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Impact of COVID-19 on 75 Immunocompromised Patients: Does Immunosuppression Alter the Clinical Course?

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ABSTRACT

Backgrounds: Currently, clinical details of immunosuppressed patients suffering from COVID-19 are limited. Some studies have shown no more severe diseases among them, but others have highlighted that immunosuppressed patients may have high levels of viral load and impaired immune responses. Herein, this study aimed to specifically address the symptoms, prognosis, laboratory tests, clinical course, and the outcome of SARS-CoV-2 infected immunocompromised patients at a tertiary referral center.

Materials & Methods: Clinical and laboratory information of 75 non-congenital immunosuppressed patients with COVID-19 disease was obtained at a referral center for immunodeficiency diseases and infectious disorders in Tehran, Iran. Three groups of immunocompromised patients were evaluated, including patients with a history of organ transplantation, autoimmune patients receiving medical therapy, and cancer patients undergoing chemotherapy.

Findings: Among 75 immune-deficient patients with COVID-19, there were 32 patients with a kidney transplant, 23 patients with malignancies, and 19 patients with autoimmune disorders. One patient had both malignancy and multiple sclerosis. The mean length of hospitalization was 10.82 days. By the end of the study, 24 (32%) patients were dead, and 51 (68%) patients were discharged. Dyspnea was the most common (64%) symptom. Low levels of O2 saturation and lymphopenia at admission time significantly affected the mortality rate of patients.

Conclusion: This study showed that mortality rate among immunocompromised patients was 32%. It seems that COVID-19 has a worse outcome and a more severe clinical course in immunocompromised patients regardless of age, gender, and underlying diseases.

Keywords: COVID-19, Immun ocompromised patients, Cancer, Kidney transplant.

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Introduction

As of December 8, 2019, many cases of unknown-origin pneumonia were identified in Wuhan, China [1-2]. Deep sequencing analysis of respiratory tract samples indicated a novel coronavirus, which was officially called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [3-4]. Presently, this virus could be transmitted from human-to-human through close contact, respiratory droplets, or fomites. Latest studies have also pointed to the fecal-oral and fecal-aerosol transmission routs. Recent data have demonstrated that viral load reaches the maximum within 2 days after the initiation of symptoms.

Transmission from asymptomatic individuals has also been recorded despite the lower viral load. [5-6]. Prognosis of some patients with COVID-19 is not good, and some complications such as severe pneumonia, acute respiratory distress syndrome, organ failure, and death may occur [1, 7].

Since the COVID-19 outbreak, there have been justifiable concerns about the possible effects and complications of SARS-CoV-2 infection among immunocompromised individuals who are at high risk of infection and complications [7-9]. The highest case-fatality rates have been recorded in the elderly and patients with comorbidities, such as cardiac or pulmonary diseases, diabetes mellitus, hypertension, and malignancy. Also, patients with organ transplant may have high case-fatality rates due to long-term immunosuppressive therapies [7].

Currently, there is limited information on the clinical course, imaging findings, and outcomes of COVID-19 among immunosuppressed patients. Some recent studies have shown no more severe diseases among immunocompromised patients with COVID-19 [10], while other studies have highlighted that immunosuppressed patients may have high levels of viral load and impaired immune responses [11].

Objectives: Herein, this study aimed to specifically address the symptoms, prognosis, laboratory tests, clinical period, and outcomes of immunocompromised patients suffering from SARS-CoV-2 infection at a tertiary referral center.

Materials and Methods

Data collection: In this single-center survey, 75 individuals were recruited with confirmed COVID-19 infection and drug-induced immunosuppression from March 1 to May 15, 2020, at Labbafinejad hospital, a referral center for immune deficiency and infectious disorders in Tehran, Iran. The study was approved by the Ethics Committee of Shahid Beheshti University of Medical Sciences. Informed written consent was obtained from participants or their relatives when data were retrospectively collected. Three groups of non-congenital immunocompromised patients were participated in this descriptive study, including patients with a history of organ transplantation, autoimmune patients receiving medical therapy, and cancer patients undergoing chemotherapy.

Required data were collected from patients' medical records, including epidemiological and demographic data, clinical and paraclinical results, management, signs and symptoms at admission time, comorbidities, chest computed tomography (CT) findings, length of hospitalization, transplant details, medications, and outcomes. If any information was missing in the documents, or any definition was required, the intended information was gathered by direct contact with attending doctors.

Laboratory analyses: Laboratory confirmation of COVID-19 cases was based on a positive result on real-time reverse transcriptase polymerase chain reaction (RT-PCR) assay of nasal and pharyngeal swab specimens or in

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terms of pulmonary involvement, based on compatible and highly suggestive CT scans associated with clinical symptoms [12]. RT-PCR assays were conducted according to the WHO protocol [13]. Laboratory assessments comprised a complete blood count, serological tests, O2 saturation, creatinine, and C-reactive protein.

Definitions: The COVID-19 severity degree was determined using the following criteria. Patients with mild conditions have slight clinical symptoms with no imaging findings associated with pneumonia [14]. Severe COVID-19 is characterized with breath shortness, 30 or more breaths in each minute, a blood oxygen saturation of 93% or less, the ratio of arterial oxygen partial pressure to fractional inspired oxygen fraction (PaO_2/FiO_2) less than 300 mmHg, or the presence of infiltrates in more than half of the lung field within 1 or 2 days after the initiation of symptoms [15]. Those who have COVID-19 but do not meet the above criteria are considered as "moderate". Fever was described as an axillary temperature of 37.5 °C or higher. Lymphocytopenia was identified as a lymphocyte count of less than 1500 cell/mm^3. Thrombocytopenia was characterized as a platelet count of less than 150,000 cell/mm^3. Acute kidney insufficiency was defined based on the highest serum creatinine level or urine output criteria consistent with the Kidney Disease Improving Global Outcomes (KDIGO) guidlines [16].

Statistical analysis: If normally distributed, continuous variables were expressed as mean; otherwise, they were summarized as medians and interquartile ranges. Categorical variables were presented as counts and percentages. The laboratory results were also evaluated to determine whether the measurements were outside the normal range. Statistical analyses were performed using SPSS software, Version 19.0 by employing different tests, such as Chi-squere, Mann-Whitney, and Fisher exact tests as well as Spearman's rho correlation.

Findings

In this study, 75 immune-deficient patients with COVID-19 infection were surveyed. All participants were tested with nasopharyngeal swab, of whom 39 cases were positive for COVID-19. Other 36 patients were considered as infected according to their lungs involvement shown in CT scan. The mean length of hospitalization was 10.82 days, ranging from 3 to 36 days (median: 8.0 days).

Among all patients, there were 32 patients with a kidney transplant, 23 patients with malignancies, and 19 patients with autoimmune disorders. One patient had both malignancy and multiple sclerosis. Also, 56.8 % of patients were male with a mean age of 59.37 years, and 43.2 % were female with a mean age of 50.3 years. Based on the present study results, gender and age had no significant effect on mortality rate among patients ($p > .05$). Autoimmune disorders included systemic lupus erythematosus (SLE), multiple sclerosis (MS), myasthenia gravis, psoriasis, pyoderma gangrenosum, rheumatoid arthritis (RA), systemic sclerosis, and Wegener's granulomatosis. By the end of the research, 51 (68%) individuals were discharged, and 24 (32%) cases were dead (Figure 1). According to the statistical results, there was no meaningful association between the mortality rate and immune deficiencies in patients in three groups of autoimmune disorders, kidney transplants, and cancer ($p > .05$). Among 24 patients with cancer, the mortality rate in 20 cases with solid tumors and 4 cases with hematological malignancies was 25 and 50%, respectively. Overally, the mortality rate among 375 COVID-19 patients admitted to the hospital during the study period was 13.3 % (50 patients). Also, the mortality rate

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among 300 immunocompotent patients was 8.6% (26 patients), which was significantly less than the mortality rate of 32% (24 patients) among immunocompromised patients ($p < .05$).

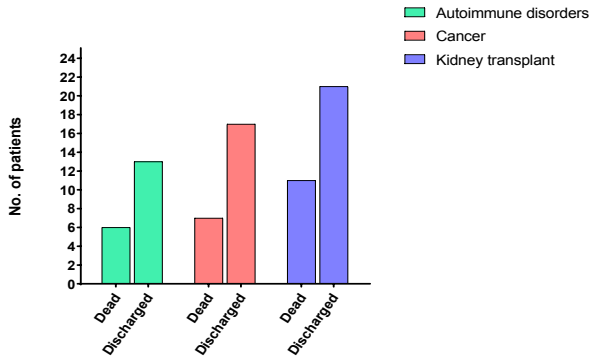

Figure 1) Final outcomes according to patients' hospital records

Dyspnea was the most common (64%) symptom among patients, followed by cough (53.3%), fever (40%), myalgia (25.3%), gastrointestinal tract (GIT) symptoms (12%), and headache (5.3%).

Leukopenia was present (5000-10000 per mcL of blood) in 24 (32%) patients, and lekocytosis was present in 16 (21.3%) patients. Also, 48 (64%) patients had lymphocyte counts below the normal range (20-40% of overall WBC count or 1000-2000 per mcL of blood) [17]. Among 62 patients tested, hemoglobin was below the normal range in 34 patients [18]. Also, 55 patients underwent liver functional tests, and 13 individuals had varying degrees of liver function abnormality with alanine aminotransferase (ALT) or aspartate aminotransferase (AST) above the normal range [19]. In addition, 43 (57.3%) patients had varying degrees of kidney function failure with high serum creatinine level [20]. All participants were examined for C-reactive protein (CRP); 71 out of 75 patients had elevated levels of CRP [21]. Also, 14 (32%) individuals needed an invasive ventilator to support ventilation.

According to the statistical analysis results, there was a meaningful association between O2 saturation level (p= .025) and lymphocyte count (p= .038) at admission time and the outcome of patients. However, the findings showed no significant association between CRP levels (p= .798) and WBC count (p= 0.763) at admission time and the outcome of patients.

According to chest CT imaginging at the time of admission, ground-glass opacity was found in 39 (52%) patients, consolidation in 20 (26.6%) patients, and both consolidation and ground-glass opacity in 15 (20 %) patients. There was only one patient with pleural effusion and ground-glass opacity in her record.

Among all participants, 37 were admitted to the intensive care unit (ICU), and 28 patients were intubated, of whom 24 intubated patients were dead. Based on the Fisher exact test results, there was no significant association between the mortality rate of patients in three groups (autoimmune disorders, kidney transplants, and cancer) and ICU admission or intubation.

Mortality rate of patients with ICU admission and intubation is ahown in Figure 2.

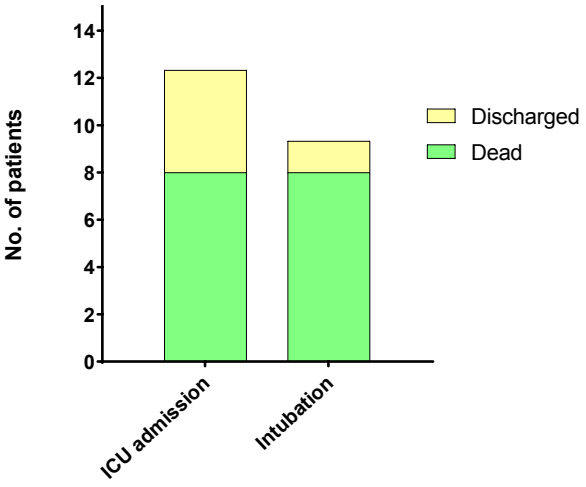

Figure 2) Mortality rate of patients with ICU admission and intubation

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Patients received antiviral treatment, including oseltamivir, hydroxychloroquine, Kaletra, intravenous immunoglobulin (IVIG), interferon, ribavirin, favipiravir, and sofosbuvir. For most patients, the duration of antiviral treatment was 7 days. Most patients received antibiotic treatment. The antibiotics used were often combination regimens, including ceftriaxone, azithromycin, vancomycin, meropenem, ciprofloxacin, teicoplanin, linezolid, colistin, caspofungin, and levofloxacin.

Table 1) Results of laboratory tests.

Disease	Laboratory Tests	Outcome						P value
		Discharge			Death			
		Mean	SD	Median	Mean	SD	Median	
Autoimmune	O2 saturation	90	5	90	89	8	90	.758
	CRP (mg/L)	38	24	41	59	50	48	.429
	WBC count (per mcL of blood)	6954	3385	5200	7683	5137	6850	.792
	Lymphocyte count (lymphocyte/mcL)	19	11	16	14	7	14	.354
Kidney transplant	O2 saturation	93	5	94	90	4	91	.067
	CRP (mg/L)	38	20	34	31	15	32	.462
	WBC count (per mcL of blood)	8448	5261	6600	6882	3057	6700	.606
	Lymphocyte count (lymphocyte/mcL)	17	7	16	16	14	10	.169
Cancer	O2 saturation	89	8	90	80	10	84	.026
	CRP (mg/L)	34	14	27	40	15	35	.367
	WBC count (per mcL of blood)	8024	3986	7000	10529	9741	7000	1.00
	Lymphocyte count (lymphocyte/mcL)	17	7	20	24	30	8	.279
Total	O2 saturation	91	6	92	87	8	88	.025
	CRP (mg/L)	37	19	32	41	29	37	.798
	WBC count (per mcL of blood)	7925	4390	6700	8146	6091	6750	.763
	Lymphocyte count (lymphocyte/mcL)	18	8	16	17	19	10	.038

McL: microliter

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A significant number of patients had underlying diseases, including blood hypertension (46.9%), diabetes mellitus (24.3%), ischemic heart diseases (0.06%), and thyroid disorders (0.05%). Patients' symptoms were recorded at admission time. The mortality rate of patients with hypertension, diabetes mellitus, ischemic heart diseases, thyroid disorders was 26.4, 44.4, 80, and 25%, respectively. Based on the obtained findings, there was no significant association between these underlying diseases and the mortality rate ($p > .05$). Also, there was no statistical association between the length of hospitalization and the results of laboratory tests, including O2 saturation, CRP, WBC count, and lymphocyte count.

Discussion

COVID-19 caused by SARS-CoV-2 is considered as a global public health concern. It is a respiratory infection resulting in high mortality and morbidity rate worldwide [22-25]. Immunocompromised patients are at higher risk of COVID-19 infection. Thus, there are serious concerns about the disease-related complications among these patients who are more likely to develop severe outcomes [7-9]. This study aimed to descriptivly explore the symptoms, prognosis, laboratory tests, clinical findings, and outcome of 75 immunocompromised patients suffering from COVID-19 infection, admitted to Labbafinejad hospital, Tehran, Iran.

All patients were tested for SARS-CoV-2 with nasopharyngeal swab, of whom just 39 were positive. Other 36 patients were considered as infected according to their lungs involvement shown in CT scan. Most earlier studies have just used PCR for the diagnose of SARS-CoV-2 infection. According to a study by Li and Xia (2020), chest CT could be a suitable method for the fast diagnosis of COVID-19 infecion; however, chest CT is not able to identify particular viruses and differentiate between them [12].

In this study, among 75 patients, the number of men was significantly higher than the number of women. Based on the results, gender and age had no significant effect on mortality rate of patients. However, a previous study by Yang et al. (2020) discussed that elderly people were more vulnerable to COVID-19; this may be due to the presence of more comorbidities in this group [26]. This incompatibility between the present and other studies findings may be related to the neutralization of gender and age impact on mortality rate by the immunosuppressed status of patients. Also, MERS-CoV and SARS-CoV tend to infect more men than women [1, 27-28]. Decreased susceptibility of women to infection may be ascribed to sex hormones and the X chromosome, which play a key role in innate and adaptive immunity [26, 29]. Interestingly, a Chinese survey indicated that the age of patients experiencing severe conditions was higher than that of patients experiencing mild or moderate conditions [2]. Another study suggested that the disease could affect everyone in different age groups, while seeming to be milder among pediatric patients [9]. It could be attributed to lower rate of smoking, fewer comorbidities, and lower expression level of ACE2 receptor.

By the end of the research, 68% of patients were discharged, and 32% were dead. This mortality rate was much higher than those reported in other studies. Chen et al. (2020) reported that among 99 patients, the mortality rate was about 11.1% [1]. In a Chinese report surveying 1099 patients, the case fatality rate was 1.4% [2]. In another study on 41 patients, 6 (14.6%) patients died [4].

In this study, there was no meaningful association between the mortality rate and immune deficiencies in patients in three

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Table 2) Demographic and clinical characteristics of patients.

Index		Kidney Transplant	Autoimmune Disorders	Cancer Disease	Total
No. of patients	Female	10	15	7	32
	Male	22	4	16	42
Mean age (age period)		49 (27-73)	51.2 (19-83)	68.3 (39-85)	55.8 (19-85)
length of hospitalization (day)		11.75	10.05	9.13	10.51
No. of patients with ICU admission		16	10	11	37
No. of patients with intubation		12	7	9	28
PCR test	Positive	19	12	7	39
	Negative	13	7	17	36
Clinical symptoms	GI symptoms	7	1	1	9
	Cough	14	15	11	40
	Dyspnea	17	7	17	41
	Headache	3	1	0	4
	Myalgia	10	7	4	21
	Fever	15	8	7	30
Laboratory data	First WBC count (per mcL of blood)	7909	7226	10845	8676
	Lymphocyte count (lymphocyte/mcL)	1265	1258	1912	1470
	No. of patient with lymph count <1000	21	12	12	59
	CRP (mg/L)	35.43	45.68	35.66	38.10
	First O2-sat level	91.84	90.05	85.79	89.45
	Creatinine (mg/dL)	2.63	1.59	1.75	2.09
Mortality (%)		11 (34.37)	6 (31.57)	7 (29.16)	24 (32)

groups of autoimmune disorders, kidney transplants, and cancer. Among three groups of patients (autoimmune disorders, kidney transplants, and cancer), ICU admission and intubation had no significant effect on the mortality rate of patients in comparison with each other.

Previous studies have suggested that patients with chronic comorbidities are more susceptible to be infected with a virus, as a result of impaired immune responses in these group [27-31]; however, it

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is in contrast with other studies claiming that immunodeficient patients are not at higher risk of COVID-19 infection [7,10]. D'Antiga expressed that immunosuppressive treatment had adverse impact on neutrophil function, as well as on B and T-cells function, which could put patients at elevated risk of serious infections caused by several viruses, including adenovirus and influenza. However, it does not appear to have a role in conditions like COVID-19 given the etiology of the coronavirus family [10].

T cells, CD8+ T cells, and CD4+ T cells, play a key role in the development of some infections, especially β-coronaviruses infections. Virus-specific antibodies are produced by B cells activated by CD4+ T cells. Discharge of CD4+ T cells may decrease lymphocytes and cytokine production in lung tissue and neutralize antibody utilization. This condition could cause severe interstitial pneumonitis and delay the clearance of the virus. In some reports, humoral immunity has been suggested to play a key role in controlling the persistent phase of COVID-19 infection. Also, survived patients with MERS-CoV have been reported to have more antibodies [32]. Recent studies have demonstrated that the T-helper 1 type response has a significant role in the control of SARS-CoV, MERS-CoV, and maybe SARS-CoV-2 [33]. Thus, humoral and cellular immunodeficiency may alter the clinical findings and outcome of COVID-19 patients. A significant number of patients had underlying diseases, including blood hypertension, diabetes mellitus, ischemic heart diseases, and thyroid disorders. Based on the findings, none of these underlying diseases could affect the mortality rate. Although the mortality rate of diabetic patients was high (44.4%) but not statistically significant, it is presumably due to the low number of our patients. A case-control study on seasonal influenza conducted by Hong et al. (2014) demonstrated that diabetes mellitus and chronic cardiac disease were associated with more complications [34]. Another study demonstrated that diabetes mellitus and cardiac disease were the risk factors of MERS-CoV infection [35]. Lubetzky et al. (2020) reported that among patients with kidney transplants and COVID-19, comorbidities could affect the rate of admission to hospital and the disease severity, especially cardiac diseases [8]. In a review study by Chan et al. (2020), underlying comorbidities like hypertension, diabetes, and coronary heart disease were suggested to be related to severe presentation [6].

Dyspnea was the most common symptom among patients, followed by cough, fever, myalgia, GIT symptoms, and headache, this finding is in contrast to the finding of some previous studies introducing fever as the most common symptom. It may be due to the effect of immunosuppression condition on the manifestation of fever. In a study by Chen et al. (2020), the most common clinical findings were as follows: fever (83%), cough (82%), dyspnea (31%), myalgia (11%), headache (8%), and GIT symptoms (3%) [1]. Alkaline et al. (2020) surveyed 36 patients with kidney transplants and confirmed COVID-19. In their study, fever was the most common symptom among patients (58%), and diarrhea was reported in 22% of patients [31]. Guan et al. (2020) reported that the most common symptom among patients was fever (88.7%), followed by cough (67.8%). Nausea, vomiting, and diarrhea (8.8%) were less frequent [2].

Earlier studies have shown that fever and cough were the most frequent symptoms, and gastrointestinal complains were infrequent, indicating a variance in viral tropism in comparison with SARS-CoV, MERS-CoV, and seasonal influenza [2, 4, 36-37].

The present study results share several similarities with previous studies reporting

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elevated levels of AST, ALT, BUN, creatinine, and CRP. Changes in levels of hemoglobin, WBC, and lymphocyte count have also been reported in other studies [1-2, 4, 8, 31,38]. A Chinese study explained that patients with severe conditions presented more noticable paraclinical abnormalities (like lymphocytopenia and leukopenia) than others with mild or moderate diseases [2]. In most patients, the absolute lymphocytes count was reduced. This finding indicated that, similar to SARS-CoV, SARS-CoV-2 affects lymphocytes, especially T-cells. SARS-CoV could speard via the respiratory mucosa and involve other cells. The viruses then generate some inflammatory responses and change white blood cells, like lymphocytes [1, 39]. This mechanism could also be attributed to novel coronavirus.

Among all patients, there was a meaningful association between O2 saturation level and lymphocyte count with the outcome of patients. However, these findings show that there is no significant association between CRP levels and WBC count with the outcome of patients. Also, there was no significant association between the length of hospitalization and the results of laboratory tests, including O2 saturation, CRP, WBC count, and lymphocyte count. Guo et al. (2019) surveyed the clinical findings of patients with viral pneumonia and found that the absolute counts of CD3+ T cell, CD3+ CD8+ T cell, and CD3+ CD4+ T cell in the survivor group were notably higher than in the dead group [40].

Chest imaging is very important for diagnosis [38]. According to CT scans, ground-glass opacity was found in 52% of patients, consolidation in 26.6% of patients, and both consolidation and ground-glass opacity in 20% of patients. There was only one patient with pleural effusion and ground-glass opacity in her record. In a study by Chen et al. (2020), 74 (75%) individuals had bilateral pneumonia, 14 (14%) patients had multiple mottling and ground-glass opacity, and one (1%) patient had a pneumothorax [1]. Also, Guan et al. (2020) expressed that the most common patterns on chest CT scans were ground-glass opacity (56.4%) and patchy bilateral shadowing (51.8%) [2]. Huang et al. (2020) demonstrated that the dominant findings of chest CT images in their patients were bilateral multiple lobular, subsegmental areas of consolidation, and bilateral ground-glass opacity [4].

Drugs used for COVID-19 patients include oseltamivir, hydroxychloroquine, Kaletra, IVIG, interferon, ribavirin, favipiravir, sofosbuvir, ceftriaxone, azithromycin, vancomycin, meropenem, ciprofloxacin, teicoplanin, linezolid, colistin, caspofungin, and levofloxacin. Hydroxychloroquine is a widely used antimalarial drug, which induces immunomodulatory effects and is used to treat autoimmune conditions. This agent has antiviral activities based on previous reports [41]. The majority of patients in this study received hydroxychloroquine. However, the evidence of its efficacy is limited. The use of hydroxychloroquine in treating SARS-Cov-2 is controversial [8]. Akalin et al. (2020) used hydroxychloroquine and tocilizumab for patients with kidney transplants and COVID-19 [31]. Oseltamivir is a neuraminidase inhibitor which prohibits the release of virus from human cells and prevents the virus spread so that the virus could not cross mucosa of the respiratory tract. This drug is broadly used due to the concern of influenza, which is clinically similar to COVID-19 [41]. By inhibiting polymerase activity, ribavirin may prohibit the initiation and elongation of RNA fragments and inhibit the synthesis of protein. Typically, it is used in combination with an interferon product to treat the RNA virus [42]. Favipiravir is a nucleoside precursor. It has been prescribed for the treatment of influenza in Japan [43-44]. Intracellular phosphoribosylation results

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in a triphosphate form that is adapted by the viral RNA-dependent RNA polymerase [45]. IVIG is a polyclonal immunoglobulin G, derived from healthy donors. It is a safe immune-modulating agent for all age stages [42]. The use of IVIG is suggested to increase the effectiveness of anti-infection therapy for patients with sever conditions [39]. Based on previous studies, interferons could reduce the viral replication of SARS in vitro [6].

The present study had several limitations. It was a descriptive study on 75 immunosuppressed cases, in which there was no control on immune-competency to compare clinical manifestation and laboratory results. Because of the small sample size, the outcomes could not be attributed to the whole society.

Conclusion

This study showed a 32% mortality rate among immunocompromised patients, which was not affected by gender and age. In conclusion, it seems that COVID-19 has a poorer prognosis and more severe clinical course in immunocompromised patients regardless of age, gender, and underlying diseases. Further research with larger sample sizes and control groups is needed to achieve more accurate results.

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