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Research Article

# Outcomes of Patients and Acute Kidney Injury in SARS-CoV-2 Infection

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## Abstract

**Objectives:** The SARS-CoV-2 virus has caused an outbreak of COVID-19 disease and severe acute respiratory syndrome. The related mortality may not be just due to respiratory complications. Here, we report acute renal injury and other outcomes of COVID-19 patients.

**Methods:** Demographic, clinical, laboratory, treatment, and outcome data of 194 COVID-19 patients were collected. We used univariable and multivariable logistic regression methods to explore the risk factors associated with the length of hospital stay and in-hospital death. A survival analysis of COVID-19 patients was included in conditions of basal elevated creatinine values and development of AKI as secondary outcome.

**Results:** 37 patients who were followed up from outpatient clinics and 157 hospitalized patients of whom 149 were discharged and 8 died in hospital were included in this study. Age over 45 was found to increase the time required to spend in hospital. Patients with COPD and AKI were significantly more likely to die.

**Conclusion:** Baseline decreased renal function in COVID-19 patients was asssociated with poor prognosis. Preexisting CKD and/or abnormal serum creatinine levels must be detected on admission in order to identify the most risky patients.

**Keywords:** SARS-CoV-2, renal functions, prognosis

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SARS-COV2 is a novel coronavirus. It arised in Wuhan, China and resulted in a pandemic. Most countries suffered from the virus as a healthcare problem resulting in many deaths. The COVID-19 agent causes primarily respiratory illness, both upper respiratory tract and also lower respiratory tract.[1]

COVID-19-related mortality rate varies widely among countries. Risk factors increasing disease mortality of COVID-19 patients needs to be described clearly. Comorbid diseases present at first may have a worsening effect on the clinical course. So identifying the poor prognostic factors could save limited healthcare capacities of the countries. In studies focusing on this issue, increased risk of developing more severe complications were reported in COVID-19 patients with certain preexisting chronic diseases.[2]

Chronic kidney disease (CKD) is widely accepted as an immunsupressive condition. Regardless of the primary disease, CKD patients usually have multiple defects of both the innate and adaptive in immune systems characterized by consistent low-grade inflammation.[3]

CKD prevalance is higher in people aged over 70 years according to a large scale study.[4] COVID-19 disease is also known to be more mortal in elderly, possibly as a result of co-existing health problems.[5] From this view, baseline renal functional capacities have some potential to increase

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the mortality of COVID 19 disease in the elderly.

In fact, COVID-19 was detected to affect mainly the respiratory system and rapidly progressing to acute respiratory distress syndrome (ARDS) in some of the patients but other organ functions were considered to be less involved in the earlier stages.[1] Pneumonia and resultant hypoxia is still accepted as the major mortality reason.[6] Hypoxia is also known to cause renal injury.[7] The kidney injury induced by hypoxia and ischemia-reperfusion usually causes irreversible renal fibrosis, a process that develops into CKD. Imbalances between circulatory demands and perfusion leading to renal ischemia as well as adverse events of drugs may be the causes of acute kidney injury (AKI) during COVID 19 infection. But besides mortality and renal injury through respiratory disease and drugs, this new virus has the potential to influence other organs like eyes, heart and kidneys. Renal injury and resultant GFR decline may be also a result of renal SARS-CoV-2 infiltration in addition to potentially increasing mortality.

Increased serum creatinine (SCr) values were reported in COVID 19 patients that were admitted to intensive care units (ICU).[2] Some of the COVID 19 patients need advanced life support in ICUs. Critically ill patients in ICU need further support to preserve the function of their vital organs like kidney and they may need dialysis treatment.[8] The dialysis facilities may not be adequate in every healthcare unit so identifiying the patients under risk of dialysis during outbreaks like COVID 19 is crucial. Thus, predicting the renal progression of COVID 19 patients and the effects or renal disease on mortality is necessary in COVID-19 patients. Clinicians must follow changes in the clinical situation of the patients carefully in order to organize the treatments, prevent renal failure and improve outcomes. Here, we performed a study in order to identify the role of COVID 19 infection on estimated glomerular filtration rate (eGFR) and the effect of basal eGFR on disease severity and mortality among COVID-19 patients.

## Methods

This study was a retrospective observational research study. The approval was received from the local ethics committee. (TÜTF-BAEK 2020/274) It was conducted in COVID 19 patients who were followed up. Written informed consents were obtained from all patients included in the study. The study was based on the record analysis of COVID-19 patients of either sex without any age bar.

### Selection and Description of the Cases

The participants were the patients that were hospitalized in our COVID-19 inpatient clinic and the severe ones that were transferred to our ICU. All the patients had been treated according to the COVID-19 guidelines that were suggested by the Health Ministery of Turkey. Oxygen therapy, oral and/or intravenous hydration, antipyretic therapy, deep venous thrombosis prophylaxis with subcutaneous enoxaparin and gastrointestinal ulcer propylaxis were used in every patient in need.

### Technical Information

Age and gender were noted as demographical data of the patients. Presence of hypertension, Diabetes Mellitus, coronary artery disease, active malignancy and any other immunsuppresive condition or disease data were recorded as comorbidities. The medication history of the patients were taken comprehensively. The CKD and AKI was diagnosed based on biochemical parameters, clinical findings and imaging studies. All data were checked by physicians.

CKD definition of decreased kidney function shown by a GFR of less than 60 mL/min per 1, 73 $m^2$, or markers of kidney damage (albuminuria, urinary sediment abnormalities, electrolyte or other abnormalities due to tubular disorders, abnormalities on histology, structural abnormalities detected by imaging and having a history of a kidney transplantation), or both, of at least 3 months duration, regardless of underlying cause was used.[9] AKI was defined as an increase in SCr by ≥ 0,3 mg/dl (≥ 26,5 µmol/l) within 48 hours or to ≥ 1,5 times of baseline, or a decline in eGFR to more than 25% from baseline value, or a urine volume lower than 0.5 mL/kg/h for 6 h which is known or presumed to have occurred within the prior 7 days.[10] The medical records were noted at the beginning, just before the discharge or just before death. Serum biochemical tests including serum urea, creatinine, sodium, potassium, chloride, CRP, SGPT, SGOT, complete blood count, lactate dehydrogenase, which had been analyzed at our central laboratory were obtained. Estimated GFR values were calculated by using CKD-EPI formula. Thorax computed tomography scans that were taken for all pnemonia suspected patients without contrast administration were also obtained.

The Microbiology Laboratory was responsible for SARS-CoV-2 infection detection in respiratory specimens by real-time polymerase chain reaction (RT-PCR) methods. SARS-CoV-2 RNA were detected by microbiology laboratory. CoV-2 PCR throat-swab specimens for SARS- were re-collected 2 days after clinical remission of symptoms. The criteria for discharge were clinical remission of respiratory symptoms, and two throat-swab samples negative for SARS-CoV-2 RNA obtained at least 24 h apart and absence of fever for at least 3 days.

## Statistical Analysis

Data analysis was performed using SPSS version 22. Numeric variables were expressed as median (Inter-Quartile Range, IQR) and compared with the Mann-Whitney U test. Categorical variables were presented as number and percentage (%) and compared with the Chi-square test. The survival probability of COVID-19 patients in hospital were calculated using the Kaplan-Meier method, and the significance and the hazard ratio of the risk variables were estimated by fitting a Cox proportional hazards model. A significance level was considered statistically significant for $p<0.05$.

## Results

A total of 194 patients were included in this study, of whom 157 were discharged and 8 died in hospital. 29 patients were still under treatment at hospital. 104 patients were women (53%), and the mean age was 45±18 years. Fourteen patients (7,2%) were treated in the ICU. Hypertension was the most common comorbidity (40 [20,6%] patients), followed by DM (18 [9,3%] patients) and hypothyroidism (10[5,2%] patients). Seven (3,6%) patients had AKI (Table 1).

Older age, especially over 45 was found to increase the time required to spend in hospital. Baseline serum creatinine value was found to increase the time required to spend in hospital. Presence of diabetes mellitus was found to increase the time required to spend in hospital (Table 2).

Age of 45 and older was found to increase the death risk. Presence of acute renal failure and chronic obstructive pulmonary disase (COPD) were found to increase the death risk significantly (Table 3).

Up to 57,1% of the patients with acute renal failure were found to have lymphopenia at initial presentation. Lymphopenia was found to increase acute renal failure risk significantly (p=0,004) .

The mean length of hospital stay was 9.7 days with a standard deviation of 6.9. The median length of hospital stay was 8 days (minimum 3-maximum 54 days). The treatment was heterogenous; 151 patients (77.8%) were given hydroxychloroquine, 145 patients (74.7%) were given aziythromycin, 139 patients (71.6%) were given oseltamivir, 19 patients (9.8%) were given favipiravir and 9 patients (4.6%) were given rotinavir.

**Table 1.** Demographical and clinical characteristics of the subjects

| | |
|---|---|
| Age, year | |
| Median (Interquartile range) | 45 (33-58) |
| Mean±standard deviation | 45±18 |
| Gender, n (%) | |
| Female | 104 (53.6) |
| Male | 90 (46.4) |
| Comorbidity, n (%) | |
| Hypertension | 40 (20.6) |
| Diabetes mellitus | 18 (9.3) |
| Coronary artery disease | 5 (2.6) |
| Chronic obstructive pulmonary disease | 7 (3.6) |
| Hypothyroidism | 10 (5.2) |
| Malignancy | 8 (4.1) |
| Hospitalization, n (%) | 157 (80.9) |
| CT-based pneumonia presence, n (%) | |
| Unilateral ground-glass opacity | 16 (8.2) |
| Bilateral ground-glass opacity | 93 (47.9) |

CT: computed tomography.

## Discussion

As SARS-CoV-2 enters the human tissues through the ACE2 and DPP4 receptors, and as those receptors are expressed mainly in the renal tubules, it was supposed that renal tubules would be more prone to be harmed by SARS-CoV-2 than some other tissues.[11-13] As a supporting evidence, plasma urea and creatinine levels were found to increase in some of COVID-19 patients by Li et al. when biochemical parameters were considered. Also a greater proportion of patients were found to have proteinuria. In addition, a significant proportion of the patients had renal abnormalities on computed tomography (CT) scan in that study.[14] When histological evidences are taken into account, a recent postmortem analysis of 26 COVID-19 patients showed some renal pathological abnormalities related to SARS-CoV-2 such as obstruction the capillary lumens, diffuse proximal tubule injury and necrosis. Hypoxia, coagulation defects, and possible drug adverse effects or rhabdomyolysis were detected as AKI causes but also the direct effects of SARS-CoV-2 had an impact. Coronavirus particles were shown with electron microscopy. This effect was detected to be directly related to the invasion of SARS CoV-2 into kidney tissue.[15]

As a different point, Zhou et al. found that acute kidney injury had been detected in only 1% of SARS-CoV-2-infected patients who survived but this rate was as high as 50% among non-survivors. From this aspect having AKI anytime on clinical course can be accepted as a precursor of death. [16] Likewise, baseline serum creatinine value was found to increase the time to completely recover and be discharged from the hospital in our study supporting the results of those findings. In the same way, presence of AKI was found to increase the death risk in our study. Additionally, COPD was found to be a statistically important factor on mortality as an other risk factor.

In a study investigating the renal effects of COVID-19, 29% of the patients were detected to have acute renal injury

**Table 2.** Clinical determinants of the hospitalization duration (≥7days)

| | Univariate analysis | | Multivariate analysis | |
|---|---|---|---|---|
| | HR (95% CI) | p | HR (95% CI) | p |
| Age, ≥45 years | 4.45 (1.94-10.19) | <0.001 | 3.12 (1.30-7.47) | 0.01 |
| Gender, male | 1.75 (0.85-3.62) | 0.12 | | |
| Baseline urea, mg/dL | 1.01 (0.97-1.04) | 0.56 | | |
| Baseline creatine mg/dL | 0.56 (0.05-6.30) | 0.64 | 5.42 (1.02-28.91) | 0.04 |
| Baseline eGFR, <60 | 0.98 (0.96-1.01) | 0.30 | | |
| Baseline lymphocyte | 0.99 (0.99-1.00) | 0.12 | | |
| Baseline hemoglobin | 0.78 (0.58-1.05) | 0.11 | | |
| Baseline SGPT (ALT) | 0.99 (0.95-1.03) | 0.84 | | |
| Baseline SGOT (AST) | 1.02 (1.01-1.04) | 0.01 | | |
| Baseline LDH | 1.001 (1.001-1.002) | 0.01 | | |
| Baseline CRP | 1.01 (0.99-1.02) | 0.14 | | |
| DM, presence | 0.03 (0.01-587.7) | 0.49 | 4.64 (1.57-13.69) | 0.005 |
| HT, presence | 1.5 (0.26-5.08) | 0.84 | | |
| COPD, presence | 22.87 (4.34-120.47) | <0.01 | | |
| Malignancy, presence | 4.55 (0.50-40.91) | 0.17 | | |
| ARF, presence | 6.27 (1.11-35.73) | 0.04 | | |

eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; ARF: acute renal failure.

**Table 3.** Clinical characteristics related to death

| | Univariate analysis | |
|---|---|---|
| | HR (95% CI) | p |
| Age, ≥45 years | 4.45 (1.94-10.19) | <0.001 |
| Gender, male | 1.75 (0.85-3.62) | 0.12 |
| Baseline urea, mg/dL | 1.02 (1.01-1.05) | 0.02 |
| Baseline creatine | 7.76 (1.56-38.44) | 0.01 |
| Baseline eGFR, <60 | 0.97 (0.95-0.98) | 0.001 |
| Baseline lymphocyte | 0.99 (0.98-0.99) | 0.02 |
| Baseline hemoglobin | 1.02 (0.83-1.26) | 0.81 |
| Baseline SGPT (ALT) | 1.01 (0.98-1.01) | 0.93 |
| Baseline SGOT (AST) | 1.02 (1.01-1.04) | 0.03 |
| Baseline LDH | 1.01 (1.01-1.02) | 0.001 |
| Baseline CRP | 1.01 (1.0-1.02) | 0.05 |
| DM, presence | 5.96 (2.12-16.73) | <0.01 |
| HT, presence | 4.17 (1.88-9.23) | <0.01 |
| COPD, presence | 1.48 (0.26-8.44) | 0.65 |
| Malignancy, presence | 1.80 (0.41-7.89) | 0.43 |
| ARF, development | 2.07 (0.33-12.93) | 0.43 |

eGFR: estimated glomerular filtration rate; DM: diabetes mellitus; HT: hypertension; COPD: chronic obstructive pulmonary disease; ARF: acute renal failure.

on admission to hospital.[17] Similarly, 27% of COVID-19 patients were reported to present with AKI in another study by Diao et al.[18] However, in a study that was conducted within 11 patients, COVID-19 was found not to result in AKI. In addition COVID-19 patients with CKD were found to save their renal functions in that study.[19] We found COVID-19 not to have a statistically significant impact on AKI risk.

Both cellular and humoral immunity are known to weaken due to uremia. This situation leads to defective elimination of intracellular pathogens like viruses. CKD patients infected by SARS-CoV-2 virus were found to be to have deeper lymphopenia than patients without CKD to prove this immune deficiency and they were unfortunately more prone to death.[20] In addition, presence of renal disease was found to be related with disease severity in a meta-analysis that was conducted in COVID-19 patients.[21] However, in a study, only 3% of patients were found to have CKD as a comorbidity. Related fatality rate in that study was 16.[22] We found lymphopenia in our patients in a statistically significant rate in our patients as in other studies. We detected 57,1% of the patients with acute renal failure to have lymphopenia at presentation. We found lymphopenia to increase acute renal failure risk significantly (p=0.004). This renal disease associated immune suppression may explain the increased length of hospital stay and increased mortality risk in our patients.

Some limitations were present in our study. First of all, this was a retrospective study. Second, the number of patients included in the study was small. Third, patients that represented with suspicious COVID-19 clinical pattern were excluded from the study if their PCR test results were negative.

Baseline higher creatinine values of COVID-19 patients

were associated with poor prognosis regarding longer hospitalization time in COVID-19 patients. Baseline higher creatinine values of COVID-19 patients were associated with poor prognosis regarding higher mortality rate in COVID-19 patients. In addition, older age, presence of COPD and presence of diabetes mellitus were associated with poorer outcomes in COVID-19 patients.

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**Disclosures**

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**Conflict of Interest:** None declared.

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