Evaluation of mortality predictors in hospitalized COVID-19 patients: Retrospective cohort study

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ABSTRACT

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Introduction: Evaluation of parameters that will predict prognosis in COVID-19 disease ensures correct determination of treatment strategy. In this study, it was aimed to determine the clinical, radiological and laboratory parameters affecting mortality and to evaluate the risk factors.

Materials and Methods: Patients hospitalized with the diagnosis of COVID-19 in September 2020 were included in the study. Clinical features, laboratory parameters, and radiological findings at admission were recorded. The relationship of these parameters with 30-day mortality was evaluated. Statistical analysis was performed with SPSS for Windows 16.0 Package Program.

Results: Three hundred and sixty patients (female/male, n= 228/132) hospitalized in the specified period were included in the study. 30-day mortality rate was 14.4% in all patients. In multiple logistic regression analysis, age, presence of heart failure, admission oxygen saturation, body temperature higher than 38.2 and high ferritin levels were evaluated as independent risk factors for 30-day mortality.

Conclusion: The relationship between clinical and laboratory markers and mortality is very important for the correct orientation of healthcare services and the correct determination of treatment strategy during the COVID-19 pandemic.

Key words: COVID-19; pandemic; prognosis; mortality; ferritin
INTRODUCTION

Coronavirus disease-19 (COVID-19) outbreak that emerged in December 2019 in Wuhan still goes on unabated worldwide. Since the clinical course varies from mild disease to death (1,2), there is a need for certain parameters that can predict the prognosis at the time of patient’s admission to the hospital and enable the relevant healthcare professionals to make the appropriate treatment decisions (3).

The rate of the patients, who were provided intensive care support among the patients admitted to the hospitals, had reached 6% in China and that the respective rates in U.K. and in Europe in general were even higher. Therefore, availability of such data that can be used to predict mortality or severe course of the disease would enable the healthcare professionals to properly distribute and use their energy and the available medical support (2,4).

During the pandemic period, clinics started to rapidly share their data in order to be able to create a common treatment modality and a follow-up approach. A review of the published studies reveals the differences between these laboratory data, which might be helpful in predicting the prognosis (2,3).

Hence, it was aimed with this study to investigate the relationship between clinical, laboratory and radiological findings and mortality in hospitalized patients and to determine the risk factors related to the prognosis.

MATERIALS and METHODS

The ethics committee approval was obtained from the local ethics committee in which the study was conducted.
Radiology

Radiological findings (chest X-ray and computed tomography (CT)) on first day visit were noted. Chest X-ray findings were categorized into three groups: normal, unilateral, and bilateral infiltrates. Additionally, CT findings were re-evaluated by two experienced clinicians. CT findings were categorized both based on the number of lobes involved (unilateral or bilateral), and the location of the involvement (central and/or peripheral). While on CT, findings with ground glass and/or consolidation detected in more than 50% of the total area were defined as “diffuse involvement”, those with less than 50% were defined as “limited involvement”. CT scans performed during the hospital stay were not taken into consideration.

These clinical, laboratory and radiological findings were reviewed within the scope of the 30-day medical surveillance period to determine the factors affecting mortality.

Statistical Analysis

Statistical analysis of the study was performed with SPSS for Windows 16.0 Package Program. Normality analysis of continuous data was performed with Shapiro-Wilk test, QQ-plot and histogram graphics. It was accepted that a p< 0.05 level in the Shapiro-Wilk test did not provide the assumption of normality. For normally distributed variables, Independent Samples-t test was used for mean comparisons between two independent groups, and variables were expressed as mean, standard deviation and 95% confidence interval. For the variables assumed to be not normally distributed, Mann-Whitney U test was used for comparisons between two independent groups, and variables were expressed as median and interquartile range. Chi-square tests were used to compare the frequency distributions of categorical variables, and these variables were expressed with sample count and percentage. Multiple logistic regression analysis was performed for parameters evaluated to be significantly in terms of survival in univariate analyses. In this analysis, Odds ratios are presented with 95% confidence intervals for the potential predictors of mortality. p< 0.05 level was used for statistical significance.

RESULTS

Three hundred and sixty patients (228/132, M/F) admitted to the hospital and received inpatient between September 1st and September 30th, 2020 were included into the study. Mean age of patients was 62.3 ± 14.1. 88.3% of the patients who received inpatient were discharged, whereas 11.7% of them had died. The patients’ 30-day mortality rate after being diagnosed with COVID-19 was 14.4% (Table 1).

According to the univariate analysis of the factors affecting 30 day mortality, 76.9% (n= 40) of the patients were male in the mortality group, which indicated that mortality rate was significantly higher in male patients (p< 0.05) (Table 1).

While mean age was as 60.8 ± 13.7 years in the survival group, it was 71.2 ± 13.0 years in the mortality group (p< 0.05). Mean BMI was 28.6 (26.3-31.7) and 27.9 (24.1-30.2) in the survival and mortality group, respectively. No significant relationship was found between BMI and mortality (p= 0.066). Although the patients’ complaints at admission included cough, shortness of breath (dyspnea), sore throat, fever (>38.2°C), diarrhea, taste and smell loss, and myalgia, mortality was found to be statistically higher in patients presented with dyspnea (p< 0.05). Median time elapsed from the onset of symptoms till the admission to the hospital was determined in the surviving group as seven days (min: 4, max: 8 day), and it was detected significantly longer than according to the mortality group [4 days (min: 3, max: 7), (p< 0.05)] (Table 1).

In patients with at least one comorbidity, survival and mortality rates were determined as 69.2% and 88.5%, respectively (p< 0.05). When mortality rate was reviewed by comorbidities, it was significantly higher in patients with congestive heart failure (CHF) and chronic obstructive pulmonary disease (COPD) (p< 0.05 and p< 0.01, respectively). No statistically significant relationship was found between mortality and comorbidities such as hypertension (HT), diabetes mellitus (DM), coronary artery disease (CAD), asthma, malignancy, chronic kidney disease (CKD), interstitial lung disease (ILD) and rheumatologic diseases. Median value of oxygen saturation recorded at admission was found to be significantly higher in the survival group than in the mortality group [90 (85-94), 80 (75-88), respectively, p< 0.001] (Table 1).

The analysis of the relationship between laboratory parameters and mortality revealed that lymphocyte count was statistically significantly higher in the survival group than in the mortality group, whereas
neutrophil count, creatinine, CRP, D-dimer, ferritin, and troponin levels were statistically significantly higher in the mortality group than in the survival group (p < 0.001) (Table 2) (Figure 1).

Although hemoglobin, AST and calcium levels in the mortality group were also found statistically significantly higher, these results were not considerable clinically. The relationship between radiological findings and mortality was not statistically prominent. However, a statistically expressive was determined in terms of mortality rates between the patients with limited and diffuse involvement on CT. The ratio of patients with diffuse involvement was 59% in the mortality group (p < 0.05) (Table 3). There was no mortality in the patient group who needed no oxygen

| Table 1. Univariate analysis in groups according to 30-day survival- demographics |
|-----------------|-----------------|-----------------|-----------------|
| Variables       | Survival n=308 (85.6%) | Mortal n=52 (14.4%) |
| Age, mean ± SD (%95 CI) | Median (IQR) | Median (IQR) | p |
| BMI‡            | 28.6 (26.3-31.7) | 27.9 (24.1-30.2) | 0.066 |
| Hospitalization (day)‡ | 7 (4-9) | 7 (3-10) | 0.468 |
| Time to admission‡ | 7 (4-8) | 4 (3-7) | 0.006 |
| Sex*            | 188 (82.5) | 40 (17.5) | 0.028 |
| Male            | 120 (90.9) | 12 (9.1) | 0.000 |
| Female          | 166 (86.0) | 27 (14.0) | 0.792 |
| Shortness of breath* | 193 (81.8) | 43 (18.2) | 0.005 |
| Sore throat*    | 46 (83.6) | 9 (16.4) | 0.660 |
| Fever*          | 139 (83.2) | 28 (16.8) | 0.244 |
| Diarrhea*       | 31 (86.1) | 5 (13.9) | 0.909 |
| Taste/smell loss§ | 16 (94.1) | 1 (5.9) | 0.485 |
| Myalgia*        | 200 (87.7) | 28 (12.3) | 0.125 |
| Contact history* | 105 (84.7) | 19 (15.3) | 0.731 |
| Comorbid disease* | 213 (82.2) | 46 (17.8) | 0.004 |
| HT*             | 125 (83.3) | 25 (16.7) | 0.311 |
| DM*             | 87 (83.7) | 17 (16.3) | 0.513 |
| CAD*            | 50 (82.0) | 11 (18.0) | 0.382 |
| CHF§            | 12 (60.0) | 8 (40.0) | 0.004 |
| COPD*           | 35 (68.6) | 16 (31.4) | <0.001 |
| Asthma§         | 20 (80.0) | 5 (20.0) | 0.383 |
| Malignancy*     | 29 (78.4) | 8 (21.6) | 0.193 |
| CKD§            | 10 (71.4) | 4 (28.6) | 0.128 |
| ILD§            | 1 (50.0) | 1 (50.0) | 0.270 |
| Rheumatological§ | 8 (80.0) | 2 (20.0) | 0.643 |

IQR: Interquartile range, SD: Standard deviation, CI: Confidence interval, BMI: Body mass index, HT: Hypertension, CAD: Coronary artery disease, CHF: Congestive heart failure, COPD: Chronic obstructive pulmonary disease, CKD: Chronic kidney disease, ILD: Interstitial lung disease.

* Independent Samples-t test [mean ± SD (%95 CI)].
‡ Mann-Whitney U test [median (IQR)].
§ Pearson Chi-square test [n (%)].
¶ Fisher’s exact test [n (%)].
therapy at admission. However, mortality rate was found significantly higher in patients requiring oxygen by reservoir masks or high-flow nasal oxygen (HFNO) at admission or during follow-up. Twenty-three of the patients were transferred to the intensive care unit (Table 4).

In the multiple regression analysis performed for 30-day mortality variable, age, presence of heart failure, admission oxygen saturation, body temperature greater than 38.2, and ferritin level were determined as independent predictors. The odds ratios for 30-day mortality were 1.057 for each 1-year increase in age,
7.117 for the presence of congestive heart failure, 0.002 for each one-unit increase in admission oxygen saturation, 0.027 for body temperature above 38.2 degrees Celsius, and 1.0013 for each one-unit increase in ferritin level (Equation: \( \text{logit}(p) = 1.623 + (0.055 \times \text{age}) + (1.963 \times \text{CHF}) + (-0.079 \times \text{SO}_2) + (1.593 \times \text{high BT}) + (0.001 \times \text{ferritin}) \)) (Table 5).

**DISCUSSION**

In this retrospective clinical study, the clinical features of COVID-19 patients were thoroughly reviewed to predict prognosis and mortality. Mean ages of the patients in the mortality group were older (71.2 y), which is in line with the results of a prospective study demonstrating that being over the age of 65 is a risk factor for mortality (5). Similarly, in a study conducted on 3841 patients, mean ages in the survival and mortality groups have been reported as 54.7 and 73.4, respectively (Odds Ratio (OR): 1.07), and the ratio for male to female has been found as 3/2 in the mortality group (1). Along these lines, in a study conducted as a single-center study in January 2020 in China, the very first study in which the mortality rates were investigated by sex, mortality rates were reported as 12.8% in male and 7.3% in female patients (6). In comparison, 30 day mortality rates were a bit higher in this study, 9.09% (n= 12) in female and 17.5% (n= 40) in male.

There was no statistically significant difference between the survival and mortality groups in terms of BMI, but the minimum BMI levels were >24 in both groups. So, the fact that no significant difference was found between the groups in terms of BMI may be attributed to the fact that the groups were homogeneous and almost all of the patients were overweight or obese.

When the relationship between admission symptoms and mortality was examined, a relationship between headache, increased sputum, fatigue, shortness of breath and increased mortality was found in the literature. In contrast, no relationship was found between symptoms other than dyspnea and mortality or disease severity in this study (5). In a comprehensive study involving 1157 patients, mortality rates have been found significantly higher in advanced age and male patients, furthermore, the rate of referral to intensive care units has been detected higher in young patients of non-white ethnicity. Additionally, comorbidities such as DM, HT and chronic lung disease have been demonstrated to be significantly associated with mortality and the need for intensive...
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Care (7). Also, mortality rates have been found higher in patients with cardiovascular or cerebrovascular comorbidities (5). A meta-analysis has demonstrated hypertension, chronic lung diseases, cardiovascular disease and DM were high risk factors for mortality due to COVID-19 (8). In distinctive from, mortality rates were detected notably higher only in patients with heart failure and COPD in this study, which may be explained by the extent of the impairment in the immune status of the patients with different comorbidities compared to their healthy peers (9,10). Intercalarily, the impairment in immunity may be the reason for the severe course of COVID-19 in patients with comorbidities. However, COVID-19 is a new disease and the immune response to this disease is not clearly understood. Various comorbidities reported as associated with COVID-19-induced mortality in several studies make it even more difficult to predict the prognosis of the disease.

In many studies in the literature, different results have been obtained in terms of blood cell counts associated with immune response. In a meta-analysis, high leukocyte and neutrophil counts and low lymphocyte counts have been found to be associated with COVID-19 severity (8). Risk scoring consisting of 12 parameters reported in another meta-analysis includes: over 40 years age, male sex, non-white race, <93% SO2, radiological severity score >3, neutrophil count >8.0 x 10^9/L, CRP >40 mg/L, Albumin <34 g/L, creatinine >100 μmol/L, DM, HT and chronic lung disease (7). In our study, lymphocyte count was found to be statistically lower in the mortal group.

### Table 3. Univariate analysis in groups according to 30-day survival-imaging

| Variables                  | Survival n (%) | Mortal n (%) | p   |
|----------------------------|----------------|--------------|-----|
| PA-CXR sign*               |                |              |     |
| None                       | 35 (97.2)      | 1 (2.8)      | 0.109 |
| Unilateral                 | 93 (83.8)      | 18 (16.2)    |     |
| Bilateral                  | 180 (84.5)     | 33 (15.5)    |     |
| CT-number of lobes- Median (IQR)‡ | 4 (2-5) | 5 (3-5) | 0.072 |
| CT (performed?)            |                |              |     |
| Yes                        | 248 (86.1)     | 39 (13.9)    | 0.360 |
| No                         | 60 (83.3)      | 13 (16.7)    |     |
| CT sign†                   |                |              |     |
| None                       | 7 (100.0)      | 0 (0.0)      |     |
| Unilateral                 | 24 (80.0)      | 6 (20.0)     | 0.405 |
| Bilateral                  | 217 (86.8)     | 33 (13.2)    |     |
| CT- lobes†                 |                |              |     |
| None                       | 7 (100.0)      | 0 (0.0)      |     |
| Upper lobes                | 14 (100.0)     | 0 (0.0)      | 0.225 |
| Bases                      | 93 (88.6)      | 12 (11.4)    |     |
| All lobes                  | 134 (83.2)     | 27 (16.8)    |     |
| CT involvement‡            |                |              |     |
| None                       | 7 (100.0)      | 0 (0.0)      |     |
| Central                    | 8 (100.0)      | 0 (0.0)      | 0.029 |
| Peripheral                 | 150 (90.4)     | 16 (9.6)     |     |
| Diffuse                    | 83 (78.3)      | 23 (21.7)    |     |
| CT involvement*            |                |              |     |
| Localized                  | 165 (91.2)     | 16 (8.8)     | 0.002 |
| Diffuse                    | 83 (78.3)      | 23 (21.7)    |     |

PA-CXR: Posteroanterior chest X-ray, CT: Computed tomography, IQR: Interquartile range.
* Pearson Chi-square test n (%).
† Mann-Whitney U test - median (IQR).
‡ Pearson Chi-square test (the number of cases is not sufficient for the analysis; not reliable).
Table 4. Univariate analysis in groups according to 30-day survival treatment and prognosis

|                | Survival | Mortal | p   |
|----------------|----------|--------|-----|
|                | Column n (%) | Column n (%) |    |
| **Initial O2 therapy** |           |        |     |
| None           | 37 (12)   | 0 (0)  | <0.001 |
| Nasal          | 267 (86.7)| 43 (82.7)|       |
| NIMV           | 0 (0)     | 1 (1.9) |       |
| Venturi mask-reservoir | 2 (0.6) | 7 (13.5) |       |
| HF             | 2 (0.6)   | 1 (1.9)  |       |
| **Advanced O2 therapy** |       |        |     |
| None           | 289 (93.8)| 30 (57.7)|       |
| Venturi mask-reservoir | 14 (4.5) | 5 (9.6) | <0.001 |
| HF             | 4 (1.3)   | 15 (28.8) |       |
| NIMV           | 1 (0.3)   | 2 (3.8)   |       |
| ICU transfer†  | 6 (1.9)   | 17 (34)   | <0.001 |
| ICU transfer day- mean ± SD (%95 CI)‡ | 4.3 ± 1.5 (0.5-8.1) | 8.9 ± 4.6 (6.4-11.3) | 0.116 |
| Result*        | Mortal    |        | <0.001 |
| Discharge      | 302 (98.4)| 10 (19.2)|       |
| ICU            | 5 (1.6)   | 12 (23.1) |       |

PA-CXR: Posteroanterior chest X-ray, CT: Computed tomography, IQR: Interquartile range.
* Pearson Chi-square test, n (%).
† Mann Whitney U test, median (IQR).
‡ Pearson Chi-square test (the number of cases is not sufficient for the analysis; not reliable).

Table 5. Multiple logistic regression analysis for 30-day mortality

| Variables        | B** | Sig. | Odds ratio* (95% CI) |
|------------------|-----|------|----------------------|
| Step 1a          |     |      |                      |
| Age              | 0.055 | 0.015 | 1.057 (1.011-1.105) |
| Sex (1)          | -0.173 | 0.756 | 0.841 (0.283-2.501) |
| Shortness of breath (1) | 0.298 | 0.614 | 1.347 (0.422-4.296) |
| COPD (1)         | 0.325 | 0.608 | 1.384 (0.400-4.787) |
| CHF (1)          | 1.963 | 0.011 | 7.117 (1.579-32.087) |
| SO2 (admission)  | -0.079 | 0.002 | 0.924 (0.878-0.973) |
| BT (1)           | 1.593 | 0.027 | 4.920 (1.196-20.241) |
| Lymphocyte       | 0.000031 | 0.631 | 1.000 (1.000-1.000) |
| CRP              | 0.001 | 0.811 | 1.001 (0.994-1.007) |
| D-dimer          | -0.000085 | 0.256 | 1.000 (1.000-1.000) |
| Ferritin         | 0.001 | 0.026 | 1.0013 (1.000-1.002) |
| Troponin         | 0.008 | 0.107 | 1.008 (0.998-1.018) |
| CT-diffuse (1)   | 0.763 | 0.144 | 2.146 (0.771-5.968) |
| Constant         | 1.623 | 0.552 | 5.069 |

* Odds of mortal vs. survival.
CI: Confidence interval, COPD: Chronic obstructive pulmonary disease, CHF: Congestive heart failure, SO2: Oxygen saturation, CRP: C-reactive protein, CT: Computed tomography, BT: Body temperature (if >38.2 degrees Celsius).
** Equation: logit (p) = 1.623 + (0.055 x age) + (1.963 x CHF) + (-0.079 x SO2) + (1.593 x high BT) + (0.001 x ferritin).
(<750 x 10^9/L). Lymphopenia and neutrophilia were found to be associated with mortality.

In our study, increased CRP and creatinine were found to be associated with high mortality rate. Strong correlation between CRP increase and acute lung injury in COVID-19 cases has been previously shown in a study (11). In another analysis, it has been shown that CRP was higher in the group with high severity (12). In addition, increased CRP has been associated with heart damage, ARDS development, and death in COVID-19 patients (13).

Excessive immune response resulting in cytokine storm plays an important role in disease severity. High levels of cytokine release may occur with over-activation of leukocytes (14). In addition, this may cause neutrophil infiltration in pulmonary capillaries, organ damage and ARDS (15). Lymphocytes play an important role against bacterial, viral, fungal and parasitic infections and their blood levels increase; however, the immunological response that develops against COVID-19 is not clearly understood (16). On the other hand, according to a study conducted in Wuhan, myocardial damage has been detected in 82 of 416 patients (19.7%), and significantly high leukocyte count and low lymphocyte count have been found in these patients (p< 0.001) (17).

Massive inflammatory response that develops against SARS-CoV-2 also affects the endothelial cells and, consequently, an increase in coagulation, disseminated intravascular coagulation and fibrin breakdown occurs (18). High fibrin and D-dimer levels may explain venous thromboembolism in severe COVID-19 patients (19,20). Moreover, one study has found that pulmonary embolism and deep vein thrombosis were also detected in patients with severe COVID-19, which indicates that D-dimer could play an important role in predicting the severity of COVID-19 patients (8). In comparison, in this study, mean D-dimer levels in the survival and mortal groups were determined as 755 and 1440, respectively, supporting the findings in the literature.

Hyperferritinemia, which occurs as a result of excessive inflammation due to infection, is associated with the need for intensive care and high mortality and guides treatment changes to control inflammation in high-risk patients (21,22). High ferritin was found to be associated with high mortality rate in our study. Wu et al. have found that high ferritin levels were associated with the development of ARDS but not associated with mortality (23). Cecconi et al. have emphasized that high ferritin levels can be used in the early period to identify patients in need of intensive care or with high mortality risk (24). In a large meta-analysis (n= 10614), ferritin was found to be elevated in patients with at least one comorbid disease, associated with severe liver damage, and predictive of the need for intensive care unit and mechanical ventilation (25).

In a study conducted with COVID-19 patients, troponin has been found to be high and increased gradually in the mortal group, and its levels were found to be stable in the surviving group (26). Therefore, monitoring of troponin levels in hospitalized patients may be necessary for early detection of cardiac damage. Malignant arrhythmias such as unstable ventricular tachycardia or ventricular fibrillation were found to be higher in patients with high troponin levels (p< 0.001) (27). Similarly, in our study, mortality was found higher in patients with high levels of troponin at admission.

In COVID-19 cases, chest X-ray can be seen superior to other imaging methods because it is a common, easily accessible and easy-to-use tool. Diffuse infiltration in chest X-ray is considered as a predictor for intensive care and mortality (7). Already, the American College of Radiology, the Society of Thoracic Radiology and WHO do not recommend Thoracic CT scan for screening and diagnostic purposes (28,29). However, in some local approaches, it is still recommended to perform CT scans to determine severity (30). We think that follow-up with chest X-ray is more appropriate due to the need to minimize movement in hypoxic patients and high admission burden. In our study, no significant difference was found in the mortality rate between patients with unilateral and bilateral involvement in chest X-ray (Table 3). Initial chest X-ray findings may be misleading in determining prognosis. During the expected cytokine storm period, findings may increase, or new findings may develop on chest X-ray. Chest X-ray at admission is not predictive for prognosis, therefore we think that bedside chest X-ray performed during follow-up is necessary.

In this study, in-hospital mortality was found as 11.7%, whereas 30-day mortality was found as 14.4%. In the multiple regression analysis in terms of 30-day mortality rate, age, presence of heart failure, admission SO_2, body temperature greater than 38.2,
and ferritin level were determined as independent predictors. As expected, mortality rate was found to be higher in patients who needed supplemental oxygen treatment at the beginning and who required high flow oxygen therapy during the follow-up depending on the SO₂ level.

CONCLUSION

In summary, the clinical findings of the patients at admission are more important than laboratory parameters in predicting disease prognosis. However, we can say that laboratory parameters provide more reliable information than radiological examinations. The relationship between clinical markers and prognosis is very important in terms of accurately directing the healthcare services during the COVID-19 pandemic and revealing the importance of fast and efficient sharing of the clinical data.

Ethical Committee Approval: The study was obtained from University of Health Sciences, Ataturk Chest Diseases and Chest Surgery Training and Research Hospital Medical Specialty Education Board (Decision no: 696, Date: 08.10.2020)

CONFLICT of INTEREST

The authors of this meta-analysis declare that they have no conflict of interest.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: MUŞ, AÖ, MY
Analysis/Interpretation: MUŞ, AÖ, SK, AŞ
Data Acquisition: MUŞ, MY, SK, FÖE
Writing: MUŞ, AŞ, AÖ
Clinical Revision: All of authors
Final Approval: All of authors

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