Prognosis score system to predict survival outcome of COVID-19: a Korean nationwide cohort study

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Abstract

Background: As the coronavirus disease 2019 (COVID-19) pandemic continues, initial risk-adapted allocation is crucial for managing medical resources and providing intensive care.

Objective: This study aimed to identify factors that predict COVID-19 mortality and develop a COVID-19 prognosis score (COPS) based on these factors.

Methods: This study retrospectively analyzed nationwide cohort of laboratory-confirmed COVID-19 cases between January and April 2020 in Korea. This study identified factors associated with mortality, subsequently constructing a multivariable model to develop the scoring system. Each variable's score in the COPS system was a log-scaled converted value of the adjusted odds ratio.

Results: Among the 5,594 patients included in this analysis, 234 died after COVID-19 diagnosis. Survivors stayed in a hospital significantly longer than non-survivors (26.1±10.7 vs. 15.6±13.3 days); moreover, length of hospital stay and disease severity were directly associated in survivors (P<.001). Twelve parameters were significantly related to mortality: advanced age; male sex; heart rate ?110/min; dyspnea, and mental disturbance; diabetes; chronic renal failure; cancer in active treatment; dementia; and cytopenia (hemoglobin <12.5 g/dL, absolute lymphocyte count <1,000/mm3, and platelet count <100,000/mm3). Accordingly, the COPS system was developed and risk groups were created: very low-risk (score ?3.72), low-risk (3.73–4.96), intermediate-risk (4.97–6.20), high-risk (6.21–8.68), and very high-risk (>8.68), presenting mortality probabilities of 0.1%, 4.5%, 17.8%, 41.3%, and 83.3%, respectively (P<.001). Receiver operating characteristics curve analysis achieved an area under the curve of 0.959.

Conclusions: The newly developed predictive COPS system may assist in risk-adapted decisions for medical resources allocation, including intensive care, during the COVID-19 pandemic.

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Prognosis score system to predict survival outcome of COVID-19: a Korean nationwide cohort study

Abstract

Background: As the coronavirus disease 2019 (COVID-19) pandemic continues, initial risk-adapted allocation is crucial for managing medical resources and providing intensive care. This study aimed to identify factors that predict COVID-19 overall survival rate and develop a COVID-19 prognosis score (COPS) based on these factors. Also, severity of patients' illness and length of hospital stay were analyzed.

Methods: This study retrospectively analyzed nationwide cohort of laboratory-confirmed COVID-19 cases between January and April 2020 in Korea. The cohort was split randomly into the development cohort and the validation cohorts with 2:1 ratio. In the development cohort (n=3,729), we tried to identify factors associated with overall survival (OS) and create a scoring system to predict OS using identified parameters by Cox proportional hazard regression model with bootstrapping methods. The prediction accuracy was evaluated in the validation cohort (n=1,865) using the area under the curve (AUC) by receiver operating characteristics curves. Each variable's score in the COPS system was rounded off following the log-scaled conversion of the adjusted hazard ratio.

Results: Among the 5,594 patients included in this analysis, 234 died after COVID-19 diagnosis. In the development cohort, six parameters were significantly related to poor overall survival: advanced age; dementia; chronic renal failure; dyspnea; mental disturbance; and absolute

lymphocyte count <1,000 /mm^3. Afterward, the COPS system was developed, and risk groups were created: low-risk (score, 0-2), intermediate-risk (score, 3), high-risk (score, 4), and very high-risk (score, 5-7). The COPS system yielded an AUC of .918 for predicting 14-days survival rate and .896 for predicting 28-days survival rate in the validation cohort. Using the COPS system, 28-days overall survival rates were discriminatively estimated as 99.8%, 95.4%, 82.3%, and 55.1% in low-risk, intermediate-risk, high risk, and very high-risk groups in the total cohort, respectively (P <.001). Length of hospital stay and disease severity were directly associated with the survivors (P <.001), and survivors stayed in a hospital significantly longer than non-survivors (26.1±10.7 vs. 15.6±13.3 days).

Conclusions: The newly developed predictive COPS system may assist in risk-adapted decisions for medical resources allocation, including intensive care, during the COVID-19 pandemic.

Keywords: COVID-19; length of stay; mortality; prognosis; triage; digital health

Introduction

Since the outbreak of unexplained pneumonia in Wuhan, China in December 2019, which was subsequently identified as the coronavirus disease (COVID-19) caused by the newly discovered pathogen severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the COVID-19 pandemic remains active in over 180 countries [1, 2]. Globally, as of November 6, 2020, 1,231,017 out of 48,534,508 COVID-19 confirmed patients have died, representing an overall infection-fatality rate of 2.54% [3, 4]. The clinical spectrum of COVID-19 includes asymptomatic or pre-symptomatic, upper and lower respiratory tract infections, and acute respiratory distress syndrome (ARDS) [5-8]. Although the majority of viral infections are self-limiting, severe (*i.e.* dyspnea, hypoxia, or >50% of lung involvement on imaging within 24–48 h) or critical (*i.e.* respiratory failure, shock, or multiple organ failure) COVID-19 cases are global concerns and require medical resources for intensive care. The proportion of severe or critical cases and case-fatality rate vary by region and country, ranging from 10–30% [8-10] and 2–10%, respectively [3, 4].

Most severe or critical cases occur in older patients or those with underlying comorbidities such as cancer, chronic obstructive pulmonary diseases, heart failure, or diabetes [11-13]. The clinical course of COVID-19 patients also depends on multiple factors, including immune status of the host, viral load of SARS-CoV-2, genetic diversity of the virus, and underlying diseases. However, details of viral factors and host immune status (*e.g.* patient-released cytokines) are difficult to analyze in a real-world setting. Therefore, prognosis prediction systems should comprise basic factors such as initial symptoms at diagnosis, vital signs, hemogram parameters, and major underlying comorbidities.

As the global pandemic continues, the ability to timely detect COVID-19 patients with a high risk of death and provide them with intensive care is important. Accordingly, the assessment of disease severity or mortality probability can be used to establish a sustainable strategy. Therefore, this study aimed to develop an easy and simple scoring system that can predict COVID-19 mortality according to initial presentation and several major underlying comorbidities. Additionally, this study investigated the length of hospital stay according to disease severity and survival status of patients.

Methods

Study design and data source

This was a nationwide retrospective cohort study on COVID-19 cases in Korea. This study defined COVID-19 cases based on laboratory confirmation of infection and positive results on SARS-

CoV-2 reverse transcription polymerase chain reaction assays using the Korea Ministry of Food and Drug Safety approved kit, irrespective of clinical signs and symptoms [14, 15]. Clinical data of patients in this cohort were managed by the Korea Disease Control and Prevention Agency (KDCA) and disclosed to researchers after application and permission for research purposes in July 2020. The released clinical and epidemiological information included 5,628 COVID-19 cases collected between January and April 2020. The KDCA is an organization that aims to protect the population from diseases—including emerging infectious diseases such as COVID-19—through national surveillance, healthcare research, and promotion of policies regarding disease prevention management. Patient data included demographic and epidemiological characteristics, hemogram parameters at admission, maximal severity, and clinical outcome obtained from designated hospitals. Patients in the final cohort were randomly allocated, two-thirds into the "development cohort" and the remaining third to the "the validation cohort," using a random number generator: The predictive score was developed from the development cohort whereas the power of prediction was explored in the validation cohort.

This study was approved by the institutional review board of Seoul St. Mary's Hospital, Seoul, Korea (KC20ZADI0654). Individual patient consent was waived due to the anonymity and publicity of the data.

COVID-19 management setting

In Korea, all suspected or confirmed cases of COVID-19 should be reported to the KDCA as part of the notifiable infectious diseases. All laboratory-confirmed COVID-19 patients were admitted to designated hospitals or residential treatment centres for isolation, monitoring of symptoms, and treatment. Clinical severity was categorized into eight levels according to patient performance, oxygen requirement, and organ failure as follows [16]: (1) no limit of activity, (2) limited activity without oxygen supplementation, (3) requirement of oxygen supply with nasal cannula, (4) requirement of oxygen supply with facial mask, (5) requirement of non-invasive ventilation, (6) requirement of invasive ventilation, (7) requirement of ECMO for multiple organ failure, or (8) death. Death outcomes were evaluated regardless of maximum severity. Cases that required oxygen supply with invasive ventilation or ECMO were defined as invasive intensive care.

Statistical analysis

Normally distributed numerical variables are shown as mean ± standard deviation. Categorical variables are shown as numbers (%). Student's *t-test* was used to compare the hospital stay duration of two independent groups. Overall survival (OS) was defined as the time from COVID-19 diagnosis to death from any cause or date of the last follow-up; death event was censored at the time of hospital discharge for a subject who was discharged. OS rates at 14 days and 28 days were calculated using the Kaplan-Meier method and compared using the Log-rank test.

Within the development cohort, all risk factors with a *P* value < .05 in the univariable analysis were entered into the multivariable model to identify factors associated with OS: multivariable analysis was performed using the Cox proportional hazard regression model. We identified potential variables for the final prediction model based on 2,000 bootstrap sampled datasets; when a parameter occurred in 60% or more of the bootstrap models, it was evaluated in the final multiple logistics regression model. We then computed the hazard ratio (HR), 95% confidence interval (CI), and *P*-value of all metrics over the bootstrapped datasets in the final regression model. The final parameters used in the scoring system were defined by a *P* value <.05 in the final regression model; to confirm the risk score for each significant parameter, we adjusted the HR values to a Log_e scale, followed by the conversion of the respective Log_e scale to a rounded

integer point. In the validation cohort, the area under the curve (AUC) of the receiver operating characteristics (ROC) curve was measured to evaluate the prediction accuracy of the survival rates after 14 and 28 days. A value above 0.8 of AUC was considered reliable. Among the developed risk groups, we compared the hospitalized days using one-way ANOVA. For all statistical analysis, this study used R statistical software (ver. 3.6.1, R Foundation for Statistical Computing, Vienna, Austria, 2019). Statistical significance was set at $P < .05$.

Results

Patient Characteristics

In total, 5,628 COVID-19 confirmed cases occurred between January and April 2020. Cases with post-mortem diagnosis (n=7) or lack of clinical course data after diagnosis (n=27) were excluded from the analysis. As shown in Figure 1, 5,594 COVID-19 patients were included in this cohort. Overall, 41.2% of patients were male (n=2,307), and 52.2% were 50 years old or older (n=2,919). Baseline demographics are summarized in Table 1. In the total cohort, the most frequent age distribution was 50–59 years (n=1,140, 20.4%), followed by 20–29 years (n=1,110, 19.8%), and 60–69 years (n=905, 16.2%). Frequent symptoms were sputum (n=1,610, 28.8%), fever (n=1,300, 23.2%), and dyspnea (n=662, 11.8%). Common underlying comorbidities were hypertension (n=1,196, 21.4%) and diabetes (n=686, 12.3%). Moreover, 224 (4.0%) patients had dementia and 179 (3.2%) had cardiac diseases. Distribution of these variables between the validation (n=3,729) and development cohorts (n=1,865) are listed in table 1.

Clinical course, outcome, and length of hospital stay in the total cohort

Among the 5,594 patients included in the analysis, 234 died after COVID-19 diagnosis, resulting in a cohort infection-fatality rate of 4.2%. Excluding death, the maximal clinical severity during hospitalization was as follows: (1) no limit of activity in 4,455 (79.6%) patients, (2) limited activity without oxygen supplementation in 330 (5.9%) patients, (3) requirement of oxygen supply with nasal cannula in 469 (8.4%) patients, (4) requirement of oxygen supply with facial mask, or (5) advanced device (such as non-invasive ventilation or high flow oxygen therapy) in 76 (1.4%) patients, and invasive intensive care such as (6) invasive ventilation for ARDS or (7) extracorporeal membrane oxygenation (ECMO) for multiple organ failure in 30 (0.5%) patients (Figure 2).

Overall, The duration of hospital stay was 25.6±11.0 days. Hospital stay was significantly longer in survivors (26.1±10.7 days) than that in non-survivors (15.6±13.3 days) (P <.001). As shown in Figure 2, among survivors, the higher the severity of clinical course, the longer the hospitalization duration: 25.4±10.2, 27.6±10.6, 29.8±12.0, 32.5±14.0, and 41.0±15.4 days for the no limit of activity, limit of activity without oxygen supplement, oxygen supply with nasal cannula, oxygen supply with facial mask or advanced device, and invasive intensive care groups, respectively.

Analysis of factors associated with overall survival in the development cohort

The univariable analysis identified the following potential factors associated with poor OS: age (≥70 or 50–69 years compared to <50 years); male sex; comorbidities such as hypertension, diabetes, dementia, chronic cardiac disease, cancer in active treatment, chronic pulmonary disease, and chronic renal failure; dyspnea, fatigue, mental disturbance, high systolic blood pressure (≥140 mmHg), lower diastolic blood pressure (<80 mmHg), tachycardia (heart rate ≥110/min), and fever (≥38℃) at diagnosis; and cytopenia (hemoglobin level <12.5 g/dL, absolute lymphocyte counts [ALCs] <1,000 /mm^3, and platelet count <100,000 /mm^3) as shown in table 2.

COVID-19 prognosis score (COPS) for predicting overall survival

In the bootstrap analysis, we identified that advanced age (50–69, or ≥70 years), and comorbidities including dementia, chronic renal failure, presentation of dyspnea, mental disturbance at diagnosis, and ALCs <1,000 /mm^3 were significantly associated with poor OS. Assigned risk scores obtained by rounding the Log-scale of hazard ratio are shown in Table 3: age (50–69 years, 2 points; ≥70 years, 3 points), underlying dementia (1 point), chronic renal failure (1 point), dyspnea (1 point), mental disturbance (1 point), ALCs <1,000/mm^3 (1 point). We developed COPS (COVID-19 Prognosis Score), using the obtained risk score for each subject by summing the respective score of the six parameters. The total prediction score ranged between 0 and 8.

We explored the clinical prediction score in the validation cohort using ROC curve analysis. It achieved an AUC of .918 (95% CI, .91-.927) for 14-day survival rate and .896 (95% CI, .872-.911) for 28-day survival rate, indicating a reliable discrimination through the COPS system (Figure 3).

Thereafter, we applied the scoring system to the total cohort, which resulted in a score range of 0 – 7 points (Figure 4A). Scoring system discriminately divided patients into eight score groups: 28-day OS rates were predicted as 99.9% (95% CI, 99.7-100) in the 0-point group (n=2,348), 99.7% (95% CI, 99.1-100) in the 1-point group (n=317), 99.6% (95% CI, 92.9-99.9) in the 2-point group (n=1,511), 95.4% (95% CI, 93.9-97.1) in the 3-point group (n=815), 82.3% (95% CI, 78.5-86.4) in the 4-point group (n=395), 60.0% (95% CI, 39.2-52.8) in the 5-point group (n=170), 32.9% (95% CI, 20.6-52.7) in the 6-point group (n=36), and 50.0% (95% CI, 12.5-100) in the 7-point group (n=2), as shown in Figure 4A (*P* <.001). We then determined the risk groups of the final COPS system including the low-risk group (0-2 points, n=4,167) with 99.8% (95% CI, 99.6-99.9) 28-day OS rate, the intermediate-risk group (3 points, n=774) with 95.4% (95% CI, 93.9-97.1) 28-day OS rate, the high-risk group (4 points, n=321) with 82.3% (95% CI, 78.5-86.4) 28-day OS rate, and the very-high risk group (≥ 5 points, n=98) with 55.1% (95% CI, 48.5-62.5) 28-day OS rate (Figure 4B, *P*<.001). The developed COPS calculator is presented in the online calculator at https://ymdtech.kr/covid19-os.

Also, there was a significant trend of longer hospital days as the risk group advanced: 25.4 ± 10.4 days in the low-risk, 27.2 ± 10.9 days in the intermediate-risk group, and 30.8 ± 11.9 days in the high-group or very high-risk groups, respectively (*P* <.001).

Table 1. Demographics of cohorts

Variables	Total Cohort (N= 5,594)	Sub-cohorts	
		Development cohort (n=3,729)	Validation cohort (n=1,865)
Age			
0 - 9 years	66 (1.2%)	46 (1.2%)	20 (1.1%)
10 - 19 years	205 (3.7%)	146 (3.9%)	59 (3.2%)
20 - 29 years	1,110 (19.8%)	725 (19.4%)	385 (20.6%)
30 - 39 years	564 (10.1%)	378 (10.1%)	186 (10.0%)
40 - 49 years	739 (13.2%)	487 (13.1%)	252 (13.5%)
50 - 59 years	1,140 (20.4%)	768 (20.6%)	372 (19.9%)
60 - 69 years	905 (16.2%)	605 (16.2%)	300 (16.1%
70 - 79 years	542 (9.7%)	364 (9.8%)	178 (9.5%)
≥ 80 years	323 (5.8%)	210 (5.6%)	113 (6.1%)
Male, n (%)	2,307 (41.2%)	1,536 (41.2%)	1,094 (58.7%)
Comorbidity			
Hypertension (missing n=3)	1,196 (21.4%)	795 (21.3%)	401 (21.5%)
Diabetes (missing n=3)	686 (12.3%)	452 (12.1%)	234 (12.5%)
Dementia (missing n=329)	224 (4.0%)	150 (4.0%)	74 (4.0%)
Cardiac disease (missing n=19)	179 (3.2%)	122 (3.3%)	57 (3.1%)
Cancer in active treatment[†] (missing n=4)	143 (2.6%)	90 (2.4%)	53 (2.8%)
Asthma (missing n=3)	128 (2.3%)	82 (2.2%)	46 (2.5%)
Chronic hepatic disease[‡] (missing n=326)	82 (1.5%)	47 (1.3%)	35 (1.9%)
Heart failure (missing n=3)	58 (1.0%)	36 (1.0%)	22 (1.2%)
Chronic renal failure (missing n=3)	55 (1.0%)	36 (1.0%)	19 (1.0%)
Chronic obstructive lung disease (missing n=3)	40 (0.7%)	25 (0.7%)	15 (0.8%)

Autoimmune disease (missing n=332)	38 (0.7%)	31 (0.8%)	7 (0.4%)
Symptoms (missing n=4)			
Sputum	1,610 (28.8%)	1,114 (29.9%)	496 (26.6%)
Fever	1,300 (23.2%)	852 (22.8%)	448 (24.0%)
Dyspnea	662 (11.8%)	454 (12.2%)	208 (11.2%)
Diarrhea	516 (9.2%)	345 (9.3%)	171 (9.2%)
Nausea/vomiting	244 (4.4%)	168 (4.5%)	76 (4.1%)
Fatigue	233 (4.2%)	164 (4.4%)	69 (3.7%)
Mental disturbance	32 (0.6%)	22 (0.6%)	10 (0.5%)
Systolic blood pressure (missing n=135)			
<120 mmHg	1,306 (23.3%)	907 (24.3%)	399 (21.4%)
120 - 129 mmHg	1,138 (20.3%)	733 (19.7%)	405 (21.7%)
130 - 139 mmHg	1,084 (19.4%)	705 (18.9%)	379 (20.3%)
140 - 159 mmHg	1,418 (25.3%)	960 (25.7%)	458 (24.6%)
≥160 mmHg	513 (9.2%)	330 (8.8%)	183 (9.8%)
Diastolic blood pressure (missing n=135)			
<80 mmHg	2,102 (37.6%)	1,401 (37.6%)	701 (37.6%)
80 - 89 mmHg	1,797 (32.1%)	1,201 (32.2%)	596 (32.0%)
90 - 99 mmHg	1,056 (18.9%)	686 (18.4%)	370 (19.8%)
≥ 100 mmHg	504 (9.0%)	347 (9.3%)	157 (8.4%)
Heart rate (missing n=122)	85.8 ± 15.1	85.8 ± 15.1	85.8 ± 15.1
<110 /min	5,136 (91.8%)	3,374 (90.5%)	1,709 (91.6%)
≥110 / min	336 (6.0%)	272 (7.3%)	117 (6.3%)
Body temperature (missing n=37)	36.9 ± 0.6	36.9 ± 0.6	36.9 ± 0.6
<38℃	5,348 (95.6%)	3,523 (94.5%)	1,752 (93.9%)
≥38℃	209 (3.7%)	179 (4.8%)	103 (5.5%)
Baseline hemogram			
Hemoglobin (missing n=1519)	13.3 ± 1.8	13.3 ± 1.7	13.3 ± 1.8
≥12.5 g/dL	2,882 (51.5%)	1,923 (51.6%)	959 (51.4%)
<12.5 g/dL	1,193 (21.3%)	773 (20.7%)	420 (22.5%)
Absolute lymphocyte count (missing n=1542)	1,691 ± 1,054	1,697 ± 955	1,681 ± 1,225
≥1,000/mm^3	3,266 (58.4%)	2,161 (58.0%)	1,105 (59.2%)
<1,000/mm^3	786 (14.1%)	518 (13.9%)	268 (14.4%)
Platelet count (missing n=1517)	236,814 ± 82,846	238,377 ± 82,789	233,760 ± 82,900
≥100,000/mm^3	3,986 (71.3%)	2,634 (70.6%)	1,352 (72.5%)
<100,000/mm^3	91 (1.6%)	62 (1.7%)	29 (1.6%)
Median follow-up, days (95% CI)	25 (24-25)	25 (24-25)	25 (24-25)

Data are presented as n (%) or mean ± SD (standard deviation). All values are data at the time of COVID-19 diagnosis.
[†]Cases that achieved complete cure of cancer were excluded.
[‡]Cases with chronic hepatitis were included in this category.

Table 2. Univariable analysis for potential factors associated with overall survival in the development cohort

	N	Overall survival rate (95% CI)		*p*
		At 14 days	At 28 days	
Age				<.001
< 50 years	1,782	99.9% (99.8-100)	99.8% (99.5-100)	
50 - 69 years	1,373	98.6% (98.0-99.2)	98.0% (97.2-98.8)	
≥ 70 years	574	87.0% (84.3-89.8)	81.6% (78.3-85.0)	
Sex				0.013
Female	2,193	97.8% (97.2-98.4)	96.8% (96.0-97.6)	
Male	1,536	96.9% (96.0-97.8)	95.2% (94.1-96.4)	
Comorbidity				
Hypertension				<.001
No	2,932	98.7% (98.3-99.1)	98.0% (97.4-98.6)	
Yes	795	92.7% (90.9-94.6)	89.7% (87.4-91.9)	
Diabetes				<.001
No	3,275	98.3% (97.8-98.7)	97.3% (96.7-98.0)	
Yes	452	91.5% (88.9-94.1)	88.1% (85.0-91.3)	
Dementia				<.001

No	3,359	98.3% (97.9-98.7)	97.3% (96.7-97.9)	
Yes	150	74.5% (67.8-81.8)	67.4% (60.1-75.6)	
Chronic cardiac disease[†]				<.001
No	3,582	97.7% (97.2-98.2)	96.7% (96.0-97.3)	
Yes	147	91.1% (86.6-95.8)	85.8% (79.9-92.0)	
Cancer in active treatment				0.034
No	3,636	97.5% (97.0-98.0)	96.3% (95.7-97.0)	
Yes	90	95.5% (91.2-99.9)	89.8% (82.5-97.7)	
Chronic pulmonary disease[‡]				<.001
No	3,628	97.6% (97.1-98.1)	96.5% (95.9-97.2)	
Yes	101	92.0% (86.8-97.5)	85.3% (77.9-93.3)	
Chronic hepatic disease				.6
No	3,463	97.3% (96.7-97.8)	96.0% (95.2-96.7)	
Yes	47	97.9% (93.8-100)	95.3% (89.1-100)	
Chronic renal failure				<.001
No	3,691	97.5% (97.0-98.0)	96.3% (95.7-97.0)	
Yes	36	85.7% (74.9-98.1)	81.2% (68.4-96.4)	
Autoimmune disease				.56
No	3,476	97.3% (96.7-97.8)	96.0% (95.3-96.7)	
Yes	31	96.8% (90.8-100)	90.7% (78.7-100)	
Symptoms				
Sputum				.59
No	2,612	97.4% (96.8-98.1)	96.0% (95.2-96.9)	
Yes	1,114	97.4% (96.4-98.3)	96.5% (95.4-97.7)	
Dyspnea				<.001
No	3,272	98.3% (97.9-98.8)	97.4% (96.8-98.0)	
Yes	454	90.9% (88.2-93.6)	87.6% (84.4-90.9)	
Diarrhea				.81
No	3,381	97.4% (96.8-97.9)	96.1% (95.4-96.8)	
Yes	345	98.0% (96.5-99.5)	96.8% (94.8-98.8)	
Nausea/vomiting				0.2
No	3,558	97.5% (97.0-98.1)	96.3% (95.6-97.0)	
Yes	168	95.1% (91.8-98.5)	94.3% (90.8-98.0)	
Fatigue				.006
No	3,562	97.5% (97.0-98.1)	96.4% (95.7-97.1)	
Yes	164	95.0% (91.7-98.5)	91.9% (87.6-96.5)	
Mental disturbance				<.001
No	3,704	97.7% (97.3-98.2)	96.5% (95.9-97.2)	
Yes	22	45.5% (28.8-71.8)	40.4% (24.2-67.5)	
Systolic blood pressure				.022
< 140 mmHg	2,345	97.8% (97.2-98.4)	96.8% (96.0-97.6)	
≥ 140 mmHg	1,290	96.9% (95.9-97.9)	95.3% (94.0-96.6)	
Diastolic blood pressure				.011
< 80 mmHg	1,401	96.7% (95.7-97.6)	94.9% (93.7-96.2)	
≥ 80 mmHg	2,234	98.0% (97.4-98.6)	97.1% (96.3-97.8)	
Heart rate				.005
< 110 /min	3,374	97.7% (97.2-98.2)	96.4% (95.7-97.1)	
≥ 110 / min	272	94.4% (91.6-97.2)	93.5% (90.6-96.6)	
Body temperature				<.001
< 38℃	3,523	97.8% (97.3-98.3)	96.4% (95.8-97.1)	
≥ 38℃	179	93.2% (89.6-97.0)	93.2% (89.6-97.0)	
Baseline hemogram				
Hemoglobin				<.001
≥12.5 g/dL	1,923	97.9% (97.2-98.5)	96.8% (95.9-97.7)	
<12.5 g/dL	773	93.6% (91.8-95.3)	90.8% (88.7-93.1)	
Absolute lymphocyte count				<.001
≥1,000 /mm^3	2,161	98.3% (97.8-98.9)	97.7% (97.0-98.4)	
<1,000 /mm^3	518	89.7% (87.1-92.4)	84.3% (81.0-87.8)	

Platelet count				<.001
≥100,000 /mm^3	2,634	96.9% (96.2-97.5)	95.2% (94.3-96.1)	
<100,000 /mm^3	62	85.3% (76.9-94.7)	83.5% (74.7-93.4)	

All values were collected data at the time of initial COVID-19 diagnosis.
†Chronic cardiac disease was a composite variable including heart failure and cardiac disease.
‡Chronic pulmonary disease was a composite variable including asthma and chronic obstructive lung disease.

Table 3. The final scoring model in the development cohort

	Adjusted hazard ratio (95% CI)*	*p**	Log$_e$ value of hazard ratio	Final score
Age				
< 50 years	1 (reference)		0	0
50 - 69 years	6.7 (1.09-43.93)	.047	1.831	2
≥ 70 years	26.03 (4.26-169.8)	<.001	3.186	3
Sex				
Female	1 (reference)		-	
Male	1.35 (.85-2.15)	.3	-	
Comorbidity				
Hypertension				
No	1 (reference)		-	
Yes	1.21 (.75-1.94)	.476	-	
Diabetes				
No	1 (reference)		-	
Yes	1.71 (1.08-2.7)	.61	-	
Dementia				
No	1 (reference)		0	0
Yes	3.92 (2.33-6.61)	<.001	1.35	1
Chronic cardiac disease†				
No	1 (reference)		-	
Yes	1.15 (.61-2.15)	.573	-	
Cancer in active treatment				
No	1 (reference)		-	
Yes	1.83 (.72-4.71)	.302	-	
Chronic pulmonary disease‡				
No	1 (reference)		-	
Yes	1.76 (.857-3.625)	.246	-	
Chronic renal failure				
No	1 (reference)		0	0
Yes	3.48 (1.39-8.85)	0.045	1.205	1
Symptoms				
Dyspnea				
No	1 (reference)		0	0
Yes	2.31 (1.44-3.69)	.006	.821	1
Fatigue				
No	1 (reference)		-	
Yes	.69 (.3-1.57)	.38	-	
Mental disturbance				
No	1 (reference)		0	0
Yes	4.04 (1.72-9.53)	.041	1.268	1
Systolic blood pressure				
< 140 mmHg	1 (reference)		-	
≥ 140 mmHg	.93 (.57-1.54)	.594	-	
Diastolic blood pressure				
< 80 mmHg	1 (reference)		-	
≥ 80 mmHg	1.03 (.63-1.68)	.628	-	
Heart rate				

< 110 /min	1 (reference)		-	
≥ 110 / min	1.88 (.96-3.68)	.177	-	
Body temperature				
< 38℃	1 (reference)		-	
≥ 38℃	.79 (.39-1.63)	.459	-	
Baseline hemogram				
Hemoglobin				
≥12.5 g/dL	1 (reference)		-	
<12.5 g/dL	1.14 (.71-1.83)	.553	-	
Absolute lymphocyte count				
≥1,000/mm^3	1 (reference)		0	0
<1,000/mm^3	2.71 (1.66-4.43)	<.001	.982	1
Platelet count				
≥100,000/mm^3	1 (reference)		-	-
<100,000/mm^3	1.68 (.77-3.7)	.344	-	-

All values were collected at the time of initial COVID-19 diagnosis.
*Based on 2,000 Bootstrap samples.
†Chronic cardiac disease was a composite variable including heart failure and cardiac disease.
‡Chronic pulmonary disease was a composite variable including asthma and chronic obstructive lung disease.

Figure 1. Flow diagram of the nationwide COVID-19 patients cohort
Overall, 5,628 confirmed COVID-19 cases occurred between January and April 2020. Cases with post-mortem diagnosis (n=7) or lack of clinical course data after diagnosis (n=27) were excluded from the analysis. A total of 5,594 COVID-19 patients were included in this cohort. **Abbreviations.** COVID-19, Coronavirus disease-2019

Figure 2. Maximal COVID-19 severity and duration of hospital stay
Hospital stay duration (days) differed significantly according to maximal disease severity in COVID-19 patients. Days were presented as mean ± standard deviation. **Abbreviations.** COVID-19, Coronavirus disease-2019

Figure 3. Receiver operating characteristic curve analysis of the newly developed COVID-19 prognosis score system in the validation cohort.
A receiver operating characteristic curve analysis achieved an area under the curve of (A) .918 (95% confidence interval, .91–.927) for 14-day survival and (B) .896 (95% confidence interval .872-.911) for 28-day survival. Abbreviations. COVID-19: Coronavirus disease-2019

Figure 4. (A) Probability of overall survival in COVID-19 patients according to each score and (B) in the final COVID-19 prognosis score system. Overall survival rates at 14 and 28 days were as follows: 99.9% (95% CI 99.7-100) and 99.8% (95% CI 99.6–99.9) in the low-risk group (scores 0-2); 97.4% (95% CI 96.3-98.5) and 95.4% (95% CI 93.9-97.1) in the intermediate-risk group (score 3); 88.8% (95% CI, 85.7-91.9) and 82.3% (95% CI 78.5-86.4) in the high-risk group (score 4); 66.2% (95% CI, 60.1-73.5) and 55.1% (95% CI, 48.5-62.5) in the very high-risk group (score ≥5), respectively. The Log-rank test showed significant differences in the overall survival among the risk groups (P < .001). **Abbreviations.** CI: Confidence interval; COVID-19: Coronavirus disease-2019

Discussion

This study developed a new scoring system to predict the mortality of COVID-19 patients

using nationwide data of 5,594 COVID-19 patients. The COPS system comprises basic demographics, initial symptoms, vital signs, and hemogram results at diagnosis. The risk score was stratified into four risk groups: low-risk, intermediate-risk, high-risk, and very high-risk associated with 28-day OS rate probabilities of 99.8%, 95.4%, 82.3%, and 55.1%, respectively. The ROC curve analysis indicated that the prediction ability of the COPS system is excellent in the validation cohort.

Comorbidities identified in this study included dementia and chronic renal failure. Those with the highest impact on mortality were dementia (adjusted HR 3.92) followed by chronic renal failure (adjusted HR 3.48). Moreover, the prognosis was poor when mental disturbance (adjusted HR 4.04) was present at the time of diagnosis or the patient had underlying dementia (adjusted HR 3.92). These two factors are related to the presence of SARS-CoV-2 infection clusters in nursing homes or long-term care facilities between February and April 2020 in Korea. Therefore, establishing screening and infection control strategies for long-term healthcare facilities are necessary [17-20].

In this study, an ALC of <1,000/mm^3 affected the survival rate of COVID-19 patients. ALC has been used as a prognostic factor for common respiratory viruses, including respiratory syncytial virus, or other viral reactivation in immunocompromised hosts [21]. A recent meta-analysis reported that lymphopenia on admission was associated with poor outcomes in patients with COVID-19 [22]. Further immunological studies on COVID-19 patients are needed to elucidate the mechanism of lymphopenia and T cell reactivation, as well as cytokines [23].

Regarding severity, approximately 87% of patients did not need oxygen supplementation. Approximately 10% of the patients required oxygen supplementation; of these, 25% received oxygen via a simple mask or mechanical ventilators. From a national strategy for new infectious disease crisis perspective, determining the proportion of critically ill patients and length of hospital stay according to severity is important to prepare medical resources, such as critical care beds. This study found that the hospitalization period was significantly longer in survivors than in that non-survivors; moreover, among survivors, length of hospital stay and disease severity were directly associated.

In this cohort, the infection-fatality rate after COVID-19 diagnosis was 4.18% (234/5,594 patients). However, until April 30, 2020, the cumulative number of confirmed COVID-19 cases in Korea was 10,765 with 247 deaths, representing an actual mortality rate of 2.29% during the same period [24]. As of November 6, 2020, the total cumulative number of confirmed cases and deaths are 27,195 and 476, respectively, representing an infection-fatality rate of 1.75% in Korea [24]. This mortality disparity is caused by not all data being entered at the time this cohort was released. However, considering the large number of patients included in this cohort and collection of most deceased cases, the findings of this study are still meaningful and carry little statistical bias. In addition, remdesivir was not available in Korea during the study period, and infectious disease prevention and control measures were less established in the early phase of the COVID-19 pandemic. Thus, several mass infection episodes might have caused the relatively high mortality rate in the earlier pandemic phase in Korea.

Several studies have attempted to determine predictive factors for severe or fatal COVID-19. A study on risk factors for fatal COVID-19 performed in China proposed a scoring system including age, procalcitonin, aspartate aminotransferase level, coronary heart disease, and cerebrovascular disease developed using data of 1,590 COVID-19 inpatients until January 2020. The nomogram showed discriminatory power with a C-index of 0.91 to predict survival [13]. Another study analyzed the risk of intensive care unit admission and death in 4,997 individuals under investigation at an academic hospital in New York. In this study, age, heart rate, procalcitonin, lactate dehydrogenase, heart failure, and chronic obstructive pulmonary disease were used to predict intensive care unit

care and death, yielding an accuracy of 0.74 and 0.83, respectively [25]. In the UK, a similar study was conducted on 17 million individuals included in the OpenSAFELY database, a near-real-time primary care patient record, which pseudonymously identified 10,926 COVID-19-related deaths. This study identified male sex, older age and deprivation, diabetes, and severe asthma as significant risk factors for death [26]. However, this study did not analyze survival and death among patients with a confirmed COVID-19 diagnosis. In addition to studies attempting to predict death in COVID-19 patients, other studies have focused on severity index to predict severe or critical cases [10, 27-30]. More recently, machine learning-based warning system for mortality risk prediction of COVID-19 patients was reported, and timely risk stratification using multiple laboratory and clinical factors was improved [31].

Compared with the abovementioned studies, our study has the following strengths: first, the risk factors of death were analyzed using a nationwide cohort including a large number of COVID-19 patients, resulting in a scoring system that can be widely used for triaging laboratory-confirmed COVID-19 cases. Second, the COPS system was developed using easily accessible information, such as age, underlying disease, dyspnea, mental disturbance, and hemogram parameters. We believe that if a scoring system using only simple laboratory tests, such as hemogram parameters, can be constructed and still shows good predictability, it is more cost-effective than including other biomarkers such as procalcitonin or cytokine levels. Third, the discriminatory power of our system for predicting death probability was excellent. Finally, this study further analyzed length of hospital stay according to disease severity, which may assist in preparing medical resources based on patient classification. However, this study is limited by the lack of external verification for our scoring model. Therefore, the current model of OS for the diagnosis of COVID-19 would need to be validated in a future cohort.

In conclusion, our study provides a simple scoring system based on information collected at diagnosis for predicting mortality in COVID-19 patients in a timely manner. Early triaging of COVID-19 patients using the COPS system can provide new insights for risk-adaptive strategies and optimize the use of medical resources.

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Conflicts of interest. All authors declare no competing interests.

Abbreviations

COVID-19: Coronavirus disease-19
SARS-CoV-2: severe acute respiratory syndrome coronavirus-2
ARDS: acute respiratory distress syndrome
KDCA: Korea Disease Control and Prevention Agency
ECMO: Extracorporeal membrane oxygenation
SD: standard deviation
HR: Hazard ratio
CI: confidence intervals

AUC: area under the curve
ROC: receiver operating characteristics
ALC: absolute lymphocyte count
COPS: COVID-19 prognosis score

Supplementary calculator

Calculator of COVID-19 prognosis score system. Provided calculator to make calculate risk scores of COVID-19 easier.

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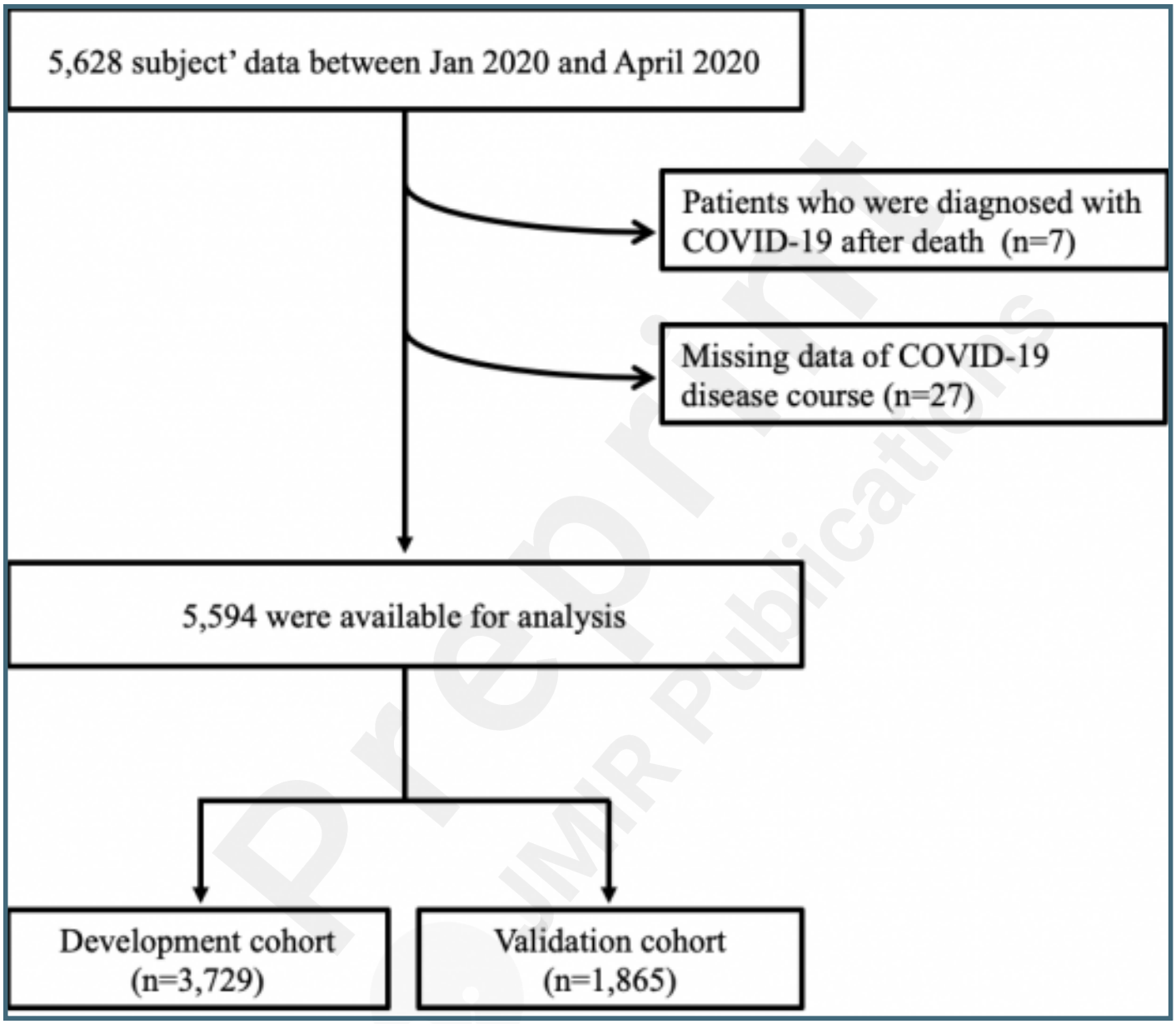
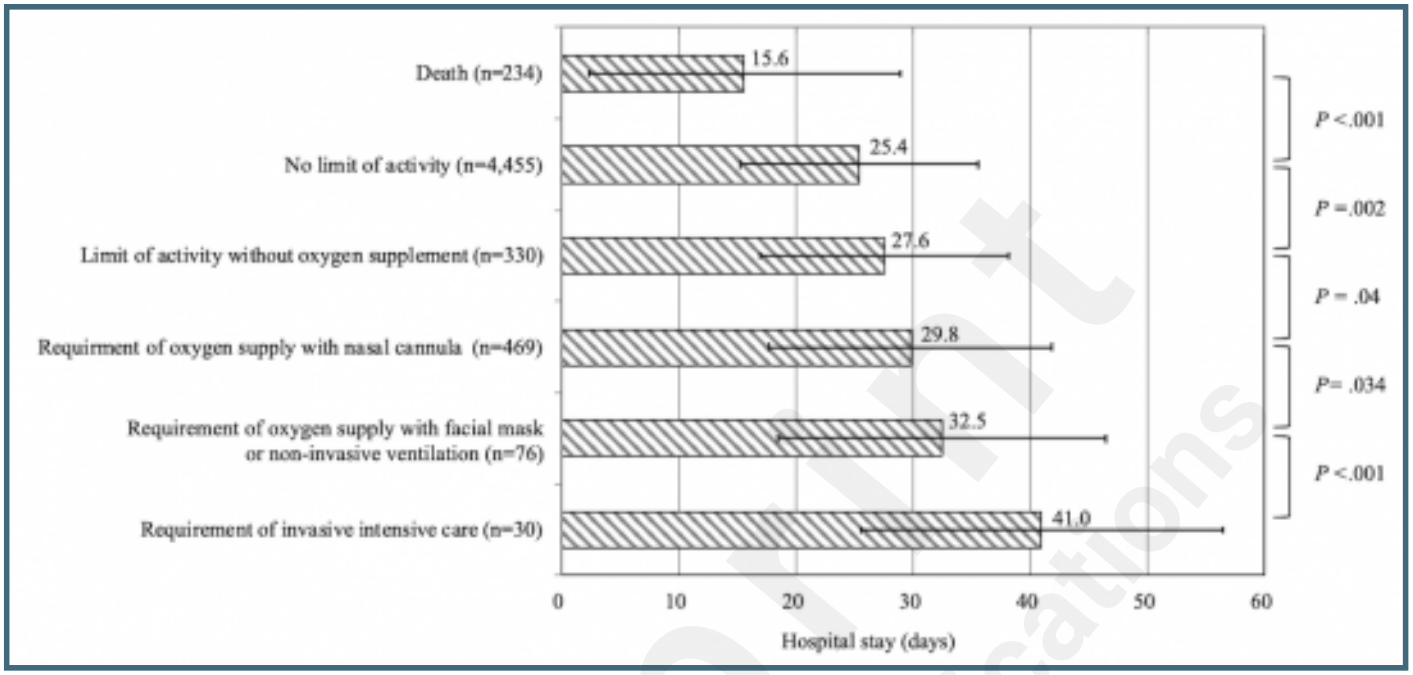
Supplementary Files

Figures

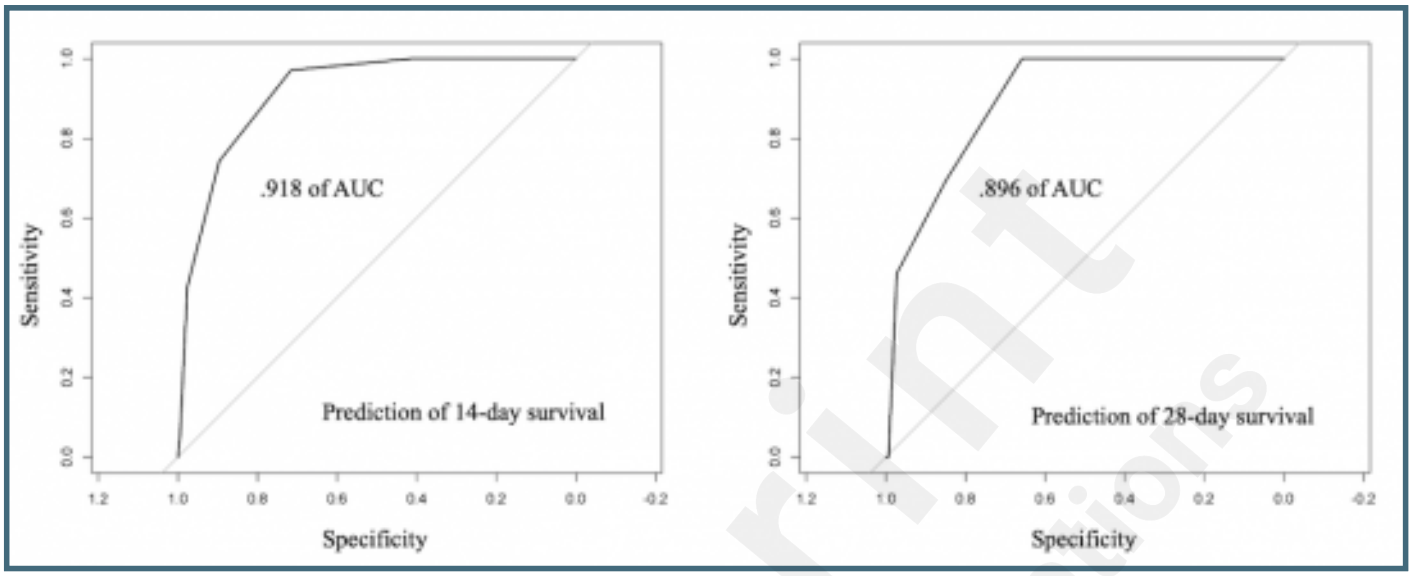
Flow diagram of the nationwide COVID-19 patients cohort Overall, 5,628 confirmed COVID-19 cases occurred between January and April 2020. Cases with post-mortem diagnosis (n=7) or lack of clinical course data after diagnosis (n=27) were excluded from the analysis. A total of 5,594 COVID-19 patients were included in this cohort. Abbreviations. COVID-19, Coronavirus disease-2019.



Maximal COVID-19 severity and duration of hospital stay Hospital stay duration (days) differed significantly according to maximal disease severity in COVID-19 patients. Days were presented as mean ± standard deviation. Abbreviations. COVID-19, Coronavirus disease-2019.



Receiver operating characteristic curve analysis of the newly developed COVID-19 prognosis score system in the validation cohort. A receiver operating characteristic curve analysis achieved an area under the curve of (A) .918 (95% confidence interval, .91–.927) for 14-day survival and (B) .896 (95% confidence interval .872-.911) for 28-day survival. Abbreviations. COVID-19: Coronavirus disease-2019.



(A) Probability of overall survival in COVID-19 patients according to each score and (B) in the final COVID-19 prognosis score system. Overall survival rates at 14 and 28 days were as follows: 99.9% (95% CI 99.7-100) and 99.8% (95% CI 99.6–99.9) in the low-risk group (scores 0-2); 97.4% (95% CI 96.3-98.5) and 95.4% (95% CI 93.9-97.1) in the intermediate-risk group (score 3); 88.8% (95% CI, 85.7-91.9) and 82.3% (95% CI 78.5-86.4) in the high-risk group (score 4); 66.2% (95% CI, 60.1-73.5) and 55.1% (95% CI, 48.5-62.5) in the very high-risk group (score ?5), respectively. The Log-rank test showed significant differences in the overall survival among the risk groups (P < .001). Abbreviations. CI: Confidence interval; COVID-19: Coronavirus disease-2019.