Development and Validation of a Multivariable Predictive Model for Mortality of COVID-19 Patients Demanding High Oxygen Flow at Admission to ICU: AIDA Score

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Introduction. Risk stratification is an important aspect of COVID-19 management, especially in patients admitted to ICU as it can provide more useful consumption of health resources, as well as prioritize critical care services in situations of overwhelming number of patients. Materials and Methods. A multivariable predictive model for mortality was developed using data solely from a derivation cohort of 160 COVID-19 patients with moderate to severe ARDS admitted to ICU. The regression coefficients from the final multivariate model of the derivation study were used to assign points for the risk model, consisted of all significant variables from the multivariate analysis and age as a known risk factor for COVID-19 patient mortality. The newly developed AIDA score was arrived at by assigning 5 points for serum albumin and 1 point for IL-6, D dimer, and age. The score was further validated on a cohort of 304 patients admitted to ICU due to the severe form of COVID-19. Results. The study population included 160 COVID-19 patients admitted to ICU in the derivation and 304 in the validation cohort. The mean patient age was 66.7 years (range, 20–93 years), with 68.1% men and 31.9% women. Most patients (76.8%) had comorbidities with hypertension (67.7%), diabetes (31.7), and coronary artery disease (19.3) as the most frequent. A total of 316 patients (68.3%) were treated with mechanical ventilation. Ninety-six (60.0%) in the derivation cohort and 221 (72.7%) patients in the validation cohort had a lethal outcome. The population was divided into the following risk categories for mortality based on the risk model score: low risk (score 0–1) and at-risk (score > 1). In addition, patients were considered at high risk with a risk score > 2. By applying the risk model to the validation cohort (n = 304), the positive predictive value was 78.8% (95% CI 75.5% to 81.8%); the negative predictive value was 46.6% (95% CI 37.3% to 56.2%); the sensitivity was 82.4% (95% CI 76.7% to 87.1%), and the specificity was 41.0% (95% CI 30.3% to 52.3%). The C statistic was 0.863 (95% CI 0.805-0.921) and 0.665 (95% CI...
critical care services in situations of an overwhelming num-
ment of COVID-19 mostly due to the need to prioritize
severe lung involvement, and immune response [11, 12].
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focusing on clinical risk, ICU care, and in-hospital mortality
[8–10]. Patients with the severe form of the disease were more
likely to be older, associated with multiple comorbidities,
severe lung involvement, and immune response [11, 12].
Risk stratification is a very important part of the manage-
ment of COVID-19 mostly due to the need to prioritize
critical care services in situations of an overwhelming num-
ber of patients. A proper risk stratification could provide
more useful consumption of health resources, as well as to
reorient more attention to the patients most likely to develop
a severe form of the disease [13–15]. In certain studies, it is
shown that predictive models using laboratory parameters
had stronger discriminatory power compared to the clinical
models [16]. Careful monitoring of laboratory and clinical
parameters followed by a purposeful risk stratification
of patients admitted to ICU could allow a forehead reaction in
case of disease progression, reducing further deterioration
and overall mortality.
In this multicenter study, we aimed to develop and
validate a multivariable predictive model for mortality of
COVID-19 patients admitted to ICU.

2. Materials and Methods
The AIDA score was developed according to the results and
methodology of the previous study by Popadic et al. [17],
combining all significant variables from the multivariate
logistic regression analysis including serum albumin, inter-
leukin-6, and D-dimer, accompanied by age.

2.1. Study Population and Risk Factors. The derivation group
consisted of 160 COVID-19 patients with moderate to severe
ARDS admitted to the Respiratory Intensive Care Unit
between June 23, 2020, and October 2, 2020, in University
Clinical Hospital Center Bezanijska kosa, Belgrade, Serbia,
while further analysis and validation were performed on
additional consecutive 318 patients admitted to ICU between
October 2, 2020, and January 14, 2021, in University Clinical
Hospital Center Bezanijska kosa, Belgrade, Serbia (160
patients), and University Clinical Hospital Center Zvezdara,
Belgrade, Serbia (158 patients). The patients in both groups
were treated by the National Protocol of the Republic of
Serbia for the treatment of COVID-19 infection, as explained in
Materials and Methods of the development study by
Popadic et al. [17].
The Institutional Review Boards of the University Clinical
Hospital Center Bezanijska kosa and University Clinical Hos-
pital Center Zvezdara approved the conducting of the study.

2.2. Predictive Model Development. The predictive model was
developed using data completely from a development cohort,
which consisted of 160 patients. Patient characteristics were
first assessed by univariate logistic regression analysis, fol-
lowing with the final model being developed using a stepwise
multivariate logistic regression analysis. The characteristics
of patients admitted to ICU could allow a forehead reaction in
in-hospital mortality (p value < 0.10 in univariate analysis). The var-
iance inflation factor (VIF) was used to examine covariates
for collinearity. The risk prediction score was developed using
coefficients from the final regression multivariate model with
the addition of age from univariate analysis. Missing data was
rare (<5%) among characteristics considered for the final
model development, and no imputations were performed.
Patients who had their data missing for an outcome (14
patients in total) were excluded from the analysis. Wilson
procedure, including continuity correction, was used to
evaluate differences between characteristics frequency in the
development and validation cohorts, shown with a 95% con-
fidence intervals (CI). Patients were divided into 2 risk
groups according to the risk score once the final model had
been defined.

2.3. Model Validation. The validation cohort (304 patients)
was used to assess the final model. Definitions, measure-
ments, and outcomes used in the validation study were the
same as the ones used in the development study. Model discrimi-
ination performance was tested by means of sensitivity,
specificity, positive, and negative predictive values. C statis-
tic, representing the area under the receiver operating
characteristic curve, was used for overall assessment of the
predictive model. Larger values of C statistics indicated
improved discrimination. For the statistical analysis, the
SPSS version 25 statistical software (Chicago, USA) was used.

3. Results
3.1. Patient Characteristics. The study population included
160 COVID-19 patients admitted to ICU in the derivation
and 304 in the validation cohort. The two cohorts were well
balanced concerning the most assessed patient characteristics
(Table 1). The mean patient age was 66.7 years (range, 20–93
years), with 68.1% men and 31.9% women. Most patients
(76.8%) had comorbidities with hypertension (67.7%), diabe-
tes (31.7), and coronary artery disease (19.3) as the most
frequent. Obesity was present in 16.5% of patients and was more prevalent in the validation cohort. A total of 316 patients (68.3%) were treated with mechanical ventilation, and 89 (19.2%) received Tocilizumab. Ninety-six (60.0%) in the derivation cohort and 221 (72.7%) patients in the validation cohort had a lethal outcome.

3.2. Risk Assessment Model. In the derivation cohort, the following variables were associated with the mortality of patients admitted to ICU due to COVID-19-related pneumonia in univariate logistic regression analysis: age (RR = 3.495, 95% CI 1.801–6.779), albumin (RR = 22.286, 95% CI 9.319–53.294), D-dimer (RR = 2.111, 95% CI 1.091–4.085), IL-6 at admission to ICU (RR = 6.100, 95% CI 2.857–13.023), and CT score (RR = 2.362, 95% CI 1.120–4.980). In the multivariate analysis, serum albumin (RR = 25.740, 95% CI 7.491–88.443), IL-6 (RR = 6.245, 95% CI 1.937–20.129), and D-dimer at admission to ICU (RR = 4.574, 95% CI 1.375–15.212) were independently associated with mortality [17]. Subsequently, the regression coefficients from the final multivariate model were used to assign points for the risk model. The newly developed AIDA score included all significant patient characteristics from the multivariate analysis and age as a known risk factor for COVID-19 patient mortality. The AIDA score was arrived at by assigning 5 points for serum albumin and 1 point for IL-6, D dimer, and age (Table 2). Finally, based on the risk prediction score, the population consisted of the following division risk categories for mortality: low risk (score 0–1) and at risk (score > 1). In addition, patients were considered at high risk with a risk score > 2.

3.3. Accuracy and Validation of AIDA Risk Model. In the development cohort, for patients classified as at risk (score > 1), the AIDA risk model produced a positive predictive value (probability of a lethal outcome in patient designated at risk) of 73.8% (95% CI 68.9% to 78.2%) and a negative predictive value (probability of recovering in patients designated low risk) of 91.2% (95% CI 76.7% to 97.0%). The sensitivity (probability of being classified as at risk in patients with the lethal outcome) was 96.9% (95% CI 91.1% to 99.4%), and the specificity (probability of being classified as low risk in patients recovered) was 48.4% (95% CI 35.8% to 61.3%). A high-risk AIDA score > 2 had a positive predictive value (probability of a lethal outcome in patient designated at high risk) of 81.2% (95% CI 74.6% to 86.4%) and a negative predictive value (probability of recovering in patients designated as not being at high risk) of 76.3% (95% CI 65.9% to 84.3%). The sensitivity (probability of being classified as at high risk in patients with the lethal outcome) was 85.4% (95% CI 76.7% to 91.8%), and the specificity (probability of being classified as not at high risk in patients recovered) was 70.3% (95% CI 57.6% to 81.1%).

The AIDA risk model was then tested for accuracy in the validation cohort (n = 304), where the positive predictive value was 78.8% (95% CI 75.5% to 81.8%); the negative predictive value was 46.6% (95% CI 37.3% to 56.2%); the sensitivity was 82.4% (95% CI 76.7% to 87.1%), and the specificity was 41.0% (95% CI 30.3% to 52.3%). The C statistic was 0.863 (95% CI 0.805-0.921) and 0.665 (95% CI 0.598-0.732) in the development (Figure 1) and validation cohorts (Figure 2), respectively. Both cohorts were similar according to AIDA score accuracy, as well as the frequency of patients classified into each risk category.

4. Discussion

The clinical setting of COVID-19 infection could be diverse, affecting multiple organs and provoking various symptoms

| Table 1: Characteristics of patients in both development and validation cohorts. |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Patient characteristics         | Development cohort | Validation cohort | Difference | 95% CI for the difference |
| Gender, n (%)                   | Development cohort | Validation cohort | Difference | 95% CI for the difference |
| Male                            | 110 (68.8)        | 206 (67.8)       | -0.010     | -0.100 to 0.080         |
| Female                          | 50 (31.3)         | 98 (32.2)        |            |                          |
| Age, mean ± sd                  | 65.6 ± 14.0       | 67.2 ± 12.6      | -1.559     | -4.067 to 0.499         |
| CT score, mean ± sd             | 19.0 ± 4.9        | 17.6 ± 6.0       | 1.394      | 0.009 to 2.778          |
| Mechanic ventilation, n (%)     | 107 (66.9)        | 209 (69.0)       | -0.021     | -0.111 to 0.069         |
| Comorbidities, n (%)            | Development cohort | Validation cohort | Difference | 95% CI for the difference |
| Hypertension                    | 109 (69.4)        | 203 (66.8)       | 0.027      | -0.064 to 0.117         |
| Diabetes                        | 52 (33.1)         | 94 (31.0)        | 0.021      | -0.069 to 0.111         |
| Obesity                         | 14 (8.9)          | 62 (20.4)        | -0.115     | -0.168 to -0.044        |
| HOBP                            | 8 (5.1)           | 13 (4.3)         | 0.008      | -0.032 to 0.049         |
| Asthma                          | 6 (3.8)           | 14 (4.6)         | -0.008     | -0.047 to 0.032         |
| Coronary disease                | 28 (17.8)         | 61 (20.1)        | -0.022     | -0.099 to 0.054         |
| Cardiomyopathy                  | 14 (8.9)          | 24 (7.9)         | 0.010      | -0.043 to 0.063         |
| Total number of patients with comorbidities, n (%) | 120 (75.9) | 235 (77.3) | -0.014 | -0.095 to 0.068 |
| Total number of patients with 2+ comorbidities, n (%) | 72 (45.6) | 137 (45.1) | 0.005 | -0.091 to 0.101 |
| Tocilizumab, n (%)              | 38 (23.8)         | 51 (16.8)        | 0.070      | -0.006 to 0.145         |
and signs, making it more difficult to enable an appropriate risk stratification of these patients [18]. Also, the clinical course of the disease in terms of different pathophysiological mechanisms and complications, including acute respiratory distress syndrome, superinfection, shock, acute heart, liver, and kidney injury, is unpredictable and is leaving a limited timespan to bring the right treatment decision in a real clinical scenario [19, 20].

In the present study, we reported a process of development and validation of a multivariable predictive model for mortality of COVID-19 patients demanding high oxygen flow at admission to ICU.

In order to develop a simple but highly predictable risk score, we have started by identifying credible predictors of mortality in a group of patients with the worst possible clinical condition, considering respiratory status as the most important aspect. This is why the derivation group consisted only of patients with moderate to severe ARDS and on invasive, noninvasive mechanical ventilation and high flow oxygen therapy. The main aim of the following analysis was to extract only those clinical and laboratory parameters which are most likely to be linked with the poor clinical outcome. In the final multivariate analysis, serum albumin, interleukin-6, and D-dimer, accompanied by age and CT severity score as parts of univariate analysis, were marked as independent predictors of mortality. It is important to underline that these predictors are reflecting the three most probable pathophysiological mechanisms of a lethal outcome, infection with sepsis and shock, procoagulable state provoking micro and macrothrombosis, and cytokine storm as a potential trigger of multiorgan failure [21]. Different risk scores have been developed to stratify hospitalized COVID-19 patients, with very few being applicable in patients admitted to ICU. AIDA score primarily relies on the high sensitivity (being 82.4% (95% CI 76.7% to 87.1%) in the validation group) and positive predictive value (78.8% (95% CI 75.5% to 81.8%)), as the most important part of the risk stratification in COVID-19 patients was to identify patients at risk, but not to eliminate the subgroup of low-risk patients, as that would be a two-edged sword, considering the unpredictability of the disease and rapid progression of certain clinical forms. One of the most important advantages of this score is a quite respectable sample size in both derivation and validation groups, encompassing more than 460 patients admitted to ICU with a severe form of the disease. The validation group consisted of patients from two different hospital centers but treated according to the same therapy protocol, while the baseline characteristics between the derivation and validation group did not differ significantly (Table 1). The score is easy to use, as it includes usual laboratory parameters for every COVID-19 patient. Also, the significance of CT severity score was already marked as an important part of risk stratification, although it was not statistically analyzed in our study, due to the lack of data in the external validation group. However, it can be helpful as an additional factor considering the results of the univariate logistic regression model where values of CT severity score above 20 were highly predictive for poor clinical outcome among patients admitted to ICU.

Interleukin-6 values above 72 pg/mL were significant for predicting poor clinical outcomes, which may be helpful in the decision-making process, as immunomodulatory therapy should be administrated earlier in the clinical course. According to the results, the interleukin-6 receptor antagonists might be effective in patients with elevated values of interleukin-6 (but below 72 pg/mL), and before the clinical deterioration in terms of respiratory failure and need for mechanical ventilation, as positive results in terms of lower
mortality rate among this subset of patients are still to be demonstrated [22]. As presented in our derivation study, the mortality rates did not differ between the groups that received and did not receive Tocilizumab in ICU, although the baseline characteristics were not significantly different.

It is of great importance to note that a low value of serum albumin, below 33 g/L, is already highly significant as a predictor of mortality and is a sufficient parameter to stratify patients into a high-risk group. Following the worsening of the patient's condition, the values of interleukin-6 and D-dimer were usually already elevated above their significant values, while the value of serum albumin was preserved a certain amount of time before further clinical worsening. In patients with a severe form of COVID-19, hypoalbuminemia should be considered the most pertinent marker of an advanced clinical condition and is usually followed by the further rising of proinflammatory parameters and D-dimer, indicating a coupling of progressing shock and an increased procoagulable state [23]. This is meaningful as it can point out that various important regulatory mechanisms are already expanded, initiating an irreversible condition refractory to a wide specter of different therapeutic modalities [24]. The potential therapeutic benefit of albumins in patients with COVID-19 is yet to be established [25].

The main limitation of the study is a lack of a more comprehensive external validation in a condition of different therapy protocols being used. It is still unknown if different therapeutic modalities in the earlier phase of the disease can significantly affect the credibility of the score, although this score is primarily intended for the risk stratification of patients admitted to ICU. The score could be developed further by implementing different ICU scoring systems to encompass a wider image of the patient’s current condition.

5. Conclusion

Risk stratification of patients with COVID-19 is an important aspect of everyday practice, having in mind the unpredictability of clinical course and possible complications of the disease. AIDA score could be a reliable tool capable of identifying patients with a higher risk of poor clinical outcomes at admission to the ICU, providing more space to deliver an appropriate therapy on time. Further validation on a larger group of patients will provide more insights into the utility and definitive clinical significance of this score.

Abbreviations

COVID-19: Coronavirus disease 19
ICU: Intensive care unit
ARDS: Acute respiratory distress syndrome
CT: Computerized tomography
IL-6: Interleukin-6.

Data Availability

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

Disclosure

The authors state that no relationship with industry exists. The funders had no role in preparation of the manuscript or the decision to publish.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Authors’ Contributions

Collaborator details are as follows: Nina Rajovic3 MD; Jasna GACIC1, 2 MD, PhD; Lijilana Denic Markovic1, 2 MD, PhD; Aleksandra Petrovic1 MD; Natasa Stanisavljevic1 MD, PhD; Igor Nadj4 MD; Uros Marjanovic5 MD; Aleksandra Duminic5 MD; Simona Petricevic1 MD; Maja Popovic4 MD; Filip Lukic1 MD; Zdravko Kalaba1 MD; Aleksandar Davidovic6, 10 MD, PhD; Natasa Markovic Nikolic2, 8 MD, PhD; Gordana Mihajlovic2, 8 MD, PhD; Miljanka Vuksonovic2, 8 MD, PhD; Milica Marjanovic Petkovic2, 8 MD, PhD; Natasa Petrovic Stanojevic8, 10 MD, PhD. 1University Clinical Hospital Center, Beznajiska kosa, Belgrade, Serbia. 2Faculty of Medicine, University of Belgrade, Belgrade, Serbia. 3Institute for Medical Statistics and Informatics, Faculty of Medicine University of Belgrade, Belgrade, Serbia. 4Clinical Center of Serbia, Belgrade, Serbia. 5Institute of Cardiovascular Diseases “Dedinje,” Belgrade, Serbia. 6Department of Medical Sciences, Serbian Academy of Sciences and Arts. 7Clinic for Hematology, Clinical Center of Serbia, Belgrade, Serbia. 8University Clinical Center Zvezdara, Belgrade, Serbia. 10Faculty of Stomatology, University of Belgrade, Belgrade, Serbia.

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References


