



# 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), 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

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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 (SpO<sub>2</sub>), oxygen concentration (FiO<sub>2</sub>, 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), natremia (Na), kalemia (K), chloremia (Cl), urinalysis, urea, creatinine, estimated glomerular filtration rate (eGFR), fasting glycemia, vitamin D (25(OH)D<sub>3</sub>), 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 SpO<sub>2</sub> of 93% or less without oxygen supplementation, a ratio of the partial pressure of arterial oxygen to the fraction of inspired oxygen (PaO<sub>2</sub>/FiO<sub>2</sub>) 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 *R*<sub>s</sub> was equal to or less than 0.4, moderate when *R*<sub>s</sub> 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(±SD 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/m <sup>2</sup> )	31.4 (±6.6)	28.5 (±5.1)*
time from onset to hospital admission (days)	8.1 (±4.8)	8.8 (±4.5)
WHO Ordinary Scale on admission – 4	0 (0%)	21 (15.6%)
5	42 (100%)	114 (84.4%)
SpO <sub>2</sub> /FiO <sub>2</sub> on admission	189 (±47)	276 (±115)*
MEWS score on admission	2.4 (± 1.7)	1.0 (± 1.2)*
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 (±17)	37 (±19)
Comorbidities:		
CCI	3.6 (± 2.8)	2.7 (±2.3)*
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 (35.7%)	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:		
CQ/HCQ	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 (64.3%)	77 (57.0%)
remdesivir	27 (64.3%)	81 (60.0%)
antibiotics	39 (92.9%)	104 (77.0%)
heparin (LMWH or UHF)	40 (95.2%)	128 (94.8%)
other anticoagulants (VKA, DOAC)	7 (16.7%)	11 (7.4%)
antiplatelet therapy (ASA, P2Y <sub>12</sub> i)	7 (16.7%)	23 (17.0%)

\* P &lt;0.05, Mann-Whitney U-Test or chi2 test

BMI – body mass index, WHO – World Health Organization, SpO<sub>2</sub> – arterial blood saturation measured with finger pulse oximeter, FiO<sub>2</sub> – oxygen concentration, MEWS – Modified Early Warning Score, qSOFA – quick Sequential Organ Failure Assessment Score, RR – Respiratory Rate, CTSS – Chest Computed Tomography Severity Score, CT – computed tomography, CCI – Charlson Comorbidity Index, CKD – chronic kidney disease, COPD – chronic obstructive pulmonary disease, CQ – chloroquine, HCQ – hydroxychloroquine, LPV/RTV – lopinavir/ritonavir, GCS – glucocorticosteroids, LMWH – low molecular weight heparin, UHF – unfractionated heparin, VKA – vitamin K antagonists, DOAC – direct oral anticoagulants, ASA – acetylsalicylic acid, P2Y<sub>12</sub>i – P2Y<sub>12</sub> adenosine diphosphate receptor antagonists

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:

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

Risk factor	OR	95%CI	P value
leukocytosis (WBC > 11*10 <sup>3</sup> /μL)	4.44	1.73 – 11.38	0.002
neutrophilia (neutrophils > 7.7*10 <sup>3</sup> / μL)	4.92	2.16 – 11.20	< 0.001
severe lymphopenia (lymphocytes < 0.6*10 <sup>3</sup> / μL)	2.85	1.33 – 6.11	0.006
INC > 0.06*10 <sup>3</sup> / 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 ng/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 (MDRD) < 60 ml/h/1.73m <sup>2</sup>	5.60	2.24 – 14.03	<0.001
proteinuria > 0.5 g/L	5.60	2.41 – 10.91	<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 (MDRD) – 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 (99 <sup>th</sup> 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*10 <sup>3</sup> / μL	4.06	1.35–12.20	0.012
proteinuria > 0.5 g/L	2.94	1.04–8.31	0.043

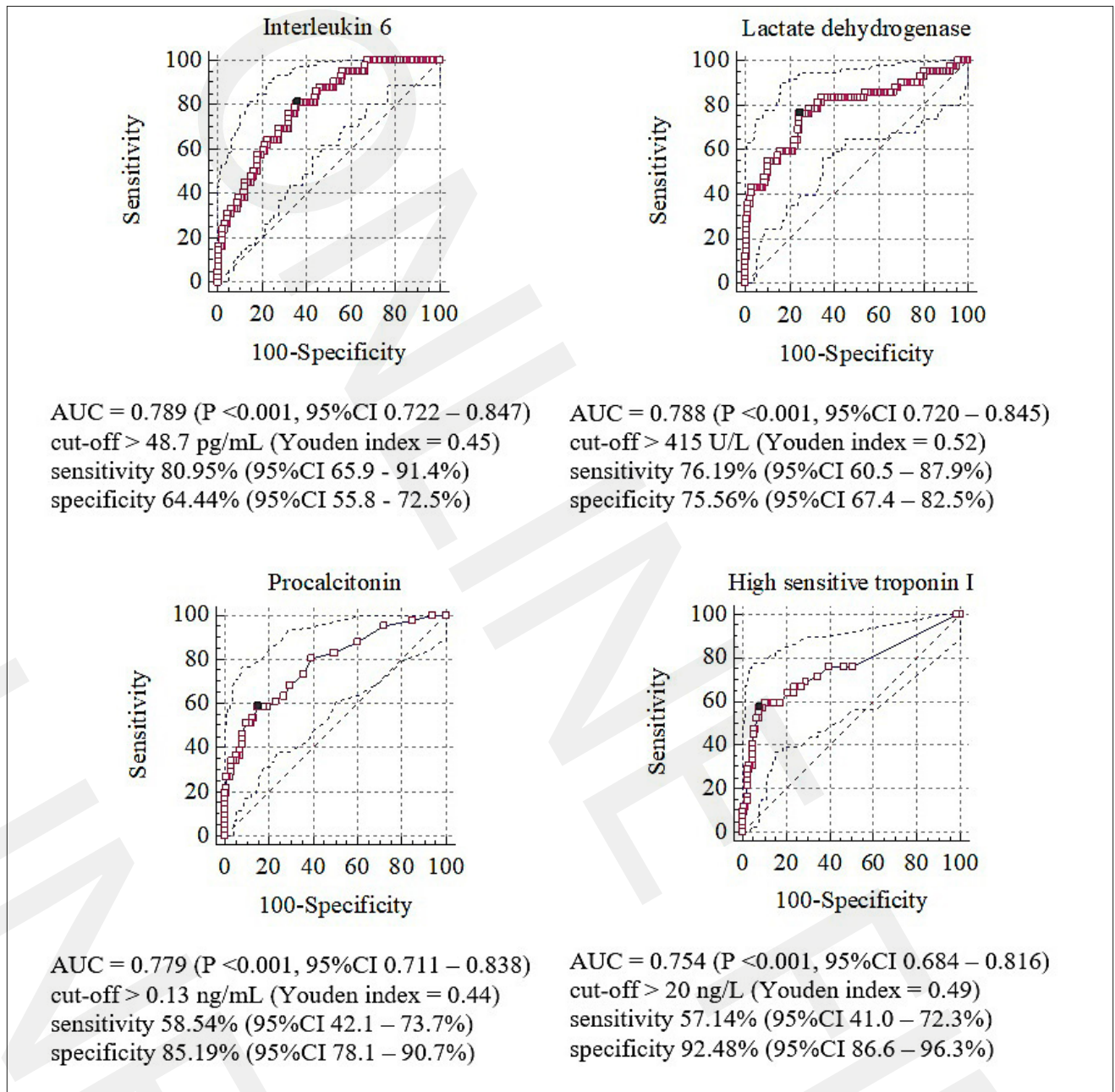
OR – odds ratio, 95%CI – 95% confidence interval, hs-TnI – high sensitivity troponin I, NMR – neutrophils to monocytes ratio, IL-6 – interleukin 6, INC – immature neutrophils count

$$\text{logit}(Y) = -5.007 + 2.599 \cdot \text{TnI} + 1.735 \cdot \text{NMR} + 1.708 \cdot \text{IL6} + 1.557 \cdot \text{glc} + 1.402 \cdot \text{INC} + 1.077 \cdot \text{UPC} \text{ where:}$$

TnI = 1 if hs-TnI concentration is > 26 ng/L;  
 NMR = 1 if neutrocytes to monocytes ratio > 15;  
 IL6 = 1 if IL-6 concentration is >50 pg/mL;  
 glc = 1 if fasting glycaemia > 6.8 mmol/L;  
 INC = 1 if immature neutrocytes 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-





**Figure 1.** Receiver operating characteristic (ROC) curves for predictors with highest predictive value in univariate analysis

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 ( $SpO_2/FiO_2$ ) 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-Tnl > 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 <sup>3</sup> /μL	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 R <sup>2</sup>	0.40
Nagelkerk R <sup>2</sup>	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-Tnl – 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 SpO<sub>2</sub>/FiO<sub>2</sub> ratio on admission to the hospital

Laboratory parameter	CTSS RS	P value	SpO <sub>2</sub> /FiO <sub>2</sub> 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-Tnl	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-Tnl – 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  $\gamma$ -interferon lead to increase in insulin resistance and higher insulin demand.  $\beta$  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 [24, 25]. It was also proved that diabetes is associated with more significant COVID-19 related mortality, hyperglycaemia and diabetes are independent risk factors of COVID-19 critical course and mortality [24, 26].

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 neutrophils and their precursors in peripheral blood is an evidence of emergency myelopoiesis, 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 glycocalyx 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 (SpO<sub>2</sub>/FiO<sub>2</sub>) factors, although most of them were weak (Tab. 5). Moderate correlations were found between CTSS and LDH, CRP, AST and NMR, whereas LDH and glycaemia

moderately negatively correlated with SpO<sub>2</sub>/FiO<sub>2</sub> ratio. No strong correlations between laboratory alterations and radiological extent of infiltrates or SpO<sub>2</sub>/FiO<sub>2</sub> 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 SpO<sub>2</sub>/FiO<sub>2</sub> 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]. Bennouar et al. developed a risk score of COVID-19 severity and in-hospital mortality comprising age, natraemia, 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, natraemia, 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 homogenous; 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. With an 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.

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