

Severity of Covid-19 Infection Among Kidney Transplant Recipients in Duhok City, Kurdistan Region, Iraq

Zana Sidiq Mohammed Saleem*

Department of Internal Medicine, College of Medicine, University of Duhok, Duhok, Iraq.

*Correspondence to: Zana Sidiq Mohammed Saleem (E-mail: zanasidik@gmail.com)

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Abstract

Background: Kidney transplant recipients are risky group population in whom greater morbidity and mortality reported in comparison to general population.

Methods: We examined a prospectively cohort of 80 SOT kidney transplant recipients with first-wave COVID-19, participants assessed and grouped into severe and non-severe illness.

Results: Eighty kidney transplant recipients involved in our study, with average age of 46.6 ± 12.2 years and kidney transplant duration of 6.4 ± 3.5 years. Fifty four were male (67.5%). Comorbidities included hypertension (60%), diabetes mellitus (18.8), coronary heart disease (3.8), and hypothyroidism (2.5). Twelve patients had severe Covid-19 infection (15%) and sixty eight with non-severe (85%). Risk factors for severe COVID-19 infection in this study were male gender, old age, comorbidities, obesity, longer duration of COVID-19 symptoms, kidney transplantation duration, C-reactive protein > 24 mg/L, Interlukine-6 > 26 pg/mL and D-Dimer level > 1000 ng/mL. Modulation of immunosuppressive drugs done only for severe cases. Eight transplant recipients needed admission to hospital and one necessitate mechanical ventilation.

Conclusion: Kidney transplant recipients are at high risk of acquiring opportunistic infections including COVID-19 infection. The most important strategy in kidney transplant recipients to prevent COVID-19 infection is through adopting preventive measures in particular the use of masks and avoidance of crowded non-ventilated places. Risk stratification and poor outcome factor is crucial strategy to prevent spread of the infection.

Keywords: COVID-19, Duhok, Iraq, severity, kidney transplant

Introduction

Coronavirus disease 2019 (COVID-19) is caused by the single strand RNA virus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has become a worldwide threat at beginning of 2020. The first human case of COVID-19 was reported in Wuhan, China, in December 2019, and within a few weeks the infection spread around the world, becoming a pandemic.¹

Symptoms like fever, fatigue and dry cough are the most common and patients may also experience dyspnea, muscle pain, sore throat and gastrointestinal (GI) symptoms.² Patient receiving immunosuppressant drugs have been one of the populations most vulnerable to COVID-19 and many reports have been published. In this setting, immunomodulation has emerged as a promising option for patients with COVID-19-related cytokine storm.³ Moreover, COVID-19 has had a big impact on wait-listed patients, highlighting the need to properly balance the risks and benefits of transplantation in the setting of an ongoing pandemic.⁴

Acute kidney injury (AKI) is a common complication in patients with COVID-19 and it's multifactorial and is associated with increased intensive care unit (ICU) admission and mortality.^{5,6} AKI incidence is higher in patients admitted to the ICU due to COVID-19 than in patients admitted for other reasons.⁷

Renal transplant recipients may be at high risk of developing severe COVID-19 disease due to chronic immunosuppression, comorbidities and frequent contact with the healthcare system. Kidney transplant recipient may be diagnosed earlier when they have symptoms due to closer follow-up at the transplant center.⁸⁻¹⁰ In kidney transplantation, the most widely used interventions were the modification of immunosuppression, reducing or suspending the

antimetabolite or inhibitors of the mammalian target of rapamycin, while the calcineurin inhibitor was suspended in patients at risk for interaction with protease inhibitors.¹¹⁻¹⁵

A British population-based study showed that solid organ transplant patients had one of the highest in-hospital risks of death (HR 4.23) due to COVID-19.¹⁶

Risk factors for mortality included age >65 years, chronic heart failure, chronic lung disease and obesity.

Focusing on renal transplants, a recent systematic review based on 20 studies from different countries revealed a patient mortality higher than in general population, ranging between 18% and 43%,¹⁷ versus 1% and 14% in the general population.¹⁸⁻²⁰

Risk factors for severe disease in the general population include older age and comorbidities,²¹ but the impact of chronic immunosuppression related to transplantation on COVID-19 is not well known. Despite widespread concern that COVID-19 clinical phenotypes may be more severe among solid organ transplant recipients (SOTRs) due to a poorer inflammatory response and greater organ injury, data on this population are limited to a few case series and generally small retrospective cohorts.²²⁻²⁵

Previous reports suggest that immunosuppression may reduce the frequency of cytokine storms, a significant cause of mortality.^{26,27}

Methods

Study Design and Participants

This prospective study from 15th July, 2020 to January 22, 2021.

Eighty kidney transplant recipients visiting Duhok Kidney Diseases and Transplantation Center diagnosed with SAR-Cov-19 infection after confirmation by real time polymerase chain reaction (RT-PCR).

Patient demographics (age, gender), body mass index (BMI), duration of kidney transplantation, comorbidities, medications history, concomitant infections, clinical presentation, immunosuppression regimen and subsequent adjustment, laboratory investigation in form of complete blood count (CBC), liver function tests, serum creatinine, IL-6, CRP, D-dimer, LDH, imaging, clinical course, and treatment modalities were collected.

Covid-19 Infection Classification

Severity of infection based on World Health organization (WHO) classification, and patient management based on the severity of infection in regard of hospital or home management.

Immunosuppression was reduced or stopped like antimetabolite (mycophenolate mofetil (MMF) or azathioprine) with or without adjustment of calcineurin inhibitors such as tacrolimus (FK) or cyclosporine. Steroids were either kept at the maintenance dose or converted to intravenous for stress dosing. Confirmed cases who were not admitted were managed by instructed to self-isolate, monitor temperature and partial oxygen saturation (SpO₂), and scheduled for weekly follow-up.

Normal weight for adults is usually when body mass index (BMI) is 18.5 to less than 25, overweight when BMI is 25–29.9 and obesity is when BMI is 30 and more according to Center for Disease control and prevention.²⁸

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories.

Asymptomatic or Presymptomatic Infection: Individuals who test positive for SARS-CoV-2 using a virology test (i.e., a nucleic acid amplification test [NAAT] or an antigen test) but who have no symptoms that are consistent with COVID-19. **Mild Illness:** Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. **Moderate Illness:** Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have oxygen saturation (SpO₂) ≥94% on room air at sea level. **Severe Illness:** Individuals who have SpO₂ 30 breaths/min, or lung infiltrates >50%.²⁹

Statistics

We analyzed the result using SSPS (version 17). We used the student's *t*-test for comparing the means. The significance level was at $P < 0.05$.

Ethics

This study was approved by the Ethics Committee in the College of Medicine, University Duhok. Written consent was obtained from all recruited patients.

Results

Eighty kidney transplant recipients involved in our study, characteristics of participants are shown in Table 1.

Male constitutes two third of participants, mean age were 46.6 and mean duration of transplantation is 6.4 years. Eighty eight percent of participants were managed at home. Hypertension was the most common comorbid disease in our study.

Fever, dyspnea, cough and diarrhoea were the most common presenting symptoms as shown in Table 2. AKI was the presenting symptom in four percentages (Figure 1).

In the current study, severe COVID-19 infection seen more in male gender, elderly, obese, longer duration of symptom, kidney transplantation, and those with more comorbidities as shown in Table 3.

Table 1. Characteristic of participants in the study

Characteristic	No. (%)
Male	54 (67.5)
Female	26 (32.5)
Age (Mean)	46.6 ± 12.2
Weight	47 (58.75)
Normal	23 (28.75)
Overweight	10 (12.5)
Obese	4 (5)
Smoking	71 (88.75)
Home management	9 (11.25)
Hospital management	6.4 ± 3.5
Mean duration of kidney transplantation in year	6.2 ± 3.2
Mean duration of symptoms (days)	48 (60)
Comorbidities	15 (18.8)
Hypertension	3 (3.8)
Diabetes Mellitus	2 (2.5)
Ischemic Heart Disease	3 (3.8)
Stroke	3 (3.8)
Hypothyroidism	3 (3.8)
Others	25 ± 14.7 mg/l
Mean CRP	26 ± 12.4 pg/mL
Mean IL-6	1085 ± 390 ng/mL
D-Dimer	12 (15)
Severe COVID-19	2 (2.5)
Death	

Table 2. Clinical presentation of Covid-19 among participants

Presentation	No. (%)
Fever	28 (35)
Dyspnea	11 (14)
Diarrhoea	11 (14)
Cough	10 (13)
Fatigue	7 (9)
Headache	5 (6)
Acute kidney injury	3 (4)
Loss of smell	2 (3)
Others	4 (5)

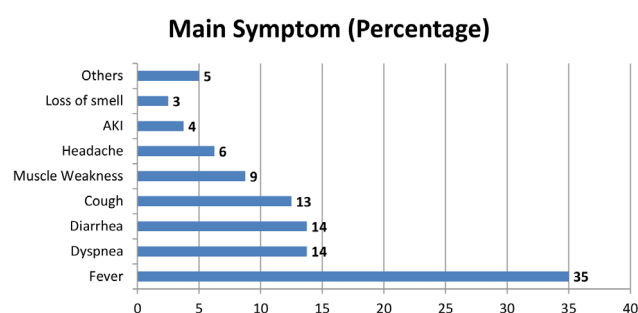


Fig. 1 Main symptoms of covid-19 infection among participants.

Table 3. Characteristic of severe cases in the study

Characteristic	No. (%)
Male	9 (75)
Female	3 (25)
Age (Mean)	50.3 ± 12.2
Weight	2 (16.7)
Normal	4 (33.3)
Overweight	6 (50)
Obese	1 (8.3)
Smoking	4 (33.3)
Home management	8 (66.6)
Hospital management	12 (100)
Mean duration of kidney transplantation in year	9.8 ± 3.7
Mean duration of symptoms (days)	6.2 ± 2.9
Comorbidities	48 ± 24.5
Mean CRP	56 ± 32.6
Mean IL-6	1873 ± 1024
D-Dimer	2 (16.6)
Death	

There was no difference in regard of severity of covid-19 infection among transplant recipient with Cyclosporine and Tacrolimus group.

There was significant difference of inflammatory markers like CRP, IL-6 and D-Dimer among severe and non-severe group (P value of 0.001, P value of $< < 0.0000001$, P value of $< < 0.0000001$ respectively).

Case fatalities were two, one male from ARDS and one female from acute coronary syndrome.

Twelve of 80 patients underwent modification in the immunosuppression drugs. Immunosuppression reduction was done in the severely affected patient. The strategic change in immunosuppression regimen was in form of complete cessation of antimetabolites (mycophenolate mofetil, mycophenolic acid, or azathioprine) and reducing tacrolimus dose. No change in immunosuppression regimen done in non-hospitalized and mild form cases.

Discussion

In this study of kidney transplant recipients affected by COVID-19 with follow-up of six months, 15% were with severe COVID-19 infections, 11.25% required hospital admissions and only one patient needed ICU admission. The case fatality of this study population was two patients (2.5%). May be the low rate of infection and mortality in this risky group attributed to that this group of patients are using precautious measure of infection transmission directly after kidney transplantation before the pandemic of COVID-19 and also may be they are on continuous small dose of steroid which decrease mortality in severe covid-19.³⁰

Risk factors for severe COVID-19 infection in this study were male gender, old age, comorbidities, obesity, longer duration of COVID-19 symptoms and kidney transplantation duration. Delay seeking health facilities also found risk factor in this study for severe COVID-19 infection. And lastly earlier post-transplant SARS-CoV-2 infection also was demonstrated as a risk factor for severe infection.

Fever, dyspnea, cough and diarrhoea were the most common presenting symptoms among this study population, which were significantly associated with a poor clinical outcome (P value < 0.001). This was similar to other study done at Spain.³¹

Three cases presented as AKI (4%), in this study this rate is lower in comparison to other studies.³²

Inflammatory markers were significantly higher among severe covid-19 cases in comparison to non-severe cases.

Two cases of 12 severe cases died (16.6%) this rate is lower to study done in China were the rate was 28%.³³ But comparable to subsequent publications, these rates were reported to be 8% in New York, 14% in Italy, and 12% in Spain.³⁴ This is attributed mostly because of age and comorbidity among the study groups.

There was no difference in the outcomes of COVID-19 infection in transplant recipients receiving cyclosporine and tacrolimus.³⁵

Conclusion

Kidney transplant recipients are on immunosuppressive regimen and they are at high risk for opportunistic infection acquisition like COVID-19 infection. Risk stratification and poor outcome factor is crucial strategy to prevent spread of the infection. Early diagnosis and proper treatment is also important to prevent unfavorable COVID-19 infection sequelae in this risky group population.

The most important strategy in kidney transplant recipients to prevent COVID-19 infection is through adopting preventive measures in particular the use of masks and avoidance of crowded non-ventilated places. The ultimate strategy to effectively prevent COVID-19 is vaccination against SARS-CoV-2.^{36,37}

Our protocol in managing transplant recipients with COVID-19 infection was based on new and updating reports. Larger and longer duration studies needed to adopt the best protocol in managing such risky group of patients. ■

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