Independent predictors of in-hospital mortality and the need for intensive care in hospitalized non-critical COVID-19 patients: a prospective cohort study

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Abstract
One of the most helpful strategies to deal with ongoing coronavirus pandemics is to use some prudence when treating patients infected with SARS-CoV-2. We aimed to evaluate the clinical, demographic, and laboratory parameters that might have predictive value for in-hospital mortality and the need for intensive care and build a model based on them. This study was a prospective, observational, single-center study including non-critical patients admitted to COVID-19 wards. Besides classical clinic-demographic features, basic laboratory parameters obtained on admission were tested, and then new models for each outcome were developed built on the most significant variables. Receiver operating characteristics (ROC) analyses were performed by calculating each model’s probability. A total of 368 non-critical hospitalized patients were recruited, the need for ICU care was observed in 70 patients (19%). The total number of patients who died in either ICU or wards was 39 (10.6%). The first two models (based on clinical features and demographics) were developed to predict ICU and death, respectively; older age, male sex, active cancer, and low baseline saturation were noted to be independent predictors. The area under the curve values of the first two models were noted 0.878 and 0.882 (p < .001; confidence interval [CI] 95% [0.837–0.919], p < .001; CI 95% [0.844–0.922]). Following two models, the third and fourth were based on laboratory parameters with clinic-demographic features. Initial lower sodium and lower albumin levels were determined as independent factors in predicting the need for ICU care; higher blood urea nitrogen and lower albumin were independent factors in predicting in-hospital mortality. The area under the curve values of the third and fourth model was noted 0.938 and 0.929, respectively (p < .001; CI 95% [0.912–0.965], p < .001; CI 95% [0.895–0.962]). By integrating the widely available blood tests results with simple clinic demographic data, non-critical patients can be stratified according to their risk level. Such stratification is essential to filter the patients’ non-critical underlying diseases and conditions that can obfuscate the physician’s predictive capacity.

Keywords COVID-19 · SARS-CoV-2 · Albumin · Sodium · Blood urea nitrogen · In-hospital mortality · Intensive care unit

Introduction
Coronavirus disease 2019 (COVID-19) has already affected millions of people. Most patients with COVID-19 are asymptomatic or experience mild illness; however, some patients rapidly progress to a critical stage of the disease. The proportion of hospitalized patients who develop acute respiratory distress syndrome (ARDS) during the course of the disease is between 16 and 29% [1–3]. The fatality rate has been documented to be 40.5% in critically ill COVID-19 patients, similar to ARDS [4]. However, the fatality rate remains obscure among those hospitalized but not admitted as severe or critical since considerable variation has occurred from time to time, institute to institute and country to country. Nevertheless, the case fatality rate of hospitalized COVID-19 patients can be assumed to be between 4.3 and 15% [2, 5, 6].

Previous reports defined an array of prognostic factors for predicting the disease course. Older age, male sex, and
pre-existing medical conditions are also associated with increased mortality [7, 8]. Besides these classical features, numerous investigations have been carried out to reveal factors associated with the severity. Various studies have gathered evidence on impaired interferon response, serum levels of cytokines, and the effect of concentrations of trace elements [9–11]. But a significant focus on inpatient management should be on ensuring a feasible, sustainable, and reliable risk categorization that can be adjusted to various non-critical cases. Recent studies have reported some nomograms and scoring systems; however, they did not satisfy the need for practical and reliable tools [12–16].

This study aimed to describe the clinical features and outcomes of a medium-scaled population consisting of non-critical cases and investigate all independent factors associated with in-hospital mortality and the need for intensive care. The second aim was to develop a model for a prediction tool that will lead to more proper and faster triage of these non-critical patients.

**Patients and methods**

**Study design and participants**

This prospective, observational, single-center study was conducted in a cohort of laboratory-confirmed COVID-19 patients hospitalized in a tertiary university hospital, Ankara, Turkey, between 15 June 2020 and 15 October 2020. The period was chosen with intention since the admission criteria before July were highly subjective. Even asymptomatic patients were hospitalized due to the ambiguity and lack of knowledge of the disease (Fig. 1).

All adult patients with suspected symptoms of COVID-19 presented to the emergency room, or COVID-19 outpatient clinics at our hospital were tested with a nasopharyngeal swab for virus identification by SARS-CoV-2 real-time reverse transcription-polymerase chain reaction (RT-PCR). Consultant physicians managed the medical treatment and decisions of admission, discharge, and intensive care unit (ICU) transfer regarding the relevant national guidelines and regulations. As this was an observational study, there was no intervention in the patient’s medical management and decisions.

**Data collection**

All patients or their official guardians signed the written informed consent to participate in the study. The medical registry was built according to the ethical principles and the medical data anonymization process details. The complete blindness of the caring physicians or nurses to the researchers was explained to the patients and their official guardians.

The demographics (age, gender, travel history), medical history (concurrent medical illnesses, contact history with COVID-19, detailed medication history), and symptoms were obtained directly from the patients or their first-degree relatives on admission. Concurrent medical conditions included a detailed list of the diseases (Supplementary File 1). Vital signs were recorded from the electronic database since primary caring physicians and nurses were not involved in the study. The blood tests included in routine admission protocol were recorded and not intervened by data collecting researchers.

The patients were tracked until discharge, transfer to the ICU, or death in the wards. The primary endpoint was the need for intensive care or death in the wards. The secondary endpoint was in-hospital mortality.

**Clinical assessment**

Judgment of the severity of COVID-19 pneumonia and subsequent stratification was made according to WHO Clinical Management Guideline: COVID-19 Clinical management [17]. Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia were classified as mild. Patients with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air, were classified as moderate. Patients with clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; respiratory distress; or SpO2 < 90% on room air were classified as severe disease. Critically ill patients requiring intensive care at the time of admission were excluded. The ICU admission criteria of our hospital were adapted according to national regulations.

Supportive and antiviral therapy was provided to all eligible patients soon after admission, and each individual was assessed by infectious disease specialists at the bedside upon admission and then daily. Favipiravir was the only approved and commercially available antiviral drug for COVID-19 treatment in Turkey [18]. Antibiotics were only administered to clinically suspected cases for bacterial co-infection, and the treating physician made the decision along with infectious disease specialists.

**Statistical analysis**

Patients were stratified into two groups based on the ICU requirement or death before ICU transfer (discharged without ICU requirement vs. either deceased before ICU transfer or transferred to ICU) and the survival outcome (discharged vs. deceased in the hospital).

Continuous variables were given as median ± interquartile range, as many variables were not distributed normally.
Categorical variables were summarized as counts and percentages. The Chi-squared test ($\chi^2$ test) or Fisher’s exact test was used for categorical variables, and the Mann–Whitney U test was used for continuous ones.

After the descriptive analysis of the data, univariate logistic regression analyses were performed, any variable having a significant univariate test at some arbitrary level was selected as a candidate for the multivariate analysis, based on the Wald test from logistic regression and a p-value cut-off point of 0.2. Through using the ‘backward stepwise’ method, four multivariate logistic regression models (mv-model) were developed to identify predictors for each endpoint (need for ICU care and in-hospital mortality); mv-model ICU-1 and ICU-2 were developed to predict ICU transfer. The mv-model SUR-1 and SUR-2 were developed to predict in-hospital mortality. Interactions were also tested.

Fig. 1 Flow chart of patients included and excluded in the study
by adding interaction-term into models. The probability of the event occurring versus the model parameters (the data where \( y_i \in \{-1, 1\} \) and \( x_i \in \mathbb{R}^p \)) was calculated through the formula below:

\[
f(x) = \frac{1}{1 + \exp(-\alpha + \beta_1 x_1 + \beta_2 x_2 + \beta_3 x_3 + \beta_4 x_4)} = p(y = 1 | \beta, x)
\]

The probability of each model (\( p \in \{0, 1\} \)) was tested with receiver operating characteristic curves (ROC) with the area under the curve (AUC) statistics.

All analyses were conducted using the IBM SPSS Software version 22.0 (SPSS Inc., Chicago, IL) licensed to the institution where the study was carried on. Two-sided significance testing was performed, and \( p \) values < 0.05 were considered significant.

Results

Demographics and clinical data

We recorded 849 adult patients (≥ 18 years old) hospitalized in COVID-19 wards during the specified period (Fig. 1). After excluding patients who had inadequate radiological data (\( n = 122 \)), inadequate or conflicting clinical data (\( n = 78 \)), a history of readmission (\( n = 79 \)), were hospitalized less than a day (\( n = 56 \)), initially admitted to the intensive-care unit (\( n = 23 \)) or did not have PCR confirmation (\( n = 99 \)) and patients who did not want to be a participant to our cohort (\( n = 24 \)), a total of 368 patients were recruited into our study. Among these, six patients (1.6%) were deceased before ICU transfer. Nevertheless, they met the admission criteria for ICU and they were also included in the group of patients requiring ICU care.

Three hundred twenty-eight (89.1%) patients were treated with the recommended dosage of favipiravir; those who were not eligible for the treatment with favipiravir were only observed with supportive therapy except for six patients (1.6%) who received remdesivir in the scope of a clinical trial.

Our cohort had a slightly female dominance (total \( n = 197; 53.5\% \)) and a median age of 57 years (IQR 31). The most common comorbidities were arterial hypertension (AH) (\( n = 140, 38\% \)) and diabetes mellitus (DM) (\( n = 89, 24.2\% \)). As can be seen from Table 1, 64 patients were transferred to ICU, six patients died before ICU transfer, so the need for ICU care was observed/assumed in 70 patients (19%). The total number of patients who died in either ICU or wards was 39 (10.6%).

With regards to endpoints (need for intensive care and mortality), patients who experienced any of these events were significantly older (ICU group vs. non-ICU group: 68 vs. 52 years, \( p < 0.001 \), non-survivors vs. survivors: 68 vs. 53 years, \( p < 0.001 \) and predominantly male (ICU group vs. non-ICU group: 27.5% versus 11.7%; \( p < 0.001 \), non-survivors vs. survivors: 16.5% versus 5.6%; \( p = 0.001 \)), compared to those who did not (Table 1).

Patients who required intensive care had a higher prevalence of AH (\( p < 0.001 \)), coronary artery disease (CAD) (\( p = 0.001 \)), congestive heart failure (CHF) (\( p = 0.002 \)), active cancer (\( p = 0.002 \)) and higher median CCI (\( p < 0.001 \)) than the non-ICU group. Smoking was not different between the ICU group and the non-ICU group. Prevalences of certain comorbidities were also higher among the deceased patients (Table 1). Smoking habits did seem to be different among groups in regard to mortality outcomes. The difference comes mainly from ex-smokers (\( p = 0.002 \), Bonferroni correction was made for each 2 × 2 cross-table). The known epidemiological link was higher in patients who did not require intensive care (\( p < 0.001 \); however, it was not statistically significant between survivors and non-survivors (\( p = 0.241 \)).

Among patients who required intensive care, the history of using diuretics, beta-blockers, anti-platelet therapy were significantly higher than the patients who were discharged without any event (Table 1). In patients who did not survive, the history of being treated by RAS blockers, diuretics, beta-blockers, and anti-platelet therapy was significantly higher than the patients who survived.

The need for oxygen support upon admission and baseline low saturation (< 90%) were significantly higher in ICU and non-survivor groups. The median duration between the onset of symptoms and PCR confirmation was 2 (IQR 3.25) days, and admission was 3 (IQR 3) days. The median length of stay in the wards was 5 (IQR 4) days. These intervals were not different between groups.

Laboratory parameters

Patients who required intensive care had significantly lower hemoglobin levels, lymphocyte, thrombocyte counts, but higher neutrophil counts (Table 2). Similar pattern was observed among those who didn’t survive; however, neutrophil counts were not different between survivors and non-survivors. Blood urea nitrogen (BUN), uric acid, AST, GGT, lactate dehydrogenase (LDH), ferritin, C-reactive protein (CRP), brain natriuretic peptide, erythrocyte sedimentation rate, procalsitonin, IL-6, fibrinogen, INR, d-dimer levels were significantly higher, and LDL, sodium, albumin levels were significantly lower in patients who required intensive care. A similar pattern was observed in the non-survivor group; however, HDL was also significantly lower, ESR and fibrinogen were not significantly different. Cardiac-specific enzymes were significantly higher in groups representing poor outcome in both endpoints.
Table 1 The comparison of demographic and clinical features between groups by each outcome

| Total population (n & %) | Total | Non-ICU | ICU | P | Survivors | Non-survivors | P |
|--------------------------|-------|---------|-----|---|-----------|---------------|---|
| Age (Median ± IQR)       | 57    | 31      | 23  | 18| 68        | 53            | 23 |
| Sex (n & %)              |       |         |     |   |           |               |    |
| Female                   | 197   | 53.5    | 174 | 88.3| 23        | 11.7          | <0.001 |
| Male                     | 171   | 46.5    | 124 | 72.5| 47        | 27.5          | <0.001 |
| Comorbidity (n & %)      |       |         |     |   |           |               |    |
| Arterial hypertension    | 140   | 38      | 100 | 71.4| 40        | 28.6          | <0.001 |
| Diabetes mellitus        | 89    | 24.2    | 67  | 75.3| 22        | 24.7          | 0.116 |
| Coronary artery disease  | 53    | 14.4    | 34  | 64.2| 19        | 35.8          | 0.001 |
| Congestive heart failure | 12    | 3.3     | 5   | 41.7| 7         | 58.3          | 0.002 |
| Dysrhythmia              | 25    | 6.8     | 18  | 72  | 2         | 28            | 0.288 |
| Asthma                   | 31    | 8.4     | 25  | 80.6| 6         | 19.4          | <0.001 |
| Chronic obstructive airway disease | 18 | 4.9 | 12 | 66.7 | 6 | 33.3 | 0.125 |
| Cerebrovascular disease  | 16    | 4.3     | 16  | 80  | 4         | 20            | 0.203 |
| Chronic kidney disease   | 20    | 5.4     | 11  | 68.8| 5         | 31.3          | 0.9  |
| Chronic liver disease    | 3     | 0.8     | 3   | 100 | 0         | 100           | NA |
| Active cancer            | 26    | 7.1     | 15  | 57.7| 11        | 42.3          | 0.002 |
| History of cancer        | 31    | 8.5     |     |     |           |               |    |
| No history               | 337   | 91.6    | 279 | 82.8| 58        | 17.2          | 0.004 |
| Solid tumour             | 30    | 8.2     | 19  | 63.3| 11        | 36.7          | 0.04 |
| Haematological           | 1     | 0.3     | 0   | 0   | 1         | 100           | 0.01 |
| Chronic viral infection  | 2     | 0.5     | 2   | 100 | 0         | 100           | NA |
| Connective tissue        | 17    | 4.6     | 12  | 70.6| 5         | 29.4          | 0.337 |
| Hypothyroidism           | 30    | 8.2     | 24  | 80  | 6         | 20            | 0.887 |
| Peptic ulcer disease     | 2     | 0.5     | 2   | 100 | 0         | 100           | NA |
| Dementia                 | 10    | 2.7     | 4   | 40  | 6         | 60            | 0.001 |
| Allergy                  | 29    | 8.8     | 23  | 79.3| 6         | 20.7          | 0.598 |
| Pregnancy                | 5     | 1.5     | 5   | 100 | 0         | 7             | 0.788 |
| Smoking                  |       |         |     |   |           |               |    |
| Active smoker            | 26    | 7.5     | 22  | 84.6| 4         | 15.4          | 0.11 |
| Ex-smoker                | 52    | 17      | 41  | 78.8| 11        | 21.2          | 0.08 |
| Non-smoker               | 227   | 74.4    | 203 | 89.4| 24        | 10.6          | 0.105 |
| Charlson comorbidity index (median ± IQR) | 2 | 4.25 | 1 | 3 | 4 | 3.25 | <0.001 |
| Medications (n & %)      |       |         |     |   |           |               |    |
| Metformin                | 57    | 15.5    | 47  | 82.5| 10        | 17.5          | 0.792 |
| RAS blockers             | 102   | 27.7    | 78  | 76.5| 24        | 23.5          | 0.172 |
| Diuretics                | 22    | 6       | 12  | 54.5| 10        | 45.5          | 0.003 |
| Calcium channel blockers | 33    | 9       | 25  | 75.8| 8         | 24.2          | 0.423 |
| Beta blockers            | 69    | 18.8    | 49  | 71  | 20        | 29            | 0.019 |
| Antiplatelet therapy     | 67    | 18.2    | 48  | 71.6| 19        | 28.4          | 0.031 |
| Oral anticoagulants      | 21    | 5.7     | 19  | 90.5| 2         | 9.5           | 0.253 |
| Statins                  | 43    | 11.7    | 33  | 76.7| 10        | 23.3          | 0.452 |
| Anti-anginal treatment   | 16    | 4.3     | 13  | 81.3| 3         | 18.8          | 0.977 |
| Immunomodulatory drugs   | 15    | 4.1     | 11  | 73.3| 4         | 26.7          | 0.4  |
| Oral steroids            | 12    | 3.3     | 9   | 75  | 3         | 25            | 0.706 |
| Chemotherapeutics        | 9     | 2.4     | 7   | 77.8| 2         | 22.2          | 0.804 |
| Anti-depressants         | 30    | 8.2     | 21  | 70  | 9         | 30            | 0.11 |
| Antipsychotics           | 16    | 4.3     | 12  | 75  | 4         | 25            | 0.537 |
Vital signs and symptomatology

Symptoms, vital signs, and the comparison of the proportions between groups are shown in Table 3. The most common two symptoms were fever (61.4%) and non-productive cough (54.6%). There were no statistically significant differences between groups regarding these symptoms. Sputum production was observed significantly higher in the ICU group than the non-ICU group \((p=0.039)\). The proportion of dyspnea was noted to be lower in the survivor group than non-survivors \((p=0.04)\). In contrast, sore throat and headache were recorded as significantly lower in the ICU group.

The vital signs were similar in both groups with both outcomes, besides baseline saturation on room air were significantly lower in groups who experienced the endpoints than those who did not.

Logistic regression models

The univariate binary logistic regression analysis for each variable for each endpoint is shown in Supplementary Table 1. Several demographic, clinical and laboratory parameters including; sex, smoking history, CCI score, the severity of the disease, medication history, requiring oxygen support on admission and baseline low \(O_2\) saturation on room air, sputum, higher neutrophil count, acute phase reactants, ferritin, LDH, GGT, AST, uric acid, d-dimer, cardiac enzyme levels and lower thrombocyte count, lymphocyte count, hemoglobin, sodium and albumin, LDL levels were recorded as significant predictors for ICU need. Having a lower HDL, in addition to LDL, was also a significant predictor for in-hospital mortality.

Four models were developed for different purposes (Table 4). The first two models (MV model ICU-1 and SUR-1; based on same variables) were developed to predict ICU need, built on clinical variables and demographics, without laboratory parameters. The third and fourth models (MV model ICU-2 and SUR-2) were based on clinical data and demographics plus laboratory parameters. In the multivariate model ICU-1; age, male sex, active cancer, baseline saturation on room air lower than 90\% were noted to be significant independent predictors. The probability of the model was tested with ROC analysis, and the AUC value was noted to be 0.878 (Fig. 2). The same parameters were also modelled for predicting mortality (MV model SUR-1), found to be independent and...
significant. The latter was also tested with ROC analysis and AUC value was 0.882 (Fig. 2).

Third model and fourth model (named model-ICU-2 and model-SUR-2, respectively) were developed by investigating significant blood parameters and clinic-demographic data. In model-ICU-2, older age, male sex, need for supplemental oxygen during the first 48 hours after admission, lower sodium and albumin level were significant and
independent predictors for ICU need. Having a lymphocyte count lower than 800 was not independently significant but contributed to the model. The probability of the model was tested with ROC analysis and AUC value was 0.938. In model-SUR-2, older age, gender, active cancer, higher BUN, and lower albumin levels were noted to be significant independent predictors; however, hypertension was not found to be significant but has contributed to the model positively. AUC value of the model-SUR-2 was 0.929 (Fig. 2).

### Discussion

In this study, we tested the extent to which clinical, demographic, and routine laboratory parameters predicted the poor outcomes, represented as the need for intensive care and in-hospital mortality in a group of patients being treated for non-critical COVID-19 pneumonia in wards. According to these new models, besides older age and male sex, independent predictors for ICU requirement were the need for oxygen support upon admission, and lower sodium and albumin levels. On the other hand, independent predictors for in-hospital mortality included confounding active cancer, the need for oxygen support, lower albumin, and higher blood urea nitrogen levels.

Previous studies have reported descriptive, predictive, and prognostic models based on many parameters from routine blood tests, radiological findings, medical history, and symptoms [11, 19, 20]. The best-known scoring systems include ISARIC-4c score, COVID-GRAM score, and quick COVID-19 Severity Index (qCSI) [13, 21, 22]. NEWS score, which was validated for adult patients to predict unexpected ICU admission or death was also tested and modified for COVID-19 patients [23]. These scores were also compared in one large-scale study [24]. However, none of those

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**Table 3** Symptomatology and vital signs of patients and the comparison of the groups by outcome

|                      | Total | Non-ICU | ICU | P         | Survivors | Non-survivors | P         |
|----------------------|-------|---------|-----|-----------|-----------|---------------|-----------|
| **Signs & symptoms on admission (n & %)** |       |         |     |           |           |               |           |
| Fever                | 226   | 61.4    | 180 | 79.6      | 46        | 20.4          | 0.41      |
| Cough                | 201   | 54.6    | 168 | 83.6      | 33        | 16.4          | 0.163     |
| Dyspnoea             | 84    | 22.8    | 63  | 75        | 21        | 25            | .112      |
| Sputum               | 30    | 8.2     | 20  | 66.7      | 10        | 33.3          | 0.039     |
| Sore throat           | 71    | 19.3    | 64  | 90.1      | 7         | 9.9           | 0.029     |
| Rhinorrhea           | 11    | 3       | 10  | 90.9      | 1         | 9.1           | 0.698     |
| Chest pain           | 10    | 2.7     | 8   | 80        | 2         | 20            | 0.93      |
| Back pain            | 19    | 5.2     | 18  | 94.7      | 1         | 5.3           | 0.14      |
| Fatigue              | 188   | 51.1    | 152 | 80.9      | 36        | 19.1          | 0.861     |
| Myalgia              | 148   | 40.3    | 119 | 80.4      | 29        | 19.6          | 0.749     |
| Arthralgia           | 67    | 18.2    | 53  | 79.1      | 14        | 20.9          | 0.666     |
| Nausea-vomiting      | 38    | 10.3    | 32  | 84.2      | 6         | 15.8          | 0.827     |
| Diarrhoea            | 52    | 14.1    | 44  | 84.6      | 8         | 15.4          | 0.471     |
| Altered sense of smell | 35    | 9.5     | 30  | 85.7      | 5         | 14.3          | 0.453     |
| Altered sense of taste | 36  | 9.8     | 30  | 83.3      | 6         | 16.7          | 0.699     |
| Eye dryness          | 6     | 1.6     | 6   | 100       | 0         | 0             | 0.825     |
| Red eye              | 3     | 0.8     | 3   | 100       | 0         | 0             | NA        |
| Headache             | 63    | 17.1    | 57  | 90.5      | 6         | 9.5           | 0.035     |
| Chills               | 9     | 2.4     | 9   | 100       | 0         | 0             | 0.21      |
| Neurological signs   | 5     | 1.4     | 4   | 80        | 1         | 20            | 0.95      |
| **Vital Signs (median & IQR)** |       |         |     |           |           |               |           |
| Body temperature     | 38    | 1.7     | 38  | 1.5       | 15.3      | 1.5           | 0.476     |
| Respiration rate     | 20    | 2       | 20  | 2         | 21        | 4             | 0.186     |
| Saturation on room air | 95  | 3       | 95  | 3         | 91        | 6             | <0.001    |
| Pulse                | 85.5  | 20      | 85  | 16        | 81        | 17            | 0.263     |
| Systolic Blood Pressure | 122.5 | 25 | 122  | 25.5      | 130       | 18            | 0.567     |
| Diastolic Blood Pressure | 71.5 | 18.5    | 73  | 18.5      | 73        | 20            | 0.179     |

Values are shown as median [interquartile range] or numeric values [percent]

ICU intensive care unit, IQR interquartile range
developments have been capable of slowing down global efforts to search for a practical prediction tool yet. Active cancer is the most powerful predictive factor for poor outcomes among comorbidities, which is also consistent with the COVID-gram critical illness Risk Score [13]. Upon admission, the need for oxygen support upon admission was an independent and powerful factor for poor outcomes in both endpoints. Recently introduced models also emphasized the predictive factor for baseline oxygen saturation and the need for supplemental oxygen [21, 25].

### Table 4 Multivariate logistic regression models

#### Multivariate Logistic Regression Model-ICU-1

|         | B    | OR   | p value | CI interval 95% |
|---------|------|------|---------|-----------------|
| Age     | 0.066| 1.068| <.001   | 1.043 1.094     |
| Male Sex| 1.088| 2.968| 0.001   | 1.517 5.807     |
| Active cancer | 1.341| 3.821| 0.009   | 1.390 10.507    |
| Saturation < 90% on room air | 2.424| 11.287| <.001 | 5.046 25.247 |
| Constant| -8.856|   |         |                 |

#### Multivariate Logistic Regression Model-SUR-1

|         | B    | OR   | p value | CI interval 95% |
|---------|------|------|---------|-----------------|
| Age     | 0.075| 1.078| <.001   | 1.046 1.111     |
| Male Sex| 1.356| 3.882| 0.002   | 1.674 9.003     |
| Active cancer | 1.714| 5.551| 0.002   | 1.918 16.063    |
| Saturation < 90% on room air | 0.948| 2.580| 0.034   | 1.076 6.186     |
| Constant| -8.015|   |         |                 |

#### Multivariate Logistic Regression Model-ICU-2

|         | B    | OR   | p value | CI interval 95% |
|---------|------|------|---------|-----------------|
| Age     | 0.053| 1.055| 0.001   | 1.022 1.088     |
| Male sex| 0.818| 2.265| 0.049   | 1.005 5.104     |
| Active cancer | 1.438| 4.862| 0.026   | 1.213 19.488    |
| Hypertension| 0.719| 5.632| 0.156   | 0.761 5.531     |
| Oxygen support need | 2.482| 11.287| <.001 | 5.381 26.586    |
| Albumin | -1.438| 0.237| 0.002   | 0.094 0.597     |
| Lymphocyte count < 800 | 0.775| 2.170| 0.056   | 0.953 4.942     |
| Thrombocyte count | -0.004| 0.996| 0.196   | 0.996 1.002     |
| Sodium  | -0.126| 0.882| 0.024   | 0.79 0.984      |
| Blood Urea Nitrogen | 0.017| 1.017| 0.289   | 0.985 1.05      |
| Troponin| -17.7 |   |         |                 |

#### Multivariate Logistic Regression Model-SUR-2

|         | B    | OR   | p value | CI interval 95% |
|---------|------|------|---------|-----------------|
| Age     | 0.042| 1.078| 0.03    | 1.004 1.083     |
| Male sex| 1.113| 3.882| 0.021   | 1.179 7.855     |
| Active cancer | 1.581| 4.862| 0.026   | 1.213 19.488    |
| Hypertension| 0.719| 3.105| 0.156   | 0.761 5.531     |
| Oxygen support need | 2.015| 7.502| <.001   | 2.952 19.064    |
| Albumin | -1.056| 0.348| 0.038   | 0.129 0.942     |
| Lymphocyte count < 800 | 0.775| 2.170| 0.056   | 0.953 4.942     |
| Thrombocyte count | -0.004| 0.996| 0.196   | 0.996 1.002     |
| Sodium  | -0.126| 0.882| 0.024   | 0.79 0.984      |
| Blood Urea Nitrogen | 0.017| 1.017| 0.289   | 0.985 1.05      |
| Troponin| -17.7 |   |         |                 |

![Fig. 2](image-url) Receiver Operating Characteristics Curve of Multivariate Model ICU−1/ICU−2 (A) and Multivariate Model SUR−1/SUR−2 (B)
Low oxygen saturation may reflect the extent of the alveoli-capillary unit destruction, as some patients might not always respond to non-pressurized nasal oxygen support since damaged areas of the lung could cause shunting of non-oxygenated blood from right-to-left, and result in ventilation-perfusion (V/P) mismatch [26, 27]. Extended thrombosis in aerated regions may also be responsible for V/P mismatch and can be found with right-to-left shunts [27, 28].

Among our findings, increased troponin level was not a significant independent predictor; however, the addition of the serum troponin level to the multivariate model increased the strength of the prediction ability. The interaction between the virus and the cardiovascular system has been complex, ranging from microvascular thrombosis to inflammatory myocarditis [29, 30]. The most interesting point is that even mild increases in troponin levels without overt signs or clues of a myocardial injury can be predictive of poor outcomes [31].

Another finding which needs to be highlighted was the difference in the predictors between the two models (ICU and mortality). Significant factors predicting the need for intensive care were more likely to be laboratory parameters. In contrast, parameters predicting in-hospital mortality were more likely to be pre-existing illnesses, including active cancer and arterial hypertension. This difference reflects the fact that some ICU admission might have been influenced by laboratory findings (such as; uremia, high ferritin, hyponatremia, low fibrinogen, etc.). Nevertheless, higher blood urea nitrogen and lower albumin levels on admission were also independent factors for in-hospital mortality. Low albumin can be an indicator of a couple of ongoing processes. First of all, a patient presented with lower albumin levels might have poor nutritional status. One study showed that elderly patients are more likely to be malnourished and have lower serum albumin levels on admission [32]. Lower serum albumin level is also associated with increased catabolism, decreased hepatic albumin synthesis, and increased capillary permeability [33]. All these conditions can be associated with poor prognosis in patients regardless of disease state and the predictive value of low serum albumin was appreciated by recent studies [34–37]. In the present study, the linear association of lower serum albumin levels and poor prognosis in COVID-19 patients (both ICU transfer and in-hospital mortality) has been very well demonstrated and may potentially increase the foresight capability of physicians.

Mortality seems to be predicted by increased BUN levels, as well, and this finding is consistent with COVID-19 literature [38–40]. Some of the easy-to-use nomograms include serum BUN levels [15, 41]. As being one of the most validated scoring systems, the ISARIC-4C tool also includes serum BUN level [21]. Serum BUN level may not be the best surrogate marker of kidney dysfunction but is almost always found to be increased in case of poor perfusion of the kidneys, mild-to-profound dehydration, increased catabolic processes, and can be potentially an early warning parameter for clinical deterioration.

Our work has several limitations. First of all, this was a single-center study. Secondly, the lack of validation makes the model questionable, even though six different prediction tools based on mentioned models are being reviewed under the internal validation process. The third limitation, participants weren’t vaccinated at the study time and joined our cohort before variants arose. Therefore the risk factors and the models described during this study have not been tested on subjects outside of these particular circumstances.

**Conclusion**

Even though some overt prognostic factors exist, the severity and progression of the disease remain somewhat unpredictable. Patients who are not elders, co-morbid, or critical upon admission are also highly susceptible to misjudgment. So, we demonstrate the impact of independent predictive factors which can be easily obtained and may lead to clinicians attending to high-risk patients on the proposed model more intensively.

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**Declarations**

**Conflict of interest** Authors have no competing interests to declare.

**Financial interests** The authors declare they have no financial interests.

**Ethical Approval** This study was conducted in accordance with principles defined in the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice guidelines, and approved by the relevant institutional ethics committee (31.03.2020, GO 20/354, 2020/07-33).
Human and animal rights statement  This article does not contain any studies with animals performed by any of the authors.

Consent to participate  Informed consent was obtained from each participating patient at the Hacettepe University, Ankara.

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