

Cancer has an Independent Association with Death in Hospitalized Patients with COVID-19: A Single-center Study in Iran

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ABSTRACT

Background: COVID-19 could cause severe complications in those with pre-existing conditions such as cancer. Here, we aimed to assess the outcome of COVID-19 in hospitalized patients with a history of cancer.

Methods: In this retrospective cohort study, we extracted medical records of patients with any cancer history among hospitalized patients with COVID-19. Our patients were admitted between February 20th and July 15th, 2020. The primary outcome was death, and the secondary outcomes were overall survival, COVID-19-specific mortality, admission to intensive care unit (ICU), and hospital stay. A group of individuals without cancer history was selected from the COVID-19 cohort and matched for age, gender, and pre-existing conditions. We utilized univariate and multivariate logistic regression to analyze the association between studied variables and primary outcomes.

Results: We identified 46 patients with cancer and COVID-19. The median age was 63, and 54.3% were male. According to the univariate logistic regression analysis, death was 5.3 (CI95%: 1.75-15.85) times more probable in cancer patients than controls ($p=0.003$). The multivariate analysis adjusted for having cancer and sex, age, and having any comorbidity showing this figure was 5.5 (CI95%:1.8-16.8) ($p=0.003$). The 30- and 90-day COVID-19 specific mortality was 30% (CI95%:17-43) and 33% (CI95%: 20-46), respectively.

Conclusion: Patients with COVID-19 with a history of cancer have a considerably higher risk of death irrespective of age, gender, and other pre-existing conditions. Patients with advanced cancers and concurrent bacterial infections need the most vigorous care.

Keywords: Cancer, Chemotherapy, COVID-19, Epidemic, Iran, SARS-CoV-2

INTRODUCTION:

In December 2019, an outbreak of atypical pneumonia caused by 2019 novel coronavirus (COVID-19) emerged in Wuhan, Hubei, China [1]. This new type of pneumonia that is characterized by rapid human-to-human transmission is linked to the severe adult respiratory syndrome coronavirus 2 (SARS-CoV-2) [2]. Soon, almost all parts of the world got involved with the outbreak.

Based on the available reports on cancer incidence, Iran was ranked 17th worldwide in 2017. Overall, 134,473 new cancer cases were diagnosed in 2017. The total number of cancer patients was 624,818 [3]. Cancer patients often commute to the hospital for treatment and disease surveillance, and therefore, they may be at an elevated risk of contracting SARS-CoV-2 [4]. Moreover, most individuals with cancer are at risk of a compromised immune state due to antineoplastic therapy, supportive medications such as steroids, radiation to the marrow, and cancer's immunosuppressive properties [5].

In Iran, as a developing country, there are specific challenges in protecting cancer patients against infection with SARS-CoV-2. During treatment, family members try to support patients by making frequent visits to them, which puts them at greater risk of infection, especially in crowded households. Furthermore, cancer patients frequently use overcrowded public transportation systems for commuting to the cancer centers, sometimes very remote. Finally, for a considerable proportion, providing personal protective equipment (PPE) may be unaffordable considering the high costs of cancer treatments they are already dealing with.

Due to the high transmissibility of COVID-19 and the challenges posed by cancer, understanding the disease course and factors influencing clinical outcomes of COVID-19 in patients residing in developing countries is urgently needed. Indeed, due to variations in cancer distribution worldwide, the association would be different in each part of the world. In this regard, we aimed to evaluate the demographic and clinical factors, underlying cancer, and mortality rate of COVID-19 in patients with cancer compared to non-cancer patients in a developing country setting.

Material and methods

1. Study design and participants

This retrospective study was conducted between February 20th and July 15th, 2020, in Imam Khomeini Hospital Complex, affiliated with Tehran University of Medical Sciences. In this study, we included hospitalized patients with a history of cancer and signs and symptoms suspicious for COVID-19 admitted up to April 6th. We used clinical data, chest computed tomography (CT) scan images, and real-time polymerase chain reaction (qRT-PCR) tests to differentiate real COVID-19 cases from other diagnoses. Our case definition was based on the diagnosis made by an infectious disease specialist or a pulmonologist. A positive qRT-PCR was not mandatory for confirmation of COVID-19. The institutional review board (local IRB) and the ethics committee of Tehran University of Medical Sciences approved this study (code: IR.TUMS.VCR.REC.1399.114 accessible at ethic.research.ac.ir). All patients provided written informed consent at the time of admission to allow the use of their data for research purposes, albeit confidentially.

2. Inclusion criteria and Data collection

We included hospitalized patients with an active cancer or cancer survivors out of an ongoing cohort of hospitalized patients with COVID-19. Patients had to be discharged or died to enter our study. We sought patients without any history of cancer out of the cohort that were matched to our cancer patients based on age, sex, and comorbid conditions. The ratio of controls to cases was 1:1.

Epidemiological, clinical, laboratory, and radiological data of all patients were obtained from the electronic medical records. Data were reviewed and verified by a team of physicians who are coauthors in this study. Any missing or uncertain records were re-checked with involved healthcare providers or through making phone calls to patients and their families. Detailed demographics information, comorbidities, symptoms, and disease severity of all patients were recorded or inquired on admission. Laboratory examinations, including routine blood tests and the clinical treatment details, were also included.

3. Definition of variables

We defined active cancer as those patients with hemato-

logical or solid tumors who have not been disease-free during the month before admission. By hematological tumors, we mean all lymphomas, acute and chronic leukemias, multiple myeloma, and primary central nervous system lymphoma (PCNSL). To stage solid tumors, we used TNM staging, as mentioned in the AJCC cancer staging manual, 8th edition.

4. Outcome Assessment

The primary outcome was death in the hospital or at home after discharge during the follow-up period. Our secondary outcome was admission to the intensive care unit (ICU) and COVID-19-specific mortality. The duration of follow-up was defined as hospital admission to death or the patients' last known alive status. Survivors were defined as patients discharged from the hospital or still hospitalized at the end of the study.

5. Statistical analysis

We did not have a sample size calculation before data gathering. Thus, all consecutive patients meeting our inclusion criteria were recruited. In this study, we used descriptive statistics to show the participants' baseline demographic information included in our analyses. In addition, we used uni- and multivariate logistic regression to evaluate any association between laboratory and important demographic variables and death in patients with cancer both within the group and versus those without cancer. Associations were considered statistically significant at 0.05, and the odds ratios (ORs) were provided. Multivariate analysis was limited to variables with a statistically significant relationship to death in univariate analysis. One more condition for entering into multivariate analysis was the accessibility of all patients' data for any specific variable. Moreover, survival analysis was used to evaluate patients' survival rates with cancer up within a 90-day follow-up. All statistical analysis was done using SPSS version 20, and $P < 0.05$ was considered statistically significant

RESULTS:

Out of 1,032 patients with confirmed COVID-19, we identified 46 patients with a history of cancer. Their characteristics are shown in **Table 1**. The majority of pa-

tients were male. Diabetes mellitus (DM), hypertension (HTN), and ischemic heart disease (IHD) comprised the most common comorbidities. Smokers comprised less than a tenth of patients. The most common symptoms were fever, dyspnea, fatigue, and dry cough. Among lab parameters, lymphopenia was observed in half of the patients.

The ratio of hematological to solid cancers was 1:3. Also, about two-thirds of patients had active cancer at the time of admission. The most common cancer type among females was breast cancer, while among men, prostate and lung cancer and chronic lymphocytic leukemia (CLL) were equally the most frequent. The stage of the majority of patients with solid tumors was I-III. The median interval between last cancer treatment and admission for COVID-19 was almost three weeks.

As shown in **Figure 1**, the most common cancer subsite was lymphoma, leukemia, and multiple myeloma, while the least common subsite was central nervous system (CNS) tumors. Only 4.3% of the patients had lung cancer. The incidence of cancer types in Iran is also shown in **Figure 1**, based on GLOBOCAN 2018 data (accessible at: <https://gco.iarc.fr/today/online-analysis-table>).

Based on the univariate analysis, the TNM stage, cancer status, the interval from last chemotherapy to admission, bacterial co-infection, and abnormality in the liver function test were associated with death in cancer patients

Table 1. The clinical characteristics of patients at admission

Clinical Characteristics	Confirmed COVID-19 (n=46)
Age	63 (52.7-67)
Age >70	9 (19.6%)
Sex (female)	21 (45.7)
Past Medical History	
Any comorbidity	29 (63)
Multiple comorbidities	10 (21.7)
Diabetes mellitus(DM)	14 (30.4)
Hypertension(HTN)	15 (32.6)
IHD	12 (26.1)
Chronic obstructive pulmonary disease(COPD)	1 (2.2)
Liver disease	3 (6.5)
Chronic kidney disease/End-stage renal disease(CKD/ESRD)	3 (6.5)
Smoker	3 (6.5)

Cancer Type	
Hematological	16 (34.8)
Acute myeloid leukemia(AML)	2 (4.3%)
Chronic lymphocytic leukemia(CLL)	3 (6.4%)
Chronic myeloid leukemia(CML)	0 (0%)
Multiple Myeloma	4 (8.5%)
Hodgkin Lymphoma	2 (4.3%)
Non-Hodgkin Lymphoma	5 (10.6)
Solid	30 (65.2)
Breast	6 (12.8%)
Gastric	2 (4.3%)
Colorectal	4 (8.5%)
Lung	2 (4.3%)
Bladder	2 (4.3%)
Prostate	3 (6.4%)
Central nervous system(CNS)	1 (2.1%)
Esophagus	1 (2.1%)
Liver	1 (2.1%)
Pancreas	3 (6.4%)
Germ Cell Tumor	1 (2.1%)
Endometrial	2 (4.3%)
Larynx	2 (4.3%)
-Kidney	1 (2.1%)
Cancer Status	
Active	29 (63)
Remission	17 (37)
Stage of Solid Tumors	
Stage IV	9 (30)
Stage I to III	21 (70)
Cancer-specific treatment	
History of chemotherapy	32 (69.6%)
Chemotherapy in the last 2 weeks	10 (21.7%)
History of radiotherapy	15 (32.6%)
History of cancer surgery	20 (43.5%)
History of autologous stem cell transplantation	0 (0%)
Symptom development to admission time (day)	7 (3-12)
Last treatment to admission time (day)	20 (4-156)
Length of hospital stay (day)	4 (2-8.5)
Symptoms	
Fever	31 (67.3%)
Chills	8 (17.4%)
Dry cough	17 (37%)
Productive cough	12 (26.1%)
Dyspnea	23 (50%)
Distress	6 (13%)
Fatigue	15 (32.6%)
Headache	3 (6.5%)
Myalgia	13 (28.3%)
Diarrhea	1 (2.2%)

Signs	
Initial SO2 (%)	90 (84-93)
Low SO2(%93>) 2)	32 (69.6)
Systolic/Diastolic Blood pressure (mm/Hg)	110 (100-121.2)/ 70
Systolic blood pressure < 90 or diastolic blood pressure < 60 mmHg(Low BP)	(60-80)
Systolic blood pressure > 140 or diastolic blood pressure > 90 mmHg(High BP)	
Heart Rate (beats/min)	6 (13)
Heart rate > 100(Tachycardia)	2 (4.35)
Heart rate < 60(Bradycardia)	
Respiratory rate (breath/min)	98.5 (82.7-109.2)
Respiratory rate > 20(Tachypnea)	19 (41.3)
Body temperature (°C)	1 (2.2)
	21 (18-27)
	26 (56.6)
	37.7 (36.9-38.2)
Lab tests	
WBC (*103/mcL)	7.2 (5.2-11.2)
Leukopenia (< 103*3/mcL)	6 (13)
Neutropenia (< 103*1.5/mcL)	3 (6.5%)
Lymph (*103/mcL)	0.91 (0.71-1.5)
Lymphopenia (< 103*1/mcL)	24 (52.2)
Hb (mg/dL)	11.2 (9.5-13.4)
Anemia	26 (56.5)
PLT (* 103/mcL)	188 (131.5-255.2)
Thrombocytopenia (< 103*150/mcL)	13 (28.3%)
CRP	116 (55.7-163.2)
ESR	77 (52-116.5)
LDH	722 (480-938)
Use of Medication	
Antibacterial	30 (65.2%)
Antifungal	7 (15.2%)

(Table 2). However, in the multivariate analysis, only the patients with TNM stage IV had a significantly higher death rate than those with stage I-III or hematological cancers (p=0.034). In addition, in those with active cancer, less than a 2-week interval from last chemotherapy to admission, and bacterial co-infection, there was a trend toward higher death (0.05 < p < 0.1). ICU admission rate was 26.1% vs. 17.5% in patients with cancer compared to the controls (p= 0.449). The mean hospital stay was 8.8 vs. 4.4 days in cancer and control groups, respectively (p=0.046). Patients were followed up for a median of 134.5 days (CI95%:129-138). During the study period, 18 patients (39.1%) died. Twelve deaths were caused by COVID-19 and 6 by cancer. Among control patients, the death rate was 10.9%. According to the univariate logistic regression analysis, the death was 5.3 (CI95%: 1.75-15.85) times more probable in cancer patients versus controls (p=0.003). In the multivariate analysis adjusting for hav-

ing cancer and sex, age, and having any comorbidity, this figure was 5.5 (CI95%:1.8-16.8) with the same p-value. However, our patients' 30-day and 90-day overall survival with COVID-19 was 70% (CI95%: 57-83) and 63% (CI95%: 50-76), respectively. In **Figure 2**, the Kaplan-Meier COVID-19-specific mortality curve of cancer patients is shown. The 30- and 90-day COVID-19-specific mortality was 30% (CI95%:17-43) and 33% (CI95%: 20-46), respectively.

DISCUSSION

The prevalence rate of cancer in patients with COVID-19 was 4.5%, about 15 times the national cancer incidence estimate which is 302 per 100,000 people [6]. With caution, this could point to cancer patients' susceptibility to contracting moderately to severe COVID-19 that needs hospitalization. A pooled meta-analysis reported that 2-3% of COVID-19 patient cohorts had a history of cancer, which is lower than our rate. However, this rate is in both outpatient and inpatient settings.

Numerous studies have suggested that patients with cancer are more prone to infection than normal individuals without cancer. This is assumed to be due to their systemic immunosuppressive state, mainly related to the malignancy itself and anticancer treatments, including chemotherapy or surgery. Other reasons include frequent commuting to healthcare centers and prolonged stay in cancer-treatment centers, which are more contaminated than other places. In line with these hypotheses, in the first report on the association between cancer and COVID-19, Liang et al. showed a substantially higher incidence of cancer in the COVID-19 cohort than the general Chinese population [7].

Looking at the nearest image of the distribution of cancer types in Iran based on GLOBOCAN 2018 (**Figure 1**), we see a vast difference in the share of hematological malignancies between our cohort and the national image. Hematological malignancies are ten times more common in our cohort. Aside from the inherent abnormality posed by the cancerous process in blood cells, these patients almost always receive myeloablative chemotherapeutic regimens that usually weaken the immune system. Also,

the mentioned limitations we face in developing countries to prevent infection could justify the relatively high contribution of hematological malignancies in COVID-19 infection. However, some studies from developed nations show a similar infection rate to normal populations but with more severe disease states [8]. Thus, this notion needs further assessment.

Solid tumors are somehow not so different between our cohort and national estimates. One might assume that patients with lung cancer, due to the pre-existing lung damage caused by the neoplastic process itself, surgeries to the lung parenchyma, and comorbidities that are usually attributable to smoking, might be more susceptible to SARS-CoV-2 infection. However, the rate of lung cancer was lower in our cohort compared to the national distribution. This could be due to the similarities of symptoms between lung cancer patients and those with COVID-19 that include cough, dyspnea, and fever [9]. Thus, they may be hospitalized and managed as a complication of lung cancer other than COVID-19.

We showed that cancer patients had a higher death rate compared to the matched controls without cancer. This

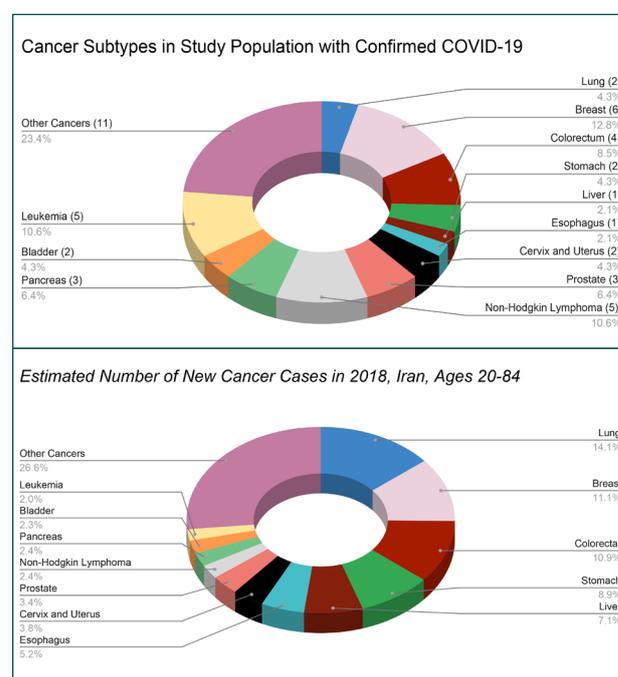


Fig. 1 Distribution of cancer types in our study and Iran based on the data of GLOBOCAN 2018

Table 2. Multivariate regression analysis in cancer patients

		Univariate analysis		Multivariate		
		Death rate	P	OR	P	OR
Sex	Male	9 (36)	0.764			
	Female	9 (42.9)				
Age group	≤ 70 years	13 (35.1)	0.284			
	> 70 years	5 (55.6)				
Comorbidity	No	14 (38.9)	0.613			
	Yes	4 (40)				
Cancer type	Solid	6 (37.5)	0.563			
	Hematological	12 (40)				
TNM stage	Solid I to III or Hematological	11 (29.7)	0.016	Ref.	0.034	Ref.
	Solid IV	7 (77.8)		8.3 (1.47-46.30)		6.9 (1.15-41.97)
	Remission	2 (11.8)		Ref.		Ref.
Cancer activity	Active	16 (55.2)	0.005	9.2 (1.78-47.92)	0.055	5.8 (0.96-35.40)
	Interval from cancer treatment to admission > 2 weeks	11 (30.6)		Ref.		Ref.
Interval from cancer treatment to admission	≤ 2 weeks	7 (70)	0.03	5.3 (1.14-24.42)	0.079	4.3 (0.84-22.40)
	Bacterial infection	2 (12.5)		0.007		Ref.
Bacterial infection	Yes	16 (53.3)	8 (1.54-41.5)		5.0 (0.77-32.91)	
	Fungal infection	No	14 (35.9)	0.258		
Yes		4 (57.1)				
Lymphopenia	No	5 (29.4)	0.160			
	Yes	12 (50)				
Neutropenia	No	14 (38.9)	0.363			
	Yes	2 (66.7)				
Anemia	No	5 (29.4)	0.219			
	Yes	12 (46.2)				
Thrombocytopenia	No	10 (32.3)	0.047	Ref.		Not entered
	Yes	8 (61.5)		3.4 (0.87-12.93)		
Liver function test abnormality (N=31)	No	9 (37.5)	0.078	Ref.		Not entered
	Yes	6 (85.7)		10 (1.03-97.04)		
Coagulopathy	No	9 (39.1)	0.105			
	Yes	7 (70)				
Renal function test abnormality (N=45)	No	10 (32.3)	0.106			
	Yes	8 (57.1)				

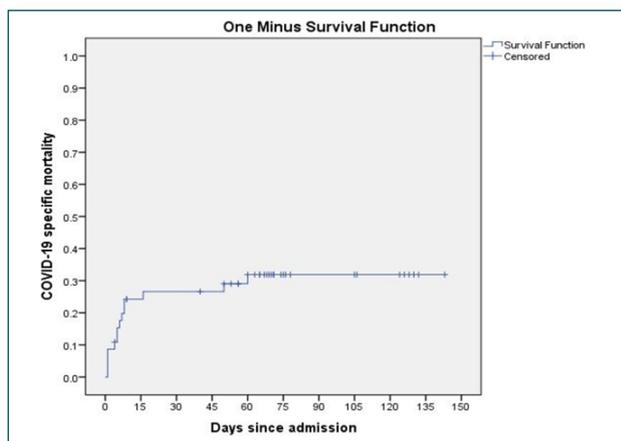


Fig. 2 Kaplan-Meier curve for COVID19- specific mortality

association has been emphasized previously in numerous reports. The mortality rate of cancer patients with COVID-19 had been between 10% and 62% in hospitalized patients [8,10]. Unfortunately, based on our results and previous studies, patients with cancer could not deal successfully with COVID-19, and they are expected to reflect severe complications. In this regard, countries with a higher rate of cancer cases should focus on these individuals' health to decrease mortality and the risk of death. Since chemo- and radiotherapy might impact immune response, close follow-up should be made because patients with cancer are prone to develop a severe condition rapidly. In addition, hospital admission and recurrent hospital visits are potential risks for SARS-CoV-2 infection, and these factors may account for the increased incidence among cancer patients. Therefore, we recommend aggressive measures to reduce the frequency of hospital visits during a viral epidemic in the future. For cancer patients who require treatment, proper isolation protocols must be in place to mitigate the risk of COVID-19 infection.

Within the group of patients with cancer, we observed that death was higher in those with stage IV disease, less than 2 weeks from last chemotherapy, active cancer, and bacterial co-infection. However, when adjusted for all factors, only the effect of stage IV disease remained significant. At the same time, patients with active cancer, shorter than 2 weeks interval from the last chemotherapy, and those with bacterial co-infection showed a

trend toward more death. In the previous studies, various factors were associated with death in multivariate analysis. In the earliest report from Wuhan city, Zhang et al. showed higher mortality in those with patchy consolidation and those having chemotherapy in the past 14 days as independent risk factors for death in COVID-19 patients [11]. In the TERAVOLT study in thoracic malignancies, only smoking was a risk factor [12]. In the UK Coronavirus Monitoring Project Team study, age, gender, and comorbidity were considered related to death, but not chemotherapy in the past month [13]. In a French cohort that included both RT-PCR positive and negative cases, male gender and low-performance status, having respiratory symptoms and cancer recurrence had a significant relationship with death [10]. In the New York hospital system in the USA, older age elevates lactate dehydrogenase (LDH), and D-dimer is significantly associated with death [14]. As is apparent, there are discrepancies in factors contributing to mortality in cancer patients with COVID-19. These may be explained by various definitions of variables and accessibility to various clinical and laboratory data in harsh epidemic situations. For example, the cut-off for the interval from the last chemotherapy was different among studies. Based on white blood cell count nadir after the most common regimens, we chose two weeks as the cut-off according to Zhang et al. [11].

Some limitations of the current study are the lack of critical information regarding the source of infection among those with COVID-19, the drug history, including steroids that affect the immune system, and the risk of re-infection at the second peak of the disease we experienced in Iran.

CONCLUSION

Patients with COVID-19 and a history of cancer have a considerably higher risk of death irrespective of age, gender, and other pre-existing conditions. Patients with advanced cancers and concurrent bacterial infections need the most vigorous care.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest

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