SHORT COMMUNICATION

Clinical characteristics of COVID-19-infected cancer patients, Isfahan, Iran

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Background: Cancer patients, as a highly vulnerable population, are receiving a great deal of attention in the current crisis of coronavirus 2019 (COVID-19). To date, shreds of evidence are not sufficient to the description of COVID-19 outcomes in patients with cancer. This study was performed to evaluate the demographic and clinical characteristics and subsequent outcomes of COVID-19 in cancer patients. **Materials and Methods:** A hospital-based study was conducted involving 66 cancer patients with a confirmed diagnosis of COVID-19 from January 15, 2020, to December 21, 2020, in Isfahan, Iran. The clinical information was collected by interview and medical records. The statistical analyses were performed to describe categorical variables as well as mean, standard deviation, median, and the interquartile range for quantitative variables. **Results:** In our study, 66 cancer patients with confirmed COVID-19 (age: 17–97 years; 50% female) were included. Leukemia and bone marrow cancer with a frequency of 25.7% were the most common types of cancer among them. Cancer patients mostly complained of fever, cough and fatigue, and shortness of breath. Among 76.9% of patients discharged from the hospital with relative recovery, 23% died; the most common cause of death was acute respiratory distress syndrome. Age, gender, and type of cancer did not affect cancer mortality. COVID-19 had no potential effect to increase the risk of side effects of anticancer therapies. **Conclusion:** The results of our studies revealed that cancer is an important risk factor for the higher rate of mortality in patients with COVID-19. These findings could help physicians for the management, treatment, and supportive care of COVID-19 cancer patients.

Key words: Coronavirus, COVID-19, neoplasms, retrospective case study, severe clinical events

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INTRODUCTION

In late 2019 and early 2020, an epidemic of new coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) infection, known as COVID-19, occurred in Wuhan, China, and has spread rapidly with large cases in the most countries of the world.[1,2] As of June 18, 2021, the World Health Organization (WHO) reported a total of 177,108,695 confirmed cases with 3,840,223 deaths.

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In the COVID-19 pandemic, cancer patients have been gained consideration as a highly vulnerable group. Cancer patients who receive systemic chemotherapy drugs appear to be at greater risk than those who do not receive chemotherapy drugs.[3] A recent investigation of 28 COVID-19 patients who had been previously diagnosed with cancer from three hospitals in Wuhan, China, found that patients with cancer had a higher risk for COVID-19 infection than those without cancer.[4] Another case report indicated that the case fatality rate reached 5.6% among cancer patients in comparison to 2.3% in the general population.[5] A cohort study in the USA, Canada, and Spain on patients with active or history of previous malignancy with confirmed SARS-CoV-2 infection showed that 30-day all-cause mortality was high among these patients.[6] However, some investigations are oppose and reported no evidence of an increase in mortality rate of cancer patients with COVID-19 compared to healthy patients with COVID-19.[3,7] Age, type of chemotherapy, higher presence of comorbidities, and type of cancer were found to be effective in influencing the rate of mortality.[8]

Other studies have also been performed regarding the prevalence and outcomes of COVID-19-infected cancer patients; however, most of them are single-center studies with a limited number of participants. On the other hand, recent systematic review and meta-analyses have also been published in this regard that included many studies from different regions of world;[9,10] however, only a few studies were included from Iran and Eastern Mediterranean region.[11,12] Due to this, the importance of further research on this topic in Eastern Mediterranean region is clear to receive effective and proper antitumor treatments in epidemic areas for cancer patients with COVID-19.

To this end, we aimed to design a retrospective case study in Isfahan, Iran, for the evaluation of the demographic and clinical characteristics and outcomes of COVID-19 patients with cancer and the assessment of cytotoxic chemotherapy effect on COVID-19 disease phenotype.

MATERIALS AND METHODS

Study design and definitions

A retrospective case study was conducted in 8 hospitals designated for COVID-19 patients in Isfahan, Iran, namely AL-Zahra, Sayyed Al-Shohada, Noor va Ali Asghar, Amin, Gharazi, Isabne Maryam Shahid Beheshti Ardestan, and Saheb Al-Zaman Shahreza hospitals. Cancer patients diagnosed with COVID-19 acute infection were identified between February 15, 2020, and December 21, 2020. In the study, patients that formerly diagnosed with cancer and had a PCR-confirmed SARS-CoV-2 infection were enrolled. Data were gained considering theWHO standardized data collection forms, which are retrieved from the medical records, including demographic characteristics, laboratory findings, clinical features, and chest computed tomography (CT) reports. All data were reviewed by three physicians (pulmonologist, oncologist, and radiologist). This study was approved by the Ethics Committee of Isfahan University of Medical Sciences (No. IR.MUI.RESEARCH.REC.1399.004) and patients have agreed to use the medical record when they are admitted to the hospital.

Statistical analysis

We used percentage to describe categorical variables as well as mean, standard deviation, median, and the interquartile range for quantitative variables. We also used regression logistics to investigate the associated factors with death considering significance level of 5% using IBM® SPSS® Statistics software, Tokyo, Japan.

All chest CT images were acquired using 16-slice Philips scanner, with low-dose protocol, with the patient in supine position, and at full inspiration, and without the injection of contrast. The images were reviewed by a radiologist with 5 years of experience in thorax imaging. The following characteristics were recorded for each CT scan: pattern, distribution (craniocaudal and transverse), and extent of disease according to semiquantitative scoring system. Furthermore, each CT scan was subclassified according to published RSNA guideline to four groups including typical, indeterminate, atypical, and negative.

RESULTS

Clinical characteristics

A total of 66 cancer patients with COVID-19 were included in the study, half of whom were female and their age was ranged from 17 to 97 years. They were admitted to 8 designated hospitals for the treatment of COVID-19 between February 15, 2020, and August 31, 2020. Clinical and demographic characteristics of the COVID-19-infected cancer patients are presented in Table 1. The majority of patients (82.6%) enrolled in the study were residents of Isfahan city.

The results showed that 71.2% of patients had solid cancer, while the most common types of cancer were leukemia and bone marrow (25.7%) and breast cancer (18.1%) [Figure 1]. The most common symptoms of patients at the time of hospitalization were fever, cough, fatigue, and shortness breath.

The challenge that cancer patients with COVID-19 in this study encounter is suffering from chronic diseases such as diabetes, chronic cardiovascular and cerebrovascular disease, and chronic pulmonary disease. About one-fifth of cases were nosocomial infections and 30% of patients had

Table 1: Demographic and baseline clinical characteristics of cancer patients with COVID-19 (*n*=66)

Characteristic	*n* (%)
Age (years), mean (SD)	61.2 (17.2)
Gender (female)	33 (50.0)
Stage 4	
Yes	18 (27.3)
No	39 (45.5)
Unknown	18 (27.3)
Chemotherapy/radiotherapy	
Chemo	26 (39.4)
Radio	5 (7.6)
Both	14 (21.2)
None	15 (22.7)
Unknown	6 (9.1)
Target immunotherapy	
Yes	59 (89.4)
No	1 (1.5)
Unknown	6 (9.1)
Last chemotherapy (day)	
Mean (SD)	376.3 (1023)
Median (range)	7 (0-4745)
Last radiotherapy (day)	
Mean (SD)	431.3 (1035)
Median (range)	0 (0-4745)
Last target therapy	
Mean (SD)	30.4 (235.6)
Median (range)	0 (0-1825)
Source of infection	
Contact person COVID-19 positive in the community	46 (69.7)
At the time of hospitalization	14 (21.2)
Unknown	6 (9.1)
Co-morbidities, *n/N* (%)	
Diabetes	6/66 (9.1)
Chronic cardio vascular	9/60 (15.0)
Cerebos vascular	0/60 (0)
Hypertension	6/60 (10.0)
Chronic lung disease	4/66 (6.1)
Chronic liver disease	0/66 (0)
Symptoms on admission, *n/N* (%)	
Fever	37/66 (56.1)
Cough	20/66 (30.3)
Fatigue	31/59 (52.5)
Shortness breath	41/66 (61.2)
Muscle pain	9/66 (13.9)
Diarrhea	11/60 (18.3)
Chest pain	14/59 (23.7)
Symptoms until hospitalization, *n/N* (%)	
0=day of hospitalization	10 (16.95)
1	19 (32.2)
2	4 (6.78)
3	5 (8.47)
4	3 (5.08)
5	4 (6.78)
6	1 (1.69)
7	7 (11.86)
10	1 (1.69)
11	1 (1.69)
12	1 (1.69)
14	2 (3.39)
21	1 (1.69)
Severe shortness of breath	9/60 (15.0)
Pulmonary embolism	3/60 (5.0)
Severe symptoms	18/60 (30.0)
Diagnosis until symptoms (days), mean (SD)	
0	54/59 (91.5)
≥1	5/59 (8.5)

SD=Standard deviation

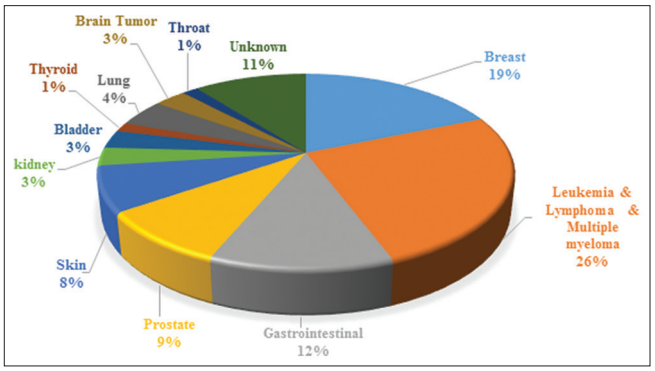

Figure 1: Types of cancer in cancer patients with COVID-19

severe symptoms; however, 91.5% of them were diagnosed on the 1st day of COVID-19 infection [Table 1].

The 49 patients (72.7%) underwent surgery after a cancer diagnosis. About 68.1% of patients had received at least one antitumor procedure [Table 1]. There are two groups of patients: those who were hospitalized to receive antitumor therapy (21.2%) and those who lived in the community (69.7%).

Clinical laboratory results

The complete blood count results showed 77.1% of patients suffered from anemia, 54.5% from leukopenia, and 60% from lymphopenia. High levels of alanine aminotransferase were detected in 13% of patients and high levels of aspartate aminotransferase were observed in 34.8% of patients. The lactate dehydrogenase levels were increased in 95.8% of patients. Elevated highly sensitive C-reactive protein levels were observed in 82.5% of patients. D-dimer was checked in 10 patients, 9 of whom (80%) showed elevated levels.

Chest computed tomography findings

Based on the RSNA guideline, typical, intermediate, atypical, and negative patterns of patients were interpreted on chest CT scan, and the chest CT imaging of 35 patients (53%) was not available. Bilateral involvement showed in 17 patients (25.7%) and the six cases showed unilateral involvement. All patients with abnormal chest CT showed a ground-glass opacity pattern (GGO) [Table 2].

Treatment

Among 66 patients, approximately 25% of patients were admitted to the intensive care unit (ICU), while 10% were ventilated because of progressive hypoxia, but in general, 80% of them underwent oxygen therapy. Hydroxychloroquine (HCQ), an antilupus erythematosus drug, plays a role in immunity regulation, antithrombotic activity, and inflammation improvement. HCQ has been commonly used in patients with COVID-19 and also was utilized in our patients. Meropenem or imipenem and HCQ were the most prescription drugs, though 18.5% and 53% of patients did not receive antiviral and corticosteroids, respectively [Table 3].

Systemic corticosteroids including dexamethasone, hydrocortisone, methylprednisolone, and Symbicort were prescribed to 32 patients (48.4%). 8 patients (12.1%) consumed a combination of some systemic corticosteroids [Table 3].

Complication

Among 66 cancer patients with COVID-19, 15 patients (23%) died and 50 patients (76.9%) were discharged from the hospital with partial recovery. Patients suffered from complications such as acute respiratory distress syndrome (ARDS) (9, 13.6%), cerebrovascular accident (2, 3%), and pulmonary embolism suspected (3, 4.5%). The most common cause of death was ARDS followed by stroke, heart failure and, pulmonary embolism. Two of the patients died due to cancer complications.

Among 30 patients with stage I/II/III, 12 patients (40%) showed severe symptoms and 9 patients (30%) died. On the other hand, among the patients who were diagnosed with stage IV (18 patients), 5 patients (27.8%) had developed severe symptoms, in which 5 patients (27.8%) passed away. These differences between the two groups were not significant ($P > 0.05$) [Table 4].

Among the 34 patients who received anticancer therapies at least 14 days before the diagnosis of COVID-19, 9 patients (26.5%) showed severe symptoms. This rate was 34.6% in people who had not been treated with anticancer drugs for <14 days of COVID-19 diagnosis, and there was not a significant difference between the two groups ($P > 0.05$) [Table 4].

Table 2: Chest computed tomography scan finding

Findings	*n* (%)
GGO	13/44 (29.6)
GGO + consolidation	10/44 (22.7)
Consolidation	3/44 (6.82)
Centrilobular nodule	9/44 (20.5)
Bronchial wall thickening	4/44 (9.1)
Reticulation	9/44 (20.5)
LAP	2/43 (6.7)
Vascular enlargement	2/44 (4.6)
Pleural effusion	7/44 (15.9)
Craniocaudal distribution	
0	10/38 (26.3)
Upper	6/38 (15.8)
Lower	10/38 (26.3)
None	12/38 (31.6)
Axial distribution	
0	10/38 (26.3)
Central	8/38 (21.1)
Peripheral	12/38 (31.6)
None	8/38 (21.1)

CT=Computed tomography; GGO=Ground-glass opacity

Table 3: Treatment for COVID-19 infected cancer patients (*n*=66)

Actions	*n*/*N* (%)
ICU	16/65 (24.6)
Oxygen therapy	51/64 (79.7)
Ventilation	7/65 (10.7)
Antibiotics	
Azithromycin	22/65 (33.9)
Meropenemorimipenem	47/65 (72.3)
Vancomycin	26/65 (40.0)
Clindamycin	2/65 (3.1)
Tetracycline	1/65 (1.5)
Cefepime	2/65 (3.1)
Cotrimoxazole	2/65 (3.1)
Colistin	3/65 (4.6)
Metronidazole	3/65 (4.6)
Tobramycin	4/65 (6.15)
Levofloxacin	20/63 (31.8)
Ceftriaxone	9/65 (13.9)
Linesolid	10/65 (15.4)
Antiviral	
No drug	12 (18.46)
HCQ	45 (69.23)
Acyclovir	2 (3.08)
Ribavirin	0
Interferon	1 (1.54)
Acyclovir + HCQ	4 (6.15)
Ribavirin + HCQ	1 (1.54)
Corticosteroid	
No drug	34 (52.31)
Dexamethasone	18 (27.69)
Methylprednisolone	3 (4.62)
Hydrocortisone	2 (3.08)
Prednisolone	0
Dexamethasone + methylprednisolone	1 (1.54)
Dexamethasone + hydrocortisone	4 (6.15)
Prednisolone + methylprednisolone	1 (1.54)
Dexamethasone + methylprednisolone + hydrocortisone	1 (1.54)
Dexamethasone + methylprednisolone + prednisolone	1 (1.54)
Improving clinical symptoms	52/60 (86.7)
Stability symptoms	1/60 (1.7)

ICU=Intensive care unit; HCQ=Hydroxychloroquine

Risk factors to develop severe event

The results showed that age, gender, type of cancer, underlying disease, chemotherapy, GGO, and GGO plus consolidation had no effect on the likelihood of death ($P > 0.05$) [Table 5].

DISCUSSION

In this study, the clinical characteristics and outcomes of 66 cancer patients with coronavirus disease-19 have been reported. The median age of participants was 61 years old and the main symptoms were fever, cough, and fatigue. Leukemia and lymphoma were the most prevalent cancer among patients followed by breast cancer. Our results showed that cancer patients had anemia, lymphopenia, and leukopenia. A quarter of our patients were admitted to the ICU and received HCQ and corticosteroids. About 71.4% of COVID-19-infected cancer patients received at least one antiviral drug, such as ganciclovir, lopinavir/ritonavir, arbidol, and ribavirin, while 32.1% were treated with two or more than two antiviral drugs. All patients with abnormal chest CT showed a GGO. The rate of mortality in cancer patients with COVID-19 was 23% and was not significantly different from among cancer COVID-19 patients with different stages.

Table 4: Outcome

Consequences after COVID-19	*n* (%)
Hospitalization (days), mean (SD)	11.48 (9.3)
Discharged, *n*/*N* (%)	50/65 (76.9)
Time from admission to discharged (days)	
Mean (SD)	8.9 (8.6)
Median (range)	7 (2-52)
Dead, *n*/*N* (%)	15/65 (23.1)
Time from diagnosis to death (days)	
Mean (SD)	17.5 (14.5)
Median (range)	15 (4-54)
Causes of death	
ARDS	7 (50.0)
CVA	2 (14.3)
Cancer	2 (14.3)
Pulmonary embolism	1 (7.1)
Cardiac arest	2 (14.3)

ARDS=Acute respiratory distress syndrome; CVA=Cerebrovascular accident; SD=Standard deviation

Table 5: Multivariate analysis for the risk of death

	OR (95% CI)*	
	Crude	Adjusted[&]
Sex (female-male)	1.62 (0.50-5.24)	1.41 (0.23-8.68)
Age	1.03 (0.99-1.06)	1.05 (0.98-1.13)
Cancer type (solid to nonsolid)	1.87 (0.45-7.68)	0.57 (0.04-6.9)
Comorbidity[#]	0.58 (0.14-2.33)	0.09 (0.00-2.47)
NLR	1.05 (0.97-1.14)	1.02 (0.87-1.19)
INR	9.1 (0.79-105.1)	6.52 (0.37-114.8)
Chemotherapy		
0	1	1
1	0.47 (0.11-2.0)	0.72 (0.04-12.33)
2	0.5 (0.04-5.7)	3.12 (0.08-115.3)
12	0.8 (0.16-3.9)	4.92 (0.20-115.5)

*The odds ratio, calculated with logistic regression, was considered significant if $P<0.05$, [#]At least had one of diseases (diabetes, chronic cardio vascular, chronic lung disease, hypertension), [&]All variable included in the adjusted logistic regression. NLR=Neutrophil to lymphocyte ratio; INR=International normalized ratio

Cancer patients have several risk factors that put them at higher risk for COVID-19 infection, such as suppressed immune systems, older age, increased comorbidities (e.g., diabetes, chronic lung disease, and cardiovascular disease), and need for frequent hospitalizations and referring to the hospital for chemotherapy.[13] According to a study conducted in the USA, increased rate of mortality in cancer patients with COVID-19 is significantly linked with older age, need for ICU support, multiple comorbidities, and elevated levels of lactate dehydrogenase, D-dimer, and lactate.[14] Three of these items including elevated levels of D-dimer, lactate dehydrogenase, and higher incidence of comorbidities were found in COVID-19-infected cancer patients in our study as well. Fatality rate in their study was 28%, which is almost similar to our result (23%). The double-arm meta-analysis by ElGohary *et al*. showed that cancer patients had a higher risk of mortality, ICU admission, severe/critical disease, and mechanical ventilation than noncancer patients, but the rate of ICU admission was not significantly different between groups in a case–control study performed in Iran ($P > 0.05$).[15] This study also reported significantly higher rate of dry cough (75.0% vs. 29.2%, $P = 0.01$) and fever (72.7% vs. 45.8%, $P = 0.02$) in COVID-19 cancer patients, but these differences were not significant in our study between these groups. In their study, gastrointestinal cancer was the most frequent type of cancer followed by breast cancer and hematologic.[16] Nine (37.5%) of their cancer patients were at stage 4, while in our study, only 20% were diagnosed with metastatic cancer. The prevalence of breast cancer in both studies was similar, 18.18% in our study versus 20.8% in study by Taghizadeh-Hesary *et al*.[16]

In our study, 77.1% of COVID-19 cancer patients had anemia, which is higher compared to prevalence of anemia in general COVID-19 population (48.2%)[17] reported by another study in Iran and 24.7% reported by Bellmann-Weiler in Austria.[18] According to their results, the rate of death was almost twice in patients with anemia compared to the rest of COVID-19 population.[17] It has been reported that the higher percentage of anemia in COVID-19 cancer patients may be the result of malnutrition and an immunosuppressive condition that leads to the increased susceptibility to respiratory pathogens.[19] According to a cohort study in the USA, on admission, anemia was independently associated with increased

risk of all-cause mortality in COVID-19 patients, but it was not significantly linked with severe outcomes during hospitalization.[20] A recent study of 259 patients with COVID-19 by Bellmann-Weiler *et al*. also confirmed these results that anemia on admission but not iron deficiency is an independent predictor of COVID-19 related mortality.[18]

For both cancer and general COVID-19 patients in our study, GGO was the most occurred feature of chest CT imaging followed by patchy consolidation, which has higher prevalence in COVID-19 cancer patients as a bilateral lung involvement than regular patients.[21] These findings are in line with the results of study by Zhang *et al*., Vuagnat *et al*., and Taghizadeh-Hesary *et al*., named the GGO as the most common imaging result.[4,16,22]

A nationwide analysis on cancer patients with coronavirus in China showed that patients undergoing chemotherapy or cancer-related surgery were more likely than general COVID-19 patients at the risk of severe clinical events.[5] Our study showed an increased risk of mortality and serious clinical events due to the COVID-19 infection in cancer patients after surgery. However, the risk of side effects from cancer treatments does not appear to increase. The true effects of COVID-19 on cancer patients will be known in the near future. Evidence suggests that cancer is associated with worse clinical outcomes in patients with COVID-19. However, elderly patients with cancer may not be at risk of death if they develop COVID-19.[23] These findings could potentially help physicians discuss with patients about their disease conditions to provide a prognosis and maybe, guide health policy. In the field of cancer, it is clear that the earlier the diagnosis of malignancy or cancer, the better the clinical outcome for the patient. Most health-care protocols have now follow safety guidelines and procedures, which have significantly reduced the risk of viral outbreaks when encountered in their health-care facilities.[24] False negative results of COVID-19 test and incomplete information of some patients are the limitations of our study.

CONCLUSION

Cancer care is affected by the global epidemic of acute respiratory syndrome, COVID-19, that has unprecedented challenges. Supportive care is one of the necessary components of cancer therapy, which seeks to prevent and manage chemotherapy side effects such as anemia, febrile neutropenia, thromboembolic events, thrombocytopenia/bleeding, and vomiting/nausea, all of them are major reasons for hospitalization. These side effects are essential to the patient's routine management, especially during an epidemic, in which physicians intend to minimize the risk of infection and patients' need for hospital visits. The results of our studies revealed that cancer is an important risk factor for the higher rate of mortality in patients with COVID-19. These findings could help physicians for the management, treatment, and supportive care of COVID-19 cancer patients.

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Conflicts of interest

There are no conflicts of interest.

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