Comparison of in-hospital mortality risk prediction models from COVID-19

Ali A. El-Solh1,2,3*, Yolanda Lawson1†, Michael Carter1†, Daniel A. El-Solh1†, Kari A. Mergenhagen1†

1 VA Western New York Healthcare System, Buffalo, New York, United States of America, 2 Department of Medicine, Division of Pulmonary, Critical Care, and Sleep Medicine, Jacobs School of Medicine, University at Buffalo, Buffalo, New York, United States of America, 3 Department of Epidemiology and Environmental Health, School of Public Health, University at Buffalo, Buffalo, New York, United States of America

These authors contributed equally to this work.
† These authors also contributed equally to this work.
* solh@buffalo.edu

Abstract

Objective

Our objective is to compare the predictive accuracy of four recently established outcome models of patients hospitalized with coronavirus disease 2019 (COVID-19) published between January 1st and May 1st 2020.

Methods

We used data obtained from the Veterans Affairs Corporate Data Warehouse (CDW) between January 1st, 2020, and May 1st 2020 as an external validation cohort. The outcome measure was hospital mortality. Areas under the ROC (AUC) curves were used to evaluate discrimination of the four predictive models. The Hosmer–Lemeshow (HL) goodness-of-fit test and calibration curves assessed applicability of the models to individual cases.

Results

During the study period, 1634 unique patients were identified. The mean age of the study cohort was 68.8±13.4 years. Hypertension, hyperlipidemia, and heart disease were the most common comorbidities. The crude hospital mortality was 29% (95% confidence interval [CI] 0.27–0.31). Evaluation of the predictive models showed an AUC range from 0.63 (95% CI 0.60–0.66) to 0.72 (95% CI 0.69–0.74) indicating fair to poor discrimination across all models. There were no significant differences among the AUC values of the four prognostic systems. All models calibrated poorly by either overestimated or underestimated hospital mortality.

Conclusions

All the four prognostic models examined in this study portend high-risk bias. The performance of these scores need to be interpreted with caution in hospitalized patients with COVID-19.
Introduction
Since the first reported case of COVID-19 in Wuhan, China, at the end of 2019, COVID-19 has rapidly spread throughout the globe, shattering world economy and traditional way of life [1]. As of August 1, 2020, more than 17 million laboratory-confirmed cases had been reported worldwide. The number of infected individuals has surpassed that of SARS and MERS combined. Despite the valiant public health responses aimed at flattening the curve to slow the spread of the virus, more than 675,000 people have died from the disease [2].

Numerous prognostic models ranging from rule-based scoring systems to advanced machine learning models have been developed to provide prognostic information on patients with COVID-19 [3]. Such information is valuable both to clinicians and patients. It allows healthcare providers to stratify treatment strategy and plan for appropriate resource allocation. As for patients, it offers valuable guidance when advance directives are to be implemented. However, initial description of these prognostic models has been based on patients from a localized geography and time frame. These evaluations may thus be limited in scope of their predictability as concerns have been raised about the applicability of such models when patient demographics change with geography, clinical practice evolves with time, and when disease prevalence varies with both [4, 5]. In response to the call for sharing relevant COVID-19 research findings, many of these models have been published in open access forums before undergoing a peer review. The quality of these models are further compromised by the relatively small sample size both in derivation and validation [6]. Recently, Wynants and colleagues [7] conducted a systematic review of COVID-19 models developed for predicting diagnosis, progression, and mortality from the infection. All models reviewed were at high risk of bias because of improper selection of control patients, data overfitting, and exclusion of patients who had not experienced the event of interest by the end of the study. Besides, external validation of these models was rarely performed. In the present study, we sought to examine the external validity of four scoring models that have shown excellent precision for predicting hospitalization outcome from COVID-19 [8–10].

Methods
Patients
We used data from the Veterans Affairs Corporate Data Warehouse (CDW) of all patients tested positive on the reverse transcriptase polymerase chain reaction assay for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) between January 1st, 2020 and May 1st 2020. Data were extracted from CDW using structure query language (SQL) with pgAdmin4 PostgreSQL 9.6 on July 16, 2020. The de-identified database contained data of demographic information, laboratory values, treatment processes, and survival data. We excluded patients who had a length of stay <24 hours, who lacked vital signs or laboratory data, and who were transferred to or from another acute care facility (because we could not accurately determine the onset or subsequent course of their illness). The median time between the date the case index tested positive for COVID-19 and the date of discharge (whether alive or dead) was referred to as the median follow-up. All data analysis was done on the VA Informatics and Computing Infrastructure workspace (VINCI). Access of the CDW for research was approved by the Institutional Review Board of the VA Western New York Healthcare System. Because the study was deemed exempt, informed consent was not required.

Missing data
Demographic and comorbidity data contained almost no missing data. However, many baseline laboratory values had up to 20% missing data. When data are missing at random,
statistical methods such as multiple imputation give less biased and realistic results compared with complete case analysis [11]. However, the ordering of a laboratory test is likely driven by factors that make assumptions underlying multiple imputation inaccurate. In the absence of a standardized method to address missing data under these conditions, we have adopted the following approach: Missing data were imputed with the centered mean. A dummy variable (called also an indicator variable) is added to the statistical model in order to indicate whether the value for that variable is available or not [12]. When using the indicator method to handle missing covariate data, the value for the missing variable is set to 1, otherwise the value is set to 0. Then, both the primary variable and the indicator variable are entered into the regression model to predict the intended outcome. Then, both the primary variable and missingness indicator were evaluated in a mixed-effects logistic regression model and the primary mean imputed variable was considered.

External validation of risk models

We conducted initially a search strategy using PubMed and Medline databases between January 1st, 2020 and May 1st, 2020. The literature was done using the following keywords in combination: 1) (COVID-19 OR SARS-CoV-2 OR 2019-nCoV) AND 2) (Mortality OR Death) AND 3) (Predictive model OR Scoring system) (“S1 Table” in S1 File). Inclusion criteria were: 1) English-written peer reviewed studies; 2) hospitalized patients with COVID-19; 3) prognostic models for predicting in-hospital mortality; and 4) sample size of no less than 100. Exclusion criteria included duplicate studies and lack of access to full documents. Studies identified by the search strategy were reviewed by title and abstract. Screening was conducted by two independent investigators (YL and DES). Any disagreements were resolved by consensus. Fifteen studies were identified. Two were concise reviews leaving 13 studies for further evaluation. Four prognostic models were selected based on availability of the predictive parameters in the CDW [8–10, 13]. For each predictive model, we replicated the methods used by the original authors to calculate the predicted hospital mortality from COVID-19. The main outcome of interest was in-hospital mortality.

We incorporated the Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) principles for validating each of the selected predictive models [14]. The risk of bias for each predictive model was evaluated by the Prediction model Risk Of Bias Assessment Tool (PROBAST) described by Moons and colleagues [15].

Statistical analysis

The normality of continuous variables was assessed using the Kolmogorov–Smirnov test. Continuous variables with and without normal distribution were reported as mean (standard deviation (SD)) and median (interquartile range (IQR)), respectively. Categorical variables were presented as number (percentage). Continuous variables with or without normal distribution between survivors and non-survivors were compared using t-test and Mann–Whitney U test, respectively. Comparisons of categorical variables were performed using Chi squares tests.

Receiver operating characteristic (ROC) curves were drawn for each model by plotting sensitivity versus one minus specificity. The area under the receiver operating characteristic curve (AUC) was used to evaluate the discriminatory capacity of the selected models [16]. An ideal discrimination produces an AUC of 1.0, whereas discrimination that is no better than chance produces an AUC of 0.5. Based on a rough classifying system, AUC can be interpreted as follows: 90–100 = excellent; 80–90 = good; 70–80 = fair; 60–70 = poor; 50–60 = fail [17]. Pairwise comparison of the area under the ROC curve for each model was performed according to the method described by Hanley and McNeil [16]. If P is less than the conventional 5% (P <
the compared areas are considered statistically different. Calibration was assessed with the Hosmer–Lemeshow goodness-of-fit $\chi^2$ estimates by grouping cases into deciles of risk [18]. The method involves sorting the predictive probabilities of death in ascending order and dividing the total number of cases into 10 equally distributed subgroups or deciles. Calibration plots were provided to show the relationship between model-based predictions of mortality and observed proportions of mortality using the loess algorithm [19]. The non-parametric bootstrapping method was used to calculate the 95% confidence intervals (CIs) of both discrimination and calibration estimates [20]. These CIs were reported using the percentile method, or bias corrected method if the estimation bias was greater than 25% of the standard error [21]. All analyses were performed using STATA 15.0 (STATA Corp). A $P$-value less than .05 was considered statistically significant.

**Results**

A total of 1634 patients were hospitalized for COVID-19 between January 1, 2020 and May 1, 2020. The majority of patients were male (95%) with 47% identified as Caucasian, 43% as African American, and 10% as Latino. Fever (65%), dyspnea (41%), and cough (32%) were the three most common manifestations at hospital admission. The mean age of the cohort was 68.8±13.4 years. Fifty percent of the group had three or more comorbidities. Hypertension was the most common comorbidity, followed by hyperlipidemia, and heart disease. The median time from illness onset to admission was 7.8 days (interquartile range 1.0–14.2). Of the 817 patients treated in the intensive care units, 478 (59%) required invasive mechanical ventilation. Overall, 73.8% received at least one antibiotic treatment during their hospital stay. Almost half of the patients had received azithromycin and/or hydroxychloroquine. After a median follow-up of 58 (IQR, 50–68) days, there were 475 deaths (overall mortality, 29%) for a mortality rate of 12 (95%CI, 11–12) per 1000 patient-days.

The clinical characteristics of survivors and non-survivors of the CDW cohort are depicted in “Table 1”. In univariate analysis, age, current tobacco smoker, high burden of comorbidities, lymphopenia, thrombocytopenia, liver function abnormalities, and elevated procalcitonin and D-dimer levels were associated with mortality. Compared with survivors, non-survivors were more likely to receive vasopressors, to require mechanical ventilation, and to develop complications including acute respiratory distress syndrome, acute renal failure, and septic shock.

A summary of models methodology is depicted in “S2 Table” in S1 File. “Table 2” shows the independent risk variables and corresponding odds ratios of the four prognostic models. All four models were classified as overall high ROB either because of flawed methods of data analysis pertaining to handling of missing data or lack of validation cohort “S3 Table” in S1 File. The predictive performances of the four models on the CDW cohort are presented in “Table 3”. The AUCs indicate inferior discriminative power across all models compared to the AUCs obtained by the derivation cohorts. Pair-wise comparisons of the AUCs were performed by using the method described by Hanley and McNeil [22] “Table 4”. Overall the best discrimination was obtained by the scoring model proposed by Shang et al. [9] which attained significance with respect to Chen et al. [8] and Yu et al. [10] models (AUCs 0.72 (95% CI 0.69–0.74) versus 0.68 (0.66–0.70) and 0.63 (95% CI 0.60–0.66); respectively) “Fig 1”. The least discriminatory model was the model described by Yu et al. [10] with an AUC of 0.63 (95% CI 0.60–0.66).

The Hosmer–Lemeshow goodness-of-fit test reveals poor calibration ($p < 0.05$) for all the models “Table 3”. Calibration was further explored by plotting the observed to expected frequency of death for each quintile of every model “Fig 2”. The Chen et al. model [8] showed a departure from expected risks at the tail of risk distribution for each of the three endpoints.
Table 1. Comparison of baseline characteristics and treatment between survivors and non-survivors of the external validation group.

|                                | Study population N = 1,634 | Missing observation (%) | Survivors N = 1,159 | Non-survivors N = 475 | P value |
|--------------------------------|----------------------------|-------------------------|---------------------|------------------------|---------|
| Age, years                     | 68.8±13.4                  | 0                       | 66.1±13.5           | 75.6±10.6              | <0.001  |
| Sex, n (%)                     |                            |                         |                      |                        | 0.004   |
| Male                           | 1553 (95)                  | 1,090 (94)              | 463 (97)            |                        |         |
| Female                         | 81 (5)                     | 69 (6)                  | 12 (3)              |                        |         |
| BMI, kg/m²                     | 28 (24–33)                 | 1.0                     | 27 (23–32)          | 29 (25–33)             | <0.001  |
| Current smoker, n(%)           | 171 (10)                   | 0                       | 104 (9)             | 67 (14)                | 0.002   |
| Comorbidities, n (%)           |                            |                         |                      |                        |         |
| COPD                           | 404 (25)                   | 0                       | 261 (23)            | 143 (30)               | 0.001   |
| Diabetes mellitus              | 801 (49)                   | 0                       | 544 (47)            | 257 (54)               | 0.008   |
| Hypertension                   | 1208 (74)                  | 0                       | 839 (72)            | 369 (78)               | 0.03    |
| CAD                            | 461 (28)                   | 0                       | 290 (25)            | 171 (36)               | <0.001  |
| Heart failure                  | 299 (18)                   | 0                       | 177 (15)            | 122 (26)               | <0.001  |
| Chronic renal failure          | 111 (7)                    | 0                       | 74 (6)              | 37 (8)                 | 0.31    |
| Liver cirrhosis                | 65 (4)                     | 0                       | 47 (4)              | 18 (4)                 | 0.8     |
| HIV infection                  | 32 (2)                     | 0                       | 22 (2)              | 10 (2)                 | 0.784   |
| Charlson Comorbidity Index     | 3 (1–6)                    | 0                       | 2 (1–5)             | 4 (2–7)                | <0.001  |
| ICU admission                  | 817 (50)                   | 0                       | 462 (39)            | 355 (74)               | <0.001  |
| Fever                          | 1064 (65)                  | 0                       | 764 (66)            | 300 (63)               | 0.29    |
| Cough                          | 530 (32)                   | 0                       | 414                 | 116 (24)               | <0.001  |
| Dyspnea                        | 666 (41)                   | 0                       | 463                 | 203 (43)               | 0.29    |
| Fatigue                        | 251 (15)                   | 0                       | 177                 | 74 (16)                | 0.87    |
| Diarrhea                       | 165 (10)                   | 0                       | 132                 | 33 (7)                 | 0.007   |
| WBC, x10⁹/L                    | 6.2 (4.8–8.4)              | 1.3                     | 6 (4.7–8)           | 6.7 (5.1–9.7)          | <0.001  |
| Lymphocytes, x10⁹/L            | 0.88 (0.58–1.25)           | 1.9                     | 0.92 (0.62–1.3)     | 0.77 (0.49–1.07)       | <0.001  |
| Hemoglobin, g/L                | 13.25 (11.7–14.6)          | 9.7                     | 13.6 (11.9–14.7)    | 12.9 (11.4–14.5)       | 0.2     |
| Platelets, x10⁹/L              | 179 (128–230)              | 5.8                     | 193 (150–246)       | 161 (102–221)          | <0.001  |
| Creatinine                     | 1.3 (1.0–1.9)              | 0.1                     | 1.21 (0.95–1.66)    | 1.52 (1.1–2.5)         | <0.001  |
| AST, U/L                       | 39 (26–58)                 | 6.7                     | 37 (25–55)          | 45 (29–71)             | <0.001  |
| ALT, U/L                       | 29 (19–44)                 | 6.7                     | 29 (1–44)           | 29 (19–46)             | 0.87    |
| Procalcitonin, ng/mL           | 0.17 (0.08–0.46)           | 9.1                     | 0.13 (0.07–0.3)     | 0.32 (0.13–1.21)       | <0.001  |
| D-Dimer, ug/mL                 | 215 (1.57–617)             | 18.7                    | 183.5 (1.2–524.0)   | 297.5 (2.7–868.5)      | <0.001  |
| Mechanical ventilation         | 478 (29)                   | 0                       | 190 (16)            | 288 (61)               | <0.001  |
| Remdesivir                     | 86 (5)                     | 0                       | 64 (6)              | 22 (5)                 | 0.46    |
| Hydroxychloroquine             | 747 (46)                   | 0                       | 493 (43)            | 254 (53)               | <0.001  |
| Interleukin6-inhibitor         | 261 (16)                   | 0                       | 182 (16)            | 79 (17)                | 0.64    |
| Vasopressors                   | 374 (23)                   | 0                       | 144 (12)            | 230 (48)               | <0.001  |
| ARDS                           | 263 (16)                   | 0                       | 115 (9.9)           | 148 (31)               | <0.001  |
| Acute renal failure            | 813 (49)                   | 0                       | 472 (41)            | 341 (72)               | <0.001  |

(Continued)
Table 1. (Continued)

|                     | Study population N = 1,634 | Missing observation (%) | Survivors N = 1,159 | Non-survivors N = 475 | P value |
|---------------------|-----------------------------|--------------------------|---------------------|-----------------------|---------|
| Septic shock        | 530 (32)                    | 0                        | 273 (24)            | 257 (54)              | <0.001  |

ARDS = Acute Respiratory Distress Syndrome  
AST = Aspartate transaminase  
ALT = Alanine transaminase  
BMI = Body Mass Index  
CAD = Coronary Artery Disease  
CVD = Cerebrovascular Disease  
COPD = Chronic Obstructive Lung Disease  

https://doi.org/10.1371/journal.pone.0244629.t001

Table 2. Odds ratios and 95% confidence intervals of the components of the three predictive models.

| Parameters          | Chen et al. [8] | Shang et al. [9] | Yu et al. [10] | Wang et al. [13] |
|---------------------|-----------------|------------------|----------------|------------------|
| Sample Size         | 1590            | 452              | 1464           | 296              |
| Age, years          |                 |                  |                |                  |
| <65                 | 1.0             |                  |                |                  |
| 65–74               | 3.43 (1.24–9.5) |                  |                |                  |
| ≥75                 | 7.86 (2.44–23.35)|                |                |                  |
| Age, years          |                 |                  |                |                  |
| <60                 | 1.0             |                  |                |                  |
| 60–75               | 1.82 (0.41–8.17)|                  |                |                  |
| >75                 | 15.07 (2.27–99.78)|            |                |                  |
| Age, years          |                 |                  |                |                  |
| <65                 | 1.0             |                  |                |                  |
| ≥65                 | 2.11 (1.39–3.21)|                  |                |                  |
| Sex                 |                 |                  |                |                  |
| Female              | 1.0             |                  |                |                  |
| Male                | 2.02 (1.37–2.99)|                  |                |                  |
| Hypertension        |                 |                  |                | 1.82 (0.5–6.63)   |
| Diabetes mellitus   |                 |                  |                | 2.52 (1.62–3.94)  |
| CAD                 | 4.28 (1.14–16.13)| 5.61 (1.39–22.62)| 3.04 (0.45–20.74)|                  |
| CVA                 | 3.1 (1.07–8.94) |                  |                |                  |
| Dyspnea             | 3.96 (1.42–11.0)|                  |                |                  |
| AST, U/L            |                 |                  |                |                  |
| >40                 | 2.2 (1.1–6.73)  |                  |                |                  |
| PCT, ng/ml          |                 |                  |                |                  |
| >0.5                | 8.72 (3.42–22.28)|                |                |                  |
| >0.15               | 20.74 (5.14–83.75)|               |                |                  |
| ≥0.05               | 3.13 (2.02–4.84)|                  |                |                  |
| Lymphocytes, %      |                 |                  |                |                  |
| <8%                 | 3.66 (1.01–13.38)|                |                |                  |
| Lymphocytes, x10^9/L|                 |                  |                |                  |
| <1.1                | 1.45 (0.98–2.15) |                  |                |                  |
| D-dimer, ug/ml      |                 |                  |                |                  |
| >0.5                | 4.45 (1.37–14.51)|                |                |                  |

https://doi.org/10.1371/journal.pone.0244629.t002
selected (14, 21, and 28 days predicted mortality) “Fig 2A–2C”. The predictions overestimated the probability of death for high risk patients. This was also the case for the model by Yu et al. [10] “Fig 2E”. In contrast, the model by Wang et al. [13] underestimated the probability of death for low risk patients and overestimated it for high risk patients “Fig 2F” while Shang et al. model [9] consistently overestimated mortality risk across the range of total scores “Fig 2D”.

Discussion

This is, to our knowledge, the first study to evaluate and externally validate risk prediction models of in-hospital mortality from COVID-19 in a large cohort. Our results showed that external validation of all four selected scores was not commensurate with the performance observed in the primary derivation cohorts underscoring that model evaluation can generally be generalizable only when the model has been tested in a separate cohort exposed to similar risk pressure.

With the rapid spread of COVID-19, healthcare providers struggle to institute clinical strategies aiming at optimizing outcomes and reducing resource consumption. In response, more than two dozen prediction models have been destined for publications in just over 12 weeks period since COVID-19 was declared a pandemic by the WHO [3]. Many of the prediction models were developed as simplified scoring system or nomograms. Despite the excellent predictive accuracy shown in the initial derivation, the validity of these models has not been confirmed independently. Based on our observations, the performance of these prognostic systems varied in their ability to discriminate between survivors and non-survivors and were labeled overall either fair or poor in contrast to their original designation as excellent or good.

We should point out that the four models originated from mainland China that was initially

Table 3. Summary of the discrimination and calibration performance for each model.

|                        | AUC_d | AUC_v | HL_k^2 | HLI(p) |
|------------------------|-------|-------|-------|--------|
| Chen et al. [8]        | 0.91  | 0.68  | 67.0  | <0.01  |
| 14d mortality          | 0.67  | 377.3 | <0.001|
| 21d mortality          | 0.68  | 1015.8| <0.001|
| 28d mortality          | 0.69  | 1805.3| <0.001|
| Shang et al. [9]       | 0.92  | 0.72  | 44.3  | <0.001|
| Yu et al. [10]         | 0.77  | 0.63  | 124.4 | <0.001|
| Wang et al. [13]       | 0.88  | 0.69  | 62.8  | <0.001|

AUC_d = Area under the curve of the derivation model; AUC_v = Area under the curve of the validation model; HL = Hosmer Lemeshow

https://doi.org/10.1371/journal.pone.0244629.t003

Table 4. Pair-wise discrimination model comparison.

|          | Chen (14d) | Chen (21d) | Chen (28d) | Shang | Yu | Diff | p | Diff | p | Diff | p | Diff | p |
|----------|------------|------------|------------|-------|----|------|---|------|---|------|---|------|---|
| Chen (14d) |            |            |            |       |    |      |   |       |   |       |   |       |   |
| Chen (21d) | 0.003 | 0.87 |            |       |    |      |   |       |   |       |   |       |   |
| Chen (28d) | 0.015 | 0.48 | 0.011 | 0.56 |    |      |   |       |   |       |   |       |   |
| Shang     | 0.044 | 0.03 | 0.041 | 0.04 | 0.029 | 0.12 |    |       |   |       |   |       |   |
| Yu        | 0.047 | 0.03 | 0.051 | 0.01 | 0.063 | 0.002 | 0.09 | <0.001 |   |       |   |       |   |
| Wang      | 0.016 | 0.46 | 0.012 | 0.54 | 0.0006 | 0.97 | 0.028 | 0.13 | 0.063 | 0.001 |

https://doi.org/10.1371/journal.pone.0244629.t004
Fig 1. Receiver-operating characteristics curves of the prognostic models.

https://doi.org/10.1371/journal.pone.0244629.g001

Fig 2. Calibration plots. The green circles denote point estimates and the green vertical lines 95% confidence intervals for risk groups. Fewer than 10 groups in a plot indicate absence of cases in decile risk groups. The dashed line represents a perfect agreement between observed and expected mortality estimates. The blue line indicates the fitted loess curve. (A-C) represent the calibration plots generated from Chen et al. (D) represents the calibration plot generated from Shang et al. (E) denotes the calibration plot generated from Yu et al. (F) illustrates the calibration plot generated from Wang et al.

https://doi.org/10.1371/journal.pone.0244629.g002
hard hit by the pandemic. With the large disparity in medical resources among the Chinese provinces [23], the expected models can only be accurate under the same clinical setting the model was derived under. As such, the risk prediction models developed in a different geographic setting can be less accurate in providing risk-adjusted outcomes when applied externally [24].

Various statistical and clinical factors may lead to a prognostic model to perform poorly when applied to other cohorts [25]. First, the models presented in this study are parsimonious, making a variety of assumptions in order to simplify applicability and avoid overfitting the limited and often incomplete data available. Even when these predictive models being constructed with similar variables such as age, presence of comorbidities, and laboratory values (procalcitonin, C-reactive protein, or D-dimer), the thresholds selected for each of these variables vary significantly for a given geographic locality [26]. Second, these models have several sources of uncertainty, including the definition of parameters entered into the final model, differences in handling missing data, and most importantly, non-comparable traits (genetic diversity), which can weaken model prognostication and lessen its discrimination accuracy [27, 28].

Even when discrimination can be useful for generic risk stratification, the observed poor calibration underlines the fact that the applicability of these prognostic scoring models to heterogeneous systems of health care delivery dissimilar to the derivation cohorts may not be feasible. The four prognostic models showed shortcomings with regard to calibration, tending to over-predict or under-predict hospital mortality. This may partly reflect the inclusion criteria of the sample—in which, for example, do not resuscitate patients were not included—and improvements in care (e.g. timing to transfer to ICU or prone position in management of ARDS) since the models were first developed. A relevant factor in explaining the divergence in performance accuracy is that the time from onset of illness to admission was not similar among all cohorts. Wang and colleagues [13] reported the shortest interval of a median of 5.0 days for survivors and 6.8 days for non-survivors while Yu and coworkers [10] reported a median of 10.0 days for both the survivors and non-survivors. Our interval was comparable to the study of Shang and colleagues [9] which may explain the higher performance of that study using the CDW cohort.

It could be argued also that our CDW cohort consisted of predominantly male, Caucasian and African American patients with multiple comorbidities which are different from the patient demographics in the original training dataset and, as such, may impose significant strain on the accuracy of the risk estimates. Age-standardized mortality in men was shown to be almost double compared to that of women across all age groups [29]. Reports have similarly suggested a disproportionate mortality rates among Black and Latino residents compared with their proportion of the US population. Age and population adjusted Black mortality was reported more than twice that for Whites [30, 31]. Accordingly, the predictive models might be expected to give different predictions of mortality risk in our validation cohort. While this may cause prognostic systems to underestimate the mortality rate at the lower end of the calibration curve, only two out of the four tested models exhibited this pattern. Multiple studies have demonstrated a decreasing ratio of observed mortality to expected mortality with time [32, 33]. Changing risk profiles, advance treatment modalities, and changes in the association of risk factors with outcomes can all contribute to poor calibration. Given that the CDW cohort overlaps the time period during which the four models were constructed, we cannot attribute the failure of the Hosmer-Lemeshow tests to this phenomenon [34]. Consideration of other variables, such as severity of comorbid diseases, lifestyle habits (smoking or alcohol intake), and prescribed treatments may improve the predictive accuracy of these models.
Alternatively, an ensemble learning model [35] which uses multiple decision-making tools can be implemented to produce a more accurate output [36].

Our study has its own strengths but also several limitations. The systematic nature of the model identification, the large sample size in which the models were validated and the opportunity to compare the performance among the predictive models are all substantial strengths. Conversely, at the time our analysis was conducted, the number of COVID-19 cases was relatively small compared to the most recent statistics of veterans infected with COVID-19. This limits the precision in re-estimating the baseline prevalence of the disease, which may have hampered the calibration performance of the model. However, CDW is undergoing continuous update and re-conducting this validation in the large expanded cohort may mitigate some of these issues related to selection bias. Such validations in large datasets have been advocated to ensure developed prediction models are fit for use in all intended settings [37]. Finally, while previous studies have shown that physicians usually overestimate patients’ mortality [38], there is limited evidence so far to suggest that prognostic models represent a superior solution when their performance in actual clinical practice is taken into consideration.

Conclusions

In conclusion, predictions arising from risk models applied to cohorts drawn from a different distribution of patient characteristics should not be adopted without appropriate validation. The variability in predicted outcomes as we have documented in this analysis highlights the challenges of forecasting the course of a pandemic during its early stages [7]. To achieve a more robust prediction model, the focus should be placed on developing platforms that enable deployment of well-validated predictive models and prospective evaluation of their effectiveness. We are actively engaged in pursuing these objectives at the Veterans Affairs.

Supporting information

S1 File.
(DOCX)

Acknowledgments

The views expressed in this manuscript do not communicate an official position of the Department of Veterans Affairs.

Author Contributions

Conceptualization: Ali A. El-Solh, Kari A. Mergenhagen.
Data curation: Ali A. El-Solh, Yolanda Lawson, Michael Carter.
Formal analysis: Ali A. El-Solh.
Methodology: Ali A. El-Solh.
Project administration: Michael Carter.
Resources: Yolanda Lawson.
Software: Daniel A. El-Solh.
Validation: Ali A. El-Solh, Daniel A. El-Solh.
References

1. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. N Engl J Med. 2020; 382(13):1199–207. Epub 2020/01/30. https://doi.org/10.1056/NEJMoA2001316 PMID: 31995857; PubMed Central PMCID: PMC7121484.

2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. The Lancet Infectious diseases. 2020; 20(5):533–4. Epub 2020/02/23. https://doi.org/10.1016/S1473-3099(20)30120-1 PMID: 32087114; PubMed Central PMCID: PMC7159018.

3. Sperrin M, Grant SW, Peek N. Prediction models for diagnosis and prognosis in Covid-19. BMJ. 2020; 369:m1464. Epub 2020/04/16. https://doi.org/10.1136/bmj.m1464 PMID: 32291266.

4. Shaw RE, Anderson HV, Brindis RG, Klein LW, McKay CR, et al. Updated risk adjustment mortality model using the complete 1.1 dataset from the American College of Cardiology National Cardiovascular Data Registry (ACC-NCDR). J Invasive Cardiol. 2003; 15(10):578–80. Epub 2003/10/02. PMID: 14519891.

5. Altman DG, Royston P. What do we mean by validating a prognostic model? Statistics in medicine. 2000; 19(4):453–73. Epub 2000/03/01. https://doi.org/10.1002/(sici)1097-0258(20000229)19:4<453::aid-sim350>3.0.co;2-5 PMID: 10694730.

6. Riley RD, Ensor J, Snell KIE, Harrell FE Jr., Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. BMJ. 2020; 368:m441. Epub 2020/03/20. https://doi.org/10.1136/bmj.m441 PMID: 32188600.

7. Wynants L, Van Calster B, Collins GS, Riley RD, Heinze G, Schuit E, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ. 2020; 369:m1328. Epub 2020/04/09. https://doi.org/10.1136/bmj.m1328 PMID: 32265220; PubMed Central PMCID: PMC7226643 at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no competing interests with regards to the submitted work; LW discloses support from Research Foundation-Flanders (FWO); RDR reports personal fees as a statistics editor for The BMJ (since 2009), consultancy fees for Roche for giving meta-analysis teaching and advice in October 2018, and personal fees for delivering in-house training courses at Barts and The London School of Medicine and Dentistry, and also the Universities of Aberdeen, Exeter, and Leeds, all outside the submitted work.

8. Chen R, Liang W, Jiang M, Guan W, Zhan C, Wang T, et al. Risk Factors of Fatal Outcome in Hospitalized Subjects With Coronavirus Disease 2019 From a Nationwide Analysis in China. Chest. 2020; 158 (1):97–105. Epub 2020/04/19. https://doi.org/10.1016/j.chest.2020.04.010 PMID: 32304772; PubMed Central PMCID: PMC7158802.

9. Shang Y, Liu T, Wei Y, Li J, Shao L, Liu M, et al. Scoring systems for predicting mortality for severe patients with COVID-19. EClinicalMedicine. 2020; 24:100426. Epub 2020/08/09. https://doi.org/10.1016/j.eclinm.2020.100426 PMID: 32766541; PubMed Central PMCID: PMC7332889.

10. Yu C, Lei Q, Li W, Wang X, Liu W, Fan X, et al. Clinical Characteristics, Associated Factors, and Predicting COVID-19 Mortality Risk: A Retrospective Study in Wuhan, China. American journal of preventive medicine. 2020; 59(2):168–75. Epub 2020/06/23. https://doi.org/10.1016/j.amepre.2020.05.002 PMID: 32564974; PubMed Central PMCID: PMC7250782.

11. Schaefer JL, Graham JW. Missing data: our view of the state of the art. Psychol Methods. 2002; 7 (2):147–77. Epub 2002/07/02. PMID: 12090408.

12. Burton A, Altman DG. Missing covariate data within cancer prognostic studies: a review of current reporting and proposed guidelines. Br J Cancer. 2004; 91(1):4–8. Epub 2004/06/10. https://doi.org/10.1038/sj.bjc.6601907 PMID: 15188004; PubMed Central PMCID: PMC2364743.

13. Wang K, Zuo P, Liu Y, Zhang M, Zhao X, Xie S, et al. Clinical and laboratory predictors of in-hospital mortality in patients with COVID-19: a cohort study in Wuhan, China. Clin Infect Dis. 2020. Epub 2020/05/04. https://doi.org/10.1093/cid/ciaa538 PMID: 32361723; PubMed Central PMCID: PMC7197616.

14. Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD). Ann Intern Med. 2015; 162(10):735–6. Epub 2015/05/20. https://doi.org/10.7326/L15-5093-2 PMID: 25984857.

15. Moons KGM, Wolf RF, Riley RD, Whiting PF, Westwood M, Collins GS, et al. PROBAST: A Tool to Assess Risk of Bias and Applicability of Prediction Model Studies: Explanation and Elaboration. Ann Intern Med. 2019; 170(1):W1–W33. Epub 2019/01/01. https://doi.org/10.7326/M18-1377 PMID: 30590876.
16. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. Radiology. 1982; 143(1):29–36. Epub 1982/04/01. https://doi.org/10.1148/radiology.143.1.7063747. PMID: 7063747.

17. Safari S, Baratloo A, Elif M, Negida A. Evidence Based Emergency Medicine; Part 4: Pre-test and Post-test Probabilities and Fagan’s nomogram. Emerg (Tehran). 2016; 4(1):48–51. Epub 2016/02/11. PMID: 26862553; PubMed Central PMID: PMC4744617.

18. Lemeshow S, Hosmer DW Jr., A review of goodness of fit statistics for use in the development of logistic regression models. Am J Epidemiol. 1982; 115(1):92–106. Epub 1982/01/01. https://doi.org/10.1093/oxfordjournals.aje.a113284 PMID: 7055134.

19. Austin PC, Steyerberg EW. Graphical assessment of internal and external calibration of logistic regression models by using loess smoothers. Statistics in medicine. 2014; 33(3):517–35. Epub 2013/09/05. https://doi.org/10.1002/sim.5941 PMID: 24002997; PubMed Central PMID: PMC4793659.

20. Margolis DJ, Bliker W, Boston R, Localio R, Berlin JA. Statistical characteristics of area under the receiver operating characteristic curve for a simple prognostic model using traditional and bootstrapped approaches. Journal of clinical epidemiology. 2002; 55(5):518–24. Epub 2002/05/15. https://doi.org/10.1016/s0895-4356(01)00512-1 PMID: 12007556.

21. Carpenter J, Bithell J. Bootstrap confidence intervals: when, which, what? A practical guide for medical statisticians. Statistics in medicine. 2000; 19(9):1141–64. Epub 2000/05/08. https://doi.org/10.1002/(sici)1097-0258(20000515)19:9<1141::aid-sim479>3.0.co;2-f PMID: 10797513.

22. Hanley JA, McNeil BJ. A method of comparing the areas under receiver operating characteristic curves derived from the same cases. Radiology. 1983; 148(3):839–43. Epub 1983/09/01. https://doi.org/10.1148/radiology.148.3.6878708 PMID: 6878708.

23. Zhang S, Guo M, Duan L, Wu F, Hu G, Wang Z, et al. Development and validation of a risk factor-based system to predict short-term survival in adult hospitalized patients with COVID-19: a multicenter, retrospective, cohort study. Crit Care. 2020; 24(1):438. Epub 2020/07/18. https://doi.org/10.1186/s13054-020-03123-x PMID: 32678040; PubMed Central PMID: PMC7364297.

24. Biagioli B, Scolletta S, Cevenini G, Barbini E, Giomarelli P, Barbini P. A multivariate Bayesian model for assessing morbidity after coronary artery surgery. Crit Care. 2006; 10(3):R94. Epub 2006/07/04. https://doi.org/10.1186/cc4951 PMID: 16813658; PubMed Central PMCID: PMC1550964.

25. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ. 2009; 338:b605. Epub 2009/05/30. https://doi.org/10.1136/bmj.b605 PMID: 19477892.

26. Chiu M, Austin PC, Manuel DG, Shah BR, Tu JV. Deriving ethnic-specific BMI cutoff points for assessing diabetes risk. Diabetes Care. 2011; 34(8):1741–8. Epub 2011/06/18. https://doi.org/10.2337/dc10-2300 PMID: 21680722; PubMed Central PMID: PMC3142051.

27. Vergouwe Y, Moons KG, Steyerberg EW. External validity of risk models: Use of benchmark values to disentangle a case-mix effect from incorrect coefficients. Am J Epidemiol. 2010; 172(8):971–80. Epub 2010/09/03. https://doi.org/10.1093/aje/kwq223 PMID: 20807737; PubMed Central PMCID: PMC2984249.

28. Pirracchio R, Petersen ML, Carone M, Rigon MR, Chevret S, van der Laan MJ. Mortality prediction models in intensive care units with the Super ICU Learner Algorithm (SICULA): a population-based study. Lancet Respir Med. 2015; 3(1):42–52. Epub 2014/12/04. https://doi.org/10.1016/S2213-2600(14)70239-5 PMID: 25466337; PubMed Central PMID: PMC4321691.

29. Mohamed MG C.; Kontopantelis E.; Doran T.; de Belder M.; Asaria M.; Luscher T.; et al. Sex differences in mortality rates and underlying conditions for COVID-19 deaths in England and Wales. Mayo Clin Proc. 2020. (In Press).

30. Pan D, Sze S, Minhas JS, Bangash MN, Pareek N, Divall P, et al. The impact of ethnicity on clinical outcomes in COVID-19: A systematic review. EClinicalMedicine. 2020; 23:100404. Epub 2020/07/08. https://doi.org/10.1016/j.eclinm.2020.100404 PMID: 32632416; PubMed Central PMID: PMC7267805.

31. NYCDo H. COVID-19 deaths by race ethnicity 2020 [July 30, 2020]. Available from: https://www1.nyc.gov/assets/doh/downloads/pdf/imm/covid-19-deaths-race-ethnicity-04242020.

32. Horwitz LI, Jones SA, Cerfolio RJ, Francois F, Greco J, Rudy B, et al. Trends in COVID-19 Risk-Adjusted Mortality Rates. Journal of hospital medicine: an official publication of the Society of Hospital Medicine. 2020. Epub 2020/11/05. https://doi.org/10.12788/jhm.3552 PMID: 33147129.

33. Auld SC, Caridi-Scheible M, Robichaix C, Coopersmith CM, Murphy DJ, Emory C-Q, et al. Declines in Mortality Over Time for Critically Ill Adults With Coronavirus Disease 2019. Crit Care Med. 2020; 48(12):e1382–e4. Epub 2020/09/30. https://doi.org/10.1097/CCM.0000000000004687 PMID: 32991356; PubMed Central PMID: PMC7708435.
34. Lung function testing: selection of reference values and interpretative strategies. American Thoracic Society. Am Rev Respir Dis. 1991; 144(5):1202–18. https://doi.org/10.1164/ajrccm/144.5.1202 PMID: 1952453.

35. Seni GE, J Ensemble methods in data mining. Grossman RF, editor: Morgan & Claypool; 2010.

36. Vaid A, Somani S, Russak AJ, De Freitas JK, Chaudhry FF, Paranape I, et al. Machine Learning to Predict Mortality and Critical Events in a Cohort of Patients With COVID-19 in New York City: Model Development and Validation. J Med Internet Res. 2020; 22(11):e24018. Epub 2020/10/08. https://doi.org/10.2196/24018 PMID: 33027032; PubMed Central PMCID: PMC7652593.

37. Riley RD, Ensor J, Snell KI, Debray TP, Altman DG, Moons KG, et al. External validation of clinical prediction models using big datasets from e-health records or IPD meta-analysis: opportunities and challenges. BMJ. 2016; 353:i3140. Epub 2016/06/24. https://doi.org/10.1136/bmj.i3140 PMID: 27334381; PubMed Central PMCID: PMC4916924.

38. Ambardekar AV, Thibodeau JT, DeVore AD, Kittleson MM, Forde-McLean RC, Palardy M, et al. Discordant Perceptions of Prognosis and Treatment Options Between Physicians and Patients With Advanced Heart Failure. JACC Heart Fail. 2017; 5(9):663–71. Epub 2017/08/22. https://doi.org/10.1016/j.jchf.2017.04.009 PMID: 28822745; PubMed Central PMCID: PMC5609812.