients had higher uric acid, LDH, AST, CRP, procalcitonin, ferritin, D-dimer, CPK, WBC, and lower sodium, calcium, albumin, hematocrit, and lymphocyte levels (Table 5). The association between old age and COVID-19 mortality is well known, therefore, we calculated age-adjusted odds ratios of the study parameters for mortality (Table 5). According to the age-adjusted analysis, heart failure, malignancy, kidney function parameters, and sodium, calcium, albumin, LDH, AST, CRP, ferritin, D-dimer, Hct, WBC and lymphocyte levels were associated with mortality.
Table 5. Demographic, clinical and laboratory findings of patients who died and those who survived.

| Parameters          | Patients who died (n=43) | Those who survived (n=293) | p     | Age adjusted OR | CI 95% (min-max) | p     |
|---------------------|--------------------------|---------------------------|-------|----------------|------------------|-------|
| Age                 | 68.5±15.2                | 53.0±15.1                 | <0.001| NA             | NA               | NA    |
| Gender, male        | 27 (62.8)                | 165 (56.3)                | 0.510 | 1.543          | 0.756-3.149      | 0.233 |
| Diabetes mellitus   | 15 (34.9)                | 48 (16.4)                 | 0.006 | 0.554          | 0.262-1.172      | 0.123 |
| Hypertension        | 22 (51.2)                | 98 (33.4)                 | 0.027 | 1.288          | 0.605-2.745      | 0.512 |
| Asthma bronchiale   | 1 (2.3)                  | 19 (6.5)                  | 0.489 | 3.087          | 0.382-24.965     | 0.290 |
| COPD                | 6 (14.0)                 | 13 (4.4)                  | 0.023 | 0.613          | 0.206-1.822      | 0.379 |
| Heart failure       | 8 (18.6)                 | 8 (2.7)                   | <0.001| 0.234          | 0.076-0.717      | 0.011 |
| Malignancy          | 17 (39.5)                | 14 (4.8)                  | <0.001| 0.046          | 0.017-0.121      | <0.001|
| Urea (mg/dL)        | 71.4±58.3                | 32.6±20.5                 | <0.001| 1.021          | 1.011-1.031      | <0.001|
| Creatinine (mg/dL)  | 1.9±1.9                  | 1.0±1.0                   | <0.001| 1.367          | 1.109-1.685      | 0.003 |
|                                | Admission eGFR (mL/min/1.73m²) | Peak creatinine (mg/dL) | Time to peak creatinine (day) | eGFR calculated using peak creatinine (mL/min/1.73 m²) | Discharge creatinine (mg/dL) | Discharge eGFR (mL/min/1.73 m²) | Uric acid (mg/dL) |
|--------------------------------|--------------------------------|------------------------|-------------------------------|--------------------------------------------------------|-----------------------------|--------------------------------|------------------|
| 59.7±37.4                     |                                 | 3.3±2.6                | 7.6±7.2                       | 30.6±27.2                                               | 2.2±1.5                     | 44.9±37.0                              | 6.0±3.1          |
| 86.5±25.6                     |                                 | 1.2±1.4                | 3.6±3.8                       | 76.4±26.5                                               | 0.9±0.9                     | 89.2±25.5                              | 5.0±1.8          |
| <0.001                         |                                 | <0.001                 | 0.001                         | <0.001                                                 | <0.001                      | <0.001                                   | 0.045            |
| 0.983                          |                                 | 1.495                  | 1.140                         | 0.947                                                  | 1.708.                      | 0.960                                   | 1.109            |
| 0.970-0.996                   |                                 | 1.227-1.821            | 1.068-1.217                   | 0.932-0.963                                             | 1.280-2.280                 | 0.948-0.973                            | 0.953-1.291      |
| 0.010                          |                                 | <0.001                 | <0.001                        | <0.001                                                 | <0.001                      | <0.001                                   | 0.182            |
| Test                      | Value 1     | Value 2     | p-value | CI          | p-value | CI          | p-value |
|--------------------------|-------------|-------------|---------|-------------|---------|-------------|---------|
| Sodium (mEq/L)           | 135.5±5.6   | 138.0±3.4   | 0.006   | 0.792--0.936| <0.001  | 0.792--0.936| <0.001  |
| Potassium (mEq/L)        | 4.2±0.7     | 4.3±0.5     | 0.411   | 0.316-1.127 | 0.112   | 0.316-1.127 | 0.112   |
| Calcium (mg/dL)          | 8.3±0.7     | 8.8±0.6     | <0.001  | 0.253-0.728 | 0.002   | 0.253-0.728 | 0.002   |
| Albumin (g/dL)           | 3.3±0.5     | 4.0±0.5     | <0.001  | 0.032-0.175 | <0.001  | 0.032-0.175 | <0.001  |
| LDH (U/L)                | 439.2±687.8 | 263.6±130.1 | <0.001  | 1.002-1.007 | <0.001  | 1.002-1.007 | <0.001  |
| AST (U/L)                | 71.8±100.6  | 33.7±67.7   | <0.001  | 1.000-1.007 | 0.046   | 1.000-1.007 | 0.046   |
| ALT (U/L)                | 66.8±215.4  | 30.5±48.4   | 0.863   | 0.999-1.011 | 0.102   | 0.999-1.011 | 0.102   |
| CRP (mg/dL)              | 146.1±83.6  | 44.9±61.0   | <0.001  | 1.008-1.017 | <0.001  | 1.008-1.017 | <0.001  |
| Procalcitonin (ng/mL)    | 3.1±9.3     | 1.1±9.3     | <0.001  | 0.980-1.037 | 0.569   | 0.980-1.037 | 0.569   |
| Ferritin (ng/mL)         | 1192.0±1910.1 | 419.3±608.7 | <0.001  | 1.000-1.001 | 0.003   | 1.000-1.001 | 0.003   |
| D-dimer (ng/mL)          | 5.0±6.6     | 1.1±1.7     | <0.001  | 1.126-1.453 | <0.001  | 1.126-1.453 | <0.001  |
| Fibrinogen (mg/dL)       | 470.8±164.0 | 439.8±165.2 | 0.280   | 0.999-1.003 | 0.385   | 0.999-1.003 | 0.385   |
|                          | Mean±SD               | Median±IQR       | P-value | OR     | 95% CI       | P-value |
|--------------------------|-----------------------|------------------|---------|--------|--------------|---------|
| **CPK (U/L)**            | 182.1±162.4           | 153.7±381.1      | 0.033   | 1.001  | 1.000-1.001  | 0.192   |
| **Hematocrit (%)**       | 32.3±6.3              | 38.9±5.1         | <0.001  | 0.833  | 0.779-0.891  | <0.001  |
| **White blood cell**     | 8576.7±5553.0         | 6313.0±2981.5    | 0.005   | 1.000  | 1.000-1.000  | 0.009   |
|                          | 883.7±532.7           | 1612.2±1676.3    | 0.005   | 0.998  | 0.997-0.999  | <0.001  |
| **Platelet (/mm³)**      | 176793.0±93824.5      | 220707.1±155927.0| 0.073   | 1.000  | 1.000-1.000  | 0.054   |

Data are expressed as mean±SD for quantitative parameters and n (%) for nominal parameters. NA: not applicable. COPD: chronic obstructive pulmonary disease, eGFR: estimated glomerular filtration rate, LDH: lactate dehydrogenase, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CRP: C-reactive protein, CPK: creatine phospho-kinase. Please refer to foot-note of Table 2 for specific number of measurements of each laboratory parameter.
We used Cox regression analysis to calculate the age-adjusted survival according to the eGFR group and prepared the survival curves accordingly (Fig 2). A baseline eGFR <60ml/min/1.73m² was associated with a reduced survival rate (p: 0.021, OR: 2.161, CI 95%, min-max: 1.121-4.167).

Finally, we constructed a multivariate model to determine the in-hospital mortality rate using the variables that were available on admission and that were significantly associated with mortality in the age-adjusted analysis. We did not include the data that was not available on admission (peak creatinine, discharge creatinine, their associated eGFRs and time to peak creatinine) and associates of eGFR (urea and creatinine) in our prediction model. According to the multivariate model, malignancy, eGFR, CRP and Hct levels on admission were independent determinants of mortality (Table 6).

Table 6. Variables associated with mortality according to the multivariate binary logistic regression model.

| Variables                  | Age adjusted OR | CI 95% (min-max) | p     |
|----------------------------|-----------------|------------------|-------|
| Malignancy                 | 29.412          | 7.194-125.000    | <0.001|
| Admission eGFR (mL/min/1.73m²) | 0.974     | 0.956-0.992      | 0.005 |
| CRP (mg/dL)                | 1.012           | 1.005-1.018      | <0.001|
| Hematocrit (%)             | 0.879           | 0.796-0.972      | 0.012 |

eGFR: estimated glomerular filtration rate, CRP: C-reactive protein.
Discussion

We showed that eGFR on admission was an independent determinant of mortality in patients with COVID-19. The association of COVID-19 with kidney function can be addressed in two reciprocal ways, which are not mutually exclusive; first, the effect of kidney disease on the course of COVID-19 can be examined, and second, the effect of COVID-19 on kidney function and development of AKI can be examined. In this paper, we mainly examined the first part of this association. Additionally, we also examined the rate of AKI. To the best of our knowledge, most studies have focused on the second part of this association from a clinical or histopathological point of view [2,8,14-18].

In addition to pulmonary infiltration, SARS-CoV-2 may have cytopathic effects in many organs, including renal tissue [3]. It has been reported that ACE2, the cell entry receptor of SARS-CoV-2, is expressed almost 100 times higher in the kidneys than in the lungs [19,20]. The pathogenesis of kidney disease in patients with COVID-19 is probably multifactorial, including direct cytopathic effects on kidney tissue, deposition of immune complexes and virus-induced cytokines or mediators [1,8]. Su et al. investigated postmortem findings of COVID-19 patients and found evidence of the direct cytopathic effect of COVID-19 on kidney tissue [3]. Hirsch et al. reported the incidence of AKI in a large cohort consisting of 5449 patients and suggested ischemic acute tubular necrosis as an important aetiology for AKI in COVID-19 [18].

We report a high rate of AKI (29.1%) and a high mortality rate in patients with AKI (34.6%). According to previous clinical studies, the detection rate of AKI in patients with COVID-19 has been reported to vary between 0.5% and 36.6% [8,16,18]. Wang et al. claimed that COVID-19 was not associated with AKI [14]. Curiously, in that study AKI was not reported even in the patients who died in the ICU. Cheng et al. reported AKI in 5.1% of a cohort of 701 patients [8]. The in-hospital death rate in that study was 16.1%, while it was calculated as high as 33.7% in those with elevated baseline serum creatinine levels. Another study from China examined 1,099 patients and found that mortality or ICU admission
rates in patients with a higher creatinine level were higher (9.6%, n=52) than those with normal creatinine levels (1%, n=700) [16]. Chen et al. evaluated the characteristics of deceased COVID-19 patients and found that AKI was more frequent in patients who died (25%) than in those who survived (1%) [15]. In another study, Pei et al. reported that 6% of their patients experienced AKI, and Lim et al. found that the median age was higher in AKI patients [17,21]. Hirsch et al. reported the highest AKI rate (36.6%) among COVID-19 patients and the mortality rate among this group was 35% [18].

Studies that analyzed the relationship between AKI or peak creatinine and the prognosis of COVID-19 might be prone to look-ahead bias. Therefore, we want to emphasize the importance of analyzing the relationship between kidney function on admission and mortality. We exclusively focused on baseline eGFR, since data on the peak creatinine level or development of AKI during the hospital stay are not available at the time of admission and risk stratification based on those characteristics might lead to a look-ahead bias. Similar to our findings, recently Cheng et al. showed that the prevalence of kidney disease during hospitalization in patients with COVID-19 was high and it was associated with in-hospital mortality [8]. However, their analysis was based on creatinine levels and they did not use eGFR as a prognostic marker [8].

Heterogeneity of the results regarding the development of AKI might be explained by differences in baseline demographics, comorbid conditions and respiratory disease severity [18]. Moreover, there were differences among countries regarding their response to the pandemic. Besides the differences in the extent and types of social isolation measures, treatment algorithms, modalities and drug use were also different. Additionally, there are demographic differences between countries; all those factors might also affect clinical endpoints. Therefore having data from different countries and geographic regions is important to better understand and manage the COVID-19 globally.

The following points summarise Turkey’s position regarding baseline characteristics and its response to the pandemic. Turkey is one of the countries with a relatively young population (30.7% of the population under age 20) and wide health coverage through
government programs [22,23]. The number of hospital beds and intensive care units per population is high [23]. Regarding COVID-19 treatment, early initiation of hydroxychloroquine was practised, favipiravir use was widely adopted, and tocilizumab was used in all patients when indicated [10].

There are several limitations of our paper. First, urine analysis was not available in a large proportion of patients and we did not collect data on kidney imaging. Therefore, we might have overlooked some patients with CKD. Second, our follow-up duration was limited by the hospital stay period of the patients. The recovery patterns of kidney function might change during a longer follow-up. Third, we did not perform a formal power analysis to determine the sample size, however, we recruited all eligible patients that were hospitalized. Fourth, our study was performed in a leading university hospital, it is possible that we might have recruited more severe patients. Finally, the generalizability of our results to other countries might be limited since countries have adopted different treatment guidelines according to local regulations and the availability of health resources.

In conclusion, eGFR on admission seems to be a prognostic marker for mortality in patients with COVID-19. We recommend that eGFR should be determined in all patients on admission and used as an additional tool for risk stratification. Close follow-up might be warranted in patients with a reduced eGFR.

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Conflict of Interest Statement:

None declared
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Legends of the figures

**Figure 1.** Flow chart showing the selection of the patients. * Definitions are based on the 
European Centre for Disease Prevention and Control [11].

**Figure 2.** Cumulative survival plots of the patients stratified by eGFR on admission. The 
plots are prepared according to age-adjusted Cox regression analysis. Green line depicts 
patients with GFR ≥60 mL/min/1.73 m² and blue line depicts patients with GFR <60 
mL/min/1.73 m².
737 patients hospitalized with COVID-19 during study period

329 “Possible” and “Probable” patients with negative PCR
72 Patients under age 18

336 “Confirmed” patients were included for the final analysis
