

AGE DEPENDENCE OF PROGNOSTIC SIGNIFICANCE
OF COMPLETE BLOOD COUNT PARAMETERS
ON MORTALITY FROM COVID-19

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Abstract

The aim of this study is to determine the age dependence of prognostic significance of complete blood count parameters at the time of admission on mortality from the SARS-CoV-2 infection. This is a single-centre retrospective analytic case-control study covering all 2132 patients with COVID-19 treated in the period 2020–2021 in the hospital. Subject of our study is to compare the diagnostic ability of parameters of the complete blood count (CBC) to predict mortality in different age groups using receiver operating characteristics (ROC) and the corresponding area under the curve (AUC) analyses. Out of the red blood cells related parameters, a sufficient accuracy demonstrates only the red blood cell distribution width (RDW-CV), with a gradual decrease of the area under the curve with ageing – from 0.796 in the age groups under 40 and up to 0.601 in the age group of 80 years and above. From the parameters characterizing platelets, the platelet count (PLT), mean platelet volume (MPV) and platelet distribution width (PDW) exhibit a sufficient accuracy only in the age group under 50 years. White blood cells related parameters – white blood count (WBC), granulocytes, granulocytes/lymphocytes ratio (G/L) – demonstrate the best prognostic significance with good accuracy for the age under 50 years – AUC above 0.7, which is retained the same only for granulocytes/lymphocytes ratio in the age group under 70 years. With ageing, we again observe a decline of the accuracy to sufficient in the age groups past 70 years.

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The results from our study give us grounds to accept that the prognostic value of complete blood count parameters for the prediction of the mortality from COVID-19 is different in various age groups, and decreases with ageing. In patients above 70 years, a limited prognostic value for unfavourable course of the disease have only the RDW-CV and G/L.

Key words: COVID-19, mortality rate, complete blood count, red blood cell distribution width, platelets count, mean platelet volume, granulocytes, lymphocytes, granulocytes/lymphocytes ratio

Introduction. The mortality of patients with COVID-19, hospitalized due to the severe course of the disease, rises exponentially with age [1]. This makes the identification of infection course predictors in older patients of a critical importance for the clinical practice.

Many parameters from the CBC are used for predicting the course of the disease. A widely accepted one is the change in the white blood cells population, which has a major role in immunity and defense against viruses [2]. From the red blood cell parameters, red blood cell distribution width is most commonly used in the prediction of the prognosis of patients [3]. This is rooted in the proven benefit of the application of RDW as a nonspecific marker of general illness [4], and also in the identified association between the high RDW and the severity of the inflammation process caused by SARS-CoV-2, described also in influenza infection cases [5, 6]. Changes in platelets count [7] and platelet indices as indicators for platelet activity [8] are also studied as predictors for the severity SARS-CoV-2 infection.

Our clinical practice observations over a two-year period indicated implications of age on the COVID-19 mortality prognostic ability of the parameters from the complete blood count. We identified that this matter is not well studied. In our study, we set a goal, based on our clinical experience, to answer the following questions – is there an age-based difference in the predictive value for mortality of the parameters from CBC at the time of admission to hospital, and which parameters are most reliable for the elderly patients?

To confirm or reject our clinical practice observations in this area, we conducted a single-centre retrospective analytic case-control study covering all patients with COVID-19, admitted and treated in the hospital during the period 2020–2021.

The study was conducted in accordance with the Declaration of Helsinki, and approved by Ethics Committee of Medical Institute of Ministry of Interior (protocol 11/15.04.2021).

Patients and methods. Patient selection and data collection. All included in the study adult patients with PCR-confirmed COVID-19 were meeting the criteria included in the second version of the WHO – COVID-19 Clinical Management – moderate, severe and critical COVID-19. ARDS diagnosis is based on the criteria of Kigali Modification of the Berlin Definition [9].

For the purpose of the study we analyzed the data of 2132 sequentially admitted patients meeting the investigation criteria with average age 60.22 ± 14.28 years (aged from 18 to 94). Eight hundred and fourteen of them were females with average age 63.29 ± 13.85 years and 1318 were males with average age 58.32 ± 14.22 years. Two groups were formed: survivor – 1823 patients (85.51%) with average age 58.58 ± 13.97 years; and non-survivor – 309 patients (14.49%) with average age 69.94 ± 12.07 years. From non-survivors 189 were male (14.34%) and 120 female (14.74%). The patients were divided into seven groups – Group 1 < 30 years, $30 \leq$ Group 2 < 40, $40 \leq$ Group 3 < 50, $50 \leq$ Group 4 < 60, $60 \leq$ Group 5 < 70, $70 \leq$ Group 6 < 80, $80 \leq$ Group 7.

Laboratory measurements. All samples were processed by the Medonic M-series automated hematology analyzer (Boule's Diagnostic AB), Alinity ci-series (Abbot) for clinical chemistry and immunoassay, Medica EassyBloodGas (Medica Corporation) for arterial blood gas test and ACL TOP 700 CTS Hemostasis analyzer (Instrumentation Laboratory). All measurements are taken within one hour from admission.

Statistical analysis. Results were captured in a Microsoft Excel spreadsheet (Microsoft[®], Redmond, Washington, USA). Statistical analyses were performed with Statistical Package for the Social Sciences[®] software 28 (SPSS[®], Chicago, IL, USA).

The data were expressed as mean $\pm$ standard deviation (SD) for normally distributed values and the median and interquartile range (IQR) for non-normally distributed data. Normality of a distribution was tested with Shapiro–Wilk test. The differences in the parameters of the survivors and non-survivors were assessed by Mann–Whitney U test. Values of two-sided $p < 0.05$ were considered statistically significant.

Receiver operating characteristics (ROC) and the corresponding area under the curve (AUC) analyses were applied to the parameters, which exhibited statistical differences in any of the age groups in the assessment with Mann–Whitney U test. For the red blood cells, the analyzed parameters were: hemoglobin concentration, mean cell volume (MCV), mean corpuscular hemoglobin (MCH) and red blood cell distribution width (RDW-CV); for white blood cells: white blood cell count (WBC count), granulocytes count, lymphocytes count, granulocytes/lymphocytes ratio (G/L); and for thrombocytes: platelets count (PLT), mean platelet volume (MPV), platelet distribution width (PDW), platelet-large cell ratio (P-LCR). AUC 0.9 to 1 was defined as excellent accuracy, 0.8 to 0.9 as very good, 0.7 to 0.8 as good, 0.6 to 0.7 as sufficient, 0.5 to 0.6 as bad, and below 0.5 as poor.

Results. The crosstabulation between the development of ARDS and survival in the different age groups shows an increase in the frequency of non-survival, as follows: Group 1 – 0%, Group 2 – 2.84%, Group 3 – 5.01%, Group 4 – 7.77%, Group 5 – 13.89%, Group 6 – 24.24%, Group 7 – 40.83%. The frequency of development of ARDS (Table 1) is increasing with age and doubles between Group 1

T a b l e 1

Crosstabulation of the survival and ARDS development in different age groups

ARDS		Age group							Total
		1	2	3	4	5	6	7	
with	Non-survivor	0	4	14	20	37	35	29	139
	Survivor	33	110	242	338	335	251	74	1383
	Total	33	114	256	358	372	286	103	1522
without	Non-survivor	0	0	3	17	33	77	40	170
	Survivor	8	27	80	101	99	99	26	440
	Total	8	27	83	118	132	176	66	610
Total	Non-survivor	0	4	17	37	70	112	69	309
	Survivor	41	137	322	439	434	350	100	1823
	Total	41	141	339	476	504	462	169	2132

and Group 7: Group 1 – 19.51%, Group 2 – 19.15%, Group 3 – 24.48%, Group 4 – 24.79%, Group 5 – 26.19%, Group 6 – 38.09%, Group 7 – 38.84%. The mortality rate in patients that develop ARDS (Table 1) is increasing with age: Group 1 – 0%, Group 2 – 0%, Group 3 – 3.61%, Group 4 – 14.41%, Group 5 – 25%, Group 6 – 43.75%, Group 7 – 60.60%.

The hematologic parameters at admission of the six groups from second to seventh were compared consecutively. For the red blood cells related parameters, there is a statistically significant difference for all tested age groups for RDW-CV and borderline values for p in some of the age groups for MCV. For platelets count and indices there is a statistically significant difference only in some of the age groups for platelets count and borderline values for p in some of the age groups for MPV and PDW. For the white blood cell related parameters, there is a statistically significant difference between survivor and non-survivor for WBC count, granulocytes count and G/L.

For the assessment of the prognostic ability of the studied parameters from the complete blood count, that exhibit a statistically significant difference for prediction of mortality rate, we applied ROC analysis. Table 2 shows the area under the curve for these parameters.

From the red blood cells related parameters, sufficient accuracy shows only RDW-CV, with area under the curve declining slowly with age.

From the platelet parameters, only PLT, MPV and PDW demonstrate sufficient accuracy in the patients' group between 40 and 50 years, and for PDW – also between 50 and 60 years. For older patients the accuracy becomes bad.

White blood cells related parameters – WBC, granulocytes, G/L – have good accuracy in Groups 2 and 3 – under 50 years, which is preserved for G/L in Group 4 – under 60 years and Group 5 – under 70 years. With age there is a decline in accuracy, which becomes sufficient in the age groups of 70 years and above.

T a b l e 2

Comparison of area under the curve between survivor and non-survivor in studied groups 2, 3, 4, 5, 6 and 7

Parameter	Area under the curve					
	Group 2	Group 3	Group 4	Group 5	Group 6	Group 7
HGB	0.301	0.396	0.472	0.501	0.485	0.459
MCV	0.172	0.459	0.472	0.493	0.545	0.561
RDW-CV	0.796	0.632	0.631	0.629	0.617	0.601
PLT	0.579	0.608	0.541	0.427	0.440	0.454
MPV	0.683	0.631	0.563	0.564	0.531	0.560
PDW	0.608	0.627	0.612	0.532	0.518	0.563
WBC	0.762	0.738	0.640	0.556	0.566	0.600
Granulocytes	0.789	0.770	0.668	0.595	0.590	0.601
Lymphocytes	0.472	0.418	0.381	0.279	0.329	0.479
G/L	0.762	0.741	0.737	0.723	0.676	0.618

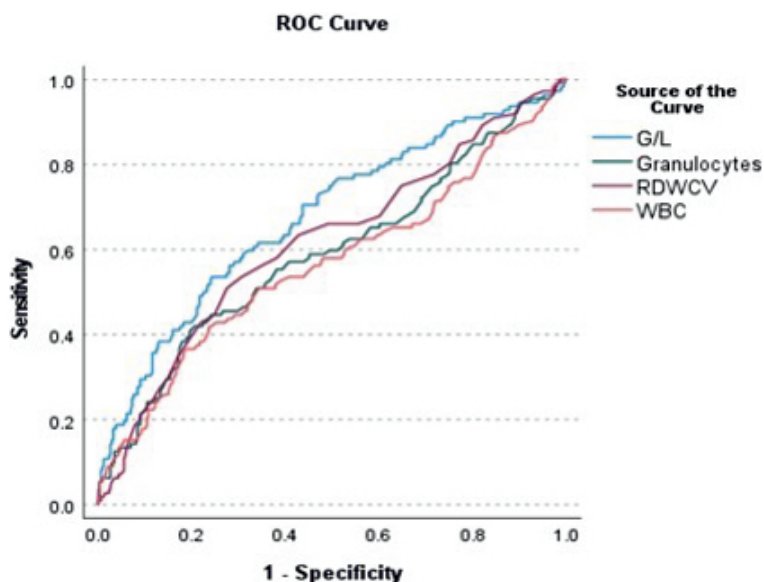
The main trend, of the COVID-19 mortality predictive ability of the haemocytometric parameters observed, is that it decreases with ageing. In age groups of 70 years and above, sufficient predictive value has only Red Blood Cell Distribution Width and granulocytes/lymphocytes ratio (Fig. 1). In the age group of 80 years and above, White Blood Cells and Granulocytes are borderline between sufficient and bad accuracy (Fig. 2).

Discussion. Our analyses confirm the conclusions of the studies of other authors that ageing itself is a prominent risk factor for severe disease and death from COVID-19 [10,11].

In our study, mortality increases from 0% in the age group under 30 years (our sample of patients in this age group is small and that can limit the statistics accuracy) to more than 40% in the age group of 80 years and above. This increase is gradual in the younger groups and after 60 years the mortality starts growing in geometrical progression. The development of ARDS is the leading cause for the mortality, and in patients of 80 years and above – 60% from those with ARDS have lethal outcome.

In our analysis, the parameters from the CBC show a declining prognostic significance with advancing age. One of the possible reasons for this is the polymorbidity of the older adults, who are also seeking medical attention earlier in the course of the infection, because of the decompensation of their chronic illnesses. In younger adults, in most of the cases, there are less comorbid conditions if any, and they are hospitalized later – after failure of the ambulatory treatment and development of respiratory insufficiency. We are analyzing only parameters at admission, which in cases of earlier in the course of the disease hospitalization are not as high as in fully developed inflammatory process.

In the hospitalized patients, there is an increase with age in the frequency of the most common comorbidities: diabetes mellitus, heart failure, chronic res-



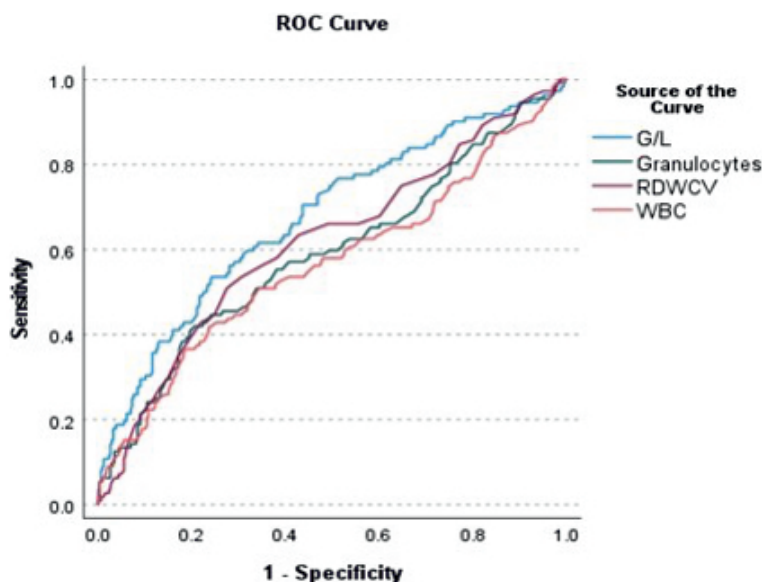
Area under the ROC curve: WBC – .566, RDW-CV – .617, Granulocytes – .590,
Granulocytes/Lymphocytes – .676

Fig. 1. ROC curve comparing sensitivity and specificity of predicting mortality between RDW-CV, White Blood Cells, Granulocytes and Granulocytes/Lymphocytes in patients' group between 70 and 80 years

piratory diseases, renal insufficiency. The worsening of these illnesses with the infection leads to earlier hospitalization of these patients. The study of GUANÍ-GUERRA et al. [12] about prognostic accuracy of the red blood cell distribution width for predicting death in COVID-19 demonstrates an increase in the sensitivity and specificity, when its values are followed during hospitalization. Similar conclusion made LIU et al. [13] about parameters of leucocytes and thrombocytes in their study analyzing “dynamic trajectories of CBC parameters” after admission.

There are also age-related changes in the reactivity of the organism. The bone marrow of a person above 80 years reveals significantly low cellularity and its proliferative activity is declining slightly in the elderly group [14]. Hematopoietic stem cells of the ageing adults show shifts in cell-surface markers [15] and with ageing there are significant changes in the immune system [16].

Changes in the main parameter characterizing red blood cells and used as a prognostic marker – red blood cell distribution width, may be associated with renal insufficiency, which in our study was with frequency of more than 8% in age of 80 years and above. Hypoxia in severe respiratory diseases leads to higher production of erythropoietin from the kidney, which stimulates erythropoiesis with rising of RDW [17]. In patients with renal failure, this stimulation is leading to a



Area under the ROC curve: WBC – .600, RDW-CV – .601, Granulocytes – .601, Granulocytes/Lymphocytes – .618

Fig. 2. ROC curve comparing sensitivity and specificity of predicting mortality between RDW-CV, White Blood Cells, Granulocytes and Granulocytes/Lymphocytes in patient group of 80 years and above

weaker increase in synthesis of erythropoietin and, respectively, to a lower increase of RDW due to the kidney damage. This relates with the observed gradually declining of values of hemoglobin in our patients of 60 years and above, as well as in those of 80 years and above – there is more than 10 g/l decline compared to those before 60 years.

Conclusion. The results from our study, give us grounds to accept that the COVID-19 mortality prognostic value of the complete blood count parameters changes in different age groups and decreases with ageing. Best prognostic significance has Granulocytes/Lymphocytes ratio, which shows good accuracy in all age groups under 70 years. In patients of 70 years and above, a limited prognostic value for unfavourable course of the disease have only the Red Blood Cell Distribution Width and Granulocytes/Lymphocytes ratio.

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