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RESEARCH ARTICLE

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Development and validation of clinical prediction model to estimate the probability of death in hospitalized patients with COVID-19: Insights from a nationwide database

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Abstract

In the current study, we aimed to develop and validate a model, based on our nationwide centralized coronavirus disease 2019 (COVID-19) database for predicting death. We conducted an observational study (CORONATION-TR registry). All patients hospitalized with COVID-19 in Turkey between March 11 and June 22, 2020 were included. We developed the model and validated both temporal and geographical models. Model performances were assessed by area under the curve-receiver operating characteristic (AUC-ROC or c-index), R^2, and calibration plots. The study population comprised a total of 60,980 hospitalized COVID-19 patients. Of these patients, 7688 (13%) were transferred to intensive care unit, 4867 patients (8.0%) required mechanical ventilation, and 2682 patients (4.0%) died. Advanced age, increased levels of lactate dehydrogenase, C-reactive protein, neutrophil–lymphocyte ratio, creatinine, albumine, and D-dimer levels, and pneumonia on computed tomography, diabetes mellitus, and heart failure status at admission were found to be the strongest predictors of death at 30 days in the multivariable logistic regression model (area under the curve-receiver operating characteristic = 0.942; 95% confidence interval: 0.939–0.945; R^2 = .457). There were also favorable temporal and geographic validations. We developed and validated the prediction model to identify in-hospital deaths in all hospitalized COVID-19 patients. Our model achieved reasonable performances in both temporal and geographic validations.

KEYWORDS
COVID-19, mortality, prediction models, prognosis

1 | INTRODUCTION

The ongoing outbreak of the novel coronavirus disease 2019 (COVID-19) has posed a challenge for public health, healthcare systems, and economies globally. It manifests with a broad clinical spectrum, ranging from asymptomatic patients to critical septic shock and a multiorgan dysfunction.[1,2] Elderly patients and those with comorbidities are at higher risk of COVID-19 complications.[3,4] Delays in the treatment of patients can be detrimental.[5] A simple and accurate clinical score for the assessment of disease severity could help identify the COVID-19 patients at a high risk of developing critical illness[6] and allow physicians to

determine which patients can be managed safely at local hospitals and which require early transfer to tertiary pandemic centers.[7]

Some prediction models have been developed to guide physicians to triage and treat high-risk patients rapidly. Wynants et al.[8] evaluated current prediction models for COVID-19 and concluded that all models reported good-to-excellent predictive performance. However, all were appraised to have a high risk of bias, owing to a combination of poor reporting and methodological conduct for the participant selection, predictor description, and statistical methods used.[8,9] They recommended that the studies should adhere to the TRIPOD statement (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis).[8,10] However, such a reliable and validated prediction model is still lacking.[8,11]

In the current study, we aimed to develop and validate a model based on our nationwide centralized COVID-19 database for predicting in-hospital deaths.

2 | METHODS

2.1 | Study design and population

We conducted an observational, retrospective, and longitudinal cohort study (CORONATION-TR registry) in accordance with the TRIPOD statement. All patients hospitalized in Turkey with at least one positive reverse transcriptase polymerase chain reaction (PCR) test for COVID-19 between March 11, 2020 and June 22, 2020 were included in the study. We did not include patients with negative PCR results, who were aged <18 years or who were not hospitalized. The Turkish Ministry of Health approved the study with a waiver of informed consent for retrospective data analysis.

2.2 | National data collection

All these data were obtained from the "public health management system (PHMS) module" to collect COVID-19-specific data (symptoms, biomarkers, medications, comorbidities, and clinical outcomes during index hospitalization). Detailed information about data collection has been published in advance.[12]

2.3 | Study outcomes

The primary outcome for this study is 30-day all-cause death.

We did not include all-cause deaths in the prehospital period, after discharge from the hospital, or in patients who were not hospitalized. Patients who were admitted to the emergency department and who died in the emergency department were also not included in this study.

2.4 | Selection of candidate predictors

We selected candidate predictors on the basis of known or plausible associations with exposure to COVID-19 infection. Candidate predictor variables obtained at the time of admission are described below.

(i) Age (years), neutrophil–lymphocyte ratio (NLR), C-reactive protein (CRP) (mg/dl), lactate dehydrogenase (LDH) [U/L], D-dimer (μg/ml), hemoglobin (Hgb) (mg/dl), albumin (mg/dl), creatinine (mg/dl), and platelet count ($\times 10^9$/L) were included in the model as continuous variables using restricted cubic spline (four knots).
(ii) Sex, coronary artery disease (CAD), peripheral vascular disease (PVD), collagen tissue disorders (CTD), malignancy, lymphoma, heart failure (HF), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), hypertension (HTN), diabetes mellitus (DM), valvular heart disease, chronic liver disease, and pneumonia on computed tomography (CT) were included in the model as categorical variables.

2.5 | Statistical analysis

All statistical analyses were performed using R-software v. 3.6.3 (R statistical software, Institute for Statistics and Mathematics, Vienna, Austria) using "rms", "CalibrationCurves", "ggplot", and "survminer" packages. Continuous variables were presented as a median and interquartile range, whereas categorical variables were presented as counts and percentages.

2.6 | Model development

The associations between prespecified candidate predictors and death were assessed using multivariable logistic regression. The associations between candidate predictors and outcome were quantified using the adjusted odds ratio (OR) with a 95% confidence interval (CI). To capture nonlinear associations, continuous predictors were modeled using restricted cubic spline transformations (four knots). The adjusted OR for continuous predictors were shown as inter-quartile OR. The final model was fitted using step-down backward variable selection ($\alpha = .05$). Overall predictive accuracy and discriminative ability of the model were evaluated using R^2 and area under the curve-receiver operating characteristic (AUC-ROC orc-index), respectively. Agreement between predicted and observed outcomes were evaluated graphically with calibration plots.

2.7 | Model validation

Validation procedures were as follows[13,14]:

TABLE 1 Baseline characteristics of all patients

Variables	All patients (*n* = 60,980)	ICU patients (*n* = 7688)	MV (*n* = 4867)	30-Day death (*n* = 2682)
Age, years	49 (36–63)	65 (52–76)	66 (54–76)	70 (61–79)
Sex, male %	53% (32,303)	60% (4590)	60% (2940)	61% (1643)
NLR	2.30 (1.46–3.81)	3.63 (2.05–6.80)	4.02 (2.20–7.71)	4.95 (2.69–9.48)
D-Dimer, μg/ml	0.40 (0.22–0.80)	0.84 (0.40–1.95)	0.92 (0.43–2.26)	1.19 (0.57–2.94)
LDH, U/L	225 (184–297)	323 (235–456)	350 (248–492)	410 (298–564)
CRP, mg/dl	6.81 (1.46–27.7)	41.4 (9.43–121)	58.7 (12.5–141)	95.0 (25.3–174)
Hemoglobin, g/dl	13.6 (12.4–14.8)	12.9 (11.4–14.2)	12.7 (11.3–14.0)	12.4 (10.9–13.8)
Platelet counts, $\times 10^9$/L	208 (169–256)	197 (155–252)	195 (153–250)	187 (147–245)
Creatinine, mg/dl	0.82 (0.69–0.98)	0.93 (0.77–1.20)	0.96 (0.78–1.26)	1.06 (0.84–1.47)
Albumin, g/dl	4.1 (3.7–4.4)	3.4 (3.0–3.9)	3.4 (2.9–3.8)	3.2 (2.8–3.5)
CAD, %	15% (9339)	32% (2452)	33% (1597)	39% (1057)
PAD, %	4.0% (2217)	7.0% (574)	8.0% (369)	9.0% (237)
CTD, %	3.0% (1857)	4.0% (291)	4.0% (198)	4.0% (118)
Malignancy, %	3.0% (1919)	6.0% (488)	7.0% (341)	9.0% (243)
Lymphoma, %	0.1% (227)	1.0% (71)	1.0% (45)	1.0% (27)
Heart failure, %	5.0% (3004)	15% (1167)	16% (773)	21% (563)
COPD, %	21% (12,581)	33% (2511)	33% (1587)	37% (979)
Cerebrovascular disease, %	7.0% (4059)	16% (1224)	17% (810)	20% (548)
Hypertension, %	37% (22,386)	62% (4768)	64% (3126)	74% (1972)
DM, %	19% (11,863)	32% (2495)	34% (1646)	39% (1036)
CKD, %	3.0% (2096)	10% (763)	10% (511)	14% (384)
Healthcare worker, %	6.0% (3557)	3.0% (194)	2.0% (103)	1.0% (15)
Pneumonia on CT, %	60% (36,778)	81% (6257)	83% (4035)	85% (2268)
Dyspnea, %	37% (22,584)	33% (2518)	32% (1564)	30% (809)
Fever, %	38% (23,083)	33% (2570)	33% (1602)	31% (827)
Valvular heart disease, %	1.0% (690)	2.0% (161)	2.0% (103)	3.0% (72)
Cardiac arrhythmias, %	7.0% (3980)	14% (1104)	15% (732)	19% (499)
Chronic liver disease, %	3.0% (1637)	4.0% (281)	4.0% (201)	5.0% (121)
Pregnancy, %	1.0% (440)	0.1% (16)	0.2% (11)	0.05% (1)
In-hospital treatments, %				
Favipiravir	23% (14,185)	63% (4852)	65% (3167)	72% (1929)
HCQ	84% (51,167)	84% (6495)	84% (4070)	81% (2169)
Lopinavir/ritonavir	3.0% (1936)	12% (892)	15% (744)	16% (439)
Oseltamivir	49% (30,138)	58% (4476)	60% (2925)	60% (1608)
High dose C-vitamin	61% (36,973)	65% (5031)	40% (1945)	44% (1173)
Azithromycin	16% (9598)	37% (2820)	65% (3175)	63% (1766)

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease, COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CTD, collagen tissue disorders; DM, diabetes mellitus; HCQ; hydroxychloroquine; ICU; intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation, NLR, neutrophil–lymphocyte ratio; PAD, peripheral artery disease.

TABLE 2 Baseline characteristics of hospitalized patients in the early and late period

Variables	Early period (*n* = 41,300)	Late period (*n* = 19,680)
Age, years	52 (39–64)	44 (31–57)
Sex, male %	53% (21,815)	53% (10,488)
NLR	2.43 (1.53–4.03)	2.10 (1.35–3.38)
D-Dimer, μg/ml	0.44 (0.23–0.89)	0.34 (0.19–0.66)
LDH, U/L	232 (187–309)	214 (178–272)
CRP, mg/dl	9.00 (1.91–36.5)	3.92 (0.90–14.7)
Hemoglobin, g/dl	13.5 (12.3–14.7)	13.8(12.6–15.1)
Platelet counts, $\times 10^9$/L	207 (167–256)	211 (172–255)
Creatinine, mg/dl	0.82 (0.69–0.99)	0.82 (0.69–0.97)
Albumin, g/dl	4.0 (3.6–4.4)	4.2 (3.8–4.5)
CAD, %	17% (7031)	12% (2308)
PAD, %	4.0% (1687)	3.0% (530)
CTD, %	3.0% (1320)	3.0% (537)
Malignancy, %	3.0% (1420)	3.0% (499)
Lymphoma, %	0.1% (171)	0.1% (56)
Heart failure, %	6.0% (2288)	4.0% (716)
COPD, %	22% (9222)	17% (3359)
Cerebrovascular disease, %	7.0% (3074)	5.0% (985)
Hypertension, %	41% (16,741)	29% (5645)
DM, %	21% (8818)	15% (3045)
CKD, %	4.0% (1616)	2.0% (480)
Healthcare worker, %	6.0% (2366)	6.0% (1191)
Pneumonia on CT, %	66% (27,112)	49% (9666)
Dyspnea, %	36% (14,799)	40% (7785)
Fever, %	37% (15,184)	40% (7899)
Valvular heart disease, %	1.0% (495)	1.0% (195)
Cardiac arrhythmias, %	7.0% (3034)	5.0% (946)
Chronic liver disease, %	3.0% (1175)	2.0% (462)
Pregnancy, %	1.0% (295)	1.0% (145)
In-hospital treatments, %		
Favipiravir	24% (10,091)	21% (4094)
HCQ	85% (35,020)	82% (16,147)
Lopinavir/ritonavir	4.0% (1823)	1.0% (113)
Oseltamivir	61% (24,996)	26% (5142)
High dose C-vitamin	64% (26,451)	53% (10,522)
Azithromycin	18% (7471)	11% (2127)
30-Day death, %	6.0% (2343)	2.0% (339)
Transferred to ICU, %	15% (6160)	8% (1528)
Mechanical ventilation, %	10% (4158)	4.0% (709)
Length of hospital stay, days	8 (5–12)	8 (5–12)

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease, COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; CT, computed tomography; CTD, collagen tissue disorders; DM, diabetes mellitus; HCQ; hydroxychloroquine; ICU; intensive care unit; LDH, lactate dehydrogenase; MV, mechanical ventilation, NLR, neutrophil–lymphocyte ratio; PAD, peripheral artery disease.

(1) Internal validation was assessed using bootstrap resampling (1000 replications).
(2) For the temporal internal–external validation, the data were split into two time periods: March 13 to April 30 (early phase) and April 30 to June 22 (late phase). We developed the model in the early phase and tested in the late phase.
(3) For the geographic internal–external validation, the data were split into two geographic regions: Istanbul (the most densely populated city in Turkey) and the rest of the Turkey (geographically called as Anatolia). We developed the model in Istanbul and tested in Anatolia.

Model performances were assessed by AUC-ROC (c-index), R^2, Brier score, and calibration plot (calibration-in-the-large, slope) in internal, temporal, and geographic validations at 30 days.

(4) Geographic internal–external validation was also assessed, as described in detail by Harrell and Steyerberg.[13] The EuroStat Nomenclature of Territorial Units for Statistics (12 NUTS)[15,16] has been considered to be the most standardized geographic unit for our model. Every NUTS is left out once, for validation of a model based on the remaining NUTSs (leave-one-NUTS-out cross-validation). The final model is based on the pooled data set, which is labeled as an internally–externally validated model. The AUC-ROC, observed/expected (O/E) ratio, calibration intercept, and slope derived from this procedure for each NUTS were pooled with a random effect model, and heterogeneity among NUTS was assessed with prediction intervals (PrI).

2.8 | Handling of missing data

The variables with missing values more than 50% were not included in the model, whereas for those with less than 50%, with the assumption of missing them at random, multiple imputations were used to minimize bias and avoid the exclusion of participants. Multiple imputations were applied for missing values using the aregImpute function (rms). Five completed data sets were analyzed, and results were combined using Rubin's rule.[17]

3 | RESULTS

The study population comprised a total of 60,980 hospitalized COVID-19 patients with positive PCR results at the 945 hospitals in Turkey between March 13 and June 22, 2020. The median age was 49 years (36–63) and almost half (53%) of the population was male. Of these patients, 7688 (13%) were transferred to an intensive care unit (ICU), 4867 patients (8.0%) required mechanical ventilation (MV), and 2682 patients (4.0%) died. The median length of hospital stays was 8 days (5–12) and that of ICU stays was 6 days (1–13). The length of hospital and ICU stays and duration of MV are demonstrated in Figure S1–S3. The baseline characteristics of all hospitalized patients, ICU patients, patients on MV, and patients who died are demonstrated in Tables 1 and 2.

A total of 12% of deaths within 30 days occurred in the first 5 days and 63% in the first 15 days. Also, 33% of the study population was less than 40 years, whereas 5% were more than 80 years. With the increase in age, the increased risk of death became prominent (0.3% for <40 years, 1.3% for 40–50 years, 3.4% for 50–60 years, 8.2% for 60–70 years, 14.4% for 70–80 years and, >80 years for 19.1%). Similarly, in patients with no comorbidity, the 30-day mortality rate was 1.25% ($n = 356$), whereas the frequency of death increased as the number of comorbidities increased, reached about 20% when the number of comorbidities were more than 7. When 356 patients who died and had no comorbidity were analyzed in detail, 25.8% ($n = 92$) were less than 50 years, 48.3% ($n = 172$) were 50–70 years, 25.8% ($n = 92$) were more than 70 years. In addition, 80.6% of these patients were male and 19.4% were female. The relationship between the number of comorbidities and death risk is shown in Figure S4. The observed frequency of death, transfer to ICU, and need for MV for number of comorbidities are summarized in Table S1.

Model development: There are 23 baseline variables available for inclusion in prognostic model. Table 3 summarizes the multivariable risk model with adjusted odds ratio and 95% CI for each predictor. After backward step-down variable selection ($\alpha = .05$), age, LDH, CRP, NLR, creatinine, D-dimer, albumin, hemoglobin, platelet counts, presence of heart failure, DM, and pneumonia on CT were found to be the strongest predictors of 30-day mortality. Age, LDH, albumin, CRP, and creatinine accounted for 80% of the variation in 30-day mortality. Figure S5 displays the relative importance of each continuous predictor based on their partial χ^2 values of in-hospital death. The relationship between continuous variables and the risk of outcomes was markedly nonlinear for majority of continuous predictors (Figure 1).

Internal validation: the multivariable logistic regression model had excellent discrimination for death (AUC-ROC = 0.942; 95% CI: 0.939–0.945; $R^2 = .457$). There were also excellent agreements between observed risk and predicted risk by model in calibration plots at 30 days (Figure 2). There was a negligible model optimism (AUC = 0.941; $R^2 = .454$) in bootstrap resampling.

Temporal validation: the present study included 42,512 patients hospitalized with COVID-19 during the early phase of the study (March 13 to April 30) and 21,060 patients hospitalized with COVID-19 during the late phase of the study (May 1 to June 22). Model were developed in the early phase and tested in the late phase. Estimated AUC was 0.933 (95% CI: 0.929–0.937) in the early phase and 0.956 (95% CI: 0.948–0.964) in the late phase. Calibration plots demonstrated that prediction model slightly underestimated the risk of death at 30 days in the late phase (Figure S6).

Geographic validation: the present study included 23,603 patients hospitalized with COVID-19 in Istanbul region and 37377 patients hospitalized with COVID-19 in the Anatolia region. The Model were developed in Istanbul region and tested in Anatolia region. Estimated AUC was 0.958 (95% CI: 0.939–0.972) in Istanbul region and 0.896 (95% CI: 0.890–0.902) in Anatolia region. Calibration plot demonstrated that prediction model moderately underestimated the risk of death at 30 days in Anatolia region (Figure S3). In Table 4, apparent, temporal, and geographic validations are summarized. The EuroStat 12-NUTS unit and total sample size/number of in-hospital

TABLE 3 Multivariable logistic regression models for 30-day death

Variables	Full model Odds ratio, and 95% CI	Simple model Odds ratio, and 95% CI
Age, year	4.24 (3.37–5.34)	4.29 (3.44–5.36)
Sex, male	0.96 (0.86–1.07)	–
NLR	1.39 (1.27–1.51)	1.38 (1.27–1.50)
D-Dimer, μg/ml	1.14 (1.05–1.24)	1.14 (1.05–1.24)
LDH, U/L	2.72 (2.44–3.03)	2.72 (2.44–3.03)
CRP, mg/dl	1.67 (1.51–1.85)	1.67 (1.51–1.84)
Hemoglobin, g/dl	1.03 (0.90–1.18)	1.01 (0.89–1.15)
Platelet counts, $\times 10^9$/L	0.66 (0.59–0.74)	0.66 (0.59–0.75)
Creatinine, mg/dl	1.64 (1.41–1.90)	1.61 (1.39–1.86)
Albumin, g/dl	0.34 (0.26–0.45)	0.34 (0.26–0.45)
Pneumonia on CT	1.52 (1.34–1.72)	1.51 (1.33–1.71)
Coronary artery disease, yes	0.94 (0.84–1.06)	–
Peripheral artery disease, yes	0.85 (0.71–1.01)	–
Collagen tissue disorders, yes	1.08 (0.86–1.36)	–
Malignancy, yes	1.02 (0.85–1.21)	–
Lymphoma, yes	1.08 (0.67–1.75)	–
Heart failure, yes	1.27 (1.11–1.46)	1.28 (1.12–1.45)
COPD, yes	1.06 (0.95–1.17)	–
Cerebrovascular disease, yes	1.18 (1.04–1.34)	–
Hypertension, yes	1.00 (0.88–1.14)	–
Diabetes mellitus, yes	1.23 (1.11–1.36)	1.23 (1.11–1.36)
Valvular heart disease, yes	1.12 (0.82–1.52)	–
Chronic liver disease, yes	1.24 (0.98–1.57)	–

Abbreviations: COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; LDH, lactate dehydrogenase; NLR, neutrophil–lymphocyte ratio.

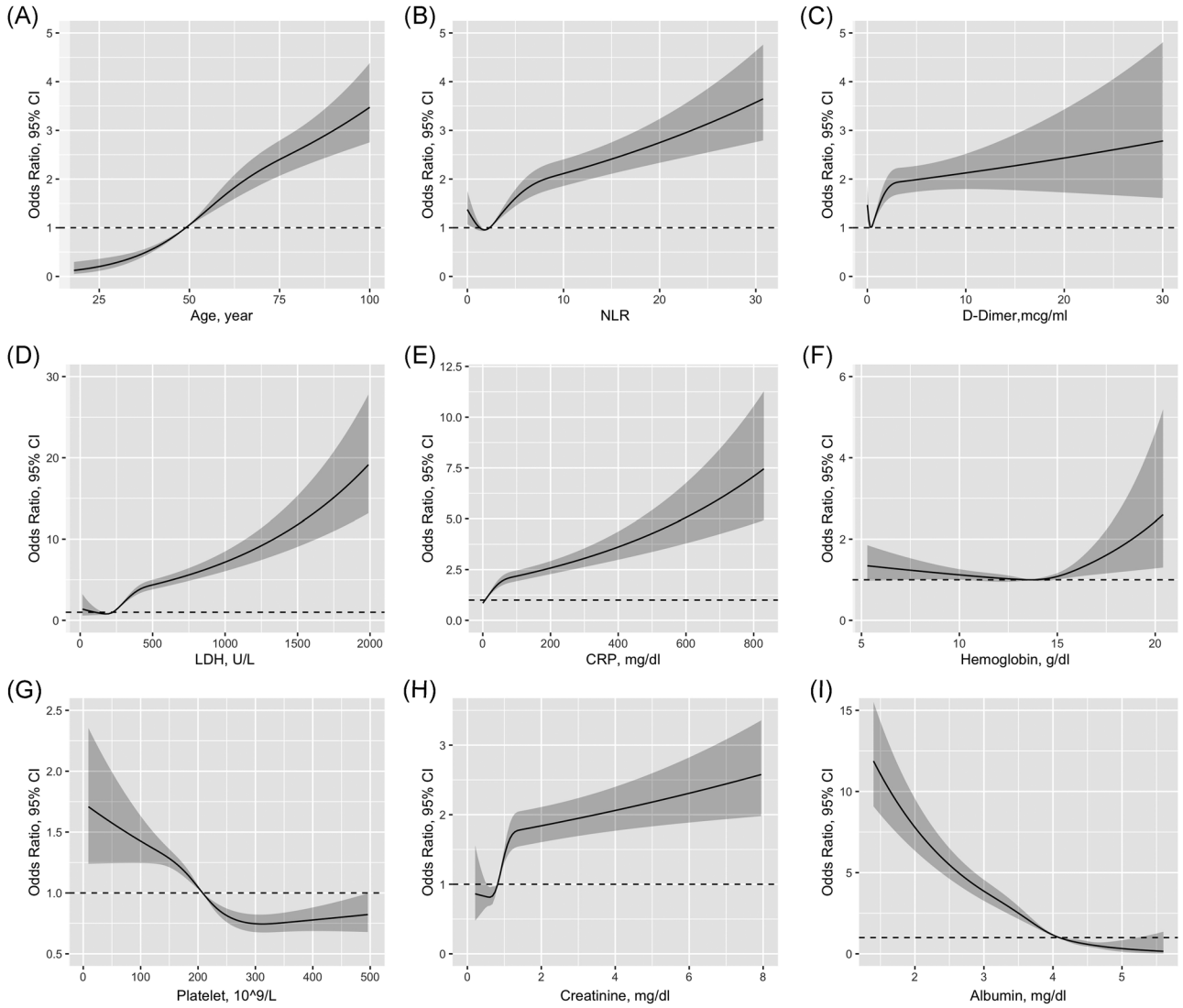

FIGURE 1 Odds ratio (95% CI) plots for the effects of continuous predictors on the outcome. CI, confidence interval

death for internal–external validations are demonstrated in Figure S3. When using the "leave-one-NUTS-out" internal–external cross-validation methods, across the geographic NUTS, AUC ranged from 0.90 to 0.97. The random effect meta-analysis estimate of mean cross-validated AUC was 0.95 (95% CI: 0.93%–0.96% and 95% PrI: 0.90–0.99) for the identification of in-hospital death in all hospitalized patients, which was similar to both apparent and the bootstrap-corrected estimate of the AUC (Table S3). The model showed good calibrations in the internal–external cross-validations.

The nomogram was based on predictors from a simple multivariable regression model (Figure S9). The calculated score ranged from 15 to 235 (Figure S10). The score less than 110 was associated with very low risk of death at 30 days (<5%), whereas more than 140 was associated with very high risk of death at 30 days (>50%). The Kaplan–Meier curve demonstrated survival probabilities according to score categories (Figure S11). The equation of the model and TRIPOD checklist are also provided (see Data S1 and S2) (http://coronation-risk.com).

4 | DISCUSSION

In this study, we developed and validated the prediction model to identify in-hospital deaths using predictors measured at admission in all hospitalized patients. Our model demonstrated reasonable performances in both temporal and geographic validations.

Although the majority of COVID prognostic models reported good-to-excellent discriminations, all were found to exhibit a high risk of bias due to a combination of poor reporting, bias in participant selection, low sample size, and the use of improper statistical methods.[8] A high risk of bias suggests that the performance of these models in new samples will probably be poor, and the estimated AUC indicating near-perfect discrimination was consistent with overfitting. We used one of the largest populations and developed the model to generalize our findings and reduce the risk of overfitting. Our model had excellent discrimination. Additionally, we validated our model on a large temporal and geographic patient cohort, providing an assessment of model generalizability with minimal

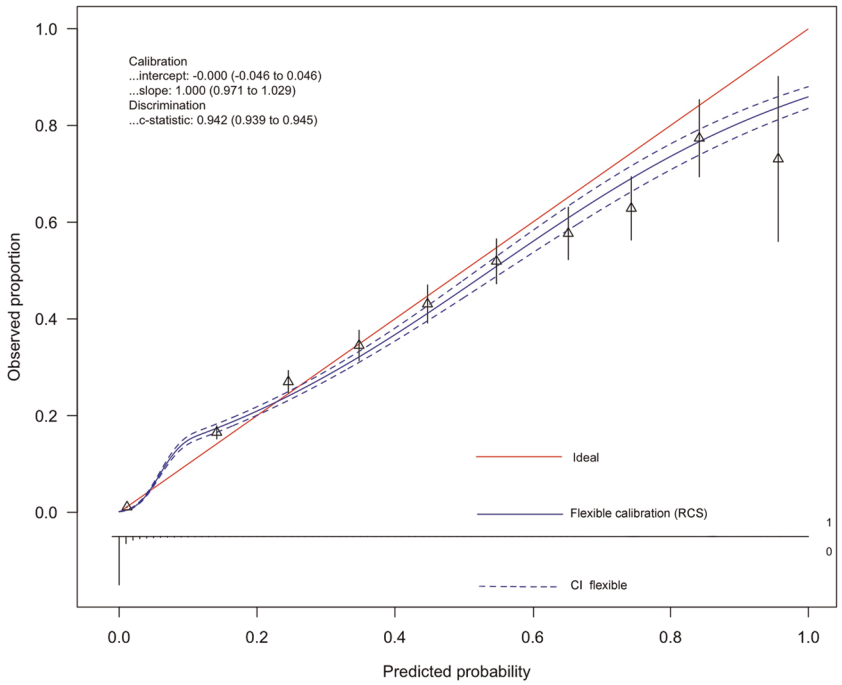

FIGURE 2 Calibration plot for overall cohorts

TABLE 4 Model performances for overall apparent, temporal, and geographic validations

	Apparent	Temporal splitting		Geographical splitting	
	All patients	Early	Late	Istanbul	Anatolia
AUC-ROC	0.942	0.933	0.956	0.958	0.896
R^2	.461	.454	.439	.531	.324
Brier-scaled	0.272	0.281	0.158	0.352	0.146
Intercept	0.000	0.000	−0.583	0.000	−0.152
Slope	1.000	1.000	1.022	1.000	0.548

(or reduced) bias. Discrimination and calibrations of the model were acceptable in both temporal and geographic validations.

The most frequently reported predictors for any outcome in patients with COVID-19 were older age, findings derived from computed tomography scans, LDH, C-reactive protein, comorbidities, NLR, and D-dimer.[1,6,8,18] In our model, the impact of age on in-hospital death was more prominent at more than 50 years of age, whereas the relation between age and in-hospital death was linear. The male sex, higher levels of LDH, CRP, D-dimer, Creatinine, and NLR, and decreased level of albumin and platelet counts were also found to be associated with the risk of death. In addition, hypertension, COPD, and CAD did not emerge as predictors in the CORONATION-TR model, despite being identified in prior studies. The individual contributions of predictors in prognostic model seem to be consistent with generally accepted scenarios for mechanisms of worsening in severe COVID-19 infections characterized by hyper-inflammatory state, cytokine storm, macrophage activation syndrome, the burden of extensive microthrombosis with consumption coagulopathy, and microangiopathic hemolytic anemia, eventually resulting in potentially lethal multisystem organ failure.[19–21]

4.1 | Study limitations

As our model was developed for predicting the outcome in hospitalized patients, the results could not allow us to generalize our risk prediction to nonhospitalized patients. Despite the lack of fully independent data for external validations of our model, the strong internal and internal-validations might obviate the need for external validation. Data were taken from PHMS records that support the accurate and fast analysis of large populations. However, we did not include patients' data that required manual review in the analysis. As our study was a retrospective study, laboratory tests such as troponin, ferritin, procalcitonin, and interleukin-6 were not available for all patients; however, complete blood count and general biochemical laboratory data were available. Also, as our study was conducted in the first month of the pandemic, more studies are needed to document changes in results as the pandemic matures. Finally, data regarding the discharge with complete recovery or occurrence of outcome events were available in up to 100% of our large study population. Thus, we used logistic regression, because censoring could not provide further benefits to our model.

5 | CONCLUSIONS

Our risk prediction model, based on a data from large nationwide COVID-19 database, can provide reliable risk prediction for in-hospital death in hospitalized patients.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests.

AUTHOR CONTRIBUTIONS

Ibrahim Halil Tanboğa, Özcan Özeke, Serkan Çay, Serkan Topaloğlu, and Cihangir Kaymaz conceived the study. Uğur Canpolat, Harun Kundi, Özcan Özeke, Serkan Çay, Osman Çelik, Murat Çağlayan, Naim Ata, and Elif Hande Özcan Çetin collected the data. Data are verified by UC, HK, OO, and EHOC. Ibrahim Halil Tanboğa and Harun Kundi cleaned data. Ibrahim Halil Tanboğa did statistical analyses. IHT, OO, CK, ST, SC, and EHOC drafted the manuscript. Ibrahim Halil Tanboğa, Harun Kundi, Uğur Canpolat, Naim Ata, Murat Çağlayan, Osman Çelik, and Cihangir Kaymaz approved the final draft.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

PEER REVIEW

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REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020;323:1239.
3. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985.
4. Tian W, Jiang W, Yao J, et al. Predictors of mortality in hospitalized COVID-19 patients: a systematic review and meta-analysis. *J Med Virol*. 2020;92:1875-1883.
5. Toniolo M, Negri F, Antonutti M, Mase M, Facchin D. Unpredictable fall of severe emergent cardiovascular diseases hospital admissions during the COVID-19 pandemic: experience of a single large center in Northern Italy. *J Am Heart Assoc*. 2020;9:e017122.
6. Liang W, Liang H, Ou L, et al. Development and validation of a clinical risk score to predict the occurrence of critical illness in hospitalized patients with COVID-19. *JAMA Intern Med*. 2020;180:1081.
7. Ji D, Zhang D, Xu J, et al. Prediction for progression risk in patients with COVID-19 pneumonia: the CALL score. *Clin Infect Dis*. 2020;71:1393-1399.
8. Wynants L, Van Calster B, Collins GS, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. *BMJ*. 2020;369:m1328.
9. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in Covid-19. *BMJ*. 2020;369:m1464.
10. Moons KGM, Altman DG, Reitsma JB, et al. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD): explanation and elaboration. *Ann Intern Med*. 2015;162(1):W1-W73.
11. Collins GS, van Smeden M, Riley RD. COVID-19 prediction models should adhere to methodological and reporting standards. *Eur Respir J*. 2020;56:2002643.
12. Kundi H, Cetin EHO, Canpolat U, et al. The role of frailty on adverse outcomes among older patients with COVID-19. *J Infect*. 2020;4453(20):30636-30638.
13. Steyerberg EW, Harrell FE, Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol*. 2016;69:245-247.
14. Harrell FE. *Regression modeling strategies: with applications to linear models, logistic regression, and survival analysis*. New York: Springer; 2001.
15. NUTS statistical regions of Turkey. https://enwikipediaorg/wiki/NUTS_statistical_regions_of_Turkey 2020.
16. Statistical regions in the European Union and partner countries — NUTS and statistical regions 2021. https://eceuropaeu/eurostat/web/nuts/publications 2020.
17. Marshall A, Altman DG, Holder RL, Royston P. Combining estimates of interest in prognostic modelling studies after multiple imputation: current practice and guidelines. *BMC Med Res Methodol*. 2009;9:57.
18. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta*. 2020;506:145-148.
19. Feldstein LR, Rose EB, Horwitz SM, et al. Multisystem inflammatory syndrome in U.S. children and adolescents. *N Engl J Med*. 2020;383:334-346.
20. Jin S, Jin Y, Xu B, Hong J, Yang X. Prevalence and impact of coagulation dysfunction in COVID-19 in China: a meta-analysis. *Thromb Haemost*. 2020;120:1524-1535.
21. Goshua G, Pine AB, Meizlish ML, et al. Endotheliopathy in COVID-19-associated coagulopathy: evidence from a single-centre, cross-sectional study. *Lancet Haematol*. 2020;7:e575-e582.

SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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