A nomogram prediction of outcome in patients with COVID-19 based on individual characteristics incorporating immune response-related indicators

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) has quickly become a global threat to public health, and it is difficult to predict severe patients and their prognosis. Here, we intended developing effective models for the late identification of patients at disease progression and outcome.

Methods: A total of 197 patients were included with a 20-day median follow-up time. We first developed a nomogram for disease severity discrimination, then created a prognostic nomogram for severe patients.

Results: In total, 40.6% of patients were severe and 59.4% were non-severe. The multivariate logistic analysis indicated that IgG, neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase, platelet, albumin, and blood urea nitrogen were significant factors associated with the severity of COVID-19. Using immune response phenotyping based on NLR and IgG level, the logistic model showed patients with the NLRhiIgGhi phenotype are most likely to have severe disease, especially compared to those with the NLRloIgGlo phenotype. The C-indices of the two discriminative nomograms were 0.86 and 0.87, respectively, which indicated sufficient discriminative power. As for predicting clinical outcomes for severe patients, IgG, NLR, age, lactate dehydrogenase, platelet, monocytes, and procalcitonin were significant predictors. The prognosis of severe patients with the NLRhiIgGhi phenotype was significantly worse than the NLRloIgGhi group. The two prognostic nomograms also showed good performance in estimating the risk of progression.

Conclusions: The present nomogram models are useful to identify COVID-19 patients with disease progression based on individual characteristics and immune response-related indicators. Patients at high risk for severe illness and poor outcomes from COVID-19 should be managed with intensive supportive care and appropriate therapeutic strategies.

Keywords
COVID-19, IgG, neutrophil-to-lymphocyte ratio, nomogram, prediction
INTRODUCTION

Since December 2019, coronavirus disease 2019 (COVID-19) due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has quickly spread to every continent except Antarctica and become a global threat to public health. The number of patients with severe disease and death is persistently high outside of China. Although the severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) have significantly higher case fatality rates than COVID-19, COVID-19 is responsible for more fatal cases because the underlying SARS-CoV-2 virus spread more easily among people by droplets produced by coughing, sneezing, or talking, leading to greater numbers of cases across the world.

A majority of COVID-19 patients have a mild disease course, but a subgroup of patients will experience continuing disease deterioration. It is urgent to identify the critical risk factors that help predict the progression and outcome of this disease. The early identification of disease deterioration and poor outcomes will help develop appropriate and necessary supportive care and reduce mortality. Previous investigations had linked clinical characteristics such as older age, multiple morbidities, and supplemental oxygen at the time of hospitalization to severe COVID-19 disease at admission. Some circulating factors, including C-reactive protein (CRP), interleukin-6, and procalcitonin (PCT), have been found to have a prognostic value in the severity of COVID-19 or the mechanical ventilation. Basically, a single risk factor failed to accurately estimate the severity and clinical outcome of individual COVID-19 patients. Moreover, a recently identified early prediction model only focused on the common laboratory variables.

Following SARS-CoV-2 infection, a high viral load and overexuberant host immune response involving innate and acquired immunity, simultaneously contribute to the pathogenesis of COVID-19 and organ injury. The baseline NLR has been identified as an independent risk factor for critical illness in COVID-19 patients. Our previous findings suggest that COVID-19 severity is associated with increased IgG response following confirmed SARS-CoV-2 infection, and an immune response phenotyping based on two immune-related indicators IgG and NLR is useful to discriminate severe and non-severe patients. Therefore, we attempt to establish immune response factors-based and factors-weighted accurate outcome risk estimation models, to help clinicians to select appropriate therapeutic decisions.

MATERIALS AND METHODS

Data collection

All included patients with COVID-19 had been admitted to the Renmin Hospital of Wuhan University, from January 13, 2020 to March 10, 2020. The confirmed diagnosis of COVID-19 was defined as a positive result by using real-time reverse-transcriptase polymerase chain reaction (RT-PCR) detection for routine nasal and pharyngeal swab specimens or anti-SARS-CoV-2 antibody assay. There were five patients with negative RT-PCR results who had typical chest computed tomography findings or clinical symptoms. The percentage of laboratory-confirmed COVID-19 patients in patients admitted to the hospital was 88.7%. Finally, a total of 197 laboratory-confirmed COVID-19 patients were included in this study.

Serum samples were collected at the convalescent phase for further analysis. We retrospectively evaluated their anti-SARS-CoV-2 antibody response, clinical disease severity at the time of IgG detection, and clinical outcome. In the present study, mild and moderate cases were recognized as "non-severe" cases, whereas severe and critical cases were "severe" cases according to a baseline clinical classification from the Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (Trial Version 7) released by the National Health Commission & National Administration of Traditional Chinese Medicine on March 3, 2020. The assessment of disease severity was carried out at the time of sampling for IgG analysis. This study received approval from the research ethics committee of the Renmin Hospital of Wuhan University, Wuhan, China (approval number: WDRY2020-K094). The research ethics committee waived the requirement of informed consent before the study started because of the urgent need to collect epidemiological and clinical data. We analyzed all the data anonymously. Anti-IgG and anti-IgM antibodies were detected using Human SARS-CoV-2 IgG and IgM Chemiluminescence Analysis (CLIA) Assays panel (Shenzhen YHLO Biotech Co., Ltd.) and the high-speed CLIA system iFlash 3000 (Shenzhen YHLO Biotech Co., Ltd.). NLR was calculated by dividing the absolute neutrophil count by the lymphocyte count.

The clinical features, including clinical symptoms, laboratory analyses, treatment, and outcome, were obtained from the hospital's electronic medical records according to previously designed standardized data collection forms. Two researchers independently reviewed the data collection forms. The laboratory measures were categorized for the convenience of clinical use to increase the accuracy of collected data. Laboratory variables including IgG, neutrophil-to-lymphocyte ratio (NLR), lactate dehydrogenase (LDH), albumin (ALB), platelet (PLT), aspartate aminotransferase (AST), CRP, white blood cell (WBC), neutrophil (NEU), lymphocyte (LYM), and hemoglobin (Hb) were stratified using the median as cut-off value. We employed quantiles as cut-off values to categorize blood urea nitrogen (BUN), PCT, and monocyte (MONO) as nonlinear effects on the outcome were found in these variables. In addition, we proposed a combined immune response phenotype by summarizing NLR and IgG into a four-level variable (NLR_IgG) using medians as cut-offs, including high NLR–high IgG (NLRhiIgGhi), high NLR–low IgG (NLRhiIgGlo), low NLR–high IgG (NLRloIgGhi), and low NLR–low IgG (NLRloIgGlo). For disease discrimination, we used severe or non-severe as a binary dependent variable. Furthermore, for the prediction of prognosis for the subgroup of severe patients in the Cox analysis, disease progression was viewed as the endpoint. Patients with disease progression consisted of patients requiring intensive care unit care and dead patients.
2.2 | Statistical analysis

Baseline characteristics of the COVID-19 patient were assessed by severe group and non-severe group and described as medians and interquartile range (IQR) for continuous variables and proportions for categorical variables. We compared the baseline characteristics using the Mann–Whitney test for continuous variables and the χ² test for categorical variables. In the present study, we first constructed two nomograms based on a logistic model with baseline information to discriminate the severe and non-severe patients. One nomogram used NLR and IgG as independent factors, and the other employed a combined immune response phenotype based on NLR and IgG levels as predictors. Nomograms based on Cox proportional hazard model in predicting the prognosis for the severe patients were built subsequently. Similar to the logistic models, we conducted two nomograms using NLR and IgG as independent predictors and the combined phenotype NLR_IgG, respectively. Each nomogram gives a score for each of the variables, and the total points of one patient are obtained by summing up the scores of all the variables. Then, the predicted probability can be estimated with a vertical line dropping down from the total points.

Variables including baseline characteristics were analyzed by multivariate regression analysis. The final models were determined incorporating both clinical hypothesis and statistical methods. Our preliminary analyses have suggested that NLR and IgG might be associated with COVID-19 severity and could be used to further predict their clinical outcome. Age has also been identified as an independent predictor in COVID-19. Therefore, the variable selection was conducted by stepwise selection technique with Akaike information criterion keeping age, IgG, and NLR in the model.

Both discrimination and calibration ability of this nomogram was evaluated using Harrell’s C-index and a calibration plot, respectively. A calibration plot was generated to validate the agreement between the probability predicted by the nomogram and the observed proportions. The bootstrap technique was employed to estimate the bias-corrected measures to validate the nomograms internally. Bias-corrected C-index and calibration were calculated by subjecting the nomogram to 1000 bootstrap resamples. All statistical analyses were performed using R version 3.6.1 with the “rms” and “forestplot” package.

3 | RESULTS

3.1 | Characteristics of patients

A total of 197 patients with complete information were included in the analysis, among which 80 (40.6%) were severe patients and 117 (59.4%) were non-severe patients. The median age was 62 years (IQR; range from 53 to 69 years). In total, 48.2% of patients were male. The median follow-up time is 20 days. As of March 10, 2020, 40 severe patients were still in the severe status and 5 patients died. No non-severe patients progressed to severe disease. Table 1

| Variables | Severe | Non-severe | χ²/z | p value |
|-----------|--------|------------|------|---------|
| Age (years) | 67 (57–75) | 59 (51–66) | 3.90 | <0.001 |
| Sex | | | | |
| Male | 43 (54) | 52 (44) | 1.23 | 0.255 |
| Female | 37 (46) | 65 (56) | | |
| IgG | | | | |
| <116.9 | 29 (36) | 64 (55) | 5.77 | 0.016 |
| ≥116.9 | 51 (64) | 53 (45) | | |
| NLR | | | | |
| <3.04 | 23 (29) | 77 (66) | 24.65 | <0.001 |
| ≥3.04 | 57 (71) | 40 (34) | | |
| NLR_IgG | | | | |
| highNLR_highIgG | 37 (46) | 18 (15) | 31.16 | <0.001 |
| highNLR_lowIgG | 14 (18) | 35 (30) | | |
| lowNLR_highIgG | 20 (25) | 22 (19) | | |
| lowNLR_lowIgG | 9 (11) | 42 (36) | | |
| LDH | | | | |
| <210 | 20 (25) | 78 (67) | 31.35 | <0.001 |
| ≥210 | 60 (75) | 39 (33) | | |
| ALB | | | | |
| <36.7 | 58 (72) | 40 (34) | 26.39 | <0.001 |
| ≥36.7 | 22 (28) | 77 (66) | | |
| PLT | | | | |
| <226 | 38 (48) | 60 (51) | 0.14 | 0.707 |
| ≥226 | 42 (52) | 57 (49) | | |
| AST | | | | |
| <24 | 32 (40) | 65 (56) | 4.00 | 0.046 |
| ≥24 | 48 (60) | 52 (44) | | |
| CRP | | | | |
| <6.6 | 32 (40) | 77 (66) | 11.78 | <0.001 |
| ≥6.6 | 48 (60) | 40 (34) | | |
| WBC | | | | |
| <6.15 | 26 (32) | 72 (62) | 14.89 | <0.001 |
| ≥6.15 | 54 (68) | 45 (38) | | |
| NEU | | | | |
| <3.9 | 23 (29) | 75 (64) | 22.36 | <0.001 |
| ≥3.9 | 57 (71) | 42 (36) | | |
| LYM | | | | |
| <1.27 | 49 (61) | 49 (42) | 6.38 | 0.012 |
| ≥1.27 | 31 (39) | 68 (58) | | |

(Continues)
summarizes the baseline characteristics of participants by the severe and non-severe groups. Age, IgG, NLR, LDH, ALB, AST, CRP, WBC, NEU, LYM, BUN, PCT, and the NLR\(^{\text{IgG}}\) phenotype were significantly different between severe and non-severe patients.

### 3.2 Disease severity discrimination nomogram

Two nomograms were established based on a logistic model with the baseline information to discriminate the severe and non-severe patients. Figure 1 shows the results of the logistic model using IgG and NLR as independent factors. The multivariate logistic analysis indicated that IgG, NLR, LDH, PLT, ALB, and BUN were significant factors associated with the severity of COVID-19 (Figure 1B). Age is not significant in the final model while it still contributes to the severity of discrimination. Figure 1A depicts the nomogram in discriminating the severe and non-severe patients using the above variables. The C-index of the nomogram was 0.86 (95% confidence interval [CI], 0.80–0.91), and the bias-corrected C-index with the bootstrap method was 0.84 (95% CI, 0.77–0.89), which indicates good discriminative performance. The slope of the calibration plot for the nomogram was close to 1, showing an agreement between the prediction and actual observation in severe illness (Figure 1C).

Figure 2 illustrates the results of the logistic model using immune response phenotyping based on NLR and IgG levels (NLR\(^{\text{IgG}}\)). Patients with the NLR\(^{\text{IgG}^\text{hi}}\) phenotype are most likely to have severe disease, especially compared to the NLR\(^{\text{IgG}^\text{lo}}\) group. Similar to Figure 1, the nomogram implies both good discrimination (C-index 0.87 [95% CI, 0.80–0.91] and bias-corrected C-index 0.84 [95% CI, 0.77–0.89]) and calibration (Figure 2C).

### 3.3 Prognosis prediction nomogram for severe patients

All patients were followed after the time of IgG analysis to establish the prognosis prediction model. As no non-severe patients progressed to severe disease, we therefore only predicted the prognosis of the severe patients. Figure 3 depicts the results of the Cox model using IgG and NLR as independent predictors in predicting the prognosis of severe patients. The multivariate Cox analysis indicates that IgG, NLR, age, LDH, PLT, MONO, and PCT were significant predictors (Figure 3B). Figure 3A shows the nomogram incorporating all the above variables for predicting the 12- and 18-day prognosis of the severe patients. The nomogram demonstrates good performance in estimating the risk of the disease progression with a C-index of 0.83 (95% CI, 0.74–0.87) and the bias-corrected C-index of 0.79 (95% CI, 0.72–0.89). In Figure 3C, the calibration plot displays good agreement between the predicted and observed probability of 12- and 18-day prognosis.

Similar results of the prediction model using immune response phenotype NLR\(^{\text{IgG}}\) are shown in Figure 4. The prognosis of severe patients with NLR\(^{\text{IgG}^\text{hi}}\) phenotype is significantly worse than the NLR\(^{\text{IgG}^\text{lo}}\) group. The C-index of the nomogram is 0.83 (95% CI, 0.75–0.88), and drops to 0.79 (95% CI, 0.73–0.89) after bootstrap correction.
The prognosis of severe patients with NLRhiIgGhi phenotype is significantly worse than the NLRloIgGhi group. A nomogram has been developed as an early quantitative predictor tool for discrimination between severe and non-severe patients using data from a single center or multiple centers with small sample size. Another nomogram generated by Gong et al. was used to predict patients at risk of progressed illness with a high AUC in the training and validation cohorts. Using fatal outcome as an endpoint, Chen et al. found that older age, coronary heart disease, cerebrovascular disease, dyspnea, and high level of PCT and aspartate aminotransferase were independent risk factors associated with poor outcomes.

**FIGURE 1** The results of the logistic model using IgG and NLR as independent factors. (A) The nomogram for discriminating the severe and non-severe patients. (B) The forest plot of the corresponding logistic model. (C) Calibration plot of the nomogram. ALB, albumin; BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet.
levels of oxygen saturation and hematocrit, higher levels of CRP, aspartate aminotransferase, and ferritin were independent risk factors for in-hospital mortality risk in COVID-19. A nomogram was established with a sufficient discriminatory power with the C-index of 0.91 (95% CI, 0.85–0.97). Our model incorporates some common laboratory variables such as LDH, PLT, ALB, BUN, as well as immune response-associated indicators NLR and IgG. High NLR is commonly presented and associated with a more severe viral infection. Recent data indicated that the NLR, an indicator of innate immunity, was identified as a powerful predictive and prognostic factor for severe COVID-19. Previous data showed severe SARS was associated with more robust serological responses including early

FIGURE 2 The results of the logistic model using immune response phenotyping based on NLR and IgG levels. (A) The nomogram for discriminating the severe and non-severe patients. (B) The forest plot of the corresponding logistic model. (C) Calibration plot of the nomogram. ALB, albumin; BUN, blood urea nitrogen; CI, confidence interval; HR, hazard ratio; IgG, immunoglobulin G; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLT, platelet.
Our previous findings suggest that COVID-19 severity is associated with increased IgG response, and an immune response phenotyping based on two immune-related indicators IgG and NLR is useful to discriminate between severe and non-severe patients. High NLR was also commonly presented and associated with a more severe viral infection. Patients with high NLR usually have high Th1 cytokine IFN-γ, inflammatory cytokines, and pro-inflammatory cytokines IL-6 and TNF-α. Furthermore, more severe cases occurred in the NLR$^{hi}$IgG$^{lo}$ or NLR$^{hi}$IgG$^{lo}$ phenotype. Recovery rates for severe patients with NLR$^{hi}$IgG$^{lo}$ (58.8%) and NLR$^{hi}$IgG$^{lo}$ (68.8%) phenotype were lower than those for severe patients with NLR$^{hi}$IgG$^{lo}$ (80.0%)
and NLR\textsuperscript{lo}IgG\textsuperscript{lo} (100%) phenotype. Dead cases only were seen in the population with the NLR\textsuperscript{hi}IgG\textsuperscript{hi} or the NLR\textsuperscript{hi}IgG\textsuperscript{lo} phenotypes.\textsuperscript{24} These results indicated that besides the antiviral efficacy, the antibody response and pro-inflammatory cytokines might result in secondary immune-mediated organ damage, which increased the severity of COVID-19 and patients' poor outcome. Interestingly, using an immune response phenotyping based on NLR and IgG level, we found patients with NLR\textsuperscript{hi}IgG\textsuperscript{hi} phenotype are most likely to have severe disease in the logistic model, especially compared to those with NLR\textsuperscript{lo}IgG\textsuperscript{lo} phenotype. This is the first study quantitatively analyzing the association between risk factors including indicators of innate and acquired immunity and the severity of COVID-19.

In the present study, we constructed two series of nomograms with different objectives. We first established nomograms to

![FIGURE 4](image-url)
discriminate the disease severity and then built a disease prognostic prediction model to identify patients with disease progression. All the results are consistent with our hypothesis from previous findings. As to the predictors, we employed a novel immune response-related phenotype based on IgG level and NLR as well as the independent predictors. The prediction model incorporating the combined phenotype showed a comparative performance with the independent predictors, while it is more user-friendly for clinicians. It suggested patients with NLRH IgGHI phenotype should be managed with intensive supportive care and appropriate medical interventions.

Our study had some limitations. First, this is a retrospective study in a single center, and more severe patients were selected in this study. The basic health profiles might influence the performance of the nomogram. The sample size is small in the present study, and further external validation should be conducted to verify the generalizability. Moreover, it is unknown whether the change or increase of IgM or IgA is related to disease severity and patients’ prognosis, and the precise mechanism responsible for the immunopathologic reaction of IgG remains unknown. Immunopathogenesis of SARS-CoV-2 infection requires further study in animal model experiments to confirm the influence of immune response on patient outcome.

Finally, most patients were treated with intravenous high-dose corticosteroids in our study. The clinical outcome for patients without high-dose corticosteroid intervention have not been addressed. In particular, intravenous high-dose corticosteroid treatment could to some extent affect some inspected parameters such as NLR, PLT, and BUN. The reason was that the number of patients without intravenous high-dose corticosteroid intervention was limited in the subgroup with different immune phenotyping, especially in severe patients.

Overall, immune response factors, including IgG, neutrophil-to-lymphocyte ratio (NLR), and general characteristics were associated with the severity of COVID-19 after admission. The current nomograms could help identify patients at risk of progression to severe disease and allow prognostic evaluation for patients with severe COVID-19. Patients at high risk for severe illness and poor outcomes from COVID-19 should be managed with intensive supportive care and appropriate medical interventions.

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CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS
Jun Wang conceived and designed the study, Bicheng Zhang and Bo Zhu prepared the data. Xiaoshuai Zhang and Fang Tang analyzed the data. Jun Wang, Xiaoshuai Zhang, and Fang Tang wrote the paper. All authors have read and approved the final manuscript.

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

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