The Comparison of Clinical, Laboratory, and Radiological Findings in Immunocompromised and Immunocompetent Patients with COVID-19: A Case-Control Study

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Research Article

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Abstract

Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19) with significant morbidity and mortality. We reported and compared the clinical and para-clinical findings of immunocompromised and immunocompetent COVID-19 patients in a case-control study at the Imam Khomeini hospital in Tehran, Iran.

Methods: A total of 107 immunocompromised COIVD patients as the case group and 107 immunocompetent COVID patients as the control group was recruited in the study. The participants were matched based on age, and sex. The patients' information was retrieved from the hospital records in an information sheet. Associations between clinical and para-clinical findings with the immune status were assessed using bivariate and multivariate analyses. The clinical trial registration number is not applicable.

Results: The initial pulse rate and recovery time were significantly higher in immunocompromised patients (P <0.05). Myalgia, nausea/vomiting, loss of appetite, headache, and vertigo were more frequently reported by the control group (P <0.05). In terms of the duration of prescribed medications, Sofosbovir time was longer in the case group; while Ribavirin time was longer in the control groups (P <0.05). The most common complication in the case group was ARDS although no major complications were observed in the control group. In the multivariate analysis, recovery time and Kaletra prescription were significantly higher in immunocompromised compared to the immunocompetent group.

Conclusions: Recovery time was significantly higher in the immunocompromised compared to the immunocompetent group. This informs the current practice of dominant COVID-19 clinical course in immunocompromised patients and communicates the related implications.

Introduction

The world is facing a new coronavirus outbreak, named severe acute respiratory syndrome coronavirus (SARS-CoV-2) causes coronavirus disease 2019 (COVID-19). It emerged in Wuhan, China in December 2019 and soon became a worldwide pandemic (1). By December 15, 2020, over 73,353,210 million people had been infected and more than 1,631,336 fatalities were reported globally. At the same time, in Iran, over 1,123,474 million people had been infected with more than 52,670 documented fatalities.

Concerns have been raised about COVID-19 outcomes in immunocompromised patients early in the pandemic. According to the Centers for Disease Control and Prevention (CDC) guidelines, these patients regard as a high-risk population for COVID-19. There are conflicting data about the influence of COVID-19 on immunocompromised hosts. Some reports demonstrated a higher risk of COVID-19 complications and poorer prognosis in immunocompromised hosts (2–6), but experiences with the severe acute respiratory syndrome (SARS), Middle East Respiratory Syndrome (MERS) coronaviruses, and present COVID-19 infection showed in contrary to other viral infectious diseases such as influenza, the immunosuppressed

hosts are not susceptible to severe pulmonary complications of coronavirus infections. This may explain the critical role of the immune system activity in coronavirus-induced pulmonary injury (7).

Almost 80% of SARS-CoV-2 infected patients are non- or mild-symptomatic (8, 9). In normal hosts, the most common presenting symptoms are cough, fever, and dyspnea. Older males with baseline comorbidities especially diabetes, hypertension, obesity, and cardiopulmonary diseases are at higher risk of severe complications. Lymphopenia and elevated inflammatory markers are valuable laboratory findings. Diffuse usually bilateral peripheral patchy ground-glass opacities, consolidation, and/or interstitial opacities are the most prevalent patterns in chest computed tomography (10–14).

Initial COVID-19 presentation in immunocompromised hosts is almost the same as for immunocompetent individuals but usually less severe and more favorable prognosis. In transplant recipients with COVID-19, cough is more common but nearly a half are afebrile and respiratory failure is less probable. Kidney transplant hosts are more prone to renal dysfunction. This might be due to the direct SARS-CoV-2 effect on the kidney, an immune reaction to viral antigens, or graft rejection following immunosuppressive dose reduction (2, 6, 12, 15). Although there are several reports in terms of the clinical presentations of COIVD-19 in immunocompromised patients, there are controversial and the differences in the clinical course with healthy individuals have not been characterized. Therefore, in the present study, we aimed to evaluate and compare the clinical, laboratory, and radiological findings of immunocompromised and immunocompetent COVID-19 patients.

Materials And Methods

Study design and participants

We conducted a case-control study. Patients were grouped based on their immune system function into the case group including immune-deficient patients with COVID-19 and the control group including immunocompetent patients with COVID-19. The hospital records of 214 patients (107 immunodeficient and 107 immunocompetent patients matched for age and sex) with COVID-19 infection were reviewed and the related information was retrieved and recorded in an information sheet separately for each group. All inpatients with either definitive (based on positive PCR of respiratory secretions) or probable (based on clinical symptoms including sore throat, cough, myalgia, weakness, lethargy, sweating, shortness of breath, diarrhea, fever, and radiological findings including lung involvement in a chest CT scan or chest x-ray) cases of COVID-19 were included. The study took place at Imam Khomeini Hospital, Tehran, Iran in July 2020. The immunodeficient patients who met the following criteria, were considered as the case group:

- More than 10 mg of corticosteroid for more than three weeks.
- Longtime low dose corticosteroids with a cumulative dose of 750 mg or more.
- Immunosuppressive or cytotoxic drugs other than corticosteroids including azathioprine, methotrexate, mycophenolate mofetil (CellCept), tacrolimus (Prograf), anti-TNF alpha, and other

biologic agents over the past six months.

- Solid organ or bone marrow transplant.
- Hematologic malignancies with or without chemotherapy during the last six months.
- Solid-organ malignancies with chemotherapy during the last six months.
- Human immunodeficiency virus (HIV) infection / Acquired immunodeficiency syndrome (AIDS)
- Primary immunodeficiency such as common variable immune deficiency (CVID) and chronic granulomatous disease (CGD).

Ethical considerations

The ethical necessities of the study were reviewed and approved by the Institutional Review Board (IRB) of the Tehran University of Medical Sciences with the file number (IR.TUMS.VCR.REC.1399.053). The ethical obligations were considered to respect the patient's rights and ensure data confidentiality.

Statistical Analysis

The information was analyzed using SPSS software version 22. Quantitative variables were reported as mean and standard deviation and qualitative variables were reported as frequency and percentage. To compare the clinical and para-clinical findings between the two groups, bivariate analysis was employed. Logistic regression analyses, adjusting for the significant variables in bivariate analysis ($p < 0.1$), assessed the associations between the study parameters with the status of the immune system in two groups. The results were reported as odds ratios (ORs) and 95% confidence intervals (CIs).

Results

A total of 107 immunocompromised COIVD patients as the case group and 107 immunocompetent COVID patients as the control group were recruited in the present study. The participants were matched based on age, and sex.

As it is shown in Table 1, comparing the vital signs and duration of the clinical course; the initial pulse rate and recovery time were significantly higher in immunocompromised patients ($P < 0.05$).

Table 1
The comparison of vital signs and duration of clinical course in the study groups, Imam Khomeini Hospital, Tehran, 2020

Characteristic	**Groups**		**P-value**
	Case	**Control**	
	Mean (SD)	**Mean (SD)**	
Respiratory rate	22.7 (10.9)	21.2 (5.3)	0.22
Temperature	37.7 (0.82)	37.5 (.88)	0.11
Pulse rate	98.3 (16.6)	92.4 (15.6)	0.008*
Oxygen Saturation (SPO2)	88.8 (8.9)	90.4 (5.2)	0.13
ICU length of stay (day)	10.0 (10.5)	8.3 (5.8)	0.51
Recovery time (The interval between the onset of the first symptom and relative recovery)	16.6 (12.5)	10.5 (8.8)	< 0.001*
Admission time (day)	8.2 (9.6)	6.5 (6.5)	0.20
Duration of the symptomatic period before admission/day	7.5 (5.4)	7.8 (3.8)	0.62

In terms of clinical manifestations (Table 2); myalgia, nausea and vomiting, loss of appetite, headache, and vertigo were more frequently reported by the control group ($P < 0.05$).

Table 2
The comparison of clinical manifestations between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Variables	Groups		OR (95% CI)	P-value
	Case N (%)	Control N (%)		
Fever	73 (68.2)	65 (60.7)	1.4 (0.79–2.43)	0.25
Myalgia	52 (48.6)	71(66.4)	0.48 (0.28–0.83)	0.009*
Generalized weakness	51 (47.7)	52 (48.6)	0.96 (0.56–1.65)	0.89
Cough	67 (62.6)	77 (72.0)	0.65 (0.37–1.16)	0.15
Nausea & vomiting	21 (19.6)	34 (31.8)	0.52 (0.28–0.98)	0.04*
Diarrhea	11 (10.3)	14 (13.1)	0.76 (0.33–1.76)	0.52
Abdominal pain	6 (5.6)	15 (14.0)	0.36 (0.14–0.98)	0.05
Appetite loss	37 (34.6)	52 (48.6)	0.56 (0.32–0.97)	0.04*
Headache	24 (22.4)	41 (38.3)	0.46 (0.26–0.85)	0.01*
Vertigo	4 (3.7)	16 (15.0)	0.22 (0.07–0.68)	0.009*
Tasteless (ageusia)	6 (5.6)	9 (8.4)	0.65 (0.221.9)	0.43
Anosmia	6 (5.6)	15 (14.0)	0.36 (0.14–0.98)	0.05

Table 3 describes the laboratory findings of the study groups. As it is shown, the first hemoglobin level was significantly higher in the control group ($P < 0.05$).

Table 3
The comparison of laboratory findings between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Characteristic	Groups		P-value
	Case Mean (SD)	Control Mean (SD)	
White Blood Cell (/µL)	9.3 (11.5)	69.1 (602.5)	0.30
Lymphocytes (/µL)	18.3 (12.7)	19.5 (8.4)	0.49
Hemoglobin (g/dL)	11.9 (2.8)	13.2 (2.1)	0.001*
Platelet count (mL)	207.9 (106.5)	219.9 (95.8)	0.40
Creatine Phosphokinase (U/L)	164.8 (281.5)	233.3 (499.1)	0.41
Erythrocyte Sedimentation Rate (mm/ hr)	76.7 (36.1)	70.2 (29.1)	0.19
C-reactive protein (mg/L)	110.1 (80.1)	99.2(82.4)	0.35
Creatinine (mg/dL)	1.2 (1.1)	1.2 (0.4)	0.27
Aspartate aminotransferase (IU/L)	49.9 (53.5)	46.4 (41.3)	0.65
Alanine transaminase (IU/L)	46.3 (41.9)	43.9 (42.4)	0.75
Lactate dehydrogenase (U/L)	652.5 (363.9)	649.4 (254.9)	0.96
Troponin (ng/mL)	21.9 (56.4)	52.7 (173.6)	0.25
B-type natriuretic peptide (pg/mL)	5120.7 (9748.4)	1958.9(6050.1)	0.12

In terms of the duration of prescribed medication (Table 4), Sofosbuvir was administered longer in the case group; while Ribavirin was administered longer in the control groups ($P < 0.05$).

Table 4
The comparison of the medication duration between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Characteristic	Groups		P-value
	Case Mean (SD)	Control Mean (SD)	
Hydroxychloroquine time(day)	7.4 (2.6)	7.6 (2.6)	0.54
Lopinavir/ritonavir (Kaletra time) (day)	6.5 (2.4)	7.5 (2.9)	0.26
Atazanavir time (day)	6.6 (2.1)	6.7 (2.4)	0.76
Steroid time (day)	4.1 (4.5)	6.3 (6.5)	0.25
Sofosbuvir time (day)	13.1 (1.8)	9.1 (4.9)	0.032*
Oseltamivir time (day)	4.9 (0.6)	4.9 (0.6)	0.84
Ribavarin time (day)	2 (0)	5 (0)	< 0.001*
Interferon time (day)	3 (0)	3.7 (1.5)	0.69
Vitamin C time (day)	2.8 (1.1)	3.7 (3.03)	0.33
Intravenous Immune Globulin time (day)	2.6 (.8)	2.5 (1.1)	0.33

Table 4 illustrates the medication type in the case and control groups, it appeared that immunocompromised patients were more likely to receive Lopinavir/Ritonavir (Kaletra) compared to the immunocompetent patients in the control group; whereas, the control group received more Atazanavir ($P < 0.05$).

Diffuse (12.2%) and anterior (77.0%) lung involvement were more prevalent among immunocompromised patients. On the other hand, in immunocompetent patients, anterior & posterior (83.9%) lung involvement was more common (Tables 6 & 7). Table 8 indicates the prevalence of complications in the case and control groups. Table 5 indicates the prevalence of different complications in the study groups. As it is shown, no complications were reported in the control group. The most common complication in the case group was acute respiratory distress syndrome (ARDS) (45%), followed by myocardial and neurological complications (20% and 25% respectively).

Table 5
The comparison of medication type between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Variables	Groups		OR (95% CI)	P-value
	Case N (%)	Control N (%)		
Hydroxychloroquine	106 (99.1)	106 (99.1)	1.0 (0.06–16.19)	> 0.9
Lopinavir/Ritonavir(Kaletra)	49 (45.8)	11 (10.3)	7.37 (3.55–15.31)	< 0.001*
Atazanavir	56 (52.3)	91 (85.0)	0.19 (0.1–0.37)	< 0.001*
Steroid	21 (19.6)	18 (16.8)	1.21 (0.6–2.42)	0.60
Sofosbuvir	9 (8.4)	11 (10.3)	0.8 (0.32–2.02)	0.64
Oseltamivir	47 (43.9)	39 (36.4)	1.37 (0.79–2.36)	0.27
Remdesivir	0 (0)	2 (1.9)	0.196 (0.01–4.14)	0.56
Ribavirin	2 (2.0)	1 (1.0)	2.1 (0.19–23.6)	0.55
Interferon	2 (2.9)	4 (4.5)	0.63 (0.113–3.57)	0.61
Altebrel	0 (0)	4 (3.8)	0.11 (0.01–2.01)	0.18
Fluconazole	2 (1.9)	0 (0)	5.10 (0.24-107.39)	0.56
Intravenous Immune Globulin	7 (6.5)	9 (8.4)	0.76 (0.27–2.13)	0.60

Table 6
The prevalence of different anatomical lung involvement in radiologic examination between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Variables	Groups		OR (95% CI)	P-value
	Case N (%)	Control N (%)		
Location of lung involvement				
Posterior	0 (0)	11 (12.6)	Ref	-
Anterior	57 (77.0)	3 (3.4)	93.8 (26.3-335.18)	< 0.01*
Anterior & Posterior	8 (10.8)	73 (83.9)	0.023 (0.01–0.06)	< 0.01*
Diffuse	9 (12.2)	0 (0)	25.4 (1.5-443.9)	0.004*

Table 7
The pattern of lung involvement in radiologic examination between the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Characteristic	Groups		P-value
	Case Mean (SD)	Control Mean (SD)	
Ground-glass opacification/opacity (%)	68 (32.7)	53.9 (32.9)	0.43
Consolidation (%)	50 (14.2)	58.3 (28.5)	0.57
Ground-glass opacity plus Alveolar (Mix)	68 (16.4)	67.9 (21.7)	0.99

Table 8
The prevalence of complications in the case and control groups, Imam Khomeini Hospital, Tehran, 2020

Variables	Groups		OR (95% CI)	P-value
	Case N (%)	Control N (%)		
Complication				
(Complications during hospitalization)	9 (45.0)	0 (0)	20.7 (1.19-360.97)	0.01*
ARDS	4 (20.0)	0 (0)	9.35 (0.50-175.80)	0.18
Neurologic	5 (25.0)	0 (0)	11.54 (0.63-211.28)	0.10
Myocarditis	2 (10.0)	0 (0)	5.095 (0.24-107.39)	0.56
Sepsis				
* Fisher exact test				

In the multivariate analysis (Table 9); adjusting for other significant factors in bivariate analysis (p value < 0.1), recovery time and Kaletra prescription were significantly higher in immunocompromised compared to the immunocompetent group.

Table 9
The final significant associated factor after adjustment; Imam Khomeini Hospital, Tehran, 2020

Associated factors	AOR*	95% CI	p-value
Recovery time	0.94	0.91–0.98	0.001
Kaletra	4.32	1.47–12.69	0.008
* AOR: Adjusted odds ratio (AOR)			

Discussion

Life-long immunosuppression increases the vulnerability of viral infections in immunocompromised patients (16). Although immunocompromised patients may be more vulnerable to SARS-CoV-2 infection, long-term immunosuppressive treatment may protect them against severe COVID-19 complications (17, 18).

In our study, some clinical manifestations were more prevalent in the control group including myalgia, nausea and vomiting, loss of appetite, headache, and vertigo. Fever (98.6%), myalgia or fatigue (69.6%), dry cough, and diarrhea are the most common in COVID-19 patients (19, 20). Although Gastrointestinal symptoms are common in immunocompetent COVID-19 patients; but rarely reported in immunocompromised COVID patients (3%-5%) (21–23).

We observed a higher level of the initial hemoglobin in the control groups. Laboratory parameters of the COVID-19 patients include elevated LDH (lactate dehydrogenase), prothrombin time, D-dimer, creatine kinase, and C-reactive protein (CRP) levels (19, 20).

In this study, ARDS was the most common complication among immunocompromised patients. SARS-CoV-2 could cause mild to severe respiratory disease and 17–29% of these lead to ARDS (24). Therefore, it is important to identify patients who are at higher risk of ARDS by monitoring the oxygen saturation (SpO2) and respiratory rate during hospitalization (25).

In the present study, Diffuse (12.2%) and anterior (77.0%) lung involvement were the most common radiologic patterns in immunocompromised patients. Similar to previous studies, the most common CT scan findings in COVID patients in our study were ground-glass opacity, and consolidation (26, 27).

Two factors that remained significantly associated with immunosuppression in multivariate analysis were recovery time and Lopinavir/Ritonavir (Kaletra). According to recent studies, recovery time in immunocompromised COIVD patients is longer than in immunocompetent COVID patients (28). Immunosuppression prolongs the course of coronavirus disease and delays virus clearance (28, 29). Although there have been several therapeutic regimens in COVID patients such as IFN-alpha, lopinavir/ritonavir, chloroquine phosphate, and ribavirin (20, 30), in immunocompromised patients such as renal transplant recipients lopinavir/ritonavir or Kaletra (protease inhibitors) was the most commonly prescribed medication so far (31). However, in a recent study, lopinavir/ritonavir (Kaletra) did not prove to improve the clinical recovery, mortality, and detectability of viral RNA in throat swabs in COVID-19 patients (32). Meanwhile, there was some evidence that indicates the effectiveness of lopinavir/ritonavir in decreasing the fatality at 28 days, ICU admissions, and hospital discharging time (33).

There are limitations in the present study such as the limited number of immunodeficient patients reduce the study power. We used the records of hospitalized patients and there were some missing data for some patients which could reduce our ability to include some factors such as the pre-hospital duration of symptoms, medication history, and underlying disease.

Conclusion

In conclusion, recovery time was significantly higher in the immunocompromised compared to the immunocompetent group. This informs the current practice of the dominant clinical course of COVID-19 in immunocompromised patients and communicates the related implications. Further, epidemiological studies are recommended to evaluate the effect of underlying diseases on the clinical course of immunocompromised COVID patients and discover new therapeutic approaches.

Declarations

The ethical necessities of the study were reviewed and approved by the Institutional Review Board (IRB) of the Tehran University of Medical Sciences with the file number (IR.TUMS.VCR.REC.1399.053). The ethical obligations were considered to respect the patient's rights and ensure data confidentiality.

Consent for publication

Not applicable

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

All authors collaborated in manuscript writing and analysis, with Zahra Ahmadinejad acting as an observer. All authors reviewed the manuscript.

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