

Long-term outcomes of COVID-19 infection in patients with solid tumors

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ABSTRACT

Objectives: We analyzed the impact of some clinical and disease-specific factors on the long-term outcomes of SARS-CoV-2 infection in patients with solid tumors.

Methods: Total of 739 patients with known solid malignancy and infected by SARS-CoV-2 before the beginning of vaccination were examined.

Results: Seventy-six cancer patients died from COVID-19 infection-related effects such as mostly pulmonary and cardiovascular system disorders after a median 16-month follow-up (67.1% and 14.5%; respectively). Compared with survivors (n = 468), non-survivors due to COVID-19 infection related effects (n = 76) were more likely to be aged ≥ 65 years and diagnosis with lung cancer ($p = 0.01$). Also, female patients were at decreased risk of mortality [OR: 0.34 (95% CI: 0.18-0.65)]. Furthermore, patients with tumor stage IV, active/stable/progressive disease and patients receiving active anticancer therapy were at increased risk of mortality ($p = 0.01$).

Conclusions: The patients with aged ≥ 65 years, diagnosed with lung cancer, receiving active anticancer therapy, with active/stable/progressive and advanced cancer stage were at increased risk of mortality from COVID-19 infection in long-term follow-up.

Keywords: Cancer patients, COVID-19, mortality, long-term outcomes

The pandemic of SARS-CoV-2 infection have led to considerably increased mortality and morbidity [1, 2]. Furthermore, it is known that COVID-19 survivors could survive many multisystem sequelae ranging from pulmonary, cardiovascular system changes to neurocognitive disorders [3, 4]. As shown in the studies, patients with a diagnosis of cancer have increased risk for worse SARS-CoV-2 infection-related outcomes compared to the healthy population [5-8]. Approximately 60%-80% of the patients with cancer

infected with SARS-CoV-2 survive infection critically [9-11].

SARS-CoV-2 infection-related case fatality rates in patients with solid cancer have been reported to range from 13% to 41% in the literature [9, 12, 13]. While ElGohary *et al.* [14] showed that a mortality rate of up to 21% and an intensive care unit hospitalization rate of 14% in patients with cancer, Barlesi *et al.* [15] did not show any difference in mortality compared to the normal population. The large population-

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based data on outcomes of 20.133 patients with COVID-19 demonstrated that mortality was significantly increased in patients with neoplasm [16]. Also, the study revealed that when needed to stay in the intensive care unit, patients with immunosuppressed systems showed increased mortality [17].

In the literature, increasing age, comorbidities and immunosuppression by the disease and/or its treatment are shown to be risk factors for poor outcomes after COVID-19 in patients with cancer [18, 19]. Also, smoking, poor performance status, oncological characteristics such as specific cancer types, tumor stage, presence of active cancer and recent systemic anti-cancer therapy may contribute to worse prognosis in patients with cancer during COVID-19 infection [13, 20-22].

Increased SARS-CoV-2 testing capacity and discovering of SARS-CoV-2 biology and clinical management of the infection and complications by several new therapies, vaccinal campaigns have improved the outcomes of COVID-19 infection in this vulnerable population [23-26]. In this report, we intended to analyze the impact of some clinical and disease specific factors on the outcomes of COVID-19 infection in patients with solid tumors before the beginning of vaccination period.

METHODS

Patient Population

A total of 739 patients, followed up with the diagnosis of solid malignancy in our department and infected by SARS-CoV-2 (positive nasopharyngeal swab) between May 2020 and December 2020 (pre-vaccine period in our country) were examined retrospectively. The patients with aged ≥ 18 years, diagnosis of SARS-CoV-2 infection confirmed by nasopharyngeal swab, diagnosis of active or in remission solid cancer were included in the study. Active cancer therapy was defined as patients who received anti-cancer treatment (Chemotherapy, hormonal therapy, immunotherapy, targeted therapy) within 4 weeks period before the diagnosis of COVID-19 infection.

Data Collection

Data about demographic characteristics, cancer diagnosis, SARS-CoV-2 infection, mortality, morbidity

and long-term outcomes of the patients were retrospectively collected from the hospital database. The cancer status of the patients was collected at the time of SARS-CoV-2 infection and at follow-up period.

The study was conducted by the Declaration of Helsinki and was approved by the Gazi University local ethics committee. Ethics Committee approval has been obtained (Date: 05.07.2022 , Decision no.: 13).

Statistical Analysis

The Statistical Package for the Social Sciences software version 23 (SPSS) was used for the statistical analysis. The presence of a normal distribution was investigated using visual and analytical methods. Categorical measurements were presented as number (n) and percentage (%). As normally distributed quantitative variables were described as mean values \pm standard deviation, non-normally distributed variables were expressed as median values (range). While, non-parametric tests were used to compare the parameters and the ordinal variables, the chisquare test was used to compare the proportions in different groups. For multivariate analysis, logistic regression analysis was performed to determine independent predictors of patient outcome. A value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 739 patients (378 males, 361 females) median aged 61 years (18-94) were included in the study. The baseline characteristics of the patients during COVID-19 infection are demonstrated in Table 1. The most common diagnosed malignancies were lung cancer, gastrointestinal cancer and breast cancer (25.7%, 24.4%, and 19.4%; respectively). Thirteen point nine percent of the patients had at least two comorbidities, such as hypertension, diabetes mellitus, chronic obstructive lung disease. Most (42.4%) of the patients had stage IV disease. While 312 (42.2%) patients were in remission from cancer, 427 (57.8%) patients were with active cancer. Also, 362 (49%) patients were on active anticancer therapy in the last 4 weeks before COVID-19 infection.

The clinical characteristics of the patients during COVID-19 infection are demonstrated in Table 2.

Table 1. Baseline characteristics of the patients (n = 739)

Characteristics	Data	
Age, n (%)	< 65 years	462 (62.5)
	≥ 65 years	277 (37.5)
Sex, n (%)	Male	378 (51.2)
	Female	361 (48.8)
Comorbidities, n (%)	0-1	636 (86.1)
	≥ 2	103 (13.9)
Cancer diagnosis, n (%)	Lung	190 (25.7)
	Gastrointestinal tract	180 (24.4)
	Breast	143 (19.4)
	Urogenital	53 (7.2)
	Gynecologic	37 (5)
	Head and neck	20 (2.7)
	Others	89 (12)
	Two primary	27 (3.6)
Tumor stage at diagnosis, n (%)	I	91 (12.3)
	II	198 (26.8)
	III	137 (18.5)
	IV	313 (42.4)
Cancer status during COVID-19 infection, n (%)	Active/stable/progressive	427 (57.8)
	Remission/no evidence of disease	312 (42.2)
Active anticancer therapy during COVID-19 infection, n (%)	Yes	362 (49)
	No	342 (46.3)
	Missing	35 (4.7)

Most of the patients were not hospitalized (n = 646, 87.4%), however 35 (4.8%) patients were hospitalized in the intensive care unit. While 22 (3%) patients needed the use of a mechanical ventilator, 42 (5.7%) patients needed to use supplemental oxygen.

The median follow-up period of the patients from the diagnosis of cancer to COVID-19 infection was 16 (1-24) months. During the follow-up, 36.7% (n = 271) of the patients died (Table 3). Most of the patients died from tumor related and other reasons (n = 195, 72%). Seventy-six cancer patients died from COVID-19 infection-related effects such as mostly pulmonary and cardiovascular system complications (67.1% and 14.5%; respectively). The mortality rate of COVID-19 infection was calculated as 14% (76/544). When

the active cancer status of the survivors was examined, it was seen that most patients were in remission (n = 336, 71.8%) (Table 3).

Compared with survivors (n = 468), non-survivors due to COVID-19 infection-related effects were more likely to be aged ≥ 65 years and diagnosis with lung cancer ($p = 0.01$) (Table 4). Also, female patients were at decreased risk of mortality ($p = 0.01$). Patients with tumor stage IV, active/stable/progressive disease and patients receiving active anticancer therapy were at increased risk of mortality ($p = 0.01$). Non-survivors were more likely to be not hospitalized for COVID-19 or COVID-19 complications in the intensive care unit ($p = 0.01$) (Table 4). Also, survivors were more likely to use supplemental oxygen ($p = 0.01$).

Table 2. Characteristics of the patients with COVID-19 infection (n = 739)

Characteristics		Data
Hospitalization for COVID-19 or COVID-19 complications, n (%)	Yes, but no intensive care	58 (7.8)
	Yes, and intensive care	35 (4.8)
	No	646 (87.4)
Use of mechanical ventilator, n, (%)	Yes	22 (3)
	No	717 (97)
Use of supplemental oxygen, n (%)	Yes	42 (5.7)
	No	697 (94.3)

When the predictors of mortality were analyzed using a multivariable ordinal logistic regression model, being aged ≥ 65 years has increased risk of mortality related to COVID-19 infection [OR: 4.07 (95% CI: 2.14-7.75)]. Also, being a female has decreased the risk of mortality [OR: 0.34 (95% CI: 0.18-0.65)].

DISCUSSION

This study underscores some clinical and disease-specific factors on outcomes of COVID-19 infection. In this report, we highlighted that gender, age, cancer diagnosis, tumor stage, cancer status and whether or not receiving active cancer therapy are important factors for mortality related to COVID-19 infection. Although a decrease in mortality has been achieved after effective vaccination programs, prevention strategies such

as organization of healthcare visits and timing of imaging for cancer patients with risk factors will significantly contribute to the decrease in mortality and morbidity.

It is known that COVID-19 has affected more than 220 million individuals worldwide [27]. Cancer patients are susceptible to infection with COVID-19 due to immunocompromised status secondary to malignancy, predisposition for malnutrition, and immunosuppressive treatment strategies and these patient population suffer worse disease outcomes [28, 29]. In the studies, it was seen that COVID-19 infection in cancer patients leads to poor illness, more need to stay in the intensive care unit and use of ventilator. In the current study, 4.8% of the patients were hospitalized in the intensive care unit. While 3% of the patients needed to use of ventilator, 5.7% of the patients needed to use supplemental oxygen.

The mortality rate of COVID-19 infection was

Table 3. Demographic and clinical characteristics of the patients at the post COVID-19 period

Characteristics		Data
Non-survivor, n (%)		271 (36.7)
Reasons for mortality, n (%)	COVID-19 infection-related effects	
	Cardiovascular system	11 (14.5)
	Pulmonary system	51 (67.1)
	Renal system	4 (5.3)
	Neurological system	2 (2.6)
	Others	8 (10.5)
	Tumor-related and others	195 (72)

Table 4. Clinical characteristics of the non-survivors due to COVID-19 infection (n = 76) compared with survivors (n = 468)

Parameter	Data	p value
Age, n (%)	< 65 years	24 (31.6)
	≥ 65 years	52 (68.4)
Gender, n (%)	Female	27 (35.5)
	Male	49 (64.5)
Comorbidities, n (%)	0-1	63 (82.9)
	≥ 2	13 (17.1)
Cancer diagnosis, n (%)	Lung cancer	39 (51.3)
	*Non-lung cancer	*37
Cancer status during COVID-19 infection, n (%)	Active/stable/progressive	64 (84.2)
	Remission/no evidence of disease	12 (15.8)
Active anticancer therapy, n (%)	Yes	56 (73.7)
	No	18 (23.7)
	Missing	2 (2.6)
Hospitalization for COVID-19 or COVID19 complications, n (%)	No	46 (60.5)
	Yes, but no intensive care	4 (5.3)
	Yes, and intensive care	26 (34.3)
Use of supplemental oxygen, n (%)	Yes	27 (35.5)
	No	49 (64.5)

*Cancer types other than lung cancer

ranges from 13% to 41% in the literature [9, 12, 13, 30-32]. In our study, mortality rate of COVID-19 infection was calculated as 14% (76/544) in accordance with the other studies.

Patients with cancer diagnosis are also at an increased risk of developing post-COVID complications including the heart, lung, kidney, skin and brain [33-35]. In our study, 76 cancer patients died from COVID-19 infection-related effects such as mostly pulmonary and cardiovascular system complications (respectively; 67.1%, 14.5%) with the median follow-up period of 16 (1-24) months.

Many risk factors for mortality related to COVID-19 infection are defined in the guidelines [36]. Increasing age, comorbidities and immunosuppression by the disease and/or its treatment have shown as the risk factors for poor outcomes after COVID-19 infection in patients with cancer in the literature [18, 19]. Immune

responses to viral infections are weaker in males than in females and compatible with this information, female patients were at decreased risk of mortality in our study ($p = 0.01$) [37]. Furthermore, ≥ 65 years was associated with dysregulated immune system, more severe disease and with a high mortality rate in the studies [38]. In our study, compared with survivors (n = 468), non-survivors due to COVID-19 infection-related effects were more likely to be aged ≥ 65 years.

The cancer patients infected with SARS-CoV-2 mostly had lung cancer, gastrointestinal cancer and breast cancer in our study which are in fact the common types of cancers. Therefore, this finding may be a related to the frequency of these tumors. In regression analysis, it was seen that non-survivors due to COVID-19 infection-related effects were more likely to be diagnosed with lung cancer ($p = 0.01$). In the studies, lung cancer during COVID-19 infection was

demonstrated to be associated with pulmonary complications and mortality [39]. Defective pulmonary architecture related to thoracic surgery or radiotherapy, smoking associated lung injury, the alterations of alveolar epithelium and pulmonary vessels lead to the development of pulmonary complications in patients with lung cancer during the SARS-CoV-2 infection [7, 39, 40]. In the literature, patients with comorbidities such as hypertension, diabetes, cardiovascular disease or cerebrovascular disease are found to have an increased risk of COVID-19 related mortality due to increased the complexity and difficulty of treatment of comorbidities after COVID-19 infection. In our study, we did not demonstrate the same association. This can be due to rigorous management of the patients with comorbidities. Furthermore, the preventive measures for COVID-19 infection especially in patients with comorbidities may be led to decreased mortality in this special population.

Cancer patients on active anticancer treatment are at increased risk of a severe form of COVID-19 infection due to their immunosuppression [41]. A meta-analysis showed that cancer patients who received active anticancer treatment within 2-4 weeks of developing COVID-19 were associated with a fourfold increased rate of mortality [42]. Our study also demonstrated that patients receiving active anticancer therapy were at increased risk of mortality ($p = 0.01$). Furthermore, in the studies, it was shown that patients with cancer stage IV and active cancer were more likely to experience severe events [43]. In our study, we also demonstrated that the patients with tumor stage IV and active/stable/progressive disease were at increased risk of mortality ($p = 0.01$).

Limitations

There were some limitations to our study. Firstly, this study had a retrospective design. Therefore, post-COVID complications and post-COVID symptoms and sequelae could not be interpreted in detailed. Also, we could not examine smoking status, Eastern Cooperative Oncology Group (ECOG) performance of the patients due to the retrospective nature of the study. Secondly, the median follow-up period was short to recognize and interpret COVID-19 sequelae. Further efforts with larger population are needed to compare the long-term outcomes between inpatients and outpatients.

CONCLUSION

The current study showed statistically significant effects of older age, male gender, diagnosis of lung cancer, active/stable/progressive and advanced cancer stage and active anticancer therapy on mortality related to COVID-19 infection. Preventive measures should be taken for these vulnerable groups to reduce the risk of mortality in COVID-19 infection.

Authors' Contribution

Study Conception: OY, NG, AÖ; Study Design: OÜ; Supervision: AÜ, AÖ; Funding: OÜ, ÖFÖ; Materials: OÜ, ÖFÖ; Data Collection and/or Processing: OÜ, OY, ÖFÖ, GŞ, NÖ; Statistical Analysis and/or Data Interpretation: OÜ, GŞ; Literature Review: OY, GŞ, NÖ, AÖ; Manuscript Preparation: OÜ, ÖFÖ, AÜ and Critical Review: OÜ, OY.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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