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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% [0.895–962]). 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

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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 $SpO_2 \geq 90\%$ 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 $SpO_2 < 90\%$ 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.

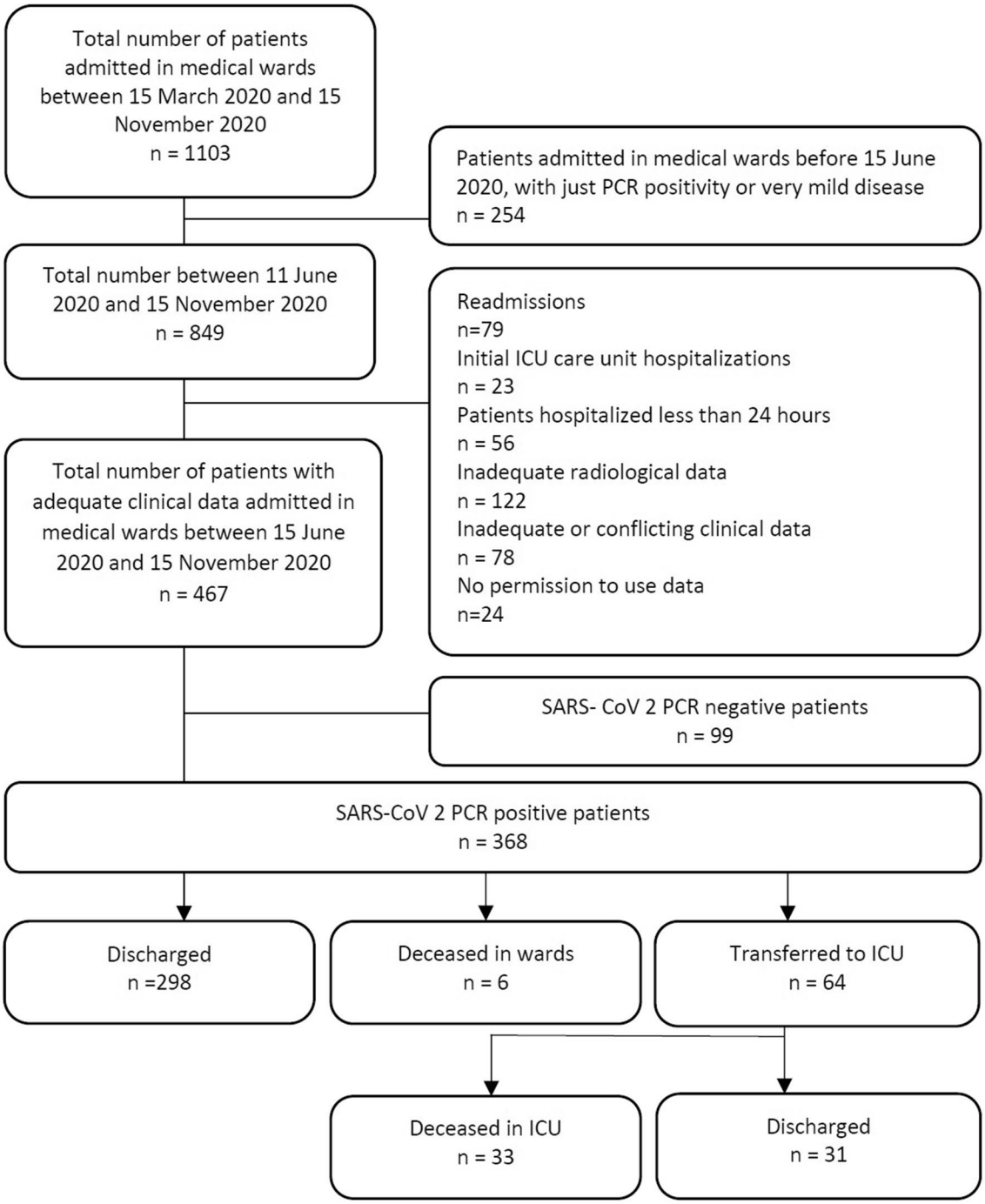

Fig. 1 Flow chart of patients included and excluded in the study

Categorical variables were summarized as counts and percentages. The Chi-squared test (χ^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

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 $x^{(i)} \in \mathbb{R}^n$) was calculated through the formula below;

$$f(x) = \frac{1}{1 + exp^{-(\alpha+\beta 1x1+\beta 2x2+\beta 3x3+\beta nxn)}} = p(y = 1|\beta, x)$$

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, procalcitonin, 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*
	368	100	298	81	70	19		329	89.4	39	10.6	
Age (Median ± IQR)	57	31	52	23	68	18	< 0.001	53	23	68	20	< 0.001
Sex (n & %)												
Female	197	53.5	174	88.3	23	11.7	< 0.001	186	94.4	11	5.6	0.001
Male	171	46.5	124	72.5	47	27.5		143	83.6	28	16.4	
Comorbidity (*n* & %)												
Arterial hypertension	140	38	100	71.4	40	28.6	< 0.001	114	81.4	26	18.6	< 0.001
Diabetes mellitus	89	24.2	67	75.3	22	24.7	0.116	77	86.5	12	13.5	0.310
Coronary artery disease	53	14.4	34	64.2	19	35.8	0.001	43	81.1	10	18.9	0.035
Congestive heart failure	12	3.3	5	41.7	7	58.3	0.002	8	66.7	4	33.3	0.029
Dysrhythmia	25	6.8	18	72	7	28	0.288	22	88	3	12	0.738
Asthma	31	8.4	25	80.6	6	19.4	0.961	29	93.5	2	6.5	0.758
Chronic obstructive airway disease	18	4.9	12	66.7	6	33.3	0.125	14	77.8	4	22.2	0.111
Cerebrovascular disease	16	4.3	16	80	4	20	0.203	18	90	2	10	0.8
Chronic kidney disease	20	5.4	11	68.8	5	31.3	0.9	14	87.5	2	12.5	0.9
Chronic liver disease	3	.8	3	100	0	0	NA	3	100	0	0	NA
Active cancer	26	7.1	15	57.7	11	42.3	0.002	17	65.4	9	34.6	< 0.001
History of cancer	31	8.5										
No history	337	91.6	279	82.8	58	17.2	0.004	308	91.4	29	8.6	< 0.001
Solid tumour	30	8.2	19	63.3	11	36.7		21	70	9	30	
Haematological	1	.3	0	0	1	100		0	0	1	100	
Chronic viral infection	2	.5	2	100	0	0	NA	2	100	0	0	NA
Connective tissue	17	4.6	12	70.6	5	29.4	0.337	13	76.5	4	23.5	0.093
Hypothyroidism	30	8.2	24	80	6	20	0.887	26	86.7	4	13.3	0.612
Peptic ulcer disease	2	.5	2	100	0	0	NA	2	100	0	0	NA
Dementia	10	2.7	4	40	6	60	0.001	5	50	5	50	0.000
Allergy	29	8.8	23	79.3	6	20.7	0.598	23	79.3	6	20.7	0.711
Pregnancy	5	1.4	5	100	0	0	0.588	5	100	0	0	0.438
Smoking												
Active smoker	26	7.5	22	84.6	4	15.4	0.11	24	92.3	2	7.7	0.002
Ex-smoker	52	17	41	78.8	11	21.2		42	80.8	10	19.2	
Non-smoker	227	74.4	203	89.4	24	10.6		216	95.2	11	4.8	
Charlson comorbidity index (median ± IQR)	2	4.25	1	3	4	3.25	< 0.001	2	3	5	4	< 0.001
Medications (*n* & %)												
Metformin	57	15.5	47	82.5	10	17.5	0.792	53	93	4	7	0.368
RAS blockers	102	27.7	78	76.5	24	23.5	0.172	86	23.4	16	15.7	0.05
Diuretics	22	6	12	54.5	10	45.5	0.003	15	68.2	7	31.8	0.005
Calcium channel blockers	33	9	25	75.8	8	24.2	0.423	26	78.8	7	21.2	0.067
Beta blockers	69	18.8	49	71	20	29	0.019	56	81.2	13	18.8	0.014
Antiplatelet therapy	67	18.2	48	71.6	19	28.4	0.031	55	82.1	12	17.9	0.032
Oral anticoagulants	21	5.7	19	90.5	2	9.5	0.253	20	95.2	1	4.8	0.371
Statins	43	11.7	33	76.7	10	23.3	0.452	39	90.7	4	9.3	0.769
Anti-anginal treatment	16	4.3	13	81.3	3	18.8	0.977	14	87.5	2	12.5	0.8
Immunomodulatory drugs	15	4.1	11	73.3	4	26.7	0.4	12	80	3	20	0.23
Oral steroids	12	3.3	9	75	3	25	0.706	11	91.7	1	8.3	0.796
Chemotherapeutics	9	2.4	7	77.8	2	22.2	0.804	7	77.8	2	22.2	0.251
Anti-depressants	30	8.2	21	70	9	30	0.11	24	80	6	20	0.112
Antipsychotics	16	4.3	12	75	4	25	0.537	12	75	4	25	0.077

Table 1 (continued)

Total population (*n* & %)	Total		Non-ICU		ICU		*P*	Survivors		Non-survivors		*P*
	368	100	298	81	70	19		329	89.4	39	10.6	
Anti-epileptics	11	3	10	90.9	1	9.1	0.698	11	100	0	0	0.246
Inhalers	22	6	18	81.8	4	18.2	0.92	22	100	0	0	0.14
Proton pump inhibitors	34	9.2	27	79.4	7	20.6	0.807	31	91.2	3	8.8	0.724
Treatment at the admission (*n* & %)												
Antibiotics (empirical)	36	9.8	26	72.2	10	2.7	0.159	31	86.1	5	13.9	0.565
O_2 need	101	28.9	38	37.6	63	62.4	< 0.001	64	63.4	37	36.6	< 0.001
Radiology: computed tomography results (*n* & %)												
Typical	257	72.2	203	79	54	21	0.205	229	89.1	28	10.9	0.713
Atypical	8	2.2	6	75	2	25		8	2.2	0	0	
Indeterminate	28	7.9	23	82.1	5	17.9		26	92.9	2	7.1	
Negative	63	17.7	57	90.5	6	9.5		67	90.5	6	9.5	
Periods (days) (median ± IQR)												
Length of stay (only wards)	5	4	5	4	6	4	0.409	5	4	6	5	0.42
Symptom-to-pcr confirmation	2	3.25	2	3.5	2	3	0.597	2	3	2	3.25	0.4
Symptom-to-admission	3	3	3	3	3	4.5	0.641	3	3	3	4.25	0.341
Known epidemiological link (*n* & %)	185	50.1	163	88.6	21	11.4	< 0.001	168	91.3	16	8.7	0.241
Severity (*n* & %)												
Mild	92	26	96.7	96.7	3	3.3	< 0.001	89	96.7	3	3.3	0.029
Moderate	257	69.8	77	53.8	59	23		223	86.8	34	13.2	
Severe	19	5.2	57.9	3	8	42.1		17	89.5	2	10.5	
Bacterial co-pneumonia (*n* & %)	26	15.6	19	73.1	7	26.9	0.075	20	76.9	6	23.1	0.002

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

ICU intensive care unit, O_2 Oxygen; *PCR* Polymerized chain reaction; *IQR* interquartile range

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

Table 2 Baseline blood parameters of the patients and comparison of the groups by outcome

	Total		Non-ICU		ICU		*P*	Survivors		Non-survivors		*P*
Complete blood count												
Haemoglobin (g/dl)	13.6	2.2	13.7	2.2	13.3	2.25	0.007	13.7	2.2	12.8	2.53	0.008
Leucocyte (per mm^3)	5200	2500	5200	2225	5500	4350	0.218	5200	2300	5700	4900	0.167
Neutrophil (per mm^3)	3400	2020	3380	1950	3740	4190	0.011	3380	1950	3740	4190	0.059
Lymphocyte (per mm^3)	1080	740	1127	722.5	790	710	< 0.001	1100	740	845	747.5	0.019
Thrombocytes $\times 10^9$ /L	188	72	194.5	63	157	91.5	< 0.001	190	65.5	159	96.5	0.043
Biochemistry												
Blood urea nitrogen (mg/dl)	14.675	2.1	14	7.15	19.3	13.4	< 0.001	14	7.31	23.85	11.49	< 0.001
Creatinine (mg/dl)	0.86	0.3	0.84	0.28	0.96	0.51	< 0.001	0.85	0.28	1.06	0.52	0.001
Sodium (mEq/L)	138	4	138	4	135	5	< 0.001	138	5	135	4	< 0.001
Potassium (mEq/L)	4.05	0.55	4.045	0.51	4.07	0.77	0.988	4.04	0.53	4.105	0.73	0.484
Magnesium (mEq/L)	1.9	0.42	1.95	0.28	1.96	0.4	0.875	1.975	0.3	1.91	0.38	0.617
Albumin (mg/dl)	4.02	0.56	4.1	2.41	3.68	0.51	< 0.001	4.08	0.52	3.66	0.95	0.001
Glucose (mg/dl)	113	48	114	49.25	120	53.25	0.563	114	45.75	120	58.25	0.797
Uric acid (mg/dl)	5.18	2.17	5.09	2.02	5.75	3.75	0.005	5.11	2.05	6.1	3.47	0.001
Alanine transaminase (u/l)	23	20	22	18	22	21	0.409	22	19	20.5	21	0.739
Aspartate transaminase (U/L)	29	19	28	17	37	28	< 0.001	28	18	37	21	0.001
Alkalen phosphatase (U/L)	73.5	32	73	30	69	42	0.443	73	31	67	48	0.967
GGT (U/L)	31	35	28.5	28	49	84	< 0.001	30	38.2	49	84	< 0.001
Lactate dehydrogenase (U/L)	222	100	216	87	284	154	< 0.001	217.5	97	268	155	0.002
Creatinine kinase (U/L)	100	113	90	104	117	137	0.15	92	111	117	172	0.052
Ferritin (mcg/L)	135.3	263.15	113.6	223.7	276.3	627.68	< 0.001	126	240.65	443	776.25	< 0.001
Myoglobin (mcg/L)	33.6	44.9	29.5	35.05	65.75	62	< 0.001	30.7	37.2	77.5	56.33	< 0.001
CK-MB (U/L)	1.1	1.3	1.1	1.1	1.4	1.53	< 0.001	1.1	1.1	1.9	1.73	0.005
Troponin (ng/mL)	3.75	4.77	3.25	3.38	8.95	12.43	< 0.001	3.5	3.9	12.7	17.7	< 0.001
C-reactive protein (mg/dl)	1.76	5.25	1.3	3.07	7.09	10.9	< 0.001	1.49	4.69	7.395	14.03	< 0.001
Sedimentation Rate (mm/h)	22	24	20.5	23	25	44	0.012	21	24	26	43	0.057
Procalcitonin (mcg/L)	0.06	0.07	0.05	0.05	0.11	0.26	< 0.001	0.05	0.06	0.11	0.3	< 0.001
Interleukin-6 (pg/mL)	16.84	37.3	14	26.2	47.51	53.11	< 0.001	14.91	29.18	49.23	38.65	< 0.001
IgG (mg/dl)	1130	317	1210	295	1080	336	0.435	1130	290	1235,28	1111	0.449
IgA (mg/dl)	191	96	178.5	100	195	99	0.846	186	103	195	80	0.642
IgM (mg/dl)	102.5	89	120	87	87.9	103	0.411	108.5	91	97.95	118	0.827
HDL (mg/dl)	36.5	14.3	38	12.7	32.5	17	0.058	38	12.8	23.5	15.6	0.004
LDL (mg/dl)	108	44.5	113.9	45.3	90.9	35.9	0.015	111	45.7	68.5	41.8	0.003
Triglycerides (mg/dl)	127	103	128	115	125	89	0.729	126	97	164	180	0.577
Coagulation studies												
Fibrinogen (mg/dl)	384.06	168.41	374.24	146	423.1	186.2	0.002	384	177.39	405.19	144.34	0.492
aPTT (s)	26.1	3.9	25.9	3.98	27	3.8	0.208	25.9	4.03	27	3.8	0.216
INR	1.05	0.13	1.04	0.12	1.12	0.13	< 0.001	1.04	0.12	1.16	0.12	< 0.001
D-dimer (ng/ml)	0.52	0.58	0.45	0.57	0.625	0.84	< 0.001	0.5	0.57	0.81	1.95	< .001

Values are shown as median [interquartile range]

CK-MB Creatinine kinase myocardial band; *Ig* immunoglobulin; *HDL* High-density lipoprotein; *LDL* Low-density lipoprotein; *aPTT* Activated Partial Thromboplastin Clotting Time; *IN*: International normalized ratio, *p* values were calculated using χ^2 test, Pearson test for categorical variables, Mann–Whitney *U* test for numerical variables

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

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	201	88.9	25	11.1	0.715
Cough	201	54.6	168	83.6	33	16.4	0.163	187	93	14	7	0.13
Dyspnoea	84	22.8	63	75	21	25	.112	70	83.3	14	16.7	0.04
Sputum	30	8.2	20	66.7	10	33.3	0.039	26	86.7	4	13.3	0.62
Sore throat	71	19.3	64	90.1	7	9.9	0.029	68	95.8	3	4.2	0.052
Rhinorrhoea	11	3	10	90.9	1	9.1	0.698	10	90.9	1	9.1	0.869
Chest pain	10	2.7	8	80	2	20	0.93	9	90	1	10	0.95
Back pain	19	5.2	18	94.7	1	5.3	0.14	10	100	0	0	0.24
Fatigue	188	51.1	152	80.9	36	19.1	0.861	170	90.4	18	9.6	0.503
Myalgia	148	40.3	119	80.4	29	19.6	0.749	130	87.8	18	12.2	0.433
Arthralgia	67	18.2	53	79.1	14	20.9	0.666	58	86.6	9	13.4	0.405
Nausea-vomiting	38	10.3	32	84.2	6	15.8	0.827	35	92.1	3	7.9	0.782
Diarrhoea	52	14.1	44	84.6	8	15.4	0.471	47	90.4	5	9.6	0.804
Altered sense of smell	35	9.5	30	85.7	5	14.3	0.453	33	94.3	3	5.7	0.324
Altered sense of taste	36	9.8	30	83.3	6	16.7	0.699	34	94.4	2	5.6	0.299
Eye dryness	6	1.6	6	100	0	0	0.825	6	100	0	0	0.402
Red eye	3	0.8	3	100	0	0	NA	3	100	0	0	NA
Headache	63	17.1	57	90.5	6	9.5	0.035	61	96.8	2	3.2	0.036
Chills	9	2.4	9	100	0	0	0.21	9	100	0	0	0.603
Neurological signs	5	1.4	4	80	1	20	0.95	4	80	1	20	0.431
Vital Signs (median & IQR)												
Body temperature	38	1.7	38	1.5	38	1.5	0.476	38	1.5	36.85	1.375	0.123
Respiration rate	20	2	20	2	21	4	0.186	20	2	20	2	0.526
Saturation on room air	95	3	95	3	91	6	<0.001	95	4	91	5	<0.001
Pulse	85.5	20	85	16	81	17	0.263	85	18	80	14	0.121
Systolic Blood Pressure	122.5	25	122	25.5	130	18	0.567	122	25	130	15.5	0.197
Diastolic Blood Pressure	71.5	18.5	73	18.5	73	20	0.179	72	17.5	73	20	0.564

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

ICU intensive care unit, *IQR* interquartile range

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 unanticipated 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

Table 4 Multivariate logistic regression models

Multivariate Logistic Regression Model-ICU-1						Multivariate Logistic Regression Model-SUR-1				
	B	OR	*p* value	CI interval 95%		B	OR	*p* value	CI interval 95%	
Age	0.066	1.068	< .001	1.043	1.094	0.075	1.078	< 0.001	1.046	1.111
Male Sex	1.088	2.968	0.001	1.517	5.807	1.356	3.882	0.002	1.674	9.003
Active cancer	1.341	3.821	0.009	1.390	10.507	1.714	5.551	0.002	1.918	16.063
Saturation < 90% on room air	2.424	11.287	< .001	5.046	25.247	0.948	2.580	0.034	1.076	6.186
Constant	− 8.856					− 8.015				
Multivariate Logistic Regression Model-ICU-2						Multivariate Logistic Regression Model-SUR-2				
	B	OR	*p* value	CI interval 95%		B	OR	*p* value	CI interval 95%	
Age	0.053	1.055	0.001	1.022	1.088	0.042	1.078	0.03	1.004	1.083
Male sex	0.818	2.265	0.049	1.005	5.104	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	2.051	0.156	0.761	5.531
Oxygen support need	2.482	11.961	< 0.001	5.381	26.586	2.015	7.502	< 0.001	2.952	19.064
Albumin	− 1.438	0.237	0.002	0.094	0.597	− 1.056	0.348	0.038	0.129	0.942
Lymphocyte count < 800	0.775	2.170	0.065	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						0.045	1.046	0.041	1.002	1.093
Troponin	0.017	1.017	0.289	0.985	1.05					
Constant	17.7					− 3.846				

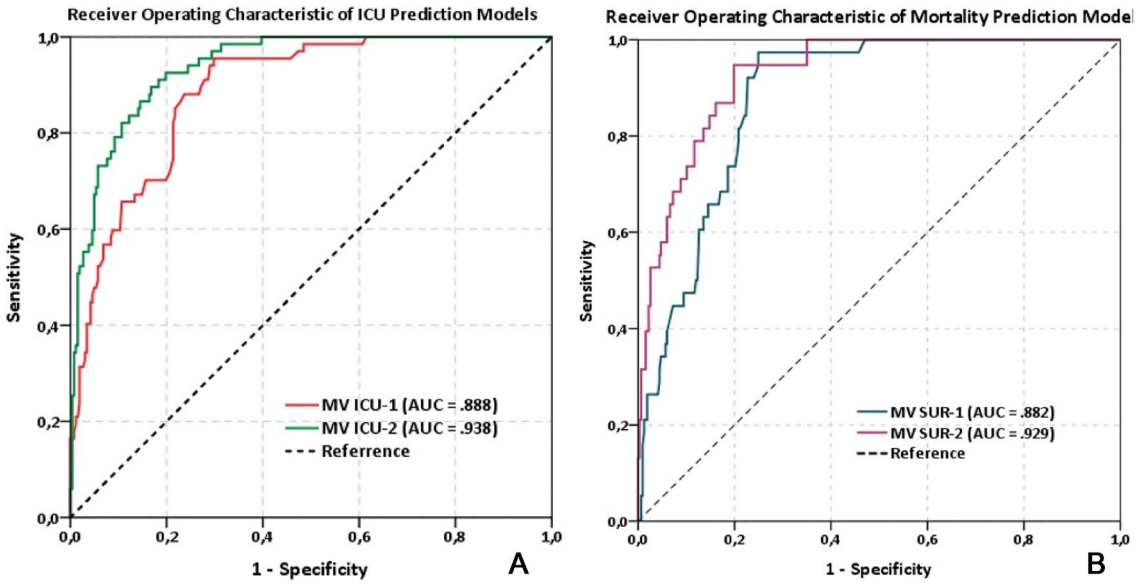

Fig. 2 Receiver Operating Characteristics Curve of Multivariate Model ICU− 1/ICU− 2 (**A**) and Multivariate Model SUR− 1/SUR− 2 (**B**)

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].

Low oxygen saturation may reflect the extent of the alveolicapillary 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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Author contributions NÇB and GSG conceptualized and designed the study, THŞ, BÖ, HO, and LÖ collected the data, OAU, MDT and MÖ analysed the data, text was written by MÖ. All authors reviewed and approved the manuscript.

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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.

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