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ORIGINAL RESEARCH

The prognostic value of laboratory parameters referring to hemopoietic stress in patients with COVID-19—a single center experience

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Abstract

In the present study we attempted to assess whether a relationship exists between laboratory signs of hemopoietic stress and fatal outcome in coronavirus disease (COVID)-19—positive intensive care unit (ICU) and non-ICU patients. Prospectively collected data of 206 COVID-19 patients (95 ICU and 111 non-ICU) were retrospectively analyzed. Beside comparing routine laboratory parameters, the analysis focused on nucleated red blood cell count (NRBC), red cell distribution width (RCDW), immature granulocyte count (IG), mean platelet volume (MPV) and platelet distribution width (PDW). In the total COVID cohort higher NRBC, RCDW, IG, MPV and PDW values were observed in patients with fatal outcome as compared to survivors. Significant differences could be observed between non-ICU and critically ill patients in NRBC (medians and interquartile range (IQR): 10/0–20/ *vs.* 20/10–60/ g/L, $p < 0.001$), IG (0.16/0.04–0.39/ *vs.* 0.42 /0.20–0.75/ g/L, $p < 0.001$), MPV (10.9 ± 1.2 *vs.* 11.4 ± 1.2 fL, $p < 0.01$) and PDW (14.5/11.6-44.7/ *vs.* 19.9/13.7–57.7/ fL, $p < 0.001$), respectively. In the ICU subgroup, RDW and MPV were higher among patients who died. Severe acute respiratory syndrome after coronavirus infection (SARS-CoV-2 infection) causes perturbation of hemopoiesis. Laboratory parameters referring to hemopoietic stress may serve as useful predictors of poor outcome in hospitalized COVID-19 patients needing intensive care.

Keywords

SARS-CoV infection; Hemopoietic stress; Intensive care

1. Introduction

In March 2020 the World Health Organization (WHO) declared a pandemic of COVID-19 and the cases showed a sudden and dramatic increase worldwide thereafter, resulting in at least two hard peaks in the number of general and critical cases. At the time of drafting this manuscript, more than 184 million positive cases were reported, leading to over 4 million deaths related to the new coronavirus disease [1]. The amount of hospitalized and —most importantly— critically ill cases challenged the healthcare systems around the world. The entire clinical spectrum of the disease was completely new for the medical systems and long term consequences are still under investigation.

Right from the beginning of the pandemic, efforts have been made to develop sensitive scoring systems that enable to pre-

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dict outcome of the disease and the necessity of intensive care treatment. Some of these risk stratification scores were merely based on basal comorbidities and the actual clinical signs at admission [2], a combination of various clinical, computed tomography (CT) and laboratory factors [3], while others tried to elaborate scoring systems that were based on laboratory parameters at admission [4, 5]. As the change of the clinical picture was very dynamic, unfortunately the majority of the scoring systems, that were based on the parameters gathered at admission, failed to show sufficient sensitivity. Additionally, the clinical picture has changed along with the appearance of the new coronavirus variants, making the outcome prediction even more complicated.

Clearly, there are laboratory parameters at admission that have been reported to be associated with worse outcome. Mortality in the general COVID population was associated with increased levels of the following parameters: white blood cell count, C-reactive protein (CRP), lactate dehydrogenase (LDH), procalcitonin (PCT), fibrinogen, D-dimer, ferritin, creatine kinase (CK) and interleukine-6 (IL-6). Among others, decreased lymphocyte count, increased neutrophil count, LDH, CK, CRP, D-dimer and pro-inflammatory cytokine levels have been shown to be associated with extensive lung damage and worse outcome [5]. Attempts have been made to develop a hemocytometric prognostic score [6] and also to find a link between early changes in laboratory parameters and outcome [7]. In the present study we attempted to assess whether a relationship exists between laboratory signs of hemopoietic stress and fatal outcome in COVID-19-positive ICU and non-ICU patients. Additionally, we intended to answer the question whether any of the laboratory parameters is specifically related to poor outcome in patients who underwent ICU treatment.

2. Methods

This is a retrospective descriptive analysis of prospectively collected data from patients who were admitted to the COVID Center of the University of Debrecen between the period of 1 February 2021 and 31 March 2021. During this period, there were 258 COVID-19 positive cases with mild symptoms, not necessitating intensive care, and 104 patients were treated at the intensive care unit. In the analysis, those patients presenting with mild symptoms but were treated in later course of their disease on ICU, were considered intensive care patients.

Pharmacological therapy was initiated according to our local therapeutic protocol that was based on international guidelines: In the early phase of the infection (stage 1) therapy was based on acetylsalicylic acid, low molecular weight heparin and antiviral medications (remdesivir, favipiravir or bamlanivimab). In stage 2 (characterized by pulmonary or other organ manifestations) in addition corticosteroid therapy or immunosuppression was considered. In stage 3 (hyperinflammatory phase) the medical therapy was based on immunosuppressive agents (tocilizumab), corticosteroids and cytosorbent therapy. Decision on ICU admission was made by the ICU physicians using the SAPS (simplified acute phsiology score) criteria. Ventilatory strategy was based on an internal protocol, that was adopted from the positions paper of the German Respiratory Society [8].

Prospectively collected clinical and laboratory data were extracted from the electronic medical records of the patients. In the present analysis only the most relevant parameters related to inflammation, coagulation and those referring to hemopoietic stress were taken into account. For the sake of clarity, in all cases the most pathological (the highest) value of each parameter measured during the course of the hospital treatment was included to the analysis, because it was meant that this would reflect most the pathological changes evoked by the COVID-19 infection.

• Hemoglobin was measured by a cyanide-free, photometry based method, where cells were lysed by the adding sodium lauryl sulphate (SLS). This way hemoglobin is converted to a sulphated derivative and light absorption is measured at 564 nm. Siemens Advia 2120i (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) hematologic analyser was applied for analysis.

• WBC (White Blood Cell number), IG (Immature Granulocyte number): After the pre-treatment, the cells pass through a laser beam one by one for hydrodynamic focusing. Forward, side scattered light and myeloperoxidase activity are detected and converted into electrical impulses. WBCs are visualized on bivariate scattergrams resulting in absolute number and subclasses of WBCs. Siemens Advia 2120i (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) hematologic analyser was applied for analysis.

• PLT (PLaTelet number), MPV (Mean Platelet Volume), PDW (Platelet Distribution Width), Htc (HemaToCrit), RDW (Red blood cell Distribution Width): Siemens Advia 2120i analysers (Siemens Healthcare Diagnostics, Deerfield, Illinois, USA) use flow cytometry for determination of platelet and red blood cell numbers (PLT and RBC) by visualising the PLTs and RBCs on bivariate scattergrams and histograms. The change in impedance is proportional to cell volume, resulting in a cell count and measure of volume. MPV, PDW and RDW is determined by PLT and RBC histograms. Htc was a calculated parameter.

• NRBC (Nucleated Red Blood Cell number): measurements were based on flow cytometric method (Sysmex XN Sysmex America, Inc. Lincolnshire, IL, USA)

• CRP (C-Reactive Protein): was assessed from venous blood using a photometry based, immunoturbidimetric method by Roche Cobas 8000 modular series (Roche Diagnostics, Mannheim, Germany)

• Procalcitonin: the PCT was measured by a two-step sandwich immunoassay with streptavidin microparticles and an electrochemiluminescence detection system (Roche Cobas 8000; Roche Diagnostics, Mannheim, Germany).

• D-dimer was assessed by latex-enhanced turbidimetric immunoassay (Instrumentation Laboratory, Bedford, Massachusetts, USA).

Statistical analysis: All row data underwent normality test to check their distribution. Normally distributed data were compared with the appropriate *t*-tests, whereas those with non-normal distribution were compared with Mann-Whitney tests. Categorical data were compared using chi-square tests. Pearson analysis was used for assessing the correlation between mean platelet volume and platelet count. A p value < 0.05 was considered as statistically significant.

TABLE 1. Most important clinical and laboratory characteristics of the entire COVID-19 cohort.

Parameter	Died (n = 76)	Survived (n = 130)	*p*-value
Age (year)	67 (59.5–74)	65 (52–71)	$p = 0.56$
Female/male	35/41	61/69	$p = 0.87$
Obesity (Yes/No)	22/54	36/94	$p = 0.84$
Hypertension (Yes/No)	62/14	97/33	$p = 0.25$
Diabetes (Yes/No)	19/57	44/86	$p = 0.14$
Cardiovascular disease (Yes/No)	43/33	63/67	$p = 0.26$
Pulmonary disease (Yes/No)	20/56	39/91	$p = 0.57$
CNS disease (Yes/No)	17/59	36/94	$p = 0.39$
Kidney disease (Yes/No)	9/67	2/128	$p < 0.01$
Malignancy (Yes/No)	8/68	14/116	$p = 0.95$
Autoimmune disease (Yes/No)	11/65	12/118	$p = 0.24$
>3 comorbidities	41/76	40/130	$p = 0.03$
Pregnancy (Yes/No)	0/76	2/130	$p = 0.28$
Lung involvement at admission CT (%)	50 (20–70)	30 (15–70)	$p = 0.08$
Hemoglobin (g/L)	116.5 (95.5–129.0)	127.5 (111.0–140.0)	$p < 0.01$
Hematocrit (%)	0.35 (0.28–0.39)	0.37 (0.34–0.41)	$p < 0.01$
WBC (g/L)	13.8 (8.8–20.1)	11.1 (7.4–15.3)	$p < 0.01$
Platelets (g/L)	202.5 (132.5–326.5)	272.0 (193.0–351.0)	$p < 0.01$
C-reactive protein (mg/L)	77.5 (21.6–168.1)	20.8 (6.1–99.8)	$p < 0.01$
Procalcitonin (µg/L)	0.35 (0.1–1.3)	0.1 (0.1–0.3)	$p < 0.01$
D-dimer (mg FEU/L)	1.51 (0.89–3.6)	1.12 (0.5–3.2)	$p < 0.05$

Grouping of the patients is based on survival vs. fatal outcome. Values are shown as medians (25–75% CI). CNS = central nervous system; WBC = white blood cell; FEU = Forty-foot Equivalent Unit.

3. Results

In our cohort 206 COVID-19-positive cases—96 females and 110 males—were included, among them 95 patients were treated at the intensive care unit during the course of hospitalisation. Mortality rate in the total hospitalized cohort was 37%. There were no age and gender differences among deceased and survived patients. The occurrence of comorbidities was the same in the two groups for all previous diseases but chronic kidney disease: it was found that chronic kidney disease was more frequent in the history of deceased patients. Also, more than 3 comorbidities were present in the group of patients with fatal outcome. Although the percentage of the pathologically involved regions on the chest CT at admission was higher among patients who deceased, this difference did not reach the level of statistical significance (Table 1).

In patients in whom intensive care treatment was necessary, age and male sex increased the probability of death. Interestingly, pulmonary affection seen at CT at admission was slightly, but not statistically significantly lower in the group of died patients (Table 2).

Laboratory parameters in the entire COVID-19 cohort: Hemoglobin and hematocrit levels were lower, white blood cell count was higher and platelet count was lower in patients with fatal outcome. An elevated C-reactive protein and procalcitonin concentration was also measured in this group. D-dimer values were significantly higher in patients who died during the course of the disease (Table 1).

Laboratory results referring to hemopoietic stress in the total COVID cohort are shown in Fig. 1, 2. In patients with fatal outcome elevated nucleated red blood cell count as well as a higher red blood cell distribution width could be observed. Similarly, both mean platelet volume and platelet distribution width were higher in COVID-19 positive patients who died. A negative relationship could be detected between MPV and platelet count in the entire cohort (Pearson correlation coefficient: –0.39; $p < 0.001$), which was also marked in non ICU patients (Pearson correlation coefficient: –0.42; $p < 0.001$). A slight, but significant increase was observed in the number of immature granulocytes in the blood of deceased patients.

Relationship between severity of lung involvement and laboratory parameters referring to hemopoietic stress in the entire cohort: No significant relationship was found between percentage of lung affection and NRBC ($r^2 = 0.03$, $p = 0.69$), MPV ($r^2 = 0.05$, $p = 0.43$), PDW ($r^2 = 0.13$, $p = 0.07$), IG ($r^2 = 0.03$, $p = 0.7$).

Comparison of clinical and laboratory parameters among ICU and non-ICU patients: When dichotomizing patients according to intensive care and non-intensive care groups, all the routine laboratory parameters and those referring to hemopoietic stress were markedly pathological in the intensive treat-

TABLE 2. Clinical and laboratory characteristics of the entire COVID-19 cohort.

	ICU (n = 95)	Non-ICU (n = 111)	*p*-value
Age (years)	65 (57–70)	67 (53–76)	$p = 0.140$
Female/male	35/60	60/51	$Chi^2 = 5.98$, $p = 0.010$
Lung involvement (%)	60 (20–80)	20 (15–50)	$p < 0.001$
Hgb (g/L)	121 (98.2–134)	126 (110.2–140)	$p = 0.030$
HTC (%)	0.36 (0.29–0.39)	0.37 (0.33–0.41)	$p = 0.060$
WBC (g/L)	14.5 (10.7–20.1)	9.2 (6.3–12.7)	$p < 0.001$
PCT (µg/L)	0.2 (0.1–0.9)	0.1 (0.1–0.3)	$p < 0.001$
C-reactive protein (mg/L)	79.5 (19.5–149.1)	19.7 (4.3–84.4)	$p < 0.001$
D-dimer (mg FEU/L)	2.1 (1.2–15.5)	0.9 (0.5–1.4)	$p < 0.001$
NRBC (g/L)	20 (10–60)	10 (0–20)	$p < 0.001$
RCDW (%)	13.8 (13.0–14.9)	13.7 (12.5–15.1)	$p = 0.600$
IG (g/L)	0.42 (0.20–0.75)	0.16 (0.04–0.39)	$p < 0.001$
MPV (fL)	11.4 ± 1.2	10.9 ± 1.2	$p < 0.01$
PDW (fL)	19.9 (13.7–57.7)	14.5 (11.6–44.7)	$p < 0.001$

Grouping of patients is based on intensive care vs. non-intensive care. Values are shown as medians (25–75% CI) or means (standard deviations), depending on the distribution of the data. ICU = intensive care unit; HGB = hemoglobin; HTC = hematocrit; WBC = white blood cell; PCT = procalcitonin; NRBC = nucleated red blood cell; RCDW = red cell distribution width; IG = immature granulocytes; MPV = mean platelet volume; PDW = platelet distribution width.

ment group, reflecting more serious stage of the disease. Data are summarized in Table 2.

Laboratory parameters within the ICU cohort: The majority of the routine laboratory parameters—hemoglobin and hematocrit, white blood cell and platelet counts, D-dimer concentrations—did not differ between survivors and non-survivors of the intensive care treatment. Statistically significant differences between the two groups could be observed only in parameters referring to inflammation, *i.e.*, CRP and procalcitonin levels (Table 3).

Laboratory parameters referring to hemopoietic stress in the ICU cohort: Number of nucleated red blood cells were comparable between the survivor and non-survivor groups, whereas red blood cell distribution width was slightly higher among patients who died. Mean platelet volume was also higher in ICU patients with worse outcome, but no significant differences could be detected in platelet distribution width (Fig. 3). The correlation between MPV and platelet count was statistically highly significant (Pearson correlation coefficient: –0.37; $p < 0.001$). This negative relationship could be verified among ICU patients who died (Pearson correlation coefficient: –0.37; $p < 0.01$), but not in the individuals who survived ICU period (Pearson correlation coefficient: –0.27; $p = 0.06$). Immature granulocyte count was similar in both groups (Median: 0.40 CI: 0.17–0.69 *vs.* 0.46 CI: 0.20–0.77; $p = 0.74$).

4. Discussion

In the present study we found signs of hemopoietic stress among hospitalized COVID-19—positive patients with worse outcome. In the entire COVID-19 population (critical plus non-critical patients) activation of early immature lines of erythropoiesis, early granulocyte forms and cell forms referring to enhanced platelet maturation were indicators of death. Among critically ill patients, red blood cell distribution width, as well as mean platelet volume were parameters, that were related to fatal outcome.

SARS-CoV-2 virus infection is characterized by a marked damage in airway epithelial protection resulting in a release of the virus and related pathogen-associated products into the blood stream. Alveolar macrophages as well as airway epithelial cells are playing a crucial role in the development of excess cytokine release leading to a systemic inflammatory response state (SIRS). During the past 1.5 years, accumulating evidence suggest, that not only the pulmonary parenchymal damage and associated hypoxia is responsible for poor outcome after COVID-19 infection, but exaggerated systemic cytokine production and a consequent perturbation of the coagulation may play also an important role [9]. Among the various organ manifestations of SIRS, cytokines are also responsible for the stimulation of the hepatocytes and a consequent stimulation of acute phase protein production. It is widely accepted that acute phase proteins play a crucial role in stimulation of hemopoiesis in various inflammatory states, resulting in hyperactivation of the bone marrow.

Nucleated red blood cells are usually not present in the blood of healthy adults. They are early erythrocyte precursors that are physiologically filtered by the fenestrations of the bone marrow and thus in normal stage they do not appear in the peripheral blood. Their presence may refer to either a gradually increased erythropoietic activity or to the failure of the filtrating mechanism [10]. The appearance of NRBCs in the peripheral blood may be seen in severe arterial hypoxic states, during systemic inflammations, and after massive hem-

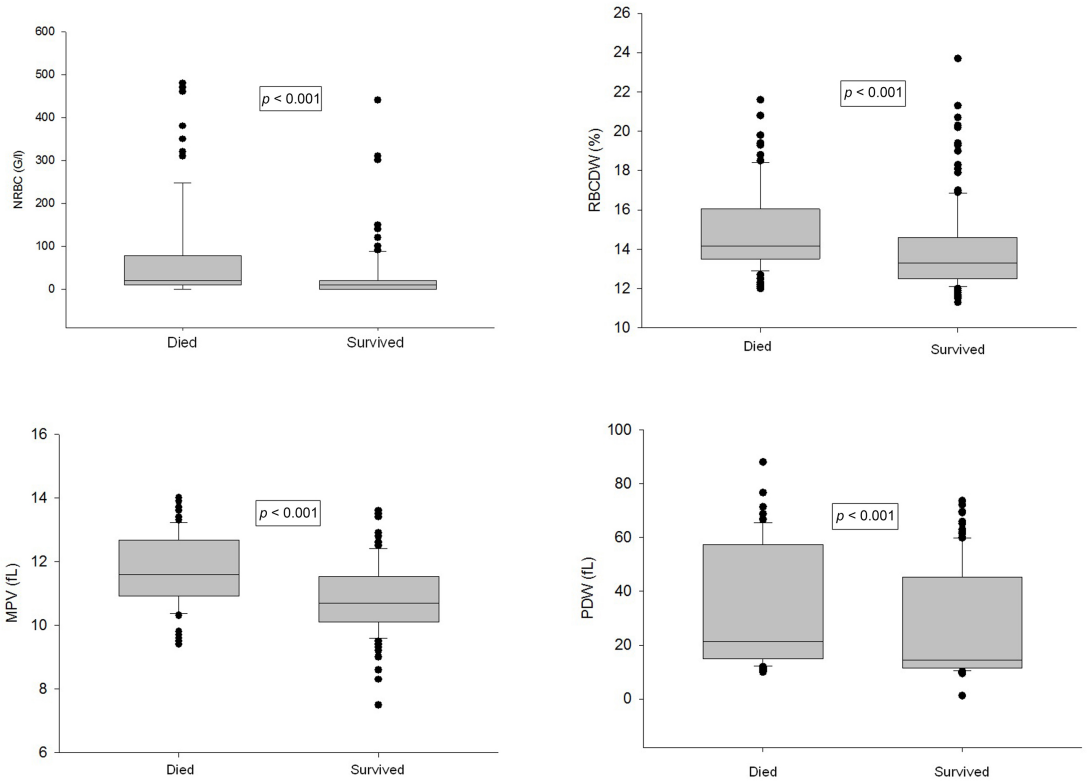

FIGURE 1. Laboratory parameters referring to hemopoietic stress in the total cohort. Grouping of the patients is based on survival *vs.* fatal outcome. NRBC indicates nucleted red blood cells, RBCDW indicates red blood cell distribution width, MPV indicates mean platelet volume, PDW indicates platelet distribution width. Values are shown as medians and 25–75 CIs.

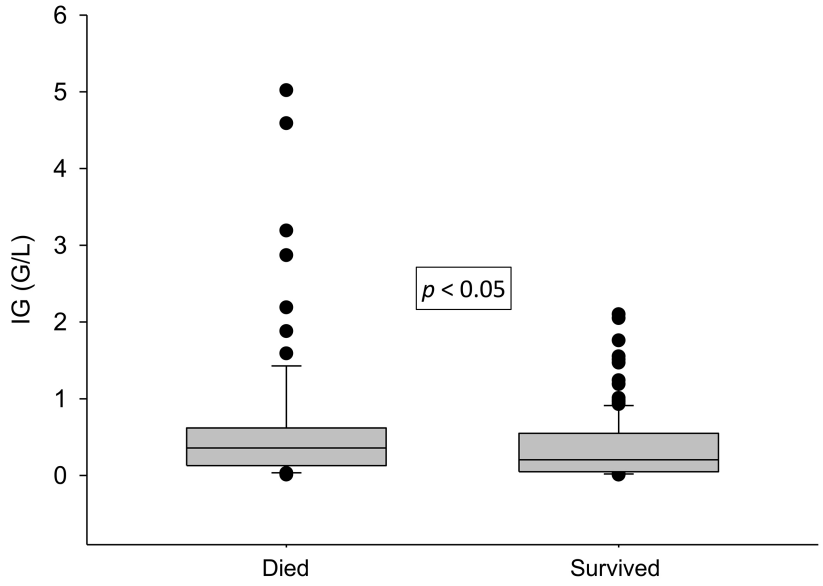

FIGURE 2. Number of immature granulocytes (IG) in the entire patient cohort. Grouping of the patients is based on survival *vs.* fatal outcome. Values are shown as medians and 25–75 CIs.

orrhages [11, 12]. A clear prognostic value of NRBCs has been demonstrated both in surgical and medical intensive care units by several authors [13–15]. Additionally, it has been also shown that a cut-off value of 220 NRBC/μL is suitable for distinguishing between fatal and non-fatal prognosis in acute respiratory distress syndrome (ARDS) [16]. Linssen *et al.* [6] attempted to develop and validate a hemocytometric score in COVID-19 patients and they detected a marked difference between the NRBC counts of critical and non-critical patients. In the present study we demonstrated an increased count of NRBC in patients suffering from COVID-19 disease. Additionally, the number of immature red blood cells was almost double in patients with fatal outcome than in patients who survived the infection (medians and IQRs: 20.0/10.0–80.0/ *vs.* 10.0/0.0–20.0/ g/L, respectively, see Fig. 1). It has to be noted that among ICU patients the differences in NRBC count

TABLE 3. Comparison of parameters measured in patients treated at the ICU.

Parameter	Died (n = 49)	Survived (n = 46)	*p*-value
Age (years)	67 (59.0–72.2)	64 (53.2–67.0)	$p < 0.05$
Female/male	15/34	20/26	$Chi^2 = 6.49$, $p = 0.01$
Lung involvement (%)	50 (28.7–76.2)	70 (20–80)	$p = 0.63$
Hemoglobin (g/L)	120.0 (95.7–129.5)	124.5 (108.0–136.0)	$p = 0.11$
Hematocrit (%)	0.35 (0.28–0.39)	0.37 (0.33–0.39)	$p = 0.16$
WBC (g/L)	15.2 (10.2–20.0)	14.3 (11.6–20.1)	$p = 0.76$
Platelets (g/L)	229.0 (128.7–365.2)	268.0 (193.0–367.0)	$p = 0.19$
C-reactive protein (mg/L)	90.8 (30.3–177.9)	52.1 (14.0–121.9)	$p < 0.05$
Procalcitonin (µg/L)	0.44 (0.1–1.5)	0.1 (0.1–0.5)	$p < 0.05$
D-dimer (mg FEU/L)	2.1 (1.4–14.2)	2.9 (1.1–16.3)	$p = 0.86$

Grouping of the patients is based on survival vs. fatal outcome. Values are shown as medians (25–75% CI). WBC = white blood cell.

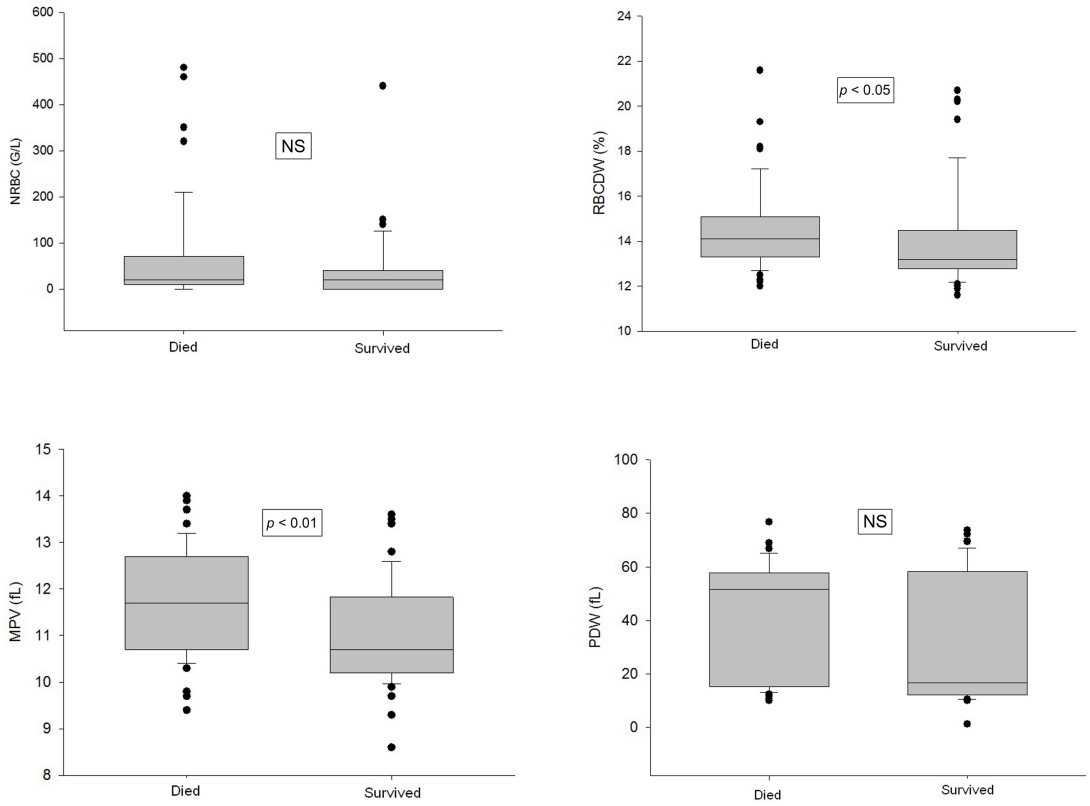

FIGURE 3. Laboratory parameters referring to hemopoietic stress in the ICU group. Grouping of the patients is based on survival *vs.* fatal outcome. NRBC indicated nucleted red blood cells, RBCDW indicated red blood cell distribution width, MPV indicates mean platelet volume, PDW indicates platelet distribution width. Values are shown as medians and 25–75 CIs. NS indicates non-significant difference.

between non-survivors and survivors could not be verified (medians and IQRs: 20.0/10.0–70.0/ *vs.* 20.0/0.0–40.0/ g/L, respectively, see Fig. 3), but differences in perturbed erythropoiesis could be detected among decreased and survived critically ill COVID patients: red blood cell distribution width was significantly higher in ICU patients with fatal, than in those with favourable outcome (medians and IQRs: 14.1/13.3–15.0/ *vs.* 13.2/12.8–14.4/, respectively, see Fig. 3). In previous clinical studies it was suggested that red cell distribution width is a sensitive parameter to predict ICU mortality even after discharge from the ICU and a cut-off value of 14.5 mg/dL is highly significantly associated with fatal outcome [17] Similar to our observations, Gowda *et al.* [18] could also demonstrate a significant association of red blood cell distribution width and increased mortality among COVID-19 patients.

The granulocyte-line of hemopoiesis has also been shown to be stimulated in patients with coronavirus disease. The number of immature granulocytes was significantly different among

critically and non critically ill patients in the study of Linssen *et al*. [6]. They could not demonstrate a marked rise in the immature granulocyte counts in non-ICU patients. In line with these observations, an increased number of immature granulocytes in the blood was associated with worse outcome in the entire COVID cohort of the present study. In contrast, we could not detect any differences between immature granulocytes of ICU survivors and those with fatal outcome. Considering the leading role of the granulocytes in the production of inflammatory cytokines and in the development of consequent cytokine storm, it is conceivable that hyperactivation granulocyte-line of the hemopoiesis takes place already in the early course of the disease and its magnitude remains stable in subsequent critical stages.

Thrombotic complications are among the most frequent and life threatening consequences of COVID-19 infection [19]. It is believed that platelet activation occurs due to different reasons after the infection. Direct binding of the pathogen on the surface of platelets, endothelial injury and a consequent release of von Willebrand factor may be elicited by the virus. Additionally, blood coagulation is also activated as part of the systemic inflammatory reaction. It is widely accepted that thrombin generation also contributes to platelet activation [20]. The importance of platelet activation is also underlined with previous observations in viral pneumonia indicating that direct platelet activation caused by respiratory viruses stimulate the inflammatory reactions of the respiratory tract and contribute to the development of systemic inflammatory reactions [21]. As a consequence, platelet counts are decreased among patients with coronavirus infection [7] and lower platelet counts are associated with worse outcome. This is in line with our observations: in the entire COVID-19 cohort we also observed lower platelet counts in patients with fatal outcome than in patients who survived the disease. Mean platelet volume, reflecting circulating large, mostly reticulated platelets has been shown as a marker of platelet activation. In previous studies differences has been found between MPV values of severe and mild COVID-19 infected patients. Higher MPV values were seen as markers of disease progression and fatal outcome [22]. Similar to these previous observations, we also found higher MPV values in patients with fatal outcome in our entire population and also among patients treated at the intensive care unit. As previous studies in critically ill patients suggested the use of MPV/platelet count ratio as a more sensitive marker of platelet activation in critical illness [23], we also plotted MPV against platelet counts in the present study. Both in the entire COVID-19 cohort and also in ICU patients a highly significant negative correlation has been detected, *i.e.*, the lower was the platelet count the higher MPV values could be detected. Although platelet distribution width (PDW), another platelet parameter reflecting immature platelets in the circulating blood, was also significantly higher in deceased patients in our entire COVID-19 cohort, this difference could not be verified among patients treated at the ICU. It has to be noted, that in previous studies PDW was useful parameter suggesting any SARS-CoV-2 infection (mild disease) when its value exceeded 12.7 fL [24] and a cut-off value of 17% increased the probability of death by 6.3 times [18]. To mirror these data gathered from our cohort, in our entire COVID-19 population a PDW of 21.4 (14.9–57.5)% was found in the deceased patients, whereas it was 14.4 (11.6–45.1)% in patients who survived the disease. Although the differences in PDW did not reach the level of statistical significance in ICU patients (51.5/15.2–57.6/% in deceased *vs.* 16.7/12.3–57.8/% in survivors, $p = 0.09$), there is a clear sign indicating that platelet activation may be an important factor determining fatal outcome in COVID-19 patients. The clinical importance of platelet activation is underlined by a recent evidence suggesting that administration of aspirin (81 mg daily) in COVID-19 patients has been associated with a nearly 50% reduction in the risk of death [25].

We have to mention the limitations of our investigations. Major limitation is the single-center, retrospective nature of the present study. Although samples for laboratory parameters analyzed here were taken in a regular, systematic fashion during protocol-based patient care of patients, grouping and statistical evaluation occurred retrospectively. A further limitation is the number of included patients. The limited number of ICU (n = 95) and non-ICU (n = 111) COVID-19 patients does not allow the definition of threshold values for the different laboratory parameters.

5. Conclusion

Laboratory parameters referring to hemopoietic stress may serve as useful predictors of poor outcome in hospitalized COVID-19 patients, especially in critically ill patients needing intensive care.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

JK and BF—conceptualization and methodology. IL, MB, ZM, LA, AK, AF and AV—data collection and investigation. NB—data curation. JK and BF—writing: review and editing. All authors wrote original draft preparation. All authors have read and agreed to the published version of the manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted according to the guidelines of the Declaration of Helsinki. Medical Ethics Committee of University of Debrecen gave approval for the study (registration number: RKEB 113/2021). All patients or their closest relatives gave written consent to participate.

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Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

[1] Johns Hopkins University Coronavirus Resource Center. 2021. Available at: https://coronavirus.jhu.edu/. (Accessed: 26 June 2021).

[2] Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, *et al*. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C mortality score. The BMJ. 2020; 370: m3339.

[3] Galloway JB, Norton S, Barker RD, Brookes A, Carey I, Clarke BD, *et al*. A clinical risk score to identify patients with COVID-19 at high risk of critical care admission or death: an observational cohort study. Journal of Infection 2020; 81: 282–288.

[4] Henry BM, de Oliveira MHS, Benoit S, Plebani M, Lippi G. Hematologic, biochemical and immune biomarker abnormalities associated with severe illness and mortality in coronavirus disease 2019 (COVID-19): a meta-analysis. Clinical Chemistry and Laboratory Medicine (CCLM). 2020; 58: 1021–1028.

[5] Lippi G, Plebani M. Laboratory abnormalities in patients with COVID-2019 infection. Clinical Chemistry and Laboratory Medicine (CCLM). 2020; 58: 1131–1134.

[6] Linssen J, Ermens A, Berrevoets M, Seghezzi M, Previtali G, van der Sar-van der Brugge S, *et al*. A novel haemocytometric COVID-19 prognostic score developed and validated in an observational multicentre European hospital-based study. eLife. 2020; 9: e63195.

[7] Kiss S, Gede N, Hegyi P, Németh D, Földi M, Dembrovszky F, *et al*. Early changes in laboratory parameters are predictors of mortality and ICU admission in patients with COVID-19: a systematic review and meta-analysis. Medical Microbiology and Immunology. 2021; 210: 33–47.

[8] Pfeifer M, Ewig S, Voshaar T, Randerath W, Bauer T, Geiseler J, *et al*. Position paper for the state of the art application of respiratory support in patients with COVID-19. Pneumologie. 2020; 74: 337–357.

[9] Polidoro RB, Hagan RS, de Santis Santiago R, Schmidt NW. Overview: systemic inflammatory response derived from lung injury caused by SARS-CoV-2 infection explains severe outcomes in COVID-19. Frontiers in Immunology. 2020; 11: 1626.

[10] Schwartz SO, Stansbury F. Significance of nucleated red blood cells in peripheral blood: analysis of 1496 cases. Journal of the American Medical Association. 1954; 154: 1339–1340.

[11] Tóth J, Debreceni IB, Berhés M, Hajdú E, Deák Á, Pető K, *et al*. Red blood cell and platelet parameters are sepsis predictors in an Escherichia coli induced lethal porcine model. Clinical Hemorheology and Microcirculation. 2017; 66: 249–259.

[12] Stachon A, Sondermann N, Imohl M, Krieg M. Nucleated red blood cells indicate high risk for in-hospital mortality. Journal of Laboratory and Clinical Medicine. 2002; 140: 407–412.

[13] Stachon A, Kempf R, Holland-Letz T, Friese J, Becker A, Krieg M. Daily monitoring of nucleated red blood cells in the blood of surgical intensive care patients. Clinica Chimica Acta. 2006; 366: 329–335.

[14] Stachon A, Segbers E, Holland-Letz T, Kempf R, Hering S, Krieg M. Nucleated red blood cells in the blood of medical intensive care patients indicate increased mortality risk: a prospective cohort study. Critical Care. 2007; 11: R62.

[15] Purtle SW, Horkan CM, Moromizato T, Gibbons FK, Christopher KB. Nucleated red blood cells, critical illness survivors and postdischarge outcomes: a cohort study. Critical Care. 2017; 21: 154.

[16] Menk M, Giebelhäuser L, Vorderwülbecke G, Gassner M, Graw JA, Weiss B, *et al*. Nucleated red blood cells as predictors of mortality in patients with acute respiratory distress syndrome (ARDS): an observational study. Annals of Intensive Care. 2018; 8: 42.

[17] Foy BH, Carlson JCT, Reinertsen E, Padros I Valls R, Pallares Lopez R, Palanques-Tost E, *et al*. Association of red blood cell distribution width with mortality risk in hospitalized adults with SARS-CoV-2 infection. JAMA Network Open. 2020; 3: e2022058.

[18] Bommenahalli Gowda S, Gosavi S, Ananda Rao A, Shastry S, Raj SC, Menon S, *et al*. Prognosis of COVID-19: red cell distribution width, platelet distribution width, and C-reactive protein. Cureus. 2021; 13: e13078.

[19] Parra-Izquierdo I, Aslan JE. Perspectives on platelet heterogeneity and host immune response in coronavirus disease 2019 (COVID-19). Seminars in Thrombosis and Hemostasis. 2020; 46: 826–830.

[20] Zhong Q, Peng J. Mean platelet volume/platelet count ratio predicts severe pneumonia of COVID-19. Journal of Clinical Laboratory Analysis. 2021; 35: e23607.

[21] Lê VB, Schneider JG, Boergeling Y, Berri F, Ducatez M, Guerin J, *et al*. Platelet activation and aggregation promote lung inflammation and influenza virus pathogenesis. American Journal of Respiratory and Critical Care Medicine. 2015; 191: 804–819.

[22] Lippi G, Henry BM, Favaloro EJ. Mean platelet volume predicts severe COVID-19 illness. Semin Thromb Hemost. 2021; 47: 456–459.

[23] Li J, Li Y, Sheng X, Wang F, Cheng D, Jian G, *et al*. Combination of mean platelet volume/platelet count ratio and the APACHE II score better predicts the short-term outcome in patients with acute kidney injury receiving continuous renal replacement therapy. Kidney and Blood Pressure Research. 2018; 43: 479–489.

[24] Wang Y, Fan Z, Wang S, Zhuang C. The diagnostic value of platelet distribution width in patients with mild COVID-19. Journal of Clinical Laboratory Analysis. 2021; 35: e23703.

[25] Meizlish ML, Goshua G, Liu Y, Fine R, Amin K, Chang E, *et al*. Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. American Journal of Hematology. 2021; 96: 471–479.

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