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Medisch Spectrum Twente
een santeon ziekenhuis

Risk factors for ICU admission, long-term stay and mortality in hospitalized COVID-19 patients

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Abstract

OBJECTIVE The aim of this study is to develop a prediction model based on demographic and clinical characteristics at hospital admission to identify risk factors for intensive care unit (ICU) admission, long-term stay, and mortality in hospitalized COVID-19 patients.

OUTCOMES Primary outcomes were ICU admission, long-term stay, and death while hospitalized.

METHOD A total of 334 eligible patients (208 [62.3%] male, median age 65.5 [58-76] years), admitted to either a general ward or ICU of Medisch Spectrum Twente were enrolled in this study. Data such as demographics, comorbidities, vital signs, respiratory condition and laboratory test results, was obtained from the electronic medical records and the Castor database of our COVID-19 cohort at hospital admission. Logistic regression was used to identify independent variables predicting the three outcomes. All three models were validated by randomly splitting the data into 80% for training and 20% for validating. Performance accuracy was evaluated using area under the receiver operating characteristic curve (AUC-ROC) analysis.

FINDINGS Eight independently significant predictors for ICU admission were BMI between 25-30 $kg \cdot m^{-2}$ compared to BMI ≤25 $kg \cdot m^{-2}$, respiratory rate ≥20/min, pH value 7.35-7.45 or ≤7.35 compared to pH value ≥7.45, HCO_3 ≥23.8 mEq/L, neutrophils ≥5.18 cells/µL, C-Reactive Protein ≥79.5 mg/L and D-dimer ≥2286 µg/L. For long-term stay (≥7 days), 6 predictors were independently significant: age ≥70 years compared to age ≤50 years, use of immunosuppressive therapy, respiratory rate ≥20/min, pH value ≤7.35 compared to pH value ≥7.45, HCO_3 ≥23.8 mEq/L and D-dimer ≥2286 µg/L. In case of death while hospitalized, age ≥70 years compared to age ≤50 years, male gender, sodium ≥136 mmol/L, D-dimer ≥2286 µg/L, and oxygen therapy ≤4 L compared to no oxygen therapy were found as the 5 best predictors. The prediction model of the validation set yielded an AUC-ROC of 0.94 (95% CI [0.88-1.00], p <0.001) for ICU admission, a AUC-ROC of 0.63 (95% CI [0.49-0.77], p = 0.081) for long-term stay and a AUC-ROC of 0.68 (95% CI [0.48-0.89], p = 0.093) for death while hospitalized.

CONCLUSION This study identified key independent predictors for ICU admission, long-term stay and death while hospitalized with COVID-19. These predictors offer the potential to stratify patients based on risk factors so that they can triage COVID-19 patients more effectively.

Keywords: COVID-19, SARS-CoV-2, prediction model, risk factors, outcomes

1. Introduction

Coronavirus lung disease 2019 (COVID-19) is a severe acute respiratory syndrome. The Coronavirus-2 (SARS-CoV-2) outbreak initially appeared in Wuhan, China, in December 2019 (1), but has evolved into a rapidly spreading pandemic (2). As from June 22th 2021, a total of 180 million cases of COVID-19 have been reported, including 3,89 million deaths. In the Netherlands, a total of 1,68 million cases and 18 thousand deaths have been reported (3). On February 27th 2020, the first Dutch person with COVID-19 was diagnosed in the Elisabeth-TweeSteden Ziekenhuis (ETZ), the Netherlands (4).

There is an immediate urgency to provide clinicians with adequate support in the effective triage of patients in the COVID-19 pandemic (5). Based on the data obtained between March 2020 and June 2021, the Netherlands has a COVID-19 case fatality rate (CFR) of 1.1% which is considerably higher than the CFR of the influenza virus (0.1%) (6). It is therefore crucial that the clinical characteristics of those with worse/fatal outcome are identified, so that physicians can properly assess which patients have poor prognosis and therefore might benefit from early intensive treatment.

As the pandemic progresses, more becomes clear about the clinical and demographic characteristics of hospitalized COVID-19 patients. Most common symptoms of COVID-19 are fever, cough, shortness of breath, fatigue, muscle aches, headache, loss of taste or smell and nasal congestion (7–10). Zhang et al. (11) reported that patients with chronic comorbidities were more likely to have more severe COVID-19. Especially patients with previous cardiovascular or metabolic diseases and underlying immune disorders or chronic lung diseases are at greater risk of developing more severe COVID-19 (12,13). Mortality due to COVID-19 in the intensive care unit (ICU) occurs mainly in overweight men of advanced age. Elderly patients are at high-risk for developing COVID-19 with a rapidly progressive clinical deterioration. It is therefore of importance to offer individual therapeutic approaches to the elderly weighing the beneficial and adverse effects of therapeutic decisions (14).

Albitar et al. (15) analyzed global data and assessed predictors for death in COVID-19. They found that there is considerable variation in COVID-19 mortality based on geographical location. Many studies have been conducted worldwide (16–22) to describe the risk factors for COVID-19 patients, but none of the studies are representative of the demographic characteristics of the Dutch COVID-19 population (23). A recent study in the Netherlands showed (24) that mortality increases in ICU patients with comorbidities – such as hypertension, chronic neurological, nephrological, cardiac disease, or diabetes mellitus type 2 (25) – but a comprehensive overview on risk factors is lacking.

The aim of this study is to develop a predictive model based on clinical characteristics at admission for outcomes such as ICU admission, long-term hospitalization, and mortality in order to identify risk factors in hospitalized COVID-19 patients in the Netherlands.

2. Methods

2.1 Study- design and population

This retrospective cohort study was conducted at Medisch Spectrum Twente (MST), a large teaching hospital in Enschede, the Netherlands. Between March 2020 and April 2021, all patients with laboratory-confirmed SARS-CoV-2 infection and admitted to a hospital ward or the ICU after deterioration of their medical condition were enrolled in the study database.

Conform WHO guidance (26), laboratory confirmation for SARS-COV-2 was defined as a positive result of real-time reverse transcriptase–polymerase chain reaction (RT-PCR) assay of oropharyngeal or nasopharyngeal swabs. This guidance has been implemented in MST to diagnose COVID-19 patients. Patients with neither laboratory confirmation for SARS-CoV-2 infection (RT-PCR), nor CT thorax abnormalities consistent with COVID-19, nor clinical judgement only, or patients with an incomplete medical history (no data of vital signs and or laboratory values at all), or who were still hospitalized at the time of the analysis were excluded from the present report. Patients referred to the ICU from the general ward were considered as ICU patients. Data obtained at first day of ICU admission was used in respective analyses. Subjects whose prognosis was too poor to be admitted to the ICU or who chose not to be intubated (in consultation with the physician) were excluded from the analyses for ICU admission. Subjects who were palliative discharged or transferred to another facility were considered as alive in the analyses for death while hospitalized. This study was approved by the Ethical Review Board of MST.

2.2 Data collection

Predictors

Data was obtained from the electronic medical records and the Castor database of our COVID-19 cohort (27). For all patients hospitalized with proven COVID-19, the following data were systematically recorded: demographics (age, gender, and body mass index (BMI)), COVID-19 symptoms, comorbidities, medication, vital signs (temperature, heart rate, respiratory rate, blood pressure, and oxygen saturation), respiratory condition (SaO_2, pO_2, pCO_2, pH value, HCO_3, and base excess value), laboratory test results (hemoglobin, leukocytes, lymphocytes, neutrophils, hematocrit, thrombocytes, glucose, lactate, creatinine, sodium, potassium, C-Reactive Protein, LDH, CK, ferritin, and D-dimer), outcomes (discharged alive, duration of hospitalization, palliative care and discharge with impending death, and all cause death), complications, radiology results (chest x-ray and CT thorax), and treatment. All possible predictors (demographics, comorbidities, vital signs, respiratory condition, laboratory test results) were assessed on the first day of hospital admission or on the first day of ICU admission.

Outcomes

The main outcomes of the study were admission to the ICU, long-term hospitalization, and death while hospitalized. Long-term hospitalization is defined as hospitalized for a period of days greater than the median COVID-19 hospital stay (≥7 days).

2.3 Statistical analysis

Clinical characteristics are reported as means with standard deviations or median with interquartile ranges (IQR) for continuous variables, as appropriate, or as numbers with corresponding percentages for categorical variables. Pearson Chi-square tests or Fisher's exact tests are used comparing study groups for categorical, unpaired variables, as appropriate. Student's t-test or the Mann-Whitney U test are used to compare study groups for continuous variables. Total data were randomly split into 80% for a training set and 20% for a validation set. Logistic regression models were made for ICU admission against general ward admission as dependent variable. Similarly, logistic regression models were made for long-term hospitalization against short-term hospitalization as dependent variable. Finally, logistic regression models were made for death while hospitalized against discharged alive as dependent

variables. Coefficients obtained from the logistic regressions in the training set were fixed and used in the validation set for predicting the outcomes. In all three models, pre-selection (only including variables $p \leq 0.001$) was used to reduce the number of independent variables. Subsequently, forward selection was performed to include only the significant independent variables in the final models ($p<0.05$). Demographic data that had previously been reported as potential risk factors (age, gender and BMI) were included in each analysis. Continuous variables were categorized based on either the median or crucial values to obtain the best fit for the models, using the -2 Log likelihood: gender = male, age: ≤50 years, 50-70 years and ≥70 years, BMI: ≤25 $kg \cdot m^{-2}$, 25-30 $kg \cdot m^{-2}$ and ≥30 $kg \cdot m^{-2}$, respiratory rate ≥20/min, pH: ≤7.35, 7.35-7.45 and ≥7.45, HCO_3 ≥23.8 mEq/L, hemoglobin ≥8.20 mmol/L, glucose ≥7.70 mmol/L, neutrophils ≥5.18 cells/µL, sodium ≥136 mmol/L, potassium ≥4.03 mmol/L, LDH ≥358 U/L, C-Reactive Protein ≥79.5 mg/L, D-dimer ≥2286 µg/L, ferritin ≥1298 µg/L and oxygen supply at hospital admission ≤4 L or >4 L. Possible predictors are also shown as continuous variables in the descriptive tables for clarification. Cox regression models were similarly made for time till death while hospitalized as a dependent variable, with corresponding hazard ratios. Kaplan-Meier curves were made to estimate the overall survival over time.

Area under the receiver operating characteristic (AUC-ROC) curve analysis was used to estimate the performance for all three logistic regression models. Different cut-offs are considered (Youden index, high sensitivity, high specificity) to identify the best predictive values. For each threshold value, the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) was calculated. Ultimately, the cut-off points with the highest NPVs are used. Complications are reported as dichotomous variables. A p-value of $p<0.05$ is considered significant and 95% confidence intervals are reported where appropriate. IBM SPSS Statistics 25 is used for analysis of all data.

3. Results

3.1 Study population

A total of 350 subjects, hospitalized between 26th February 2020 and 3rd January 2021, were registered in the Castor database and included in the current study. After applying the beforementioned inclusion criteria, 334 subjects were selected for analysis. The training set consisted of 268 subjects, with a median age of 68 years and 64.2% male. Of all 268 subjects, 213 (79.5%) had at least one comorbidity. The most common comorbidity was hypertension in 91 (34.0%) subjects (Appendix 1).

3.2 Predictor selection

A total of 105 variables, measured at hospital admission, were included in the univariate logistic regression model (Appendix 1). After pre- and forward selection, 14 variables remained suitable as predictors for ICU admission. Inclusion of these variables in the multivariate logistic regression resulted in 10 variables that remained independently significant as predictors for ICU admission. This method was also applied to identify significant predictors for long-term admission and for death during hospital admission. In case of long term-admission, 17 variables remained significant resulting in 6 independently statistically significant predictors. For death, 5 out of 17 significant variables were independently statistically significant predictors.

ICU admission vs. general ward

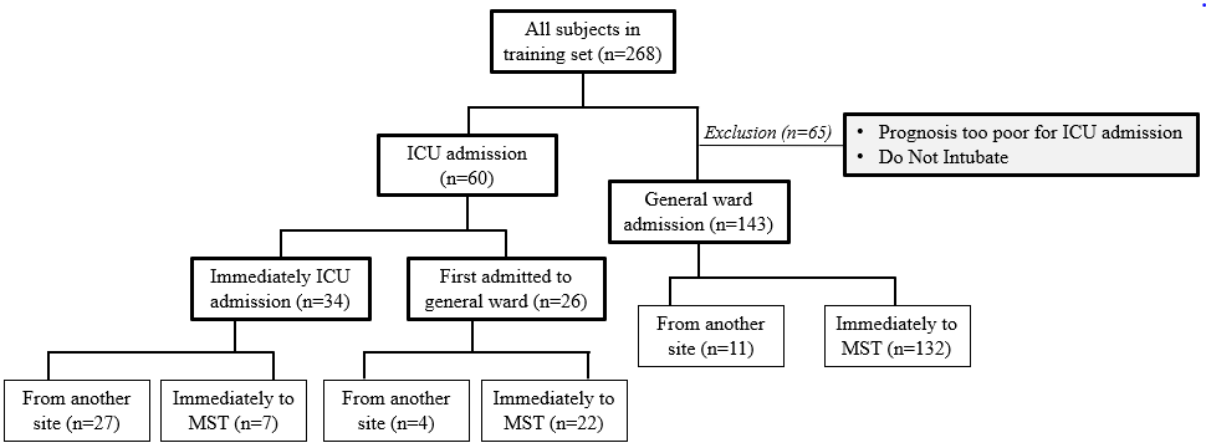
Regarding the univariate and multivariate analyses for ICU admission, subjects whose prognosis was too poor to be admitted to the ICU or who chose not to be intubated (n=65) were excluded from analysis. A small overview of the distribution of the mortality of these patients is shown in Table 1. The admission process of both ICU admission and general ward is shown in figure 1.

TABLE 1 Subjects who chose DNI or those who were not admitted to the ICU in consultation with the physician (n=65)

	Died at general ward (n=28)		**Leaving general ward alive (n=37)**	
DNI	1	3.6%	1	2.7%
No ICU	25	89.3%	34	91.9%
DNI and No ICU	2	7.1%	2	5.4%

DNI; do not intubate. ICU; intensive care unit.

Figure 1 Flowchart of admission process



As summarized in Table 2, the median age of subjects admitted to the general ward was 63 years and that of subjects admitted to the ICU was 66.5 years. Males were overrepresented in both general ward and ICU admissions, with a much higher proportion in the ICU (78.3% vs 61.5%, p=0.007). No significant difference was found in age for ICU admission. Subjects admitted to ICU significantly more often had a BMI >25 $kg \cdot m^{-2}$ compared to a BMI ≤25 $kg \cdot m^{-2}$ than those admitted to general ward (p = 0.006). A low pH value of <7.45 occurred significantly much more frequently in subjects admitted to ICU than those who remained at a general ward (p <0.001). Furthermore, subjects admitted to the ICU showed significantly more abnormal laboratory values (all p <0.001). In univariate analysis, male gender, BMI between 25-30 $kg \cdot m^{-2}$ compared to BMI ≤25 $kg \cdot m^{-2}$, pH value between 7.35-7.45 and pH value ≤7.35 compared to pH value ≥7.45, respiratory rate ≥20/min, HCO_3 ≥23.8 mEq/L, neutrophils ≥5.18 cells/µL, sodium ≥136 mmol/L, C-Reactive Protein ≥79.5 mg/L, D-dimer ≥2286 µg/L and ferritin ≥1298 µg/L all have a strong positive association with admission to the ICU. The multivariate logistic regression model (see table 1) identified the best predictors for ICU admission to be BMI between 25-30 $kg \cdot m^{-2}$ compared to BMI ≤25 $kg \cdot m^{-2}$, respiratory rate ≥20/min, pH value 7.35-7.45 or ≤7.35 compared to pH value ≥7.45, HCO_3 ≥23.8 mEq/L, neutrophils ≥5.18 cells/µL, C-Reactive Protein ≥79.5 mg/L and D-dimer ≥2286 µg/L. Of all 7

predictors, a pH ≤7.35 had the strongest association with ICU admission (mOR 49.8 [95% CI 4.77-519]).

TABLE 2 Characteristics of subjects admitted to ICU vs. general ward admission

	ICU admission (n=60)		General ward (n=143)		p-value	OR	95% CI	mOR	95% CI
Demographics[+,*]									
Age, years	66.5	56.8-72.0	63.0	54.0-75.0	0.704	-	-	-	-
≤50	11	18.3%	29	20.3%	0.648	1	-	-	-
50-70	29	48.3%	59	41.3%	-	1.30	0.57-2.96	-	-
≥70	20	33.3%	55	38.5%	-	0.96	0.41-2.27		
Male gender	47	78.3%	88	61.5%	0.007	2.26	1.12-4.55	-	-
BMI, $kg \cdot m^{-2}$, mean±SD	28.3	±1.9	28.1	±4.2	0.591	-	-	-	-
≤25	1	1.7%	30	21.0%	0.006	1	-	1	-
25-30	52	86.7%	87	60.8%	-	17.9	2.37-135	15.3	1.54-151
≥30	7	11.6%	26	18.2%	-	8.08	0.93-70.0	5.67	0.46-69.6
Clinical values[+,*]									
Respiratory rate, rate/min	22.7	20.0-29.5	20.0	16.0-24.0	0.009	-	-	-	-
≥20	49	81.7%	73	51.0%	<0.001	4.27	2.06-8.88	3.68	1.25-10.9
pH value	7.44	7.37-7.49	7.48	7.45-7.51	<0.001	-	-	-	-
≥7.45	23	38.3%	108	75.5%	<0.001	1	-	1	-
7.35-7.45	24	40.0%	34	23.8%	-	3.32	1.66-6.61	4.24	1.35-12.6
≤7.35	13	21.7%	1	0.7%	-	61.0	7.60-490	49.8	4.77-519
HCO_3, mEq/L	25.0	23.3-27.0	23.0	21.0-24.8	<0.001	-	-	-	-
≥23.8	43	71.7%	61	42.7%	<0.001	3.40	1.77-6.53	2.94	1.07-8.07
Laboratory values[+,*]									
Neutrophils, cells/µL	6.99	5.8-10.3	4.49	3.35-6.12	<0.001	-	-	-	-
≥5.18	49	81.7%	54	37.8%	<0.001	7.34	3.52-15.3	4.11	1.35-12.6
Sodium, mmol/L	137	135-141	135	133-138	<0.001	-	-	-	-
≥136	42	70.0%	65	45.5%	0.001	2.80	1.47-5.33	2.60	0.96-7.07
C-Reactive Protein, mg/L	132	96.2-276	60.0	28.0-99.3	<0.001	-	-	-	-
≥79.5	49	81.7%	50	35.0%	<0.001	8.29	3.96-17.3	4.09	1.28-13.1
D-dimer, µg/L	3740	2452-7136	1842	811-2693	<0.001	-	-	-	-
≥2286	49	81.7%	53	37.1%	<0.001	7.56	3.62-15.8	5.44	1.86-15.9
Ferritin, µg/L	2004	1179-3588	1044	670-1582	<0.001	-	-	-	-
≥1298	45	75.0%	59	41.3%	<0.001	4.27	2.18-8.37	-	-

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. OR; odds ratio. mOR; multivariate odds ratio. CI; confidence interval. [*]Pearson χ^2-test; [+]Student's t-test.

Long-term admission vs. short-term admission

In order to classify subjects into either short-term or long-term admission, the median hospital stay (≥7 days) was used. Subjects who were hospitalized long-term were significantly older (p =0.004), but no significant differences were found in gender nor BMI. Dyslipidemia and pre-hospitalization use of immunosuppressive therapy were more common in those with long-term admission (14.2% vs. 5.5% and 11.3% vs. 3.9%, respectively). All laboratory values were significantly more abnormal in those with long-term admission: hemoglobin, glucose, sodium, C-Reactive Protein, D-dimer and ferritin (p ≤0.001). A complete overview is shown in Table 3. In univariate analyses, age ≥70 years compared to age ≤50 years, dyslipidemia, use of immunosuppressive therapy, respiratory rate ≥20/min, pH value ≤7.35, HCO_3 ≥23.8 mEq/L, sodium ≥136 mmol/L, C-Reactive Protein ≥79.5 mg/L, D-dimer ≥2286 µg/L and ferritin ≥1298 µg/L have a strong positive association with long-term admission. The multivariate logistic

regression model identified the best predictors for long-term admission to be age ≥70 years compared to age ≤50 years, use of immunosuppressive therapy, respiratory rate ≥20/min, pH value ≤7.35 compared to pH value ≥7.45, HCO_3 ≥23.8 mEq/L and D-dimer ≥2286 µg/L. Of all 6 predictors, a pH ≤7.35 compared to a pH ≥7.45 had the strongest association with long-term admission (mOR 14.71 [95% CI 1.67-130]).

TABLE 3 Characteristics of long-term admission vs. short-term admission

	Long-term (n=141)		**Short-term (n=127)**		**p-value**	**OR**	**95% CI**	**mOR**	**95% CI**
Demographics[+,*]									
Age, years	70.0	61.5-76.0	64.0	54.0-76.0	0.004	-	-	-	-
≤50	14	9.9%	27	21.3%	0.024	1	-	1	-
50-70	52	36.9%	48	37.8%	-	2.09	0.98-4.45	2.23	0.95-5.22
≥70	75	53.2%	52	40.9%	-	2.78	1.33-5.81	2.75	1.21-6.27
Male gender	90	63.8%	82	64.6%	0.635	0.97	0.59-1.60	-	-
BMI, $kg \cdot m^{-2}$, mean±SD	28.1	±3.24	27.9	±3.91	0.900	-	-	-	-
≤25	21	14.9%	26	20.5%	0.404	1	-	-	-
25-30	99	70.2%	80	63.0%	-	1.53	0.80-2.92	-	-
≥30	21	14.9%	21	16.5%	-	1.24	0.54-2.85	-	-
Dyslipidemia	20	14.2%	7	5.5%	0.019	2.83	1.16-6.95	-	-
Immunosuppressive therapy	16	11.3%	5	3.9%	0.024	3.12	1.11-8.79	5.59	1.70-18.4
Clinical values[+,*]									
Respiratory rate, rate/min	22.0	18.0-27.0	20.0	16.0-24.0	0.015	-	-	-	-
≥20	96	68.1%	64	50.4%	0.003	2.10	1.28-3.45	2.24	1.26-4.00
pH value	7.46	7.41-7.49	7.47	7.44-7.50	0.001	-	-	-	-
≥7.45	80	56.7%	86	67.7%	0.025	1	-	1	-
7.35-7.45	46	32.6%	40	31.5%	-	1.24	0.73-2.08	1.59	0.87-2.90
≤7.35	15	10.6%	1	0.8%	-	16.1	2.08-125	14.7	1.67-130
HCO_3, mEq/L	24.1	22.0-26.0	23.0	21.0-24.3	0.004	-	-	-	-
≥23.8	89	63.1%	45	35.4%	<0.001	3.12	1.89-5.14	3.56	2.01-6.29
Laboratory values[+,*]									
Hemoglobin, mmol/L	8.1	7.2-9.0	8.5	7.7-9.1	0.001	-	-	-	-
≥8.20	63	44.7%	80	63.0%	0.003	0.48	0.29-0.77	-	-
Glucose, mmol/L	7.9	6.6-9.9	7.5	6.3-8.6	0.001	-	-	-	-
≥7.70	76	53.9%	58	45.7%	0.178	1.39	0.86-2.25	-	-
Sodium, mmol/L	136	134-140	135	133-138	<0.001	-	-	-	-
≥136	93	66.0%	60	47.2%	0.002	2.16	1.32-3.54	-	-
C-Reactive Protein, mg/L	99.3	49.0-176	60.0	25.0-99.3	<0.001	-	-	-	-
≥79.5	86	61.0%	48	37.8%	<0.001	2.57	1.57-4.21	-	-
D-dimer, µg/L	2728	1685-4869	1882	941-2667	<0.001	-	-	-	-
≥2286	89	63.1%	45	35.4%	<0.001	3.12	1.89-5.14	3.02	1.72-5.30
Ferritin, µg/L	1560	883-2309	1014	671-1582	<0.001	-	-	-	-
≥1298	86	61.0%	48	37.8%	<0.001	2.57	1.57-4.21	-	-

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. OR; odds ratio. mOR; multivariate odds ratio. CI; confidence interval. *Pearson χ^2-test; +Student's t-test.

Death while hospitalized vs. discharged alive

As shown in Table 4, subjects who died while hospitalized were significantly older (p <0.001) and more often male than subjects who were discharged alive (79.6% vs 60.7%, p = 0.013). No difference was found in BMI. Comorbidities such as chronic cardiac disease, chronic neurological disease and prior malignity were significantly more frequent in subjects who died

while hospitalized (p = 0.001, p = 0.001 and p = 0.049, respectively). The pH value was significantly lower in subjects who died while hospitalized than in subjects who were discharged alive (p = 0.028). In addition, subjects who died while hospitalized had significantly more abnormal laboratory values compared to subjects who were discharged alive: sodium (139 mmol/L vs 136 mmol/L, p <0.001), potassium (4.3 mmol/L vs 4.0 mmol/L, p =0.001), D-dimer (2978 µg/L vs 2065 µg/L, p = 0.003), and LDH (406 U/L vs 341 U/L, p = 0.002), respectively. Age ≥70 years compared to age ≤50 years, male gender, chronic cardiac disease (CCD), chronical neurological disease (CND), having a prior malignity, pH ≤7.35 compared to pH ≥7.45, sodium ≥136 mmol/L, D-dimer ≥2286 µg/L, LDH ≥358 U/L and oxygen supply >4 L compared to no oxygen therapy were found as having a positive association with death while hospitalized in the univariate analysis. The multivariate logistic regression model identified the best predictors for death while hospitalized to be age ≥70 years compared to age ≤50 years, male gender, sodium ≥136 mmol/L, D-dimer ≥2286 µg/L, and oxygen therapy ≤4 L compared to no oxygen therapy. Of all 5 predictors, male gender had the strongest association with death while hospitalized (mOR 3.53 [95% CI 1.50-8.31]). A flow chart of different subjects considered as alive is shown in figure 2.

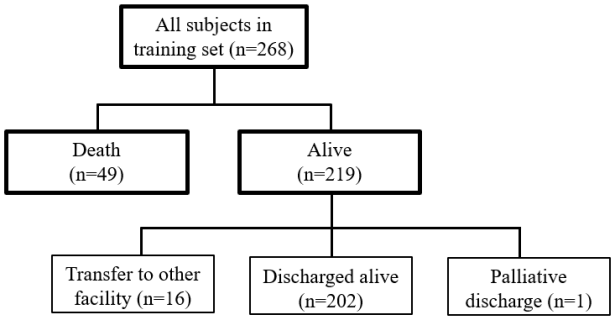
TABLE 4 Characteristics of subjects who died while hospitalized vs. discharged alive

	Death (n=49)		**Alive (n=219)**		**p-value**	**OR**	**95% CI**	**mOR**	**95% CI**
Demographics[+,*]									
Age, years	77.0	69.0-83.0	66.0	56.0-75.0	<0.001	-	-	-	-
≤50	1	2.0%	40	18.3%	<0.001	1	-	1	-
50-70	11	22.4%	89	40.6%	-	4.94	0.62-39.6	4.72	0.56-40.0
≥70	37	75.5%	90	41.1%	-	16.4	2.18-124	2.30	2.30-152
Male gender	39	79.6%	133	60.7%	0.013	2.52	1.20-5.31	3.53	1.50-8.31
BMI, kg·m−2, mean±SD	27.5	± 2.6	28.1	± 3.8	0.299	0.71	0.28-1.79	-	-
≤25	9	18.4%	38	17.4%	0.768	1	-	-	-
25-30	34	69.4%	145	66.2%	-	0.99	0.44-2.24	-	-
≥30	6	12.2%	36	16.4%	-	0.70	0.23-2.18	-	-
CCD	17	34.7%	32	14.6%	0.001	3.10	1.55-6.24	-	-
CND	8	16.3%	8	3.7%	0.001	5.15	1.83-14.5	-	-
Prior malignity	14	28.6%	36	16.4%	0.049	2.03	0.99-4.16	-	-
Clinical values[+,*]									
pH value	7.45	7.39-7.47	7.46	7.44-7.50	0.001	-	-	-	-
≥7.45	23	46.9%	143	65.3%	0.028	1	-	-	-
7.35-7.45	20	40.8%	66	30.1%	-	1.88	0.97-3.67	-	-
≤7.35	6	12.2%	10	4.6%	-	3.73	1.24-11.3	-	-
Laboratory values[+,*]									
Sodium, mmol/L	139	136-142	136	133-138	<0.001	2.90	1.51-5.58	-	-
≥136	39	79.6%	114	52.1%	<0.001	-	-	3.27	1.46-7.35
Potassium, mmol/L	4.3	3.8-4.6	4.0	3.7-4.3	0.001	1.87	0.99-3.54	-	-
≥4.03	31	63.3%	102	46.6%	0.035	-	-	-	-
D-dimer, µg/L	2978	2053-5568	2065	1387-2741	0.003	3.42	1.72-6.80	-	-
≥2286	36	73.5%	98	44.7%	<0.001	-	-	3.16	1.46-6.81
LDH, U/L	406	328-501	341	259-427	0.002	2.41	1.25-4.63	-	-
≥358	33	67.3%	101	46.1%	0.007	-	-	-	-

Oxygen therapy*										
No oxygen	22	44.9%	145	66.2%	0.011	1	-	1	-
≤4 L	13	26.5%	45	20.5%	-	1.90	0.89-4.08	3.00	1.23-7.33
>4 L	14	28.6%	29	13.2%	-	3.18	1.46-6.94	2.44	0.96-6.19

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; CCD: chronical cardiac disease; CND: chronical neurological disease; SD: standard deviation: OR: odds ratio; mOR: multivariate odds ratio; CI; confidence interval. *Pearson χ^2-test; +Student's t-test.

Figure 2 Flow chart of different subjects considered as alive

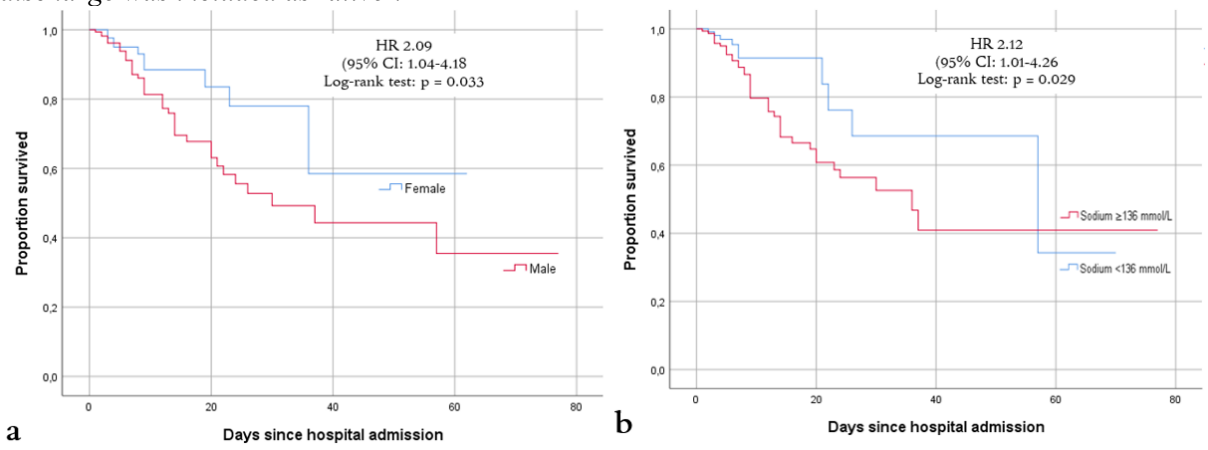


Survival analysis

To illustrate, we have created Kaplan-Meier curves for gender and sodium level. For male gender, the proportion survived after 20 days was estimated around 63.1% (std. error 5.8%). By contrast, for female, the proportion survived after 20 days was estimated around 83.5% (std. error 6.3%), log rank test: p = 0.033. The corresponding hazard ratio (HR) for male gender was 2.09 (95% CI: 1.04-4.18). In case of sodium <136 mmol/L, the proportion survived after 20 days was estimated around 91.4% (std. error 3.5%). Conversely, for sodium ≥136 mmol/L, the proportion survived after 20 days was estimated around 60.8% (std. error 5.7%), log rank test: p = 0.029. The corresponding HR for sodium ≥136 mmol/L was 2.12 (95% CI: 1.01-4.26). Both results are shown in figure 2. All other Kaplan-Meier curves can be found in Appendix 2.

Figure 2 Differences in survival of hospitalized COVID-19 patients

a) differences in survival between gender; b) differences in survival between sodium values. Palliative discharge was included as 'alive'.



3.3 Validation set

The validation set consisted of 66 subjects, with a median age of 70 years, 54.5% male and BMI of 27.96 ±3.3 $kg \cdot m^{-2}$. Demographic characteristics between both subsets were very similar (Table 5). The only variable that showed a significant difference was CCD (p = 0.031), with a higher percentage of patients with 30.3%.

TABLE 5 Characteristics of subjects classified in either training set or validation set

	Training set (n=268)		**Validation set (n=66)**		**p-value**
Demographics[+,*]					
Age, years	68.0	58.0-76.0	70.0	57.8-77.5	0.538
≤50	40	14.9%	9	13.6%	0.791
50-70	110	41.0%	25	37.9%	0.639
≥70	118	44.0%	32	48.5%	0.515
Male gender	172	64.2%	36	54.5%	0.148
BMI, $kg \cdot m^{-2}$, mean±SD	28.0	± 3.6	28.1	± 3.3	0.925
≤25	47	17.5%	11	16.7%	0.867
25-30	179	66.8%	44	66.7%	0.985
≥30	42	15.7%	11	16.7%	0.843
CCD	49	18.3%	20	30.3%	0.031
CND	16	6.0%	8	12.1%	0.083
Prior malignity	50	18.7%	11	16.7%	0.708
Dyslipidemia	27	10.1%	5	7.6%	0.646
Immunosuppresive therapy	21	7.8%	5	7.6%	1.000
Clinical values[+,*]					
Respiratory rate, rate/min	20.0	16.0-24.6	21.2	18.8-24.0	0.729
pH value	7.46	7.43-7.49	7.47	7.44-7.50	0.172
≥7.45	181	67.5%	46	69.7%	0.736
7.35-7.45	71	26.5%	17	25.8%	0.903
≤7.35	16	6.0%	3	4.5%	1.000
HCO_3, mEq/L	23.8	21.0-26.0	23.5	21.8-25.0	0.551
Laboratory values[+]					
Hemoglobin, mmol/L	8.2	7.5-9.0	8.1	7.0-8.9	0.455
Glucose, mmol/L	7.70	6.40-9.18	7.20	6.10-8.70	0.447
Neutrophils, cells/µL	5.18	3.60-7.56	5.49	3.96-7.44	0.850
Sodium, mmol/L	136	134-139	136	134-138	0.605
Potassium, mmol/L	4.03	3.70-4.30	4.00	3.60-4.40	0.472
C-Reactive Protein, mg/L	79.5	37.6-128	64.0	24.8-127	0.409
D-dimer, µg/L	2286	1434-3118	1855	935-3155	0.438
Ferritin, µg/L	1298	735-1739	1089	581-1883	0.469
LDH, U/L	358	276-443	331	235-444	0.287
Oxygen therapy[*]					
No oxygen	167	62.3%	35	53.0%	0.167
≤4 L	58	21.6%	20	30.3%	0.136
>4 L	43	16.0%	11	16.7%	0.902

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. [*]Pearson χ^2-test; [+]Student's t-test.

Performance of the training model

Prediction performance in the training set yielded an AUC-ROC of 0.94 for ICU admission, 0.78 for long-term admission and 0.83 for death. Cut-offs were chosen resulting in the most appropriate NPV. For ICU admission, a sensitivity of 95.0% and a specificity of 67.4% was obtained from the training set. For long-term admission and death, a sensitivity of 92.2% and 93.9% and a specificity of 39.4% and 39.7% were obtained, respectively. ICU admission showed a PPV of 54.8% and a NPV of 97.0%. Long-term admission presented a PPV of 62.8% and a NPV of 82.0%. The PPV of death was 25.8% with a NPV of 96.7% (Table 6).

Table 6 Indication of considered cut-off points and predicting performance of the three investigated outcomes (Training)

	Yes/no (%)	Cut-off	Based on	Sensitivity	Specificity	PPV	NPV	AUC-ROC	95% CI
		0.241	Youden index	90.0%	83.9%	70.1%	95.2%		
ICU admission	60/143 (29.6%)	0.087	High sensitivity	95.0%	67.4%	54.8%	97.0%	0.94	0.90-0.97
		0.386	High specificity	83.3%	90.2%	78.1%	92.8%		
		0.506	Youden index	73.8%	71.7%	74.3%	71.1%		
Long-term admission	147/127 (54.9%)	0.312	High sensitivity	92.2%	39.4%	62.8%	82.0%	0.78	0.73-0.84
		0.677	High specificity	45.4%	92.9%	87.7%	60.5%		
		0.233	Youden index	65.3%	85.4%	50.0%	91.7%		
Death	49/219 (18.3%)	0.068	High sensitivity	93.9%	39.7%	25.8%	96.7%	0.83	0.76-0.89
		0.388	High specificity	59.2%	90.9%	59.2%	90.9%		

PPV: positive predictive value; NPV: negative predictive value; AUC-ROC: area under the receiver operating curve.

Validation of prediction model

Regarding the validation set for ICU admission, subjects whose prognosis was too poor to be admitted to the ICU or who chose not to be intubated (n=11) were excluded from validation. In case of ICU admission, the multivariate logistic regression analysis based on the statistically significant predictors showed a sensitivity of 100%, a specificity of 64.7%, a PPV of 47.8% and an NPV of 100%. This corresponded with an AUC-ROC of 0.94 (95% CI 0.88–1.00). In long-term admission, a sensitivity of 88.5%, specificity of 25.0%, a PPV of 43.4% and an NPV of 76.9% were found, with an AUC-ROC of 0.63 (95% CI 0.49-0.77). For death, the model showed a sensitivity of 87.5%, a specificity of 58.6%, a PPV of 50.0% and a NPV of 97.1%. This corresponded with an AUC-ROC of 0.68 (95% CI 0.48-0.89) (Table 7).

TABLE 7 Predicting performance of the three investigated outcomes (Validating)

	Yes/no (%)	Cut-off	Sensitivity	Specificity	PPV	NPV	AUC-ROC	95% CI
ICU admission	11/34 (24.4%)	0.087	100%	64.7%	47.8%	100%	0.94	0.88-1.00
Long-term admission	26/40 (39.4%)	0.312	88.5%	25.0%	43.4%	76.9%	0.63	0.49-0.77
Death	8/58 (12.1%)	0.068	87.5%	58.6%	50.0%	97.1%	0.68	0.48-0.89

PPV: positive predictive value; NPV: negative predictive value; AUC-ROC: area under the receiver operating curve.

4. Discussion

This study investigated risk factors for ICU admission, long-term stay and mortality in hospitalized COVID-19 patients. To our knowledge, this is the first comprehensive overview of risk factors for those three outcomes on a Dutch COVID-19 cohort.

BMI, respiratory rate, pH, HCO_3, neutrophils, C-Reactive Protein and D-dimer are associated with ICU admission. Interestingly, unlike other studies (28,29), age was not found as a predictor for ICU admission. Furthermore, in another study only obesity (BMI ≥30 $kg \cdot m^{-2}$) was found as a predictor for ICU admission (30), whereas our result showed that being overweight (BMI 25-30 $kg \cdot m^{-2}$) was the strongest predictor for ICU admission. Zhao et al. (31) already showed that an elevated respiratory rate is significantly associated with ICU admission. No prior findings in literature were found about pH and HCO_3 values as predictors for ICU admission. This can perhaps be explained by the fact that a low pH and an abnormal HCO_3 are already an indication for ICU admission. It is very likely that these are process variables rather than predictors. Just as our study can confirm, Kiss et al. and Elshazli Id et al. (32,33) showed that increased neutrophils and C-Reactive Protein values were predictors for ICU admission. Like other studies (34,35), our model finds elevated D-dimer to be amongst the predictors for ICU admission.

The best predictors for long-term admission are age, use of immunosuppressive therapy, respiratory rate, pH, HCO_3 and D-dimer. No previous literature has investigated whether any of these variables are predictors of long-term hospitalization. In future studies, long-term hospitalization may be considered as a valuable outcome for hospital capacity management.

For death while hospitalized, the best predictors are age, male gender, sodium, D-dimer, and oxygen therapy. Several studies (36,37) demonstrated that increasing age and male gender were independently significant predictors for death while hospitalized. Tzoulis et al. (38) stated that abnormal sodium levels during hospitalization are risk factors for a poor prognosis, with hypernatremia (≥145 mmol/L) being associated with a greater risk of death (adjusted hazard ratio 2.34). This comes close to our hazard ratio of 2.12, with a lower cut-off of ≥136 mmol/L. A higher cut-off of ≥145 mmol/L in this study may resulted in a different hazard ratio. Soni et al. (39) showed that subjects with elevated D-dimer (≥2010 µg/L) had a much higher risk for death while hospitalized than subjects with a lower D-dimer (<2010 µg/L). They chose this value as optimum cut-off, calculated using the ROC curve. Our analysis indeed confirms that finding with nearly the same threshold (D-dimer ≥2286 µg/L). Oxygen therapy as a predictor for mortality was not found in previous literature. In our assumption, the need for oxygen therapy is caused by underlying suffering. The SpO_2 may be improved, but this does not necessarily apply to a patient's clinical condition. It is therefore too premature to use oxygen therapy as a predictor.

For ICU admission, long-term stay, and death while hospitalized, cut-offs considered based on the Youden index, a high sensitivity, and a high specificity. For ICU admission, a cut-off was chosen to obtain a high NPV, which attempts to diminish the probability that people are incorrectly referred to the ICU, given that subjects admitted to the ICU can develop a post-ICU syndrome (40). In the case of long-term admission, a cut-off point was chosen to obtain a high NPV, so that a clear estimate can be made of subjects who will be staying in hospital for a short-term. This could create a proper assessment of the patient flow. In death while hospitalized, a cut-off for a high NPV was chosen to rule out a subject’s death.

Limitations

This study had several limitations. Although our model identified some risk factors for ICU admission, long-term stay and mortality, these cannot be interpreted independently. These risk factors serve to determine the patient's treatment trajectory in combination with the decision of the attending physician. Another possible limitation is the fact that we considered people transferred to another hospital or with palliative discharge to be alive. This may give a biased view, as it is not known whether they were still alive. Furthermore, only clinical patient data at presentation were included in the study. Validation was performed with subjects from the same database as used for training. It would be preferable to at least redo the validation with an external dataset. It is also important to note that patient burden and available medical resources differ from hospital to hospital, both at a regional and global level. Additionally, in both ICU admission vs. general ward and death while hospitalized vs. discharged alive, there were imbalanced sample sizes between the groups as well as small sample sizes. It is therefore advisable to train this model again with data from other hospitals or regions. In addition, this was a single-centre study conducted on a relatively small population, and its confirmation on a larger, multicentre cohort is warranted to achieve generalisability. It was decided to choose a p-value ≤ 0.001 when selecting variables, so that not too many variables remained that had to be included in the final model. As a result, there is a considerable risk that potential predictors have been overlooked.

In conclusion, this study identified key predictors for ICU admission, long-term admission and death while hospitalized associated with hospitalized COVID-19 patients. Predictors for ICU admission are BMI, respiratory rate, pH, HCO_3, neutrophils, C-Reactive Protein and D-dimer. For long-term admission, predictors are age, use of immunosuppressive therapy, respiratory rate, pH, HCO_3 and D-dimer. Predictors for death while hospitalized are age, male gender, sodium, D-dimer, and oxygen therapy. These predictors have the potential to provide physicians to stratify patients based on risks so that they can triage COVID-19 patients more effectively.

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Appendix

Appendix 1

Complete descriptive tables of ICU admission vs. general admission, long-term admission vs. short-term admission and death while hospitalized vs. discharged alive.

TABLE 1 Characteristics of subjects admitted to general admission or ICU admission

	ICU admission (n=60)		General admission (n=143)		p-value
Demographics[*,+]					
Age, years	66.5	56.8-72.0	63.0	54.0-75.0	0.704
Male gender	47	78.3%	88	61.5%	0.021
BMI, $kg \cdot m^{-2}$, mean±SD	28.35	±1.87	28.12	±4.15	0.591
Symptoms[*,&]					
Fever	32	53.3%	99	69.2%	0.031
Cough	26	43.3%	63	44.1%	0.925
Sore throat	1	1.6%	24	16.8%	0.002
Rhinorrhea	8	13.1%	10	7.0%	0.147
Ear pain	0	0.0%	1	0.7%	1.000
Wheezing	1	1.6%	4	2.8%	1.000
Chest pain	4	6.6%	15	10.5%	0.394
Myalgia	8	13.1%	26	18.2%	0.399
Arthralgia	1	1.6%	2	1.4%	1.000
Malaise	29	48.3%	95	66.4%	0.016
Dyspnea	35	58.3%	100	69.9%	0.110
Lower chest wall indrawing	2	3.3%	1	0.7%	1.000
Headache	7	11.5%	38	26.6%	0.020
Confusion	4	6.6%	11	7.7%	1.000
Seizures	0	0.0%	2	1.4%	1.000
Abdominal pain	1	1.6%	20	14.0%	0.010
Vomiting	6	9.8%	31	21.7%	0.049
Diarrhea	10	16.4%	34	23.8%	0.262
Skin rash	1	1.6%	1	0.7%	0.505
Lymphadenopathy	0	0.0%	1	0.7%	1.000
Bleeding hemorrhage	1	1.6%	0	0.0%	0.296
Comorbidities[*,&]					
Chronic cardiac disease	9	14.8%	16	11.2%	0.451
Hypertension	16	26.2%	44	30.8%	0.384
Dyslipidemia	10	16.4%	7	4.9%	0.006
PAOD	3	4.9%	1	0.7%	0.078
Chronic pulmonary disease	2	3.3%	7	4.9%	1.000
Asthma	7	11.5%	18	12.6%	0.855
Chronic kidney disease	2	3.3%	9	6.3%	0.395
Liver disease	0	0.0%	1	0.7%	1.000
Mild liver disease	2	3.3%	0	0.0%	0.086
Chronic neurological disease	2	3.3%	4	2.8%	1.000
Malign neoplasm	10	16.4%	17	11.9%	0.360
Chronic hematologic disease	0	0.0%	2	1.4%	1.000
Obesity	7	11.5%	26	18.2%	0.251
Diabetes	16	26.2%	26	18.2%	0.173
Rheumatic disease	9	14.8%	12	8.4%	0.158
Dementia	0	0.0%	1	0.7%	1.000
Malnutrition	0	0.0%	2	1.4%	1.000
Myocardial infarct	7	11.5%	7	4.9%	0.082

Atrium fibrillation	15	24.6%	22	15.4%	0.105
CVA	3	4.9%	9	6.3%	1.000
OSAS	3	4.9%	7	4.9%	1.000
Muscle disease	2	3.3%	1	0.7%	0.209
Immuno-suppressive therapy	4	6.6%	9	6.3%	1.000
Auto-immune disease	6	9.8%	9	6.3%	0.384
Prior malignity	10	16.4%	21	14.7%	0.720
COPD	2	3.3%	11	7.7%	0.352
Cancer diagnosis	8	13.1%	18	12.6%	0.885
Lymphocytopenia	10	16.7%	28	19.6%	0.627
Other	11	18.0%	20	14.0%	0.432
Vital signs[+]					
Temperature, °C	38.0	37.1-38.8	37.9	37.2-38.6	0.450
Heart rate, beats/min	90.1	78.0-102	89.0	75.0-100	0.935
Respiratory rate, rate/min	22.7	20.0-29.5	20.0	16.0-24.0	0.009
Systolic blood pressure, mmHg	139	123-150	137	125-146	0.979
Diastolic blood pressure, mmHg	75.0	70.0-83.5	80.0	70.0-88.0	0.049
Oxygen saturation, %	94.3	92.1-97.0	96.0	94.0-97.0	0.011
Respiratory condition[+]					
SaO_2, %	94.0	91.0-96.8	94.0	92.0-96.0	0.146
pO_2, kPa	9.9	8.8-11.6	10.4	8.7-11.6	0.283
pCO_2, kPa	5.3	4.4-6.2	4.2	3.8-4.6	<0.001
pH value	7.44	7.37-7.49	7.48	7.45-7.51	<0.001
HCO_3, mEq/L	25.0	23.3-27.0	23.0	21.0-24.8	<0.001
Blood condition[+]					
Hemoglobin, mmol/L	8.1	7.1-8.8	8.6	7.9-9.2	<0.001
Hematocrits, %	39.0	35.0-42.0	41.4	38.0-44.0	0.001
Leukocytes, x 10^9/L	8.48	6.86-11.6	6.09	4.64-8.83	<0.001
Lymphocytes, x 10^9/L	0.64	0.40-0.98	1.04	0.72-1.39	0.235
Neutrophiles, cells/µL	6.99	5.76-10.3	4.49	3.35-6.12	<0.001
Thrombocytes, x 10^9/L	245	198-297	211	166-274	0.075
Glucose, mmol/L	7.8	6.7-9.2	7.7	6.4-8.8	0.358
Ureum, mmol/L	8.9	6.7-11.7	5.8	4.3-9.2	0.818
Creatinine, µmol/L	89.5	67.3-108	80.0	65.1-102	0.863
Sodium, mmol/L	136	135-141	135	133-138	<0.001
Potassium, mmol/L	4.1	3.9-4.4	3.9	3.6-4.2	0.005
C-Reactive Protein, mg/L	132	96.2-276	60.0	28.0-99.3	<0.001
D-dimer, µg/L	3740	2452-7136	1842	811-2693	<0.001
LDH, U/L	433	348-555	329	257-407	<0.001
CK, U/L	174	69.3-364	112	59.0-238	0.134
Ferritin, µg/L	2004	1180-3588	1044	671-1582	<0.001
Medication[*]					
Antivirals	20	32.8%	20	14.0%	0.002
Antibiotics	51	85.0%	100	69.9%	0.025
Corticosteroids	39	63.9%	60	42.0%	0.003
Side effects medication[&]	3	4.9%	6	4.2%	0.725
Length of stay[+] (days, mean±sd)	24	16-33	5	3-8	0.001
Outcomes[*,&]					
Discharged alive	32	52.5%	137	95.8%	<0.001
Transfer to other facility	12	19.7%	1	0.7%	<0.001
Palliative discharge	0	0.0%	0	0.0%	-

Death	16	26.7%	5	3.5%	<0.001
Treatment[*,&]					
Chloroquine	33	55.0%	34	23.8%	<0.001
Antivirals	14	23.0%	18	12.6%	0.055
Oxygen therapy	55	91.7%	92	64.3%	<0.001
Non-invasive ventilation	27	45.0%	30	21.0%	0.001
Invasive ventilation	52	85.2%	1	0.7%	<0.001
Inotropes or vasopressors	31	50.8%	0	0.0%	<0.001
Infection[*,&]					
Influenza	2	3.3%	2	1.4%	0.583
Bacteremia	17	28.3%	10	7.0%	<0.001
Clinical pneumonia	42	70.0%	64	44.8%	0.001
Complication due to treatment[*,&]					
Pulmonary	37	60.7%	4	2.8%	<0.001
Cardiac	12	19.7%	2	1.4%	<0.001
Hematologic	19	31.1%	6	4.2%	<0.001
Renal	14	23.0%	1	0.7%	<0.001
Other	24	39.3%	6	4.2%	<0.001
Radiology results[*]					
Chest X-ray infiltrates	39	65.6%	80	55.9%	0.232
CT thorax consistent with COVID-19	50	83.3%	60	42.0%	<0.001

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. [*]: Pearson χ^2-test; [+]: Student's t-test. [&]: Fisher's exact test for groups < 5.

TABLE 2 Characteristics of subjects in short-term admission or long-term admission

	Long-term (n=141)		Short-term (n=127)		p-value
Demographics[*,+]					
Age, years	70.0	61.5-76.0	64.0	54.0-76.0	0.004
Male gender	90	63.8%	82	64.6%	0.635
BMI, $kg \cdot m^{-2}$, mean±SD	28.13	±3.24	27.91	±3.91	0.900
Symptoms[*,&]					
Fever	85	60.3%	86	67.7%	0.206
Cough	55	39.0%	59	46.5%	0.218
Sore throat	11	7.8%	20	15.7%	0.042
Rhinorrhea	15	10.6%	9	7.1%	0.309
Ear pain	0	0.0%	1	0.8%	0.474
Wheezing	4	2.8%	6	4.7%	0.525
Chest pain	9	6.4%	12	9.4%	0.351
Myalgia	24	17.0%	20	15.7%	0.779
Arthralgia	2	1.4%	2	1.6%	1.000
Malaise	82	58.2%	84	66.1%	0.179
Dyspnea	86	61.0%	86	67.7%	0.252
Lower chest wall indrawing	2	1.4%	2	1.6%	1.000
Headache	20	14.2%	33	26.0%	0.015
Confusion	10	7.1%	16	12.6%	0.128
Seizures	3	2.1%	3	2.4%	1.000
Abdominal pain	8	5.7%	17	13.4%	0.030
Vomiting	24	17.0%	25	19.7%	0.573
Diarrhea	30	21.3%	25	19.7%	0.747
Skin rash	2	1.4%	1	0.8%	1.000
Lymphadenopathy	1	0.7%	0	0.0%	1.000
Bleeding hemorrhage	1	0.7%	0	0.0%	1.000
Comorbidities[*,&]					
Chronic cardiac disease	30	21.3%	19	15.0%	0.182
Hypertension	53	37.6%	38	29.9%	0.186
Dyslipidemia	20	14.2%	7	5.5%	0.019
PAOD	4	2.8%	1	0.8%	0.216
Chronic pulmonary disease	10	7.1%	10	7.9%	0.808
Asthma	11	7.8%	18	14.2%	0.094
Chronic kidney disease	11	7.8%	13	10.2%	0.486
Liver disease	2	1.4%	0	0.0%	0.499
Mild liver disease	2	1.4%	0	0.0%	0.499
Chronic neurological disease	11	7.8%	5	3.9%	0.182
Malign neoplasm	27	19.1%	16	12.6%	0.145
Chronic hematologic disease	4	2.8%	2	1.6%	0.486
AIDS / HIV	1	0.7%	0	0.0%	1.000
Obesity	21	14.9%	21	16.5%	0.712
Diabetes	40	28.4%	23	18.1%	0.048
Rheumatic disease	18	12.8%	9	7.1%	0.123
Dementia	3	2.1%	3	2.4%	1.000
Malnutrition	3	2.1%	0	0.0%	0.249
Myocardial infarct	17	12.1%	6	4.7%	0.032
Atrium fibrillation	35	24.8%	22	17.3%	0.134
CVA	17	12.1%	10	7.9%	0.256
OSAS	9	6.4%	6	4.7%	0.555
Muscle disease	3	2.1%	0	0.0%	0.249
Immunosuppressive therapy	16	11.3%	5	3.9%	0.024
Auto-immune disease	14	9.9%	7	5.5%	0.179

Prior malignity	32	22.7%	18	14.2%	0.074
COPD	10	7.1%	12	9.4%	0.483
Cancer diagnosis	26	18.4%	16	12.6%	0.239
Lymphocytopenia	28	19.9%	26	20.5%	0.900
Other	27	19.1%	18	14.2%	0.277
Vital signs[+]					
Temperature, °C	37.9	37.2-38.8	38.0	37.2-38.4	0.521
Heart rate, beats/min	90	76-102	88	75-98	0.647
Respiratory rate, rate/min	22	18-27	20	16-24	0.015
Systolic blood pressure, mmHg	137	124-150	136	123-145	0.542
Diastolic blood pressure, mmHg	76	68-84	80	73-87	0.008
Oxygen saturation, %	95	93-97	96	94-98	0.005
Respiratory condition[+]					
SaO_2, %	94	91-96	94	92-97	0.699
pO_2, kPa	10.1	8.6-11.5	10.2	8.7-11.5	0.281
pCO_2, kPa	4.6	4.2-5.3	4.3	3.8-4.6	<0.001
PH value	7.46	7.41-7.49	7.47	7.44-7.50	0.001
HCO_3, mEq/L	24.1	22.0-26.0	23.0	21.0-24.3	0.004
Blood condition[+]					
Hemoglobin, mmol/L	8.1	7.2-9.0	8.5	7.7-9.1	0.001
Hematocrits, %	39.0	36.0-43.0	41.0	38.0-44.0	0.006
Leukocytes, x 10^9/L	7.29	5.27-10.10	6.29	4.87-8.48	0.057
Lymphocytes, x 10^9/L	0.80	0.53-1.07	1.03	0.68-1.36	0.063
Neutrophiles, cells/µL	5.86	4.19-8.31	4.68	3.38-6.56	0.007
Thrombocytes, x 10^9/L	217.0	158-284	228	177-273	0.784
Glucose, mmol/L	7.9	6.6-9.9	7.5	6.3-8.6	0.001
Ureum, mmol/L	8.6	5.8-11.5	5.9	4.3-10.5	0.504
Creatinine, µmol/L	90.0	69.5-113	84.0	69.0-104	0.403
Sodium, mmol/L	136	134-140	135	133-138	<0.001
Potassium, mmol/L	4.1	3.8-4.4	4.0	3.7-4.3	0.006
C-Reactive Protein, mg/L	99.3	49.0-176	60.0	25.0-99.3	<0.001
D-dimer, µg/L	2728	1685-4869	1882	941-2669	<0.001
LDH, U/L	379	298-487	325	254-406	<0.001
CK, U/L	153	70-284	113	60.0-284	0.409
Ferritin, µg/L	1560	883-2309	1014	671-1582	<0.001
Medication[*]					
Antivirals	38	27.0%	13	10.2%	0.001
Antibiotics	111	78.7%	90	70.9%	0.138
Corticosteroids	82	58.2%	47	37.0%	0.001
Length of stay[+]	14	9-24	4	2-5	<0.001
ICU admission[&] **(days, mean±sd)**	58	41.1%	3	2.4%	<0.001
Outcomes[*,&]					
Discharged alive	93	66.0%	109	85.8%	<0.001
Transfer to other facility	4	2.8%	2	1.6%	0.004
Palliative discharge	1	0.7%	0	0.0%	1.000
Death	33	23.4%	16	12.6%	0.022
Treatment[*,&]					
Chloroquine	54	38.3%	31	24.4%	0.015
Antivirals	29	20.6%	13	10.2%	0.020
Oxygen therapy	116	82.3%	81	63.8%	0.001

Non-invasive ventilation	48	34.0%	24	18.9%	0.005
Invasive ventilation	52	36.9%	1	0.8%	<0.001
Inotropes or vasopressors	32	22.7%	0	0.0%	<0.001
Infection[*,&]					
Influenza	3	2.1%	1	0.8%	0.366
Bacteremia	27	19.1%	7	5.5%	0.001
Clinical pneumonia	73	51.8%	61	48.0%	0.541
Complication due to treatment[*,&]					
Pulmonary	42	29.8%	4	3.1%	<0.001
Cardiac	16	11.3%	1	0.8%	<0.001
Hematologic	23	16.3%	4	3.1%	<0.001
Renal	16	11.3%	2	1.6%	0.001
Other	34	24.1%	5	3.9%	<0.001
Radiology results[*]					
Chest X-ray infiltrates	83	58.9%	71	55.9%	0.625
CT thorax consistent with COVID-19	87	61.7%	47	37.0%	<0.001

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. [*]: Pearson χ^2-test; [+]: Student's t-test. [&]: Fisher's exact test for groups < 5.

TABLE 3 Characteristics of subjects who discharged alive or who died while hospitalized

	Death (n=49)		Alive (n=219)		p-value
Demographics[*,+]					
Age, years	77.0	69.0-83.0	66.0	56.0-75.0	<0.001
Male gender	39	79.6%	133	60.7%	0.013
BMI, $kg \cdot m^{-2}$, mean±SD	27.5	±2.6	28.1	±3.8	0.299
Symptoms[*,&]					
Fever	33	67.3%	138	63.0%	0.568
Cough	17	34.7%	97	44.3%	0.219
Sore throat	2	4.1%	29	13.2%	0.084
Rhinorrhea	6	12.2%	18	8.2%	0.372
Ear pain	0	0.0%	1	0.5%	1.000
Wheezing	3	6.1%	7	3.2%	0.397
Chest pain	1	2.0%	20	9.1%	0.139
Myalgia	4	8.2%	40	18.3%	0.092
Arthralgia	1	2.0%	3	1.4%	0.556
Malaise	24	49.0%	142	64.8%	0.039
Dyspnea	31	63.3%	141	64.4%	0.883
Lower chest wall indrawing	2	4.1%	2	0.9%	0.154
Headache	3	6.1%	50	22.8%	0.006
Confusion	5	10.2%	21	9.6%	0.895
Seizures	3	6.1%	3	1.4%	0.077
Abdominal pain	1	2.0%	24	11.0%	0.057
Vomiting	6	12.2%	43	19.6%	0.226
Diarrhea	8	16.3%	47	21.5%	0.421
Skin rash	0	0.0%	3	1.4%	1.000
Lymphadenopathy	0	0.0%	1	0.5%	1.000
Bleeding hemorrhage	0	0.0%	1	0.5%	1.000
Comorbidities[*,&]					
Chronic cardiac disease	17	34.7%	32	14.6%	0.001
Hypertension	18	36.7%	73	33.3%	0.649
Dyslipidemia	7	14.3%	20	9.1%	0.279
PAOD	2	4.1%	3	1.4%	0.227
Chronic pulmonary disease	6	12.2%	14	6.4%	0.159
Asthma	3	6.1%	26	11.9%	0.314
Chronic kidney disease	7	14.3%	17	7.8%	0.148
Liver disease	2	4.1%	0	0.0%	0.033
Mild liver disease	0	0.0%	2	0.9%	1.000
Chronic neurological disease	8	16.3%	8	3.7%	0.001
Malign neoplasm	10	20.4%	33	15.1%	0.357
Chronic hematologic disease	2	4.1%	4	1.8%	0.302
AIDS / HIV	1	2.0%	0	0.0%	0.183
Obesity	6	12.2%	36	16.4%	0.465
Diabetes	14	28.6%	49	22.4%	0.355
Rheumatic disease	4	8.2%	23	10.5%	0.795
Dementia	3	6.1%	3	1.4%	0.077
Malnutrition	2	4.1%	1	0.5%	0.087
Myocardial infarct	8	16.3%	15	6.8%	0.032
Atrium fibrillation	13	26.5%	44	20.1%	0.319
CVA	10	20.4%	17	7.8%	0.008
OSAS	3	6.1%	12	5.5%	0.742
Muscle disease	0	0.0%	3	1.4%	1.000
Immunosuppressive therapy	4	8.2%	17	7.8%	1.000
Auto-immune disease	3	6.1%	18	8.2%	0.775

Prior malignity	14	28.6%	36	16.4%	0.049
COPD	5	10.2%	17	7.8%	0.574
Cancer diagnosis	11	22.4%	31	14.2%	0.149
Lymphocytopenia	9	18.4%	45	20.5%	0.731
Other	11	22.4%	34	15.5%	0.241
Vital signs[+]					
Temperature, °C	38.0	37.4-38.7	37.9	37.2-38.6	0.287
Heart rate, beats/min	91.0	87.0-95.0	89.0	75.0-100.0	0.615
Respiratory rate, rate/min	23.0	19.1-29.0	20.0	16.0-24.0	0.025
Systolic blood pressure, mmHg	137	121-151	136	124-146	0.658
Diastolic blood pressure, mmHg	78.0	71.5-82.5	79.0	70.0-87.0	0.613
Oxygen saturation, %	94.0	91.0-97.0	96.0	94.0-97.0	0.047
Respiratory condition[+]					
SaO_2, %	93.0	90.9-95.3	94.0	92.0-96.0	0.654
pO_2, kPa	9.5	8.3-11.7	10.2	8.7-11.5	0.734
pCO_2, kPa	4.6	4.2-5.7	4.4	3.9-4.8	0.007
PH value	7.45	7.39-7.47	7.46	7.44-7.50	0.001
HCO_3, mEq/L	23.8	20.5-27.5	23.8	21.3-25.0	0.538
Blood condition[+]					
Hemoglobin, mmol/L	7.9	6.9-8.6	8.3	7.6-9.1	0.011
Hematocrits, %	39.0	35.0-44.0	40.0	38.0-44.0	0.135
Leukocytes, x 10^9/L	7.58	5.56-10.15	6.75	5.05-8.99	0.098
Lymphocytes, x 10^9/L	0.76	0.51-1.04	0.95	0.61-1.22	0.761
Neutrophiles, cells/µL	6.36	4.40-8.94	5.09	3.53-7.02	0.038
Thrombocytes, x 10^9/L	219	157-316	226	167-275	0.661
Glucose, mmol/L	7.6	6.3-9.8	7.7	6.4-9.1	0.480
Ureum, mmol/L	12.3	8.7-15.8	6.6	4.5-10.5	0.714
Creatinine, µmol/L	114.0	93.0-151	82.0	66.0-104	0.023
Sodium, mmol/L	139	136-142	136	133-138	<0.001
Potassium, mmol/L	4.3	3.8-4.6	4.0	3.7-4.3	0.001
C-Reactive Protein, mg/L	107	66.5-167	70.0	33.0-118	0.005
D-dimer, µg/L	2978	2053-5568	2065	1387-2741	0.003
LDH, U/L	406	328-501	341	259-427	0.002
CK, U/L	222	110-397	110	58.0-280	0.242
Ferritin, µg/L	1580	978-3165	1151	690-1670	0.017
Medication[*]					
Antivirals	20	40.8%	31	14.2%	<0.001
Antibiotics	47	95.9%	154	70.3%	<0.001
Corticosteroids	32	65.3%	97	44.3%	0.008
Length of stay[+] **(days, mean±sd)**	9	5-17.5	6	4-14	0.572
Outcomes[*,&]					
Discharged alive	0	0.0%	202	92.2%	<0.001
Transfer to other facility	0	0.0%	16	7.3%	0.049
Palliative discharge	0	0.0%	1	0.5%	1.000
Death	49	100.0%	0	0.0%	<0.001
Treatment[*]					
Chloroquine	15	30.6%	70	32.0%	0.854
Antivirals	16	32.7%	26	11.9%	<0.001
Oxygen therapy	43	87.8%	154	70.3%	0.012
Non-invasive ventilation	18	36.7%	54	24.7%	0.085
Invasive ventilation	16	32.7%	37	16.9%	0.012

Inotropes or vasopressors	6	12.2%	26	11.9%	0.942
Infection[*,&]					
Influenza	2	4.1%	2	0.9%	0.154
Bacteremia	8	16.3%	26	11.9%	0.397
Clinical pneumonia	21	42.9%	113	51.6%	0.269
Complication due to treatment[*]					
Pulmonary	14	28.6%	32	14.6%	0.019
Cardiac	5	10.2%	12	5.5%	0.220
Hematologic	8	16.3%	19	8.7%	0.108
Renal	7	14.3%	11	5.0%	0.019
Other	11	22.4%	28	12.8%	0.083
Radiology results[*]					
Chest X-ray infiltrates	34	69.4%	120	54.8%	0.062
CT thorax consistent with COVID-19	30	61.2%	104	47.5%	0.082

Data are presented as median with interquartile range or n (%) unless otherwise stated. BMI: body mass index; SD; standard deviation. [*]: Pearson χ^2-test; [+]: Student's t-test. [&]: Fisher's exact test for groups < 5.

Appendix 2

Kaplan-Meier curves of all relevant predictors for death while hospitalized.