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COVID-19 Adverse Outcomes in Immunocompromised Patients

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is a devastating viral pandemic infecting millions of people with a wide range of symptoms from fever to death. It has been suggested that immunocompromised patients are at a higher risk of severe disease, poor clinical outcomes, and mortality. However, these patients' risk factors and COVID-19-related outcomes are not well characterized.
Objectives: We evaluated the COVID-19-related outcomes among immunocompromised patients ranging from solid tumors, hematological malignancies, and HIV to autoimmune disease and transplant recipients who received immunosuppressive agents. We also aimed at finding risk factors related to mortality among immunocompromised patients with COVID-19.
Methods: This cross-sectional study was conducted in Khansari Hospital, Iran between March and November 2021. We included immunocompromised patients with nasal swab positive SARS-CoV-2 polymerase chain reaction (PCR) results in the study. Patient outcomes, including hospitalization ward and the mortality rate, were assessed till three months after COVID-19 infection were evaluated in all patients. Moreover, the relation between risk factors and the rate of the mortality rate was analyzed in immunocompromised patients with COVID-19.
Results: A total number of 74 immunocompromised patients with solid tumors, hematologic malignancies, autoimmune diseases, acquired immunodeficiencies, and solid-organ transplant recipients were included in the study. Results indicated that the male gender and ICU hospitalization significantly increase the mortality risk. Surprisingly, chemotherapy is associated with a lower risk of mortality.
Conclusions: Identifying the risk factors can improve the decision-making on cancer patients' management during the COVID-19 infection. A further large cohort of patients would be required to identify risk factors relating to poor clinical outcomes and mortality rates in immunocompromised patients with COVID-19.

Keywords: Coronavirus Disease-2019, Immunocompromised Patients, Immunosuppressed Patients, Cancer, Mortality

1. Background

Coronavirus disease 2019 (COVID-19) is an emerging and rapidly evolving infectious disease that has spread worldwide since December 2019 (1). In humans, COVID-19 infection can lead to a wide range of respiratory symptoms, from mild signs like dry coughs to severe ones such as acute respiratory distress syndrome (ARDS) (2). Among the infected cases, 1% - 3% progress to multi-organ failure and finally be overwhelmed by the disease. Although all people are at risk of COVID-19 infection, some individuals are more susceptible to developing severe disease. Older age and some comorbidities, including diabetes, hypertension, or cardiac disease, increase the hospitalization period and intensive care unit (ICU) requirement (3).

Preliminary reports suggested that patients with cancer have a higher risk of severe disease and COVID-19-related mortality (4). A study by Kim et al. reported a 24% mortality related to COVID-19-induced pneumonia in cancerous cases compared with 3% in non-cancerous cases (5). Williams et al. declared that most malignancies cause a > 5% mortality risk in case of COVID-19 infection (6). As different malignancies, radiotherapy and chemotherapy cause immune suppression to different degrees, patients undergoing radical radiotherapy or active chemotherapy and those with hematologic malignancies are more susceptible to ARDS (7).

Immunocompromised statuses like immunosuppressive treatments for cancer treatments or transplantation, autoimmune diseases, and such as human immunodeficiency virus (HIV) cause concern about severe COVID-19 consequences (8). However, some scientists suggested that the attenuated immune system in patients with cancer

could alleviate COVID-induced inflammatory response (4). Despite the initial beliefs about the increased risk of severe COVID-19 in immunosuppressed patients, receiving immunosuppressive therapies for autoimmune diseases decrease the ARDS risk due to reducing the excessive inflammatory responses (9). COVID-19 hospitalized patients with autoimmune diseases do not show any increased risk of ICU requirement, intubation, or mortality compared to other patients (10). CD4+ cells depletion in HIV cases acts as a double-edged sword that compromises the anti-viral defense and eases the cytokine storm; thus, there are controversial findings regarding the COVID-19 infection outcome in HIV cases (11). Overall, studies warn that HIV patients are at a higher risk of hospital admission and mortality for COVID-19 (12).

The pandemic has significantly affected transplantation activity worldwide. Transplant communities suggested postponing non-urgent transplantations, such as kidney transplants, whereas performing life-saving transplantations like lung, heart, and liver transplants (13). This decision increased the mortality risk on the waiting list. Besides, the mortality rate in solid organ transplantation recipients reached 35% (14). Similarly, autologous and allogeneic recipients of hematopoietic stem cell transplantation have shown poor overall survival (15).

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2. Objectives

Here, we described the characteristics, clinical state, and COVID-19-related outcomes in patients with cancer, autoimmune diseases, HIV infection, and transplantation.

3. Methods

3.1. Study Design and Patients

We conducted a cross-sectional, single-center, descriptive observational study in Khansari Hospital, Iran between March and November 2021. Immunosuppressed patients with cancer, autoimmune disease, HIV, and transplant recipients who had positive SARS-CoV-2 PCR results from nasal swab specimens were included in the study. Patients with diabetes, hypertension, asthma, chronic obstructive pulmonary disease (COPD), liver failure, and renal failure were excluded from the study. According to medication history regarding chemotherapy and immunosuppressive drugs use, the included patients were categorized into three groups: Patients who completed the chemotherapy course, those who had been receiving chemotherapy meanwhile, and those who had been receiving immunosuppressive agents at the time of COVID-19 infection. The group receiving immunosuppressive agents included patients who had undergone transplantation and received anti-rejection therapies, as well as HIV and autoimmune patients. All patients with cancer had been subjected to standard chemotherapy regimens according to diagnosis. Patients did not receive combination therapy, targeted therapy, and immunotherapy. Radiotherapy was just performed on two patients with lung and breast cancers.

Patient outcomes were followed up till three months after the COVID-19 infection. The hospitalization ward and the mortality rate were evaluated in all patients. Ethical approval was waived by the local Ethics Committee of Arak University of Medical Sciences (IR.SBMU.REC.1399.108). In view of the study's retrospective nature, all the procedures performed were part of routine care.

3.2. Statistical Analysis

In the descriptive analysis, the categorical variables were reported as frequencies and percentages, while the continuous variables were expressed as means ± standard deviation (SD). The difference in frequency of variables between outcomes was analyzed by the chi-square test. For estimating the mortality risk, the odds ratio (OR) and its 95% confidence interval (CI) were calculated. The significance level was set at 0.05. The data were analyzed using SAS (version 9.4; SAS Institute Inc., Cary, NC, USA).

4. Results

4.1. Patients

A total number of 74 patients were included in this study. The clinical characteristics of the patients are presented in Table 1. The mean age of the patients was 55.74 ± 11.69. Thirty-five (47.3%), 25 (33.8%), 6 (8.1%), 3 (4.1%), and 5 (6.8%) patients were diagnosed with solid tumors, hematologic malignancies, autoimmune diseases, acquired immunodeficiencies, and transplantation, respectively. Fifty-nine (79.17%) cases expired and 15 (20.3%) experienced remission.

4.2. Association of Factors with Outcome

Variables including gender, ward of hospitalization, and previous and current disease-related treatment had significant associations with mortality in univariate analysis (P-values = 0.03, 0.01, and 0.01) (Table 2). Based on the results, in male cases, the proportion of mortality was higher than remission (80% vs. 49.15%). Also, male cases had a 4.13 times higher risk of mortality than female cases [OR = 4.13, CI 95% (1.05 - 16.19), P = 0.03]. The outpatients had a significantly lower mortality risk than the ICU hospitalized patients [OR = 0.03, CI 95% (0.001 - 0.70), P = 0.002]. Surprisingly, patients who underwent chemotherapy had a lower

Table 1. Clinical Characteristics of Patients (N = 74) [a]

Characteristics	Values
Age	55.74 ± 11.69
< RL	36 (48.6)
≥ RL	38 (51.4)
Gender	
Male	41 (55.4)
Female	33 (44.6)
Disease diagnosis	
Solid tumor	35 (47.3)
Hematologic malignancy	25 (33.8)
Autoimmune disease	6 (8.1)
Acquired immunodeficiency	3 (4.1)
Transplant related to disease	5 (6.8)
Treatment process	
With chemotherapy	50 (67.6)
Without chemotherapy	19 (25.7)
Immunosuppressive drugs	5 (6.8)
Unit	
Hospital department	46 (62.2)
ICU	11 (14.9)
Outpatient	17 (23)
Outcome	
Remission	59 (79.7)
Death	15 (20.3)
Reference level: 60 (y)	

Values are expressed as Mean ± SD or No. (%).

risk of mortality than those without chemotherapy [OR = 4.46, CI 95% (1.33 - 15), P = 0.01]. Significant variables in univariate analysis were not influential on mortality in multiple analyses.

5. Discussion

Various small and large cohorts investigated the mortality risk factors in malignant patients with COVID-19 infection. They introduced age, sex, and comorbidities as the chief risk factors (16).

Although senility and comorbidities are the main factors associated with mortality in COVID-19 cases, the male sex is also related to worse outcomes and a higher mortality rate (17). Several studies have claimed that males are more likely to exhibit enhanced disease severity, prolonged hospitalization, and mortality than females (18). Similarly, in the present study, the mortality rate was higher in males than females, which was in accordance with other studies. This sex-specific bias in COVID-related mortality is due to the higher expression and activity of the angiotensin convertase enzyme (ACE2) protein in males than in females (19, 20).

During the COVID-19 pandemic, several cohort studies were conducted about the impact of cancer on the COVID-19 outcome and mortality. Abouesheia et al. indicated a high frequency of long-term hospitalization, ICU admission, and mortality in patients with cancer compared to non-cancer patients (21). Consuming that cancer generally worsens the COVID-19 outcome, in the present study, we evaluated the impact of cancer type and chemotherapy on the hospitalization ward and the mortality in patients with cancer.

Some studies have stated that cancer type might affect COVID-related outcomes in cancerous patients (22). For instance, patients with hematological malignancies showed an increased risk of COVID-19-related mortality compared to solid tumors (23). It may be because, unlike solid tumors, hematological malignancies can directly compromise the immune system (24). Despite other studies, the present study declared no significant difference in COVID-19 outcomes in cancer types, whether solid tumors or hematological malignancies. It is probably due to the insufficient sample size.

In addition to the mentioned risk factors of COVID-19 infection in cancer cases, it is anticipated that chemotherapy can affect COVID-19 outcomes too. Some studies believe that anti-cancer therapy makes patients more susceptible to COVID-19 adverse outcomes due to the suppressed immune system (25). On the other hand, Jee et al. and Lee et al. reported that although cancer cases were at a higher risk of poor outcomes, there was no significant correlation between the mortality rate and chemotherapy (26, 27). Surprisingly, in the present study, patients who underwent chemotherapy showed a lower mortality rate than those without chemotherapy. There is a possibility that chemotherapy agents inhibit the virus replication, or it is again due to the insufficient sample size.

There are some recommendations for the management of patients with cancer during the pandemic. Chemotherapy regimens with low-intermediate risk for febrile neutropenia and administration of low-toxicity agents in metastatic patients could reduce COVID-19 risk in patients with cancer. Also, it has been suggested that delaying radiotherapy or applying alternative therapy, and discontinuing target therapies with more than 10% leukopenia could help cancer patient management in COVID-19 (28).

Although studies warn that HIV patients are at a higher

Table 2. Association of Variables with Patients Mortality Status

Variables	Univariate Analysis				Multiple Analysis	
	Death, No. (%)	Remission, No. (%)	OR (CI 95%)	P-Value	AOR (CI 95%)	P-Value
Age			0.64 (0.20 - 2.03)	0.45		
< 60	6 (40.0)	30 (50.85)		0.45		
≥ 60 (RL)	9 (60.0)	29 (49.15)				
Gender			4.13 (1.05 - 16.19)	0.03 [a]	1.72 (0.79 - 3.70)	0.16
Male	12 (80.0)	29 (49.15)		0.03		
Female (RL)	3 (20.0)	30 (50.85)				
Disease diagnosis				0.32		
Stratum 1 vs stratum 5	8 (100.0)	27 (84.38)	3.4 (0.17 - 67.98)	0.23		
	0 (0.0)	5 (15.63)				
Stratum 2 vs stratum 5	7 (100.0)	18 (78.26)	4.45 (0.21 - 91.09)	0.17		
	0 (0.0)	5 (21.74)				
Stratum 3 vs stratum 5	0 (0.0)	6 (54.55)	NA	NA		
	0 (0.0)	5 (45.45)				
Stratum 4 vs stratum 5	0 (0.0)	3 (37.5)	NA	NA		
	0 (0.0)	5 (62.5)				
Hospitalization unit type				0.01 [a]		0.70
Section vs ICU	10 (66.7)	36 (85.71)	0.33 (0.08 - 1.32)	0.10	34.55 (inf)	0.93
	5 (33.3)	6 (14.29)				
Outpatient vs ICU	0 (0.0)	17 (73.91)	0.03 (0.001 - 0.70)	0.002	0 (inf)	0.92
	5 (100.0)	6 (26.09)				
Treatment process				0.01 [a]		0.09
Without chemo vs chemo	8 (53.33)	11 (20.37)	4.46 (1.33 - 15)	0.01	89.29 (inf)	0.95
	7 (46.67)	43 (79.63)				
Immunosuppressive drugs vs chemo	0 (0.0)	5 (10.42)	0.52 (0.02 - 10.55)	0.37	0.001 (inf)	0.96
	7 (100.0)	43 (89.58)				

Abbreviations: RL, reference level (60 y); AOR, adjusted odds ratio.
[a] Significant at 0.05.
[b] Stratum 1: Solid tumor, Stratum 2: Hematologic malignancy, Stratum 3: Autoimmune disease, Stratum 4: Acquired immunodeficiency, Stratum 5: Transplant recipients.

risk of mortality for COVID-19 (12), our results were contra versa. Once more, due to the low sample size.

5.1. Conclusions

Although the male gender and ICU hospitalization significantly increase the mortality risk, chemotherapy is associated with lower mortality risk. However, identifying the risk factors can improve the decision-making on cancer patients' management during the COVID-19 infection. Although the small sample size was a limitation of our study, all patients were followed during the treatment period and a minimum of three months after discharge. Our results would be valuable for designing future large cohort studies. Further studies with large sample sizes can provide reliable indications for managing immunocompromised patients during the COVID-19 pandemic.

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Footnotes

Authors' Contribution: SH. SH., A. H, conception and design; P. CH, analysis and interpretation of data; H. GH, draft-

ing the article or revising it critically for important intellectual content. All authors revised final approval of the version to be submitted for publication.

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