

## RESEARCH ARTICLE

# Mortality risk factors in kidney-transplanted patients with COVID-19: A systematic review and regression analysis

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## Abstract

**Background and aims:** The kidney transplant patients who receive immunosuppressive and specific medication may lead to different mortality risk factors between kidney transplant patients with COVID-19 and the general population. We aimed to provide a model predictor and a risk analysis of mortality in kidney transplant COVID-19 positive patients.

**Methods:** We performed our search using PubMed, MEDLINE, Web of Science, Scopus, and Google Scholar to identify English articles published from the beginning of December 2019 through August 2020. Excluded manuscripts had no full text, lacked information, were not the original article, or consisted of less than three cases. We gathered information about demographic information, comorbidities, COVID-19 symptoms, lung radiographic findings, history of medication therapy, and changes in the kidney maintenance therapy after confirming their COVID-19 on the data extraction forms.

**Results:** We found a total of 31 eligible articles. We set a 10% mortality rate as our cutoff point. The most common sign and symptoms were cough (53.22 [29.42]), dyspnea (50.80 [24.55]). In the bivariate analysis, fatigue ( $P = .04$ , OR of 0.92; 95% CI: 0.85-1.00), hypertension ( $P = .07$ , OR of 1.03; 95% CI: 1.00-1.07), and dyspnea ( $P = .08$ , OR of 1.04; 95% CI: 1.00-1.09) showed a statistically significant relationship with increases in mortality.

In multivariate regression analysis, an independent association was only found between hypertension and mortality ( $P = .035$ ; AOR of 1.064; CL: 1.004-1.127).

**Conclusion:** Clinicians should pay special attention to modifiable risk factors for COVID-19 infection mortality, such as hypertension among kidney transplant patients, because it may be possible to decrease mortality by controlling these factors.

## KEYWORDS

COVID-19, kidney transplant, mortality

Yasaman Navari and Amir Behzad Bagheri contributed equally to this study.

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## 1 | BACKGROUND

In December 2019, a worldwide pandemic respiratory syndrome started in Wuhan, China, which caused a multi-organ infection named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).<sup>1,2</sup>

As the disease continued to spread rapidly, in March 2020, the World Health Organization proclaimed coronavirus disease 2019 (COVID-19) as a global pandemic.<sup>3</sup> By 29 December 2020, the total number of confirmed cases had reached over 79 million, and over 1.7 million cases of confirmed patients had died.<sup>4</sup>

In several published articles like systematic reviews and case reports about COVID-19, an increase in age and chronic diseases such as hypertension, diabetes, chronic respiratory disease, and cardiovascular disease could increase the severity of the disease.<sup>5,6</sup> Due to a lack of curative treatment, supportive care is the only option available.<sup>7,8</sup> Immunosuppressive medication such as dexamethasone is one of the main treatments for COVID-19.<sup>9-12</sup> The majority of kidney transplant patients receive immunosuppressive medication such as corticosteroids. There is neither an established course of the disease nor a specific absolute therapeutic method for them.<sup>13</sup> Hence, we decided to review published articles about kidney transplant patients infected with COVID-19, discuss their symptoms, the different medication regimens given, and address the possible relation between any of these variables with mortality COVID-19 positive patients.

## 2 | METHODS

### 2.1 | Data sources

We performed our search using PubMed, MEDLINE, Web of Science, Scopus, and Google Scholar to identify English articles published from the beginning of December 2019 through August 2020. We used keywords including “COVID-19,” “SARS-CoV-2,” “Coronavirus 2,” “coronavirus 2019,” “renal transplant,” and “kidney transplant” to identify articles.

### 2.2 | Study selection

After collecting studies, the full texts and abstracts were evaluated for excluding criteria. Every article had been reviewed by two individuals, and the final observation over the reviewed articles was performed by the third party.

Duplicated studies, the protocols and management guidelines, letters to the editor, abstracts, studies with lack of information about demographic data of the patients, radiographic findings, medication therapy, or mortality, and articles with no available full text, were excluded. Also, we excluded studies on less than three cases due to the small population and chance of bias. Any disagreements during data collection were solved through group discussion.

### 2.3 | Data extraction

We gathered information about authors and year of publication, patient age, gender, comorbidities, COVID-19 symptoms, lung radiographic findings, history of medication therapy, and kidney maintenance therapy changes after confirming their COVID-19 on the data extraction forms. Our gathered data included only kidney-transplanted recipient cases. Two independent inspectors carried out the data extraction and any disagreement during the process was solved by the third member.

### 2.4 | Quality assessment

To ensure the quality of the selected articles, we made a checklist consisting of 15 questions (Table 1). The quality of papers was scored based on the checklist.<sup>14</sup> The results were reported in three groups: Low quality (0-5), medium quality (6-10), and high quality (11-15). The authors discussed the qualified full texts to make the final decision. After reading the full text of these papers, the authors decided to include/exclude each of them.

### 2.5 | Data synthesis

A quantitative synthesis of identified characteristics was done. These findings were then analyzed based on frequencies (n) to make data

**TABLE 1** Quality assessment checklist for the articles

No.	Question
1	Does the study address any research question(s) or objective(s)?
2	Does the study provide any theoretical framework for the evaluation method?
3	Does the theoretical framework of the study include any health promotion theory?
4	Does the study provide a time frame for the data collection?
5	Does the study identify the country where the search was conducted?
6	Does the study mention that the reviewed current evidence was downloaded for evaluation?
7	Does the study discuss the selection criteria for current evidence to be included or excluded for review?
8	Does the study provide a clear description of the evaluation method?
9	Are there at least two independent data extractors with a consensus procedure in place in case of disagreement?
10	Is a list of the reviews of current evidence provided?
11	Does the study discuss the findings of the evaluation?
12	Does the study look at the reviewed evidence to promote or enable behavioral change?
13	Does the study discuss any limitations?
14	Does the study provide any future recommendations in general?
15	Does the study state any conflict of interest?

**TABLE 2** List of the variables extracted from the articles and used in the data analysis

<b>Demographics</b>	
Male	Mean age
<b>Signs, symptoms, and related morbidities and outcomes</b>	
Fever	Nausea/vomiting
Cough	Myalgia
Dyspnea	Intubated
Gustatory dysfunction	Still in hospital
Dysgeusia, Hypogeusia, Phantogeusia, Ageusia	Recover/discharge
Fatigue	
<b>Changes in kidney transplant medications and medications for COVID-19</b>	
Antimetabolite stopped	Antimetabolite dose reduction
Steroids stopped or lower the dose	Calcineurin stopped
Calcineurin dose reduction	Antiviral
Antibiotic	Tocilizumab
Hydroxychloroquine	IVIG
<b>Imaging studies</b>	
Lung involvement in CT/X-ray	Unilateral lung involvement
Bilateral lung involvement	
<b>Comorbidities</b>	
Hypertension	Heart disease
Diabetes mellitus	Lung disease
Cancer	

interpretation easier. We used SPSS Statistics software (version 22, SPSS Inc., Chicago, Ill., USA) for data analysis. We considered all variables quantitative. Besides, we used univariate, bivariate, and multivariate analysis methods in this study. Odds ratio (OR) with the corresponding 95% confidence interval (CI) was calculated for each analysis. The data were analyzed by the variables listed in Table 2.

### 3 | RESULTS

In this systematic review study, we found a total of 140 articles. After initial review, six duplicates were identified and excluded. The remaining articles were evaluated by their abstract and title, which excluded 103 other studies (Figure 1). The mean score of quality assessment for the remaining articles was 13.5 (range 12 to 15), which showed that the included study had a high quality (the characteristic data of included studies can be found in the Appendix S1).<sup>1,7,11,12,18,26-51</sup>

Our included studies resulted in finding 903 kidney-transplanted patients with confirmed COVID-19 PCR tests. For this research, based on the clinical findings from a similar study, we set a 10% mortality rate as the cutoff point.<sup>5,6</sup>

### 3.1 | The most common signs and symptoms

The seven most common sign and symptoms with the highest mean among included articles were cough (53.22 [29.42]), dyspnea (50.80 [24.55]), myalgia (26.21 [23.96]), fatigue (8.04 [19.79]), fever (79.13 [17.78]), gustatory dysfunction (79.13 [17.78]), and nausea/vomiting (4.59 [8.77]). Table 3 shows detailed information.

### 3.2 | Bivariate analysis

In the bivariate analysis, applying a cutoff point of  $P < .10$  for significance, among signs and symptoms, fatigue ( $P = .04$ , OR of 0.92; 95% CI: 0.85-1.00), hypertension ( $P = .07$ , OR of 1.03; 95% CI: 1.00-1.07), and dyspnea ( $P = .08$ , OR of 1.04; 95% CI: 1.00-1.09) showed a statistically significant relationship with increases in mortality.

It also showed that being intubated while in hospital ( $P = .09$ , OR of 1.11; 95% CI: 0.98-1.26) was associated with mortality rate. None of the chest X-ray findings, mean age, or different medication therapy showed significant association with mortality rate (Table 3).

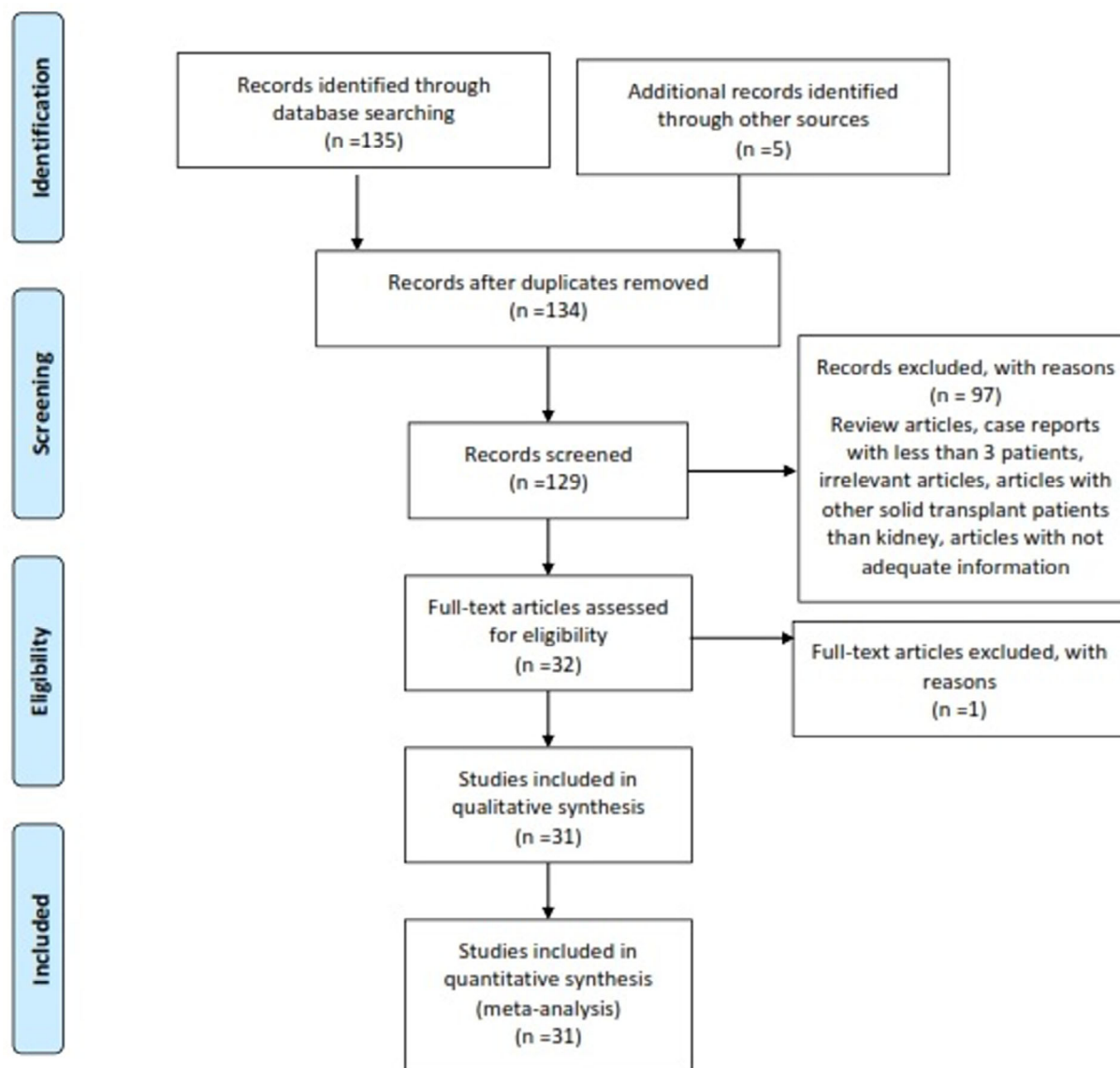
### 3.3 | Multivariate regression analysis

We additionally conducted a multivariate regression analysis of the variables that had an association with COVID-19. In this analysis, our threshold of significance ( $P$  value) was  $<.05$ . An independent association was found between hypertension and mortality ( $P = .035$ ; AOR of 1.064; 95% CI: 1.004-1.127).

## 4 | DISCUSSION

In this systematic review, we found hypertension as a major risk factor of the mortality rate in kidney transplant COVID-19 positive patients. Statistic results showed that other comorbidities, medications, or symptoms were not effective in increasing or decreasing the mortality rate of these patients. Also, cessation or dose reduction of drugs related to kidney transplant may not have a significant effect on mortality of COVID-19.

Kidney-transplanted patients may have numerous comorbidities, which may be the reason for their kidney injury.<sup>15</sup> Among all comorbidities, we only found hypertension as a risk factor to raise mortality risk. In the Pranata meta-analysis study, they also found that hypertension is a risk factor for increasing the mortality rate among COVID-19 patients.<sup>16</sup> In a study, Wu and McGoogan suggested that hypertension and cardiovascular disease impact mortality.<sup>17</sup> Besides, in another study conducted by Cravedi et al, hypertension was mentioned as the most common comorbidity affecting 95% of COVID-19 patients with kidney transplantation.<sup>18</sup> Zaki et al reviewed that using antihypertensive drugs such as calcium channel blockers (CCBs), angiotensin II receptor blockers (ARBs), and angiotensin-converting enzyme inhibitors (ACEIs) can reduce the risk of mortality in COVID-



**FIGURE 1** PRISMA flowchart for extracted articles for investigation of mortality risk factors in kidney-transplanted patients with COVID-19

19 patients with hypertension.<sup>19</sup> Surprisingly, it has been reported that utilization of ARBs and ACEI in patients with diabetes and hypertension leads to upregulation of angiotensin-converting enzyme 2 (ACE2) in Fang's study. SARS-CoV-2 invades the body using ACE2 receptors. Therefore, it has been hypothesized that upregulation of ACE2 in these patients may predispose them to more severe infection.<sup>20,21</sup> However, several investigations and systematic reviews have mentioned hypertension as a major comorbidity that affects mortality significantly even without medical history of kidney transplant.<sup>19,22</sup> Nevertheless, more investigations are demanded to clarify the exact mechanism of hypertension in deteriorating respiratory infections.

Lung involvement is one of the significant and life-threatening consequences of the COVID-19 infection. Some studies found lung involvement as a risk factor for predicting the outcome of COVID-19 patients,<sup>23</sup> but the current study did not support this finding and did

not show any relation between lung involvement in COVID-19 patients who had a kidney transplant. In Zhu's study in China, they concluded that kidney-transplanted patients have severe lung involvement, but it just increases their clinical course duration and has no effect on their mortality rate.<sup>12</sup> In Chen's study, they also showed that although most of their patients had chest X-ray involvement, it did not increase the mortality rate.<sup>1</sup> Other studies support our findings as well.<sup>5</sup>

Our regression analysis did not show a significant effect between stoppage or reduction of kidney transplant's medications and fatality of the COVID-19 infection. One of the medications is immunosuppressant, which reduces the risk of transplant rejection. As the COVID-19 virus pandemic started, there were several attempts to reduce or change the immunosuppressive medicines to decrease the mortality rate in these patients. This systematic review did not show any relation between reducing or stopping antimetabolite

**TABLE 3** Different variables and their associations with the hospital mortality of COVID-19 in kidney-transplanted patients in the bivariate analysis

Characteristics	Number of studies	Mean $\pm$ SD	Odds ratio (95% CI) <sup>a</sup>	P value
<b>Demographics</b>				
Male (%)	31	65.71 (13.91)	1.01 (0.95-1.07)	.75
Mean age (year)	31	64.0 (12.99)	0.93 (0.86-1.00)	.53
<b>Comorbidities</b>				
Hypertension (%)	27	74.93 (26.69)	1.03 (1.00-1.07)	.07
Diabetes mellitus (%)	23	31.21 (22.95)	0.98 (0.94-1.02)	.37
Cancer (%)	11	6.86 (10.39)	0.98 (0.90-1.06)	.60
Heart disease (%)	18	16.45 (19.45)	1.04 (0.97-1.12)	.26
Lung disease (%)	11	5.14 (7.99)	1.04 (0.91-1.19)	.53
<b>Imaging studies</b>				
Lung involvement in CT/X-ray (%)	19	81.20 (24.12)	0.96 (0.89-1.03)	.23
Unilateral lung involvement (%)	12	17.94 (16.09)	1.03 (0.96-1.11)	.37
Bilateral lung involvement (%)	19	67.74 (23.18)	0.97 (0.93-1.02)	.31
<b>Changes in kidney transplant medications and medications for Covid-19</b>				
Antimetabolite stopped (%)	22	73.00 (30.09)	0.98 (0.94-1.02)	.27
Antimetabolite dose reduction (%)	6	13.83 (30.85)	1.04 (0.96-1.12)	.37
Steroids stopped or lower the dose (%)	11	15.72 (27.60)	1.00 (0.97-1.03)	.96
Calcineurin stopped (%)	22	42.96 (34.74)	1.00 (0.98-1.03)	.82
Calcineurin dose reduction (%)	5	24.62 (38.17)	0.99 (0.96-1.03)	.71
Antiviral (%)	19	41.15 (38.03)	1.00 (0.98-1.03)	.94
Antibiotic (%)	20	55.78 (41.46)	1.00 (0.98-1.03)	.75
Hydroxychloroquine (%)	22	70.44 (38.17)	1.02 (0.99-1.04)	.17
Tocilizumab (%)	15	19.31 (27.60)	1.05 (0.97-1.14)	.23
IVIG (%)	10	12.96 (21.52)	0.99 (0.95-1.03)	.49
<b>Signs and symptoms</b>				
Fever (%)	28	79.13 (17.78)	0.99 (0.93-1.05)	.69
Cough (%)	24	53.22 (29.42)	0.98 (0.94-1.02)	.33
Dyspnea (%)	26	50.80 (24.55)	1.04 (1.00-1.09)	.08
Gustatory dysfunction (%)	2	25.30 (17.42)	1.02 (0.96-1.09)	.55
Myalgia (%)	19	26.21 (23.96)	1.02 (0.97-1.07)	.41
Fatigue (%)	6	8.04 (19.79)	0.92 (0.85-1.00)	.04
Nausea/vomiting (%)	7	4.59 (8.77)	0.95 (0.86-1.06)	.37
<b>Morbidities and outcomes</b>				
Intubated (%)	17	23.11 (21.25)	1.11 (0.98-1.26)	.09
Recover/discharge (%)	27	54.63 (20.24)	0.98 (0.93-1.04)	.56
Still in hospital (%)	11	12.71 (20.56)	0.97 (0.92-1.01)	.14

<sup>a</sup>Two-sided 95% CI.

(methotrexate) and calcineurin inhibitor medication with reducing mortality. Also, an unclear effect of immunosuppressant as a risk factor on morbidity and mortality of COVID-19 patients has been mentioned in several published articles.<sup>18,24</sup> Besides, a meta-analysis study conducted by Tassone et al concluded that immunosuppressants cannot be a significant risk factor for COVID-19 infection.<sup>25</sup> Our analysis also showed no mortality risk enhancement with starting antiviral or antibiotic drugs as well. Nair et al study in New York, which was done on 10 patients, stopped giving antibiotics as a routine treatment plan to their patients, as it did not show any impact on their outcomes.<sup>26</sup> Trujillo had

reported that even after reduction of kidney transplant's drugs, there was no observation of organ rejection or increment of donor-specific antibodies.<sup>27</sup>

## 5 | LIMITATIONS AND STRENGTHS

We did an immense systematic review of mortality in kidney-transplanted patients who had COVID-19. We extracted and analyzed a vast group of articles. Some studies had a small study population,

though, which did not help us obtain adequate information from them. We omitted these studies to prevent any bias in our analysis results. Due to the novelty of COVID-19, we also had a scarcity of information regarding treatment protocols and published articles regarding some risk factors and possible effective therapy. Availability of medication and facilities to all the population was a debate. The authors did not have access to primary data, and they worked on secondary data. Thus, in some articles, the authors had just median, and in some others, they had mean and SD.

## 6 | CONCLUSION

Our analysis showed that 24.12% of cases showed lung involvement in their chest radiography or CT scan. Among those, 23.18% had bilateral involvement. Our statistical analysis findings suggest that hypertension, fatigue, dyspnea, and intubation in the course of hospitalization, have increased the mortality rate among kidney transplant patients who are COVID-19 positive. However, in the multivariate analysis, only hypertension showed an independent relationship with increased mortality. We suggest that further research be done to examine other risk factors with COVID-19 in kidney-transplanted patients.

### ACKNOWLEDGMENT

None.

### FUNDING

All affiliations with or financial involvement in any entity with a financial interest in, or in competition with, the manuscript's subject matter are disclosed. This includes stock ownership, employment, consultancies, honoraria, grants, patents, and royalties. This research did not receive any specific assistance from funding agencies in the public, commercial, or not-for-profit sectors.

### CONFLICT OF INTEREST

There is no conflict of interest regarding the publication of this manuscript.

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All authors have read and approved the final version of the manuscript.

Corresponding author had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. This article has not been published and is not under consideration for publication elsewhere.

### TRANSPARENCY STATEMENT

Ali Asadollahi-Amin affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

### ETHICS STATEMENT

We also declare that the study was performed according to the international, national, and institutional rules considering animal experiments, clinical studies, and biodiversity rights.

### DATA AVAILABILITY STATEMENT

All information provided in this article can be obtained from the author on request.

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#### SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

**How to cite this article:** Navari Y, Bagheri AB, Akhavan Rezayat A, et al. Mortality risk factors in kidney-transplanted patients with COVID-19: A systematic review and regression analysis. *Health Sci Rep.* 2021;4:e427. doi:10.1002/hsr2.427