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Research Article

Prognostic Factors and Clinical Outcomes of Hospitalized Cancer Patients Diagnosed with COVID-19 Infection: Single Center Experience

Asli Yildirim,[1] **Leman Delen Acun**[2]

[1]Department of Medical Oncology, Malatya Training and Research Hospital, Malatya, Turkey
[2]Department of Anesthesia, Malatya Training and Research Hospital, Malatya, Turkey

Abstract

Objectives: Several studies have demonstrated that COVID-19 infection has been related with poor prognosis in cancer patients. On account of these findings, we aimed to analyze cancer patients infected with COVID-19 in terms of their laboratory and clinical findings. The relationship between the number of metastases with the outcome of COVID-19 infection was also examined.

Methods: A total of 56 patients—with 25 females and 31 males—were enrolled in this retrospective study. The presence of COVID-19 infection was proven through the use of nasopharyngeal swab and PCR technique laboratory tests. Diagnosis of cancers were confirmed with pathological findings on the biopsy or surgery specimens. The IBM SPSS Statistics 26.0 program was used in the statistical analysis of the research.

Results: Existence of 4 or more metastases were found in 21 patients who died during their follow-up period (p=0.000), as well as increased serum ferritin levels with a median of 905.3 ng/ml in death patients as compared to 173.1 ng/ml in surviving patients (p=0.01). Other laboratory findings that were found statistically significant between non-surviving and surviving patients, older age and being of the male gender were accepted as worse prognostic factors in this study. In addition, 15 of 26 non-surviving patients who received chemotherapy in their last month had worse prognosis than patients who had received chemotherapy more than one month ago (p=0.045).

Conclusion: As a result, the management of cancer patients during the pandemic process, and particularly those with widespread metastasis, is quite challenging. Therefore, medical follow-up of patients with 4 or more metastases is of particular importance.

Keywords: Cancer, COVID-19 infection, prognostic factors

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The novel coronavirus (SARS-CoV-2), termed as the COVİD-19 infection, was first detected in individuals working at sea animal markets in the Wuhan Province of China during the month of December 2019. Following its rapid spread to other countries around the globe, it was accepted as a pandemic disease by the World Health Organization (WHO) on March 11, 2020. The COVID-19 infection can cause a variety of symptoms in humans, ranging from a mild flu to severe acute respiratory distress syndrome. The latter can be fatal, especially in individuals with comorbid diseases, such as diabetes mellitus (DM), coronary artery disease (CAD), hypertension (HT), and immunosuppressed

Address for correspondence: Asli Yildirim, MD. Malatya Egitim ve Arastirma Hastanesi Tibbi Onkoloji Anabilim Dali, Malatya, Turkey
Phone: +90 552 340 39 44 **E-mail:** dr.asliyldrm@gmail.com
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conditions like cancer diseases. It has been observed that cancer patients are more vulnerable to COVID-19 infection, and it appears that these individuals are in a higher risk group than the standard population according to studies conducted from the beginning of this pandemic process.[1] Individuals with cancer are more vulnerable to COVID-19 infection, not only because of their underlying cancer disease, which is thought to be the most important reason for their immunosuppressed conditions, but also as a result of their malnutrition statuses and the treatment-related side effects contributing to their comorbidities. Finally, previous research has demonstrated that these individuals are more prone to develop complications and require admission to intensive care units (ICUs). As a consequence, this research revealed that patients with cancer disease have increased death rates when compared to those without cancer disease.[2, 3]

Cancer patients infected with COVID-19 were analyzed in terms of their outcome, as well as in terms of prognostic factors that included clinical and laboratory findings. These findings were proven by nasopharyngeal swab laboratory tests using the PCR technique. Diagnosis of cancers were confirmed with pathological findings via biopsy and/or surgery specimens. The relationship between the presence and number of metastases with the prognostic factors and outcome of COVID-19 infection was also examined in this study. According to our knowledge, this was not evaluated adequately in previous studies.

Methods

Study Design and Participants

Ethics approval of this retrospective, single-center cohort study was obtained from the Ethics Committee of Malatya Training and Research University Hospital in Turkey. Written consent was obtained from all patients participating in this study. Files were evaluated from 4000 patients who were admitted to our hospital from 01 June to 31 December 2020. These individuals had a SARS-CoV-2 infection diagnosis based on their positive PCR test results. Out of these individuals, 56 patients with a history of malign tumors were enrolled. This study included only cancer patients whose diagnoses were confirmed in their histopathological specimen and whose diagnoses of COVID-19 infection was confirmed through PCR tests. All of the patients in this study were older than 18 years of age. Furthermore, patients hospitalized in the service and intensive care units, whose data we can easily access, were enrolled in this study. It was almost impossible to access data of outpatients that were not hospitalized due to the intense working conditions of the emergency services.

Data Collection

Data were obtained from electronic medical records, hospital files and the interview with the patients and their relations, and this included the following: vital signs with oxygen saturation levels; information about hemogram and biochemical data evaluated at the time of COVID-19 diagnosis; the history, stage, and date of last oncologic treatment received; comorbidities of patients including acute renal failure (ARF), chronic obstructive pulmonary disease (COPD), CAD, DM, HT; and symptoms at the beginning of COVID-19 infection. Cancer stages of the patients were defined by using the American Joint Committee on Cancer (AJCC) TNM Staging Classification for Carcinoma (8th edition, 2017) and the performance status of patients were defined according to the Eastern Cooperative Oncology Group (ECOG) performance score system. International Severe Acute Respiratory and Emerging Infection Consortium forms were used to define the severity of pneumonia in terms of a standard evaluation. All metastatic and pneumonic lesions of patients were defined according to their thorax computer tomography (CT) scan findings at diagnosis. SARS-CoV-2 infection was diagnosed by using RT-PCR and samples were collected using nasopharyngeal swabs.

Statistical Analysis

The Statistical Package for the Social Sciences program (SPSS) 26.0 was used in the statistical analysis of the research and the performing of conformity tests of all data to normal distribution. Continuous variables that are suitable for normal distribution (parametric) were compared with the Student's t test and non-parametric variables were compared with the Mann-Whitney U test. Pearson method was used for parametric correlation analysis and Spearman tests were used for non-parametric correlation analysis. In each analysis, a p-value of < 0.05 was considered as statistically significant.

Results

A total of 56 patients—composed of 25 (44.6%) females and 31 (55.4%) males—were enrolled in this study. The vast majority of these patients (80.3%) were found symptomatic at presentation. Symptoms of the patients at the time of their diagnosis are shown in Table 1. The median age of women at the time of diagnosis was 70.24 years, whereas it was calculated as 76.19 years for men. The most common lung finding was diffuse bilateral infiltration detected in 34 (60.7%) patients. Based on their radiologic and clinical findings, it was observed that 27 (48.2%) patients had mild pneumonia, while 20 (35.7%) patients had severe pneumonia at diagnosis.

Lung cancer was found as the most common cancer type with a rate of 30.4%, followed by breast cancer with a rate of 28.6%. Moreover, 51 (91.1%) of the patients included in this study had solid cancer. On the contrary, the remaining 5 (8.9%) patients had hematological malignancies. All cancers detected in our patients are shown in Table 2.

In addition to these findings, 28 (50%) patients had stage 4 cancer disease, followed by stage 3 cancer disease detected in 15 (28.6%) patients according to the cancer TNM staging system. Furthermore, almost half of patients had a poor ECOG performance score, which was defined by the WHO performance score system. The number of patients with an ECOG performance level of greater than three (>3) was 22 (39.3%).

A total of 16 (28.6%) patients included in this study did not initially have any accompanying comorbidity, such as DM, HT, CAD, COPD or obesity. However, at least one comorbidity was observed in the remaining 40 (71.4%) patients, with the most common type of DM with HT found in 8 (14.3%) patients at the time of diagnosis. The prevalence and number of comorbidities found in patients is summarized in Table 3.

Majority of patients (29 patients with a percentage of 51.8%) needed ICU care during their follow up periods. Four of them had to be continuously treated in ICUs without ever being transported to services because of their clinical conditions. A total of 26 patients, 8 females and 18 males (p=0.034), died during their treatment periods. A total of 21 of these patients had widespread metastatic cancer disease (p=0.000). In addition, 15 patients who died had received chemotherapy in the last month (p=0.045).

When women and men were compared with each other in terms of their treatment durations, the total period of hospital stays were statistically longer in women, with an average 14.96 days as opposed to the 12.45 days for men (p=0.038).

During their follow up, complications were observed in 33 (59%) of the patients participating in this study. According

Table 1. Symptoms of patients at diagnosis

Symptoms	Number of Patients (n)	Percentage (%)
Cough	7	12.5
No symptom	6	10.7
Fatigue	5	8.9
Dyspnea	5	8.9
Fatigue + dyspnea + cough	5	8.9
Fever + cough	5	8.9
Fever + dyspnea + cough	4	7.1
Fever + dyspnea	3	5.4
Fever	3	5.4
Tachycardia	2	3.6
Nausea-vomiting	2	3/6
Dyspnea + nausea + vomiting	2	3,6
Myalgia	2	3.6
Diarrhea	2	3.6
Dyspnea + diarrhea	1	1.8
Unconsciousness	1	1.8
Cough + Dyspnea	1	1.8
Total	56	100

Table 2. Cancer Types in Patients

Cancer Types	Number of Patients (n)	Percentage (%)
Lung	17	30.4
Breast	16	28.6
Colon	11	19.6
Lymphoma	3	5.4
Prostate	2	3.6
Thyroid	1	1.8
Renal	1	1.8
Myeloma	1	1.8
Gastric	1	1.8
Cervix	1	1.8
Endometrium	1	1.8
Renal	1	1.8
Total	56	100

Table 3. Number and Frequency of Comorbidities in Patients

Comorbidities	Number of patients (n)	Percentage (%)
Without Comorbidity	16	28.6
HT + DM	8	14.3
HT	7	12.5
HT + CAD	4	7.1
COPD	3	5.4
Obesity + DM + HT + CAD	3	5.4
HT + DM + CAD	3	5.4
DM	2	3.6
COPD + HT	2	3.6
Renal Failure	1	1.8
CAD	1	1.8
Obesity	1	1.8
Obesity + DM	1	1.8
Obesity + HT	1	1.8
COPD + DM	1	1.8
Cardiac Failure	1	1.8
COPD + HT + CAD	1	1.8
Total	56	100

to these complications shown in Table 4, sepsis was the most common complication observed, with a total of 12 (21.4%) patients who experienced it.

Prognostic laboratory findings are summarized in Table 5, detailing statistically significant differences between patients who survived and those who did not. According to these findings, the following were identified: increased level of serum blood urea nitrogen (BUN), creatinine, lactate dehydrogenase (LDH), creatinine kinase (CK), D-dimer, fibrinogen, sedimentation rate, pro-brain natriuretic peptide (pro-BNP), procalcitonin, ferritin, respiratory and heart rate per minute, and older age. On the other hand, decreased level of serum albumin, hemoglobin, leukocyte, neutrophil, thrombocyte, and systolic blood pressure were all statistically related with poor prognosis in this study.

Table 4. Complications During the Follow-up Period

Complications	Number of patients (n)	Percentage (%)
Without Complication	23	41.1
Sepsis + Acute Renal Failure (ARF)	6	10.7
Arrhythmia	5	8.9
ARF + Hypernatremia	3	5.4
Embolism	3	5.4
Congestive Cardiac Failure (CCF)	3	5.4
Sepsis	2	3.6
Sepsis + Arrhythmia + CCF	2	3.6
Cerebrovascular Event	2	3,6
Atrial Fibrillation + Embolism	2	3.6
Hepatic Failure	2	3.6
Septic Shock	1	1.8
Sepsis + ARF + Hypernatremia	1	1.8
ARF	1	1.8
Total	56	100

Table 5. Statistically Significant Prognostic Lab. Findings Between Deaths and Survivors

Prognostic Factors	Non-survivors	Survivors	p
Age (year)	79.88	68.03	0.012
Systolic Blood Pressure (mmHg)	107.8	134.86	0.004
Respiratory Rate/per minute	29	14	0.000
Heart Rate/per minute	141	95	0,014
Hemoglobin (g/dL)	10.78	13.7	0.008
Leukocyte count (10^3/uL)	8256.89	8582.77	0.020
Neutrophil count (10^3/uL)	5344	6864	0.000
Thrombocyte count (10^3/uL)	134.764	240.533	0.04
Albumin (g/dL)	2.9	3.9	0.002
BUN (mg/dl)	98	41.6	0.000
Creatinine (mg/dl)	1.51	0.81	0.004
LDH (IU/L)	692	182.5	0.001
CK (U/L)	280.29	91.98	0.002
D-dimer (mg FEU/ml))	1.042	0.18	0.000
Fibrinogen (mg/dL)	827.2	149.27	0.013
Sedimentation Rate (mm/hour)	100	50.67	0.021
Pro-calcitonin (ng/ml)	0.62	0.21	0.001
Pro-BNP (pg/ml)	265.7	106.9	0.020
Ferritin (ng/ml)	905.38	173.1	0.010

Discussion

Prior literature has demonstrated that cancer patients are more likely to be infected with COVID-19 disease, tend to have a much worse prognosis, and are expected to have higher risk of serious pneumonia than non-cancer patients. One of the reasons for higher tendency to be infected with COVID-19 disease may be due to their obligation to visit hospitals more often than non-cancer patients.[4] In a study conducted by Xu and colleagues, bilateral lung lesions were detected in 53 of 90 (58.8%) patients, and this was also the most common lung finding detected in 34 (42.8%) patients within our study.[5] Consistent with other studies, severe pneumonia was detected in 20 (35.7%) patients while mild pneumonia was detected in 27 (48.2%) patients on CT at the time of diagnosis. Beyond those findings, the most common symptom at presentation was dyspnea (37.5%), followed by cough (32.1%) and fever (26.8%), respectively, as shown in Table 1.

Studies have demonstrated that increasing age, underlying comorbidities, being of the male gender, and receiving chemotherapy recently were considered as factors that contribute to worse prognosis.[2, 6] Likewise, the mean age of our patients was calculated as 70.24 years for women and 79.16 years for men, and there was a statistically significant difference between non-surviving and surviving patients (median age for non-survivors was 79.88 years and 68.03 years for survivors; p=0.012). Beyond this, the mortality rate of our male patients was found to be higher than that of female patients (18 and 8 patients, respectively; p=0.034). In addition, 15 of 26 patients who died had received chemotherapy in the last month (p=0.045) in this study. The fact that majority of patients who died had received active chemotherapy in the last one month supports the opinion that chemotherapy agents which are related with less cytopenia and administered at longer intervals without affecting cancer-related surveillance may be better options for cancer treatments during the pandemic process. Another option is switching intravenous chemotherapy to less toxic oral treatments, if possible.[7] Although other studies[1-3] found statistically significant lower levels of lymphocyte count—which may prove the decreasing effect of SARS-CoV-2 infection on the host immune system that is defending against viruses—no statis-

tically significant difference was found between non-surviving and surviving patients in terms of lymphocyte level in our study. However, there was still a higher trend in favor of surviving patients with a mean level of 964 (10^3/uL) when compared with non-surviving patients whose mean level was calculated as 387.9 (10^3/uL) (p=0.690). Moreover, the thrombocyte level of non-surviving patients was found statistically lower when compared to survivors, which may also be related with poor prognosis (p=0.04).[8] The reason why both leukocyte and neutrophil counts were found statistically higher in our surviving patients compared to our non-surviving patients may be due to the diminishing effect of the chemotherapy that majority of non-surviving patients received in the last month on their leukocyte and neutrophil values (p=0.020 and 0.000 respectively).

Ferritin level is not only a marker of iron storage in the circulating blood system, but also a marker that can be elevated in inflammatory conditions such as infections. In our study, the statistically significant lower level of ferritin level in survived patients may be because of the increased inflammatory process due to severe COVID-19 infection in patients who died (p=0.010).[10] In addition to this finding, some studies suggest that serum ferritin level may be increased in malignancy and this increased level of ferritin is generally related with poor survival in various cancers.[11] On the contrary, when C-reactive protein—which was expected to be elevated due to inflammatory processes in circulating blood system—was evaluated, there was no statistically significant difference between the surviving and non-surviving patients, even when a trend for increase in non-survived patients was detected (mean value for non-surviving patients was 6.17 mg/dL and 2.22 mg/dL for survivors; p=0.333). The statistically significant higher sedimentation rate value in the patients who died supports the notion that ferritin level may increase due to inflammatory processes and may also be a worse prognostic factor.[12] Since the levels of iron, iron binding, and transferrin saturations were not evaluated at the time of COVID-19 diagnosis, the relationship between these values with the ferritin level could not be investigated in our study. All prognostic factors found statistically significant between surviving and non-surviving patients are summarized in Table 5.

Despite the fact that all patients were provided adequate hydration in this study, acute renal failure was diagnosed in 12 patients, with hypernatremia accompanying 3 of them. The reasons for this situation may be the drug-drug interactions that may occur as a result of intensive supportive treatment, including antibiotics, the negative effects of recent chemotherapy on the kidneys,[13] or the contribution of underlying comorbidities such as HT and DM to renal failure.[14] Whether the COVID-19 infection itself might cause acute renal failure is an area of investigation. Other frequent complications included cardiac failure in 5 patients and arrhythmia in 9 patients, which developed during the follow-up of patients included in this study. Pro-brain natriuretic peptide (pro-BNP) may be elevated due to cardiac complications. On the other hand, in a study designed by Raymond Pranata et al., it was found that elevated pro-BNP was independently associated with mortality in COVID-19 pneumonia. In alignment with this study, we found statistically significant higher levels in the pro-BNP along with the CK level in our patients who died (p=0.020 and 0.002, respectively).[15,16] Complications that developed during follow-up periods are shown in Table 4.

Finally, another situation that draws our attention in this study is the presence of widespread radiological metastases in 21 of the patients who died, if the number of metastases of 4 or more is considered to be widespread metastatic status (p=0.000). None of our patients with a number of 3 or less in metastatic lesions died during the follow-up period. This finding may also be a warning sign for clinicians when selecting an oncologic treatment option, since presence of wide spread metastasis may also contribute to worse prognosis of COVID-19 infection.

The factors limiting our study were the small number of our patients, the absence of evaluation of other mediators such as Interleukin 6 (IL-6), exclusion of other patients being followed-up with in the outpatient clinic from the study due to the inability to access their files, and the inability to compare these patients and hospitalized patients in terms of prognostic factors.

Conclusion

In conclusion, increased number of metastasis are defined as worse prognostic factor in our study. As the COVID-19 pandemic disease continues, it seems that it may become more difficult to manage patients with extensive metastases. As a consequence, more specific approaches may be required for these patients before the pandemic ends.

Disclosures

Ethics Committee Approval: Malatya Research and Training Hospital, 25.02.21; E-23536505-604.02.

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Concept – A.Y.; Design – A.Y.; Supervision – A.Y.; Materials – L.A.D.; Data collection &/or processing – A.Y., L.A.D.; Analysis and/or interpretation – A.Y.; Literature search – A.Y.

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