



## COVID-19 in Cancer and Non-cancer Patients

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### Abstract

**Background:** There is a global concern for the susceptibility of patients with cancer to the adverse effects of novel coronavirus disease (COVID-19). Nevertheless, there is a signal of potentially increased vulnerability of patients with cancer to more COVID-19-induced mortality, this notion needs to be further evaluated in various societies with different cancer epidemiology and practice.

**Objectives:** To investigate the outcomes of cancer patients admitted due to COVID-19 and compare them with data of COVID-19 infected patients without a history of cancer.

**Methods:** In this case-control study, the medical records of patients with cancer (Ca<sup>+</sup> patients) who infected with COVID-19 were evaluated and compared with patients without a medical history of cancer (Ca<sup>-</sup> patients). Clinical data were collected from 19 February 2020 to 17 May 2020. The extracted data were classified into demographics, underlying medical conditions, clinical manifestations, imaging and laboratory findings, and clinical outcomes.

**Results:** A total of 24 Ca<sup>+</sup> patients were compared with 44 Ca<sup>-</sup> patients in terms of clinical manifestations and outcomes of COVID-19. The Ca<sup>-</sup> patients significantly developed more dry cough (75.0% vs 29.2%, P = 0.01) and fever (72.7% vs 45.8%, P = 0.02). Findings of the chest CT scan was comparable between groups, except for pleural effusion and lymphadenopathy that exclusively reported in Ca<sup>+</sup> patients. (3% and 4%, respectively). At the end of observation, 13 (19.1%) patients died from COVID-19. This rate was significantly higher in Ca<sup>+</sup> patients (41.7 vs 6.8%, P = 0.01). Likewise, Ca<sup>+</sup> patients experienced more mechanical ventilation (25.0 vs 4.7%, P = 0.01). However, the rate of ICU admission was comparable between groups (P = 0.29).

**Conclusions:** The patients with cancer had a higher rate of mechanical ventilation and COVID-19-induced mortality.

**Keywords:** Cancer, COVID-19, Mortality

### 1. Background

Since the end of 2019, the novel coronavirus disease (COVID-19) has been a major health issue all over the world. It is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and has led to 645,482 deaths worldwide as of 26 July 2020 with an average crude mortality rate of 3% - 4% (1, 2). Considering the immune-compromised status of patients with cancer, they are expected to experience more morbidity and mortality (3). However, the existing findings are controversial. As the initial report of the effects of cancer on COVID-19 prognosis, Liang et al. (4) re-

ported a significantly higher incidence of death and intensive care unit (ICU) admission in patients with cancer versus without. However, they overlooked the effect of age on COVID-19 mortality and morbidity. So far, several investigators have evaluated the effects of cancer on the natural history and prognosis of COVID-19 (3, 5, 6). However, these results may not be generalizable to all populations with different cancer epidemiology and practice. Moreover, there is a lack of information for direct comparison of patients with versus without cancer in terms of clinical manifestations and outcomes of COVID-19.

## 2. Objectives

In this retrospective study, we aimed to address the effects of cancer on the natural history of COVID-19 among Iranian patients.

## 3. Methods

### 3.1. Study Design, Participants, and Treatment

This retrospective case-control study of the clinical outcomes of COVID-19 in patients with cancer was carried out at the Vasei Hospital of Sabzevar, Razavi Khorasan, Iran which is one of the four COVID-19 specific treatment centers in the northeast of Iran (after the report of the first case of COVID-19 in Iran, a hospital in each city has been specified to evaluate, hospitalize, and treat patients who are suspected or infected by COVID-19). Being a retrospective analysis of clinical outcomes of patients, additional ethical clearance was waived by the Institutional Review Board of Sabzevar University of Medical Sciences (code: IR.MEDSAB.REC.1399.048).

Between 19 February 2020 and 17 May 2020 case records of the patients who were previously diagnosed with cancer (Ca<sup>+</sup> patients) and had a laboratory- or imaging-confirmed COVID-19 infection were compared with patients with COVID-19 infection without a medical history of cancer (Ca<sup>-</sup> patients). All chest computed tomography (CT) scans were independently reviewed by 2 experienced radiologists blinded to the clinical data. Clinical data were retrospectively retrieved from the medical record. Two designated research collaborators (FZ and SAJ) independently extracted the data. Demographic and clinical data were collected, including age at diagnosis, gender, comorbidities, type and stage of cancer, anti-cancer treatment during infection, clinical features, laboratory and imaging findings, and clinical outcomes. The management of patients was in keeping with the national protocol for the management of patients with COVID-19 (7-9).

### 3.2. Endpoints

This study primary endpoints were to compare the clinical features, laboratory and imaging findings, and clinical outcomes (i.e. discharge from hospital or death). The criteria for discharge of patients were defined based on the national guideline, as follows: (1) Resolution of fever for 72 hours without antipyretics; (2) blood oxygenation (SpO<sub>2</sub>) > 93% on room air; and (3) stable vital signs (9).

### 3.3. Statistical Analysis

All patients with cancer who were admitted in the our center during the first wave of the COVID-19 pandemic were enrolled. To compare data, patients without any history of malignancies whom were admitted during the same time were selected randomly using a table of random numbers generated by <https://www.random.org>. To summarize the data, we used frequencies (%) and mean [standard deviation (SD)] for categorical and continuous variables, respectively. We applied the chi-square test of independence (or Fisher's exact test) and independent sample t-test to compare categorical and continuous variables, respectively. To evaluate the normal distribution of continuous variables we applied the Kolmogorov Smirnov test. Furthermore, to omit the effect of age as the confounder on mortality rate, we run the Cochran-Mantel-Haenszel test and stratified the patients to < 65 and ≥ 65 years old (10). All analyses were performed using IBM SPSS Statistics, version 26. The statistical significance level was set to 0.05.

## 4. Results

From 19 February 2020 to 17 May 2020, medical records of 24 Ca<sup>+</sup> patients who had a laboratory- or imaging-confirmed COVID-19 were analyzed. The gastrointestinal system was the most frequent site of cancer (25.0%), followed by breast cancer (20.8%), and hematologic and head and neck malignancies (each 12.5%). Nine (37.5%) patients were diagnosed with metastatic cancer. Table 1 summarizes baseline information on cancer history. Sixteen (66.7%) patients received antitumor therapies during the COVID-19 outbreak, such that 10 (41.6%) patients only received chemotherapy, 1 (4.1%) patient only received radiotherapy, and 5 (20.9%) patients received both treatment modalities. For comparison, medical records of 44 Ca<sup>-</sup> patients with COVID-19 were extracted. RNA testing and chest CT scans were performed for all patients. A total of 67 patients were diagnosed with COVID-19, based on either a positive SARS-CoV-2 polymerase chain reaction (PCR) test (n = 53 patients) or, in the case of negative results, based on radiologic findings (n = 14 patients). Forty-six patients had positive results for either PCR or chest CT scan. One patient only reported symptoms suggestive of COVID-19 without confirming by PCR test and chest CT scan. Demographics and clinical characteristics of patients are summarized in Table 1. Overall, patients were predominantly male (61.8%) and the mean age (± SD) was 51.8 (± 17.3) years. The Ca<sup>+</sup> patients were significantly older (mean 59.1 vs 47.8 years, P = 0.01), however, were comparable to the Ca<sup>-</sup> group in terms of gender and comorbidities.

Table 2 summarizes the clinical manifestations of COVID-19. Dyspnea and fever were the most common

**Table 1.** Patients' Demographics and Clinical Characteristics

Characteristics	Total, No. (%)	Ca <sup>+</sup> , No. (%)	Ca <sup>-</sup> , No. (%)	P-Value
<b>Number of patients</b>	68	24	44	
<b>Age at diagnosis, y</b>				0.01
Mean ± SD	51.8 ± 17.3	59.1 ± 15.1	47.8 ± 17.3	
Range	17-87	27-85	17-87	
<b>Gender</b>				0.34
Male	42 (61.8)	13 (54.2)	29 (65.9)	
Female	26 (38.2)	11 (45.8)	15 (34.1)	
<b>Comorbidities<sup>a</sup></b>	4 (5.9)	3 (12.5)	1 (2.2)	0.25
<b>Primary cancer site</b>				
Gastrointestinal	-	6 (25.0)	-	-
Breast	-	5 (20.9)	-	-
Hematologic	-	3 (12.5)	-	-
Head and neck	-	3 (12.5)	-	-
Other	-	7 (29.1)	-	-
<b>Stages of cancer</b>				
Non-metastatic		15 (62.5)		
Metastatic		9 (37.5)		

Abbreviations: Ca<sup>+</sup>, patients with cancer; Ca<sup>-</sup>, patients without cancer; SD, standard deviation.

<sup>a</sup>Including ischemic heart disease, diabetes mellitus, chronic obstructive pulmonary disease, and chronic kidney disease.

symptom and sign in both groups, respectively. The Ca<sup>-</sup> patients significantly more experienced dry cough (75.0 vs 29.2%,  $P = 0.01$ ) and fever (72.7 vs 45.8%,  $P = 0.02$ ), however, there was no significant difference for other signs and symptoms. On physical examination, comparable SpO<sub>2</sub> ( $P = 0.59$ ) and body temperature ( $P = 0.12$ ) were recorded. Approximately 88% of the patients had abnormal CT findings. The most reported radiographic finding was ground-glass opacification (GGO) found in 66% of patients. Bilateral and multi-lobar involvement were more detected in Ca<sup>-</sup> patients. CT findings were comparable in both groups, except for pleural effusion and lymphadenopathy (LAP) that were only detected in Ca<sup>+</sup> patients. Pleural effusion was detected in 2 cases with gastrointestinal cancer and 1 patient with a brain tumor. Mediastinal LAP was reported in the same patient with a brain tumor, one patient with breast cancer, one with lung cancer, and another one with hematologic malignancy. Among 48 patients evaluated for c-reactive peptide (CRP), 83.3% had elevated results with no significant difference between groups ( $P = 0.27$ ).

The clinical outcomes of patients are also demonstrated in Table 2. The Ca<sup>+</sup> patients more experienced mechanical ventilation (25.0 vs 4.7%,  $P = 0.01$ ), while the rate of admission to the Intensive Care Unit (ICU) was comparable between groups (29.2 vs 18.2%,  $P = 0.29$ ). Ten Ca<sup>+</sup>

patients died during the observation period, including 6 (60%) patients with advanced disease. Of note, the Ca<sup>+</sup> patients' mortality rate was significantly higher (41.7 vs 6.8,  $P = 0.001$ ), considering the effect of age as a confounder [odds ratio (OR) = 8.4, 95% confidence interval (CI) 2.0-34.6,  $P = 0.001$ ]. Neither chemotherapy nor radiotherapy during the COVID-19 outbreak correlated with the mortality rate ( $P = 0.69$  and  $P = 0.88$ , respectively).

## 5. Discussion

This case-control study went beyond previous studies by comprehensively comparing the clinical characteristics and outcomes of COVID-19 in Ca<sup>+</sup> versus Ca<sup>-</sup> patients. Both groups shared common status in terms of gender and underlying medical conditions, although Ca<sup>+</sup> patients were approximately 11 years older on average. Dyspnea and fever were the most presenting symptoms and signs in the patients. However, other studies have shown that cough and fever are the most common symptoms and signs in COVID-19 (5, 6, 11, 12). Also, we found that Ca<sup>-</sup> patients more developed dry cough and fever. On physical examination, blood oxygenation and body temperature had comparable results in both groups.

Overall, the most common findings in the chest CT

**Table 2.** Clinical Manifestations and Outcomes of Patients<sup>a</sup>

Characteristics	Total	Ca <sup>+</sup>	Ca <sup>-</sup>	P-Value
<b>Number of patients</b>	68	24	44	
<b>Presenting signs and symptoms</b>				
Dyspnea	57 (83.8)	19 (79.2)	38 (86.4)	0.44
Dry cough	40 (58.8)	7 (29.2)	33 (75.0)	0.01
Productive cough	3 (4.4)	0 (0.0)	3 (6.8)	0.19
Fever	43 (63.2)	11 (45.8)	32 (72.7)	0.02
Malaise	15 (22.1)	5 (20.8)	10 (22.7)	0.85
Nausea and vomiting	7 (10.3)	1 (4.2)	6 (13.6)	0.21
Diarrhea	6 (8.8)	3 (12.5)	3 (6.8)	0.43
Other <sup>b</sup>				
<b>Vital signs at admission</b>				
Body temperature, °C	37.1 ± 1.0	37.4 ± 0.7	37.0 ± 1.1	0.12
SpO <sub>2</sub> , %	89.6 ± 7.0	89.0 ± 6.4	89.9 ± 7.4	0.59
<b>Chest CT scan findings</b>				
Abnormal appearance	60 (88.2)	21 (87.5)	39 (88.6)	0.88
Consolidation	23 (33.8)	9 (37.5)	14 (31.8)	0.63
GGO	45 (66.2)	16 (66.7)	29 (65.9)	0.95
Number of lesions	5 (7.4)	3 (12.5)	2 (4.5)	0.66
Single				
≤ 10	14 (20.6)	5 (20.8)	9 (20.5)	
> 10	41 (60.3)	13 (54.2)	28 (63.6)	
Location of lesions				0.53
Multiple lobes	32 (47.1)	10 (41.7)	22 (50.0)	
Peripheral	22 (32.4)	8 (33.3)	14 (31.8)	
Base	4 (5.9)	1 (4.2)	3 (6.8)	
Central	1 (1.5)	1 (4.2)	0 (0.0)	
Peribronchovascular	1 (1.5)	1 (1.5)	0 (0.0)	
Apical lobes	0 (0.0)	0 (0.0)	0 (0.0)	
Bilateral involvement	49 (72.1)	15 (62.5)	34 (77.3)	0.19
Pleural effusion	3 (4.4)	3 (12.5)	0 (0.0)	0.01
Lymphadenopathy	4 (5.9)	4 (16.7)	0 (0.0)	0.005
<b>Laboratory findings</b>				
Elevated CRP <sup>c</sup>	40 (83.3)	12 (75.0)	28 (87.5)	0.27
<b>Clinical condition at admission</b>				
ICU admission	15 (22.1)	7 (29.2)	8 (18.2)	0.29
Mechanical ventilation	8 (11.9)	6 (25.0)	2 (4.7)	0.01
<b>Clinical outcome</b>				
Discharge from hospital	55 (80.9)	14 (58.3)	41 (93.2)	0.001
Death	13 (19.1)	10 (41.7)	3 (6.8)	

Abbreviations: Ca<sup>+</sup>, patients with cancer; Ca<sup>-</sup>, patients without cancer; CRP, c-reactive peptide; CT, computed tomography; GGO, ground glass opacity; ICU, Intensive Care Unit.

<sup>a</sup>Values are expressed as mean ± SD or No.(%).

<sup>b</sup>Including hemoptysis, seizure, loss of consciousness, sore throat, and headache.

<sup>c</sup>CRP was available in 48 patients

scan was GGO located mainly in peripheral pulmonary sites in a bilateral and multilobar fashion. Mediastinal LAP and pleural effusion were exclusively reported in patients with cancer. These findings may occur secondary to the involvement by cancer; albeit mediastinal LAP and pleural effusion are not in the natural history of brain tumors.

These findings are in line with the Zhang et al.'s study (5) on 28 COVID-19-infected cancer patients, that GGO was the most common finding followed by consolidation. Likewise, Vuagnat et al. (6) named the GGO as the most common imaging finding that was found in half of 78 patients with breast cancer. In a retrospective evaluation, Bai et al.

found comparable results in 219 patients with COVID-19 (irrespective of their cancer history) and reported that GGO (91%) was the most common finding followed by consolidation (69%) and vascular thickening (59%). They found pleural effusion and mediastinal LAP in 4% and 3% of patients, respectively (13).

Also, we found a comparable elevation of CRP in Ca<sup>+</sup> and Ca<sup>-</sup> patients. Notwithstanding previous studies have named the elevated CRP as a poor prognostic factor in patients with COVID-19 (14), in our study, the rate of elevated CRP was insignificantly lower in patients with cancer who have a potentially poorer prognosis (3, 15). This controversial finding needs further evaluation in larger studies.

Based on our observations, the rate of ICU admission was similar, however, Ca<sup>+</sup> patients required more mechanical ventilation. This may be due to the adverse effects of prior chemotherapy or radiotherapy on the respiratory capacity of patients (16, 17). In a retrospective analysis, Miyashita et al. (3) found that a history of cancer significantly increased the intubation rate in patients aged 66 - 80 years [relative risk (RR):1.76, 95% CI 1.15 - 2.70].

We detected a higher crude mortality rate of COVID-19 for Ca<sup>+</sup> patients. This notion remained true following the omission of the confounding effect of age, as a major risk factor for COVID-19 mortality (18). According to Miyashita et al.'s study (3), the increased mortality rate is limited to patients younger than 50 years. Of note, chemotherapy and/or radiotherapy did not enhance the mortality rate of our patients. This interesting finding is consistent with the previous reports (19).

The present study had some limitations that should be considered before interpreting the results. Firstly, the absence of stratification according to risk factors of mortality was a limitation of the study that may affect the results. Secondly, the heterogeneity of cancer types with varying stages and prognosis may affect our findings. Thirdly, the small sample size could have biased the results. Fourthly, retrospective analysis of medical records made poor control of covariates of mechanical ventilation and mortality. Another potential limitation of this study was its single-center condition; therefore, the composition of participants, management protocols, resources, and staffing characteristics are potentially limiting to the generalizability of our results. To solve these critical issues, larger multi-center prospective studies are necessary.

Although these limitations are important, this study is one of the few that highlights the effects of cancer on clinical characteristics and outcomes of COVID-19 by comparison with patients without a medical history of cancer.

## 5.1. Conclusions

The findings support the vulnerability of patients with cancer in the COVID-19 pandemic. We demonstrated that they had a higher rate of mechanical ventilation and COVID-19-related mortality. Further studies are warranted for a better understanding of the risk of COVID-19 in patients with cancer.

## Footnotes

**Authors' Contribution:** SAJ, PP, BPS, MH, and SS conceived and designed the evaluation and drafted the manuscript. FTH, MH, and DS participated in designing the evaluation, performed parts of the statistical analysis and helped to draft the manuscript. WM re-evaluated the clinical data, revised the manuscript and performed the statistical analysis and revised the manuscript. SAJ, BK, MMF, and FR collected the clinical data, interpreted them and revised the manuscript. SAJ, MMF, and MS re-analyzed the clinical and statistical data and revised the manuscript. All authors read and approved the final manuscript.

**Conflict of Interests:** There is no conflict of interest to be reported.

**Ethical Approval:** Being a retrospective analysis of clinical outcomes of patients, additional ethical clearance was waived by the Institutional Review Board of Sabzevar University of Medical Sciences (code: IR.MEDSAB.REC.1399.048).

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