sciendo
ПРИЛОЗИ. Одд. за мед. науки, XLIII 2, 2022 МАНУ
CONTRIBUTIONS. Sec. of Med. Sci., XLIII 2, 2022 MASA

10.2478/prilozi-2022-0029 ISSN 1857-9345

HEMATOLOGICAL FINDINGS AND ALTERATION OF OXIDATIVE STRESS MARKERS IN HOSPITALIZED PATIENTS WITH SARS-COV-2

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ABSTRACT

Background/aim: Hematological parameters are the starting point in COVID-19 severity classification. The aim of this study was to analyze oxidative stress in hospitalized COVID-19 patients and to determine its association with D-dimer, neutrophil to lymphocyte ratio (NLR), and platelets to lymphocyte ratio (PLR) as markers for disease progression.

Materials and methods: 52 patients with moderate and severe forms of COVID-19 were enrolled. A hematological and coagulation profile was performed for each patient. PAT (total antioxidant power, iron-reducing) and d-ROMs (plasma peroxides) were determined in serum at admission and 7 days after hospitalization.

Results: The severe group presented parameters that indicated a poor prognosis. Patients that recovered had a significant reduction in d-ROM (t-test, $p<0.01$) and improvement in oxidative stress index (t-test, $p<0.05$). Patients that died had significantly decreased PAT ($p<0.01$) resulting in an increase in oxidative stress. Except for d-ROM vs PLR in both groups and d-ROM vs D-dimer in the severe group, a good correlation between oxidative stress parameters and D-dimer, PLR, and NLR was demonstrated ($p<0.01$).

Conclusion: Our results show that oxidative stress markers can be used as a tool for disease progression in COVID-19. This analysis is easily accessible and affordable in addition to conventional hematological parameters performed for severity classification.

Keywords: COVID-19, oxidative stress, D-dimer, neutrophil to lymphocyte ratio, platelets to lymphocyte ratio

INTRODUCTION

The coronavirus disease (COVID-19) has rapidly evolved from an epidemic outbreak in China [1] into a pandemic infecting individuals worldwide. The majority of patients with COVID-19 develop only a mild or moderate form of the disease, but approximately 10–15 % progress to severe disease, requiring oxygen support, and 5 % have a critical form of the disease with complications affecting different organ systems. [2]

It is well known that respiratory viral infections are accompanied by increased cytokine production, inflammation and other pathophysiological processes linked to redox imbalance or oxidative stress. [3] Oxidative stress is a dis-

proportion between the reactive oxygen species (ROS) and altered antioxidant capacity that leads to a disturbance of redox signaling and irreversible protein damage. [4] In addition to the present inflammation, processes like the inhibition of ACE-2 activity, [5] endothelial dysfunction, [6] disseminated intravascular coagulation, and hemoglobin denaturation, resulting in disturbances of iron metabolism by releasing toxic free iron [7, 8], are closely related to increased oxidative stress level in COVID-19 patients. Several review articles have suggested the role of the redox system in the pathophysiology of COVID-19. [3, 9–11] Still, little information is available about the redox status of COVID-19 hospitalized patients.

As an indicator for the prediction of severity and prognosis of COVID-19, several blood tests, including platelet count, [12, 13] prothrombin time, D-dimer, [14–16] NLR and PLR [17–20] are commonly used. However, besides these routinely performed investigations, we hypothesize that an additional fast and affordable analysis, such as the measurement of oxidative stress parameters, could be useful as additional markers for evaluation of disease progression.

The aim of our study was to analyze oxidative stress parameters in 52 hospitalized COVID-19 patients with moderate and severe forms of the disease. Afterwards, we investigated the relation between the oxidative stress parameters and D-dimer, NLR, and PLR as commonly used hematological markers for disease severity classification.

MATERIALS AND METHODS

Study design (patients)

Included in this study were fifty-two (52) adult patients (≥18 years old) with a confirmed diagnosis of COVID-19 by real-time reverse transcriptase-polymerase chain reaction assay (RT-PCR) from nasal and pharyngeal swab specimens. These patients were admitted to the PHI University Clinic for infectious diseases and Febrile Conditions in Skopje, R. North Macedonia over the period of two months. The diagnosis and classification of COVID-19 was based on Interim Guidance for Clinical Management of COVID-19, issued by the WHO and were classified into two groups: moderate and severe. Patients with moderate disease were adults with clinical signs of pneumonia, but no signs of severe pneumonia, including an SpO2 > 90% on room air. Severe cases met at least one of the following conditions: SpO2 < 90% on room air, respiratory rate >30 breaths/minute, or presence of severe respiratory distress. The discharge criteria consisted of: clinical improvement upon physical examination, improvement of oxygenation, body temperature back to normal at least for three days, and an improvement of lung infiltration (proved by chest X-ray examination). Patients with signs of deterioration were transferred to the ICU. The investigation was approved by the Ethical Committee of the Medical Faculty, University of "SS Cyril and Methodius"- Skopje, Republic of North Macedonia.

Data collection and laboratory assessment

Demographic, medical history, clinical, laboratory, treatment, and outcome data were obtained from the patients' medical records. The laboratory assessment consisted of: complete blood cell count: red blood cells (RBC), hemoglobin, hematocrit, white blood cells (WBC), lymphocyte, monocytes, neutrophil, eosinophil, platelets; electrolytes: K+, Ca++, Na+, as well as a coagulation profile: D-dimer, prothrombin time (PT), activated partial thromboplastin time (aPPT), thrombin time (TT). NLR and PLR were calculated from the complete blood count by dividing the mean neutrophil and platelet counts by the mean lymphocyte count. [21] Serial hematological analyses were ordered based on the clinical condition of each patient.

Method for determination of d-ROMs, PAT, and Oxidative stress index

PAT (total antioxidant power, iron reducing) and d-ROMs (plasma peroxides) were measured on a FRAS5 analytical photometric system (H&D, Italy). The instructions of the manufacturer were followed for the both tests. The oxidative stress index (OSI) presents information obtained from d-ROMs and the PAT tests that is automatically calculated with normal reference values less than 40. Analyses were performed at the Department of Preclinical and Clinical Pharmacology and Toxicology, Medical Faculty of Ss. Cyril and Methodius University in Skopje, R. North Macedonia. Two samples (on admission and day 7 of hospitalization) were collected and analyzed. The obtained results for both groups were compared with the normal oxidative stress values of 40 healthy individuals from our previous measurements.

Statistical analysis

Data was described as number and/or percentage, or mean and standard deviation (SD) or standard error of mean (SEM), where appropriate. Differences between groups were explored using the t-test, Mann-Whitney, or ANOVA, followed with Holm-Sidak's multiple comparison test, where appropriate. A p-value less than 0.05 was considered significant. All analyses were made using the statistical program GraphPad 9 (USA).

RESULTS

Demographic characteristics

General demographic characteristics, co-existing medical conditions, and outcome of 52 confirmed COVID-19 patients included in this study are listed in Table 1. The mean age of the patients was 56.18 ±1 1.65 (range from 18–79 years). 36.5 % were over 60 years old and 63.46% were male. No significant difference was observed in terms of mean age between the groups ($p>0.05$, t-test). More comorbidities were present in the severe group of patients with hypertension being the most common, followed by diabetes, and coronary artery disease. Common clinical symptoms of COVID-19 at admission were high body temperature (82.69%), malaise (63.46 %), dyspnea (61.54 %), and cough (55.77 %) and other less common symptoms included headache, myalgia, loss of appetite, nausea, diarrhea, and rhinorrhea. The median time from onset to admission was 10.52 ± 2.29 days.

According to the severity of COVID-19 at time of admission, 21 patients were classified as moderate and 31 as severe. All patients received the standard of care, and most were treated with antibiotics, oxygen therapy, anticoagulants, and corticosteroids. If necessary, for each patient, other symptomatic and supportive therapies were applied upon the clinician's judgment. Among the 31 patients in the severe group, 6 recovered and were discharged, while 25 deteriorated and died (67.74 %). For 11 of patients that died later than the 7th day of hospitalization, a second blood sample was obtained and analyzed.

Hematological parameters

Clinical laboratory parameters of the moderate and severe group of patients upon admission and at day 7 of hospitalization are listed in detail (Table 2). In the moderate group at admission, laboratory blood examinations revealed increased lymphocytes, NLR and PLR, as well as an elevation of D-dimer, despite normal values for PT, aPPT, and TT from the coagulation profile. By day 7, normalization in lymphocyte count, a statistically significant decrease by 25 % in NLR, was observed when compared to the admission values ($p = 0.001$). Even though PLR and D-dimer were decreased by 25 % and 15 %, respectively, the difference was not statistically significant in comparison to the admission values ($p = 0.065$).

In the severe group of patients, increased WBC, neutrophils, NLR, PLR, as well as lymphopenia were noted. The coagulation profile revealed D-dimer elevation, prolonged PT with normal aPPT, and TT. Among the recovered patients from the severe group, a statistically significant difference was observed for NLR and PLR ($p = 0.0019$), and the values were decreased for 70 % and 67 %, respectively, in comparison to admission values. In addition, lymphocytes were increased by 53 % ($p = 0.001$). Decreases of WBC for 18%, neutrophils for 11%, platelets for 19 %, PT for 22 % and D-dimer for 85 % were noticed, but the difference was not statistically significant ($p = 0.074$).

In patients that died, further deterioration of the condition was observed as a continuous increasing in WBC and neutrophils (34 %), NLR (55 %), decreasing in lymphocytes (42 %), PT (18 %) and D-dimer (50 %). A statistically significant difference was observed only for lymphocytes compared to admission values.

Oxidative stress parameters

Oxidative stress parameters (PAT, d-ROM and OSI) of COVID-19 patients are listed in Table 3. Both moderate and severe group, upon admission, had significantly increased plasma peroxides and an increased OS index level, in comparison with previously determined values in healthy individuals from our laboratory (t-test, $p < 0.01$).

In the moderate group by day 7, parallel to the improvements in hematological parameters, a significant reduction in d-ROM and OSI in comparison to admission values was noticed (t-test, $p < 0.05$). Similar decreases of d-ROM and OSI were also seen in the severe group at day 7 of hospitalization in patients that recovered. By contrast with patients that died, PAT significantly decreased ($p < 0.01$), thus resulting in an increase in OSI by day 7 (Fig. 1A).

Table 1. *Demographic and characteristics and clinical manifestations of COVID-19 patients (Mean ± SD*)

Demographic	**Total (n=52)**	**Moderate group (n=21)**	**Severe group (n=31)**
Age (years)	56.18 ± 11.65	53.05 ± 13.3	58.37 ± 9.97
Gender (M/F)	33 / 19	10 / 11	23 / 8
Body weight (kg)	85.48 ± 13.7	86.15 ± 16.20	84.75 ± 11.03
Days from onset to admission	10.52 ± 2.29	10.29 ± 2.15	10.61 ± 2.42
Comorbidities (%)	36 (69.23%)	12 (57.14%)	24 (77.42%)
Comorbidities in each patient	1.59 ± 0.55	1.38 ± 0.51	1.69 ± 0.56
Co-existing medical conditions (%)			
Hypertension	20 (38.46%)	6 (28.57%)	14 (45.16%)
Diabetes	13 (25%)	4 (19.05%)	9 (29.03%)
COPD, asthma	1 (1.92%)	/	1 (3.23%)
Thyroid disease	3 (5.77%)	2 (9.52%)	1 (3.23%)
Hematological disease	4 (7.69 %)	2 (9.52%)	2 (6.45%)
Cardiomyopathy	1 (1.92%)	1 (4.76 %)	/
GI disease	2 (3.85%)	1 (4.76 %)	1 (3.23%)
Coronary artery disease	5 (9.62%)	/	5 (16.13%)
Arrhythmia	1 (1.92%)	1 (4.76 %)	/
Urological disease	3 (5.77%)	1 (4.76 %)	2 (6.45%)
Neurological disease	1 (1.92%)	/	1 (3.23%)
OUTCOME (recovered/ deceased)	27/ 25	21/0	6/ 25

Table 2. *Clinical laboratory parameters of COVID-19 patients (Mean ± SEM)*

Parameter	**Moderate (n=21) Admission**	**Moderate (n=21) Day 7**	**Severe (n=31) Admission**	**Severe (n=6) Day7** *Recovered*	**Severe (n=11) Day7** *Died*	**Ref. values**
RBC ($x10^3\mu L$)	4491 ±79.22	4512 ±95.69	**4780 ±11[3]**	4332 ±335.9	**4684 ±281.6[2]**	4000-5500
Hemoglobin (g/L)	127.3 ±2.42	129.3 ±3.11	137.97 ±2.74	121.8 ±9.82	**145.4 ±2.98[1]**	115-180
Hematocrit (%)	37.87 ±0.93	38.25 ±0.93	**40.8 ±1.04[4]**	37.73 ±2.54	**48.85 ±5.65[2]**	35-50
WBC ($x10^3\mu L$)	7.686 ±0.81	8.929 ±0.75	**24.17 ±10.03[4]**	11.58 ±0.77	21.84 ±2.46	4.0-11.0
Lymphocytes (%)	0.4176 ±0.18	0.2490 ±0.02	**0.0603 ±0.01[3]**	**0.15 ±0.01[1]**	**0.03 ±0.01[2]**	0.21-0.25
Monocytes (%)	0.083 ±0.01	0.096 ±0.01	0.0413 ±0.004	**0.07 ±0.10[1]**	0.037 ±0.04	0.02-0.10
Neutrophil (%)	0.6948 ±0.04	0.6462 ±0.03	**0.8971 ±0.01[4]**	0.79 ±0.02	0.92 ±0.01	0.40-0.70
Eosinophils (%)	0.02 ±0.01	0.02 ±0.01	0.02 ±0.007	0.016 ±0.01	/	0.01-0.06
Platelets ($x10^3\mu L$)	340.6 ±32.07	363.7 ±32	292.74 ±21.51	234.7 ±39.14	294.5 ±31.39	150-400
NLR	6.54 ±1.56	**5.037 ±1.51[1]**	**19.73 ±1.98[4]**	**5.81 ±0.81[1]**	44.16 ±10.78	< 3.0
PLR	318.2 ±51.34	243.4 ±43.96	**512.36 ±75.84[4]**	**170.5 ±32.69[1]**	553.1 ±80.05	50-200
PT (s)	12.87 ±0.93	12.15 ±0.36	15.85 ±3.6	12.37 ±0.51	12.97 ±0.46	9.8-14.2
aPPT (s)	34.11 ±1.81	**29.79 ±1.48[1]**	34.14 ±4.03	29.52 ±1.77	28.92 ±1.16	27.9-37.7
TT (s)	19.04 ±0.95	**21.59 ±1.14[1]**	19.87 ±0.59	21.65 ±1.87	18.96 ±0.67	16.1-24.1
D-dimer (ng/mL)	866 ±81.98	734.5 ±63.51	**8852 ±22[4]**	**1286 ±119.1[1]**	4411 ±892.7	0-500
K^+ (mmol/L)	4.34 ±0.56	4.17 ±0.71	4.19 ±0.68	4.1 ±0.58	3.47 ±0.6	3.5-5.5
Ca^{++} (mmol/L)	2.21 ±0.21	2.23 ±0.14	2.19 ±0.38	2.11 ±0.02	2.22 ±0.52	2.1-2.5
Na^+ (mol/L)	139.1 ±3.35	141.1 ±3.21	139.61 ±4.5	138.8 ±2.86	141.6 ±9.17	135-145

[1] $p<0.01$, [2]$p<0.05$ admission compared to Day 7 of illness for both groups, [3]$p<0.05$, [4]$p<0.01$ moderate group admission compared to severe group admission

Table 3. *Oxidative stress parameters (PAT, d-ROM, and OSI) of COVID-19 patients (Mean ± SEM)*

Parameter	**PAT**	**d-ROM**	**OSI**
Moderate, (n=21) Admission	2885±97.15 [1]	431.1±24.05[1]	94.24±12.54 [1]
Moderate, (n=21) Day 7	2650±154.4 [3]	335±13.21[4]	52.24±5.32[3]
Severe, (n=31) Admission	2783±83.21[2]	411.9± 15.45[1]	83.33±7.74[1]
Severe, (n=6) Day7*, Recovered*	2853±209.6	326±22.44 [6]	41.33±9.54[5]
Severe, (n=11) Day 7, *Died*	2245±192.5[7]	399.1±49.04	105.1±17.16
Healthy group, (n=40)	2489±79.96	282±6.78	24±3.014
Reference values	2200-2800	250-300	<40

[1] p<0.01, [2] p<0.05 normal group compared to moderate and severe group on admission;
[3]p<0.05, [4]p<0.01 moderate group admission compared to moderate group Day 7 of illness;
[5]p<0.05, [6]p<0.01 severe group admission compared to severe group Day 7 of illness/recovered; [7] p<0.01 severe group admission compared to severe group Day 7 of illness/died.

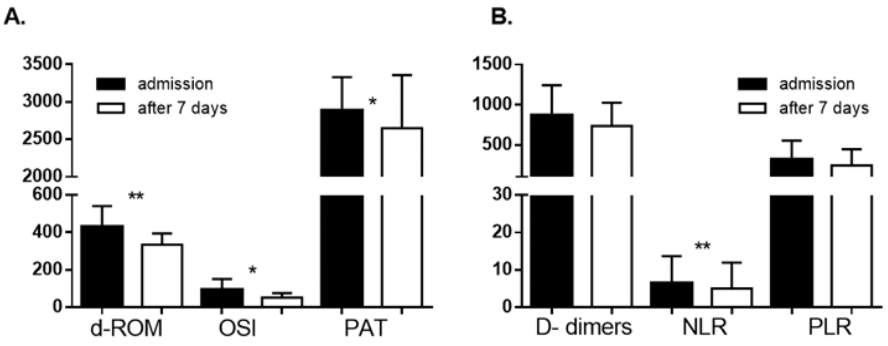


Figure 1. A.) Oxidative stress parameters in moderate group (n=21) at admission and after 7 days of hospitalization B.) D-dimer, NLR and PLR in moderate group (n=21) at admission and after 7 days of hospitalization. Results are shown as Mean ± SEM. **p<0.01, *p<0.05.

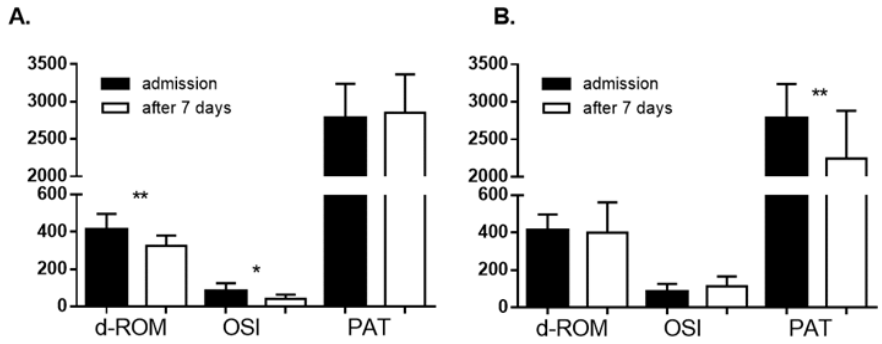


Figure 2. Oxidative stress parameters in severe group at admission (n=31) and after 7 days of hospitalization in patients (n=6) that survived (A) and patients (n=11) that died (B). Results are shown as Mean ± SEM. **p<0.01, *p<0.05.

Three common hematological abnormalities between the moderate and severe groups (NLR, PLR and D-dimer) were compared to oxidative stress parameters upon admission. Among the moderate cases (n=21), a good correlation was demonstrated between all investigated parameters (d-ROM, PAT, OSI, D-dimer, PLR and NLR) ($R2 = 0.98$, $p < 0.02$, ANOVA). Additionally, Holm Sidak's multiple comparison test showed a significant difference ($p < 0.01$) between all investigated parameters except d-ROM vs PLR ($p > 0.05$) (Fig. 1B).

Among the severe cases (n = 31), a good correlation was demonstrated between all investigated parameters (d-ROM, PAT, OSI, D-dimer, PLR and NLR) ($R2=0.4174$, $p < 0.001$, ANOVA). Additionally, Holm Sidak's multiple comparison test showed a significant difference ($p < 0.01$) between all investigated parameters except d-ROM vs PLR and d-ROM vs D-dimer ($p > 0.05$).

The oxidative stress parameters for the severe group are shown in Fig. 2, where a statistically significant difference was obtained for the values of d-ROM and OSI in the group of patients that survived (Fig. 2A), and for PAT value in the group of patients that died (Fig. 2B).

DISCUSSION

The enormous efflux of COVID-19 patients has created a need for a fast, reliable, but affordable, set of analyses that can assist clinicians in formulating a tailored treatment approach.

This study was designed with a hypothesis that oxidative stress parameters can be used as a marker for disease progression. Patients with a continuous increase of the OS index after hospital admission are more likely to develop a severe form of the disease or complications during hospitalization, including death. In contrast, if the OS index decreases, a better outcome can be predicted. In our study, in order to further confirm our hypothesis, we have analyzed the oxidative stress parameters and hematological laboratory parameters of 52 patients with moderate and severe form of COVID-19, hospitalized at the University Clinic for Infectious Diseases and Febrile Conditions in our country.

Similar to previously published results [22–25], our study showed that patients in both the moderate and severe groups had significantly higher values for d-ROMs at admission and therefore an increased OS index level in comparison to healthy individuals.

In the severe group, upon admission, several hematological parameters indicating poor prognosis were observed: an increase in WBC, neutrophils, NLR, PLR, as well as a decreasing trend of lymphocytes. The pathophysiology of viral pneumonia includes the activation of several defense mechanisms, like the influx of activated phagocytes, polymorphonuclear neutrophils, and macrophages. Neutrophils and macrophages destroy pathogens by activating ROS, thereby increasing oxidative stress in the lung. This local inflammation process can proceed to a systemic inflammatory response. Oxidative stress is a contributing factor in pneumonia [26]. Lymphopenia is a predictor of poor prognosis, the need for ICU treatment [27, 28], and the development of ARDS [29]. Several factors contribute to COVID-19 associated lymphopenia: direct infection and lysis of lymphocytes due to surface expression of the ACE2 receptor [30] and lymphocyte apoptosis promoted by the cytokine storm [31, 32]. Patients with severe COVID-19 are often lymphopenic, whereas the number of neutrophils is increased [28]. The formation of neutrophil-platelet complexes facilitates the recruitment of neutrophils to inflamed tissue and platelets, inducing neutrophils to produce neutrophil extracellular traps (NETs) that protect from viral infection [33]. Several authors suggest that NLR [34, 35] and PLR [36] can be used as an independent prognostic marker which differentiates severe from non-severe COVID-19 patients. In our study, NLR and PLR upon admission were increased in both groups, but NLR was significantly higher in the severe group of patients. In patients that recovered within both the moderate and severe group, NLR significantly decreased and was comparable, but in patients that died, NLR increased. In severe patients that recovered, the PLR normalized in contrast to patients that died where a rising trend for PLR was noted.

D-dimer is a fibrin degradation product involved in the diagnostic algorithm of thrombosis and thrombosis-conditioned diseases. An increase in D-dimer can be physiological and pathological (malignant diseases, chronic liver diseases, pregnancy, inflammation) [37]. Coagulation disorders are frequently detected among COVID-19 patients [22]. High levels D-dimer admission, accompanied by increasing D-dimer trends, are associated with a greater risk

of all-cause mortality, the need for mechanical ventilation, and venous thromboembolism [38]. Procoagulant response is associated with the inflammatory effects of cytokines in the vascular endothelium, including an increased vascular permeability and damage due to immune-cell infiltration [37]. Our study showed increased values for D-dimer levels in both the moderate and severe groups, and prolonged PT in the severe group. Values for aPPT and TT were within the normal range. This is in accordance to results published by several authors [27, 39–41]. In addition to the hematological parameters, our results suggested that the oxidative stress parameters of these patients correlate with NLR, PLR, and D-dimer.

The authors would like to suggest several study limitations. Namely, the study was performed on 52 COVID-19 patients in a single center, serving as a tertiary hospital that mostly treats patients with fast condition deterioration or patients referred from a secondary healthcare setting. Laboratory assessment was not performed daily. A more frequent blood sampling schedule, shorter than 7 days, should be employed, especially in severe patients at risk of developing complications.

CONCLUSION

Oxidative stress parameters (d-ROM, PAT and OSI) displayed a good correlation between NLR, PLR, and D-dimer upon admission. Our results suggest that these parameters can be used as a marker for disease progression in COVID-19 patients and an easier classification of disease severity. This analysis is easily accessible and affordable, in addition to conventional hematological parameters, performed for the classification of disease severity. We believe that patients in the earlier course of the disease will have greater benefits because of this analysis.

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Резиме

ХЕМАТОЛОШКИ НАОДИ И ПРОМЕНИ ВО МАРКЕРИТЕ НА ОКСИДАТИВЕН СТРЕС КАЈ ХОСПИТАЛИЗИРАНИ ПАЦИЕНТИ СО SARS-COV-2

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Вовед/цел: Хематолошките параметри се почетната точка при класификувањето на сериозноста на болест кај пациентите со дијагностициран КОВИД-19. Целта на оваа студија беше да се анализира оксидативниот стрес кај хоспитализираните пациенти со КОВИД-19 и да се определи нивната поврзаност со вредностите за д-димерите, односот на неутрофилите и лимфоцитите (NLR) и односот на тромбоцитите со лифоцитите (PLR).

Материјал и методи: Во испитувањето беа вклучени 52 пациенти со умерена и тешка клиничка слика на КОВИД-19. За секој пациент беше направен хематолошки профил и коагулациски статус. Вредностите за PAT (вкупен антиоксидативен капацитет) и d-ROM (пероксиди во плазма) беа одредувани во серум, при прием и по 7 дена од хоспитализацијата на пациентите.

Резултати: Во групата на пациенти со тешка клиничка слика забележавме влошување на некои параметри, кои укажуваат на дополнително влошување на нивната здравствена состојба. Во групата со пациенти што имаа средна клиничка слика, по оздравувањето беше забележано значително намалување на вредностите за d-ROM (t-test, $p < 0,01$) и подобрување на индексот на оксидативен стрес (t-test, $p < 0,05$). Пациентите што- починаа имаа значително намалени вредности за PAT ($p < 0,01$), кои доведоа до покачување на оксидативниот стрес. Резултатите покажаа добра корелација меѓу параметрите на оксидативен стрес и д-димерите, PLR и NLR ($p < 0,01$), освен за d-ROM, наспроти PLR, во двете групи и d-ROM наспроти д-димери во групата на пациенти со потешка форма на болеста.

Заклучок: Резултатите од ова испитување покажуваат дека маркерите за оксидативен стрес може да се користат како алатка за процена на прогресијата на болеста. Оваа анализа е економски прифатлива и лесно достапна, и може да се користи како дополнителна анализа, заедно со конвенционалните хематолошки параметри, при класификацијата на болеста кај пациентите со КОВИД-19.

Клучни зборови: КОВИД-19, оксидативен стрес, Д-димери, однос на неутрофили наспроти лимфоцити, однос тромбоцити наспроти лифоцити