Original Article

# Chronic Kidney Disease and COVID-19 Infection: A Case–Control Study

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## Abstract

**Background:** To organize efforts to manage the coronavirus disease 2019 (COVID-19), it is necessary to understand which groups are at higher risk of infection. Kidney disease seems to be substantial in COVID-19 patients, but there are limited data on COVID-19 incidence and fatality among chronic kidney disease (CKD) patients. In this study, we intend to examine the association between CKD and susceptibility to COVID-19 infection.

**Materials and Methods:** Participants were selected from those recruited in a population-based cross-sectional survey of CKD prevalence and associated risk factors in Iranian people 18 years and older. A three-part questionnaire was used for COVID-19 infection clinical symptoms and epidemiologic and hospitalization data.

**Results:** A total of 962 individuals including 403 CKD patients and 559 healthy controls were recruited in this study. Healthy controls were suffering more from common cold signs, cough, fever, sore throat, headache, anosmia, dyspnea, and abdominal pain (all $P < 0.05$). Furthermore, the number of healthy individuals with myalgia was marginally higher compared to the CKD patients ($P = 0.057$). Data regarding the number of CKD patients with/without COVID-19 infection throughout different CKD stages revealed that there was no significant difference between the two groups in terms of COVID-19 infection in different stages of CKD ($P = 0.956$).

**Conclusion:** We found that some of the clinical presentations of COVID-19 including common cold symptoms, cough, fever, sore throat, headache, anosmia, dyspnea, and abdominal pain were higher among healthy individuals compared to the CKD group. On the other hand, the susceptibility to COVID-19 infection was not significantly different in various early stages of CKD.

**Keywords:** Case–control study, chronic kidney disease, coronavirus disease 2019, Iran, prevalence

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## Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS CoV-2), was declared as a global public health emergency on January 30, 2020.[1] Ever since, it has led to substantial morbidity and mortality worldwide.[2] According to the initial reports, the mortality rate associated with COVID-19 was reported to be about 3.5%; however, following the spread of the disease, the actual rates appeared to be different from the initial reports.[3]

The primary symptoms of the disease include fever, cough, shortness of breath, and other nonspecific symptoms.[4] Patients are classified into three categories of mild, moderate, and severe, based on their clinical manifestations. Most of these

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patients do not need hospitalization; however, severe cases require hospitalization and may have symptoms of septic shock and multiple organ failure.[5,6]

Data from China, the United States, and Europe reveal that individuals with major comorbidities including chronic kidney disease (CKD), hypertension (HTN), diabetes mellitus (DM), chronic obstructive pulmonary disease, and malignancy seem to be at higher risk than those without these conditions for severe COVID-19 complications.[7-10] Furthermore, a recent study by Williamson *et al*. reported that patients with severe forms of CKD have a very high risk of COVID-19 mortality.[11] Based on a recent review, the prevalence of CKD was 3.5% in all COVID-19 cases and up to 9.6% in all fatal cases.[12] Overall, there are limited data on COVID-19 and CKD, with mortality data varying from 16% to 53%.[13,14]

The association between CKD and COVID-19 is not well studied, and limited data are available on this topic. Additional studies are needed to improve our understanding and to develop effective preventative and therapeutic strategies. It is imperative to understand the epidemiology of the disease and to understand what groups are at high risk of infection to be able to organize efforts to manage this pandemic.

Therefore, in this study, we intend to examine the association between CKD and susceptibility to COVID-19 infection.

## Materials and Methods

This study was reported following the Strengthening the Reporting of Observational Studies in Epidemiology statement.[15]

### Study design and setting

This is a case–control study using data from a large cross-sectional population-based study conducted in cooperation with Isfahan University of Medical Sciences, Isfahan, Iran. Participants were recruited from those visiting the health-care centers located within Isfahan, Iran. The study protocol was approved by the Ethics Committee of Isfahan University of Medical Sciences (IR. MUI. MED. REC.1399.162), and investigations were performed according to the Declaration of Helsinki. All studied individuals provided written informed consent.

### Cases and controls

Patients were selected from participants in a cross-sectional population-based survey of CKD prevalence and associated risk factors in people 18 years and older which was conducted between July 2020 and September 2020 in Isfahan, Iran, as CKD epidemiology in Isfahan (CKD-EI study, data not published yet). CKD diagnosis was based on the following criteria: decreased renal function for more than 3 months determined by the estimated glomerular filtration rate <60 mL/min/1.73 $m^2$[16] or persistent proteinuria and/or hematuria.[17] The CKD patients of the current study ranged from stage 1 A1 to stage 4 A3 without any individual receiving renal replacement therapy (RRT) including hemodialysis or peritoneal dialysis. The age- and sex-matched control group for this study was randomly selected from non-CKD individuals who participated in the CKD-EI study.

### Study data collection

#### COVID-19

Furthermore, a three-part questionnaire was used regarding COVID-19 infection with questions about (1) clinical symptoms in the past 3 months (common cold symptoms, cough, fever, body pain, asthenia, sore throat, headache, ageusia and anosmia, shortness of breath, abdominal pain, diarrhea, nausea/vomiting, and other symptoms), (2) epidemiologic data (recent travel history, contact with COVID-19 patients, and any close family member diagnosed with COVID-19), and (3) hospitalization data (confirmed COVID-19 infection, admission in a hospital ward or an ICU, quarantine without hospitalization, recovery, or death). All information regarding COVID-19 and related clinical manifestation were gathered through phone calls and were based on self-report.

#### Anthropometric measurements

Weight was measured using a mechanical scale (Zyklusmed *ZYK-MS01*, China) with 0.01-kg accuracy with minimal clothing and no shoes. Furthermore, a nonstretched tape was installed for height measurement to the nearest 1 mm without shoes (Seca). To calculate body mass index (BMI), the "weight (kg)/height$^2$ ($m^2$)" equation was utilized. Waist circumference (WC) was measured midpoint between the top of the iliac crest and the lower margin of the last palpable rib in the midaxillary line to the nearest 0.5 cm. Hip circumference (HC) was measured as the distance around the largest part of the hips also to the nearest 0.5 cm. To obtain waist-to-hip ratio, WC was divided by HC.[18]

#### Blood pressure

Systolic and diastolic blood pressures (SBP and DBP) were measured by digital sphygmomanometers (Omron BF511; Omron Corp., Kyoto, Japan) on the right arm. If the first BP was equal to or above 140/90 mmHg, a second measurement was performed with a break of 5 min between measurements, and BP was defined as the mean of two measurements.

#### Other variables

Demographic data including age, sex, educational status, marital status, cigarette smoking, opium use, or drinking alcohol and personal history of diseases including DM, HTN, cardiovascular disease (CVD), and cerebrovascular accidents (CVAs) were collected using a general questionnaire.

### Statistical analysis

Statistical analysis was done using SPSS software version 21 (SPSS Inc., Chicago, IL, USA). The Kolmogorov–Smirnov test was used to assess the normality of quantitative variables. All data were presented as mean ± standard deviation or number. The between-group comparison was done using independent samples *t*-test for continuous and Pearson's Chi-square test and Fisher's exact test (if expected counts were ≤5) for categorical variables. $P < 0.05$ was considered statistically significant.

## Results

A total of 962 individuals including 403 CKD patients and 559 healthy controls were included in this study. Table 1 provides the information regarding the comparison of demographic characteristics of the participants between CKD and control groups. Age, BMI, and SBP of the CKD group were significantly higher than the healthy controls (all $P < 0.05$). Furthermore, the educational status of the control group was better than the CKD group, since there were more illiterate CKD patients ($P < 0.001$). Furthermore, there were significant differences between the two groups in terms of marital status and alcohol consumption (all $P < 0.05$). Moreover, the history of DM, HTN, and CVAs was higher in the CKD group compared to the controls (all $P < 0.05$).

**Table 1: Comparison of demographic and clinical characteristics of patients with chronic kidney disease and controls**

| Variables | CKD (*n*=403) | Control (*n*=559) | *P* |
|---|---|---|---|
| Age (year), mean±SD | 53.56±14.97 | 47.18±13.52 | <0.001* |
| BMI (kg/m$^2$), mean±SD | 27.56±4.76 | 26.76±5.05 | 0.011* |
| WHR, mean±SD | 0.92±0.09 | 1.02±2.95 | 0.487* |
| SBP (mmHg), mean±SD | 127.86±22.53 | 118.91±18.72 | <0.001* |
| Sex, *n* (%) | | | |
| Male | 145 (36) | 187 (33.5) | 0.416** |
| Female | 258 (64) | 372 (66.5) | |
| Educational status, *n* (%) | | | |
| Illiterate | 73 (81.1) | 58 (10.4) | <0.001** |
| Diploma | 109 (27) | 204 (36.6) | |
| Below diploma | 158 (39.2) | 166 (29.8) | |
| Bachelor degree | 5513.63) | 98 (17.6) | |
| Master's degree and higher | 8 (2) | 31 (5.6) | |
| Marital status, *n* (%) | | | |
| Away from wife/husband | 4 (1) | 4 (0.7) | <0.001** |
| Death of wife/husband | 45 (11.2) | 12 (2.2) | |
| Married | 325 (80.6) | 489 (87.8) | |
| Single | 29 (7.2) | 52 (9.3) | |
| Cigarette smoking, *n* (%) | | | |
| Yes | 26 (6.5) | 34 (6.1) | 0.679** |
| No | 377 (93.5) | 524 (93.9) | |
| Opium, *n* (%) | | | |
| Yes | 5 (1.2) | 15 (2.7) | 0.122** |
| No | 398 (98.8) | 544 (97.3) | |
| Alcohol, *n* (%) | | | |
| Yes | 10 (2.5) | 30 (5.4) | 0.027** |
| No | 392 (97.5) | 527 (94.6) | |
| Diabetes mellitus, *n* (%) | | | |
| Yes | 92 (22.8) | 62 (11.1) | <0.001** |
| No | 311 (77.2) | 497 (88.9) | |
| Hypertension, *n* (%) | | | |
| Yes | 133 (33) | 94 (16.8) | <0.001** |
| No | 270 (67) | 465 (83.2) | |
| Cardiovascular disease, *n* (%) | | | |
| Yes | 21 (5.2) | 17 (3) | 0.088** |
| No | 382 (94.8) | 542 (97) | |
| Cerebrovascular accident, *n* (%) | | | |
| Yes | 114 (28.3) | 92 (16.5) | <0.001** |
| No | 289 (71.7) | 467 (83.5) | |

*Calculated by independent samples *t*-test, **Calculated by Chi-square test or Fisher's exact test, $P<0.05$ was considered statistically significant. CKD: Chronic kidney disease, SD: Standard deviation, BMI: Body mass index, WHR: Waist-to-hip ratio, SBP: Systolic blood pressure

Early signs, symptoms, and information regarding the COVID-19 are shown in Table 2. Healthy controls were suffering more from common cold signs, cough, fever, sore throat, headache, anosmia, dyspnea, and abdominal pain (all $P < 0.05$). Furthermore, the number of healthy individuals with body pain was marginally higher compared to the CKD patients (all $P < 0.1$). Furthermore, there were more subjects with history of contact with COVID-19 patients and infection of close family members in the control group compared to the CKD group (all $P < 0.05$). Moreover, Figure 1 illustrates that there were no significant differences between the CKD and control groups regarding the prevalence of COVID-19 infection ($P = 0.368$).

Data regarding the comparison of the number of CKD patients with/without COVID-19 infection throughout different stages of CKD are presented in Table 3. The overall findings revealed that there was no significant difference between the two groups in terms of COVID-19 infection prevalence in different stages of CKD ($P = 0.956$).

## Discussion

In this large population-based study conducted in Isfahan, Iran, we did not observe any association between CKD and the prevalence of COVID-19 infection. On the other hand, susceptibility to COVID-19 infection was not linked with different stages of CKD. It should be noted that some of the clinical presentations of COVID-19 including common cold symptoms, cough, fever, sore throat, headache, anosmia, dyspnea, and abdominal pain were higher among healthy individuals compared to the CKD group. However, it should be considered that data were self-reported and studies indicate that underreporting of symptoms holds true for patients with different health issues,[19] which could explain the lower symptom presentation in COVID-19 patients.

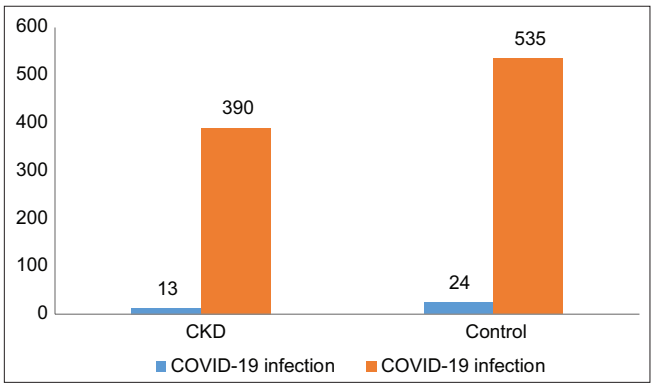


**Figure 1:** Comparison of coronavirus disease 2019 infection prevalence in chronic kidney disease patients and controls

**Table 2: Comparison of early signs, symptoms, or information regarding coronavirus disease 2019 in chronic kidney disease patients and controls during the recent 3 months**

| Variables | CKD (*n*=403), *n* (%) | Control (*n*=559), *n* (%) | *P* |
|---|---|---|---|
| Common cold signs | | | |
| Yes | 23 (5.8) | 36 (6.4) | <0.001 |
| No | 367 (94.1) | 522 (93.6) | |
| Cough | | | |
| Yes | 21 (5.3) | 33 (5.9) | 0.002 |
| No | 373 (94.7) | 526 (94.1) | |
| Fever | | | |
| Yes | 17 (4.3) | 39 (7) | 0.002 |
| No | 379 (95.7) | 520 (93) | |
| Myalgia | | | |
| Yes | 28 (7) | 49 (8.8) | 0.057 |
| No | 368 (93) | 508 (91.2) | |
| Asthenia | | | |
| Yes | 17 (4.2) | 29 (5.2) | 0.157 |
| No | 379 (95.8) | 527 (94.8) | |
| Sore throat | | | |
| Yes | 17 (4.2) | 30 (5.4) | 0.012 |
| No | 378 (93.8) | 528 (94.5) | |
| Headache | | | |
| Yes | 10 (2.5) | 35 (6.3) | <0.001 |
| No | 385 (97.5) | 524 (93.7) | |
| Ageusia | | | |
| Yes | 6 (1.5) | 15 (2.7) | 0.133 |
| No | 392 (98.5) | 542 (97.3) | |
| Anosmia | | | |
| Yes | 6 (1.5) | 21 (3.8) | 0.014 |
| No | 392 (98.5) | 537 (96.2) | |
| Dyspnea | | | |
| Yes | 8 (2) | 23 (4.1) | 0.012 |
| No | 389 (98) | 535 (95.9) | |
| Abdominal pain | | | |
| Yes | 4 (1) | 7 (1.3) | 0.015 |
| No | 391 (99) | 551 (98.7) | |
| Diarrhea | | | |
| Yes | 7 (1.8) | 12 (2.2) | 0.108 |
| No | 391 (98.2) | 546 (97.8) | |
| Nausea/vomiting | | | |
| Yes | 4 (1) | 9 (1.6) | 0.231 |
| No | 393 (99) | 547 (98.4) | |
| Sinusitis | | | |
| Yes | 2 (0.5) | 0 | 0.124 |
| No | 400 (99.5) | 559 (1) | |
| Recent travel history | | | |
| Yes | 25 (6.7) | 35 (6.6) | 0.489 |
| No | 349 (93.3) | 497 (93.4) | |
| Recent history of contact with COVID-19 patients | | | |
| Yes | 7 (1.8) | 54 (9.7) | <0.001 |
| No | 391 (98.2) | 501 (90.3) | |
| Recent history of contact with COVID-19 treatment staff | | | |
| Yes | 1 (0.3) | 4 (0.7) | 0.209 |
| No | 395 (99.7) | 551 (99.3) | |
| Recent travel history abroad | | | |

*Contd...*

**Table 2: Contd...**

| Variables | CKD (*n*=403), *n* (%) | Control (*n*=559), *n* (%) | *P* |
|---|---|---|---|
| Yes | 1 (0.3) | 1 (0.2) | 0.330 |
| No | 395 (99.7) | 554 (99.8) | |
| Infection of close family members to COVID-19 | | | |
| Yes | 20 (5) | 78 (14) | <0.001 |
| No | 380 (95) | 476 (86) | |
| Approved COVID-19 infection | | | |
| Yes | 13 (3.2) | 24 (4.3) | 0.368 |
| No | 390 (96.8) | 535 (95.7) | |
| Quarantine without hospitalization | | | |
| Yes | 11 (84.6) | 20 (83) | 0.920 |
| No | 2 (15.4) | 4 (17) | |
| Hospitalization in the ward due to COVID-19 | | | |
| Yes | 2 (15.4) | 3 (12.5) | 0.806 |
| No | 11 (84.6) | 21 (87.5) | |
| Hospitalization in the ICU due to COVID-19 | | | |
| Yes | 0 | 1 (4.1) | 0.456 |
| No | 13 (100) | 23 (95.9) | |
| Recovery or death of approved cases | | | |
| Recovery | 12 (92.3) | 24 (100) | 0.168 |
| Death | 1 (7.7) | 0 | |

*P*<0.05 was considered statistically significant. CKD: Chronic kidney disease, COVID-19: Coronavirus disease 2019, ICU: Intensive care unit

**Table 3: Comparison of coronavirus disease 2019 infection prevalence in different stages of chronic kidney disease**

| Stages of CKD | No infection to COVID-19 (*n*=390), *n* (%) | Infection to COVID-19 (*n*=13), *n* (%) | *P* |
|---|---|---|---|
| CKD stage 1 A1 | 73 (18.7) | 4 (30.9) | 0.894 |
| CKD stage 1 A2 | 69 (17.7) | 1 (7.6) | |
| CKD stage 1 A3 | 7 (1.8) | 0 | |
| CKD stage 2 A1 | 72 (18.5) | 4 (30.9) | |
| CKD stage 2 A2 | 85 (21.8) | 0 | |
| CKD stage 2 A3 | 4 (1) | 1 (7.6) | |
| CKD stage 3a A1 | 47 (12.1) | 2 (15.4) | |
| CKD stage 3a A2 | 12 (3.1) | 1 (7.6) | |
| CKD stage 3a A3 | 1 (0.2) | 0 | |
| CKD stage 3b A1 | 6 (1.5) | 0 | |
| CKD stage 3b A2 | 7 (1.8) | 0 | |
| CKD stage 4 A1 | 1 (0.3) | 0 | |
| CKD stage 4 A3 | 6 (1.5) | 0 | |

*P*<0.05 was considered statistically significant. CKD: Chronic kidney disease, COVID-19: Coronavirus disease 2019

Based on previous data from patients infected by earlier SARS-CoV, histochemical examination revealed antigens, RNA, and virions in the lung and other organs, including the kidney.[20,21] This may explain the multi-organ manifestations of COVID-19 and hence the kidney involvement.[22,23] A recent meta-analysis by Pranata *et al*. revealed that CKD patients present a nearly three-fold higher risk of mortality and severe COVID-19, and this relationship is affected by DM, HTN, CVD, and age.[24] Furthermore, it was discussed that individuals with CKD have elevated levels of circulating angiotensin-converting enzyme 2 (ACE2),[25] which accelerates the SARS-CoV-2 entrance and may subsequently be downregulated by the virus, leading to unregulated angiotensin-2 activity and multiple organ failure.[26-28] Furthermore, it should be mentioned that most of the included patients in this meta-analysis had serum creatinine within the normal range which leads to the hypothesis of whether different stages of CKD are correlated with COVID-19. The present study was designed to answer this issue but failed to provide any significant association.

Lowering blood pressure is the fundamental part of CKD management for slowing the progression of CKD and reduces the risk for cardiovascular disease.[29-31] ACE inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) are the best-studied antihypertensive agents that have been recommended for CKD patients as a first-line therapy even in the absence of high blood pressure.[32,33] There have been assumptions that these drugs may diminish the COVID-19 severity since previous documents have revealed that taking ACEI/ARB by hypertensive subjects was associated with a dramatic decrease in COVID-19 severity and mortality.[34,35] Some of the clinical manifestations of COVID-19 were higher among healthy controls than the CKD group in the current study which might be linked with their medication including ACEI/ARB, although data regarding patients' medication were missed.

Pranata *et al*. reported that RRT is associated with significantly poor outcomes, including severity, need for intensive care, acute respiratory distress syndrome, mortality, and use of mechanical ventilator in COVID-19 patients.[24] The CKD patients of the current study ranged from stage 1 A1 to stage 4 A3 without any individuals receiving RRT including hemodialysis or peritoneal dialysis. It could be conjectured

that there are no differences between stages of CKD regarding COVID-19 infection susceptibility in nondialysis cases of CKD. A mechanism related to this finding may be due to the copious expression of ACE2 in tubular cells of the kidney which is subsequently affected directly by SARS-COV-2.[22]

Previous data from China, Italy, and the United States have reported that obese patients, older patients, male patients, and patients with comorbidities were more susceptible to COVID-19 infection and adverse outcomes and mortality.[36-40] Based on our findings, the CKD group was older and with a higher BMI. Moreover, DM, HTN, and CVAs were more prevalent in the CKD group compared to the controls. Nevertheless, there were no significant differences in terms of the number of COVID-19 cases between the CKD and the healthy groups, which is inconsistent with previous data. A probable explanation for this finding could be discussed through ACE2 expression. Previous *in vivo* studies have reported that ACE2 expression in the kidney of the male is higher than the female which may explain the higher susceptibility to COVID-19 among male individuals.[41] In the present study, the gender distribution of the CKD patients and healthy controls was not significantly different which may provide additional evidence regarding nonsignificant findings of the current study.

As a final point, it is noteworthy that results indicate a significantly lower history of close contact with COVID-19 patients among CKD patients as compared to the controls. This could be the result of better isolation in the CKD group which could reduce the risk of COVID-19 infection.

Although we described a large population-based study regarding the association between COVID-19 and CKD among Iranian population, there are several limitations to this study. This is a single-center investigation, so regional diversities and disease spectrum should be considered during the interpretation of the findings. The risk of COVID-19 infection in CKD patients cannot be inferred from the present study. Since the information regarding COVID-19 and related clinical manifestations were self-reported and gathered through phone calls, the reliability of data is diminished, and this should be considered as a limitation of the current study.

## Conclusion

In the present population-based study among Iranian individuals, there were no significant differences between the CKD and control groups regarding the prevalence of COVID-19 infection. We found that some of the clinical presentations of COVID-19 including common cold symptoms, cough, fever, sore throat, headache, anosmia, dyspnea, and abdominal pain were higher among healthy individuals compared to the CKD group. On the other hand, the susceptibility to COVID-19 infection was not linked to different stages of CKD. The findings of the current study should be interpreted with cautious, since data were self-reported and gathered through phone calls.

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Nil.

### Conflicts of interest

There are no conflicts of interest.

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