BMC Nephrology

RESEARCH

Open Access

Improved kidney function is associated with Colchicine treatment in COVID-19 patients

Yeter Eylul Bayram[1*], Mustafa Ilteris Bardakci[2] and Gulhan Ayhan Albayrak[2]

Abstract

Background The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2 virus) has been a major cause of significant morbidity and mortality. Acute kidney injury (AKI) has been seen in COVID-19-infected subjects, and it has frequently resulted in an abnormal estimated glomerular filtration rate. Colchicine, an immunomodulatory drug, was used in several studies in the early stages of the pandemic. Colchicine has been shown to prevent the development of renal failure in patients with Familial Mediterranean Fever (FMF). It has also been reported to reduce fibrosis, which plays a role in chronic kidney disease. We, therefore, aimed to investigate whether using Colchicine, in addition to standard care, was associated with better renal function in patients with severe COVID-19 infection.

Methods This retrospective cohort study comprised 118 out of 605 hospitalized COVID-19 subjects. Some of the subjects ($n=50$) received oral Colchicine plus standard care, called the Col (+) group. The others ($n=68$) received only the standard care, called the Col (-) group. The estimated glomerular filtration rate (eGFR) and other laboratory findings, including lymphocytes, D-dimer, and CRP, were analyzed.

Results The D-dimer and serum creatine levels were significantly reduced in both groups. The number of lymphocytes showed a significant increase in both groups at discharge. The level of C-reactive protein (CRP) was significantly higher in the Col (+) group than in the Col (-) group at admission. The reduction of SCr was considerably higher in the Col (+) group than in the Col (-) group. Similarly, the improvement of eGFR was higher in the Col (+) group than in the Col (-) group at discharge and 6–12 mounts follow-up.

Conclusion Our findings indicated the use of Colchicine plus standard care was associated with improved renal function in hospitalized patients with severe COVID-19 infection.

Keywords COVID-19, Acute kidney injury, SARS-CoV-2, Estimated glomerular filtration rate, Colchicine

Background

COVID-19 has a characteristic of high transmission and diverse clinical symptoms [1]. The prognosis of the disease might be mild, moderate, severe, or critical [2]. SARS-CoV-2-induced disease progression is presented in three stages: an early infection phase, infiltrating host cells; the pulmonary phase, lung tissue injury; and systemic hyperinflammation, called a cytokine storm [3, 4]. Cytokine storm is the acute overproduction and uncontrolled release of proinflammatory markers locally and systematically. Furthermore, the induction of IL-1β recruits large numbers of leukocytes from the marrow, which in turn undergo more cytokine production,

*Correspondence:
Yeter Eylul Bayram
ytrbayram@hotmail.com
[1] Department of Internal Medicine, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey
[2] Department of Pulmonology, Sisli Hamidiye Etfal Education and Research Hospital, Istanbul, Turkey

including CRP, TNF-α, and IL-6 [5–7]. IL-1β and IL-6 are involved in priming neutrophils for activation by chemoattractant [8], resulting in neutrophil diapedesis and infiltration into the COVID-19-infected organs [3]. Additionally, neutrophils are involved in platelet activation by releasing the serine protease neutrophils elastase, the most potent activator of platelets [9–11]. Activated other leukocytes also contributed more platelet activation to exacerbate thrombosis [12].

Even though COVID-19 infection mostly has deteriorated pulmonary health [7], COVID-19 compromised the tubular structure of kidneys [13]. Moreover, an abnormal estimated glomerular filtration rate (eGFR) and elevated level of proteinuria have been reported in patients with COVID-19 infection [13, 14].

Acute kidney injury (AKI) associated with COVID-19 has been reported in 28% of hospitalized patients in Europe and the United States [15, 16]. Importantly, it has been shown that more than 45% of patients with AKI who required ICU care and 1 in 5 patients admitted to the ICU received kidney replacement therapy (KRT) [16]. Therefore, addressing or treating AKI would reduce the risk of KRT in patients with COVID-19. Multiple mechanisms have been proposed to explain the pathobiology of kidney damage in the COVID-19 infection, including severe proximal tubular injury, peritubular erythrocyte aggregation, glomerular fibrin thrombi, and/or collapsing glomerulopathy [16]. COVID-19 infection compromised kidney function through the immune system and cytokine storm by inducing sepsis, shock, hypoxia, or rhabdomyolysis [17].

Colchicine is an alkaloid derived from Colchicum (autumn crocus) and has many exciting features. The primary mechanism of Colchicine is to block the tubulin polymerization [18]. Microtubules, critical cytoskeleton components, are involved in various cellular mechanisms, including maintaining cell shape, intracellular trafficking, cytokine and chemokine secretion, cell migration, regulation of ion channels, and cell division [18, 19]. Reducing the function and infiltration of granulocyte cells resulted in exerting anti-inflammatory and antifibrotic effects [18, 19], leading to the subsequent downregulation of downstream cellular functions of leucocytes [18, 20]. Reduced production of a potent proinflammatory cytokine, such as IL-1β, has also resulted in a reduced amount of other proinflammatory, including IL-6, CRP, and TNF-α [6, 7, 21].

Renal failure is considered one of the significant complications of COVID-19. Around 27.06% of COVID-19 patients exhibited acute renal failure, indicating renal function impairment is relatively common in COVID-19 patients [13]. Colchicine has been used effectively in treating various diseases such as FMF, gout, hepatic diseases, cardiovascular diseases, and Behcet's syndrome [18]. It is well known that Colchicine prevented the development of renal failure in patients with FMF [18]. Since Colchicine has reduced fibrosis, it would be a plausible treatment alternative for patients with chronic kidney disease [22].

Anti-inflammatory properties, favorable safety profile, and widespread availability of Colchicine have prompted the investigation of it as an adjunct treatment for COVID-19. Colchicine has several interesting mechanisms, such as inhibiting pathogenetic pathways involved in kidney diseases [22]. The effect of Colchicine on kidney function in the short and long term has not been addressed clearly in patients with COVID-19 infection. We, therefore, aimed to show whether using Colchicine, in addition to standard care, is associated with improved kidney function in patients with COVID-19 infection.

Methods

Subjects between 30 and 60 years old were included from Jan 2021 to Jun 2021 in Istanbul (Turkey). All subjects were hospitalized and diagnosed with COVID-19 infection. Six hundred-five subjects' clinical records were screened, and 118 patients were included in this retrospective study. The following group of patients were excluded from the study: unconfirmed RT-PCR for COVID-19, younger than 30 years old; older than 60 years old patients who were presenting eGFR < 60; patients presenting the level of sCr > 1.29 mg/dL, and patients using nephrotoxic drugs (Fig. 1). Subjects who were presenting ischemic cardiovascular, chronic kidney disease or cancer were excluded from the study. We also excluded patients who were using pulse steroids (prednisolone > 250 mg/day, 1 to 3 days), showed radiologically a sign of embolism, were admitted to the intensive care unit, or died patients (Fig. 1). Informed consent was signed by the subjects before admission. This study was approved by the Seyrantepe Sisli Etfal Education and Research Hospital's Ethics Committee (protocol #3600; Date: July 05, 2022). The subjects were confirmed positive for COVID-19 infection from nasopharyngeal swab samples using a quantitative RT-PCR (qRT-PCR). Severe COVID-19 was defined as those who had SpO_2 < 91%, a respiratory rate > 30 breaths/min, or lung infiltration of infection > 50% [2]. The patient's lungs were topographically assessed using the COVID-19 Reporting and Data System (CO-RADS). CO-RADS assesses a level of suspicion of pulmonary involvement of COVID-19 in a category very low (CO-RADS category 1) to very high (CO-RADS category 5) in the chest CT [23, 24]. All subjects were CO-RADS category 5 (Fig. 2). The subjects were divided into two groups. A total of 50 patients in the Col (+) group were treated with standard care plus

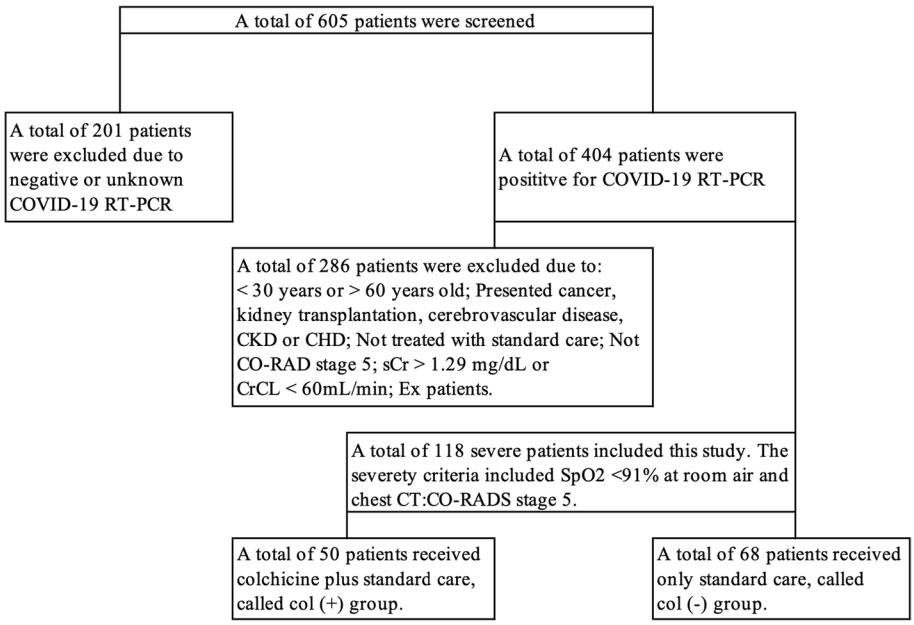

Fig. 1 Screened patients. A total of 605 patients' records were screened. A total of 487 patients were excluded from the study due to either a negative result of RT-PCR for COVID-19 (201 patients) or presented systemic diseases (286 patients). A total of 118 patients were included in this study. Col: Colchicine; CDH: Chronic Heart Disease; CKD: Chronic Kidney Disease

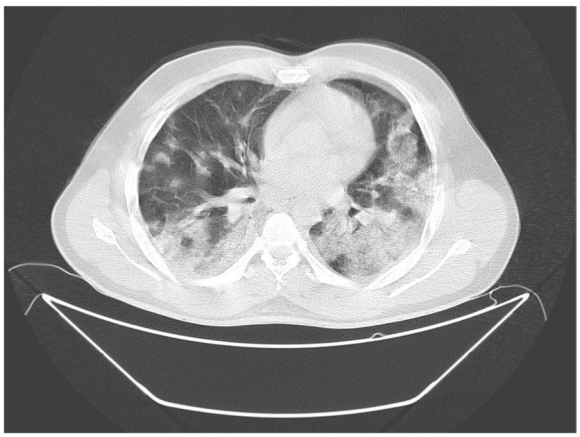

Fig. 2 CT CO-RADS-5 view at admission. Multiple and un-sharply delineated ground-glass areas that outlined the shape of numerous adjacent secondary pulmonary lobules were seen. Specifically, paving patterns were observed at intralobular lines

Colchicine. A total of 68 patients in the Col (-) group received standard care. The standard care consisted of COVID-19 anti-viral agents, steroids, antithrombotic agents, and oxygen therapy. The medications in the standard care, which was approved by The Turkish Health Minister at this period [25], included favipiravir (200mg, 2×8 tablets on the first day, then 2×3 tablets for five or ten days), high dose of steroids (prednisolone, 30 to 100 mg/day) [26], and sodium low molecular weight heparin (enoxaparin) (Table 1). Paracetamol and antibiotics (fluoroquinolone: Levofloxacin 500 mg/daily or Moxifloxacin 400 mg/daily) were given as needed. When the level of saturated pO_2 dropped less than 91%, the patients were supported with conventional oxygen therapy. A nasal cannula or face mask provided it with a limited flow rate (< 15 L/min). Patients received oxygen therapy at a flow rate of a nasal cannula or face mask without oxygen reservoir (5–8 L/min) or masks with oxygen reservoirs (9–15 L/min) [27]. In the Col (+) group, Colchicine was given as prescribed: 500μg of Colchicine every 12 h until the patient's discharge or for a maximum of 10 days. It was given 500μg per day to the patients who presented a body weight less than 70 kg (Table 1). Clinical records and laboratory findings were reviewed for all the patients. Subjects who had at least two different measurements (excluding at discharge) of SCr during the hospital stay were included in this study. The maximum level of CRP during the hospitalization stays and the level of D-dimer at admission was determined. Delta CRP was calculated by subtracting the maximum level of CRP from the level of CRP at discharge. Similarly, the delta SCr level was determined by subtracting the level of SCr determined at the initial admission from the level at discharge. The estimated glomerular filtration rate (eGFR) was calculated using the 2021 CDK-EPI Creatine equation based on SCr level, sex, and age [28]. Delta eGFR was calculated

Table 1 Treatments were given to the subjects

Treatments	Col (+)	Col (-)
Standard care	+	+
Favipiravir, 200 mg 1. day: 2×8 tablets, then 2×3 tablets for 10 days		
High dose of prednisolone (30 – 100 mg/day)	+	+
Low molecule weight heparin 400 ng/unit/day	+	+
Mask#	+	+
Colchicine: 1 mg on the first day, 0.5 mg after 12 h, then 0.5 mg 2×1 for 10 days	+	

The Col (+) group received Colchicine and standard care. The Col (-) group received only standard care

Oxygen mask was provided when O_2 saturation less than 91%

by subtraction of the level of eGFR at the initial admission from eGFR at discharge. A long-term delta level of eGFR was also determined in 6 to 12-month follow-up. Simply, it was calculated by subtracting the lowest level of eGFR at admission from the level measured in the follow-up. The level of SCr was utilized by Kidney Disease Improving Global Outcomes (KDIGO) to determine if patients presented AKI [29]. AKI was defined when the creatinine level showed more than 1.29 mg/dL in patients with no chronic kidney disease (CKD) history. AKI during hospitalization was defined as [1] an increase in creatinine by ≥ 0.3 mg/dL from the initial level at admission or [2] an increase of creatinine more than 1.5 times as compared to the initial level in patients with no AKI at admission [29]. Renal recovery was defined as the serum creatinine level decreasing to the reference range and/or to > 30% decrease compared to the initial values at admission [30].

Statistical analysis

Statistical analysis Statistical analyses were performed using GraphPad Prism version 9.0 (GraphPad Software, Inc., San Diego, CA, USA). The prespecified primary outcomes included D-dimer, number of lymphocytes, CRP, and SCr, and they were analyzed between the Col (+) and Col (-) groups. These primary outcome differences were determined by using the paired or paired student's t-test, Welch's t test and Fisher's exact test. To determine the possible effect of independent variables, including hypertension, diabetes (type 2),or antibiotic (fluoroquinolone) on the level of GFR at discharge was determined using the multiple logistic regression analysis.

Table 2 Demographic, medication, and medical history of the subjects

	Col (+)	Col (-)	*P* value
Sex			0.852
Male, *n* (%)	25 (50)	36 (53)	
Female *n* (%)	25 (50)	32 (47)	
Age, year, mean ± SD	48.22 ± 9.3	47.63 ± 10.0	0.746
Mask			0.002
Yes, *n* (%)	28 (60.87)	18 (39.13)	
No, *n* (%)	22 (30.56)	50 (69.44)	
Hospitalized day, mean ± SD	9.66 ± 3.5	8.69 ± 3.8	0.165
25% of subjects, day	6.75	6	
75% of subjects, day	12	10.7	
Minimum, day	5	4	
Maximum day	22	21	
Comorbidity, *n* (%)	22 (44)	18 (26)	0.52
T2D, *n*	6	6	
T2D and hypertension, *n*	4	5	
HT, *n*	9	5	
T2D and Asthma, *n*	0	1	
HL, *n*	1	0	
Asthma, *n*	0	1	
Hypothyroidism, *n*	1	0	
HT, HL *n*	0	1	
AKI KDIGO (stage 1), *n* (%)	12 (24)	19 (27)	0.676

Continuous variables including age and duration of hospitalized stay were described in mean and standard deviation (SD). Number and frequencies (%) were used for categorical variables, including using O_2 masks and systemic diseases

T2D Type 2 Diabetes, *HT* Hypertension, *HL* Hyperlipidemia, *AKI* Acute Kidney Injury, *KDIGO* Kidney Disease Improving Global Outcomes. Student's t-test and Fisher's exact test were used for continuous and categorical variable analysis, respectively

Results

Characteristics of the subjects

From March 2021 to Jun 2021, a total of 118 subjects were included in this study. All patients were hospitalized due to the severe COVID-19 infection. The characteristics of the subjects are shown in Table 2. The mean age of the subjects was 48.2 ± 8.8 years old. The Col (+) group consisted of 50 subjects (25 females and 25 males) with a mean age of 48.2 years. The Col (-) group included 68 subjects (32 females and 36 males) with a mean age of 47.6 years old. The percentage of patients requiring the usage of the reservoir O_2 mask was 50.0% and 26.4% among the subjects in the Col (+) and the Col (-) groups, respectively ($p = 0.002$). The mean of the length of the hospitalized stay was slightly longer in the Col (+) group (9.6 days) than that of the Col (-) group (8.6 days), but the mean difference between groups, 0.9668 ± 0.69, was not statistically significant ($p = 0.165$). Similarly, both groups showed a very similar percentage of comorbidity disease,

including type 2 diabetes, hypertension, asthma, hyperlipidemia, or hypothyroidism. (Table 2). Furthermore, we determined if any change in the level of GFR was affected by other systemic factors, including age, sex, hypertension, diabetes (type 2), or antibiotic usage (fluoroquinolone) in both groups. We found these factors were not associated with a change in the level of GFR at discharge (Table 3).

Improved systemic inflammatory biomarkers

To determine the severity of COVID-19 infection, we measured D-dimer, lymphocyte number, and CRP during the stay in the hospital. The level of D-dimer at admission was reduced to 392.8 from 567.9 ng/dL with a mean difference of 175 ± 62.6 ng/dL in the Col (+) group (Fig. 3a). In the Col (-) group, the level of D-dimer reduced from 629.6 ng/dL to 453.8 ng/dL with a mean difference of 175.8 ± 69.5ng/dL (Fig. 3b). The reduction of D-dimer levels in both groups was statistically significant.

The number of total lymphocytes was also determined at admission and discharge. At admission, the minimum number of lymphocytes was 0.9×10^9/L and 1.0×10^9/L in the Col (+) and Col (-) groups, respectively (Fig. 4a). These differences were not statistically significant ($p=0.798$). The total number of lymphocytes significantly increased from 0.9×10^9/L to 2.3×10^9/L with a mean difference of $1.30\pm0.49\times10^9$ /L in the Col (+) group at discharge (Fig. 4b). Similarly, the total lymphocytes increased from 1.0×10^9/L to 2.26×10^9/L with a significant mean difference of $1.26\pm0.15\times10^9$ /L in the Col (-) group at discharge (Fig. 4c). The increased mean differences between the groups were not statistically significant (0.417 ± 0.21, $p=0.055$) at discharge (Fig. 4d).

The maximum levels of CRP were 124.3 mg/dL and 96.93 mg/dL in the Col (+) and Col (-) groups, respectively (Fig. 5a). The mean difference between the groups was statistically significant ($p=0.015$) and it was 27.42 ± 11.11 mg/dl. (Fig. 5a). We next determined whether Colchicine was associated with improved CRP levels at discharge in both groups. The mean of delta CRP was 112.3 mg/dL and 89.3 mg/dl in the Col (+) and Col (-) groups, respectively. The mean differences between

Table 3 Variables were not associated with a change in the level of GFR

	Col (+)			Col (-)		
Variables	**Patients**	**ORs**	***p* value**	**Patients**	**ORs**	***p* value**
Age	50	1.059	0.2428	68	0.9649	0.2778
Sex	M: 25; F:25	0.5006	0.4119	M:36; F;32	1.407	0.5278
Hypertension	13	0.1816	0.1648	11	1.345	0.6969
Diabetes (type 2)	10	0.6759	0.7468	11	1.139	0.8263
Antibiotic	43	0.5301	0.6286	40	1.585	0.5498

Independent variables including age, sex, hypertension, diabetes (type-2), or antibiotic (fluoroquinolone), were analyzed using the multiple logistic regression test in the Col (+) and Col (-) groups at discharge. The odd ratios were 1.059, 0.5006, 0.1816, 0.6759, 0.5301, and 0.2485 for age, sex, hypertension, diabetes (type-2), or antibiotic in the Col (+) group, respectively. Similarly, the odd rations were 0.9649, 1.407, 1.345, 1.139, 1.585, and 0.2627 for age, sex, hypertension, diabetes (type-2), or antibiotic usage in the Col (-) group, respectively. *M* Male, *F* Female, *ORs* Odd ratios

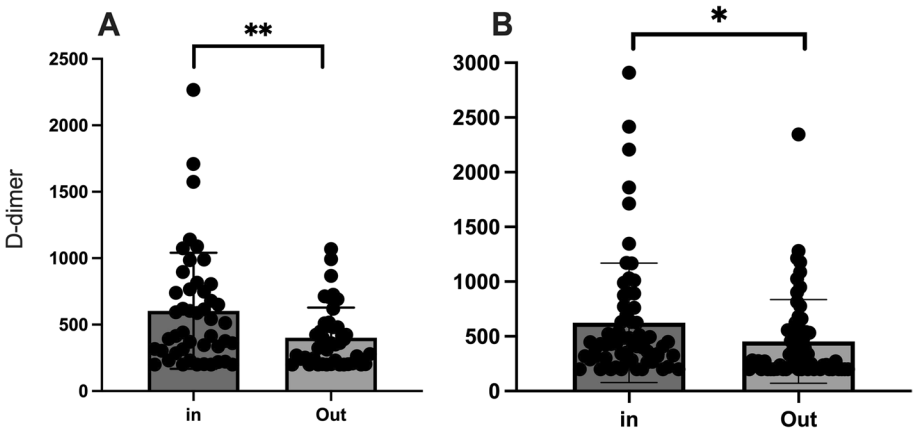

Fig. 3 The level of D-dimer was improved in both groups. The level of D-dimer was significantly reduced to 392.8 ng/dL in the Col at discharge (**A**). The level of D-dimer was reduced to 453.8 ng/dL in the Col (-) group (**B**). ** $p=0.007$; * $p=0.01$

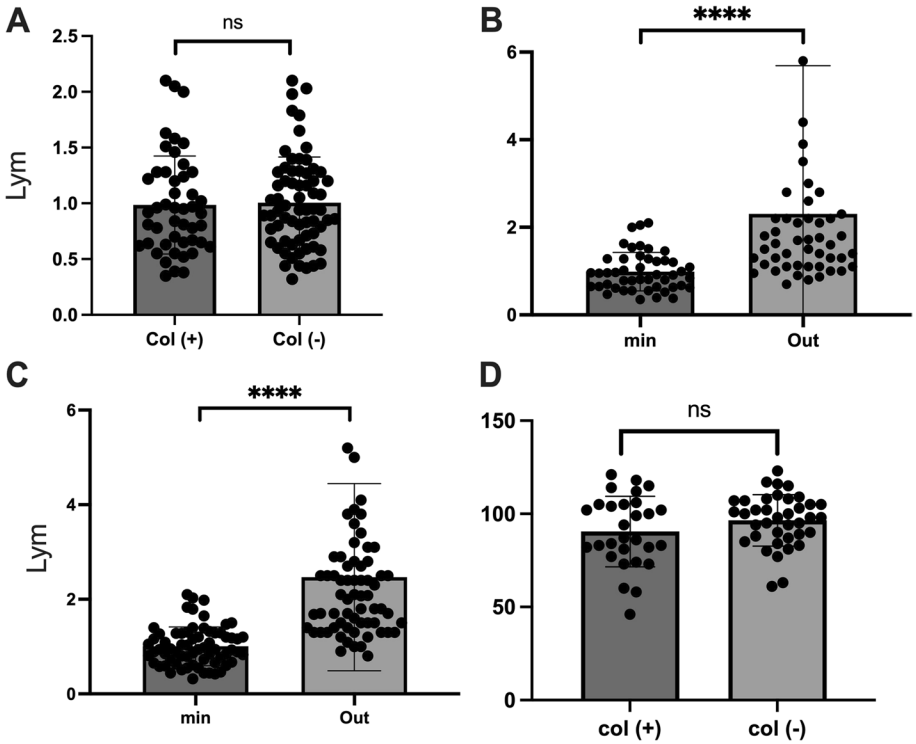

Fig. 4 The number of lymphocytes. The number of lymphocytes in the Col (+) and Col (-) groups was 0.9×10^9/L and 1.0×10^9/L at admission, respectively (**A**). The number of lymphocytes increased to 2.2×10^9/L in the Col (+) group (**B**), and it increased to $2.2\times10.^9$/L in the Col (-) group (**C**). The mean difference between the groups was 0.336 ± 0.213 ($p=0.11$) at discharge (D). ns: not significant; *** $p=0.0001$

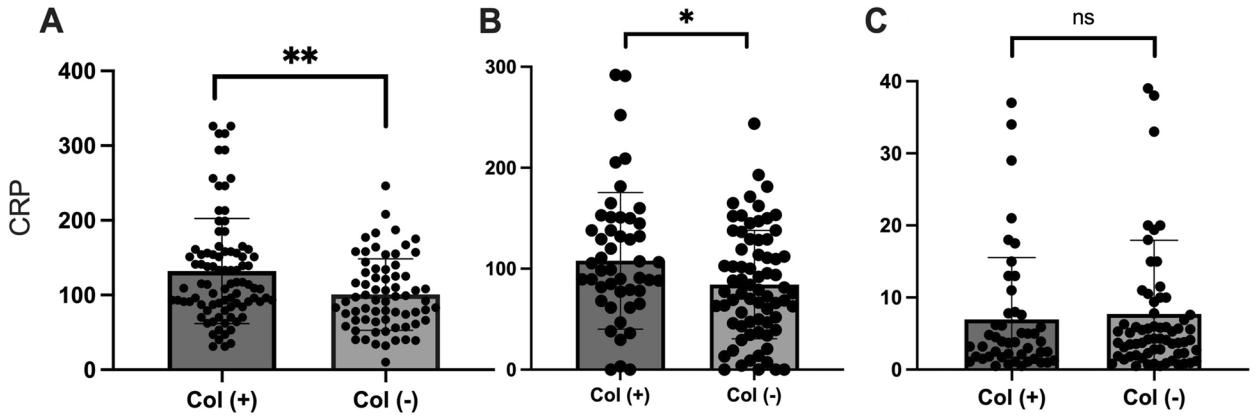

Fig. 5 The level of CRP was reduced in both groups. The mean maximum of CRP was 124.3 mg/dL and 96.9 mg/dL in the Col (+) and Col (-) groups at admission, respectively (**A**). The level of delta CRP (subtracting the max CRP from the level of CRP at discharge) was 112.3 mg/dL and 89.2 mg/dl in the Col (+) and Col (-) groups, respectively (**B**). The levels of CRP were reduced to 6.9 mg/dL and 7.7 mg/dL in the Col (+) and Col (-) groups at the discharge, respectively (**C**). ns: not significant; $p=0.68$; * $P=0.036$ ** $p=0.015$

the groups (23.03 ± 10.87, $p=0.036$) were statistically significant (Fig. 5b). The level of CRP was reduced to 6.9 mg/dL and 7.7 mg/dL in the Col (+) and Col (-) groups at the discharge, respectively. The mean difference of this reduction was 0.75 ± 1.82 between the groups, but it was not statistically significant (Fig. 5c).

Colchicine treatment was associated with a reduced level of serum creatinine

Next, we determined the level of SCr to evaluate kidney function. Initially, we determined if the level of SCr showed differences at initial admission. We found the level of SCr was 0.83 mg/dL and 0.79 mg/dL in the Col

(+) and Col (-) groups, respectively (Fig. 6a). The mean of these differences was not statistically significant ($p=0.238$). The level of SCr was reduced from 0.83 mg/dL to 0.73 mg/dL with an essential mean of 0.10 ± 0.01 mg/dL in the Col (+) group (Fig. 6b). The level of SCr was reduced from 0.79 mg/dL to 0.76 mg/dL in the Col (-) group (Fig. 6c). This difference was not statistically significant ($p=0.056$). We also determined if the levels of delta SCr in both groups showed a significant difference. The level of delta SCr was 0.104 mg/dL and 0.031 mg/dL in the Col (+) and Col (-) groups with a significant mean difference of 0.072 ± 0.024 ($p=0.003$), respectively (Fig. 6d). The level of SCr was reduced to 0.73 mg/dL and 0.76 mg/dL in the Col (+) and Col (-) groups, respectively, with no mean differences between the groups at discharge (Fig. 6e). Interestingly, we found that the level of delta SCr was reduced to 0.12 and 0.0012 in the Col (+) and Col (-) groups, respectively in the long term (Fig. 6f). This mean difference was statistically significant, and it was 0.1203 ± 0.04370 ($p=0.007$).

Colchicine treatment is associated with improved kidney function in short and long-term

We next investigated if Colchicine treatment was associated with improved renal function. Initially, we determined if the level of eGFR showed differences between the groups at admission. The level of eGFR was 97.44 mL/min/1.73m^2 and 101.2 mL/min/1.73m^2 in the Col (+) and Col (-) groups, respectively. The mean difference was 3.73 ± 2.80 mL/min/1.73m^2, but it was not statistically significant (Fig. 7a). We found the level of eGFR showed an increase from 97.44 mL/min/1.73m^2 to 107.0 mL/min/1.73m^2 in the Col (+) group at discharge. The mean difference (9.58 ± 1.69 mL/min/1.73m^2) was statistically significant (Fig. 7b). Similarly, the level of eGFR showed an increase from 101.2 mL/min/1.73m^2 to 104.7 mL/min/1.73m^2 in the Col (-) group. The mean difference, 3.4 ± 1.41mL/min/1.73m^2 was statistically significant (Fig. 7c). We next determined if the improved level of eGFR was better in the Col (+) group than the Col (-) group. Delta eGFR in the Col (+) and Col (-) groups were 9.58 mL/min/1.73m^2 and 3.48 mL/min/1.73m^2, respectively, with a significant mean of 6.09 ± 2.19 (Fig. 7d).

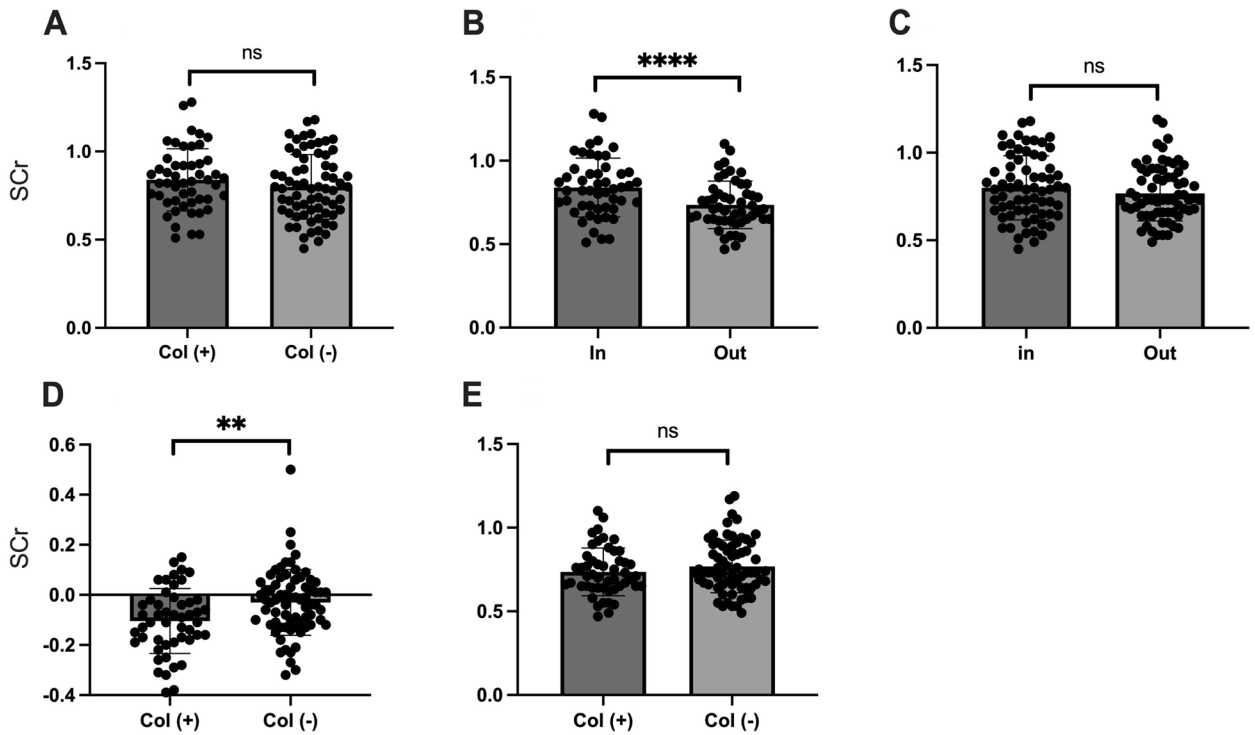

Fig. 6 The level of SCr in both groups. The level of SCr was 0.83 mg/dL and 0.79 mg/dL in the Col (+) and Col (-) groups, respectively (**A**). The level of SCr was reduced from 0.83 mg/dL to 0.73 mg/dL and from 0.79 mg/dL to 0.76 mg/dL in the Col (+) group (**B**) and the Col (-) group (**C**), respectively. The level of delta SCr level (subtracting the level of SCr at admission from the level of SCr at discharge) was 0.104 mg/dL and 0.030 mg/dL in the Col (+) and Col (-) groups, respectively (**D**). The level of SCr was reduced to the level of 0.73 mg/dL and 0.76 mg/dL in the Col (+) and Col (-) groups at discharge, respectively (**E**). The level of delta SCR (subtracting the highest level of SCr at admission from the level of SCr in 6–12 months) was reduced to 0.12 and 0.0012 in the Col (+) and Col (-) groups, respectively in 6–12 months follow-up (**F**). This mean difference was statistically significant, and it was 0.1203 ± 0.04370 ($p=0.007$). ns: not significant; ** $p=0.007$; **** $p<0.0001$

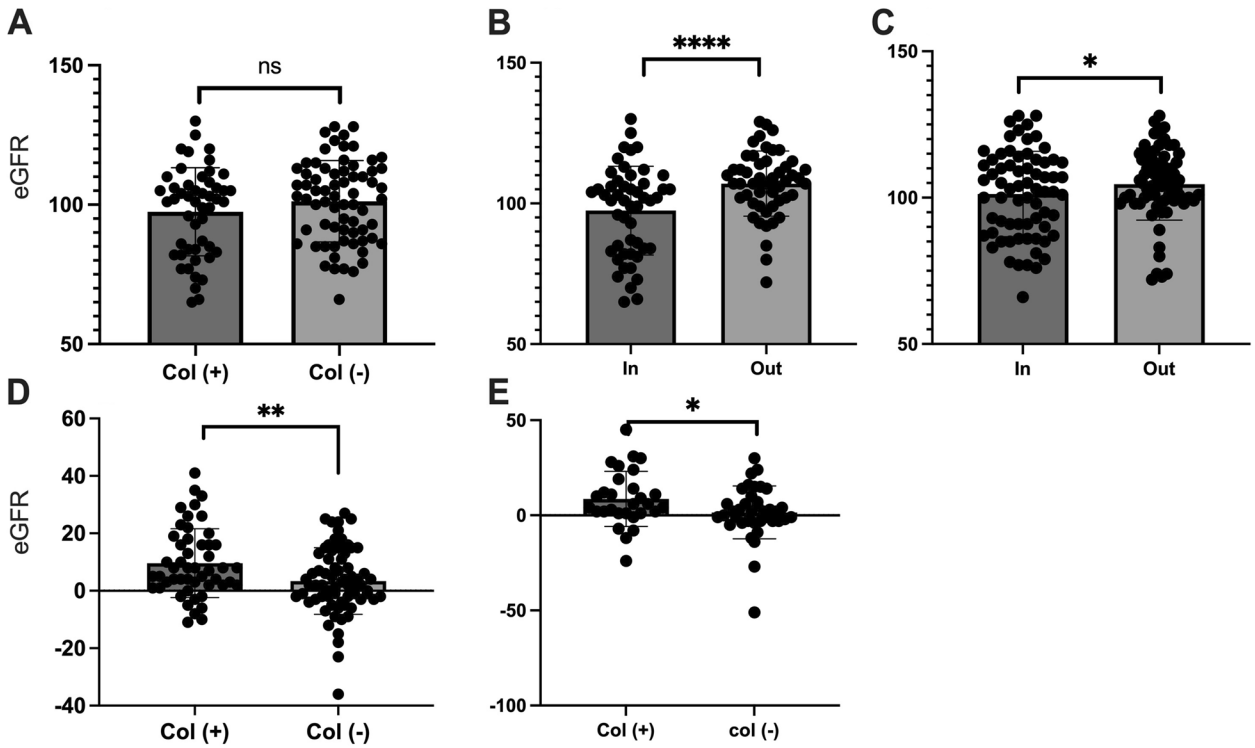

Fig. 7 An improved level of eGFR was associated with the treatment of Colchicine. The level of eGFR was 97.44 mL/min/1.73m^2 and 101.2 mL/min/1.73m^2 in the Col (+) and Col (-) groups at admission, respectively (**A**). The value of eGFR was increased from 97.44 mL/min/1.73m^2 to 107.0 mL/min/1.73m^2 in the Col (+) group at discharge (**B**). The value of eGFR was increased from 101.2 mL/min/1.73m^2 to 104.7 mL/min/1.73m^2 in the Col (-) group at discharge (**C**). Delta eGFR (subtracting the level of eGFR at admission from the level of eGFR at discharge) in the Col (+) and Col (-) groups were 9.58 mL/min/1.73m^2 and 3.48 mL/min/1.73m^2, respectively (**D**). The level of delta eGFR was 8.66 mL/min/1.73m^2 and 1.26 mL/min/1.73 m.^{2} in the Col (+) and Col (-) groups, respectively (**E**). ns: not significant; * $p=0.016$; ** $p=0.006$; **** $p<0.0001$

We finally aimed to determine the effect of Colchicine on kidney health in the long term (6–12 months). We were able to observe 27 (out of 50) and 41 (out of 68) patients' records in the Col (+) and Col (-) groups, respectively. The minimum level of eGFR during the hospitalization stay was subtracted from the level of eGFR measured at 6 to 12 months follow-up. We found that the level of eGFR was 99.4 mL/min/1.73m^2 and 97.4 mL/min/1.73m^2 in the Col (+) and Col (-) group in 6–12 months follow-up, respectively (Table 4). Similarly, the lowest level of eGFR during the stay in hospital was determined 90.7 mL/min/1.73m^2 and 95.9 mL/min/1.73m^2 in the Col (+) and Col (-) groups, respectively (Table 4). However, we found that the level delta eGFR (8.66 mL/min/1.73m^2) was significantly higher in the Col (+) group than that of the Col (-) group (1.26 mL/min/1.73m^2, $p=0.015$) suggesting that the use of Colchicine was associated with improved renal function in the long-term (Fig. 6e). During the acute phase of the infection, we found that 28% of the patients presented less than 90 mL/min per 1.73m^2 of eGFR. Among these patients, 34% and 25% were in the Col (+) and Col (-) groups, respectively. These ratios dropped to 6% and 10% in the Col (+) and Col (-) groups at discharge, respectively (Table 4). We also found that 11% and 24% of the patients showed reduced eGFR at the follow-up period in the Col (+) and Col (-) groups, respectively ($p=0.036$, Table 3).

Discussion

SARS-CoV-2 infection may affect multiple organs beyond the lungs, such as kidneys. Early prediction of kidney function trajectory in patients with COVID-19-associated AKI plays a crucial role in protecting morbidity and mortality rates. We sought to identify whether using Colchicine, in addition to standard care, was associated with short and long-term improved kidney function. This current study was the first to show Colchicine treatment had been associated with improved estimated glomerular filtration in COVID-19-infected patients.

An increased acute phase CRP levels and reduction in lymphocytes have been reported to reflect severe inflammation and the cytokine storm in patients with COVID-19 [1]. We observed that subjects in the Col (+) group

Table 4 The level of eGFR

	Total	col (+)	col (-)	*p*-value
Patient #	118	50	68	
eGFR < 90 mL/min per 1.73 m^2				
Admission, *n* (%)	34(28.0)	17 (34)	17 (25)	0.309
Discharge, *n* (%)	10(8.47)	3(6)	7 (10)	0.514
Delta eGFR (mL/min per 1.73 m^2)		9.58	3.48	0.006
eGFR (mL/min per 1.73 m^2) at admission		97.44	101.2	0.188
eGFR (mL/min per 1.73 m^2) at discharge	17(25.0)	107	104.7	0.296
Followed (6–12 M) Patient #	68	27	41	
eGFR (mL/min per 1.73 m^2) in 6–12 M		99.44	99.46	0.5932
The lowest level of eGFR at admission		90.78	95.95	0.2413
The level of delta eGFR in 6–12 M		8.667	1.268	0.0158
Reduced eGFR > 3 mL/min per 1.73 m^2 in 6-12M, *n* (%)		3 (11.1)	12 (24.26)	0.133
eGFR < 90 mL/min per 1.73 m^2				
lowest level of eGFR at admission, *n* (%)		11 (40.7)	15 (36.5)	0.801
Follow-up (6–12 M), *n* (%)		8 (29.62)	9 (21.9)	0.57
eGFR < 60 mL/min per 1.73 m^2				
Follow-up (6–12 M), *n* (%)		0	1 (2.43)	0.999

A total of 68 subjects could be able to follow up (6 to 12 months). There were 27 and 41 patients in the Col (+) and Col (-) groups, respectively. The level of eGFR was 8.66 mL and 1.26 mL min per 1.73 m^2 in the Col (+) and Col (-) groups, respectively ($p = 0.015$)

Delta eGFR was calculated by subtracting the minimum level of eGFR during the hospital stay from the level of eGFR measured during the follow-up (6–12 months)

The calculation of eGFR was determined based on the Asian-modified Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. *M* Month

showed an increased level of CRP compared to the Col (-) group within a few days of the following admission. Similarly, the maximum level of CRP was also significantly higher in the Col (+) group than in the Col (-) group. We observed that the ratio of patients required to use a reservoir O_2 mask in the Col (+) group was higher than that of the Col (-) group (Table 2). During this period of the epidemic, similar to other clinicians who used a low-dose Colchicine to treat cytokine storms in patients with SARS-CoV-2 infection as an adjunct to different therapeutic agents.

In contrast to SARS, seen in 2003, AKI has been more frequently observed in COVID-19 [31]. Assessing renal function accurately and promptly is challenging and critically important to reduce morbidity and mortality. Renal problems have been considered one of the big problems in COVID-19 infection following discharge [32]. AKI is relatively common following COVID-19 infection. AKI is most often observed in the 3^{rt} phase of the disease, even though it could occur at any stage [33]. Management of AKI in COVID-19-infected patients would be a similar fashion to the other AKIs. It has been reported that a high incidence of AKI (28.4%) was associated with increased organ failure and high mortality in hospitalized COVID-19-infected patients [34]. Another study by Fisher et al. compared the incidence of acute kidney injury in hospitalized patients with and without COVID-19 and showed an increased incidence of AKI in patients with COVID-19 [35]. A meta-analysis also reported that AKI was observed in 28–34% of inpatients and 46–77% of patients who were in intensive care units [36].

Moreover, 66% of the severe patients have developed AKI following the infection [37]. It has been reported that 50.5% of the 12,891 patients had at least one episode of AKI during their hospitalization [32]. On the other hand, 67.5% of the subjects among patients with AKI survived, and around 39.2% of the subjects could not recover kidney function at 90 days post-AKI [32]. The rates of renal recovery also have been reported in 65% to 74.1% of COVID-19 patients [30]. Even if the subjects in this study showed severe clinical conditions, we found that 24% of the patients developed AKI (Table 2), which was lower than in previous studies. We thought this difference could be due to the anti-viral drug not having a side effect on kidneys; the subjects who were presented a level eGRF of less than 60 or patients using nephrotoxic agents were excluded from the study; and steroid treatment, which has shown to reduce the rate of dialysis [36]. Ritonavir-boosted nirmatrelvir (Paxlovid), remdesivir, and molnupiravir have been used as anti-viral treatments in COVID-19 infection [38]. Favipiravir, which was used in our subjects, was prescribed during this pandemic. It has been shown that it does not have a nephrotoxicity effect [39], which eliminated being a nephrotoxicity

agent in our study. Regardless, our results indicated that using Colchicine was associated with improved kidney function in patients with severe COVID-19 since the independent variables, including age, sex, systemic diseases (hypertension or diabetes), or usage of antibiotics were not associated with a change of the GFR level at discharge (Table 3). During the acute phase of the infection, we found that 34% of patients in the Col (+) and 25% of the patients in the Col (-) group showed less than 90 ml/min/1.73 m^2 of eGFR at admission. Then, the ratio became 6% and 10% of the patients in the Col (+) and Col (-) groups, respectively, at discharge, suggesting starting Colchicine treatment might be a plausible approach in COVID-19-infected patients presenting a low level of eGFR (< 90 ml/min/1.73 m^2) at admission.

Even though the effect of Colchicine on the treatment of COVID-19 is still controversial [3, 40–43], its anti-inflammatory properties, favorable safety profile, and widespread availability have prompted the investigation of Colchicine for the treatment of kidney diseases. In the present study, the improved level of eGFR was higher in the Col (+) group than the Col (-) group in the short and long term (Table 4). Regarding kidney function, it has been reported that 47.7% of the severe patients showed a reduced level of eGFR (60–89 mL/min/1.73 m^2) in two years following COVID-19 infection [35]. Similarly, it was found that 25% of patients had decreased eGFR (< 90 ml/min/1.73 m^2) at six months after hospital discharge of COVID-19-infected patients [31, 44]. As aforementioned, COVID-19 infection can deteriorate kidney function in the long term. We observed a complete renal recovery of 75%, which was relatively higher than in the other studies mentioned above. We also found that 11% and 24% of the patients showed reduced eGFR during the follow-up period in the Col (+) and Col (-) groups, respectively (Table 4). Compared to the studies above, our results suggested that using Colchicine and standard care could reduce the risk of diminished kidney function in patients with COVID-19 in the long term. Possible mechanisms of Colchicine to protect kidney function might include reducing inflammation through blocking inflammasome activation [18], disrupting tubulin polymerization [18] and/or anti-fibrosis effect [22].

Multiple factors may influence the trajectory of kidney injury in patients who experience severe diseases. There were several limitations of this study. Firstly, all patients were enrolled in one hospital, possibly introducing a selection bias. Secondly, the participants were recruited during the wave of epidemics in Turkey, and we were unable to determine whether the subjects were vaccinated against the infection. Long-term manifestations of these patients may differ from those who were infected with the SARS-CoV-2 variants or those who received advanced treatments. Thirdly, pre-existing undiagnosed CKD may be underestimated before admission for COVID-19 since a possible pre-existing kidney problem was determined based on the patient's verbal information. We had no urinalysis data for diagnosing the cause of AKI and identifying abnormalities such as hematuria and/or proteinuria, which are frequently observed in these patients [45]. Fourthly, the organ dysfunctions may not be specific to COVID-19 as our study did not include populations without SARS-CoV-2 infection as a control. Finally, we found that most of the patients presented hypertension and/or diabetes mellitus, which could affect kidney function. We were unable to determine these factors on kidney function in our study, and it could not be resolved the temporal relationship of ACE-i/ARBs in patients who had prior exposure to ACE-i/ARBs, which has shown to affect the kidney [46].

In conclusion, the occurrence of AKI in hospitalized patients with COVID-19 was associated with a significant increase in the risk of death [47]. In this retrospective cohort study, we found that Colchicine, in addition to standard care, would be considered an independent drug of renoprotection for patients presenting severe COVID-19 clinical conditions in the short and long term. Overall, our data suggested that Colchicine treatment would be considered for the COVID-19-infected patients presenting an increased level of CRP, SCr, pulmonary damage, and or reduced eGFR at admission. However, there is a need for more studies that have more sample numbers and longer follow-ups.

Abbreviations

SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
Col	Colchicine
SCr	Serum Creatinine
CRP	C-reactive protein
ACE-i/ARB	Angiotensin-Converting Enzyme Inhibitors)/ Angiotensin II Receptor Blockers
Co-RADS	COVID-19 Reporting and Data System
AKI	Acute Kidney Injury
CKD	Chronic Kidney Disease
KRT	Kidney Replacement Therapy
eGFR	estimated Glomerular Filtration Rate
FMF	Familial Mediterranean Fever
CHD	Chronic Heart Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03817-2.

Supplementary Material 1.

Acknowledgements
We sincerely thank Mehmet Akif Eskan DDS, Ph.D., University at Buffalo School of Dental Medicine Department of Periodontics and Endodontics, for editing this manuscript.

Authors' contributions
YEB analyzed and interpreted the patient data regarding the patient clinical and lab findings after the patient was admitted by the COVID-19 service. The other authors helped to collect samples and follow the patient as needed. All authors read and approved the final manuscript.

Funding
This paper was not supported by any grant.

Data availability
The corresponding author can be contacted if further supporting data is needed. Raw data is provided as a supplementary file.

Declarations

Ethics approval and consent to participate
This study was approved by the Seyrantepe Sisli Etfal Education and Research Hospital's Ethics Committee (protoCol #3600; Date: July 05, 2022). Informed consent was signed by the subjects before admission.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

Received: 8 July 2023 Accepted: 10 October 2024
Published online: 12 November 2024

References

1. Hu J, Wang Y. The clinical characteristics and risk factors of severe COVID-19. Gerontology. 2021;67(3):255–66.
2. Clinical Spectrum of SARS-CoV-2 Infection. Available from: https://www.covid19treatmentguidelines.nih.gov/overview/clinical-spectrum/.
3. Reyes AZ, Hu KA, Teperman J, Wampler Muskardin TL, Tardif JC, Shah B, et al. Anti-inflammatory therapy for COVID-19 infection: the case for colchicine. Ann Rheum Dis. 2021;80(5):550–7.
4. Akhmerov A, Marbán E. COVID-19 and the Heart. Circ Res. 2020;126(10):1443–55.
5. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033–4.
6. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954.
7. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934–43.
8. Uriarte SM, Hajishengallis G. Neutrophils in the periodontium: interactions with pathogens and roles in tissue homeostasis and inflammation. Immunol Rev. 2023;314(1):93–110.
9. Clark SR, Ma AC, Tavener SA, McDonald B, Goodarzi Z, Kelly MM, et al. Platelet TLR4 activates neutrophil extracellular traps to ensnare bacteria in septic blood. Nat Med. 2007;13(4):463–9.
10. Harari R, Bangalore S, Chang E, Shah B. COVID-19 complicated by acute myocardial infarction with extensive thrombus burden and cardiogenic shock. Catheter Cardiovasc Interv. 2021;97(5):E661–6.
11. Ruf W, Ruggeri ZM. Neutrophils release brakes of coagulation. Nat Med. 2010;16(8):851–2.
12. Arber N, Berliner S, Pras E, Arber L, Fishelson Z, Kahn Y, et al. Heterotypic leukocyte aggregation in the peripheral blood of patients with leukemia, inflammation and stress. Nouv Rev Fr Hematol (1978). 1991;33(3):251–5.
13. Diao B, Wang C, Wang R, Feng Z, Tan Y, Wang H, et al. Human kidney is a target for novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. medRxiv. 2020:2020.03.04.20031120.
14. Kellum JA, van Till JWO, Mulligan G. Targeting acute kidney injury in COVID-19. Nephrol Dial Transplant. 2020;35(10):1652–62.
15. Palevsky PM. COVID-19 and AKI: Where Do We Stand? J Am Soc Nephrol. 2021;32(5):1029–32.
16. Silver SA, Beaubien-Souligny W, Shah PS, Harel S, Blum D, Kishibe T, et al. The prevalence of acute kidney injury in patients hospitalized with COVID-19 Infection: a systematic review and meta-analysis. Kidney Med. 2021;3(1):83–98.e1.
17. Ahmadian E, Hosseiniyan Khatibi SM, Razi Soofiyani S, Abediazar S, Shoja MM, Ardalan M, et al. Covid-19 and kidney injury: Pathophysiology and molecular mechanisms. Rev Med Virol. 2021;31(3):e2176.
18. Leung YY, Yao Hui LL, Kraus VB. Colchicine-Update on mechanisms of action and therapeutic uses. Semin Arthritis Rheum. 2015;45(3):341–50.
19. Nuki G. Colchicine: its mechanism of action and efficacy in crystal-induced inflammation. Curr Rheumatol Rep. 2008;10(3):218–27.
20. Sukeishi A, Isami K, Hiyama H, Imai S, Nagayasu K, Shirakawa H, et al. Colchicine alleviates acute postoperative pain but delays wound repair in mice: roles of neutrophils and macrophages. Mol Pain. 2017;13:1744806917743680.
21. Slobodnick A, Shah B, Krasnokutsky S, Pillinger MH. Update on colchicine, 2017. Rheumatology (Oxford). 2018;57(suppl_1):i4–11.
22. Marinaki S, Skalioti C, Boletis JN. Colchicine in Renal Diseases: Present and Future. Curr Pharm Des. 2018;24(6):675–83.
23. Kwee RM, Adams HJA, Kwee TC. Diagnostic Performance of CO-RADS and the RSNA Classification System in Evaluating COVID-19 at Chest CT: A Meta-Analysis. Radiol Cardiothorac Imaging. 2021;3(1):e200510.
24. Prokop M, van Everdingen W, van Rees Vellinga T, Quarles van Ufford H, Stöger L, Beenen L, et al. CO-RADS: a categorical CT assessment scheme for patients suspected of having COVID-19-definition and evaluation. Radiology. 2020;296(2):E97–e104.
25. Ayyildiz A, Yildirim OT, Ucan A, Ayyildiz FA. Evaluation of steroid therapy in COVID-19 patients; in the right dose at the right time to the right patients. Niger J Clin Pract. 2023;26(3):280–6.
26. Gensler LS. Glucocorticoids: complications to anticipate and prevent. Neurohospitalist. 2013;3(2):92–7.
27. Calligaro GL, Lalla U, Audley G, Gina P, Miller MG, Mendelson M, et al. The utility of high-flow nasal oxygen for severe COVID-19 pneumonia in a resource-constrained setting: a multi-centre prospective observational study. EClinicalMedicine. 2020;28:100570.
28. Muiru AN, Madden E, Scherzer R, Horberg MA, Silverberg MJ, Klein MB, et al. Effect of adopting the new race-free 2021 chronic kidney disease epidemiology collaboration estimated glomerular filtration rate creatinine equation on racial differences in kidney disease progression among people with human immunodeficiency virus: an observational study. Clin Infect Dis. 2023;76(3):461–8.
29. Lameire NH, Levin A, Kellum JA, Cheung M, Jadoul M, Winkelmayer WC, et al. Harmonizing acute and chronic kidney disease definition and classification: report of a Kidney Disease: Improving Global Outcomes (KDIGO) Consensus Conference. Kidney Int. 2021;100(3):516–26.
30. Arikan H, Ozturk S, Tokgoz B, Dursun B, Seyahi N, Trabulus S, et al. Characteristics and outcomes of acute kidney injury in hospitalized COVID-19 patients: a multicenter study by the Turkish society of nephrology. PLoS ONE. 2021;16(8):e0256023.
31. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15.
32. Tan BWL, Tan BWQ, Tan ALM, Schriver ER, Gutiérrez-Sacristán A, Das P, et al. Long-term kidney function recovery and mortality after COVID-19-associated acute kidney injury: an international multi-centre observational cohort study. EClinicalMedicine. 2023;55:101724.
33. Adamczak M, Surma S, Więcek A. Acute kidney injury in patients with COVID-19: epidemiology, pathogenesis and treatment. Adv Clin Exp Med. 2022;31(3):317–26.
34. Sánchez AV, Pérez AN, Pérez-Carrasco M, Sonet MT, Buendia YD, Ballujera PO, et al. Acute kidney injury in critically ill patients with COVID-19: The AKICOV multicenter study in Catalonia. PLoS ONE. 2023;18(4): e0284248.
35. Li D, Liao X, Liu Z, Ma Z, Dong J, Zheng G, et al. Healthy outcomes of patients with COVID-19 two years after the infection: a prospective cohort study. Emerg Microbes Infect. 2022;11(1):2680–8.

36. Matsumoto K, Prowle JR. COVID-19-associated AKI. Curr Opin Crit Care. 2022;28(6):630–7.
37. Chen K, Lei Y, He Y, Xiao F, Yu Y, Lai X, et al. Clinical outcomes of hospitalized COVID-19 patients with renal injury: a multi-hospital observational study from Wuhan. Sci Rep. 2021;11(1):15205.
38. Paraskevis D, Gkova M, Mellou K, Gerolymatos G, Psalida N, Gkolfinopoulou K, et al. Real-world effectiveness of molnupiravir and Nirmatrelvir/Ritonavir as treatments for COVID-19 in patients at high risk. J Infect Dis. 2023;228(12):1667–74.
39. Mohamadi Yarijani Z, Najafi H. Kidney injury in COVID-19 patients, drug development and their renal complications: Review study. Biomed Pharmacother. 2021;142: 111966.
40. Recovery Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet Respir Med. 2021;9(12):1419–26.
41. Tardif JC, Bouabdallaoui N, L'Allier PL, Gaudet D, Shah B, Pillinger MH, et al. Colchicine for community-treated patients with COVID-19 (COLCORONA): a phase 3, randomised, double-blinded, adaptive, placebo-controlled, multicentre trial. Lancet Respir Med. 2021;9(8):924–32.
42. Mikolajewska A, Fischer AL, Piechotta V, Mueller A, Metzendorf MI, Becker M, et al. Colchicine for the treatment of COVID-19. Cochrane Database Syst Rev. 2021;10(10):Cd015045.
43. Sharaf S, Ashmawy R, Saleh E, Salama M, El-Maradny YA, Zari A, et al. Saturation in Hospitalized COVID-19 Patients and Its Relation to Colchicine Treatment: A Retrospective Cohort Study with an Updated Systematic Review. Medicina (Kaunas). 2023;59(5):934.
44. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. Lancet. 2021;398(10302):747–58.
45. Ruault A, Philipponnet C, Sapin V, Evrard B, Bouzgarrou R, Calvet L, et al. Epidemiology and Outcome of Early-Onset Acute Kidney Injury and Recovery in Critically Ill COVID-19 Patients: A Retrospective Analysis. Biomedicines. 2023;11(4):1001.
46. Tetlow S, Segiet-Swiecicka A, O'Sullivan R, O'Halloran S, Kalb K, Brathwaite-Shirley C, et al. ACE inhibitors, angiotensin receptor blockers and endothelial injury in COVID-19. J Intern Med. 2021;289(5):688–99.
47. Nadim MK, Forni LG, Mehta RL, Connor MJ Jr, Liu KD, Ostermann M, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. Nat Rev Nephrol. 2020;16(12):747–64.

Publisher's Note