On-admission laboratory predictors for developing critical COVID-19 during hospitalization – a multivariable logistic regression model

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Abstract

Introduction and Objective. Recognition of patients with COVID-19 who will progress clinically and need respiratory support remains challenging. The aim of the study was to identify abnormalities in on-admission laboratory results that can precede progression from moderate or severe to critical COVID-19.

Materials and method. Laboratory data analyzed of 190 patients admitted with moderate or severe COVID-19 to our ward. Laboratory results taken into analysis were obtained during the first 48 hours of hospitalization. Multivariate logistic regression was performed using risk factors obtained in the univariate analysis as dependent variables.

Results. 42 patients were identified who developed critical COVID-19. In univariate analysis, 22 laboratory risk factors were detected that were used in logistic regression and in building model with following predictors: high-sensitive troponin I concentration (hs-TnI) >26 ng/mL (OR 13.45; 95%CI 3.28–55.11; P = 0.001), interleukin-6 (IL-6) >50 pg/mL (OR 5.52; 95%CI 1.86–16.37; P = 0.001), fasting glycaemia >6.8 mmol/L (OR 4.74; 95%CI 1.65–13.66; P = 0.002), immature neutrophils count >0.06/µL (OR 4.06; 95%CI 1.35–12.2; P = 0.012) and urine protein concentration >500 mg/L (OR 2.94; 95%CI 1.04–8.31; P = 0.043).

Conclusions. The most significant risk factors of developing critical COVID-19 during hospitalization are: elevated hs-TnI, IL-6, and glucose serum concentrations, increased immature neutrophil count, neutrophils to monocytes ratio, and proteinuria during the first 48 hours after admission. The model built with these predictors achieved better predictive performance than any other univariately analysed laboratory markers in predicting the critical development COVID-19.

Key words
respiratory failure, laboratory tests, covid-19, sars-cov-2

INTRODUCTION

We have been facing the coronavirus disease 2019 (COVID-19) global pandemics caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) for more than a year [1, 2]. COVID-19 pathogenesis is complicated with infectious, inflammatory, and thrombotic mechanisms involved [3]. Thus, it manifests variably and is characterized by a set of symptoms individual for each patient [4]. Characterization of manifestations including mild, moderate, severe, and critical COVID-19 have been published accompanied by various predictive models [5, 6, 7, 8].

Even though our knowledge about COVID-19 is growing every month, we still encounter research gaps. Most prognostic models published so far focus on COVID-19 diagnosis or prognosis of severe COVID-19 defined as patients needing oxygen therapy [6]. Thus, most hospitalized patients meet the criteria of severe COVID-19. We lack proper prognostic models of patients admitted to a hospital who will develop critical COVID-19, defined as respiratory failure needing respiratory support – high-flow nasal oxygen therapy, non-invasive ventilation, or invasive ventilation [9].

OBJECTIVE

The aim of the study was to analyze predictive factors of developing critical COVID-19 during hospitalization among patients admitted with moderate or severe COVID-19. Identification of on-admission laboratory predictors of such a course of the disease among routinely performed tests may contribute to better triage of hospitalized patients on hospital wards, especially when resources are limited.

MATERIALS AND METHOD

Study design, setting and patients. A retrospective, cross-sectional single-centre study was performed in our COVID-19 ward. Patients eligible for the study must have
met inclusion criteria: positive SARS-CoV-2 RNA RT-PCR (ribonucleic acid reverse transcriptase polymerase chain reaction) test and ground-glass opacities in chest computed tomography (CT) performed within the first 48 hours after hospital admission. Permission was obtained from the local ethical committee of Poznan University of Medical Sciences for the non-experimental character of the research on 3 February 2021.

Data collection. Data available in hospital documentation was collected with the use of a questionnaire prepared for this research. Clinical factors comprised age, gender, body-mass-index (BMI), symptoms, time from symptoms onset to hospital admission, World Health Organization Ordinal Scale [10], heart rate, temperature, arterial blood saturation measured with finger pulse oximeter (SpO2), oxygen concentration (FiO2, estimated with the method by Wettstein et al.) [11], systolic and diastolic blood pressure (SBP and DBP), respiratory rate (RR), Modified Early Warning Score (MEWS) [12], quick Sequential Organ Failure Assessment Score (qSOFA) [13], comorbidities and Charlson Comorbidity Index (CCI) [14] and treatment instituted throughout hospitalization. Chest Computed Tomography Severity Score was obtained from radiologists’ assessment description from our Radiology Department [15]. Laboratory data included: complete blood count (CBC), C-reactive protein (CRP), procalcitonin (Pct), interleukin 6 (IL-6), ferritin, total protein, albumin, lactate dehydrogenase (LDH), creatine kinase (CK), thyrotropin (TSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyltransferase (GGT), alkaline phosphatase (ALP), natrium (Na), kalemia (K), chloremia (Cl), urinalysis, urea, creatinine, estimated glomerular filtration rate (eGFR), fasting glycemia, vitamin D (25(OH)D3), high-sensitive troponin I (hs-TnI), B type natriuretic peptide (BNP), D-dimer, activated partial thromboplastin time (aPTT), prothrombin time (PT), international normalized ratio (INR), fibrinogen and blood type in ABO and Rh system. All analyzed laboratory results were obtained on-admission, defined as first 48h from hospital arrival and were obtained using laboratory analyzers (Roche Cobas c501, Siemens ADVIA Centaur CP, Abbott ARCHITECT i1000SR, Sysmex XN-100,0 and Werfen ACL Top 700). Severe COVID-19 was defined as RR of 30 or more, a SpO2 of 93% or less without oxygen supplementation, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO2/FiO2) of less than 300 mm Hg (in ABG performed during hospitalization), or infiltrates in more than 50% of the lung field [6]. Critical COVID-19 was defined as respiratory failure needing respiratory support, intensive care, or death (WHO Ordinal Scale scores 6–10) [9]. Patients, who deteriorated despite low-flow oxygen supplementation were treated with high flow nasal cannula (HFNC). Those who did not tolerate the treatment or worsened despite HFNC, were consulted by anaesthesiologists, who qualified patients individually into treatment in the ICU based predominantly on the ABG results, clinical status and comorbidities. Critical COVID-19 was defined as respiratory failure needing respiratory support, intensive care, or death (WHO Ordinal Scale scores 6–10). Patients who developed critical COVID-19 were classified into study group, whereas those who did not deteriorate were included into control group.

Statistics. Statistical analysis was conducted with the use of Statistica v.13.3 and MedCalc v.19.8. In the univariate analysis, the chi-square test was used to compare categorical data, when the expected frequency was small, Fisher exact test was applied. Continuous data without normal distribution were evaluated with the Mann-Whitney U test, whereas continuous data with normal distribution were analyzed with the t-Student or Welch test (depending on equality of variances). Then, multivariate binary stepwise logistic regression was performed using risk factors obtained in the univariate analysis as dependent categorical variables. Interactions between the above-mentioned variables were considered before building the model (i.e. between inflammatory markers including IL-6, CRP and procalcitonin). Independent predictors of developing critical COVID-19 were identified with the use of the backward elimination method. Calibration was assessed with the Hosmer and Lemeshow ‘goodness of fit’ test. Internal validation was performed with the use of 10-fold cross-validation. Discrimination was evaluated via area under curve (AUC) analysis of the ROC curve and the estimated ROC curve of the model. Statistical significance was defined with p value equal to or less than 0.05. Correlations of ordinal or continuous data without normal distribution were established with Spearman’s rank correlation coefficient. Correlation was assessed as weak when Rs was equal to or less than 0.4, moderate when Rs was between 0.4 – 0.7, and strong when it was equal to or more than 0.7.

RESULTS

190 patients hospitalized from 16 March 2020 – 31 January 2021 with COVID-19 were screened with the questionnaire, and 177 were found eligible for the study. 13 were excluded due to having critical COVID-19 on admission. 42 patients developed critical COVID-19 during hospitalization and were classified as the study group. In the control group, 116 patients met the criteria of severe COVID-19 during hospitalization and 19 patients were classified as having moderate disease. Descriptive characteristics and treatment in the study and control group are presented in Table 1. Patients who developed critical COVID-19 had significantly higher BMI, MEWS, and qSOFA scores on admission (due to respiratory rate included in both scores). They also significantly differed in comorbidities burden measured with CCS and had more severe lung involvement assessed with CTSS. The mean time from admission to critical COVID-19 development was 3.5(±2.2) days. Mortality in the study group was high – 27 (64.3%), whereas all patients in the control group survived hospital discharge. 21 (50%) patients in patients with critical COVID-19 needed treatment in the intensive care ward.

BNP, CK, and vitamin D concentration were available in less than half of the patients included in the study, and these parameters were excluded from the analysis. Apart from ferritin concentration available in 130 (73.4%) patients, all other laboratory results were available in all patients. 22 risk factors we found of developing critical COVID-19 in univariate analysis (Tab. 2). ROC curves of all above-mentioned factors and four with the best predictive value (highest AUC) are presented in Figure 1.
**Table 1.** Descriptive characterization of studied and control groups and instituted treatment; N(%) or mean±(SD)

| Characteristic                     | Study group | Control group |
|------------------------------------|-------------|---------------|
| patients                           | 42 (23.7%)  | 135 (76.3%)   |
| age (years)                        | 63.8 (±15.7)| 60.4 (±14.5)  |
| sex (male)                         | 27 (64.2%)  | 70 (51.9%)    |
| BMI (kg/m²)                        | 31.4 (±6.6) | 28.5 (±5.1)*  |
| time from onset to hospital admission (days) | 8.1 (±8.4)  | 8.8 (±4.5)    |
| WHO Ordinary Scale on admission    | 4 (0%)      | 21 (15.6%)    |
| SpO2/FIO2 on admission             | 189 (±47)   | 276 (115)*    |
| MEWS score on admission            | 2.4 (±1.7)  | 3.1 (±2.3)*   |
| qSOFA score on admission           | 0.5 (±0.7)  | 0.1 (±0.4)*   |
| RR on admission (breaths/min)      | 22.1 (±7.8) | 14.9 (±3.2)*  |
| CTSS                               | 17.8 (±4.2) | 9.5 (±4.6)*   |
| lung involvement in CT (%)         | 71 (±7)     | 37 (±19)      |

**Comorbidities:**
- CCI: 3.6 (±2.8) 2 (7.3%)
- hypertension: 26 (61.9%) 70 (51.8%)
- chronic kidney disease: 4 (9.5%) 5 (3.7%)
- end-stage CKD: 3 (7.1%) 0 (0%)*
- ischaemic heart disease: 8 (19.0%) 17 (12.6%)
- heart failure: 2 (4.7%) 6 (4.4%)
- diabetes mellitus: 15 (35.3%) 29 (21.5%)
- connective tissue disorders: 1 (2.4%) 5 (3.7%)
- post transplant: 4 (9.5%) 1 (0.7%)*
- asthma/COPD: 6 (14.3%) 11 (8.1%)
- neoplastic disease: 1 (2.4%) 5 (3.7%)
- inflammatory bowel disease: 0 (0%) 2 (1.5%)
- chronic hepatic disorder: 1 (2.4%) 2 (1.5%)

**Treatment:**
- CO/HCO: 2 (4.8%) 30 (22.2%)
- LPV/RTV: 2 (4.8%) 4 (3.0%)
- GCS: 38 (90.5%) 101 (74.8%)
- tocilizumab: 22 (52.4%) 33 (24.4%)
- convalescent plasma: 27 (63.4%) 77 (57.0%)
- remdesivir: 27 (63.4%) 81 (60.0%)
- antibiotics: 39 (92.9%) 104 (77.0%)
- heparin (LMWH or UFH): 40 (95.2%) 128 (94.8%)
- other anticoagulants (VKA, DOAC): 7 (16.7%) 11 (7.4%)
- antiplatelet therapy (ASA, P2Y12i): 7 (16.7%) 23 (17.0%)

**Table 2.** Risk factors of developing critical COVID-19 identified in univariate analysis

| Risk factor                              | OR   | 95%CI            | P value |
|------------------------------------------|------|-----------------|---------|
| leukocytosis (WBC > 11*10³/µL)           | 4.44 | 1.73 - 11.38    | 0.002   |
| neutrophilia (neutrophils > 7.7*10³/µL)  | 4.92 | 2.16 - 11.20    | <0.001  |
| severe lymphopenia (lymphocytes < 0.6*10³/µL) | 2.85 | 1.33 - 6.11    | 0.006   |
| INC > 0.06*10³/µL                       | 5.55 | 2.55 - 12.06    | <0.001  |
| NLR = 8                                  | 4.29 | 2.07 - 8.89     | <0.001  |
| NMR > 15                                 | 6.17 | 2.90 - 13.04    | <0.001  |
| CRP > 10 mg/dL                           | 3.67 | 1.78 - 7.54     | <0.001  |
| IL-6 > 50 pg/mL                          | 6.65 | 2.94 - 15.04    | <0.001  |
| Pct > 0.1 mg/mL                          | 5.45 | 2.60 - 11.43    | <0.001  |
| LDH > 440 U/L                            | 5.38 | 2.56 - 11.27    | <0.001  |
| AST > 35 U/L                             | 4.19 | 1.86 - 9.43     | <0.001  |
| urea > 7.1 mmol/L                        | 3.39 | 1.53 - 7.52     | 0.002   |
| creatinine > 115 µmol/L                  | 4.80 | 2.07 - 11.12    | <0.001  |
| eGFR (MORI) < 60 ml/h/1.73m²             | 5.60 | 2.24 - 14.03    | <0.001  |
| proteinuria > 0.5 g/L                    | 5.60 | 2.41 - 9.10     | <0.001  |
| leukocyturia (> 6 WBC/µL)                | 2.74 | 1.31 - 5.76     | 0.006   |
| erythrocyturia (>5 RBC/µL)               | 2.40 | 1.12 - 5.17     | 0.022   |
| fasting glycaemia > 6.8 mmol/L           | 3.31 | 1.30 - 8.42     | 0.001   |
| hs-TnI > 26 ng/L                         | 16.62| 6.29 - 43.96    | <0.001  |
| D-dimer > 1.0 µg/mL                      | 3.48 | 1.69 - 7.19     | <0.001  |
| INR > 1.2                                | 2.46 | 1.21 - 5.01     | 0.001   |
| ferritin > 1500 ng/mL                    | 6.86 | 1.84 - 25.61    | 0.002   |

**OR – odds ratio, 95%CI – 95% confidence interval, WBC – white blood cells, INC – immature neutrophils count, NLR – neutrophils to lymphocytes ratio, NMR – neutrophils to monocytes ratio, CRP – C-reactive protein, IL-6 – interleukin 6, Pct – procalcitonin, LDH – lactate dehydrogenase, AST – aspartate transaminase, eGFR (MORI) – glomerular filtration rate estimated with Modification of Diet in Renal Disease Study Group equation, RBC – red blood cells, hs-TnI – high sensitivity troponin I, INR – international normalized ratio

**Table 3.** Independent risk factors of developing critical COVID-19 identified in the logistic regression model

| Risk factor                              | adjusted OR | 95%CI            | P value* |
|------------------------------------------|-------------|-----------------|---------|
| hs-TnI > 26 ng/L (99th percentile)        | 13.44       | 3.28 – 55.11    | <0.001  |
| NMR > 15                                 | 5.67        | 1.97 – 16.36    | 0.001   |
| IL-6 > 50 pg/mL                          | 5.52        | 1.86 – 16.37    | 0.002   |
| fasting glycaemia > 6.8 mmol/L           | 4.74        | 1.65 – 13.66    | 0.004   |
| INC > 0.06*10³/µL                        | 4.06        | 1.35 – 12.20    | 0.012   |
| proteinuria > 0.5 g/L                    | 2.94        | 1.04 – 8.31     | 0.043   |

**OR – odds ratio, 95%CI – 95% confidence interval, hs-TnI – high sensitivity troponin I, NMR – neutrophils to monocytes ratio, IL-6 – interleukin 6, INC – immature neutrophils count**

Due to the lack of ferritin concentration result in all patients, this parameter was excluded from further analysis. All other 21 identified risk factors were included in the logistic regression model. 6 independent prognostic factors are presented in Table 3. An equation was devised to predict the probability of developing critical COVID-19 as follows:

\[
\text{logit}(Y) = -5.007 + 2.599 \cdot \text{TnI} + 1.735 \cdot \text{NMR} + 1.708 \cdot \text{IL-6} + 1.557 \cdot \text{glc} + 1.402 \cdot \text{INC} + 1.077 \cdot \text{UPC}
\]

Where:

- TnI = 1 if hs-TnI concentration is > 26 ng/L;
- NMR = 1 if neutrophils to monocytes ratio > 15;
- IL-6 = 1 if IL-6 concentration is >50 pg/mL;
- glc = 1 if fasting glycaemia > 6.8 mmol/L;
- INC = 1 if immature neutrophils count > 60/µL;
- UPC = 1 if urine protein concentration > 0.5 g/L;

otherwise these variables have the value of 0.

The summary of the model is shown in Table 4. Statistical significance of model parameters was proved with Wald test (P <0.001), the goodness of fit was shown with Hosmer-
Lemeshow test ($P = 0.47$), while the difference between AUC and estimated AUC was minimal, proving that model is not over-fitted. Moreover, identified risk factors are available in most laboratories in COVID-19 facilities, which makes it valuable.

Correlation between radiological (CTSS) and clinical ($\text{SpO}_2$/FiO$_2$) severity and laboratory parameters is presented in Table 5.

**DISCUSSION**

21 laboratory risk factors of critical COVID-19 development were identified in univariate analysis and 6 independent prognostic laboratory markers found in the logistic regression model, all easily and widely accessible for clinicians, especially in COVID-19 healthcare facilities. The parameters identified as risk factors of critical COVID-19 development can be easily classified into subgroups – inflammatory markers such as CRP, Pct, IL-6, leukocytosis, neutrophilia; coagulation test – D-dimer and INR; tissue and organ damage indicators – hs-TnI, LDH, AST and renal dysfunction markers – proteinuria, haematuria, elevated creatinine and urea. Independent risk factors found included: hs-TnI $>26$ ng/L, NMR (neutrophils to monocytes ratio) $>15$, IL-6 $>50$ pg/mL, fasting glycaemia $>6.8$ mmol/L, INC (immature neutrophils count) $>60/\mu L$, and proteinuria $>0.5$ g/L. Troponin I – a marker of direct or indirect cardiac injury that can significantly contribute to COVID-19 severity and mortality [16]. Its elevation can be associated with many cardiac and extracardiac COVID-19 manifestations and complications with myocarditis, acute coronary syndromes, pulmonary embolism, sepsis-related cardiac damage and cytokine storm syndrome among them [17].
Table 4. Selection of independent variables of developing critical COVID-19 identified in logistic regression model and summary of the model

| Risk factor | B      | 95% CI        | Standard error | Wald  | df |
|-------------|--------|---------------|----------------|-------|----|
| hs-TnI > 26 ng/L | 2.599  | 1.19-4.01     | 1.19           | 13.04 | 1  |
| NMR > 15    | 1.735  | 0.68-2.80     | 0.54           | 10.31 | 1  |
| IL-6 > 50 pg/mL | 1.708  | 0.62-2.80     | 0.78           | 9.48  | 1  |
| fasting glycaemia > 6.8 mmol/L | 1.557 | 0.50-2.62 | 0.54 | 8.32 | 1 |
| INC > 0.06*10^11/L | 1.402 | 0.30-2.50 | 0.56 | 6.24 | 1 |
| proteinuria > 0.5 g/L | 1.077 | 0.03-2.12 | 0.53 | 4.11 | 1 |
| constant    | -5.007 | -6.53-(-3.49) | 0.78           | 41.69 | 1  |

Summary of the model

| Wald test          | P < 0.001 |
|--------------------|-----------|
| Cox-Snell R²       | 0.40      |
| Nagelkerk R²       | 0.60      |
| Likelihood Ratio   | 88.49     |
| Hosmer-Lemeshow test | P = 0.47 |
| AUC                | 0.917     |
| estimated AUC      | 0.892     |

OR = odds ratio, 95%CI = 95% confidence interval, hs-TnI – high sensitivity troponin I, NMR – neutrophils to monocytes ratio, IL-6 – interleukin 6, INC – immature neutrophils count, AUC – area under curve

Table 5. Correlations between laboratory parameters, extent of pulmonary infiltrates measured with CTSS and SpO2/FiO2 ratio on admission to the hospital

| Laboratory parameter | CTSS RS | P value | SpO2/FiO2 RS | P value |
|----------------------|---------|---------|--------------|---------|
| WBC                  | 0.20    | 0.009*  | -0.08        | 0.285   |
| Neutrophils          | 0.27    | <0.001* | -0.16        | 0.035*  |
| Lymphocytes          | -0.20   | 0.006*  | -0.19        | 0.011*  |
| INC                  | 0.25    | <0.001* | -0.14        | 0.058   |
| NLR                  | 0.33    | <0.001* | -0.24        | 0.001*  |
| NMR                  | 0.41    | <0.001* | -0.29        | 0.001*  |
| CRP                  | 0.52    | <0.001* | -0.31        | <0.001* |
| IL-6                 | 0.05    | 0.535   | 0.02         | 0.393   |
| Pct                  | 0.38    | 0.282   | -0.06        | 0.776   |
| LDH                  | 0.63    | <0.001* | -0.45        | <0.001* |
| AST                  | 0.43    | <0.001* | -0.33        | <0.001* |
| urea                 | 0.26    | 0.001*  | -0.20        | 0.011*  |
| creatinine           | 0.12    | 0.101   | -0.18        | 0.020*  |
| eGFR (MDRD)          | -0.03   | 0.713   | 0.14         | 0.069   |
| UPC                  | 0.29    | <0.001* | -0.23        | 0.003*  |
| glycaemia            | 0.35    | <0.001* | -0.44        | <0.001* |
| hs-TnI               | 0.22    | <0.001* | -0.33        | <0.001* |
| D-dimer              | -0.07   | <0.001* | -0.22        | 0.004*  |
| INR                  | 0.27    | 0.001*  | -0.20        | 0.007*  |
| ferritin             | 0.24    | 0.005*  | -0.32        | 0.018*  |

* P < 0.05

CTSS – Chest Computed Tomography Severity Score, WBC – white blood cells, INC – immature neutrophils count, NLR – neutrophils to lymphocytes ratio, NMR – neutrophils to monocytes ratio, CRP – C-reactive protein, IL-6 – interleukin 6, Pct – procalcitonin, LDH – lactate dehydrogenase, AST – aspartate transaminase, eGFR (MDRD) – glomerular filtration rate estimated with Modification of Diet in Renal Disease Study Group equation, UPC – urine protein concentration, hs-TnI – high sensitivity troponin I, INR – international normalized ratio

NMR may reflect an immunological imbalance in patients with COVID-19 as its elevation is associated with increased intra-tissue monocytes migration [18]. It was shown that hyperactivity of neutrophils contributes to hyperinflammation and tissue damage, whereas subpopulations of monocytes predominantly decreased in severe COVID-19 are involved in anti-inflammatory pathways [19, 20].

High IL-6 concentration is well-known risk factor of COVID-19 severity and associated mortality [21, 22, 23]. It is one of the most potent pro-inflammatory cytokines that plays a crucial role in COVID-19 associated hyperinflammation and cytokine storm. It also proved to be helpful as a predictive marker [21].

Elevated fasting glycaemia is associated with critical COVID-19 development risk in many ways. Inflammatory cytokines, such as interleukin-6, and antiviral response through γ-interferon lead to increase in insulin resistance and higher insulin demand. β cells can be directly infected with SARS-CoV-2 due to high ACE2 expression. It can also be related to previously undiagnosed pre-diabetes or diabetes – 34 (49%) of patients with fasting glycaemia > 6.8 mmol/L had no such history. Moreover, patients with well-controlled diabetes can achieve fasting glycaemia below that level, as was case in 9 (20%) diabetic patients in the investigated group. As most of these patients were GCS-naïve on admission to the ward, and fact that GCS predominantly affect postprandial glucose concentrations, treatment-induced hyperglycaemia was probably neglectable in this case, as was case in 9 (20%) diabetic patients in the investigated group. As most of these patients were GCS-naïve on admission to the ward, and fact that GCS predominantly affect postprandial glucose concentrations, treatment-induced hyperglycaemia was probably neglectable in this case, as was case in 9 (20%) diabetic patients in the investigated group.

Increased INC can reflect the severity of the infection and is associated with sepsis or acute respiratory distress syndrome [27]. Severe COVID-19 is associated with dysregulated myeloid cell department [28]. Presence of immature neutrocytes and their precursors in peripheral blood is an evidence of emergency myeloipoiesis, with occurrence of signs of recent activation, similarly to sepsis [28].

Significant proteinuria (>0.5 g/L) was found to be a predictive factor of progression to critical COVID-19. Elevated urine protein concentration, predominantly transient, was reported in up to 44% of COVID-19 patients and may reflect early direct or indirect renal damage. It was proved that SARS-CoV-2 can directly infect proximal tubule and glomerular cells (podocytes and endothelium), leading to cell apoptosis and glycoalcyx disruption [29, 30].

ROC curves analysis enabled the distinguishing of single laboratory tests that can predict progression critical COVID-19. The most sensitive factor was IL-6 concentration >50 pg/mL, the most specific – high sensitivity troponin I >20 ng/L, whereas LDH activity showed both satisfying specificity and sensitivity as a single prognostic test. It must be emphasized that the probability of finding a single diagnostic test that will predict critical COVID-19 is unlikely, and in clinical practice, many biomarkers should be analyzed concomitantly with the clinical and radiological abnormalities.

Many significant correlations were found between laboratory parameters and radiological (CTSS) or clinical (SpO2/FiO2) factors, although most of them were weak (Tab. 5).
moderately negatively correlated with SpO2/FiO2 ratio. No strong correlations between laboratory alterations and radiological extent of infiltrates or SpO2/FiO2 ratio were identified. These findings are in accordance with other studies – laboratory factors correlate weakly or moderately with CT severity scores and predominantly in the early stage of the disease due to slower regression of radiological changes in comparison with higher laboratory markers dynamics [31, 32, 33, 34]. Similarly, negative correlations between SpO2/FiO2 ratio and laboratory parameters, such as LDH, D-dimer or ferritin concentrations, were also weak to moderate [35].

Most studies published to-date have focused on mortality or severe COVID-19, although the findings were similar to those in the current study [36, 37, 38]. Statsenko et al. identified prognostic factors of ICU transmission due to acute respiratory failure, including troponin, WBC, lymphocytes, LDH, bilirubin, AST, ALT, D-dimer, CK, ferritin, aPTT, fibrinogen, and CRP [39]. Bennoura et al. developed a risk score of COVID-19 severity and in-hospital mortality comprising age, natriaemia, blood urea, CRP, NLR, LDH, and albumin [40].

In the conditions prevailing in Poland, due to limited resources, patients with acute respiratory failure are hospitalized on hospital wards other than ICU in case they do not need respiratory support different than high-flow oxygen therapy systems. Thus, the criteria of ICU administration may differ between COVID-19 healthcare facilities and countries, or even within one facility, depending on the availability of ICU beds.

Some of factors found in the above-mentioned studies differ from those in the current study. First of all, most studies did not analyse the immature neutrophil count, a simple and widely available marker. Moreover, proteinuria was also scarcely reported; thus urinalysis seems to be one of the crucial tests in risk stratification of developing critical COVID-19. Interestingly, serum albumin, natriaemia, ALT, and fibrinogen were not identified as significant risk factors of progression to critical COVID-19 in the analysis in the current study. Thirdly, most of our patients received glucocorticosteroids, antibiotics, remdesivir, convalescent plasma and/or tocilizumab, therefore the results of the current study may differ due to different treatment schemes [41].

Limitations of the study. Firstly, the population of the study was homogeneous; all patients were Caucasian. Thus, extrapolation of the results on other populations may be biased. Secondly, only laboratory findings without clinical and radiological context were interpreted – the study and control groups differed in these aspects, though no strong correlations we found between laboratory, radiological and clinical factors. Building a model with clinical and radiological findings would need a larger study population. However, the model in the current study, built solely with laboratory markers, had satisfactory predictive performance based on AUC. Moreover, in comparison with other publications on the subject of COVID-19 in Polish patients, including research on large, multi-thousand cohorts, number and character of comorbidities that we encountered in our patients in the study and control groups, were comparable to those found by the authors of above-mentioned study [42]. Thus, the presented model can perform in real-life situations where analysis of laboratory data is hampered by many clinical factors, such as comorbidities that differ significantly between patients and influence laboratory results. Thirdly, the generalization of the obtained results may be biased due to the retrospective single-centre design. The presented findings should be confirmed in prospective multi-centre trials. Last but not least, there is a lack of publications on all interpreted laboratory results in mild and moderate COVID-19 patient in the current study. The inclusion of the above-mentioned groups that do not need hospitalization would take all spectrum of the disease into consideration and seems to be understudied.

CONCLUSIONS

Risk stratification in COVID-19 based on laboratory parameters remains challenging. This study has emphasized the need of considering many biomarkers in concomitance with radiological and clinical data. Six independent laboratory prognostic factors of developing critical COVID-19 were found: hs-TnI, NMR, IL-6, fasting glycaemia, INC, and proteinuria. They are widely available, and it is believed that the presented results can contribute to early recognition of patients who may develop respiratory failure and will need treatment intensification. Witan AUC of 0.91, the presented model achieved better predictive performance than any of the univariately analysed laboratory markers; therefore providing a simple to calculate tool ready for use by clinicians to more accurately stratify the risk of a critical course of COVID-19.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. N Engl J Med. 2020; 382(8): 727–733. doi: 10.1056/NEJMoa2001017
2. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet. 2020; 395(10223): 507–513. doi: 10.1016/S0140-6736(20)30211-7
3. Brodin P. Immune determinants of COVID-19 disease presentation and severity. Nat Med. 2021; 27(1): 28–33. doi: 10.1038/s41591-020-01202-8
4. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020; 323(13): 1239–1242. doi: 10.1001/jama.2020.2468
5. Gandhi RT, Lynch JB, Del Rio C. Mild or Moderate Covid-19. N Engl J Med. 2020; 383(18): 1757–1766. doi: 10.1056/NEJMc2009249
6. Berlin DA, Gulick RM, Martinez FL. Severe Covid-19. N Engl J Med. 2020; 383(25): 2451–2460. doi: 10.1056/NEJMc2009575
7. Del Sole F, Farcomeni A, Loffredo L, et al. Features of severe COVID-19: A systematic review and meta-analysis. Eur J Clin Invest. 2020; 50(10): e13378. doi: 10.1111/eci.13378
8. Wynants L, Van Calster B, Collina GS, et al. Prediction models for diagnosis and prognosis of covid-19 infection: systematic review and critical appraisal. BMJ. 2020; 369: m1328. doi: 10.1136/bmj.m1328
9. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020; 20(8): e192–e197. doi: 10.1016/S1473-3099(20)30483-7
10. A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis. 2020; 20(8): e192–e197. doi: 10.1016/S1473-3099(20)30483-7
11. Wetzstein RB, Shelley DC, Peters JI. Delivered oxygen concentrations using low-flow and high-flow nasal cannulas. Respir Care. 2005; 50(5): 604–609.
12. Subbe CP, Kruger M, Rutherford P, et al. Validation of a modified Early Warning Score in medical admissions. QJM Mon J Assoc Physicians. 2001; 94(10): 521–526. doi: 10.1093/qjmed/94.10.521
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13. Seymour CW, Liu VX, Iwashyna TJ, et al. Assessment of Clinical Criteria for Sepsis: For the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3). JAMA. 2016; 315(8): 762–774. doi: 10.1001/jama.2016.0288

14. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987; 40(5): 373–383. doi:10.1016/0021-9681(87)90171-8

15. Chang YC, Yu CJ, Chang SC, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. Radiology. 2005; 236(3): 1067–1075. doi:10.1148/radiol.2363040958

16. Chan WT, Toh HS, Liao CT, et al. Cardiac Involvement of COVID-19: A Comprehensive Review. Am J Med Sci. 2021; 361(1): 14–22. doi:10.1016/j.amjms.2020.10.002

17. Piccioni A, Brigida M, Loria V, et al. Role of troponin in COVID-19 pandemic: a review of literature. Eur Rev Med Pharmacol Sci. 2020; 24(19): 10293–10300. doi: 10.26355/eurrev_2020_12_2350

18. Pourbughari-Sigaroodi A, Bashash D, Fateh F, et al. Laboratory findings in COVID-19 diagnosis and prognosis. Clin Chim Acta Int J Clin Chem. 2020; 510: 475–482. doi:10.1016/j.cca.2020.08.019

19. Hemmat N, Derakhshani A, Bannazadeh Baghi H, et al. Neutrophils, Crucial, or Harmful? Immune Cells Involved in Coronavirus Infection: A Bioinformatics Study. Front Genet. 2020; 11: 641. doi: 10.3389/fgen.2020.00641

20. Gatti A, Radrizzani D, Viganò P, et al. Decrease of Non-Classic and Intermediate Monocyte Subsets in Severe Acute SARS-CoV-2 Infection. Cytom Part J Int Soc Anal Cytol. 2020; 97(9): 887–890. doi:10.1002/cyto.a.24188

21. Mcgonagle D, Sharif K, O’Regan A, et al. The Role of Cytokines including Interleukin-6 in COVID-19 induced Pneumonia and Macrophage Activation Syndrome-Like Disease. Autoimmune Rev. 2020; 19(6): 102537. doi: 10.1016/j.autrev.2020.102537

22. Coomes EA, Haghbayan H. Interleukin-6 in Covid-19: A systematic review and meta-analysis. Rev Med Virol. 2020; 30(6): 1–9. doi:10.1002/cyto.a.24188

23. Liu F, Li L, Xu M, et al. Prognostic value of interleukin-6, C-reactive protein, and procalcitonin in patients with COVID-19. J Clin Virol. 2021; 127: 104370. doi: 10.1016/j.jcv.2020.104370

24. Lim S, Bae JH, Kwon HS, et al. COVID-19 and diabetes mellitus: from pathophysiology to clinical management. Nat Rev Endocrinol. 2021; 17(1): 11–30. doi:10.1038/s41574-020-00435-4

25. Enej H, Alsharani A, Zafar A, et al. COVID-19 and comorbidities: Deleterious impact on infected patients. J Infect Public Health. 2020; 13(12): 1833–1839. doi:10.1016/j.jiph.2020.07.014

26. Wu ZH, Tang Y, Cheng Q. Diabetes increases the mortality of patients with COVID-19: a meta-analysis. Acta Diabetol. 2021; 58(2): 139–144. doi:10.1007/s00592-020-01546-0

27. Ronit A, Berg RMG, Bay JT, et al. Compartmental immunophenotyping in COVID-19 ARDS: A case series. J Allergy Clin Immunol. 2021; 147(1): 81–91. doi:10.1016/j.jaci.2020.09.009

28. Schulte-Schrepping J, Reusch N, Paclik D, et al. Severe COVID-19 Is Marked by a Dysregulated Myeloid Cell Compartment. Cell. 2020; 182(6): 1419–1440.e23. doi: 10.1016/j.cell.2020.08.001

29. Perico L, Benigni A, Casiraghi F, Ng LFP, et al. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. Nat Rev Nephrol. 2021; 17(1): 46–64. doi: 10.1038/s41581-020-00357-4

30. Pei G, Zhang Z, Peng J, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. J Am Soc Nephrol JASN. 2020; 31(6): 1157–1165. doi: 10.1681/ASN.2020030276

31. Canovi S, Besutti G, Bonelli E, et al. The association between clinical laboratory data and chest CT findings explains disease severity in a large Italian cohort of COVID-19 patients. BMC Infect Dis. 2021; 21(1): 157. doi: 10.1186/s12879-021-05855-9

32. Zhang B, Zhang J, Chen H, et al. Novel coronavirus disease 2019 (COVID-19): relationship between chest CT scores and laboratory parameters. Eur J Nucl Med Mol Imaging. 2020; 47(9): 2083–2089. doi:10.1007/s00259-020-04854-3

33. Zhou M, Dong C, Li C, et al. Longitudinal changes in COVID-19 clinical measures and correlation with the extent of CT lung abnormalities. Int J Med Sci. 2021; 18(5): 1277–1284. doi: 10.7150/ijms.51279

34. Francone M, Iafrafe M, Masci GM, et al. Chest CT score in COVID-19 patients: correlation with disease severity and short-term prognosis. Eur Radiol. 2020; 30(12): 6808–6817. doi:10.1007/s00330-020-07033-y

35. Piqueu-Gonzáles JM, Hernández-Pérez JM, Acosta Sorensen M, et al. Biomarkers of acute respiratory distress syndrome in adults hospitalised for severe SARS-CoV-2 infection in Tenerife Island, Spain. BMC Res Notes. 2020; 13: 555. doi: 10.1186/s13104-020-05402-w

36. Macias-Muñoz L, Wijngaard R, González-de la Presa B, et al. Value of clinical laboratory test for early prediction of mortality in patients with COVID-19: the BGM score. J Circ Biomark. 2021; 10: 1–8. doi: 10.3393/jcb.2021.2194

37. Mehta AA, Haridas N, Belgundi P, et al. A systematic review of clinical and laboratory parameters associated with increased severity among COVID-19 patients. Diabetes Metab Syndr. 2021; 15(2): 535–541. doi: 10.1016/j.dsx.2021.02.020

38. Nijman G, Wientjes M, Ramjith J, et al. Risk factors for in-hospital mortality in laboratory-confirmed COVID-19 patients in the Netherlands: A competing risk survival analysis. PloS One. 2021; 16(3): e0249231. doi: 10.1371/journal.pone.0249231

39. Stasenko Y, Al Zahmi F, Habuza T, et al. Prediction of COVID-19 severity using laboratory findings on admission: informative values, thresholds, ML model performance. BMJ Open. 2021; 11(2): e044500. doi: 10.1136/bmjopen-2020-044500

40. Bennouar S, Bachir Cherif A, Kesssra A, et al. Development and validation of a laboratory risk score for the early prediction of COVID-19 severity and in-hospital mortality. Intensive Crit Care Nurs. Published online January 9, 2021:103012. doi:10.1016/j.iccn.2021.103012

41. Leszczyński P. COVID-19: a short message to rheumatologists. Reumatologia. 2020; 58(3): 130–133. doi: 10.5114/rev.2020.96685

42. Kaneki K, Nitsch-Osuch A, Goryński P, et al. Hospitalizations for COVID-19 in Poland: a study based on data from a national hospital register. Pol Arch Intern Med. 2021; 131(6): 535–540. doi:10.20452/pamw.15946