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External validation and update of prediction models for unfavorable outcomes in hospitalized patients with COVID-19 in Japan

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Abstract

Introduction: Most of the currently used prognostic models for COVID-19 are based on Western cohorts, but it is unknown whether any are applicable to patients with COVID-19 in Japan.

Methods: This retrospective cohort study included 160 patients with COVID-19 who were admitted to the National Center for Global Health and Medicine between January 26, 2020 and July 25, 2020. We searched PubMed for prognostic models for COVID-19. The predicted outcome was initiation of respiratory support or death. Performance of the candidate models was evaluated according to discrimination and calibration. We recalibrated the intercept of each model with our data. We also updated each model by adding β2-microglobulin (β2MG) to the model and recalculating the intercept and the coefficient of β2MG.

Results: Mean patient age was 49.8 years, 68% were male, 88.7% were Japanese. The study outcomes occurred in 15 patients, including two deaths. Two-hundred sixty-nine papers were screened, and four candidate prognostic models were assessed. The model of Bartoletti et al. had the highest area under receiver operating characteristic curve (AUC) (0.88; 95% confidence interval 0.81–0.96). All four models overestimated the probability of occurrence of the outcome. None of the four models showed statistically significant improvement in AUCs by adding β2MG.

Conclusions: Our results suggest that the existing prediction models for COVID-19 overestimate the probability of occurrence of unfavorable outcomes in a Japanese cohort. When applying a prediction model to a different cohort, it is desirable to evaluate its performance according to the prevalent health situation in that region.

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infections and more than 120,000 deaths worldwide [1], with 100,618 infections and 1773 deaths in Japan [2].

Some patients with COVID-19 become severely ill, requiring ICU management and invasive ventilation, or might die. The risk factors for severe illness have been identified, and a number of prediction models for severe disease have been developed using these risk factors [3]. Prognostic models are useful for (1) making decisions about treatment strategies, (2) allocating medical resources appropriately, (3) selecting appropriate subjects for clinical research, and (4) comparing treatment outcomes among institutions, and thus, are important from both clinical and research perspectives [4].

In a systematic review of 145 prediction models related to COVID-19, it was pointed out that many of the models are at high-risk of bias, and need to be updated before being used in local settings. For external validation, discrimination and calibration of these models should also be evaluated [3].

Most of the currently used prediction models are based on Western cohorts, but it has been suggested that the background and prognosis of Japanese patients with COVID-19, such as underlying diseases and prognosis, are different from those in Western countries [5]. Since direct application of models based on overseas data to Japanese patients might result in over- or underestimation of the probability of occurrence of the outcome, updating of the model based on local settings is necessary. In addition, although recent studies have suggested that urinary β2-microglobulin (β2MG) might be useful in predicting the severity of COVID-19 [6], to the best of our knowledge, no prediction model that includes β2MG has been investigated to date.

The purpose of this study was to examine the external validity of the existing prognostic models for COVID-19 in confirmed COVID-19 patients admitted to a tertiary care center in Japan, and to recalibrate the models. Furthermore, we aimed to update each model by adding urinary β2MG as a new predictor in the model.

2. Methods

2.1. Subjects

This retrospective cohort study included patients aged 18 years or older, admitted to the National Center for Global Health and Medicine (NCGM) between January 26, 2020, and July 25, 2020, who were diagnosed with COVID-19 by reverse transcriptase polymerase chain reaction (RT-PCR) testing. Patients who were transferred from other hospitals to our hospital for admission were excluded from the study. This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Review Committee of NCGM (NCGM-G-003494-0). Information regarding opting out of our study is available on the registry website.

2.2. Measurements

Data from the COVID-19 registry Japan (COVIREGI-JP) of the NCGM were used in this study. The study data were collected and managed using REDCap (Research Electronic Data Capture), a secure, web-based data capture application hosted at the JCRAC (Joint Center for Researchers, Associates and Clinicians) data center of the NCGM [7].

Data included for the analyses were patient background factors, symptoms & signs, blood and urine test results on admission, chest radiographs on admission, and vital signs on admission. Blood samples for β2MG assessment were collected between 11 November 2020 and 25 July 2020. Since most of the subjects in this study were Japanese, obesity was defined as body mass index (BMI) ≥25 kg/m² based on the cutoff value for obesity for Asians proposed by the World Health Organization (WHO) [8]. Immunosuppression was defined by the presence of any of the following criteria: neutropenia, steroid use within the past month, chemotherapy within the past 3 months, blood transplantation, solid organ transplantation, use of immunosuppressive drugs within the past 3 months, asplenia syndrome, and primary immunodeficiency syndrome. Since direct bilirubin was not routinely measured in the data used in this study, total bilirubin was used instead of direct bilirubin when required in the calculation of the prediction model.

2.3. Outcome

The predicted outcome was initiation of respiratory support (continuous positive airway pressure/bilevel positive airway pressure, high flow nasal oxygen, invasive mechanical ventilation or extra-corporeal membrane oxygenation) or death. This corresponds to a score of 6 or higher on the WHO clinical progression scale for COVID-19 proposed by the WHO Working Group [9]. All patients were followed until discharge or death.

2.4. Search strategy for the prediction model

We searched the literature using the following procedure:

Step 1: We searched PubMed for articles published in English by November 1, 2020. The main keywords were COVID-19, prediction model, prognostic model, and logistic regression. Details of the keywords searched are described in the Supplementary data section. In addition, we hand searched several journals related to infectious diseases and emergency medicine. Step 2: We selected articles whose outcome was severe illness or death in hospitalized COVID-19 patients. Step 3: We selected articles that presented the intercept and coefficient β of the logistic regression model. If the intercept or coefficient β was not provided in the article, we requested the first author of the article to provide the missing information by e-mail. As a result, four models were selected.

2.5. Statistical analysis

Summary statistics of the patients’ background factors at admission were calculated. Mean (SD), median (interquartile range), or percentage (%) values were used as appropriate.

Discrimination of each model was examined by the area under the receiver operating characteristic (ROC) curve (AUC, area under the curve). Calibration was evaluated using a calibration plot with the predicted probability on the x-axis and the observed probability.
| Characteristic                                      | Cases with available data | Total (N = 145) | Critical illness (N = 15) |
|----------------------------------------------------|---------------------------|----------------|--------------------------|
| Days from symptom onset to hospitalization         |                           |                |                          |
| Demographics                                       |                           |                |                          |
| Age (yr), mean (SD)                                | 160                       | 49.8 (18.8)    | 48.1 (18.1)              |
| Sex (male), n (%)                                  | 160                       | 109 (68.1)     | 97 (66.9)                |
| BMI (kg/m²), mean (SD)                             | 157                       | 23.8 (4.3)     | 23.6 (4.3)               |
| Ethnicity                                          | 159                       |                |                          |
| Japanese, n (%)                                    |                           | 141 (88.7)     | 127 (88.2)               |
| Asian excl. Japanese, n (%)                        |                           | 11 (6.9)       | 11 (7.6)                 |
| White, n (%)                                       |                           | 6 (3.8)        | 5 (3.5)                  |
| Others, n (%)                                      |                           | 1 (0.6)        | 1 (0.7)                  |
| Smoking status                                     | 140                       |                |                          |
| Current, n (%)                                     |                           | 39 (27.9)      | 36 (28.8)                |
| Former, n (%)                                      |                           | 34 (24.3)      | 28 (22.4)                |
| Never, n (%)                                       |                           | 67 (49.7)      | 61 (48.8)                |
| Alcohol                                            | 136                       |                |                          |
| Excessive, n (%)                                   |                           | 33 (24.3)      | 28 (23.0)                |
| Sometimes, n (%)                                   |                           | 64 (47.1)      | 59 (48.4)                |
| None, n (%)                                        |                           | 39 (28.7)      | 35 (28.7)                |
| Vital signs at hospitalization                     |                           |                |                          |
| Heart rate (/min), mean (SD)                       | 160                       | 85.7 (14.4)    | 84.7 (13.3)              |
| Respiratory rate (/min), mean (SD)                 | 152                       | 18.8 (4.2)     | 18 (2.6)                 |
| Systolic blood pressure (mmHg), mean (SD)          | 160                       | 123.1 (16.1)   | 122.8 (15.6)             |
| Diastolic blood pressure (mmHg), mean (SD)         | 160                       | 75.2 (12.6)    | 75.1 (12.8)              |
| Glasgow coma scale, mean (SD)                      | 155                       | 15 (0.2)       | 15 (0.1)                 |
| Laboratory data at hospitalization                 |                           |                |                          |
| White blood cells (10⁹/L), median (IQR)            | 156                       | 4.96 (3.9–6.27)| 5.03 (3.9–6.14)          |
| Neutrophils (10⁹/L), median (IQR)                  | 146                       | 3.39 (2.4–4.53)| 3.32 (2.3–4.46)          |
| Lymphocytes (10⁹/L), median (IQR)                  | 147                       | 1.12 (0.79–1.43)| 1.16 (0.86–1.51)         |
| Hemoglobin (g/dL), median (IQR)                    | 156                       | 143 (12.9–15.4)| 143 (13.0–15.3)          |
| Platelets (10⁹/L), median (IQR)                    | 156                       | 195 (160–253)  | 198 (163–259)            |
| Albumin (g/dL), mean (SD)                          | 147                       | 3.8 (0.6)      | 3.9 (0.6)                |
| Total bilirubin (mmol/L), median (IQR)             | 154                       | 9.2 (6.8–10.3) | 9.0 (6.8–10.3)           |
| AST (IU/L), median (IQR)                           | 155                       | 31 (22–46)     | 30 (21.5–41.5)           |
| ALT (IU/L), median (IQR)                           | 156                       | 27 (18–45)     | 27 (18–45)               |
| LDH (IU/L), median (IQR)                           | 156                       | 233.5 (181.5–316.5)| 227 (175–291)        |
| CRP (mg/dL), median (IQR)                          | 155                       | 2.69 (0.43–8.57)| 2.03 (0.36–6.88)         |
| BUN (mg/dL), median (IQR)                          | 153                       | 14.5 (7.0)     | 13.7 (6.0)               |
| Creatinine (mg/dL), mean (SD)                      | 156                       | 0.9 (0.7)      | 0.8 (0.7)                |
| Sodium (mmol/L), median (IQR)                      | 156                       | 139 (135.5–142.0)| 140 (137–142)           |
| Potassium (mmol/L), median (IQR)                   | 156                       | 3.95 (3.6–4.2) | 4 (3.6–4.2)              |
| Underlying disease                                 |                           |                |                          |
| Myocardial infarction, n (%)                       | 160                       | 1 (0.6)        | 0 (0)                    |
| Congestive heart failure, n (%)                    | 160                       | 1 (0.6)        | 1 (0.7)                  |
| Peripheral vascular disease, n (%)                 | 160                       | 1 (0.6)        | 0 (0)                    |
| Cerebrovascular disease, n (%)                     | 160                       | 5 (3.1)        | 5 (3.4)                  |
| Hemiplegia, n (%)                                  | 160                       | 3 (1.9)        | 3 (2.1)                  |
| Dementia, n (%)                                    | 160                       | 6 (3.8)        | 5 (3.4)                  |
| Asthma, n (%)                                      | 160                       | 9 (5.6)        | 9 (6.2)                  |
| Liver disease, n (%)                               | 160                       | 2 (1.3)        | 2 (1.4)                  |
| Diabetes, n (%)                                    | 160                       | 22 (13.8)      | 18 (12.4)                |
| Obesity (BMI ≥ 25 kg/m²), n (%)                    | 157                       | 56 (35.7)      | 49 (34.5)                |
| Solid tumor, n (%)                                 | 160                       | 4 (2.5)        | 4 (2.8)                  |
| Collagen disease, n (%)                            | 160                       | 3 (1.9)        | 3 (2.1)                  |
| HIV, n (%)                                         | 160                       | 5 (3.1)        | 5 (3.4)                  |
| COPD, n (%)                                        | 160                       | 3 (1.9)        | 3 (2.1)                  |
| Hypertension, n (%)                                | 160                       | 34 (21.3)      | 28 (19.3)                |
| Hyperlipidemia, n (%)                              | 160                       | 25 (15.6)      | 21 (14.5)                |
| Immune suppression, n (%)                          | 160                       | 2 (1.3)        | 2 (1.4)                  |
| Chronic kidney disease, n (%)                      | 156                       | 31 (19.9)      | 23 (16.3)                |
| Baseline medication                                |                           |                |                          |
| ACE inhibitor, n (%)                               | 157                       | 2 (1.3)        | 2 (1.4)                  |
| ARB, n (%)                                         | 157                       | 17 (10.8)      | 12 (8.4)                 |
| Oral anticoagulant, n (%)                          | 159                       | 2 (1.3)        | 1 (0.7)                  |
| Antiplatelet, n (%)                                | 159                       | 8 (5)          | 7 (4.9)                  |
| Symptoms at hospitalization                        |                           |                |                          |
| Fever ≥ 38°C, n (%)                                | 160                       | 41 (25.6)      | 34 (23.4)                |
| Cough, n (%)                                       | 160                       | 93 (58.1)      | 85 (58.6)                |
| Sputum, n (%)                                      | 160                       | 34 (21.3)      | 30 (20.7)                |
| Hemoptyisis, n (%)                                 | 160                       | 2 (1.3)        | 2 (1.4)                  |

(continued on next page)
on the y-axis. The calibration plot is a graphical representation of
the actual observed probability against the model’s predicted
probability; if the model’s prediction of the outcome probability is
correct, it will overlap on the line $y = x$. The calibration plot was
smoothed using the locally estimated scatterplot smoothing
(LOESS) method. To update the models, we first recalibrated the
intercept of each model with our data [10]. Next, to examine the
effect of adding urinary $\beta_{2}$MG to the model, we first selected pa-
tients with $\beta_{2}$MG data and created a subpopulation. Using this
subpopulation, we updated each model by adding $\beta_{2}$MG to the
existing prediction model and recalculating only the intercept and
the coefficient of $\beta_{2}$MG. $\beta_{2}$MG was treated as a binary variable and
the cutoff value was set at 2457 mg/dL, as previously suggested [6].
We re-evaluated the performance of these updated models and
tested whether there was a difference in AUC before and after the
update.

Since this was an observational study, all available patient data
were used in the analysis. All reported P values were two-sided P
values, and the statistical significance level was set at $P < 0.05$. All
analyses were performed with SAS software, version 9.4 (SAS
Institute, Cary, NC).

3. Results

3.1. Patient background characteristics at admission

During the study period, 172 patients were included in the
study, of whom 12 patients who were transferred from other
hospitals were excluded and 160 patients were included in the final
analysis (Fig. 1). The background characteristics of the patients at
the time of admission are shown in Table 1. Mean patient age was
49.8 years, 68% were male, the majority were Japanese (88.7%), and
95.6% were Asian including Japanese. The median time from onset
to hospitalization was 7 days. The study outcomes occurred in 15
patients, including 2 deaths.

3.2. Summary of the selected prediction models

We screened 269 papers by title and abstract. As a result, 16
papers were screened for full-text and four prediction models were
finally selected (Fig. 2). A summary of the selected models is shown
in Table 2.

3.3. Discriminatory power of the prediction models

Fig. 3 shows the ROC curves and AUCs of the four prediction
models. The model of Bartoletti et al. [12] had the highest AUC
(0.88; 95% confidence interval [CI] 0.81–0.96). Supplementary
Table 1 shows the sensitivity, specificity, positive predictive value, and negative predictive value at different cutoff values with application of Bartoletti et al.’s model to our cohort.

3.4. Calibration plots and recalibration of the prediction models

Fig. 4 shows the original calibration plots and post-recalibration plots of the four prediction models, and Supplementary Table 2 shows the newly estimated intercept. All four models overestimated the probability of occurrence of the outcome when the original version was applied to our cohort. Even when calibration of Bartoletti et al.’s model was assessed separately for the first wave (before June 1, 2020) and second wave (after June 1, 2020) of the pandemic in Japan [15], the model overestimated the probability of occurrence in both periods (Supplementary Fig. 1). The post-recalibration model, in which the intercept was re-estimated using our data, showed that the Bartoletti et al. model adequately predicted the probability of outcome in our cohort.

3.5. Update of the prediction models by adding β2-microglobulin

Of the 160 patients, 133 had β2MG data and were eligible for analysis. Table 3 shows the AUCs of the original and updated models using the data of the 133 patients. The newly estimated intercept and regression coefficients for β2MG are shown in Supplementary Table 3. None of the four models showed statistically significant improvement in AUCs by adding β2MG to the model.

4. Discussion

In this study, we evaluated the performance of original and updated versions of four existing prediction models for the occurrence of the selected study outcomes of respiratory support and death in COVID-19 patients, using data from patients with confirmed COVID-19 admitted to a tertiary care hospital in Japan. The study was conducted at a single medical institution where
Fig. 4. Calibration plots of the four previous prediction models (original and recalibrated models).
relatively uniform treatment and supportive care are provided, and therefore, accurate evaluation of the prediction model was possible. The data of this study showed that the discriminatory performance of the prediction model of Bartoletti et al. was most suitable for use in Japanese subjects, with an AUC of 0.88, and it also showed good calibration.

When calibration was evaluated, all four models calculated lower observed proportions of events than the predicted proportions of events. In other words, the prediction models overestimated the probability of occurrence of the outcomes. It has been pointed out that the rate of severe disease in Japanese patients with COVID-19 is lower than that in patients in other countries, which could be the reason why the predicted probability of the original model deviated from the observed probability in Japan [5]. The reason for the lower incidence of severe disease in the Japanese population might be fewer of the comorbidities that are reportedly associated with severe disease. For example, patients in our cohort were younger than in the other cohorts. In the studies of Bartoletti et al., Salto-Alejandre et al., and Ryan et al., the mean or median ages were 65.7, 64, and 57 years, respectively, whereas the mean age in our cohort was 49.8 years. Although data on some variables were not available in the four studies, our cohort tended to have a lower BMI and lower prevalence of hypertension, diabetes, cardiovascular disease, chronic lung disease, malignancy, and immunodeficiency. In Japan, we experienced the first wave of the pandemic (before June 1, 2020) and the second wave (after June 1, 2020), and hospitalized patients in the second wave had a shorter time between disease onset and admission than those in the first wave [15]. Moreover, since the preliminary results of the RECOVERY trial were announced on June 16, 2020, patients in the second wave in our cohort were more likely to have had a chance to receive corticosteroids, which might have contributed to the lower rate of disease severity in the second wave [16]. Another reason for the lower incidence of severe disease might be preservation of medical resources due to absence of a significant surge in the number of patients, and other factors that are not yet clear, such as genetic predisposition. The background diseases and medical situations of the population for which a model is constructed might differ greatly from those of other populations, suggesting that, as shown in this study, it is important to recalibrate the model according to the actual conditions of each region.

In this study, we assessed data from NCCM, an urban tertiary care center, that tends to include more patients with a severe condition or comorbidities as compared to other hospitals. Therefore, if the four models are evaluated in other Japanese hospitals, the models might overestimate the probability of occurrence of the outcomes even more.

When we attempted to update the four prediction models by adding 2MG, none of the four models showed statistically significant improvement. A possible explanation is that although 2MG is associated with elevated levels of inflammatory cytokines [17,18], the original prediction models already incorporated factors that reflect inflammatory cytokines, such as fever and CRP. Hence, addition of 2MG in the new model does not increase its discriminatory performance.

Many prognostic models for COVID-19 patients have been proposed [3], and in future, rather than developing new models, the external validity of existing models and updates of models should be verified. To our knowledge, this is the first such study in Japanese patients, making the methodology and findings of this study valuable. Gupta et al. externally validated 22 clinical prediction models using data from 411 inpatients in London [19]. They found that AUCs ranged from 0.56 to 0.78 in their new data and that calibration of all models was visually poor, which was consistent with the result of the present study. In the current study, we assessed four new prediction models that they did not evaluate. We also updated the models to be more suitable for predicting unfavorable outcomes in our cohort by recalibrating the models.

This study has several limitations. First, this was a single-center study, which has the advantage of accurate assessment due to the high quality of data and the relatively uniform treatment, although the number of subjects was small (n = 160), and thus, the calibration plot might not have been accurate. A study with a larger number of patients is necessary. Second, because direct bilirubin was not measured in all patients at our hospital at the time of admission, data on direct bilirubin was missing in most patients. Therefore, total bilirubin was used in evaluating the model of Liang et al., which might have introduced bias. Third, because COVID-19 is a new infection, the treatment options are still in a state of continuous flux. Patients admitted to our hospital up to July 31 were used in the analysis of this study. If treatment or prevention with significant impact on outcomes becomes available in future (e.g., widespread use of vaccines), the predicted probability of severe COVID-19 might change, in which case the clinical application of this study would require caution.

In conclusion, we present the findings of an updated prediction model that can be used to predict the severity of COVID-19 in a predominantly Japanese cohort that inherently has fewer of the known COVID-19 comorbidities. Our results suggest that existing prediction models overestimate the probability of occurrence of the outcomes of death and the need for respiratory support when used in tertiary care hospitals in Japan. Our results also suggest that when applying a prediction model to a different cohort, it is desirable to evaluate its performance according to the prevalent health situation in that region.

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Authorship statement

All authors meet the ICJME authorship criteria. All authors have seen and approved the final version of the manuscript, and contributed significantly to the work. Study concept and design: GY, KH, YA, and NM. Acquisition of data: KH, YA, NM, HO, MH, YY, DK, MT, MS, RS, YM, MI, SM and SS. Statistical analysis and interpretation of data: GY, KH, and YA. Manuscript drafting: GY, KH, and YA. Critical revision of the manuscript for important intellectual content: KH, MH, KK, RS, TO, and NO. Study supervision: NO.

Declaration of competing interest

None.
Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jiac.2021.04.008.

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