Clinical Evaluation of Patients with COVID-19 Within the Framework of Comorbidities

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Abstract

Objectives: 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 Mayis University between March 16, 2020, and December 1, 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, and 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 hemoglobin, 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. It was detected that all three groups with CSD and cancer were worse than Group 1 in terms of intensive care need, intubation, and survival.

Keywords: Cancer, Chronic systemic disease, Comorbidity, COVID-19

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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.¹¹
Several comorbidities have been associated with the clinical course and severity of the disease as well as mortality in patients with COVID-19. Among these, the most common chronic systemic diseases (CSD) include hypertension, diabetes mellitus, and coronary artery diseases. Patients with cancer are more susceptible to infections due to additional CSD, poor general health, and immunosuppressive conditions caused by anticancer treatments. Therefore, they have a higher risk of being infected with SARS-CoV-2 and a poor prognosis. There are many studies which examine the relationship of cancer and CSD with COVID-19. 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.

Methods
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 Mayis 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 KAEEK 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 hematological), clinical symptoms, treatments used, biochemical parameters (counts of platelets, leukocytes, and lymphocytes, neutrophil/lymphocyte ratio [NLR], clotting tests and levels of hemoglobin [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.

Statistical Analysis
After the data obtained from the study were encoded, they were analyzed 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. Univariate and multivariate logistic regression models were used to determine the factors affecting mortality. Only variables determined to have significant differences between groups were included in the models, and one of the two variables with high correlation between them was preferred, and then odds ratio (ORs) and 95% confidence intervals (CIs) were calculated. Statistical significance level of all tests was accepted as p<0.05.

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 tumors, and 39.4% (n=26) had hematological 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 1st day of hospitalization 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<0.001).

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<0.001). 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<0.001). 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=0.004) and levels of LDH and CRP; and the median values of this group were significantly lower than those of the other three groups (p<0.001). 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<0.001).

Tables 4 and 5 show which factors were effective in predicting the risk of death for each group in univariate and multivariate logistic regression analyses. While different risk factors were determined for each group according to the univariate models, advanced age, intubation, presence of complications, and high LDH were important risk factors only for Group 2 according to the multivariate model (p<0.05).

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 tumor | 40 (60.6) | Hematological tumor | 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 (%) | 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)   |
| Dyspnea 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) |                      |
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.[7] 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.[8]

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.[9] In a meta-analysis examining the prevalence of comorbidities, the most frequently reported ones were hypertension and diabetes.[10] Similarly, the most common CSDs in the patients in our study were diseases related to
### Table 4. Factors predictive of death in hospitalised patients with COVID-19 by univariate logistic regression model

| Covariates                     | Group 1 (n=242) | Group 2 (n=442) | Group 3 (n=27) | Group 4 (n=39) |
|--------------------------------|-----------------|-----------------|----------------|----------------|
| Age (year)                     | 1.07* (1.01–1.14)** | 1.06 (1.03–1.08) | 0.99 (0.93–1.06) | 0.99 (0.92–1.07) |
| P                              | 0.034           | <0.001          | 0.97           | 0.92           |
| Intensive care                 | 76.3 (7.2–807.7) | 35.8 (18.8–68.1) | 3232296 (0.0–NA) | 1092971 (0.0–NA) |
| P                              | <0.001          | <0.001          | 0.99           | 0.99           |
| Intubation                     | 237.0 (147.7–3800.1) | 214.8 (63.0–732.8) | 169648 (0.0–NA) | 576955 (0.0–NA) |
| P                              | <0.001          | <0.001          | 0.99           | 0.99           |
| Complications                  | 2809521 (0.0–NA) | 16.7 (9.3–29.7)  | 12.5 (1.1–130.6) | 11.5 (1.9–68.5) |
| P                              | 0.99            | <0.001          | 0.03           | 0.007          |
| Hemoglobin                     | 0.91 (0.53–1.57) | 0.78 (0.68–0.88) | 0.72 (0.46–1.13) | 0.75 (0.56–1.02) |
| P                              | 0.75            | <0.001          | 0.16           | 0.07           |
| Neutrophil/Lymphocyte ratio    | 1.04 (0.93–1.18) | 1.09 (1.05–1.12) | 1.02 (0.92–1.12) | 1.10 (0.98–1.22) |
| P                              | 0.44            | <0.001          | 0.66           | 0.08           |
| Lactic acid dehydrogenase      | 1.00 (1.00–1.01) | 1.007 (1.005–1.008) | 1.00 (0.99–1.00) | 1.00 (0.99–1.00) |
| P                              | 0.06            | <0.001          | 0.86           | 0.23           |
| Ferritin                       | 1.00 (1.00–1.01) | 1.001 (1.001–1.001) | 1.00 (0.99–1.00) | 1.00 (1.00–1.00) |
| P                              | 0.26            | <0.001          | 0.91           | 0.44           |
| D-dimer                        | 1.00 (1.00–1.001) | 1.00 (1.00–1.00)  | 1.00 (1.00–1.00) | 1.00 (1.00–1.00) |
| P                              | 0.17            | <0.001          | 0.55           | 0.04           |
| C-reactive protein             | 1.009 (1.00–1.01) | 1.01 (1.01–1.017) | 1.00 (0.99–1.01) | 1.01 (1.002–1.02) |
| P                              | 0.04            | <0.001          | 0.97           | 0.014          |

*Odds Ratio, **95 % Confidence Interval, Bold values denote statistical significance at P<0.05.

### Table 5. Factors predictive of death in hospitalized patients with COVID-19 by multivariate logistic regression model

| Covariates                     | Group 1 (n=242) | Group 2 (n=442) | Group 3 (n=27) | Group 4 (n=39) |
|--------------------------------|-----------------|-----------------|----------------|----------------|
| Age (year)                     | 96.8* (0.00–NA)** | 1.1 (1.05–1.16)  | 0.41 (0.00–NA)  | 0.85 (0.58–1.26) |
| P                              | 0.97            | <0.001          | 0.99           | 0.44           |
| Intensive care                 | 2.3 (0.00–NA)   | 2.1 (0.53–8.20) | 3.600 (0.0–NA) | 4.4 (0.0–NA)   |
| P                              | 0.97            | 0.28            | 0.99           | 0.99           |
| Intubation                     | 2.9 (0.00–NA)   | 98.2 (15.3–627.5) | 6.5 (0.0–NA)  | 0.06 (0.0–NA)  |
| P                              | 0.97            | <0.001          | 1.0            | 0.10           |
| Complications                  | 1.8 (0.0–NA)    | 7.6 (2.4–23.5)  | 0.0 (0.0–NA)   | 48.4 (0.001–NA) |
| P                              | 0.97            | <0.001          | 0.99           | 0.49           |
| Hemoglobin                     | 0.001 (0.0–NA)  | 0.93 (0.71–1.21) | 0.01 (0.0–NA)  | 1.3 (0.29–6.2) |
| P                              | 0.98            | 0.60            | 0.99           | 0.69           |
| Neutrophil/Lymphocyte ratio    | 0.001 (0.0–NA)  | 0.99 (0.93–1.05) | 2.96 (0.0–NA) | 1.1 (0.46–2.75) |
| P                              | 0.97            | 0.79            | 0.99           | 0.78           |
| Lactic acid dehydrogenase      | 1.13 (0.00–10207.08) | 1.003 (1.000–1.007) | 1.008 (0.0–2.6) | 1.006 (0.98–1.02) |
| P                              | 0.97            | 0.02            | 1.00           | 0.61           |
| Ferritin                       | 1.004 (0.26–3.79) | 1.00(1.000–1.001) | 0.98(0.00–750785.3) | 1.00(0.99–1.002) |
| P                              | 0.99            | 0.25            | 0.99           | 0.62           |
| D-dimer                        | 1.009 (0.45–2.24) | 1.00 (1.00–1.00)  | 0.99 (0.04–276.7) | 1.00 (0.99–1.003) |
| P                              | 0.98            | 0.68            | 1.00           | 0.89           |
| C-reactive protein             | 1.27 (0.00–141E+5.01) | 1.006 (0.99–1.013) | 1.02 (0.0–6.2)  | 1.02 (0.98–1.06) |
| P                              | 0.97            | 0.11            | 1.00           | 0.25           |

*Odds Ratio, **95% Confidence Interval, NA: Not applicable, Bold values denote statistical significance at P<0.05.
Patients with anemia 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. Ferritin not only has a role in iron storage, but also is a well-known acute phase reactant. 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. 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 hematological cancers under the title of cancer and higher frequency of anemia 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.

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. In addition, in these patients, it was observed that SARS-CoV-2 infection
had a clinically worse prognosis and fatal course compared to those of without comorbidity. 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.

Disclosures

Ethics Committee Approval: Ethical approval for this study was obtained from the Ondokuz Mayis University Ethics Committee with the decision number OMU KAEEK 2021/730.

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