Clinical evaluation of patients with COVID-19 within the framework of comorbidities

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Abstract

Background: Chronic systemic diseases (CSD) and cancer are closely related to the clinical course, severity and mortality of COVID-19 due to the immunosuppressive conditions caused by these diseases. The purpose of this study was to investigate the differences between the effects of cancer and CSD on the clinical and laboratory parameters of patients with COVID-19. Methods: The study included patients who received inpatient treatment with the diagnosis of COVID-19 at Ondokuz Mayıs University between 16 March, 2020, and 1 December, 2020. The participants were divided into four groups as follows: those without comorbidities (Group 1), those with only CSD (Group 2), those with only cancer (Group 3), and those with both CSD and cancer (Group 4). Comparative statistical evaluation was performed in terms of clinical symptoms, biochemical parameters, admission to intensive care and survival. Results: In total, 750 patients were included: 242 patients in Group 1, 442 in Group 2, 27 in Group 3, and 39 in Group 4. The mean age of the patients was 57.1 ± 9.4 years, and 53.7% were male. Patients of Group 1 were significantly different from those of the other groups in terms of age, requirement for intensive care and intubation, complications, survival, white blood cell and lymphocyte count, neutrophil/lymphocyte ratio and levels of haemoglobin, lactic acid dehydrogenase, ferritin, D-dimer and C-reactive protein (for each $p < 0.001$). Conclusion: No difference was observed among laboratory parameters, intensive care admission, intubation need, complication frequency and survival rates in patients with CSD or cancer.

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care and intubation, complications, survival, white blood cell and lymphocyte count, neutrophil/lymphocyte ratio and levels of haemoglobin, lactic acid dehydrogenase, ferritin, D-dimer and C-reactive protein (for each $p < 0.001$).

Conclusion: No difference was observed among laboratory parameters, intensive care admission, intubation need, complication frequency and survival rates in patients with CSD or cancer.

Keywords: COVID-19, chronic systemic disease, cancer, comorbidity

What's known

Several comorbidities have been associated with the clinical course and severity of the disease in patients with COVID-19.

Patients with cancer have a higher risk of being infected with SARS-CoV-2 and a poor prognosis.

What's new

- Benignity or malignancy of the comorbid chronic processes does not have a significant effect on the COVID-19.
- The presence of chronic systemic disease and cancer is associated with mortality.
- High ferritin and low haemoglobin levels are clinically significant differences between patients with chronic systemic disease and cancer.

1 INTRODUCTION

The fight against coronavirus disease (COVID-19) disease continues globally. All aspects of scientific research on this subject are of great importance. The clinical picture of COVID-19 in adults ranges from asymptomatic infection to severe pneumonia that may be associated with multi-organ failure.[1]

Several comorbidities have been associated with the clinical course and severity of the disease as well as mortality in patients with COVID-19.[2] Among these, the most common chronic systemic diseases (CSD) include hypertension, diabetes mellitus and coronary artery diseases.[3] Patients with cancer are more susceptible to infections due to additional CSD, poor general health and immunosuppressive conditions caused by anticancer treatments.[4] Therefore, they have a higher risk of being infected with SARS-CoV-2 and a poor prognosis.[5]There are many studies which examine the relationship of cancer and CSD with COVID-19.[6,7] The purpose of our study was to evaluate patients who had cancer and/or CSD or no comorbidities who received COVID-19 treatment in our hospital by grouping them in terms of clinical and laboratory parameters, intensive care requirement and survival. In addition, it was planned to determine whether there was a difference between the effects of cancer and CSD on COVID-19, and if there was a difference, which condition affected patients with COVID-19 more and why.

2 MATERIAL AND METHOD

In this analytical study, the records of 824 patients with positive COVID-19 reverse-transcriptase polymerase-chain-reaction (RT-PCR) test result who received inpatient treatment between March 16, 2020, and December 1, 2020, at Ondokuz Mayıs University Medical Faculty Hospital were retrospectively reviewed. Pregnant patients (n = 20) and patients younger than 18 years (n = 54) were not included in the study. Permission was obtained from the Ministry of Health for this study, and approval was obtained from the local ethics committee (decision number OMU KAEK 2021/730). The study was performed in accordance with the Declaration of Helsinki.

A confirmed case of COVID-19 was defined as a positive result for real-time RT-PCR assay for nasal and oropharyngeal swab specimens. SARS-CoV-2 (2019-nCoV) RT-PCR Detection Kit (Bioeksen Bio-Speedy R&D Co, Ltd, Turkey) was used to demonstrate the presence of SARS-CoV-2. Patients were divided into four groups based on their disease status: those without comorbidities (Group 1), those with only CSD (Group 2), those with only cancer (Group 3) and those with both CSD and cancer (Group 4). CSD was recorded under the title of the relevant disease category and not separately. Patients' demographic

characteristics, CSD status, presence of cancer (solid and haematological), clinical symptoms, treatments used, biochemical parameters (counts of platelets, leucocytes and lymphocytes, neutrophil/lymphocyte ratio (NLR), clotting tests and levels of haemoglobin (Hb), lactic acid dehydrogenase (LDH), C-reactive protein (CRP), procalcitonin, D-dimer and ferritin), need for intensive care, intubation, complications and survival were evaluated comparatively.

2.1 Statistical analysis

After the data obtained from the study were encoded, they were analysed using SPSS (Version 22 for Windows, SPSS Inc, Chicago, IL, USA) package program. During data analyses, continuous variables were expressed as mean ± standard deviation and median (min–max), and frequency data were expressed as number and percentage (%). The compliance of all measurement variables to normal distribution was evaluated with the Kolmogorov–Smirnov test. Pearson chi-square test was used for comparison of frequency data. In the intergroup comparisons of continuous variables, Kruskal–Wallis test was used for comparisons between the groups as the data did not conform to normal distribution, and subsequently, Mann–Whitney U test with Bonferroni correction was used to determine the group which led to the difference for variables with significant differences. Statistical significance level of all tests was accepted as $p < .05$.

3 RESULTS

The mean age of 750 patients with COVID-19 included in the study was 57.1 ± 9.4 (min: 18–max: 96) years, and 53.7% were male. It was determined that 58.9% of the patients had at least one CSD, 5.2% (n = 39) had both CSD and cancer and 3.6% (n = 27) had cancer not accompanied by another CSD. Of the 66 patients with cancer, 60.6% (n = 40) had malignant solid tumours, and 39.4% (n = 26) had haematological cancer. Some of the demographic characteristics and distribution of patients with COVID-19 based on their CSD status are presented in Table 1. We observed that 32% of the participants had one CSD and 24.7% had two, whereas 11.3% had three or more CSDs.

The most common complaints of the participants associated with COVID-19 were cough (58.4%), fever (38.9%) and myalgia (38.7%), in order. The main treatments were enoxaparin (90.3%), favipiravir (86.1%) and steroids (50.5%). The clinical symptoms of the patients and treatments used are presented in Table 2.

Whereas 122 (16.3%) of all patients were treated in the intensive care unit, 67 (8.9%) of them were intubated. Intubation frequency was 54.9% (n = 67) among those who were followed up in the intensive care unit. Mean duration of hospital stay was 9.4±7.1 (min: 2–max: 63) days/patient for all patients, whereas it was 17.2±9.3 (min: 2–max: 52) days/patient for those in the intensive care unit. Complications developed in 18.8% of all participants, and 13.5% died.

The comparison of some sociodemographic and clinical characteristics of patients with COVID-19 based on their current CSD and cancer status as well as the laboratory results on the first day of hospitalisation is presented in Table 3. Accordingly, there was no statistically significant difference between the groups in terms of sex, white blood cell and platelet count and activated partial thromboplastin time. In the evaluation of other parameters, it was found that there was a highly significant difference between the groups ($p < .001$).

On the basis of the pair-wise comparisons of the groups, there was a difference in age in all compared pairs except in Group 2 and Group 4, ($p < .001$). Regarding other categorical variables, the patients in Group 1 were significantly different from those of the other groups in terms of age group, intensive care and intubation requirement, complication status and survival ($p < .001$). It was determined that there was no statistical difference among the other three groups in terms of these parameters. Similarly, patients in Group 1 were different from those of the other groups in terms of lymphocyte count, NLR, prothrombin time ($p = .004$) and levels of LDH and CRP, and the median values of this group were significantly lower than those of the other three groups ($p < .001$). The other groups did not differ significantly from each other in terms of these parameters. There was no difference in median values of Hb and ferritin between Group 3 and Group 4. However, the median Hb value of both groups was lower than those of Groups 1 and 2, whereas the ferritin values were significantly higher ($p < .001$).

4 DISCUSSION

In this study, the comparison of CSD and cancer examined as comorbidities in patients with COVID-19 was investigated for the first time in the literature to the best of our knowledge. It was observed that patients with CSD and/or cancer were at higher risk in terms of intensive care admission, intubation, rate of complications and survival compared to patients without comorbidities. In addition, there was no significant difference in clinical parameters and survival between those with cancer and those with CSD, except that Hb and ferritin levels were significantly different in those with cancer.

In a large COVID-19 clinical study conducted in China, the mean age of participants was 47 years, and 58% of the participants were male.[8] However, in our study, the mean age was lower, and the proportion of males was almost similar. The absence of patients under the age of 18 years may be the main reason for the mean age difference in our participants. In addition, the mean age of patients with CSD and cancer was higher than that of patients without comorbidities. This situation can be explained by the higher prevalence of CSD in older patients.[9] The most common symptoms in the patients in our study were cough, fever and myalgia, which was similar to the results reported in the literature.[10]In a meta-analysis examining the prevalence of comorbidities, the most frequently reported ones were hypertension and diabetes.[11] Similarly, the most common CSDs in the patients in our study were diseases related to the cardiovascular and endocrinological systems. Evaluation of hypertension under the title of cardiovascular system diseases and diabetes under the title of endocrinological system diseases could have had an effect on this result.

CRP is an acute phase reactant induced by interleukin (IL)-6 produced by the liver and is a sensitive biomarker in various inflammatory conditions such as infection and tissue damage.[12] An increase in serum CRP levels has been observed in many studies as a reliable indicator of the presence and severity of SARS-CoV-2 infection.[13,14] Damage to any of the multiple cell types containing LDH results in increased serum LDH levels. Therefore, elevated LDH is common in critically ill patients with COVID-19 and is believed to indicate poor prognosis.[12] D-dimer is another important biomarker investigated as a potential prognostic factor of disease severity in COVID-19. It was found that compared to patients with D-dimer levels of $<$2.0 μg/mL, those with higher D-dimer levels had a higher incidence of comorbidities such as diabetes, hypertension, coronary artery disease and stroke.[15] In our study, CRP, LDH and D-dimer levels were significantly higher in and patients with CSD and cancer compared to those without comorbidities.

NLR has been used as a prognostic indicator for conditions such as acute-on-chronic hepatitis B liver failure[16] and as a mortality risk factor for malignancy, acute coronary syndrome and cerebral haemorrhage.[17,18,19] Recent studies suggest that NLR is an early predictor of critical illness in SARS-CoV-2 infection.[20] It is reported that patients with severe COVID-19 have higher neutrophil count and lower lymphocyte count compared to nonsevere patients, and therefore, NLR tends to be higher in patients with severe infection.[21] This explains why NLR was significantly higher in patients with cancer and CSD along with COVID-19 compared to patients with COVID-19 without comorbidities in our study.

Patients with CSD who are also infected with SARS-CoV-2 require more medical attention, such as intensive care admission and mechanical ventilation therapy.[22] Similarly, patients with cancer have a higher incidence of intensive care admission, mechanical ventilation and complications.[23,24] In our study, the rate of referral to the intensive care unit exceeded 20% in patients with cancer and CSD, whereas this rate was 5% in patients without comorbidities. Whereas 25% of the patients admitted to the intensive care unit without comorbidities required intubation, this rate exceeded 50% in those with CSD and cancer. Similar to the literature, in our study, intensive care admission and need for mechanical ventilation in patients with CSD and cancer were clinically significantly higher. However, there was no significant difference between patients with CSD and those with cancer. It is observed that the benignity or malignancy of the comorbid chronic processes does not have a significant effect on the COVID-19 clinical picture; this information is contributed to the literature for the first time in this study.

The survival rates of those with CSD and cancer were significantly lower than those without comorbidities. It was not surprising that the mortality rates were high (33.3%) in the group with both cancer and CSD

(Group 4). Similar to the results reported in many studies, the presence of CSD and cancer was associated with mortality in our study.[25,26]

In a meta-analysis, it was demonstrated that patients with severe COVID-19 had lower Hb levels than those with moderately severe COVID-19. This suggests that the severity and prognosis of the disease in patients with COVID-19 may be associated with lower Hb levels.[27] Patients with anaemia have a higher prevalence of comorbidities such as hypertension, cardiovascular disease or chronic kidney disease, all of which are known risk factors for COVID-19-related death.[2] Ferritin not only has a role in iron storage, but also is a well-known acute phase reactant.[28] Ferritin H chain may be important in activating macrophages to increase the secretion of inflammatory cytokines observed in patients with COVID-19. The clinical picture in critical patients with COVID-19 resembles that of those with macrophage activating syndrome, which is often associated with high levels of ferritin and cytokine storms.[29] In our study, unlike other parameters, there was a clinically significant difference only in high ferritin and low Hb levels between patients with CSD and those with cancer. Patients with cancer were significantly different from patients of other groups in this regard. One of the most important factors for this difference may be that the release of inflammatory cytokines is higher in patients with cancer than in those with other CSDs. In addition, the grouping of haematological cancers under the title of cancer and higher frequency of anaemia in these patients may be another factor.

This study has some limitations. The number of samples was not homogeneously distributed among the groups. As the study was retrospective, the severity of comorbidities and compliance of patients with medical prescriptions could not be evaluated. It is known that some metabolic variables can reach pathological values in COVID-19 as well as some chronic inflammatory processes. Since there are no subjects without COVID-19 among our participants, it cannot be demonstrated to what extent COVID-19 affects the current values of these measurements.

5. CONCLUSION

This study has demonstrated that there is no clinically significant difference in the levels of laboratory parameters, intensive care admission, intubation requirement, rate of complications and most importantly, survival rates in patients with CSD and those with cancer who are infected with SARS-CoV-2, except in Hb and ferritin levels. Additionally, in these patients, it was observed that SARS-CoV-2 infection had a clinically worse prognosis and fatal course compared to those of normal population. Therefore, these patients should adhere more strictly to general protection measures. It is recommended to plan the treatment of patients with cancer and CSD infected with SARS-CoV-2 based on a careful risk-benefit analysis by multidisciplinary teams.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request

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TABLE 1 Some demographic characteristics of the patients and their distribution based on chronic systemic disease status

Sex n (%)	Male	403 (53.7)
	Female	347 (46.3)
Age (mean ± standard deviation), years		57.1 ± 9.4
Age group (years) n (%)	18–64	471 (62.8)
	65–84	258 (34.4)
	[?]85	21 (2.8)
Chronic systemic diseases^{+} n (%)	Cardiovascular disease	341 (45.5)
	Endocrinological disease	212 (28.3)
	Chest disease	76 (10.1)
	Nephrological disease	57 (7.6)
	Neurological disease	55 (7.3)
	Rheumatological disease	21 (2.8)
	Gastrointestinal disease	15 (2.0)
	Urological disease	14 (1.9)
	Psychiatric illness	11 (1.5)
	None	242 (32.3)
Presence of cancer n (%)	Solid tumour	40 (60.6)
	Haematological tumour	26 (39.4)

$^{+}$More than one option could be marked.

TABLE 2 Clinical symptoms of the patients and distribution of the treatment options used

Clinical symptoms n (%)	Clinical symptoms n (%)	Treatment used n (%)	Treatment used n (%)
Cough	438 (58.4)	Enoxaparin	677 (90.3)
Fever	292 (38.9)	Favipiravir	646 (86.1)
Myalgia	290 (38.7)	Steroids	379 (50.5)
Dyspnoea	283 (37.7)	Chloroquine	153 (20.4)
Weakness	261 (34.8)	Azithromycin	97 (12.9)
Headache	236 (31.5)	Anticoagulant	83 (11.1)
Throat ache	140 (18.7)	Aspirin	55 (7.3)
Loss of smell and taste	97 (12.9)	Tocilizumab	26 (3.5)
Diarrhoea	91 (12.1)	Oseltamivir	14 (1.9)
Runny nose	54 (7.2)	Plasma	13 (1.7)
Nasal congestion	40 (5.3)	Remdesivir	6 (0.8)
Sputum	33 (4.4)	Anakinra	1 (0.1)
Nausea and vomiting	32 (4.3)		

TABLE 3 Comparison of sociodemographic and clinical characteristics among the groups

Variables	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	*P*
Sex Male Female	141 (58.3) 101 (41.7)	224 (50.7) 218 (49.3)	16 (59.3) 11 (40.7)	22 (56.4) 17 (43.6)	.25
Age^{+}	43 (18-90)	65 (21-96)	55 (18-75)	68 (45-80)	**<.001***
Age group (years) 18–64 65–84 [?]85	216 (89.3) 25 (10.3) 1 (0.4)	219 (49.5) 203 (45.9) 20 (4.5)	20 (74.1) 7 (25.9) 0 (0.0)	16 (41.0) 23 (59.0) 0 (0.0)	**<.001***
Intensive care Yes No	12 (5.0) 230 (95.0)	91 (20.6) 351 (79.4)	9 (33.3) 18 (66.7)	10 (25.6) 29 (74.4)	**<.001***
Intubation Yes No	3 (1.2) 239 (98.8)	53 (12.0) 389 (88.0)	4 (14.8) 23 (85.2)	7 (17.9) 32 (82.1)	**<.001***
Complications Yes No	27 (11.2) 215 (88.8)	94 (21.3) 348 (78.7)	11 (40.7) 16 (59.3)	9 (23.1) 30 (76.9)	**<.001***
Survival Survived Died	238 (98.3) 4 (1.7)	364 (82.4) 78 (17.6)	21 (77.8) 6 (22.2)	26 (66.7) 13 (33.3)	**<.001***
Hospitalisation (days)$^{+}$	6 (2-30)	8 (2-63)	13 (2-31)	9 (2-27)	**<.001***
White blood cell count^{+}, 10^3/uL	5.9 (2.0-24.7)	6.2 (0.5-24.1)	5.8 (0.5-27.3)	5.5 (2.0-29.2)	.141
Haemoglobin^{+}, g/dL	13,7 (7.1-17.9)	12,6 (3.6-19.0)	10,7 (6.0-16.0)	10,6 (6.4-16.4)	**<0.001***
Platelet count^{+}, 10^3/uL	200 (13-570)	192 (16-594)	170 (11-435)	180 (8-591)	0.078
Lymphocyte count^{+}, 10^3/uL	1.4 (0.3-3.9)	1.1 (0.1-9.1)	0.9 (0.2-6.9)	0.8 (0.2-13.4)	**<.001***
Neutrophil/Lymphocyte ratio^{+}	2,9 (0.1-41.0)	3.8 (0.1-63.6)	2.9 (0.1-39.0)	3.3 (0.3-32.0)	**<.001***
Prothrombin time^{+}, s	12.0 (10.2-16.9)	12.3 (10.0-29.1)	12.4 (10.5-17.5)	12.4 (10.2-33.7)	**.004***
Activated partial thromboplastin time^{+}, s	27.6 (3.1-50.0)	28.3 (18.1-70.2)	26.9 (20.1-41.7)	29.5 (18.8-55.8)	.206
Lactic acid dehydrogenase^{+}, U/L	255 (23-908)	293 (90-2172)	320 (139-1634)	294.5 (133-3600)	**<.001***
Ferritin^{+}, ng/mL	208.5 (6-7256)	336 (13-10000)	1105 (60-6322)	733.5 (29-8397)	**<.001***
D-dimer^{+}, ng/mL	325 (50-8490)	721 (38-10000)	1581 (84-10000)	1188.5 (193-10000)	**<.001***

Variables	Group 1 n (%)	Group 2 n (%)	Group 3 n (%)	Group 4 n (%)	*P*
C- reactive protein^{+}, mg/L	12 (3-435)	45 (3-422)	33 (3-300)	51 (3-282)	**<.001***
Number of participants	242	442	27	39	

$^{+}$Median (Range)

*With Bonferroni correction