Ann Med Res

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Annals of Medical Research

journal page: www.annalsmedres.org

Risk factors for 30-day mortality in patients with cancer and COVID-19 in Turkey: A single center retrospective study

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ARTICLE INFO

Keywords:
COVID-19; cancer; neutrophil lymphocyte ratio; pandemia

Received: Apr 20, 2021
Accepted: Jul 16, 2021
Available Online: Feb 15, 2021
DOI:10.5455/annalsmedres.2021.04.349

Abstract

Aim: We aimed to investigate the factors affecting mortality in cancer patients with COVID-19.
Materials and Methods: 120 cancer patients followed-up in Erciyes University Medical Oncology Department were included in the study. Patients with a diagnosed cancer over the age of 18 years and diagnosis of COVID-19 between April 1 and December 1 2020 were participated in the study. The relationship between clinical, demographic, laboratory values and 30-day mortality were evaluated using the Chi-square and Fisher's exact test. Risk factors for mortality were identified by univariable and multivariable logistic regression models.
Results: 120 cancer patients were accepted in the study and 30 (25%) had died within 30 days after COVID-19 positivity. Hospitalization rate of cancer patients with COVID-19 was 67.5% and 23 (19.2%) of patients were admitted to intensive care unit (ICU). 34.6% of hospitalized patients and 95.7% of those admitted in the ICU died within 30 days. In multivariable logistic regression analysis, it was concluded that the presence of lymphopenia (OR 2.2, 95% CI 1.54-13.6, p = 0.04), high neutrophil-lymphocyte ratio (NLR) (OR 3.1, 95% CI 1.21-9.8, p = 0.02), dyspnea (OR 2.5 95% CI 0.32-11.2, p = 0.04), lung cancer diagnoses (OR 3.3 95% CI 1.54-9.7, p = 0.03), male gender (OR 2.17 95% CI 1.1-7.3, p = 0.03)) were determined that increased 30-day mortality.
Conclusion: High incidence of cancer and the risk of immunosuppression in these patients increased the importance of COVID-19. Cancer patients with COVID-19 need to be treated more carefully because they are vulnerable to infection and can be mortal.

Introduction

Coronavirus Disease-2019 (COVID-19), which causes severe acute respiratory syndrome, has become a serious global health issue. A few weeks after the first COVID -19 patient was announced in December 2019 in Wuhan, China, it spread to almost all continents and the World Health Organization (WHO) announced the outbreak a pandemic (1). Older age and underlying comorbidities such as hypertension and diabetes can be considered risk factors for severe disease. Cancer patients are at particularly high risk for severe COVID-19 (2, 3). Because of the immunosuppressive effects of treatment and the disease itself, cancer patients also represent a vulnerable population. Initial reports showed that patients with malignant solid tumors were more susceptible to COVID-19 and had worse outcomes (4). Liang et al.(5) created the first nationwide analysis at cancer patients with COVID-19 in China. In this study, only 18 patients had a diagnosis of cancer. Cancer patients were more likely to experience severe COVID-19 than patients without cancer. In a study conducted in Italy with 355 patients hospitalized due to COVID-19, 20.3% of patients had active cancer (6). The Turkish Ministry of Health created a nationwide electronic recording system for COVID-19 cases on the first day of the COVID-19 in our country, and all patients with a positive polymerase chain reaction (PCR) test were instantly recorded by health personnel. We aim to show the demographic, clinical, laboratory features, and results of patients with malignant solid tumors and PCR test verified COVID-19, obtained from the Erciyes University Medical Oncology Department Database.

Materials and Methods

One hundred and twenty cancer patients followed-up in the Erciyes University Medical Oncology Department were included in the study. We conducted this study in accordance with approval from the Erciyes University Clinical Research Ethics Committee (decision number 2021/24). On March 11, 2020, after diagnosis of the first COVID-19 patient in Turkey, according to guidelines issued by the Turkish Ministry of Health, diagnosis of patients was assessed by PCR test or chest tomography according to symptoms and contact history. PCR tests were performed by taking nasopharyngeal and oropharyngeal swab samples. Patients with a diagnosed malignant solid tumor over the age of 18 years and diagnosis of COVID-19 between

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April 1 and December 1 2020 participated in the study. Patients' demographic and clinical features, cytotoxic treatment information, laboratory results, including serum biochemistry, complete blood counts, inflammatory parameters, thorax computerized tomography scanning (CT), and treatment methods for COVID-19 infection were evaluated. As the lower and upper limit of the laboratory tests, the values determined by the Biochemistry Laboratory of Erciyes University, Faculty of Medicine were taken as basis. Lymphopenia was defined as the value for lymphocyte count < 103 / μL. Leukocytosis was defined as the value for white blood cell count > 12×10^3 / μL. The neutrophil-lymphocyte ratio (NLR) was calculated by dividing the neutrophil count by the lymphocyte count. High NLR was defined as a value > 3.32. All of the patients were staged according to the tumor, node, and metastasis (TNM) cancer staging system. Those who received chemotherapy or target therapy for cancer up to 4 weeks before the diagnosis of COVID-19 infection were grouped as active cytotoxic treatment. Those receiving hormonal therapy were grouped separately and were not included in the group receiving cytotoxic therapy. For radiological evaluation, chest computer tomography was classified as typical ground-glass opacity for COVID-19 pneumonia, pneumonia present but atypical for COVID-19, and normal or other findings. The symptoms of the patients (fever, dyspnea, loss of taste and smell, diarrhea, myalgia) were recorded. Comorbid conditions of the patients (diabetes mellitus, chronic obstructive pulmonary disease (COPD), hypertension, coronary heart disease) were recorded. Patients, who received treatment for COVID-19 infection, were classified according to their status of receiving favipravir, hydroxychloroquine, tocilizumab, antibiotics, mask or nasal oxygen, and invasive or non-invasive mechanical ventilation (IMV, NIMV). It was recorded if patients were treated in the intensive care unit (ICU) or clinic. Patients, who died within 30 days after the diagnosis of COVID-19 infection, were noted and the 30-day mortality rate was evaluated.

Statistical analysis

Quantitative and qualitative variables were presented, respectively as median and percentage value. The high NLR value was found with 70% specificity and sensitivity at 95% CI using ROC analysis. High NLR was defined as a value > 3.32. The relationship between clinical, demographic, laboratory values, treatment modalities, cancer histories, radiological characteristics, high NLR values, and 30-day mortality were evaluated using the Chi-square and Fisher's exact test. In addition, patients were divided into two groups as lung cancer and extrapulmonary cancers. The relationship between lung cancer and 30-day mortality was evaluated. Risk factors for death and their odds ratios (OR) were evaluated by the univariable logistic regression model. Multivariable logistic regression analyses were evaluated to identify clinically influencing factors associated with 30-day mortality. To be included in the multivariate model, variables that showed relationships at $\alpha = 0.05$ significance level in univariate analysis were selected. OR and 95% CIs were performed with the Cox model. Statistical analysis was performed using IBM SPSS Statistics 23.0 software. We used double-sided tests and <5% type 1 error. The differences were considered statistically significant when the p value was < 0.05.

Results

From April 1 to December 1, 2020, 120 cancer patients with COVID-19 were included in the study and 30 (25%) died. The clinical, laboratory and radiological features of the patients are shown in Table 1 and Table 2. Median age of all patients was 58.17 (range: 21-80) and 57 (47%) of patients were male. 103 (85.8%) of 120 patients experienced at least one symptom during the course of COVID-19. Cough was the most common symptom, followed by myalgia, fever, and dyspnea. The hospitalization rate of cancer patients with COVID-19 in our study was 67.5% and 23 (19.2%) of patients were admitted to ICU. 67 (55.8%) of patients received oxygen therapy and 22 (18.3%) required IMV. 30 (25%) patients died within 30 days after COVID-19 positivity. 34.6% of hospitalized patients and 95.7% of those admitted in the ICU died within 30 days. Colorectal-gastric cancers (29.2%) were the most common cancer types, followed by breast cancer (24.2%), and lung cancer (19.2%). 70 (58.3%) of patients had stage 4 cancers. 63 (52.5%) of the patients had at least one comorbidity. Hypertension (33%) was the most common comorbidity, followed by diabetes mellitus (20%), coronary heart disease (14.2%), and COPD (10%). 96 (80%) of patients received cytotoxic or hormonal treatment within 4 weeks prior to the diagnosis of COVID-19; 82 (68.3%) received cytotoxic treatment, and 14 (11.7%) received hormonal treatment. Chest CT findings were compatible with ground glass opacity in 71.7% of the patients and 20.8% had normal radiological findings. 94.2% of patients received at least one treatment for COVID-19. The most commonly used drugs were favipiravir 74.2% and hydroxychloroquine plus favipiravir 15%. Antibiotherapy was given in 63.3% of the patients. Clinical, laboratory and radiological features associated with 30-day mortality as assessed by the X2 test are shown in Table 1 and Table 2.

Male gender, presence of coronary heart disease, fever, cough, dyspnea, leukocytosis, lymphopenia, hypoalbuminemia, Lactate dehydrogenase (LDH) elevation, C-reactive protein (CRP) elevation, procalcitonin elevation, NLR > 3.32, radiological ground glass opacity, stage 4 cancers, and lung cancers were the clinical and laboratory characteristics associated with high risk of mortality. When the survivors are compared with non-survivors (Table 2), non-survivors had higher NLR, leukocyte, LDH, CRP, procalcitonin, and lower lymphocyte count and albumin level.

In univariable logistic regression analysis, colorectal-gastric cancers, lung cancers, cancer stage, male sex, cough, dyspnea, coronary heart disease, leukocytosis, lymphopenia, anemia, high NLR, LDH and radiological ground glass opacity were associated with death (Table 3).

In multivariable logistic regression analysis, multiple data subsets were evaluated. The results of the univariable and multivariable logistic regression analyses are presented in Table 3. It was found that male sex, dyspnea, lymphopenia, high NLR and lung cancer diagnoses caused an increase in 30-day mortality. The presence of lymphopenia (OR 2.2 95% CI 1.54-13.6, P = 0.04), high NLR (OR 3.1, 95% CI 1.21-9.8, P = 0.02), dyspnea (OR 2.5 95% CI 0.32-11.2, P = 0.04), lung cancer diagnoses (OR 3.3 95% CI 1.54-9.7, P = 0.03), and male gender (OR 2.17 95% CI 1.1-7.3, P = 0.03) were determined that increased 30-day mortality.

Table 1. Patients characteristics

	All Patients (n:120)	Survivors (n:90)	Non-survivors (n:30)	P value
Age (years)	58.17 (21-80)	56.4 (21-80)	63.5 (21-80)	0.141
Sex				0.02
Male	57 (47.5%)	37(64.9%)	20 (35.1%)	--
Female	63 (52.5%)	53(84.1%)	10 (15.9%)	--
BMI (median)	27.6 (17.3-42)	28.3 (17.3-42)	25.3 (18.8-41)	0.225
Symptom				
Fever	77 (64.2%)	49 (63.6%)	28 (36.4%)	P < 0.001
Cough	85 (70.8%)	56 (65.9%)	29 (34.1%)	P < 0.001
Dyspnea	55 (45.8%)	26 (47.3%)	29 (52.7%)	P < 0.001
Myalgia	82 (68.3%)	59 (72%)	23 (28%)	0.365
Diarrhea	8 (6.7%)	4 (50%)	4 (50%)	0.106
Loss of taste and smell	21 (17.5%)	20 (95.2%)	1 (4.8%)	0.345
Comorbidities				
Hypertension	40 (33%)	28 (70%)	12 (30%)	0.38
COPD	12 (10%)	7 (58.3%)	5 (41.7%)	0.172
Diabetes mellitus	24 (20%)	18 (75%)	6 (25%)	0.613
Coronary heart disease	17 (14.2%)	9 (52.9%)	8 (47.1%)	0.034
Cytotoxic treatment	82 (68.3%)	58 (70.7%)	24 (29.3%)	0.085
Hormonal treatment	14 (11.7%)	12 (85.7%)	2 (14.3%)	0.258
No cancer treatment	24 (20%)	20 (83.3%)	4 (16.7%)	0.265
ECOG performance status				P < 0.001
0	5 (4.2%)	5 (100%)	0	--
1	47 (39.2%)	47 (100%)	0	--
2	37 (30.8%)	30 (81.1%)	7 (18.9%)	--
3	31 (25.8%)	8 (25.8%)	23 (74.2%)	--
4	0	0	0	--
Cancer stage				0.001
1	6 (5%)	6 (100%)	0	--
2	21 (17.5%)	20 (95.2%)	1 (4.8%)	--
3	23 (19.2%)	20 (87%)	3 (13%)	--
4	70 (58.3%)	44 (62.9%)	26 (37.1%)	--
Cancer type				0.015
Colorectal-gastric	35 (29.2%)	24 (68.6%	11 (31.4%)	--
Lung	23 (19.2%)	13 (56.5%)	10 (43.5%)	--
Breast	29 (24.2%)	28 (96.6%)	1 (3.4%)	--
Prostate	3 (2.5%)	2 (66.7%)	1 (33.3%)	--
Genitourinary system	7 (5.8%)	6 (85.7%)	1 (14.3%)	--
Pancreaticobiliary system	5 (4.2%)	3 (60%)	2 (40%)	--
Others	18 (15%)	14 (77.8%)	4 (22.2%)	--
Lung cancer	23 (19.2%)	13 (56.5%)	10 (43.5%)	0.011
Extrapulmonary cancers	97 (80.8%)	77 (79.4%)	20 (20.6%)	--
Hospitalization	81 (67.5%)	53 (65.4%)	28 (34.6%)	P < 0.001
Median duration of hospital stay (days)	5 (0-30)	5 (0-20)	9 (0-30)	P < 0.001
Intensive care unit admission	23 (19.2%)	1 (1.1%)	22 (95.7%)	P < 0.001
Antibiotics	76 (63.3%)	49 (64.5%)	27 (35.5%	P < 0.001
Treatments				0.104
Favipiravir (a)	89 (74.2%)	69 (77.5%)	20 (22.5%)	--
Hydroxychloroquine (b)	5 (4.2%)	5 (100%)	0	--
a+b	18 (15%)	11 (61.1%)	7 (38.9%)	--
Tocilizumab (c)	0	0	0	--
a+b+c	1 (0.8%)	0	1	--
Supportive care alone	7 (5.8%)	5 (71.4%)	2 (28.6%)	--
Oxygen therapy				P < 0.001
No therapy	53 (44.2%)	52 (98.1%)	1 (1.9%)	--
Nasal-mask oxygen	38 (31.7%)	31 (81.6%)	7 (18.4%)	--
NIMV	7 (5.8%)	6 (85.7%)	1 (14.3%)	--
IMV	22 (18.3%)	1 (1, 1%)	21 (95.5%)	--

Table 2. Laboratory and radiological features

	All Patients (n:120)	Survivors (n:90)	Non-survivors (n:30)	P value
Laboratory findings (median)				
WBC X 103/μL	5.65 (0.28-30.9)	5.29 (0.41-30.9)	8.36 (16.3-0.28)	0.017
Neutrophils X 103/μL	3.56 (0.03 - 26.3)	3.14 (0.13-26.3)	6.6 (14.7-0.03)	0.012
Lymphocytes X 103/μL	1.04 (0.1-4.6)	1.12 (0.1-4.6)	0.6 (3.6-0.14)	0.004
Hemoglobin g/dL	11.05 (5.4-16.2)	11.5 (5.4-16.2)	9.3 (13.6-6.6)	P < 0001
Platelet X 103/μL	191 (9-989)	196 (648-26)	129 (989-9)	0.995
Albumin g/dl	3.8 (1.4-5)	4 (2.14-5)	2.7 (4.3-1.4)	P < 0.001
CKD-EPI	85 (22-157)	85 (29-138)	82 (157-22)	0.322
C-reactive protein mg/L	26.5 (1.01-328)	15 (1.01-195)	120 (16.8-328)	P < 0.001
Procalcitonin ng/mL	0.27 (0.01-16.4)	0.2 (0.01.-6.84)	0.85 (0.06-16.4)	P < 0.001
Lactate dehydrogenase U/L	300 (126-2158)	265 (150-1980)	554 (126-2158)	P < 0.001
NLR > 3.32	58 (48.3%)	37 (63.8%)	21 (36.2%)	0.005
Lymphocytes < 103/μL	56 (46.7%)	34 (60.7%	22 (39.3%)	0.001
Radiological findings				P < 0.001
Ground-glass opacity	86 (71.7%)	58 (67.4%)	28 (32.6%)	--
Atypical findings	9 (7.5%)	7 (77.8%)	2 (22.2%)	--
Normal findings	25 (20.8%)	25 (100%)	0	--

Discussion

As of January 27, 2021, the number of COVID 19 cases worldwide was 99,638,507 and the number of deaths was 2,141,468. The worldwide mortality rate was 2.1% (7). In our study, the 30-day mortality rate of solid tumor patients with COVID-19 infection was 25%, which is much higher than mortality rate for COVID-19 in the world (2.1%). In cancer patients with COVID-19, male gender, lymphopenia, high NLR value, and lung cancer diagnosis were identified as risk factors for 30-day mortality. Receiving anticancer therapy within 4 weeks and the use of favipiravir and/or HCQ had no effect on 30-day mortality.

It was reported in previous studies that mortality rates in cancer patients with COVID-19 were higher than in those without cancer. In the first report from China, the mortality rate due to COVID-19 in cancer patients was 28.6% (8). The next two reports from China showed mortality in cancer patients with COVID-19 as 20% (8, 9). In a study conducted in the United Kingdom, mortality was found to be 28% in patients, who received active cancer treatment or received cancer treatment in the past 12 months (10). Mortality in our study was 25%, similar to the literature.

With the first case of COVID-19 in Turkey, all health institutions were on alert and most ICUs were reserved for COVID-19 patients. In many centers, elective surgical procedures were stopped and bed capacities of hospitals were increased.

Transportation of cases to the ICU were higher in our country therefore, the majority of patients who died were treated in intensive care. In our study, 19.2% of all patients and 73.3% of those who died were treated in the ICU.

In our study, receiving anticancer therapy with a COVID-19 diagnosis within 4 weeks had no effect on 30-day mortality. The National Comprehensive Cancer Network (NCCN) recommended primary granulocyte-colony stimulating factor (G-CSF) prophylaxis for cancer patients, who had previously received chemotherapy with high risk for development of febrile neutropenia (> 20%) (11). NCCN posted short-term recommendations on the COVID-19 resources page (12). According to the NCCN short-term recommendations, we applied primary G-CSF prophylaxis to all patients with high and intermediate risk (10%–20%) of developing febrile neutropenia, for those who received chemotherapy. Since we gave primary G-CSF prophylaxis to patients, the rate of neutropenia in patients decreased. Unlike other previous studies, use of primary G-CSF prophylaxis in our study may be the reason for the lack of relationship between 30-day mortality and patients receiving cytotoxic treatment (8, 13).

Neutrophils and lymphocytes are the main factors in fighting infection. Active cancer patients may have abnormal blood values due to treatment or cancer and blood values may be different during COVID-19 infection compared to patients without cancer. In our study, we showed that high NLR value and lymphopenia are associated with mortality. These markers are indicative of poor prognosis in many cancers (14). Previous studies have shown that tumor infiltration of certain immune cell types is associated with a poor prognosis of patients with cancer (15). Several studies have shown that severe cases of COVID-19 have a higher NLR (16, 17). Leukocytosis and lymphopenia i. e., the increase of NLR was found in the severe group with COVID-19 compared to the mild group (16). In our study, we found that high NLR value and lymphopenia were associated with mortality. These biomarkers can be helpful in critical patient management. However, the cause of leukocytosis may be administration of G-CSF to patients with high risk for febrile neutropenia or due to secondary bacterial infections. Thus, high neutrophil values may have caused high NLR values.

We found that, men were more at risk than women in terms of mortality. The reason for this increased risk in men may be the change in immune response due to gender difference. It has been previously shown that the T-cell and immune system response changes depending on gender (18, 19).

In this study, we found that colorectal-gastric cancer and lung cancer are associated with 30-day mortality. All lung cancer patients, who died, were stage 4. COVID-19 primarily affects the pulmonary system, so it can be predicted to have higher mortal-

Table 3. Multivariate regression analysis of potential baseline clinical variables

	Univariable OR (95% CI)	p value	Multivariable OR (95% CI)	p value
Male Sex (vs female)	2.86 (1.2-6.82)	0.017	2.17 (1.1-7.3)	0.03
Symptom				
Fever	1.85 (1.19-4.38)	0.3	--	--
Cough	2.86 (0.7-6.3)	0.006	--	--
Dyspnea	3.2 (0.4-8.2)	P < 0.001	2.5 (0.32-11.2)	0.04
Coronary heart disease (vs no)	3.27 (1.13-9.47)	0.029	--	--
Laboratory findings				
Neutrophils >12 X 10^3/μL	4.1 (3.89-13.82)	0.002	--	--
Lymphocytes <1 X 10^3/μL	4.5 (1.81-11.3)	0.001	2.2 (1.54-13.6)	0.04
Hemoglobin <10 g/dL	6.54 (2.6-15.8)	P < 0.001	--	--
Albumin <3.5 g/dl	11 (4.2-28.7)	P < 0.001	--	--
C-reactive protein >10 mg/L	1.1 (0.7-6.1)	0.39	--	--
Lactate dehydrogenase >250U/L	3.5 (0.9-8.5)	0.012	--	--
NLR > 3.32	3.34 (1.37-8.11)	0.005	3.1 (1.21-9.8)	0.02
Radiological findings				
Ground-glass opacity (vs other radiological findings)	4.64 (1.44-14.91)	0.01	--	--
ECOG performance status				
0	1 (ref)	--	--	--
1	1.15 (0.3-3.6)	0.73	--	--
2	1.8 (0.6-6.3)	0.68	--	--
3	12.3 (3.89-38.9)	P < 0.001	--	--
4	--	--	--	--
Cancer stage				
1-2	1 (ref)	--	--	--
3-4	3.2 (1.4-7.9)	0.018	--	--
Cancer type				
Others	1 (ref)	--	--	--
Colorectal-gastric	1.32 (0.16-2.33)	0.07	--	--
Lung	3.3 (1.32-7.2)	0.02	--	--
Breast	0.65 (0.23-4.2)	0.43	--	--
Prostate	1.1 (0.41-5.1	0.57	--	--
Genitourinary system	1.3 (0.45-6.2)	0.65	--	--
Pancreaticobiliary system	0.42 (0.05-3.52)	0.43	--	--
Lung cancer (vs extrapulmonary cancers)	3.42 (1.33-8.84)	0.02	3.3 (1.54-9.7)	0.03

ity in lung cancer patients. Similar to the literature, we found that COVID-19 is more fatal in lung cancer patients (20). The reason for the high 30-day mortality in patients with colorectal-gastric cancer may be that, they were in the group of common cancers in the community. In addition, the majority of patients included in this group were stage 4 patients and 7/11 of the patients who died had lung metastases. The presence of lung metastasis may have increased mortality.

There are limitations in our study. Leukocytosis developed in patients because we used G-CSF as primary prophylaxis in at risk populations. For this reason, we could not fully explain the effect of high NLR in COVID -19 and mortality.

Finally, more studies are needed to demonstrate the effect of COVID-19 on cancer patients and the power of biomarkers to show prognosis.

Conclusion

In conclusion, the high incidence of cancer and the risk of immunosuppression in these patients increased the importance of COVID-19. Cancer patients with COVID-19 need to be treated more carefully because they are vulnerable to infection and can be mortal. More studies and treatment models are needed to control the disease.

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