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Research Article

Mortality Rate and Related Factors in Patients with Active Oncological Malignancies Hospitalized for Covid-19

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Abstract

Objectives: To investigate the mortality rate and mortality-related factors for patients with oncological malignancies (cancer patients) hospitalized for Covid-19 infection.

Methods: Demographic characteristics, hematological and biochemical parameters, lung CT Severity Scores (CT-SS), and Charlson Comorbidity Indices (CCI) of living and dead oncology patients were compared. Statistical analyses of possible factors that may impact mortality were performed.

Results: The overall mortality rate of 2650 patients hospitalized for Covid-19 was 21%. Among these, 410 patients had active oncological malignancy. The mortality rate of the oncology patients was significantly higher than those without any malignancy (54% vs. 7.2%, p<0.0001). Logistic regression analyses revealed that CT-SS, neutrophil count, hemoglobin, and CCI had meaningful independent effects on mortality in patients with oncological malignancies. The mean CT-SS was significantly higher in the ex-group than the alive group (17.6±5.5 vs. 15.3±4.8, p<0.0001). On the other hand, the mean neutrophil count (2100±830 vs. 4350±660 p <0.0001) and hemoglobin level (8.4±3.2 vs. 10.7±2.8, p<0.0001) were statistically lower.

Conclusion: Covid-19 (+) oncology patients suffering from profound anemia, neutropenia, and substantial lung involvement have markedly high mortality and should be treated intensely and meticulously.

Keywords: Covid-19, cancer patients, mortality, oncological malignancy

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Covid-19 disease causing severe clinical outcomes, was first reported in the Wuhan province of China in December 2019 and followed by a worldwide fast spread resulting in a global pandemic.[1] The clinical spectrum of the disease ranged from asymptomatic and mild upper respiratory tract symptoms to pneumonia, acute respiratory distress syndrome (ARDS), and death.[2] The clinical manifestations were worse, and the mortality rate was higher in the elderly population with comorbidities such as hypertension, diabetes, obesity, chronic renal failure, chronic liver failure, chronic obstructive pulmonary disease, and malignancies.[3]

Prevalence and mortality rates of Covid-19 disease are high for patients with oncological malignancies (cancer patients). The oncological disease itself, chemotherapy, radiotherapy, and immunotherapy interventions can dysregulate and alter immune responses in these patients. The disease can be presented with more severe illness and diverse clinical and laboratory findings. So, this group of patients is accepted as sensitive and naïve to Covid-19 infection.[4-7]

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The overall death rate of Covid-19 infection was reported as 1-5% worldwide, depending on the nation.[8-10] However, the reported death rates of cancer patients are higher.[11] In a study done under the United Kingdom Coronavirus Cancer Monitoring Projects (UKCCMP) with the patients (n=800) having symptomatic Covid-19 disease and cancer, 412 patients (52%) showed light clinical problems while 226 patients (28 %) passed away.[12]

Because cancer patients seem to have more adverse clinical outcomes due to Covid-19 infection and exhibit diverse clinical and laboratory findings, they need to be monitored closely. It is important to understand which parameters besides age and comorbidities are related to the higher mortality in this group of patients. So, follow-up and treatment of critically ill patients could be more effective. This study was designed to research mortality rate and related factors that may affect mortality in patients with active-oncological malignancy hospitalized due to symptomatic Covid-19 disease.

Methods

Study Design and Participants

Patients hospitalized for symptomatic Covid-19 infection at our tertiary center's services and intensive care units between May 2020 and March 2022 were screened. Real time polymerase chain reaction (RT-PCR) technique was used for nose/throat swabs to reveal SARS-CoV-2 RNA presence in the patients. The overall mortality of hospitalized patients for Covid-19 infection was determined. Then patients with hematological malignancies were excluded from the study. The rest of the patients were grouped as patients with oncological malignancies (cancer patients) and those without any malignancy. The mortality rates of these groups were calculated and compared. Then cancer patients were divided into two groups according to their mortality statuses (Alive group and ex-group). These two groups were compared regarding demographic characteristics, laboratory and imaging parameters, and disease scores to reveal the factors that may affect mortality. Mortality was defined as a covid 19-related death in the hospital. Patients who received adjuvant or neoadjuvant chemotherapy for their cancers in the last month prior to hospitalization and metastatic cancer patients were accepted as patients with active oncological malignancy.

Data Collection

Mortality statuses of all patients were extracted from electronic medical records. Demographic characteristics, comorbid diseases, malignancies, hematological and biochemical parameters, coagulation tests, chest CT severity scores (CT-SS), Charlson comorbidity indices (CCI), SOFA, and APACHE II scores of cancer patients were analyzed from the hospital medical records.

Statistical Analysis

The data analyses were performed using IBM® SPSS® 22 (SPSS Inc., Chicago, IL, USA) software package. The suitability of the variables to normal distribution was analyzed using Kolmogorov-Smirnov/Shapiro¬Wilk tests. Descriptive analyzes were given as average±std, frequency, and percentage (%) for continuous data and categoric variables, respectively. In continuous data, t-test was used to compare dead and alive patients for normal distribution, while Mann Whitney U test was used in the case of non-normal distribution data. Pearson's Chi Square and Fisher's Exact Chi Square tests were used to analyze categorical data. ROC analysis was used to discriminate mortality rate and cut-off values along with sensitivity and specificity. Risk assessments of the parameters on mortality and their mathematical modeling were performed using logistic regression analyses. All the p values below 0.05 were accepted as statistically meaningful.

Results

The records of 2650 patients hospitalized for symptomatic Covid-19 infection were analyzed. Among these patients, 410 patients had active oncological malignancy, 230 patients had active hematological malignancy, and 2010 patients had no malignancy. The overall mortality rate of all patients was 21% (n=557/2650). Patients having hematological malignancy were excluded from the study. The mortality rate of the patients with oncological malignancies was significantly higher than the patients with no malignancy (n=221/410 and 54% vs. n=144/2010 and 7.2%, respectively; p<0.0001) (Fig. 1).

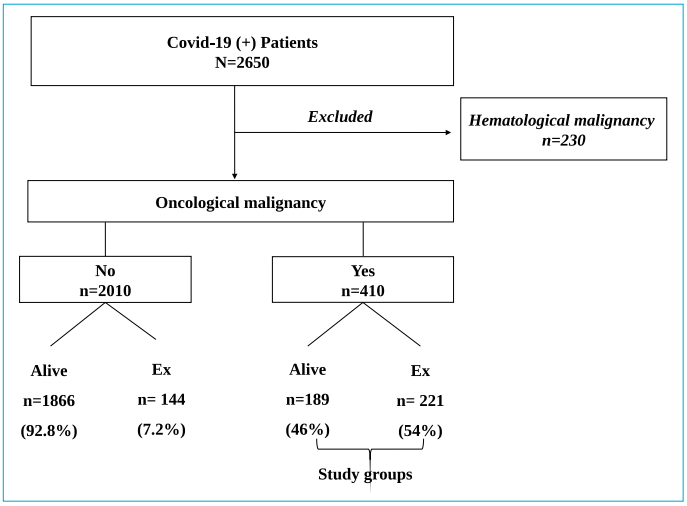

Figure 1. Research design.

Oncology Patients

The mean age of 410 patients with oncological malignancy was 62.2±17.8. Of these patients, 259 (63.2%) were male, and 151(36.8%) were female. Lung carcinomas (30.2%), breast carcinoma (15.9%), and gastrointestinal carcinomas (11%) were the main malignancies present in these patients (Table 1). Of the oncology patients hospitalized for Covid-19 infection, 46% (n=189) was surviving (Alive group), while 54% (n=221) was dead (ex-group).

Comparison of Alive and Ex Groups

There was no significant difference between both groups in terms of gender (p=.617). However, the mean age was higher in the ex-group than in the alive group (64±15 vs. 60±21 years; p=.0001). When hematological and biochemical parameters were analyzed, there was no statistical difference in the levels of LDH, glucose, urea, ALT, PT, INR, and total bilirubin between groups. On the other hand, hemoglobin (Hb), leukocyte, neutrophil, thrombocyte counts, and AST level were statistically lower in the ex-group, while D-dimer, fibrinogen, CRP, procalcitonin, ferritin, creatinine, and aPTT levels were higher (Table 2).

SOFA, APACHE II, and CCI scores were found to be significantly higher in the ex-group than in the alive group. Hospital stays were longer, and intensive care requirement rates were higher in the ex-group (Table 2). Based on the CT-SS results, lung involvement scores were higher in the ex-group (mean 17.6±5.5, range 7-34) than in the alive group (mean 15.3±4.8, range 5-28) (p <0.0001) (Table 2 and Fig. 2).

In Figure 3, different score indices that may affect mortality were evaluated, and their prediction potential on the mortality rate was analyzed. The CT-SS parameter for predicting the mortality gave 55.7% sensitivity and 56.6% specificity with a cut-off value of 16.5, while the CCI parameter showed 70.6% sensitivity and 66.7% specificity with a cut-off value of 16.5 as of statistically meaningful descriptive capacity.

Accompanied by the findings obtained from the ROC analysis, as can be seen in Table 3, in the model established by the logistic regression analysis (with Nagelkerke R^2=0.75 and 90.5% accuracy), it is predicted that the risk of death may increase with the neutrophil count less than 2000/μL with a 22.2-fold effect (CI 95% [7.1-66.7]), an increase in the CT-SS parameter with a 1.1-fold effect (CI 95% [1.0-1.2]), Hb value less than 9 g/dL with a 4.2-fold effect (CI 95% [1.4-12.8]), and an increase in the Charlson Comorbidity Index with a 1.2-fold effect (CI 95% [1.1-1.3]).

Table 1. Malignancy distributions of the Cancer patients

Malignancy	n	%
Lung	124	30.2
Breast	91	22.2
Genitourinary	65	15.9
Gastrointestinal	45	11.0
Skin	26	6.3
Sarcomas	12	2.9
Head and Neck	10	2.4
Others	37	9.0

Table 2. Comparison of demographic and clinical parameters of living and dead cancer patients

Parameters	Alive (n=189)	Ex (n=221)	p
Age (years)	60±21	64±15↑	0.0001
Gender (M/F)	118/71	141/80	0.617
Time of Stay* (days)	6.3±5.4	9.6±5.8↑	0.0001
ICU**	16% (n=30)	44% (n=97)↑	<0.0001
CT SS	15.3±4.8	17.6±5.5↑	<0,0001
CCI*	9±5	14±6↑	0.0001
SOFA Score	7.3±1.7	10.3±1.5↑	0.0001
APACHE II Score	16.1±5.4	19.1±4.4↑	0.0001
Hemoglobin (g/dL)	10.7±2.8	8.4±3.2↓	<0.0001
Leukocyte*(/μL)	8300±2300	6800±3900↓	0.0001
Thrombocyte*(/μL)	162000±120000	135000±94000↓	0.0027
Neutrophil (/μL)	4350±660	2100±830↓	<0.0001
D-Dimer*	1250.2±582.2	1400.2±782.2↑	0.0085
Fibrinogen	991.3±308.1	1121.3±588.6↑	0.0008
LDH*	199.1±161.6	218.1±171.9	0.217
Glucose* (mg/dL)	102.2±83.6	94.2±63.6	0.192
Urea* (mg/dL)	45.2±56.1	52.2±36.1	0.076
Creatinine* (mg/dL)	1.9±1.4	2.2±2.0↑	<0.0001
ALT* (U/L)	72.2±25.5	82.2±25.5	0.035
AST* (U/L)	97.7±21.0	92.7±18.1↓	0.002
PT* (seconds)	11.3±8.1	12.3±9.1	0.161
aPTT (seconds)	29.5±6.6	32.5±9.6↑	0.0001
INR*	1.8±2.0	1.8±2.1	1.000
CK* (U/L)	325.5±142.1	245.5±242.1↓	0.0001
Bilirubin-Total * (mg/dL)	1.9±1.4	2.0±1.5	0.405
CRP*	82.1±78.3	122.1±89.3↑	0.0001
Ferritin*	226.4±263.4	323.4±263.4↑	0.0001
Procalcitonin	13.8±9.5	20.9±7.4↑	0.0001

*Independent t test or Mann-Whitney U test were used, ** Categorical analysis was done using Pearson's Chi-Square test; p<0.05 was considered significant. CCI; Charlson Comorbidity Index, ICU; Intensive Care Unit, CT SS; CT severity score. The arrow shows an increase or decrease.

Discussion

The Covid-19 pandemic has affected the entire population with decreased/suspended health services, which has been more severe for individuals with chronic diseases. No-

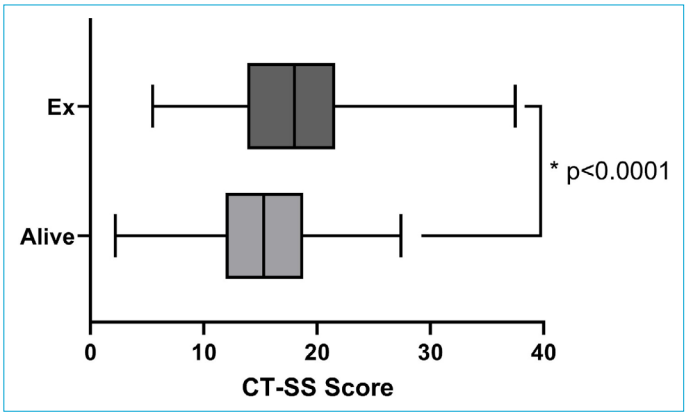

Figure 2. Comparison of CT-SS scores of ex and alive groups.

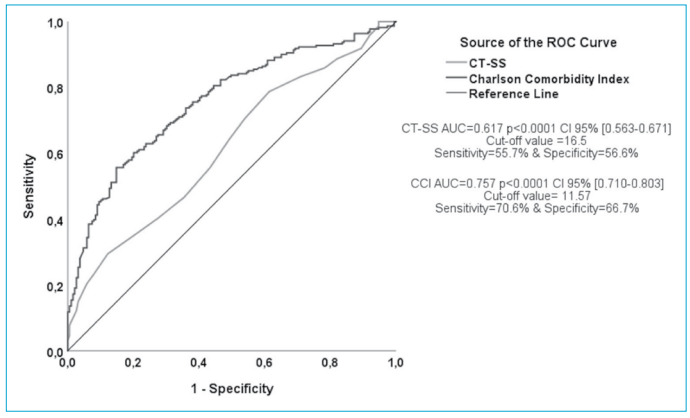

Figure 3. ROC analysis for determining mortality risk parameters CT-SS and CCI.

tably, cancer patients require consecutive visits to the hospitals, so they are more likely to get infected by the SARS-CoV-2 virus. In the early periods of the pandemic, it was speculated that immunosuppression due to cancer itself or its treatments could protect these individuals from Covid related hyper-inflammation.[7] However, the later research showed that Covid-19 infection gave more serious clinical consequences due to the immunosuppressive state, depending on the cancer type.[13] The general mortality rate of cancer patients due to Covid-19 was reported at about %20-30.[11,13,14] In our study, approximately 25% of patients hospitalized for symptomatic covid -19 infection had active malignancy, and 55% of cancer patients died due to covid-19. Since our hospital is a tertiary reference center and is a center where patients with malignancies are followed and treated intensively may have caused the high hospitalization and mortality rate of patients with oncological malignancies.

Hematological parameters of cancer patients may show dramatic changes. Chemotherapy and radiotherapy treatments for advanced malignancies, bone marrow infiltration with malignant cells, and fibrosis can cause cytopenias.[15] Especially, the risk of neutropenia may limit and guide the treatment in these patients.[16] Lee and Kuderer et al. reported no negative relation between cancer treatment and the Covid-19 clinical manifestation in two different studies. It has been reported that receiving cancer treatment in the last 30 days has no significant effect on mortality unless a level of granulocytopenia limits the treatment.[12,17] In our study, cytopenias were commonly seen abnormalities. In particular, patients with neutrophil counts below 2000/µL had the highest mortality rate, while those above 2000 had a similar mortality rate to the general group. In the ex-group, the average neutrophil count was 2100±830/µL, while that was 4350±660/µL in the alive group. The values are statistically meaningful and showed that neutrophil count is closely related to the mortality of cancer patients due to Covid-19 infection.

The other important abnormal hematological parameter seen in cancer patients is the low Hb level (anemia). Raman et al. reported that Hb level and ferritin/Hb ratio were closely associated with mortality, according to the results of their study involving 210 patients hospitalized for Covid-19.[18] Similarly, Lippi et al. reported a relationship between Hb level and Covid-19 mortality. They even recommended monitoring Hb levels to predict prognosis in hospitalized Covid-19 patients.[19] Parallel to these studies, our research also showed that a Hb level below 9 gr/dL was independently related to higher mortality in cancer

Table 3. Logistic regression analysis for determination of mortality risk parameters

Parameters/Variables	B	S.E.	Wald	Sig.	OR	95% C.I.for OR	
						Lower	Upper
Neutrophil count (<2000)	-3.099	0.577	28.814	<0.0001	22.2	7.1	66.7
CT- SS	0.094	0.036	6.764	0.009	1.1	1.0	1.2
Hemoglobin (<9 g/dL)	-1.437	0.568	6.413	0.011	4.2	1.4	12.8
Charlson Comorbidity Index	0.197	0.034	33.228	<0.0001	1.2	1.1	1.3
Constant	-1.192	0.759	2.467	0.116	0.304		

Logistic regression analysis was used, and p<0.05 was considered significant; OR: Odds Ratio, CI: Confidence Interval, SE: Standard Error.

patients. In the ex-group, the mean Hb level was 8.4±3.2 g/dL, while in the alive group, it was 10.7±2.8 g/dL. These findings clearly show that there is a meaningful relationship between the low level of Hb and increased mortality.

It is known that suppressed or dysregulated immune response in cancer patients makes the treatment harder. The infection spreads faster, which is notably worse when the infection spreads to the lungs. Pulmonary infections and the developed shortness of breath are life-treating situations.[20] CT-SS is the method to objectively monitor the lung involvement of the patients undergoing Covid-19 infection, which was shown as a powerful approach to validate the Covid-19 pulmonary involvement.[21] In our study, lung involvement severity was higher for the ex-group, where CT-SS values were 17.6±5.5 and 15.3±4.8 for the ex-group and the living group. The statistical analyses revealed a positive relationship between the lung involvement severity and mortality rate in the Covid-19(+) cancer patients.

Conclusion

Cancer patients hospitalized for symptomatic Covid-19 have markedly high mortality rates than those without any malignancy. In these patients, neutrophil count, Hb level, and lung involvement severity have positive and independent relationship with mortality. Those suffering from anemia, neutropenia, and substantial lung involvement must be closely monitored and treated intensely and meticulously.

Disclosures

Ethics Committee Approval: This study was conducted in compliance with the Declaration of Helsinki and was approved by The University of Health Sciences, Izmir Bozyaka Training and Research Hospital Clinical Research Ethics Committee (Date: 23/02/2022, No: 2022/32).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – C.Y.; Design – C.Y.; Supervision – I.D.; Materials – C.Y., I.D.; Data collection – I.D.; Analysis and interpretation – C.Y. ; Literature search – C.Y., I.D.; Writing – C.Y., I.D.; Critical Review - C.Y., I.D.

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