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Hospital and post-discharge mortality in COVID-19 patients with a preexisting cancer diagnosis in Iran

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Abstract

Background Despite the severe impact of COVID-19 on cancer patients, data on COVID-19 outcomes in cancer patients from low- and middle-income countries is limited. We conducted a large study about the mortality rate of COVID-19 in cancer patients in Iran.

Methods We analyzed data from 1,079 cancer (average age: 58.2 years) and 5,514 non-cancer patients (average age: 57.2 years) who were admitted for COVID-19 in two referral hospitals between March 2019 and August 2021. Patients were followed up until death or 31st August 2021. Multiple logistic regression models estimated the odds ratio (OR) and 95% confidence intervals (CI) of factors associated with ICU admission and intubation. The Cox regression model estimated hazard ratios (HRs) and 95% CI of factors associated with hospital and post-discharge 60-day mortalities.

Results The cancer patients had higher ICU admission (OR = 1.65, 95% CI: 1.42–1.91; *P*-value 0.03) and intubation (OR = 3.13, 95% CI = 2.63–3.73, *P*-value < 0.001) than non-cancer patients. Moreover, hospital mortality was significantly higher in cancer patients than in non-cancer patients (HR = 2.12, 95% CI: 1.89–2.41, *P*-value < 0.001). HR for the post-discharge mortality was higher in these patients (HR = 2.79, 95% CI: 2.49–3.11, < 0.001). The hospital, comorbidities, low oxygen saturation, being on active treatment, and non-solid tumor were significantly associated with ICU admission (*P*-value < 0.05) in cancer patients, while only low oxygen saturation was associated with intubation. In addition, we found that old age, females, low oxygen saturation level, active treatment, and having a metastatic tumor were associated with death due to COVID-19 (*P*-value < 0.05). Only lung cancer patients had a significantly higher risk of death compared to other cancer types (HR = 1.50, 95% CI: 1.06–2.10, *P*-value = 0.02).

Conclusion Cancer patients are at a higher risk of ICU admission, intubation, and death due to COVID-19 than non-cancer patients. Therefore, cancer patients who are infected with COVID-19 require intensive care in the hospital and active monitoring after their discharge from the hospital.

Keywords Cancer, COVID-19, Follow-up, Iran, Mortality

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Introduction

The SARS-CoV-2 (COVID-19) pandemic has had a profound impact on public health, resulting in increased mortality rates [1]. Among individuals with comorbidities, cancer patients are particularly susceptible to a higher risk of death and adverse COVID-19 outcomes [2–5]. Understanding the clinical course and outcomes of COVID-19 infection in cancer patients is crucial to update management strategies and improve patient outcomes [6].

Several cohort studies, systematic reviews, and meta-analyses have focused on COVID-19 infection in cancer patients, revealing important insights. These investigations have consistently indicated that cancer patients often exhibit lower platelet levels and higher levels of D-dimer, C-reactive protein, and prothrombin time, which increase the risk of COVID-19 infection-related complications. Therefore, diligent preventive care and early detection of COVID-19 infection are crucial for this vulnerable population [7–9]. Moreover, the mortality rate among cancer patients with COVID-19 infection is significantly higher compared to non-cancer patients [10]. An umbrella review of 10 meta-analyses, encompassing data from approximately one million cancer patients, found that the mortality rate due to COVID-19 is twice as high in cancer patients. Additionally, cancer patients are more likely to require intensive care unit (ICU) admission, highlighting the severity of the disease in this population [10].

It is important to consider the variability in outcomes observed among cancer patients with concurrent COVID-19 infection. Factors such as heterogeneous cancer populations, sample size, and ethnicity may influence patient outcomes [9, 11–13]. Previous research has indicated that advanced tumor stages and active chemotherapy treatment increase the risk of death due to COVID-19 in cancer patients [11]. Notably, lung cancer and hematologic malignancy patients face a higher risk, while breast and gynecological cancer patients exhibit a lower risk of COVID-19-related death [9]. A recent meta-analysis focusing on lung cancer and COVID-19 reported an 82% higher risk of COVID-19-related death among lung cancer patients compared to other cancer patients and more than a four-fold excess risk compared to non-cancer patients [12]. Furthermore, the complications of COVID-19 can prolong hospital stays and increase the risk of post-discharge mortality in cancer patients [13, 14]. Thus, continued care and follow-up are necessary after hospital discharge for cancer patients recovering from COVID-19. However, there is limited research on prognostic factors and post-discharge care specifically for cancer patients [15, 16]. Additionally, it is worth noting that most available data on COVID-19 and cancer patients predominantly come from high-income countries [10, 17, 18]. However, the situation may differ in low- and middle-income countries (LMIC); where the capacity for managing COVID-19 is limited.

To address these gaps, we conducted a large prospective study in Iran, to study ICU admission, intubation, hospital, and post-discharge death due to COVID-19 among cancer patients compared to non-cancer patients. Specifically, we aimed to study factors associated with the prognosis of COVID-19 among cancer patients.

Methods

Data collection

In a cohort study, we obtained the data for this study from the TUMS-COVID-19 registry, a clinical registry established in March 2019 at the Imam Khomeini Hospital Complex, Tehran University of Medical Sciences (TUMS) [23]. The registry was later expanded to include other educational hospitals within the TUMS hospital network. Six hospitals participated in the TUMS-COVID-19 registry, where clinical data from all COVID-19 patients admitted to the hospitals were collected, based on clinical diagnoses and confirmed through PCR tests or CT scan findings. The registry contains comprehensive clinical information, including symptoms, signs, chest CT scan results, personal history, comorbidities, and main outcomes such as ICU admission, intubation, and death. For this specific study, we utilized data from 7,512 COVID-19 patients admitted between March 2019 and August 2021 in two referral hospitals: Imam Khomeini and Shariati Hospitals, which are known for providing comprehensive care for cancer patients. Cancer patients were patients who had active cancer during the admission for COVID-19 or reported a history of cancer beforehand.

Cancer patients were individuals diagnosed with cancer before COVID-19 infection, while non-cancer patients were individuals admitted to hospitals due to COVID-19 but had no history of cancer. Based on treatment status, we categorized cancer patients into two groups including active and non-active treatment. The active treatment group included patients who were receiving curative treatments, such as surgery, chemotherapy, or radiotherapy, or had their cancer diagnosed within the past 12 months. While some research groups define the active cancer period as within 6 months up to 2 years, we took a conservative approach due to the potential delays in diagnosis and treatment commonly observed in low and middle-income countries, including Iran. Therefore, we considered patients who initiated their treatment within one year as having active cancer [24]. The non-active treatment group included patients who were not currently receiving active curative therapy and were either under follow-up care or receiving maintenance treatment, such as hormone therapy.

COVID-19 registry provided patient information such as age, gender, smoking status, comorbidity condition, oxygen saturation, ICU admission, intubation, and length of hospital stay, as well as available PCR-test results and CT scan findings, for all patients in the COVID-19 registry. For cancer patients, we actively extracted data on cancer type, stage of the disease, date of diagnosis, and treatment status from hospital records. In cases where information was missing in the medical records, we conducted telephone interviews with the patients or their next of kin to obtain the necessary data. Additionally, we used linkage with the death registry to ascertain the vital status of patients after their discharge from the hospital.

Inclusion and exclusion criteria

Inclusion criteria were to have a confirmed diagnosis with a PCR test or CT scan, age older than 20 years, and availability of the clinical, outcome information (Fig. 1). Exclusion criteria were COVID-19 diagnosis without confirmation by PCR test or CT scan, and being younger than 20 years old. In addition, patients with missing or inaccurate information on admission or discharge dates were excluded.

Follow-up

Patients were followed up the time they were admitted to the hospital until death or August 2021, whichever came first. In survival analysis to study hospital mortality, all patients were censored at the time death or of their discharge. The Kaplan-Meier curve showed that the mortality pattern stabilized after discharge until day 60. Therefore, we assumed that any death occurring within 60 days of admission could be attributed to COVID-19 (Fig. 2). As a result, analyses of COVID-19 related death were performed based on follow-up until the date of death or day 60, whichever came first. In these analysis, patient who were alive until 60 days, were considered as censored in the survival model.

Variables

We studied the variables associated with COVID-19 outcomes, including a history of cigarette smoking (ever/never), hospital (A/B), oxygen saturation (>95%, 90–94%, 85–89%, <85%) in which an O2 saturation higher than 95% was assumed as the reference group, and the number of comorbidities grouped into four groups (i.e., 0, 1, 2, and ≥3 comorbidities) based on the history of obesity (body mass index of higher than 35), and diabetes, hypertension, lung disease, chronic kidney disease, liver disease, cardiovascular disease, neurologic disease, or

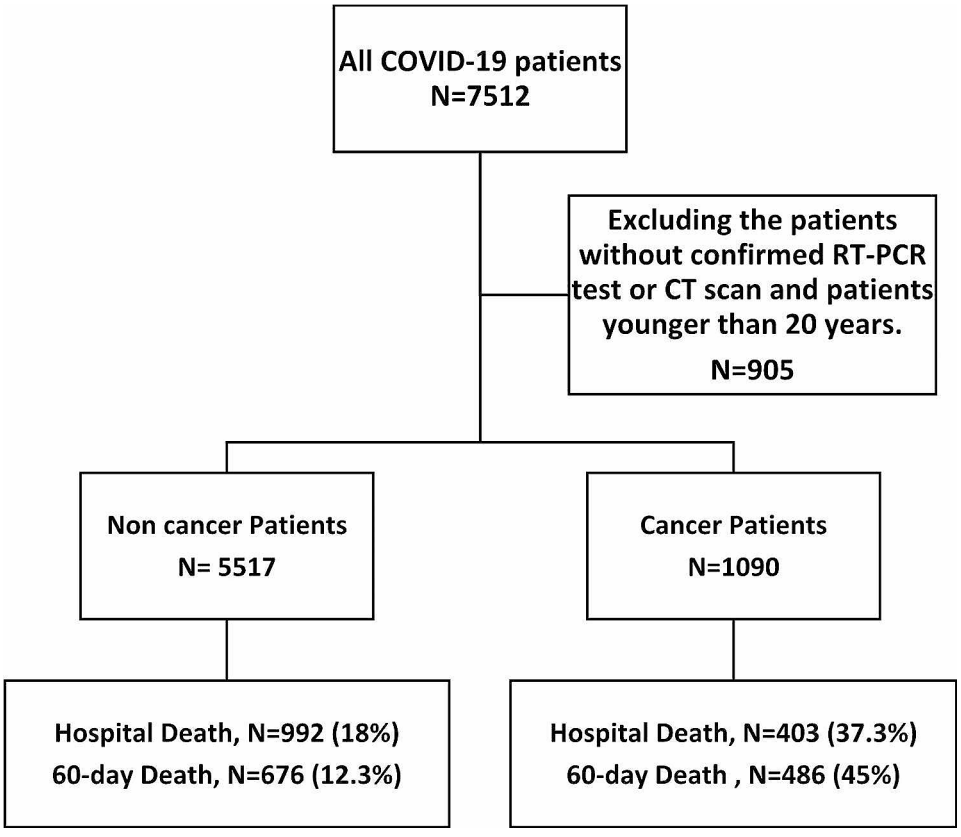

Fig. 1 The flowchart of cancer and non-cancer patients with COVID-19 recruited in this study

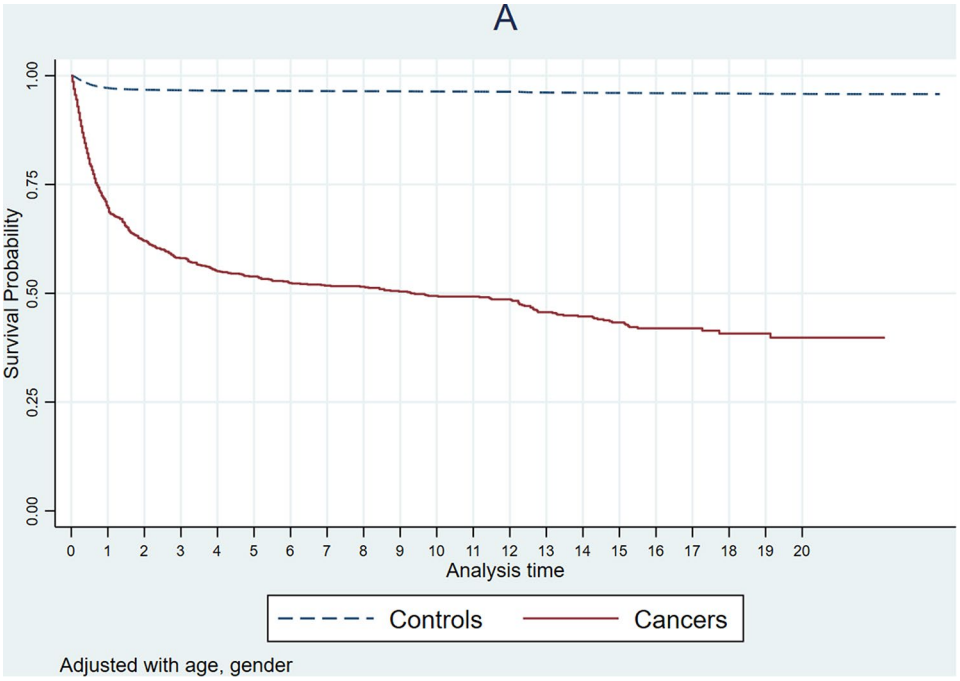

Fig. 2 Hazard line of death due to COVID-19 in cancer and non-cancer patients in Tehran, Iran

immune system disease. Additionally, we considered the metastasis status (yes/no) and treatment status (active/non-active treatment). We also studied the patient outcomes based on the more frequent cancer types defined as non-solid or hematologic cancers, including leukemia or lymphoma, and solid tumors, including lung, breast, colorectal, bladder, head and neck, breast, kidney, and prostate cancers.

Statistical analysis

First, qualitative variables were reported with frequency and percentage and quantitative variables were reported with mean and standard deviation. We used simple and multiple logistic regression to identify factors influencing the rate of hospitalization in ICU and intubation in cancer patients due to covid-19. We also used logistic regression to estimate the odds ratio of cancer patients compared to non-cancer patients in ICU admission and intubation. Finally, we used Cox regression to estimate the risk of death in the hospital and death after 60 days in cancer patients compared to non-cancer patients. In addition, Cox regression was used to identify the factors affecting hospital death and death after 60 days among cancer patients, as well as to separate solid and non-solid cancer. We also fitted separate Cox regression models for each specific cancer type to study the impact of COVID-19 outcomes by cancer subsite. To perform these analyses, simple logistic or Cox regression was performed first, and finally, to control confounders, we used the stepwise approach and included all variables with a *p*-value less than 0.25 were entered into multiple regression. All analyses were performed using Stata14 (Stata Statistical Software: Release 14, College Station, TX: Stata Corp LLC). A significance level of 5%. Statistical analyses were performed.

Results

Descriptive information of study participants

The majority of patients were male (56%), and the average age in both groups was about 58 years (Table 1). The prevalence of comorbidities was 57.5 in cancer patients and 67.8 in non-cancer patients. Dyspnea, fever, weakness, and dry cough were the most common symptoms in both groups, and these symptoms were more frequent in non-cancerous patients. About 85% of patients underwent a PCR-COVID-19 test and 90% underwent a CT scan for diagnosis of COVID-19, from which about 65.1 of cancer and 70% of non-cancer patients were positive based on PCR test and about 88% of both groups had an abnormality in favor of COVID-19 diagnosis. The duration of hospital stay was about three times longer in cancer patients (18.3 days) than in non-cancer patients (6.9 days).

Outcomes of cancer patients compared to non-cancer patients

ICU admission was significantly higher in cancer patients than in non-cancer patients (OR = 1.65, 95% CI:1.42–1.91; *P*-value < 0.001) (Table 2). Furthermore, we observed a higher intubation rate among cancer patients compared

Table 1 Descriptive information of cancer and non-cancer patients with COVID-19 infection in Tehran, Iran

Variables	Cancer Patients *N* = 1,079	Non-Cancer Patients *N* = 5,514
Age, years, Mean (±SD)	58.16 (15.78)	57.87 (16.49)
Sex N (%)		
Female	465 (43.10)	2,432 (44.11)
Male	614 (56.90)	3,082 (55.89)
Comorbidities		
No comorbidity	459 (42.54)	1,778 (32.25)
Any Comorbidity	598 (57.46)	3,736 (67.75)
1 Comorbidity	277 (25.67)	1,563 (28.35)
2 Comorbidities	198 (18.35)	1,168 (21.18)
>=3 Comorbidities	145 (13.44)	1,005 (18.23)
Cigarette Smoking		
No	866 (80.26)	5098 (92.46)
Yes	213 (19.74)	416 (7.54)
Common symptoms		
Dyspnea	512 (47.45)	3584 (65.00)
Weakness/lethargy	489 (45.32)	2586 (46.90)
Fever	436 (40.00)	3312 (60.03)
Dry cough	344 (31.88)	3063 (55.55)
Myalgia	234 (21.69)	2527 (45.83)
Trembling	183 (16.96)	1941 (35.20)
Nausea	171 (15.85)	1272 (23.07)
Vomiting	154 (14.57)	1080 (19.59)
Wet cough	105 (9.73)	629 (11.41)
Diarrhea	104 (9.64)	743 (13.47)
Sore throat	68 (6.30)	570 (10.34)
Sweating	59 (5.47)	457 (8.29)
Fatigue	10 (0.93)	145 (2.63)
PCR result		
Positive	703 (65.15)	3,919 (71.07)
Negative	170 (15.76)	950 (17.23)
Not available	206 (19.09)	645 (11.70)
CT abnormality		
Positive	962 (88.16)	4,839 (87.76)
Negative	26 (2.41)	84 (1.52)
Not available	91 (8.43)	591 (10.72)
O_2 saturation percentage, Mean (±SD)	90.39 (8.32)	88.79 (8.31)
Duration of stay, days, Mean (±SD)	12.66 (18.30)	6.92 (6.85)

SD = Standard deviation; O_2 = Oxygen; ICU = Intensive Care Unit; PCR = Polymerase Chain Reaction; CT = Computed Tomography

with non-cancer patients (OR = 3.13, 95% CI: 2.63–3.73, *P*value > 0.001). Follow-up of the patients from admission to and discharge from hospitals provided 95,337 and 16,289 person-days, 676 and 403 deaths, and mortality rates of 8.9 and 24.7 per 1000 person days for non-cancer and cancer patients, respectively. Cancer patients had more than two times higher hospital death compared to non-cancer patients (HR = 2.12, 95% CI: 1.89–2.41; *P*-value < 0.001). The 60-day mortality was higher in cancer patients than non-cancer patients (HR = 2.79, 95% CI: 2.49–3.11; *P*-value < 0.001).

Factors affecting ICU admission, intubation, hospital mortality, and death 60 days after discharge

We found a statistically significant excess rate of ICU admission in hospital B compared to hospital A (OR = 1.40, 95% CI: 1.04–1.86; *P*-value < 0.001), reporting any comorbidity (OR = 1.45, 95% CI 1.07–1.96; *P*-value = 0.02) compared to no comorbidity, an O_2 saturation of lower than 85% (OR = 2.19, 95% CI: 1.40–3.45; *P*-value = 0.001) compared to O_2 higher than 95%, being on active treatment (OR = 1.41, 95% CI: 1.05–1.87; *P*-value = 0.04) (Table 3). The ICU admission rate was significantly higher in lung (OR = 2.04, 95% CI: 1.20–3.47; *P*-value = 0.01) and colorectal (OR = 1.72, 95% CI: 1.06–2.79; *P*-value = 0.03) cancers compared to other cancer types. However, only an O_2 saturation of lower than 85% was a significantly higher risk of intubation compared to those who had a saturation of higher than 95% (OR = 2.52, 95% CI: 1.58–4.03, *P*-value < 0.001) (Table 3).

Factors affecting death due to COVID-19 in cancer patients overall and by cancer type

Survival analysis showed a statistically higher risk of death due to COVID-19 in patients who were aged between 70 and 79 years (HR = 1.42, 95% CI: 1.07–1.90, *P*-value = 0.02) or were older than 80 (HR = 1.56, 95% CI: 1.07–2.29, *P*-value = 0.02) (Table 4). In addition, the excess risk of death was statistically significant with an O_2 saturation level lower than 85% (HR = 1.65, 95% CI: 1.24–2.20, *P*-value < 0.001), having a metastasis (HR = 1.72, 95% CI: 1.42–2.10, *P*-value < 0.0001), and being on active treatment (HR = 1.32, 95% CI: 1.09–1.61; *P*-value = 0.006) compared to their reference groups. We found that the risk of COVID-19 death was higher in lung cancer compared to other cancer types (HR = 1.50, 95% CI: 1.06–2.1,0 *P*-value = 0.02). Cigarette smoking and the hospital were not associated with death due to COVID-19 in cancer patients.

In patients with a non-solid tumor, only an age higher than 80 (HR = 3.16, 95% CI: 1.36–7.35; *P*-value = 0.01) was associated with the risk of death. However, being female (HR = 0.72, 95% CI: 0.52–0.94; *P*-value = 0.006), O_2 saturation lower than 85 (HR = 1.81, 95% CI: 1.26–2.61; *P*-value = 0.001), being on active treatment (HR = 1.31, 95% CI: 1.01–1.69; *P*-value = 0.04) and metastasis status (HR = 2.10, 95% CI: 1.60–2.76; *P*-value < 0.001) increased the risk of death in cancer patients.

Discussion

Our study explored the outcomes of Iranian cancer patients who were hospitalized with COVID-19, shedding light on the impact of COVID-19 on this vulnerable population. We found that COVID-19 patients with a history of cancer had a significantly higher risk of ICU admission, intubation, and COVID-19-related

Table 2 Outcomes of cancer patients compared to non-cancer patients with COVID-19 infection in in Tehran, Iran

	Non-cancer patients *N* = 5514	Cancer patients *N* = 1079
ICU Admission		
No. of ICU admission (%)	1467 (26.61%)	389 (36.05%)
Crude OR (95% CI); *P*-value	Reference	1.55 (1.35–1.79); *P*-value < 0.001
Adjusted OR (95% CI); *P*-value*	Reference	1.65 (1.42–1.91); *P*-value < 0.001
Intubation		
No. of intubated (%)	639 (11.59%)	276 (25.58%)
Crude OR (95% CI); *P*-value	Reference	2.62 (2.23–3.07); *P*-value < 0.001
Adjusted OR (95% CI); *P*-value*	Reference	3.13 (2.63–3.73); *P*-value < 0.001
Hospital Mortality		
Person Year	95,337	16,289
N. of death	676 (12.3%)	403 (37.3%)
Mortality Rate	8.9 per 1000	24.7 per 1000
Crude HR (95% CI); *P*-value	Reference	1.79 (1.59–2.02); *P*-value < 0.001
Adjusted HR (95% CI); *P*-value*	Reference	2.12 (1.89–2.41); *P*-value < 0.001
60-day mortality		
Person Year	194946	35566
No. of death (%)	992 (18.0%)	486 (45.0%)
Mortality Rate	5.08/1000	13.64/100
Crude HR (95% CI); *P*-value	Reference	2.58 (2.48–3.13); *P*-value < 0.001
Adjusted HR (95% CI); *P*-value*	Reference	2.79 (2.49–3.11); *P*-value < 0.001

*ORs were adjusted for age, gender, number of comorbidities, O2 saturation level, and hospital. The HRs additionally were adjusted for smoking status

death compared to non-cancer patients. The excess risk of death resumed after discharge from the hospital. We found the hospital, comorbidities, low oxygen saturation, being on active treatment, and having a non-solid tumor were significantly associated with ICU admission, but only the low oxygen saturation was associated with the odds of intubation. In addition, we showed that old age, females, low oxygen saturation level at admission, active treatment, and having a metastatic tumor were associated with death due to COVID-19 in cancer patients. Lung cancer patients had a significantly higher risk of death due to COVID-19 compared to other cancer types.

Our findings are consistent with a meta-analysis based on 32 studies, which reported a higher mortality rate of COVID-19 in cancer patients compared to non-cancer patients [19]. Similar trends were observed in studies from China and Italy, where patients with different malignancies experienced a higher prevalence of COVID-19 infection and a higher mortality rate than other COVID-19 patients [20, 21]. The case fatality rate of cancer patients with COVID-19 infection varied across studies, with rates reported as 28.6%, 20% in China [5, 6, 22], and 5.1% in Turkey [19]. Moreover, a recent systematic review highlighted a summary relative risk of COVID-19 mortality in cancer patients compared to non-cancer patients, further supporting the notion that cancer patients are at a higher risk of severe outcomes [23]. Another systematic review showed that the relative risk of COVID-19 death in cancer patients appeared slightly higher in Asia compared to Europe and the US [24].

In Middle Eastern countries, the research on COVID-19 outcomes among Iranian cancer patients has been somewhat limited. One study conducted in Mashhad, northeastern Iran, involving 92 cancer patients, revealed that these patients experienced atypical symptoms and faced a higher risk of death compared to non-cancer patients [25]. A smaller study in Sabzevar city, also in the northeastern region, further supported these findings by reporting a higher mortality rate among cancer patients [26]. Similarly, a study in Hamadan City, Iran, consisting of 66 cancer patients, identified significant factors like ICU admission, mechanical ventilation, and length of hospital stay as key contributors to death risk in cancer patients during the COVID-19 infection [27]. Moreover, another study from Shariati Hospital in Tehran, which compared 66 cancer patients with 106 non-cancer patients, found that hematologic malignancies had a higher mortality rate than solid tumors, and multiple regression analyses showed a 3.5 times higher risk of death and significantly longer hospital stays in cancer patients compared to non-cancer patients [46]. A cohort study in Iran that followed 1294 cancer patients over a period of approximately 20 months reported 122 COVID-19 incidents during the follow-up, with 44 resulting in hospitalizations and only 6 deaths. This study also found that patients under palliative treatment had a significantly higher risk of COVID-19 infection. Hematological malignancies exhibited the highest incidence density of COVID-19 (24.3%), while other cancer sites had lower rates (below 11%). Head and neck cancer patients

Table 3 Factors affecting ICU admission, intubation, hospital mortality, and death 60 days after discharge among cancerpatientss in Tehran, Iran

	No. of Patients*	ICU Admission			Intubation		
		Percentage	OR** (95% CI)	*P*-value	Percentage	OR* (95% CI)	*P*-value
Age group (year)							
<60	536	34.5	Reference	-	26.1	Reference	
60–69	270	37.0	0.99 (0.70–1.41)	0.97	23.3	0.70 (0.47–1.05)	0.08
70–79	188	37.2	0.77 (0.49–1.20)	0.25	26.1	0.75 (0.47–1.20)	0.23
80+	83	41.0	1.57 (0.89–2.77)	0.12	28.9	1.08 (0.59–1.97)	0.81
Gender							
Male	614	37.1	Reference		26.2	Reference	
Female	465	34.6	0.84 (0.63–1.12)	0.23	24.7	0.90 (0.66–1.23)	0.51
Hospital							
A	586	31.4	Reference		25.6	Reference	
B	493	41.6	1.40 (1.04–1.86)	0.02	25.6	1.09 (0.80–1.49)	0.90
O2 Saturation (%)							
95+	369	30.5	Reference		21.1	Reference	
90–94	261	33.7	1.20 (0.81–1.76)	0.36	21.8	1.28 (0.73–1.72)	0..58
85–89	165	33.3	1.09 (0.69–1.74)	0.70	24.9	1.09 (0.65–1.80)	0.75
<85	155	52.3	2.19 (1.40–3.42)	0.001	40.0	2.52 (1.58–4.03)	< 0.001
Comorbidities							
No	459	31.6	Reference		23.1	Reference	
Any	620	39.4	1.45 (1.07–140)	0.02	27.4	1.32 (0.96–1.83)	0.90
1	277	37.9	1.42 (0.99–2.02)	0.05	21.1	1.29 (0.88–1.89)	0.19
2	198	41.9	1.59 (1.05–2.40)	0.01	26.0	1.37 (0.88–2.14)	0.16
3+	145	38.6	1.46 (0.91–2.34)	0.12	27.8	1.46 (0.86–2.41)	0.15
Treatment status							
Non-active	413	31.2	Reference		23.2	Reference	
Active	461	38.1	1.41 (1.05–1.87)	0.02	29.3	1.35 (0.99–1.84)	0.06
Cancer type* **							
Non-solid tumor	417	34.3	0.77 (0.58–1.03)	0.08	24.7	0.91 (0.66–1.22)	0.56
Solid tumors	662	37.2	1.29 (0.97–1.71)	0.08	26.1	1.10 (0.80–1.49)	0.56
Lung	63	52.4	2.04 (1.20–3.47)	0.01	34.9	1.54 (0.89–2.69)	0.12
Colorectal	86	54.7	1.72 (1.06–2.79)	0.03	33.7	1.72 (1.06–2.80)	0.07
Upper GI	82	41.5	1.34 (0.81–2.23)	0.26	30.5	1.24 (0.80–2.23)	0.26
Liver	42	38.1	1.03 (0.50–2.12)	0.92	26.2	1.03 (0.50–2.12)	0.92
Breast	102	30.4	0.85 (0.52–1.39)	0.52	25.5	1.03 (0.61–1.73)	0.63
Bladder	27	29.6	0.68 (0.29–1.60)	0.38	33.3	1.57 (0.68–3.65)	0.29
Head & Neck	36	44.4	1.62 (0.81–3.22)	0.17	20.6	1.28 (0.61–2.69)	0.51
Prostate	47	27.7	0.56 (0.27–1.13)	0.11	17.0	0.52 (0.22–1.20)	0.13

*The sum of the patients does not reach the total number due to missing values

**Multivariate models included Age, gender, number of comorbidities, O2 saturation level, and hospital, and treatment status

***Specific models were fitted to each cancer type, where all other cancer types were the reference group

showed the lowest risk of COVID-19 (2.8%) [28]. Despite the valuable insights provided by these studies, their small sample sizes limited the scope of analysis, especially when examining the effects of various patients and clinical factors on patient outcomes. In contrast, the current study, the largest investigation in Iran and the Eastern Mediterranean region, has significantly advanced the understanding of COVID-19's impact on cancer patients. Its larger sample size has the potential to offer a comprehensive and robust analysis of the intricate relationship between cancer and COVID-19, providing crucial information for future research and medical practices.

Covid-19 patients with a history of hematologic malignancy experience a higher mortality rate compared to other cancers in China (41-62%) (36), the USA (37%) [29], and the UK (36%) [19]. The COVID-19 Cancer Consortium (CCC19), an international collaboration of 120 institutions from the United States, European Union, Argentina, Canada, Mexico, and the United Kingdom, reported a mortality rate of 12% and 14% for solid and non-solid tumors [30]. The high mortality in

Table 4 Factors affecting death due to COVID-19 in cancer patients overall and by cancer types in Tehran, Iran

Variables	All Cancer Patients			Non-solid tumors			Solid tumor		
	No. of Death*	HR (95% CI) *	*P*-value	No. of Death*	HR (95% CI) **	*P*-value	No. of Death*	HR (95% CI)	*P*-value
Age group (year)									
<60	225	Reference		114	Reference		11	Reference	
60–69	125	1.10 (0.86–1.42)	0.42	39	1.31 (0.87–1.99)	0.19	86	1.01 (0.74–1.39)	0.73
70–79	97	1.42 (1.07–1.90)	0.02	26	1.45 (0.88–2.45)	0.15	71	1.39 (0.98-2.00)	0.07
80+	46	1.56 (1.07–2.29)	0.02	9	3.16 (1.36–7.35)	0.01	37	1.43 (0.92–2.24)	0.11
Gender									
Male	299	Reference		120	Reference		179	Reference	
Female	196	0.80 (0.65–0.98)	0.03	68	0.94 (0.68–1.31)	0.75	128	0.72 (0.56–0.94)	0.02
O2 Saturation									
95+	171	Reference		82	Reference		89	Reference	
90–94	105	0.93 (0.72–1.22)	0.57	36	0.80 (0.52–1.23)	0.32	69	0.99 (0.69–1.40)	0.94
85–89	64	0.81 (0.58–1.13)	0.30	18	0.97 (0.55–1.72)	0.93	46	0.77 (0.51–1.17)	0.22
<85	97	1.65 (1.24–2.20)	< 0.001	35	1.24 (0.77–2.09)	0.37	62	1.81 (1.26–2.61)	0.001
No. of Comorbidity									
0	209	Reference		95	Reference		110	Reference	
1	121	0.86 (0.67–1.11)	0.25	42	0.68 (0.45–1.02)	0.06	79	1.02 (0.74–1.40)	0.94
2	104	1.09 (0.83–1.42)	0.52	36	1.34 (0.87–2.09)	0.19	68	1.09 (0.77–1.55)	0.61
3+	65	0.89 (0.64–1.23)	0.45	15	0.87 (0.48–1.61)	0.69	50	0.94 (0.63–1.40)	0.77
Treatment Status									
Non-active	177	Reference		65	Reference		112	Reference	
Active **	246	1.32 (1.09–1.61)	0. 006	100	1.30 (0.96–1.7)	0.08	146	1.31 (1.01–1.69)	0.04
Metastasis status									
No	250	Reference		-	-		109	Reference	
Yes	245	1.72 (1.42–2.10)	< 0.001	-	-		198	2.10 (1.60–2.76)	< 0.001
Cancer type* **									
Non-solid tumor	188	0.95 (0.78–1.16)	0.63						
Solid tumors	307	1.05 (0.86–1.29)	0.63						
Lung	37	1.50 (1.06–2.10)	0.02						
Colorectal	43	1.21 (0.87–1.67)	0.26						
Upper GI	45	1.24 (0.90–1.72)	0.18						
Liver	21	1.12 (0.72–1.73)	0.63						
Breast	47	1.18 (0.83–1.67)	0.37						
Bladder	13	1.27 (0.72–2.24)	0.40						
Head & Neck	15	0.90 (0.54–1.52)	0.71						
Prostate	21	0.79 (0.49–1.29)	0.35						

****The sum of the patients does not reach the total number due to missing values

**Multivariate models included Age, gender, number of comorbidities, O2 saturation level, and hospital, and treatment status

**Specific models were fitted to each cancer type, where all other cancer types were the reference group

hematological malignancies has been linked to intense immunosuppressive treatment [19] and higher susceptibility to viral infection in non-solid tumors [19]. In our study, the case fatality rate due to COVID-19 in non-solid tumors was higher (41.7%) than in non-solid tumors (34.9%) overall. Notably, lung cancer showed a significantly higher risk in our study, consistent with findings from China [29, 31], the USA, the UK [19], and Turkey [11]. Involvement of the upper aerodigestive system in head and neck cancer, upper GI tract, and lung cancers, and a high prevalence of metastasis (63.5%) during COVID-19 infection increased the risk of death among solid tumors in our study [23, 32]. Differences in study designs, types of recruited cancers, study power, comorbidity prevalence, adjustment for confounding variables, access to standards of care in different countries [33], and patient recruitment at various times and phases of the COVID-19 pandemic [34] may contribute to the varying reports on mortality rates among cancer patients with COVID-19 [23, 32].

Comorbidities have been linked to a poorer prognosis in COVID-19 [40]. In our cohort study, 57.3% of cancer patients had at least one comorbidity, including hypertension (31.38%), diabetes mellitus (23.8%), and heart

disease (19.4%). However, after adjusting for confounding factors, we did not find a significant association between comorbidities and the risk of COVID-19 death among cancer patients. While some limited studies supported our findings [35], most research in a systematic review has shown an association between comorbidities and an increased risk of severe outcomes [36]. Furthermore, smoking has been associated with the progression of Covid-19 [37]. In our study, we did not find a significant relationship between smoking and the risk of death due to Covid-19 overall. However, non-solid tumors in patients who were smokers showed a higher risk of death compared to non-smokers.

In the current study, cancer patients exhibited significantly higher rates of ICU admission and intubation compared to non-cancer patients. These findings are consistent with previous research in a meta-analysis indicating that ICU admission was 45% higher in cancer patients compared to non-cancer patients [38]. A systematic review and meta-analysis also supported these results, revealing that cancer patients had a twofold higher risk of adverse outcomes, including ICU admission, compared to non-cancer patients [24]. ICU admission rates for COVID-19 patients have varied globally [9], with reports ranging from 7 to 19% [39–41] to 35% in certain reports [42].

In our study, 35.8% of cancer patients required admission to the ICU, which was relatively higher than the rates reported in some previous studies [41, 42]. The higher ICU admission rate in our cancer patients could be attributed to the perception of cancer patients as a high-risk group for severe COVID-19 infection, leading to a more cautious approach and intensive care provision. Some studies with lower ICU admission rates have mentioned that a larger number of their cancer patients met the criteria for ICU admission, but resource constraints limited the allocation to all eligible patients [39, 41].

The strengths of this study lie in its recruitment of a substantial number of cancer patients and the comprehensive collection of clinical data, including cancer stage, type, and treatment status. The inclusion of relevant confounding variables such as oxygen saturation, tobacco smoking history, and comorbidities enhances the study's validity. Notably, the analysis of 60-day mortality provides valuable insights into the importance of follow-up care after COVID-19 discharge, augmenting the existing evidence. However, the study has some limitations. Firstly, the lack of laboratory tests as prognostic indicators and markers of organ damage could limit a comprehensive understanding of disease progression. Previous research has shown the association of inflammatory markers like neutrophil to lymphocyte ratio (NLR), C-reactive protein (CRP), procalcitonin, ferritin levels, albumin status, creatinine, and troponin I with mortality risk [15,33,47–50]. Additionally, the absence of data on vaccination status, a significant factor in preventing death, may potentially confound the study's results if not considered. Despite reporting a large overall sample size, the limited number of cancer cases for each subsite might have some impact on specific subgroup analyses. However, the inclusion of a substantial comparison reference group partially mitigates this limitation.

In conclusion, this study highlights that cancer patients face a significantly higher risk of severe outcomes when infected with COVID-19, particularly those with lung cancer. The prognosis for COVID-19 is notably poor for almost all cancer types, especially in patients undergoing active treatment, with metastatic disease, and those with low oxygen saturation levels. To reduce their risk of contracting COVID-19, cancer patients must adopt strong protective measures. Furthermore, COVID-19-infected cancer patients require intensive care during their hospitalization, and close monitoring is essential even after their discharge from the hospital.

Abbreviations

CI	Confidence intervals
COVID-19	Corona Virus Disease of 2019
GI	Gastrointestinal
HR	Hazard Ratio
ICU	Intensive Care Unit
OR	Odds ratios
PCR	Polymerase Chain Reaction
SD	Standard deviation
TUMS	Tehran University of Medical Sciences

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Author contributions

MS.S: Conceptualization, Methodology, Formal analysis, Data curation, Writing-Original draft preparation, Project administration; M.R: Conceptualization, Methodology Original draft preparation, Writing- Reviewing and Editing; R.Gh: Conceptualization, Writing- Reviewing and Editing, A.N: Conceptualization, Writing- Reviewing and Editing; B.E: Conceptualization, Writing- Reviewing and Editing, Z.Sh: Original draft preparation, Writing- Reviewing and Editing; SF.A: Resources, Writing- Reviewing and Editing; K.Z: Conceptualization, Methodology, Formal analysis, Supervision. All authors read and approved the final manuscript.

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Data availability

The data underlying this article cannot be shared due to the privacy of patients who participated in the study. Anonymous data may be shared upon request from an agreement with the corresponding author. Additional permission from the IRB of the Cancer Institute of Iran will be needed.

Declarations

Ethics approval and consent to participate

Our study was approved by the Tehran University Medical Sciences Ethics Committee under code number IR.TUMS.VCR.REC.1399.309. All authors confirm that all methods were carried out under relevant guidelines and

regulations (declarations of Helsinki). Also, we confirmed that "informed consent" was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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