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Clinical manifestations and laboratory findings and mortality rate of kidney transplant recipients infected with COVID-19

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ABSTRACT

Introduction: The emergence of a novel coronavirus (COVID-19) in late December 2019 and its rapid global spread has led World Health Organization (WHO) to introduce it as a very dangerous pandemic. People with underlying disease and a history of organ transplantation are at higher risk for COVID-19 disease compared with healthy people.

Objectives: In the present study, clinical and laboratory manifestations in the patients with COVID-19 with a history of kidney transplantation has been investigated.

Patients and Methods: This study conducted on 103 COVID-19-positive kidney transplant patients as a descriptive epidemiological study. Clinical and laboratory symptoms of hospitalized renal transplanted patients have been assessed. Statistical analysis of the collected data conducted using SPSS (Statistical Package for Social Sciences, version 22).

Results: This study consisted of 103 COVID-19 patients with a history of kidney transplant, of which 64 males (62.1%) and 39 females (37.9%) with an average age of 48.5 ± 13.1 years. The most common clinical manifestations were headache (67%) and shortness of breath (66%). Elevated lactate dehydrogenase (LDH) levels, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) has been observed in 100%, 98.1% and 93.2% of patients, respectively. In 12.6% and 41.7% of patients, the degree of lung involvement was above 75% and 50%-75%, respectively. Moreover, 79.6% of patients has been discharged after improved, while 20.4% of patients died.

Conclusion: We found, kidney transplantation may increase COVID-19-related mortality when compared to COVID-19-related mortality in the general population.

Implication for health policy/practice/research/medical education:
This study consisted of 103 COVID-19 patients with a history of kidney transplant, of which 64 males (62.1%) and 39 females (37.9%) with an average age of 48.5 ± 13.1 years. We found, kidney transplantation may increase COVID-19-related mortality when compared to COVID-19-related mortality in the general population.

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Introduction

The coronavirus, which was the cause of acute respiratory syndrome, appeared in December 2019 in Wuhan, China (1). The virus has been spread rapidly around the world and has been introduced as COVID-19 and a pandemic by World Health Organization (WHO) (1). Many people around the world are dying every day from COVID-19 infection every day (1). The primary symptoms of this condition include fever, cough, loss of smell (anosmia), and loss of taste (ageusia) (2). The risk of developing dangerous symptoms of COVID-19 may be increased in people with underlying health conditions (2). One of the underlying conditions that increases the severity of infection in COVID-19 patients is a history of kidney transplantation (3). Numerous studies showed that immunosuppression in the patients with kidney transplantation lead to an exacerbation of Middle- East respiratory syndrome coronavirus (MERS-CoV) (4, 5).

Considering the similarity of the genetic structure of this virus with severe acute respiratory syndrome (SARS) virus in terms of its binding to the receptor cell, it reported that COVID-19 virus, like SARS virus, enters the cells

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via the receptor of the angiotensin-converting enzyme 2 (ACE2) (6,7). An ACE2 receptor expression level in any type of kidney damage, such as transplanted kidneys, is higher than normal kidneys (7). Administration of immunosuppressant drugs in kidney transplant recipients increases the severity of COVID-19 among them (8). COVID-19 has a roughly 28% mortality rate in persons with a history of renal illness, according to the findings of investigations (9). Furthermore, when COVID-19 patients with a history of kidney transplantation has been compared to COVID-19 patients without a history of kidney transplantation, a decrease in the number of tissue dendritic cells in the blood was evident (10). Since kidney transplant recipients' immune systems are compromised, providing intense care to these patients to avoid COVID-19 is a large and significant problem.

Objectives

Regarding the limited studies and the importance of subject, the clinical and laboratory manifestations and mortality rate of COVID-19 patients with a history of kidney transplantation referred to Razi and Golestan hospitals in Ahvaz has been investigated.

Patients and Methods

Study design

This descriptive epidemiological study conducted on 103 COVID-19 patients with a history of kidney transplantation (at least three years duration of kidney transplantation) who had been admitted to Razi and Golestan hospitals in Ahvaz from February 2020 to February 2021. Fever, respiratory distress, and leukopenia or lymphocytopenia were among the early diagnostic criteria. The final diagnostic criteria for COVID-19 was the observation of pulmonary abnormalities in chest computed tomography (CT) images and positive findings in a real-time polymerase chain reaction (PCR) test. Two pulmonary and infectious disease subspecialists made the diagnosis. The exacerbation of dyspnea, and tachypnea more than 30%, oxygen saturation less than or equal to 90% or PaO2/FiO2 ratio less than 300 mm Hg, and involvement of more than 50% of lung on CT scan are considered as criteria for disease severity(11). Scoring and grading of lung involvement in CT images conducted based on the method of Francone et al (12). Demographic characteristics, underlying disease, clinical manifestations of patients including fever, shortness of breath, cough, body aches, and fatigue, and gastrointestinal symptoms such as diarrhea and vomiting and anosmia has been recorded by ward nurses for each patient. The patients' files contained laboratory data such as electrolytes tests, liver function tests (aspartate aminotransferase, alanine transaminase, alkaline phosphatase), lactate dehydrogenase (LDH), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), D-dimer and medications. In addition, the length of the patients' hospitalization, the length of their stay in the intensive care unit (ICU), and the result of their hospitalization were all recorded.

Statistical analysis

The collected data has been statistically analyzed using SPSS (Statistical Package for Social Sciences, version 22), and through descriptive tests, independent *t* test, Mann-Whitney U test, ANOVA and Kruskal-Wallis test. A *P* value less than 0.05 (typically ≤ 0.05) was considered statistically significant.

Results

Among 103 COVID-19 patients had a history of kidney transplantation at least 3 years ago and has been admitted to Golestan and Razi hospitals in Ahvaz, 64 were male (62.1%) and 39 were female (37.9%) and the mean age of patients was 48.5 ± 13.1 years (Table 1).

Besides, after checking the patients for underlying disease, 45.6% of them had hypertension and 31.1% had diabetes (Table 2).

Table 3 shows the outcomes of clinical complaints based on patient signs and symptoms. The most prevalent symptoms among patients were headaches (67%) and shortness of breath (66%) respectively. Fever was the most common complaint among patients, accounting for 15% of them, and cough for 3% of cases (Table 3).

The results of the laboratory findings are shown in Table 4. The increased LDH levels seen in 100% of patients.

Table 1. Frequency distribution of demographic variables in the studied patients

Variable	
Gender, No. (%)	
Men,	64 (62.1)
Women	39 (37.9)
Age (year), Mean ± SD	48.5 ± 13.1
Time elapsed since kidney transplantation (year), Mean ± SD	5 ± 2.1

Table 2. Frequency distribution of underlying disease in the studied patients

Underlying disease	No. (%)
Diabetes	32 (31.1)
Hypertension	47 (45.6)
Heart failure	2 (1.94)
Cancer	1 (0.97)
Ischemic heart disease	4 (3.88)
Focal segmental glomerulosclerosis	2 (1.94)
Glomerulonephritis	1 (0.97)

Table 3. Frequency distribution of clinical complaints based on signs and symptoms

Clinical complaints	No. (%)
Shortness of breath	69 (67.0)
Headache	68 (66.0)
Weakness and fatigue	42 (40.7)
Gastrointestinal symptom	130 (29.1)
Myalgia	16 (15.5)
Fever	15 (14.5)
Cough	31 (2.91)

Moreover, the increased ESR was in 98.1% of patients, while serum CRP level increment was detected in 93.2% of patients. The incidence of lymphocytopenia was 57.3% percent of patients, while an increased D-dimer levels was seen in 53.4% of patients.

The findings of pulmonary CT imaging are shown in Table 5. Based on the data presented in this table, in more than half of the patients, more than 50% of both lungs has been involved. The most prevalent pattern of lung involvement was in the form of bilateral ground-glass opacification/opacity (GGO). Only one patient had a mosaic attenuation pattern in the lungs. Furthermore, the degree of lung involvement was greater than 75% in 12.6% of patients, and between 50% and 75% in 41.7% of patients.

Table 6 shows the data about the hospitalization profile of the studied patients. According to the data presented in this table, the duration of patients' hospitalization in the ward and in the ICU was 2.8 ± 5.1 and 1.7 ± 4.5 days, respectively. Our study also has showed 79.6% of ICU patients discharged since 20.4% of them died.

Discussion

The challenging and global spread of COVID-19 has caused health researchers to take swift action to control its epidemic. Since the beginning of the pandemic, various studies has been conducted in this field. However, it shown that kidney transplant patients are among the virus's most susceptible victims, with a greater death rate owing to COVID-19 illness in these patients than in healthy people. COVID-19 virus has been shown to have a longer viral life and induce a greater viral load in kidney transplant recipients (13). Immune suppression, administration of corticosteroids, and malnutrition are among the causes of vulnerabilities of kidney transplant patients to COVID-19 and other types of coronaviruses (14). Previous studies showed that mortality rates in terms of SARS and MERS were higher in transplant patients compared to the individuals with healthy immune systems (15). Despite these results, there are many ambiguities regarding the prevalence and lethality of COVID-19 in patients who received a connective tissue, including kidney.

Other factors which increase the risk for COVID-19 infection in kidney transplant patients include underlying diseases such as hypertension and diabetes (16). Our results show that around 46% of kidney transplant patients had hypertension and 31% of them had diabetes, which is

Table 4. Frequency distribution of laboratory findings in the studied patients

Laboratory findings	No. (%)
Increased LDH levels	103 (100.0)
Increased aspartate aminotransferase levels	31 (30.1)
Increased creatine phosphokinase levels	22 (21.4)
Increased alanine aminotransferase levels	14 (13.6)
Increase ESR level	101 (98.1)
Increase CRP level	96 (93.2)
Lymphocytopenia	59 (57.3)
Increase the level of D-dimer	55 (53.4)
AKI	20 (19.4)
Thrombocytopenia	18 (17.5)
Leukopenia	12 (11.7)
Leukocytosis	9 (8.70)
Thrombocytosis	1 (0.97)

AKI, Acute kidney injury, LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

Table 5. CT Imaging features in the studied patients

Imaging features/findings	No. (%)
Severity of lung involvement	
0%	2 (1.90)
<5%	0 (0.0)
5-25%	0 (0.0)
25-50%	45 (43.7)
50-75%	43 (41.7)
>75%	13 (12.6)
Pattern of lung involvement	
One-sided ground-GGO)	1 (0.97)
Bilateral ground-GGO	100 (97.1)
CT mosaic pattern of lung	1 (0.97)
Pleural effusion	1 (0.97)

GGO, glass opacification/opacity.

Table 6. Hospitalization profile of the studied patients

Hospitalization profile	
Duration of hospitalization, day (mean ± SD)	2.8 ± 5.1
ICU length of stay, days (mean ± SD)	1.7 ± 4.5
Need for dialysis, number (%)	11 (10.7)
Result of hospitalization	
Clearance, No. (%)	82 (79.6)
Mortality, No. (%)	21 (20.4)

consistent with the results of the study by Shaikh et al (17). In terms of clinical symptoms, headache and shortness of breath were reported by 67% and 66% of patients, respectively, while fever and cough were reported by 15% and 3% of patients, respectively. Immune suppression causes disease manifestations to show with unique signs or/and reduced symptoms in organ transplant recipients (18). As a result, the identification of the condition in these people is delayed, resulting in additional harm and consequences among them. The incidence of shortness of breath in two-thirds of kidney transplant patients with COVID-19 and ultimately the death of 20% of them indicates that the diagnosis of COVID-19 in these patients done at the stage of progression of disease. Besides, the presence of fever in a low percentage of kidney transplant patients with COVID-19 (3%) could be due to the late diagnosis of the disease (9).

Contrary to the results of this study, previous studies have shown that the clinical manifestations of COVID-19 patients with a history of organ transplantation and the general population are similar (19,20). Regarding serum parameters, ESR value and LDH and CRP levels increased in nearly all of patients. Lymphocytopenia has been observed in 57.3% of patients. The increment of inflammatory factors and lymphopenia in organ transplant patients could be in terms of lymphocytopenia as a result of consumption of immunosuppressive drugs (21). The increment of LDH value in nearly 100% of kidney transplant patients who affected by COVID-19, is a sign which might conduct as a diagnostic marker in renal transplant individuals. In accordance with our findings, kidney transplant patients with COVID-19 and a more severe degree of lung involvement had elevated levels of serum LDH and D-dimer (21). Acute kidney injury (AKI) and the requirement for dialysis are COVID-19 disease complications in kidney transplant patients (22). The incidence of AKI observed in 20% of the patients, which is in line with the results of the study of Elhadedy et al (16). About 10% of kidney transplant patients needed dialysis. In a UK study, Banerjee et al (22) reported that 57% of kidney transplant patients with COVID-19 had to use dialysis.

COVID-19 caused a 20.4% death rate in kidney transplant recipients. According to the findings of this investigation, the death rates of organ transplant patients owing to COVID-19 were reported to be 20.4% and 27.8%, respectively, in the study by Fernández-Ruiz et al (21). According to the study conducted by Akalin et al (9) in the United States, the death rate of COVID-19-positive kidney transplant patients is 28%, compared to 1-5% in the general population. Akalin et al (9) reported in a study in the United States that the mortality rate of kidney transplant patients with COVID-19 is 28% and this rate is 1 to 5% in the general population. The rate of lung involvement in 41.7% and 12.6% of kidney transplant patients was 50%-75% and more than 75%, respectively. The results of several studies showed that the administration of immunosuppressive drugs in organ transplant patients increases the severity of COVID-19 (9,23). Moreover, it has been reported an association between chronic kidney disease and the severity of COVID-19 (24).

Conclusion

Besides the cough and fever, shortness of breath were the main clinical symptoms of COVID-19 in kidney transplant patients. Therefore, this result may indicate late referral of patients to medical centers and happening changes in their usual clinical symptoms due to the use of immunosuppressive agents. The increment of LDH serum levels, and D-dimer has been observed in a high percentage of kidney transplant patients with COVID-19. According to the findings of this study, kidney transplantation may increase COVID-19-related mortality when compared to COVID-19-related mortality in the general population. As a result, it is advised that kidney transplant patients adhere to the health standards more carefully.

Limitations of the study

The limitations of this study were the difficult access to the disease diagnostic methods, the lack of an assessment and examination of serum interloon-1 and procalcitonin and the relatively small sample size.

Authors' contribution

Conceptualization: LS. Methodology: SS, MSM and LS. Validation: HS and AG. Formal Analysis: AG. Investigation: AG, ZM and LS. Resources: MSM. Data Curation: MSM. Writing—Original Draft Preparation: MSM. Writing—Review and Editing; MSM, AG. Visualization: SS and LS. Supervision: AG, HS and ZM. Project Administration: SS, SMS and LS. Funding Acquisition: SS.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The study protocol conforms to the ethical guidelines of 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee. Moreover, each participant asked to sign the informed consent forms. The institutional ethical committee at Ahvaz Jundishapur university of medical sciences approved all study protocols (IR.AJUMS.1400.275). The present research extracted from the nephrology

fellowship dissertation of Maryam Sadat Mavalizadeh at this university (proposal code: CRD-0004). Besides, ethical issues (including plagiarism, data fabrication and double publication) have been completely observed by the authors.

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