The effect of malignancy on prognosis in ICU patients with COVID-19

Elmas Uysal, Fatih Seğmen, Gamze Kılıçarslan, Deniz Erdem

Ankara City Hospital, Intensive Care Clinic, Ankara, Turkey

ABSTRACT

Background: It is known that COVID-19 has a worse and poorer progression, which often might lead to death in those with comorbidities. Multiple studies have recently examined the clinical course of cancer patients with COVID-19 and new guidelines have been developed to manage this group of patients. This study aimed to evaluate the clinical course and mortality rate of cancer patients admitted to the intensive care unit (ICU) for COVID-19.

Material and Method: The demographic characteristics, detailed medical history and laboratory findings of 140 patients with malignancy, who were treated in the COVID-19 Intensive Care Unit of Ankara City Hospital, were evaluated retrospectively. Gender, age, comorbidity, length of stay in the ICU, mortality rates, length of stay on a mechanical ventilator, cytokine storm scores, ferritin, interleukin 6 (IL-6), C-reactive protein (CRP), procalcitonin (PCT), D-dimer, lactate dehydrogenase (LDH), lymphocyte count and treatment options were compared. The patients were divided into two groups: solid and hematological malignancies.

Results: One hundred eight of 140 patients were diagnosed with solid organ malignancy and 32 with hematological malignancy. The most common comorbidity was found to be hypertension. A total of 94 patients died during their ICU stay. While the most common solid organ malignancies were malignancies of the lower gastrointestinal tract and lung cancers, multiple myeloma (MM) was the most common hematological malignancy. There was no significant difference between the two groups in terms of cytokine storm scores , duration of hospitalization and mechanical ventilation. Levels of Ferritin and LDH were found to be significantly higher in patients with hematological malignancies, while D-dimer was significantly higher in solid organ malignancies. A high level of CRP and IL-6 was associated with COVID-19 mortality. Lymphopenia was associated with increased mortality in patients with solid organ malignancy. However, there was no difference in mortality rate among both groups. Although the mortality was significantly higher in the patient group receiving chemotherapy, there were no significant differences in mortality for the duration of receiving chemotherapy.

Conclusion: The results of this study suggested that cancer was associated with severe clinical outcomes and a 67% mortality rate among patients with COVID-19. However, despite the changes in patients' demographic, clinical and laboratory characteristics, no difference in mortality rate was detected in patients with hematological and solid organ malignancies due to COVID-19 infection.

Keywords: COVID-19, coronaviruses, hematological malignancies, malignancy, solid malignancies, mortality

INTRODUCTION

Coronavirus disease 2019 (COVID-19) disease started in the Wuhan region of China in December 2019, spread all over the world and was declared a pandemic by the World Health Organization (WHO) as of March 12, 2020 (1-3). COVID-19 can be asymptomatic depending on the host's immune response and comorbidities or it can cause life-threatening multi-organ dysfunction. COVID-19 can affect all body areas (especially the respiratory system, arterial-venous system endothelial cells, lymphoid tissue, glial cells in the brain, heart, bone, spleen, urinary tract, intestines, nasal mucosa, skin and muscle tissue). Fever, cough and shortness of breath, which can progress to organ failure are the most common symptoms of COVID-19. In respiratory failure, which occurs with clinical worsening in the later stages of the disease, follow-up in the intensive care unit (ICU) is required according to the need for respiratory support (4). The mortality rate is high in patients with COVID-19. Advanced age, male sex, hypertension, immunodeficiency due to chronic diseases and a history of cancer are the factors affecting mortality (5).

The COVID-19 pandemic has affected the publications in the literature (6,7). Studies investigating the etiopathogenesis and prognostic factors for COVID-19 in those with underlying medical conditions increase rapidly. Comorbidity is identified as an independent poor prognostic factor for patients with COVID-19. COVID-19 uses ACE-2 receptors on the surface of host cells to enter the cell and there are studies in the literature indicating that certain comorbidities are associated with a strong ACE-2 receptor expression and higher release of proprotein convertase release (8,9). It is reported that COVID-19 patients with comorbidities have worse lung damage and more mortality rate and the most common comorbidities are hypertension, coronary artery disease and diabetes mellitus (9).

In a study in which comorbidities were evaluated, it was determined that 58.3% of COVID-19 patients had lung cancer and 41.7% of them received immunotherapy, chemotherapy or radiotherapy (8). Patients with malignancies were considered to be at higher risk for COVID-19 infection because of their immune deficiency.

The mortality rate in COVID-19 patients diagnosed with malignancy was calculated as 5.6% and it was found to be 3.5 times higher when compared to the general population (10). The mortality rate was found to be 37% in COVID-19 patients with hematological malignancies (11). It has been stated that hematological malignancies are in the higher risk group for COVID-19 due to age, immune system deficiency and risk of other infections (12). Since acute myeloid leukemia (AML) patients under therapy are highly immunosuppressive and their treatment takes a long time, they are at an incredibly high risk of developing life-threatening complications if infected with COVID-19 (13).

Studies show that patients with cancer appear to be at increased risk of mortality and severe illness due to COVID-19 infection. This study aims to provide information about the effects of COVID-19 disease in malignancy patients and to evaluate the clinical differences between hematological and solid organ malignancies.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No 1 Clinical Researches Ethics Committee (Date: 15.12.2021, Decision No: E1-21-2227). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Participants

All patients older than 18 were diagnosed with solid or hematologic malignancies prior to admission to the ICU

with the diagnosis of COVID-19 who received treatment in the COVID-19 Intensive Care Unit of Ankara City Hospital between 01.03.2020 and 01.01.2022 were included in the study. Participants were divided into two groups, hematological and solid organ malignancies and their data were analyzed retrospectively.

Study Design

Clinical follow-up data were recorded by retrospective case-note review. Firstly, COVID-19 patients with malignancies were evaluated according to their general demographic and clinical and laboratory findings. Then, they were divided into two groups, hematological and solid organ malignancies. Variables such as gender, age, comorbidity, length of stay in the ICU, mortality rates, length of stay on a mechanical ventilator, cytokine storm scores, Ferritin, IL-6, CRP, PCT, D-dimer, LDH, lymphocyte count and treatment were compared.

Statistical Analysis

SPSS (Statistical Package for Social Sciences) for Windows 16.0 program was used for statistical analysis. The compatibility of the parameters with the normal distribution was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics included frequency (n), mean, standard deviation, minimum, median and maximum values. Frequencies and percentages were given for categorical variables. Kruskal-Wallis test was used for comparisons of parameters that did not show the normal distribution in quantitative data. Mann-Whitney U test was used for comparisons between the two groups. Independent-Samples T-test was used for comparisons between two groups with normal distribution. Chi-square test analysis was used to compare the relationship between qualitative data. The results were evaluated at the 95% confidence interval and the significance was at the $p<0.05$ level.

RESULTS

One hundred forty patients with malignancy, who were treated in the COVID-19 Intensive Care Unit of Ankara City Hospital because of COVID-19 pneumonia were evaluated retrospectively (**Figure**). The demographic and clinical characteristics are presented in **Table 1**. One hundred eight of 140 (77.2%) patients were diagnosed with solid organ malignancy and 32 (22.8%) with hematological malignancy. The mean age was 70.2±12.4 (37-96 years). The most common comorbidity was found to be hypertension in 66 (47.1%) patients. Although 88 (62.8%) of the patients were given high flow nasal oxygen therapy, 94 (67%) of them needed mechanical ventilation. Ninety-four (67%) patients died during their stay in ICU.
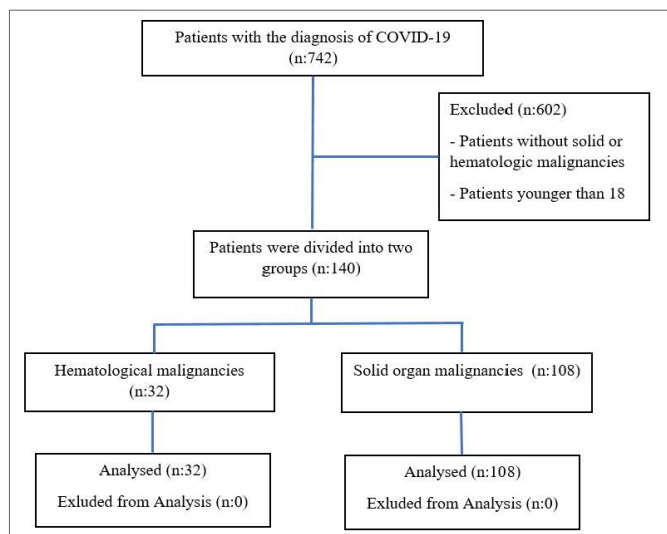
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Figure. Flowchart of the patients

Table 1. The demographic and clinical characteristics	
Variables	**All patients (n=140)**
Age	70.2±12.4 (37-96 years)
Gender (Male/female)	80 /60
Hematological malignancy	32 (22.8%)
Mean APACHE score	11.5±6.2
Mean SOFA score	5.8±3.5
Cytokine storm scores (SFS)	3.5±1.2
Duration of hospital stay	10.7±8.1 (1-40 days)
Duration of intubation	4.7±6.8 (0-35 days)
Percentage of intubation	94 (67%)
Percentage of exitus	94 (67%)
Diyabetes mellitus	38 (27.1%)
Hypertansion	66 (47.1%)
Coronery artery disease	37 (26.4%)
Chronic obstructive pulmonary disease	14 (10%)
Chronic kidney failure	9 (6.4%)
Neurological disorder	25 (17.8%)
High flow oxygen therapy	88 (62.8%)
Non-invasive mechanical ventilation	22 (15.7%)
Ferritin	1473±3157
C-reaktive protein	130±89
IL-6	267±1027
D-dimer	5.2±8.7
LDH	599±558
The lymphocytes count	2.9±13.5
Procalsitonin	2.9±11.2

The patients were divided into two groups: solid and hematological malignancies. Staging could not be performed because imaging methods (positron emission tomography -computerized tomography scans) were not available in the vast majority of patients with hematological malignancies. Solid organ malignancies were divided into subgroups among themselves; however, staging was difficult due to the same reason, so they were divided into metastatic and non-metastatic cancer groups. Sixty (55.5%) of 108 patients were found to have metastatic cancers. The most common malignancies were lower gastrointestinal

tract (20 patients, 18.5%) and lung cancers (20 patients, 18.5%). In the haematological malignancy group, nine patients (28.1%) had MM, seven patients (21.8%) had lymphoma, six patients (18.7%) had chronic lymphocytic leukaemia (CLL), three patients (9.3%) had chronic myocytic leukaemia (CML), three patients (9.3%) had AML, two patients (6.2%) had myelofibrosis, one patient (3.1%) had acute lymphocytic leukaemia (ALL) and one patient (3.1%) had myelodysplastic syndrome (MDS). All CML patients were discharged, while AML, myelofibrosis, ALL and MDS patients died in the hospital. The mortality rate was 55% in MM patients, 83% in CLL patients and 71%in lymphoma patients. **Table 2** shows the solid malignancy subgroups and and existence of metastasis.

Table 2. The solid malignancy subgroups and the existence of metastasis.			
Solid organ malignancies (n=108)	**Metastatic (n=60) (55.5%)**	**Non-metastatic (n=48) (44.5%)**	**Number of exitus**
Gastrointestinal malignancy (n=20)	8	12	13 (11.9%)
Lung cancer (n=20)	14	6	15 (13.8%)
Breast cancer (n=18)	10	8	9 (8.3%)
Prostat cancer (n=13)	5	8	11 (10.1%)
Stomach cancer (n=8)	7	1	6 (5.5%)
Bladder cancer (n=6)	3	3	5 (4.6%)
Pancreas cancer (n=4)	3	1	4 (3.7%)
Intracranial tumours (n=4)	2	2	2 (1.8%)
Renal malignancy (n=3)	1	2	1 (0.9%)
Larynx cancer (n=2)	0	2	1 (0.9%)
Liver cancer (n=2)	2	0	0 (0%)

Ninety-three patients (66.4%) did not receive active chemotherapy (CT) (>1 year), 20 patients (14.3%) had CT within 15 days, 11 patients (7.9%) received CT within 15 days-1 month and 16 patients (11.4%) had been on CT for more than 1 month. (However, there were cured malignancies as well as end-stage malignancies in the group that did not receive CT). When the patients were divided into two groups as those who received CT and those who did not, the mortality rate was found to be significantly higher in the group of patients undergoing chemotherapy (p=0.03). However, no significant correlation was found between the time of the last CT and the mortality rate (p=0.12).

When the patients were compared in terms of hematological and solid organ malignancies, the mean age of patients with hematological malignancies was 65.6±14.4 years and they were statistically younger than the patient group with solid malignancy (p=0.02). The male gender predominated in both groups. The APACHE score was significantly lower in patients with hematological malignancies at 10.2±6.8 (p=0.02). There was no significant difference between SOFA score and cytokine storm score in both groups (p=0.71, p=0.42). There was no significant

difference between the duration of hospitalization and mechanical ventilation, nor in terms of mortality rate (p=0.31, p=0.93, p=0.93).

Elevated serum ferritin and LDH levels have been found in significantly higher in hematological malignancies (p=0.04 and p=0.04). D-dimer was significantly higher in solid organ malignancies (p=0.01) (**Table 3**). Levels of PCT, IL-6 and aspartate amino transferase (AST) in hematological malignancies were significantly higher in patients who died (p=0.01, p=0.01, p=0.04, retrospectively). In solid organ malignancies, PCT and IL-6 values were found to be significantly higher in patients who died in the ICU (p=0.009 and p=0.007), while the lymphocyte count was significantly lower in this patient group (p=0.03).

Additionally, Intravenous immune globulin (IVIG) therapy was used in 16.1% of patients with hematological malignancies, while 1.8% of patients with solid organ malignancies had received this treatment (p=0.006).

DISCUSSION

Research on the course of Covid-19 disease in special disease groups such as cancer patients is limited. It is known that the high mortality rate in COVID-19 patients is associated with their comorbid conditions (9). The clinical course of the COVID-19 in malignancy patients, which is a particular group, was evaluated in our study, especially the clinical outcome between solid organ and hematological malignancies. The mortality rate was found to be significantly higher in cancer patients receiving CT. No significant difference was detected.

A study published in JAMA stated that 2,523,920 patients out of 73.4 million patients were diagnosed with malignancy. Of these patients, 16,570 were diagnosed with COVID-19 disease and 1200 patients had malignancy. In patients diagnosed within <1 year, especially leukemia, non-Hodgkin lymphoma and lung cancers were found to be associated with increased COVID-19 disease risk (p<0.01). In addition, it has been shown that patients with malignancy and COVID-19 have a higher duration of hospital stay and mortality rates (p<0.01, p<0.01) (13).

A study by Mehta et al. (11) reported that 61 patients (28%) of 218 cancer patients diagnosed with COVID-19 died in their ICU stay. Among them, the mortality rate was 37% (20/54) in those with hematological malignancies, while it was 25% in those with solid organ malignancies. They found that the mortality rate increased significantly when compared with patients without malignancy. In the same study, although the mortality rate was higher in lung and gastrointestinal cancers, it was reported that the mortality rate was lower in genitourinary and breast cancers. Among hematological malignancies, myeloid-derived hematological cancers were found to be a higher mortality rate than lymphoid-derived malignancies. The numbers of intensive care unit admission and ventilator use were slightly higher for hematological malignancies than for solid tumors (26% vs 19% and 11% vs 10%, respectively), but this finding did not show a statistical significance (11). While it was expected that patients with metastasis and newly diagnosed patients (<1 year) would show an increased mortality rate, no statistical

Table 3. Comparison of demographic, clinical and laboratory data of patients with hematological malignancies and solid organ malignancies			
	Hematological malignancies (n=32)	**Solid organ malignancies (n=108)**	**P value**
Age	65.6±14.4	71.4±11.6	<0.02
Gender (Male)(n=80)	16 (20%)	64 (80%)	>0.54
APACHE score	10.2±6.8	11.8±6.0	<0.02
SOFA score	55±31	58±36	0.71
Cytokine storm scores	36±10	34±13	0.42
Duration of hospital stay (days)	92±59	112±85	0.31
Duration of intubation (days)	40±56	49±71	0.93
Percentage of intubation (n=94)	22 (68.7%)	72 (66.6%)	0.83
Percentage of exitus (n=94)	22 (68.7%)	72 (66.6%)	0,93
Diyabetes mellitus (n=38)	8 (21%)	30 (79%)	1.0
Hypertansion (n=66)	12 (18.1%)	54(71%)	0.31
Coronery artery disease (n=37)	4 (10%)	33 (90%)	0.06
Chronic obstructive pulmonary disease (n=14)	2 (14.2%)	12 (85.8%)	0.73
Chronic kidney failure (n=9)	1 (11.1%)	8 (88.9%)	0.68
Neurological disorder (n=25)	2 (8%)	23 (92%)	0.06
Ferritin	3014±5962	1035±1442	0.04
C-reaktive protein	1377±942	1285±888	0.56
IL-6	423±1559	2231±812	0.18
D-dimer	22±18	61±97	0.01
LDH	704±802	569±468	0.04
The lymphocytes count	83±256	13±64	0.62
Procalsitonin	57±205	21±63	0.82

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significance was found (p=0.06 and p=0.09) (11). The current study calculated the total mortality rate as 67%. This rate was 68.7% in patients with hematological malignancies and 66.6% (72 out of 108) in solid organ malignancies. However, there was no statistical significance. The most common malignancies were lower gastrointestinal and lung cancers and mortality rates were higher in correlation with this study. There was no difference between the two groups regarding the duration of the ICU stay and intubation days. In parallel with Mehta et al. (11) there was no significant difference in the mortality rates of patients with metastatic disease compared to those with non-metastasis.

In a case series in which 67 patients with malignancy were evaluated, 23 patients had received active chemotherapy. The most common type of cancer was lung cancer (22.4%). It was reported that the clinical outcomes of COVID-19 disease were more severe in elderly patients and it was determined that these patients had several comorbidities. In addition, the authors stated that patients receiving active CT had a worse prognosis (14).

In a study including 28 cancer patients by Zhang et al. (15) the authors reported that patients who received CT in the last 14 days had a worse prognosis. The mortality rate was 26% and patients requiring invasive mechanical ventilation were 36%. The most common malignancy was lung cancer, which was correlated with other studies. It was also stated that 71% of these patients were given IVIG therapy (15). In our study, the intubation rate was 67% and the mortality rate was 67%. Our results showed that 66.4% of patients did not receive active CT (>1 year) and 33.6% received CT within the last year. While mortality rates were higher in patients receiving CT, no significant correlation was found with the time of receiving CT. Although the mean age and APACHE-II scores were significantly lower in hematological malignancies, there was no significant difference in mortality rate compared to solid organ malignancies. IVIG was given to 17.9% of patients and it was most frequently applied to patients with hematological malignancies.

In June 2021, the data of 1013 patients infected with COVID-19 were shared by the American Society of Hematology (ASH) and it was stated that the mortality rate ranged between 13.8% and 39% (16). Various clinical and laboratory parameters such as one or more comorbidities, age, type of malignancy (especially AML), high level of CRP, lymphopenia and neutropenia have also been reported to be risk factors for mortality in these patients (17). The most common subgroup of hematological malignancy was MM in our study. The most common mortality rate was seen in CLL patients (83%). However, there were 2 AML patients and both of them died in the ICU. When the laboratory data were analyzed, it was found that mortality was higher in patients with elevated levels of PCT, IL-6 and AST. No significant correlation was found between lymphocyte count and mortality. In addition, patients with solid organ malignancies had higher procalcitonin and IL-6 values and severe lymphopenia. While these results are in agreement with the literature data, no significant relationship was found between lymphocyte count and mortality rate.

In a study that included 3801 patients with COVID-19 and hematological malignancies with data from 132 centers, the most common subgroup was found to be non-Hodgkin Lymphoma (1084, 28.5%) and the second most common malignancy was MM (684, 18%). 73.1% of these patients were hospitalized. The average hospital stay was 15 days. 18.1% of patients needed intensive care and 65.2% were intubated. The number of patients whose primary cause of mortality was COVID-19 pneumonia was evaluated as 155 (13.1%) (18). Although the duration of stay in the ICU was not shared in this study, it was 9.2±5.9 days in our study. We found a 68.7% intubation and mortality rate. In the current study, we found that all patients with solid organ malignancies and hematological malignancies who were intubated for mechanical ventilation died during their stay in ICU. When hematological and solid organ malignancies were compared, there was no difference in mortality rate. However, when compared with this study, it can be argued that the mortality rate was higher since primary causes of mortality were not distinguished in our study. In addition, since IL-6 and PCT levels had a significant effect on mortality in both groups, it might be thought that sepsis often accompanies these patients. We detected that severe lymphopenia was significantly related to mortality in patients with solid organ malignancies. However, the evaluation of lymphopenia in hematological malignancies is complex and careful consideration should be given to using it as a basis for treatment and prognostic evaluation.

CONCLUSION

In conclusion, the mortality rate of COVID-19 patients with malignancy is high. No significant difference was found between hematological malignancies and solid organ malignancies in terms of mortality in our study. Since the mortality rate was high in patients undergoing chemotherapy, which was similar to other studies' findings, it can be recommended that primary prevention methods related to COVID-19 and special attention must therefore be given among this group. Randomized and prospective trials, including homogeneous patient groups, are needed to evaluate the data more accurately.

ETHICAL DECLARATIONS

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