Development and validation of a predictive model for critical illness in adult patients requiring hospitalization for COVID-19

Neha Paranjape MD MPH¹, Lauren L Staples MS PhD candidate², Christina Y Stradwick MA PhD candidate², Herman Gene Ray PhD³, Ian J. Saldanha MBBS MPH PhD⁴

1. Physician, Department of Infectious Disease, Wellstar Medical Group, Marietta, Georgia, USA
2. PhD candidate, Analytics and Data Science Institute, Kennesaw State University, Marietta, Georgia, USA
3. Associate Professors of Statistics, Analytics and Data Science Institute, Kennesaw State University, Marietta, Georgia, USA.
4. Assistant Professor, Center for Evidence Synthesis in Health, Department of Health Services, Policy, and Practice, Department of Epidemiology, Brown University School of Public Health, Providence, Rhode Island, USA

Corresponding author:

Neha Paranjape, MD MPH

Department of Infectious Disease, Wellstar Medical Group, Marietta, Georgia, USA

neha.paranjape@wellstar.org

ORCID 0000-0002-9375-2724

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ABSTRACT

Background: Identifying factors that can predict severe disease in patients needing hospitalization for COVID-19 is crucial for early recognition of patients at greatest risk.

Objective: (1) Identify factors predicting intensive care unit (ICU) transfer and (2) develop a simple calculator for clinicians managing patients hospitalized with COVID-19.

Methods: A total of 2,685 patients with laboratory-confirmed COVID-19 admitted to a large metropolitan health system in Georgia, USA between March and July 2020 were included in the study. Seventy-five percent of patients were included in the training dataset (admitted March 1 to July 10). Through multivariable logistic regression, we developed a prediction model (probability score) for ICU transfer. Then, we validated the model by estimating its performance accuracy (area under the curve [AUC]) using data from the remaining 25% of patients (admitted July 11 to July 31).

Results: We included 2,014 and 671 patients in the training and validation datasets, respectively. Diabetes mellitus, coronary artery disease, chronic kidney disease, serum C-reactive protein, and serum lactate dehydrogenase were identified as significant risk factors for ICU transfer, and a prediction model was developed. The AUC was 0.752 for the training dataset and 0.769 for the validation dataset. We developed a free, web-based calculator to facilitate use of the prediction model (https://icucovid19.shinyapps.io/ICUCOVID19/).

Conclusion: Our validated, simple, and accessible prediction model and web-based calculator for ICU transfer may be useful in assisting healthcare providers in identifying hospitalized patients with COVID-19, who are at high risk for clinical deterioration.
Triage of such patients for early aggressive treatment can impact clinical outcomes for this potentially deadly disease.

Keywords: COVID-19; SARS-COV2; ICU prediction model
INTRODUCTION

COVID-19 is a disease caused by SARS-CoV2, a novel coronavirus first identified in Wuhan, China in December 2019. Since then, it has spread globally resulting in an ongoing pandemic. The United States (U.S.) has been an epicenter for many months and, as of January 2021, has had over 23 million confirmed cases, with over 393,000 deaths.¹

The clinical spectrum of COVID-19 varies from a mild upper respiratory tract infection to severe life-threatening respiratory failure. Although several risk factors, such as age, sex, and certain co-morbidities, have been identified, it remains unclear why some patients recover well within a few days of hospitalization while others progress to a critical illness. While there are several ongoing clinical trials evaluating therapeutic agents for COVID-19, identifying the subset of patients that would benefit the most from these therapies remains a challenge. This is especially true during times of a case surge and/or drug shortage. Studies from China and Italy have demonstrated that certain factors, such as age, comorbidities, race, and certain laboratory markers, are associated with risk of developing severe disease.²³ The Modified Early Warning Score (MEWS) for clinical deterioration that was developed in 2015 has not shown to be accurate in predicting the need for intensive care in patients with COVID-19.⁴ Other predictive models have been developed for hospitalized COVID-19 patients in Beijing, China, New York, U.S., and Massachusetts, U.S.⁵⁶⁷ However, key differences in population demographics between China and the U.S., and among states in the U.S., indicated the need for development and validation of a prognostic predictive model for our center. Identifying factors that can predict severe disease in hospitalized patients with COVID-19 is crucial for early
recognition of at-risk individuals and for informing policy decisions regarding triage of patients who would benefit most from early treatment.

This paper describes the development and validation of a model and simple online calculator to predict ICU admission in hospitalized patients with COVID-19.

METHODS

We developed and validated a prediction model based on analysis of a retrospective sample of patients admitted to a large metropolitan health care system consisting of nine community hospitals in the state of Georgia, U.S. The study was granted exempt status and the requirement for obtaining informed consent was waived by the Wellstar Health System Institutional Review Board (Approval Number: 1611062-1). The reporting of this study adheres to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) Statement.8
Training and Validation Datasets

We analyzed de-identified data on a convenience sample of all adult patients (18 years or older) who were confirmed positive for SARS-CoV2 via a nasopharyngeal swab polymerase chain reaction (PCR) test and hospitalized with COVID-19 between March 1, 2020 and July 31, 2020. We excluded patients who were admitted directly to the ICU because they already experienced our outcome of interest (i.e., ICU transfer) at the their earliest observed time-point.

Patients admitted from March 1 through July 10, 2020 (75% of the sample) were included in the training dataset, while those admitted from July 11 through July 31, 2020 (25% of the sample) were included in the validation dataset. The cut-point determining the training/validation split was selected to provide a 75%:25% training/validation split, while maintaining temporal order.

Data Extracted and Variables Considered

We extracted all data from electronic medical records. Variables gathered included:

- Demographics, e.g., age, sex, race, body mass index (BMI);
- Temperature and oxygen saturation on room air (RA) on admission;
- Laboratory values of C-reactive protein (CRP), lactate dehydrogenase (LDH), ferritin, D-dimer, and absolute lymphocyte count on admission;
• Presence of comorbidities, e.g., hypertension (HTN), diabetes mellitus (DM), chronic kidney disease (CKD), asthma and chronic obstructive pulmonary disease (COPD), coronary artery disease (CAD); and
• Status regarding transfer to the ICU service (irrespective of the patient’s physical location).

We used the above pool of variables to develop a simple and easy to use tool for clinicians based on data commonly available at most acute care facilities, including small community or rural hospitals. For patients with multiple hospitalizations, we considered their first hospitalization for this study.

Statistical Analysis

We conducted bivariable and multivariable analyses of the associations between various independent variables and the dependent variable of interest (transfer to ICU service). Chi-square tests and simple regressions were used to provide descriptive statistics. For continuous data, such as laboratory values, outliers exceeding three times the standard deviation (3σ) were replaced with 3σ. The maximum number of outliers for each continuous variable remained low (<1.4%). Because the amount of missingness of continuous variables was low (<10%; see appendix), missing data were imputed using median values. There were no missing data for sex or race. Each comorbidity was coded as “1=present” or “0=absent”.

We conducted a multivariable logistic regression to determine the probability (from the odds) of being transferred to the ICU service, with the goal of providing a model for predicting the probability of ICU transfer for future cases. We used a backwards selection stepwise method, with a P value threshold of 0.05. To validate the model, we graphed a receiver operating characteristic (ROC) curve and calculated the area under the curve (AUC). We also calculated the sensitivity, specificity, positive predictive value, negative predictive value, and likelihood ratio.

We used Python® version 3.7.6 for preprocessing and SAS® server version 9.4 for Chi-square tests and regression analyses.9,10

**Funding Source**

None

**IRB Approval**

Approval Number: 1611062-1
RESULTS

Description of Study Population (Combined Sample)

Among all 2,685 eligible patients, the mean age was 59.7 years (standard deviation [SD] = 17.3) [Table 1]. Approximately half of the patients (49%) were of female sex. The mean BMI was 31.7 kg/m² (SD = 8.9). Forty-seven percent of patients were Black and 34% were White. HTN (72%) and DM (55%) were the most common comorbidities.

Training Dataset

The demographic characteristics and comorbidities of the 2,014 patients in the training dataset, which comprised 75% of the combined sample, were very similar to that of the combined sample [Table 1].

Validation Dataset

The mean age was slightly lower (57.8 years) in this group of 671 patients [Table 1]. Forty-two percent of patients were Black and 35% were White. The proportion of patients with each of the comorbid conditions was slightly lower in the validation dataset than the training and combined datasets.
TABLE 1. Demographic characteristic and comorbidities for patients in the training dataset (March 1 to July 10, 2020) and validation dataset (July 11 to July 31, 2020)

| Characteristic | Training Dataset (N=2,014) | Validation Dataset (N=671) | Combined Sample (N=2,685) |
|----------------|-----------------------------|-----------------------------|---------------------------|
|                | n (%)                       | n (%)                       | N (%)                     |
| Age (years)    |                             |                             |                           |
| Mean           | 60.3                        | 57.8                        | 59.7                      |
| Standard deviation | 17.4                  | 16.8                        | 17.3                      |
| Minimum        | 18                          | 19                          | 18                        |
| Maximum        | 104                         | 101                         | 104                       |
| Sex n (%)      |                             |                             |                           |
| Female         | 990 (49)                    | 315 (47)                    | 1305 (49)                 |
| Male           | 1024 (51)                   | 356 (53)                    | 1380 (51)                 |
| Body mass index (BMI) |                             |                             |                           |
| Mean           | 31.5                        | 32.4                        | 31.7                      |
| Standard deviation | 8.9                   | 8.7                         | 8.9                       |
| Minimum        | 12.8                        | 12.8*                       | 12.8*                     |
| Maximum        | 59.6                        | 59.6*                       | 59.6                      |
| Race n (%)     |                             |                             |                           |
| Black/African American | 981 (49)              | 281 (42)                    | 1262 (47)                 |
| White/Caucasian | 667 (33)                  | 236 (35)                    | 1262 (34)                 |
| Other          | 366 (18)                    | 153 (23)                    | 520 (19)                  |
| Comorbidities n (%) |                             |                             |                           |
| Hypertension (HTN) | 1495 (74)                 | 437 (65)                    | 1932 (72)                 |
| Diabetes mellitus (DM) | 1118 (56)              | 354 (53)                    | 1472 (55)                 |
| Coronary artery disease (CAD) | 620 (31)             | 155 (23)                    | 775 (29)                  |
| Chronic kidney disease (CKD) | 523 (26)             | 123 (18)                    | 646 (24)                  |
| Malignancies   | 270 (13)                    | 63 (9)                      | 333 (12)                  |
| Chronic obstructive pulmonary disease (COPD)/Asthma | 67 (3)               | 0 (0)                       | 67 (2)                    |

* Validation data values have been winsorized to the minimum/maximum values of the training dataset so as not to extrapolate.

Clinical and Laboratory Values and ICU Transfer Status (All Datasets)

Mean patient temperature, oxygen saturation, CRP level, and absolute lymphocyte count were similar across datasets [Table 2]. Compared with patients in the training dataset, patients in the validation dataset had somewhat higher levels of LDH, but somewhat lower levels of ferritin and D-dimer. In the combined sample, 37% of patients were transferred to the ICU. This percentage was 40% and 29% in the training and validation datasets, respectively.
TABLE 2. Clinical and laboratory values at admission and ICU transfer status for patients in the training dataset (March 1 to July 10, 2020) and validation dataset (July 11 to July 31, 2020)

| Characteristic                        | Training Dataset (N=2,014) | Validation Dataset (N=671) | Combined Sample (N=2,685) |
|---------------------------------------|----------------------------|----------------------------|--------------------------|
|                                       | n  | %  | n  | %  | N  | %  |
| **Temperature (F)**                   |    |    |    |    |    |    |
| Mean                                  | 98.8 | 98.6 | 98.8 | 98.8 | 98.8 | 98.8 |
| Standard deviation                    | 1.3 | 1.2 | 1.3 | 1.3 | 1.3 | 1.3 |
| Minimum                               | 94.7 | 94.7* | 94.7 | 94.7 | 94.7 | 94.7 |
| Maximum                               | 103.0 | 103.0* | 103.0 | 103.0 | 103.0 | 103.0 |
| **Oxygen saturation (%)**             |    |    |    |    |    |    |
| Mean                                  | 95.0 | 94.6 | 94.9 | 94.9 | 94.9 | 94.9 |
| Standard deviation                    | 3.2 | 3.1 | 3.2 | 3.2 | 3.2 | 3.2 |
| Minimum                               | 84.4 | 84.4* | 84.4 | 84.4 | 84.4 | 84.4 |
| Maximum                               | 100 | 100 | 100 | 100 | 100 | 100 |
| **Laboratory values at admission (mean (SD))** |    |    |    |    |    |    |
| C-reactive protein (mg/dl)            | 9.8 (8.9) | 9.9 (8.7) | 9.8 (8.9) | 9.8 (8.9) | 9.8 (8.9) | 9.8 (8.9) |
| Lactate dehydrogenase (mg/ml)         | 371.7 (196.1) | 384.1 (195.7) | 374.9 (196.0) | 374.9 (196.0) | 374.9 (196.0) | 374.9 (196.0) |
| Ferritin (ng/ml)                      | 1033.2 (1895.5) | 948.5 (1495.5) | 1011.8 (1795.3) | 1011.8 (1795.3) | 1011.8 (1795.3) | 1011.8 (1795.3) |
| D-dimer (ng/dl)                       | 1587.0 (3209.2) | 1128.0 (2829.6) | 1462.7 (3117.1) | 1462.7 (3117.1) | 1462.7 (3117.1) | 1462.7 (3117.1) |
| Absolute lymphocyte count (x10^9/dl)  | 1.2 (0.8) | 1.1 (0.6) | 1.2 (0.7) | 1.2 (0.7) | 1.2 (0.7) | 1.2 (0.7) |
| **Transferred to intensive care unit (ICU)** |    |    |    |    |    |    |
| No                                    | 1210 (60) | 479 (71) | 1689 (63) | 1689 (63) | 1689 (63) | 1689 (63) |
| Yes                                   | 804 (40) | 192 (29) | 996 (37) | 996 (37) | 996 (37) | 996 (37) |

* Validation data values have been winsorized to the minimum/maximum values of the training dataset so as not to extrapolate.

**ICU Risk Score Model Development**

In multivariable logistic regression analyses of the training dataset (2,014 patients), the following variables were predictive of ICU transfer [Table 3]:

- CAD, CKD, and DM (comorbidities): The odds of ICU transfer were higher by 32% in patients with CAD, 59% in patients with CKD, and 97% in patients with DM.
- Serum CRP: A 1-unit increase in serum CRP was associated with a 5.4% higher odds of ICU transfer.
- Serum LDH: A 1-unit increase in serum LDH was associated with a 0.4% higher odds of ICU transfer.
### TABLE 3. Final Model from Stepwise Backwards Selection, Multivariate Logistic Regression Predicting Intensive Care Unit Status.

| Variable                        | Estimate | Odds Ratio (95% CI)       | p-Value   |
|---------------------------------|----------|---------------------------|-----------|
| Intercept                       | -2.9826  | 0.0507                    | <0.0001   |
| Coronary artery disease (CAD)   | 0.2774   | 1.3197 (1.055, 1.65)      | 0.0149    |
| Chronic kidney disease (CKD)    | 0.4636   | 1.5898 (1.259, 2.007)     | <0.0001   |
| Diabetes mellitus (DM)          | 0.6756   | 1.9652 (1.599, 2.415)     | <0.0001   |
| Serum C-reactive protein (CRP)  | 0.0525   | 1.0539 (1.041, 1.067)     | <0.0001   |
| Serum lactate dehydrogenase (LDH)| 0.00397 | 1.0040 (1.003, 1.005)     | <0.0001   |

All model inputs into stepwise selection are listed in the Appendix.

### ICU Risk Score Model Validation

We validated the model using data from the 671 patients in the validation dataset. As seen in Figure 1, the model performed well in both the training and validation datasets, with AUC values of 0.752 and 0.769, respectively. At a probability cut-off of 20%, our model correctly predicted 95% of actual ICU transfers (PPV of 34%) and 27% of non-ICU transfers (NPV of 94%). The Likelihood Ratio for positive and negative prediction was 1.31 and 0.17 respectively. (Appendix E)
Based on the predictive model developed in this study, we designed a free, easy to use, online web-based calculator, to help clinicians predict the probability of hospitalized patients with COVID-19 being transferred to the ICU (https://icucovid19.shinyapps.io/ICUCOVID19/).

**DISCUSSION**

**Summary of Findings**

We developed and validated a prediction model in a total of 2,685 patients with COVID-19 to help clinicians identify patients who, at admission, are at risk for subsequent clinical deterioration, thus potentially helping appropriate triage and management of these patients. The model was developed quickly in response to local need during the
COVID-19 surge when hospitals in our health system were at crisis capacity. The potential value of this model is enhanced by the fact that its required inputs (DM, CAD, CKD, serum LDH, and serum CRP) are commonly available at most acute care facilities, including small community or rural hospitals. Measurements of these inputs are already routine in patients hospitalized with COVID-19. Our risk calculator was developed using variables on admission and is therefore is a true predictor of severe disease in absence of in-patient treatments, such as remdesivir and dexamethasone, that are now considered standard of care for hospitalized patients.

The ability to predict with reasonable accuracy which patients are most likely to deteriorate and need ICU care can be particularly useful when a hospital is at crisis capacity. In such situations of bed shortages, clinicians often need to prioritize the sickest patients for hospitalization. Some patients who would otherwise be hospitalized may be denied admission. The model and risk calculator we developed in the current study could greatly help decision-making in this context. Along with the clinicians’ judgment, patients with an ICU transfer probability score of 20% or higher may be given priority for in-patient treatment over admission to an observation unit or to be sent home.
**Comparison with Similar Studies**

While several other comorbid conditions have been identified as risk factors for severe COVID-19, our study uncovers DM, CAD, and CKD as the most significant factors.\(^{11}\) In addition to the easy availability of the variables that serve as inputs, our model’s simplicity is one of its greatest strengths. Using fewer variables, our model has similar performance (in terms of AUC) as a recent predictive model published in October 2020.\(^{7}\)

Our health system serves a metropolitan population in Georgia with significant chronic conditions and health disparities.\(^{12}\) Although age and high BMI are described as a risk factor for COVID-19 infection in the general population, these did not emerge as independent risk factors in our analysis.\(^{13, 14}\) This was likely because our study included only hospitalized patients and a majority of patients needing hospitalization were older (mean age of 62 years) and had a higher BMI (mean 31 kg/m\(^2\)).

LDH is an intracellular enzyme that catalyzes the conversion of lactate to pyruvate. It is found in most organ tissue cells and is known to be a marker of cell injury. Elevated levels of LDH have been detected in patients with COVID-19, and it has also been identified, as an independent predictor of disease severity.\(^{15}\) CRP is an acute phase protein of hepatic origin that binds to dead or dying cells and activates the complement system, promoting phagocytosis by macrophages. This biomarker has also been shown to predict disease severity.\(^{16}\)
**Strengths and Limitations**

Our study has a number of strengths. **First**, our predictive model included a limited number of variables that are easily available at hospital presentation, including small tertiary care hospitals. **Second**, we had a large sample size in both the training as well as validation datasets. **Third**, the demographics of patients in the current study are highly representative of hospitalized patients in the U.S., which are more diverse and include more vulnerable populations than elsewhere. **Fourth**, our health system includes nine community hospitals with a total capacity of over 2,500 beds. The model we developed may therefore be generalizable to other similar acute care facilities in the U.S. **Fifth**, apart from laboratory values, our analysis included presence of co-morbidities such as DM, CAD, and CKD that have been shown to be risk factors for severe disease. **Lastly**, we created an easy, ready to use, web-based calculator, freely accessible to clinicians.

Our study also has some limitations. **First**, we developed and validated the prediction model only for hospitalized patients. Thus, the model may not be applicable to non-hospitalized patients with COVID-19. **Second**, although it involved a large sample size, this study is based on a single health system. ICU transferal practices may differ across health systems. **Third**, we conducted data extraction from electronic medical records...
only. The accuracy of patient demographics and pre-existing conditions could not be independently verified. Fourth, of the laboratory values, three the variables (CRP, LDH, and D-dimer) had <10% missing values that were imputed by the median. This approach was similar to a recent predictive model published in October 2020. Lastly, we recognize that this tool may not be suitable for patient populations with significantly different genetic and socioeconomic backgrounds from ours, however similar site-specific models can be developed quickly and provide a useful tool in triage of patients during surge crises, as many centers are currently experiencing.

In summary, we developed and validated a prognostic model to predict subsequent ICU transfer in hospitalized patients with COVID-19. We do not suggest that the decision for patient transfer to the ICU be based solely on the prediction model described in the current study. The model should be used in conjunction with the treating clinical team’s evaluation in the context of all available information and history regarding an individual patient.

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APPENDICES

Appendix A: Variables Considered for Backwards Stepwise Selection for Models Predicting Intensive Care Unit Status

- Age
- Female
- Black race
- White race
- Temperature
- Oxygen saturation
- Body mass index
- Chronic obstructive pulmonary disease (COPD) or asthma
- Coronary artery disease
- Chronic kidney disease
- Diabetes mellitus
- Hypertension
- Serum lactate dehydrogenase
- Serum ferritin
- Serum D-dimer
- Serum C-reactive protein
- Absolute lymphocyte count
- Age X Race
- Age X Diabetes mellitus
- Age X Coronary artery disease
- Age X Chronic kidney disease
- Age X Hypertension
- Hypertension X Diabetes mellitus
- Serum ferritin X Serum Lactate dehydrogenase
- Serum lactate dehydrogenase x Serum D-dimer
- Serum lactate dehydrogenase x Serum C-reactive protein
- Serum ferritin x Serum D-dimer

All variables with correlations exceeding 0.20 (absolute value) were included as potential interactions. The reference group for race is Other Race. The reference group for sex is Male.
Appendix B: Correlations Between Demographic Predictor Variable Candidates.
Appendix C: Correlations Between Laboratory Predictor Variable Candidates.
## Appendix D: Missing Data

| Variable                        | %Missing |
|--------------------------------|----------|
| Age                            | 0%       |
| Sex                            | 0%       |
| BMI                            | 0%       |
| Race                           | 0.5%     |
| Temperature                    | 0.7%     |
| Oxygen Saturation              | 0.7%     |
| CRP                            | 9.8%     |
| LDH                            | 9.7%     |
| Ferritin                       | 4.2%     |
| D-dimer                        | 9.3%     |
| Absolute lymphocyte count      | 0.2%     |
Appendix E: Probability score with corresponding Sensitivity, Specificity, Positive Predictive Value, Negative Predictive Value, Positive Likelihood Ratio, Negative Likelihood Ratio and Youden Index

| Probability | Sensitivity | Specificity | PPV | NPV | LR (Pos) | LP (Neg) | Youden |
|-------------|-------------|-------------|-----|-----|----------|----------|--------|
| 10%         | 100%        | 1%          | 29% | 100%| 1.01     | 0.00     | 0.01   |
| 20%         | 95%         | 27%         | 34% | 94% | 1.31     | 0.17     | 0.23   |
| 30%         | 82%         | 53%         | 41% | 88% | 1.77     | 0.33     | 0.36   |
| 40%         | 67%         | 70%         | 47% | 84% | 2.22     | 0.48     | 0.37   |
| 50%         | 55%         | 84%         | 58% | 82% | 3.39     | 0.54     | 0.39   |
| 60%         | 40%         | 91%         | 64% | 79% | 4.51     | 0.66     | 0.31   |
| 70%         | 31%         | 95%         | 71% | 77% | 6.31     | 0.73     | 0.26   |
| 80%         | 18%         | 98%         | 81% | 75% | 10.91    | 0.83     | 0.17   |
| 90%         | 8%          | 99%         | 80% | 73% | 9.98     | 0.92     | 0.07   |
# Appendix F: Completed Checklist to Indicate Adherence to the TRIPOD Reporting Guideline for Studies Developing and Validating Multivariable Predictive Models

| Section/Topic                  | Checklist Item                                                                 | Page |
|--------------------------------|--------------------------------------------------------------------------------|------|
| **Title and abstract**         |                                                                                |      |
| Title                          | Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1    |
| Abstract                       | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 2    |
| **Introduction**               |                                                                                |      |
| Background and objectives      | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 3-4  |
| 3a                             | Specify the objectives, including whether the study describes the development or validation of the model or both. | 4    |
| **Methods**                   |                                                                                |      |
| Source of data                 | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 4    |
| 4a                             | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 4    |
| Participants                   | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | 4    |
| 5a                             | Describe eligibility criteria for participants.                               | 4    |
| 5b                             | Give details of treatments received, if relevant.                            | NA   |
| Outcome                        | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 5    |
| 6a                             | Report any actions to blind assessment of the outcome to be predicted.       | NA   |
| Predictors                     | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured. | 5    |
| 7a                             | Report any actions to blind assessment of predictors for the outcome and other predictors. | NA   |
| Sample size                    | Explain how the study size was arrived at.                                    | 4-5  |
| Missing data                   | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 5    |
| Statistical analysis methods   |                                                                 |      |
| 10a                            | Describe how predictors were handled in the analyses.                        | 5-6  |
| 10b                            | Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 5-6  |
| 10c                            | For validation, describe how the predictions were calculated.                | 5-6  |
| 10d                            | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 5-6  |
| 10e                            | Describe any model updating (e.g., recalibration) arising from the validation, if done. | NA   |
| Risk groups                    | Provide details on how risk groups were created, if done.                    | NA   |
| Development vs. validation     | For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors. | 4    |
| **Results**                   |                                                                                |      |
| Participants                   | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | 6-7  |
| 13a                            | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 6-7  |
| 13b                            | For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome). | 6    |
| Model development              | Specify the number of participants and outcome events in each analysis.       | 7-8  |
| 14a                            | If done, report the unadjusted association between each candidate predictor and outcome. | Appendix |
| Model specification            | Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 8-9  |
| 15a                            | Explain how to use the prediction model.                                     | 10-12|
| Model performance              | Report performance measures (with CIs) for the prediction model.             | 9    |
| Model updating                 | If done, report the results from any model updating (i.e., model specification, model performance). | NA   |
| Discussion                     |                                                                                |      |
| Limitations | 18 | D;V | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 11-12 |
| Interpretation | 19a | V | For validation, discuss the results with reference to performance in the development data, and any other validation data. | 11 |
| | 19b | D;V | Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. | 12 |
| Implications | 20 | D;V | Discuss the potential clinical use of the model and implications for future research. | 12-13 |
| Other information | | | | |
| Supplementary information | 21 | D;V | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | 10 |
| Funding | 22 | D;V | Give the source of funding and the role of the funders for the present study. | 1 |

*Items relevant only to the development of a prediction model are denoted by D, items relating solely to a validation of a prediction model are denoted by V, and items relating to both are denoted D;V.

Abbreviations: NA = not applicable.