Journal of Inflammation Research

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ORIGINAL RESEARCH

The Diagnostic Value of Inflammatory Markers (CRP, IL6, CRP/IL6, CRP/L, LCR) for Assessing the Severity of COVID-19 Symptoms Based on the MEWS and Predicting the Risk of Mortality

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Introduction: Various diagnostic tools are used to assess the severity of COVID-19 symptoms and the risk of mortality, including laboratory tests and scoring indices such as the Modified Early Warning Score (MEWS). The diagnostic value of inflammatory markers for assessing patients with different severity of COVID-19 symptoms according to the MEWS was evaluated in this study.

Materials and Methods: The concentrations of CRP (C-reactive protein) (immunoassay) and IL6 (interleukin 6) (electrochemiluminescence assay) were determined, and CRP/IL6, CRP/L, and LCR ratios were calculated in blood serum samples collected from 374 COVID-19 patients.

Results: We demonstrated that CRP, IL6, CRP/IL6, CRP/L, LCR inflammatory markers increase significantly with disease progression assessed based on the MEWS in COVID-19 patients and may be used to differentiating patients with severe and non-severe COVID-19 and to assess the mortality.

Conclusion: The diagnostic value of inflammatory markers for assessing the risk of mortality and differentiating between patients with mild and severe COVID-19 was confirmed.

Keywords: COVID-19, CRP, C-reactive protein, IL-6, interleukin 6, inflammatory markers, MEWS, modified early warning score

Introduction

On 30 January 2020, the World Health Organization (WHO) announced that the COVID-19 disease caused by the SARS-COV-2 virus poses a threat to the health and life of the global population.[1] Since then, more than 640 million people have been infected with the virus and 6.63 million have died from the disease (as of 24 November 2022).[2]

Despite a massive research global effort, an effective treatment for COVID-19 still is under research area, but using the corticosteroids, interleukin antagonists, antivirals, and antibody therapy have a big impact on the outcomes of COVID-19.[3] Most COVID-19 patients have mild symptoms, and some patients are even asymptomatic, but the disease can also trigger severe symptoms.[4] Clinical symptoms change rapidly, and the progression of disease can lead to hypoxia, organ dysfunctions, or even death.[5] It should be remembered that in patients with COVID-19 we observe a decrease in the immune response, and thus there are also changes in laboratory parameters (especially those related to inflammation).[6] There are some studies about the role of laboratory parameters for predicting the severity and progression of COVID-19,[7] but still the severity of the disease is assessed mainly based on clinical symptoms. Therefore,

Received: 16 February 2023
Accepted: 15 April 2023
Published: 22 May 2023

diagnostic markers for differentiating between cases of mild and severe COVID-19 should be developed to optimize treatment, improve the clinical status of patients, and reduce the risk of mortality.[8]

Research has shown that higher concentrations of C-reactive protein (CRP), interleukin 6 (IL6), procalcitonin (PCT), ferritin, D-dimers and lower concentrations of lymphocytes and eosinophils are strongly correlated with COVID-19 severity and the risk of mortality in patients infected with the SARS-CoV-2 virus.[9–13] Some studies also showed that the level of troponin, aminotransferases and erythrocytes sedimentation rate (ESR) also were higher than the reference values in the group of patients who were infected with SARS-CoV-2 virus and died.[6] A review of the literature showed a large role of laboratory testing in assessment of COVID-19 severity and mortality.[14–18] However, it is important to look for new indicators and more accurately descripted those which are commonly used.

The aim of this study was evaluating the diagnostic value of several inflammation markers (CRP, IL6, CRP/IL6 CRP/L, LCR), demographic data, and comorbidities in hospitalized patients with different severity of COVID-19 symptoms who have been diagnosed based on the MEWS. The risk of mortality in COVID-19 patients was predicted based on selected inflammatory markers. These parameters and changes in their values over time can be used to diagnose patients and select the appropriate treatment. The diagnostic value of inflammatory markers for assessing COVID-19 severity according to the MEWS was determined by analyzing the ROC curve, and the correlations between inflammatory markers, the remaining laboratory parameters, and patient data were evaluated. The role of inflammatory markers in predicting the risk of mortality in COVID-19 patients was described.

Materials and Methods

Description of the Study

A single-center, retrospective study involving COVID-19 patients (non-vaccinated) admitted to Temporary Hospital No. 2 of the Clinical Hospital of the Medical University of Białystok was conducted between November 2020 and November 2021. The study had been approved by the Bioethics Committee of the Medical University of Białystok (decision No. APK.002.353.2021).

Clinical Characteristics and Laboratory Data

Inflammatory markers (CRP, IL6) were determined in venous blood collected for routine diagnostic tests from patients infected with the SARS-CoV-2 virus. The infection was confirmed based on the presence of SARS-CoV-2 genetic material in nasal and throat swabs in the PCR assay. Epidemiological characteristics, including recent exposure history, clinical symptoms, comorbidities, treatment data, computed tomographic scan (CT) and laboratory results, were collected from digital medical records. All patients had been subjected to routine blood examinations, including CBC, coagulation profiles, and biochemical tests, as well as CT and X-ray examinations upon admission to the hospital. Treatment plans were implemented based on the diagnosis and the patients' clinical condition. Medical treatment (antibiotics, remdesivir, convalescent plasma) was continued until an improvement in the patient's condition or death. Corticosteroids, heparin also were used but we did not obtain details information about the number of patients.

The following parameters were analyzed: sex, age, hospitalization time, death, presence of comorbidities (yes, no), presence of pneumonia – inflammatory of the lung in X-ray (yes, no), hematological disorders (yes, no), diabetes (yes, no), hypertension (yes, no), obesity (yes, no), heart diseases (yes, no), history of cancer (yes, no); applied treatment – remdesivir (yes, no), antibiotics (yes, no), convalescent plasma (yes, no), intubation (yes, no), mechanical ventilation (yes, no); clinical symptoms: fever (yes, no), cough (yes, no), shortness of breath (yes, no), acute respiratory distress syndrome (yes, no), gastrointestinal symptoms (yes, no), general condition upon admission, severity of clinical symptoms according to the MEWS, blood pressure, tachypnoea (yes, no), pulse and oxygen saturation. Laboratory tests consisted of a complete blood count (CBC), including total WBCs, neutrophils, lymphocytes, monocytes, and platelets; blood chemistry analyses – alanine aminotransferase (ALT), aspartate aminotransferase (AST), amylase, total bilirubin, creatine kinase (CK), chloride (Cl^-), C-reactive protein (CRP), fibrinogen, glucose, ferritin, potassium (K^+), gamma-glutamyl transferase (GGT), creatinine, estimated glomerular filtration rate (eGFR), lactate dehydrogenase (LDH), sodium (Na^+),

procalcitonin (PCT), urea, blood urea nitrogen (BUN), interleukin 6 (IL6), and troponin levels; and coagulation profiles - activated partial thromboplastin time (APTT) and ratio, prothrombin time (PT) and activity, international normalized ratio (INR), and D-dimer.

The patients were divided into four groups based on the following vital signs that make up the MEWS (Table 1). 4-level MEWS scale (grades 1–4) used to assess the severity of COVID-19 based on the severity of symptoms: respiratory rate, systolic blood pressure, urine output, body temperature, and neurological symptoms. Stage 1 – patients are asymptomatic or mildly symptomatic. Stage 2 – patients with pneumonia without respiratory distress; stage 3 – patients with severe pneumonia with respiratory distress; stage 4 – patients with multiple organ failure.[19] Inflammatory markers were determined on the day of hospital admission, after 4–6 days, and after 10 days of hospitalization.

Analytical Methods

Interleukin 6 levels were determined in the electrochemiluminescent immunoassay (ECLIA) with the Roche Cobas e411 analyzer. C-reactive protein concentration was determined in the turbidimetric immunoassay with the Abbott Allinity analyzer.

The Roche Elecsys IL6 test is a non-competitive (sandwich) chemiluminescent immunoassay. In the first step, 18 µL of the sample is incubated with IL6-specific antibodies, and then with IL6-specific antibodies labeled with ruthenium complexes to create a sandwich complex. The formed complexes are captured magnetically, and voltage induces chemiluminescent emission that is directly proportional to the concentration of IL6. The assay has a measuring range of 1.5–5000 pg/mL, limit of quantitation (LOQ) of 2.5 pg/mL, and inter-assay precision (CV) of 17.4% (at 1.82 pg/mL) and 2.0% (at 4461 pg/mL). The reference interval is <7 pg/mL.[21]

Multigent CRP Vario is a latex immunoassay which accurately and reproducibly measures blood CRP levels in serum and plasma. An antigen-antibody reaction between CRP in a sample and an anti-CRP antibody, which has been adsorbed to latex particles, leads to agglutination. Agglutination is detected as a change in absorbance (572 nm), where the rate of the change is proportional to the quantity of CRP in the sample.[22]

CRP/L, CRP/IL6, and LCR Ratios

The following inflammatory marker ratios were computed: C-reactive protein-to-lymphocyte ratio (CRP/L), C-reactive protein-to-interleukin 6 ratio (CRP/IL6), and the lymphocyte-to-C-reactive protein ratio (LCR).[18]

Statistical Analysis

Statistical analyses were performed using Statistica 13.3 (StatSoft, Poland) and GraphPad Prism 9.0 (GraphPad Software, La Jolla, USA). Data were described with the following summary statistics: number (n), percentage (%), median (M), 25th percentile (Q1), and 75th percentile (Q3). The Shapiro–Wilk test was used to determine the normality of distribution. The differences between group means were determined by Student's t-test. The Mann–Whitney *U*-test was applied to compare outcomes with non-normal distribution. Pearson's χ 2 test was used to compare categorical data between groups. The strength of the correlations between the measured parameters was determined by calculating Spearman correlation coefficients. Statistical significance was established at $p < 0.05$. The receiver operating characteristic (ROC) analysis was performed to assess the diagnostic utility of the analyzed inflammatory markers (the predictive performance of markers for mortality and detecting mild and severe patients). The area under the curve (AUC) and the optimal cut-off values were determined for each parameter to ensure high sensitivity and specificity. The predictive performance of inflammatory markers for death was evaluated by estimating AUC values. The optimal cutoff values of inflammatory markers were determined using the Youden's index. The association of inflammatory biomarkers results with the COVID-19 mortality and of correlation of chosen inflammatory parameters with laboratory tests results and clinical parameters were estimated with the use of a univariate Cox proportional hazards model. Cutoff values were calculated to determine mortality risk levels of biomarkers in COVID-19 and to detect severely infected patients.

Results

Characteristics of the Study Group

A total of 374 COVID-19 patients aged 56 to 75 were analyzed. The studied population comprised 51.9% male and 49% female subjects. The patients were divided into four groups according to MEWS classification (Table 1): stage 1 (asymptomatic) – 13.4%; stage 2 (pneumonia without respiratory distress)– 51.95%; stage 3 (severe pneumonia with respiratory distress/pre-ARDS) – 27.8%; 4 (ARDS / multiple organ failure) – 6.9%. Approximately 35% of the patients were hospitalized for less than 10 days, 48% – for 10–20 days, and 17% – for >20 days. 86% of the patients had comorbidities, mostly hypertension (52%), coronary heart disease (26%), and diabetes mellitus (20%). The most common symptoms were fever and dyspnea which were observed in 64% and 67% of the patients, respectively. Antibiotics were administered to 87% of the patients, whereas 18.5% received Remdesivir and 12% received convalescent plasma. The overall number of in-hospital deaths was 43 (12%). The main characteristics of the study group are presented in Table 2.

Comparison of Diagnostic results in COVID-19 Patients Divided into Four Groups Based on the MEWS Classification

The results of diagnostic tests performed on the day of hospital admission were compared between four groups of patients with different severity of COVID-19 symptoms. The comparison revealed that diagnostic parameters worsened with clinical deterioration. However, significant differences between groups were observed only in the values of WBC ($p=0.0419$), neutrophils ($p=0.0147$), creatinine ($p=0.0069$), and LDH activity ($p=0.0222$) (Table 3).

Comparison of Inflammatory Parameters in COVID-19 Patients Divided into Four Groups Based on the MEWS Classification

Significant differences in inflammatory markers were observed in COVID-19 patients divided into four groups based on the MEWS classification: CRP ($p=0.0037$), IL6 ($p<0.0001$), CRP/L ($p=0.0065$), LCR ($p=0.0072$). Also significant difference in inflammatory markers were observed in CRP value between group 1 vs 4 ($p<0.001$), 2 vs 4 ($p<0.001$), 3 vs 4 ($p<0.05$) and in CRP/IL-6 value in group 2 vs 4 ($p<0.01$) and 3 vs 4 ($p<0.05$) (Table 4).

ROC Analysis of CRP, CRP/L, LCR, and IL6 for Differentiating Patients with Severe and Non-Severe COVID-19

The ROC analysis demonstrated that CRP, CRP/L, LCR, and IL6 might be useful parameters for differentiating severe and non-severe cases of COVID-19 (Table 5). Therefore, the optimal cut-off values were calculated in the ROC analysis, and ROC curves are presented in Figure 1. The AUC values of CRP, CRP/L, LCR, and IL6 were determined at 0.601, 0.590, 0.591, and 0.645, respectively. The optimal cut-off values for CRP, CRP/L, LCR, and IL6 were determined at 75 mg/l, 88.305, 0.011, and 58.8 pg/mL, respectively.

Table 1 Modified Early Warning Score (MEWS)

Score	0	1	2	3
Respiratory rate, breaths/min	9–14	15–20	21–29 or ≤8	>29
Heart rate, bpm	51–100	101–110 or 41–50	111–129 or ≤40	>129
Systolic blood pressure, mm Hg	101–199	81–100	≤200 or 71–80	≤70
Hourly urine, mL/kg of body weight/h	>0.5		<0.5	Nil
Body temperature, °C	36.1–38	38.1–38.5 or 35.1–36	≤38.6 or ≤35	
Neurological symptoms	Alert	Responsive to voice	Responsive to pain	Unresponsive

Note: Adapted from Flisiak R, Horban A, Jaroszewicz J, et al. Management of SARS-CoV-2 infection: recommendations of the Polish Association of Epidemiologists and Infectiologists as of March 31, 2020. *Pol Arch Intern Med.* 2020; 130: 352-357. Creative Commons.[20]

Table 2 Characteristics of the Study Group

	All Patients with Covid-19	Covid-19 Severity According to MEWS				$\chi 2$	*p*
Clinical Features	**n (%)**	**1**	**2**	**3**	**4**		
Number of patients	374	45 (12.0%)	182 (48.6%)	115 (31.0%)	32 (8.4%)		
Age						9.989	0.1251
≤55	64 (17%)	14 (20.31%)	32 (19.00%)	15 (23.44%)	4 (6.25%)		
56–75	211 (57%)	20 (9.62%)	104 (57.00%)	70 (33.17%)	15 (7.21%)		
>76	99 (26%)	11 (11.22%)	44 (24.00%)	30 (30.61%)	13 (13.27%)		
Sex						3.182	0.282
Female	183 (49%)	23 (12.09%)	82 (43.96%)	62 (33.52%)	19 (0.44%)		
Male	191 (51%)	22 (11.70%)	100 (53.19%)	53 (28.19%)	13 (6.91%)		
Hospitalization time						15.934	**0.014**
≤10	131 (35%)	16 (12.50%)	54 (42.19%)	39 (30.47%)	19 (14.84%)		
10–20	181 (48%)	24 (12.78%)	99 (55.0%)	51 (28.33%)	7 (3.89%)		
>20	62 (17%)	5 (8.06%)	29 (43.55%)	25 (38.71%)	6 (9.68%)		
Comorbidities (n,%)						6.357	0.095
Absent	51 (14%)	8 (15.69%)	31 (60.78%)	9 (17.65%)	3 (5.88%)		
Present	323 (86%)	36 (11.29%)	149 (46.71%)	105 (32.92%)	29 (9.09%)		
Hypertension	194 (52%)	21 (10.94%)	88 (45.83%)	65 (33.85%)	18 (9.38%)		
Diabetes mellitus	74 (20%)	6 (8.11%)	37 (50.0%)	22 (29.73%)	9 (12.16%)		
Obesity	36 (10%)	2 (5.56%)	17 (47.22%)	9 (25.00%)	8 (22.22%)		
Coronary heart failure	97 (26%)	10 (10.31%)	41 (42.27%)	34 (35.05%)	12 (12.37%)		
Others (eg cancers, hematological)	64 (17%)	7 (10.93%)	34 (53.13%)	17 (26.56%)	6 (9.37%)		
Symptoms							
Cough						4.143	0.246
Yes	154 (41%)	19 (12.50%)	81 (53.29%)	38 (25.00%)	14 (9.21%)		
No	220 (59%)	26 (11.47%)	101 (45.41%)	76 (34.86%)	18 (8.26%)		
Fever						4.162	0.244
Yes	241 (64%)	28 (11.25%)	127 (52.08%)	71 (29.58%)	17 (7.08%)		
No	133 (36%)	17 (13.08%)	55 (42.31%)	44 (33.08%)	15 (11.54%)		
Dyspnea						4.077	0.253
Yes	251 (67%)	28 (10.93%)	119 (47.37%)	85 (34.01%)	19 (7.69%)		
No	123 (33%)	17 (13.82%)	63 (51.22%)	30 (24.39%)	13 (10.57%)		
Gastrointestinal symptoms						1.058	0.787
Yes	85 (23%)	10 (11.90%)	43 (51.19%)	26 (30.95%)	5 (5.95%)		
No	289 (77%)	35 (11.89%)	137 (47.90%)	88 (30.77%)	27 (9.44%)		
Respiratory failure						2.786	0.425
Yes	127 (34%)	30 (12.30%)	123 (50.82%)	75 (30.74%)	17 (6.15%)		
No	247 (66%)	15 (12.82%)	69 (58.97%)	28 (23.93%)	5 (4.27%)		
Treatment							
Remdesivir						2.208	0.530
Yes	69 (18.5%)	5 (11.63%)	27 (62.79%)	10 (23.26%)	1 (2.33%)		
No	305 (81.5%)	40 (12.58%)	166 (52.20%)	93 (29.25%)	19 (5.97%)		

(*Continued*)

Table 2 (Continued).

	All Patients with Covid-19	Covid-19 Severity According to MEWS				$\chi 2$	*p*
Clinical Features	**n (%)**	**1**	**2**	**3**	**4**		
Antibiotics						8.386	**0.040**
Yes	324 (87%)	34 (10.63%)	152 (47.50%)	105 (32.81%)	29 (9.06%)		
No	50 (13%)	11 (20.00%)	28 (56.00%)	9 (18.00%)	3 (6.00%)		
Convalescent plasma						5.659	0.129
Yes	46 (12%)	5 (8.89%)	16 (35.56%)	19 (42.22%)	6 (13.33%)		
No	328 (88%)	40 (12.31%)	166 (50.46%)	95 (29.23%)	26 (8.00%)		
Death						88.831	**<0.0001**
Yes	43 (12%)	1 (2.38%)	3 (7.14%)	20 (47.62%)	18 (42.86%)		
No	331 (88%)	44 (13.11%)	177 (53.96%)	94 (28.66%)	14 (4.27%)		

Notes: In total, 374 patients, 56 to 75 years old, with COVID-19 were analyzed. 51.9% were men and 49% women. Patients were divided into four groups according to MEWS classification (Table 1). In stage 1 (asymptomatic) the percentage of patients was 13.4%, in stage 2 (symptomatic with pneumonia without signs of respiratory failure) was more than half of patients – 51.95, in stage 3 (severe pneumonia with respiratory failure/pre-ARDS) – 27.8% and in stage 4 (ARDS / multiple organ failure) – 6.9%. About 35% of patients were hospitalized for less than 10 days, 48% of patients were in hospital between 10 and 20 days whereas 17% of patients were hospitalized >20 days. 86% of patients had comorbidities. The most common of them were: hypertension (52%), coronary heart failure (26%) and diabetes mellitus (20%). The most common symptoms were fever and dyspnea observed in 64% and 67% of patients. Antibiotics were applicated in 87% of patients whereas just 18.5% received Remdesivir and 12% of patients received convalescent plasma. The overall number of in-hospital deaths was 43 (12%). The bold values show statistically significant differences between groups. The main characteristics of the study group are presented in Table 2.

ROC Analysis of CRP, CRP/L, LCR and IL6 for Predicting Mortality in COVID-19 Patients

ROC curves were plotted for CRP, CRP/L, LCR, and IL6 were created to determine whether the baseline values of these biomarkers were predictive of mortality in COVID-19 patients. The AUC values of CRP, CRP/L, LCR, and IL6 were above 0.6 (Figure 2, Table 6). The optimal cut-off values were 76.34 mg/l for CRP, 89.816 for CRP/L, 0.009 for LCR, and 64.9 pg/mL for IL6. Parameters with AUC values < 0.5 and no statistical significance (p>0.05) were excluded from the analysis.

Relationship Between Inflammatory Biomarkers and COVID-19 Mortality Risk

The following parameters were subjected to multivariate and univariate Cox regression analysis: CRP/L, CRP/IL6, age, sex, diabetes mellitus, hypertension, coronary heart disease, and obesity. Patients were divided into: two groups according the level of CRP/L (cuf off: median=80,675) and into three groups according the age: ≤ 55; 55–75; >75 years. Only preterminal CRP/L and age were associated with a significantly higher risk of mortality (HR=1.001; p=0.004; HR= 1.071; p<0.0001, respectively) (Figures 3 and 4). No other variables were associated with a significantly higher risk of mortality due to COVID-19 (Table 7).

Correlations Between Inflammatory Markers and Clinical Parameters

Significant correlations between inflammatory markers and clinical parameters are presented in Figures 5 and 6. The analysis revealed a positive correlation between CRP (p=0.029, r=0.115) and CRP/L (p=0.016, r=0.126), and a negative correlation between LCR (p=0.023, r=−0.121) and comorbidities. Interestingly, a positive correlation was observed between CRP and coronary heart disease (p=0.045, r=0.106). IL6 was negatively correlated with hypertension (p=0.044, r=−0.108), tachypnea (p=0.049, r=−0.105), and saturation (p=0.004, r=−0.153). Significant correlations were also found between the CRP/IL6 ratio and pneumonia (p=0.009, r=−0.139).

Table 3 Comparison of Chosen Laboratory Tests Results Between Four Groups of Patients with Covid-19 Divided According to MEWS Classification (Median Value with Q1-Q3)

Covid-19 Severity	1	2	3	4	Anova Kruskal–Wallis Test
WBC x10^3/mm^3	6.43 (4.81–8.25)	7.19 (4.65–7.94)	7.82 (5.04–9.24)	10.81 (5.45–10.37)	**p=0.0419**
Neutrophils x10^3/mm^3	4.68 (3.02–6.68)	5.12 (3.14–6.17)	6.56 (3.63–7.60)	7.30 (3.49–8.47)	**p=0.0147**
Lymphocytes x$10^3$$mm^3$	1.15 (0.81–1.35)	1.32 (0.61–1.33)	1.29 (0.61–1.17)	1.21 (0.47–1.51)	p=0.1473
Monocytes x$10^3$$mm^3$	0.52 (0.28–0.67)	0.61 (0.27–0.60)	0.42 (0.24–0.56)	1.71 (0.27–0.68)	p=0.0980
Eosinophils x10^3/mm^3	0.034 (0.00–0.025)	0.018 (0.000–0.010)	0.020 (0.000–0.010)	0.035 (0.000–0.015)	p=0.5345
Basophils x10^3/mm^3	0.018 (0.010–0.020)	0.016 (0.010–0.020)	0.022 (0.010–0.030)	0.035 (0.010–0.030)	p=0.1387
RBC x10^6/mm^3	4.32 (3.91–4.86)	4.30 (3.97–4.66)	4.22 (3.860–4.660)	4.30 (3.90–4.77)	p=0.6029
PLT x10^3/mm^3	237.54 (160.50–266.00)	202.78 (147.000–248.000)	200.33 (129.00–258.00)	205.25 (127.00–303.00)	p=0.7166
Creatinine mg/dl	0.988 (0.785–1.150)	1.006 (0.780–1.130)	1.05 (0.765–1.18)	1.29 (0.950–1.47)	**p=0.0069**
LDH U/l	420.26 (280.00–493.00)	458.45 (323.000–561.000)	508.70 (350.000–647.000)	535.04 (415.000–667.000)	**p=0.0222**
INR	1.614 (1.080–1.300)	1.796 (1.091–1.280)	3.736 (1.040–1.245)	8.79 (1.060–1.27)	p=0.8885
Fibrinogen mg/dl	477.23 (322.00–605.00)	528.81 (385.00–623.00)	530.73 (384.00–663.00)	557.85 (441.00–623.00)	p=0.2083
D-dimers µg/l	3424.89 (605.50–1639.50)	3197.28 (590.00–1855.00)	3876.705 (638.50–1716.50)	6033.047 (498.00–2603.00)	p=0.9760

Notes: Comparison of chosen results of laboratory tests performed at the day of admission to the hospital between different stages of COVID-19 revealed increasing level pf laboratory parameters with increasing of degree of clinical deterioration. Only in the case of WBC (p=0.0419), neutrophils (p=0.0147), creatinine level (p=0.0069) and LDH activity (p=0.0222) the differences between four analysed groups were statistically significant (the bold values).

https://doi.org/10.2147/JIR.S406658

Table 4 Comparison of Inflammatory Parameters Between Four Groups of Patients with Covid-19 Divided According to MEWS Classification (Median Value with Q1-Q3)

Covid-19 Severity	1	2	3	4	Anova Kruskal–Wallis Test
CRP mg/l	70.25 (12.85–116.67)	81.5 (26.96–123.46)	102.74 (46.57–151.91)	115.11 (55.52–167.85)[acc]	**p=0.0037**
IL6 pg/mL	64.76 (13.31–68.33)	125.4 (22.77–87.5)	223.13 (36.51–138.91)	234.058 (42.71–164.11)	**p<0.0001**
CRP/IL6	2.94 (0.78–1.95)	3.09 (0.63–2.31)	2.385 (0.69–1.95)	1.176 (0.43–1.67)[ab]	p=0.2437
CRP/L	83.92 (11.57–123.75)	127.96 (25.03–146.42)	141.301 (40.35–173.61)	148.77 (47.68–185.72)	**p=0.0065**
LCR	0.125 (0.008–0.075)	0.072 (0.0068–0.040)	0.023 (0.0058–0.024)	0.033 (0.0054–0.028)	**p=0.0072**

Notes: Statistical analysis performed by Anova Kruskal–Wallis test revealed that values of CRP, IL6, CRP/L and LCR between four groups of patients divided according to MEWS classification differ statistically significant: the bold values (p=0.0037, p<0.0001, p=0.0065, p=0.0072 respectively). Statistical analysis performed by Tukey's multiple comparisons test revealed that values of CRP between group 1 vs 4, 2 vs 4, 3 vs 4 and values of CRP/IL6 between group 2 vs 4, 3 vs 4 of patients divided according to MEWS classification differ statistically significant ([a]p<0.05, [b]p<0.01, [c]p<0.001).

Table 5 Areas Under the Curve (AUC) of CRP, CRP/L, LCR, IL6, CRP/IL6 Used to Differentiate Patients with Severe and Non-Severe COVID-19

Parameter	AUC	p-value	Cut-Off	Sensitivity	Specificity	95% Confidence Interval
CRP	0.601	0.0006	75	0.583	0.581	0.543–0.659
CRP/L	0.590	0.0028	88.305	0.569	0.570	0.531–0.648
LCR	0.591	0.0024	0.011	0.573	0.564	0.532–0.65
IL6	0.645	<0.0001	58.8	0.609	0.601	0.588–0.703
CRP/IL6	0.549	0.1165	1.174	0.518	0.516	0.488–0.609

Correlations Between Inflammatory Parameters and Diagnostic Results

CRP (p<0.0001, r=0.269) and IL6 (p=0.001, r=0.166) were positively correlated with WBC values. Significant correlations were also noted between CRP and CRP/IL6 vs platelet counts (p=0.043, r=0.105; p=0.0005, r=0.182 respectively). AST activity was positively correlated with CRP (p<0.0001, r=0.241), CRP/L (p<0.0001, r=0.204), LCR (p<0.0001, r=0.216), IL6 (p<0.0001, r=0.334), and CRP/IL6 (p=0.028, r=0.116). A positive correlation was observed between APTT vs CRP/L (p=0.031, r=0.119) and IL6 (p=0.013, r=0.138), whereas LCR (p=0.039, r=−0.114) was negatively correlated with APTT. Significant correlations were also found between PT and INR vs CRP (p<0.0001, r=0.257; p<0.0001, r=0.255), CRP/L (p<0.0001, r=0.242; p<0.0001, r=0.243), LCR (p<0.0001, r=−0.237; p<0.0001, r=−0.239), and IL6 (p<0.0001, r=0.254; p<0.0001, r=0.233). Positive correlations were also observed between total bilirubin vs CRP (p=0.003, r=0.167, CRP/L (p=0.021, r= 0.131), and IL6 (p=0.002, r=0.171). LCR was negatively correlated with total bilirubin (p=0.017, r=−0.136), creatinine kinase (p=0.003, r=0.225), fibrinogen (p<0.0001, r=−0.562), ferritin (p<0.0001, r=−0.279), creatinine (p=0.009, r=−0.135), and LDH (p<0.0001, r=−0.389). A positive correlation was observed between CRP vs total bilirubin (p=0.003, r=0.167), creatinine kinase (p=0.001, r=0.253), D-dimer (p=0.015, r=0.127), fibrinogen (p<0.0001, r=0.684), ferritin (p<0.0001, r=0.311), creatinine (p=0.002, r=0.160), and LDH (p<0.0001, r=0.395). CRP/L was correlated with total bilirubin (p=0.021, r=0.131), creatinine kinase (p=0.003, r=0.226), fibrinogen (p<0.0001, r=0.562), ferritin (p<0.0001, r=0.279), creatinine (p=0.007, r=0.139), and LDH (p<0.0001, r=0.386). Significant correlations were also noted between fibrinogen vs IL6 (p<0.0001, r=0.341) and CRP/IL6 (p<0.0001, r=0.265). IL6 was also positively correlated with total bilirubin (p=0.002, r=0.131), creatinine kinase (p=0.003, r=0.226), D-dimer (p=0.02, r=0.121), ferritin (p<0.0001, r=0.328), creatinine (p<0.0001, r=0.215), LDH (p<0.0001, r=0.408), and urea (p=0.001, r=0.176).

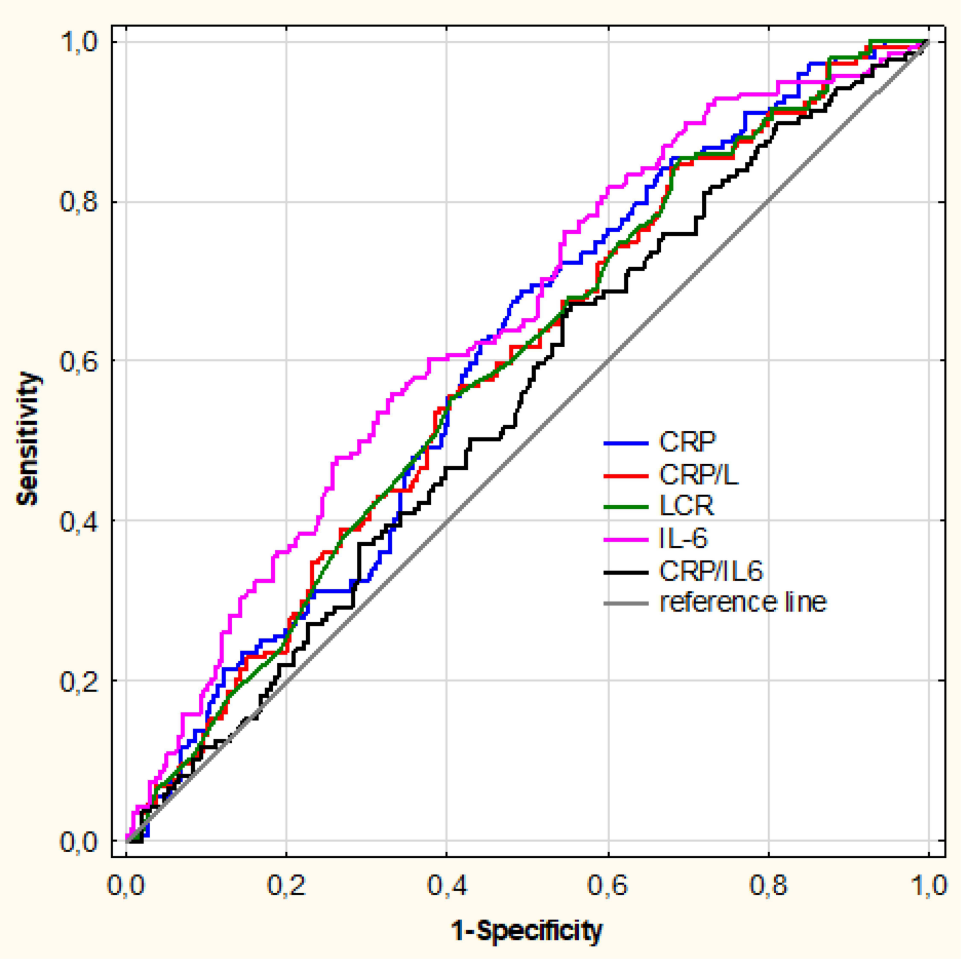

Figure 1 Receiver operating characteristic (ROC) curves of CRP, CRP/L, LCR, IL6, CRP/IL6 used to differentiate patients with severe and non-severe COVID-19.

Discussion

Scoring indexes for diagnosing disease severity are highly useful for assessing the patients' health status. More than three years after the outbreak of the COVID-19 pandemic, a scoring system for evaluating disease severity in this group of patients has not yet been developed.[23–26] The clinical state of hospitalized COVID-19 patients is evaluated with the use of generic scoring systems, such as the MEWS.[27] This study was undertaken to determine the presence of correlations between the severity of COVID-19 symptoms based on the MEWS and inflammatory markers. The results confirmed other authors' findings and demonstrated that the concentrations of two inflammatory markers (CRP and IL6) increased with the severity of COVID-19 symptoms classified based on the MEWS.

Numerous researchers have described the correlations between the concentrations of CRP and IL6 vs the severity of COVID-19,[28–30] but the patients' condition had not been evaluated based on the MEWS. According to Montesarchio et al.[18] IL6 is an effective predictor of disease severity and CRP could be a potential biomarker of response to treatment. In turn, Basina et al[31] observed that very high CRP (> 100 mg/l) in patients with COVID pneumonia upon hospital admission is an independent discriminator of critical illness. In patients with moderate and severe COVID-19, CRP could be a predictor of disease progression because the risk of disease severity increases 10-fold when CRP exceeds 53 mg/l. Similar observations were made by Liu et al[32] who reported that the probability of severe COVID-19 complications increases in patients with IL6 > 32.1 pg/mL or CRP > 41.8 mg/l. The cited authors concluded that these parameters can be used as independent indicators of disease severity. In the present study, CRP and IL6 levels rose with an increase in COVID-19 severity assessed based on the MEWS, which suggests that these markers can be considered effective tools

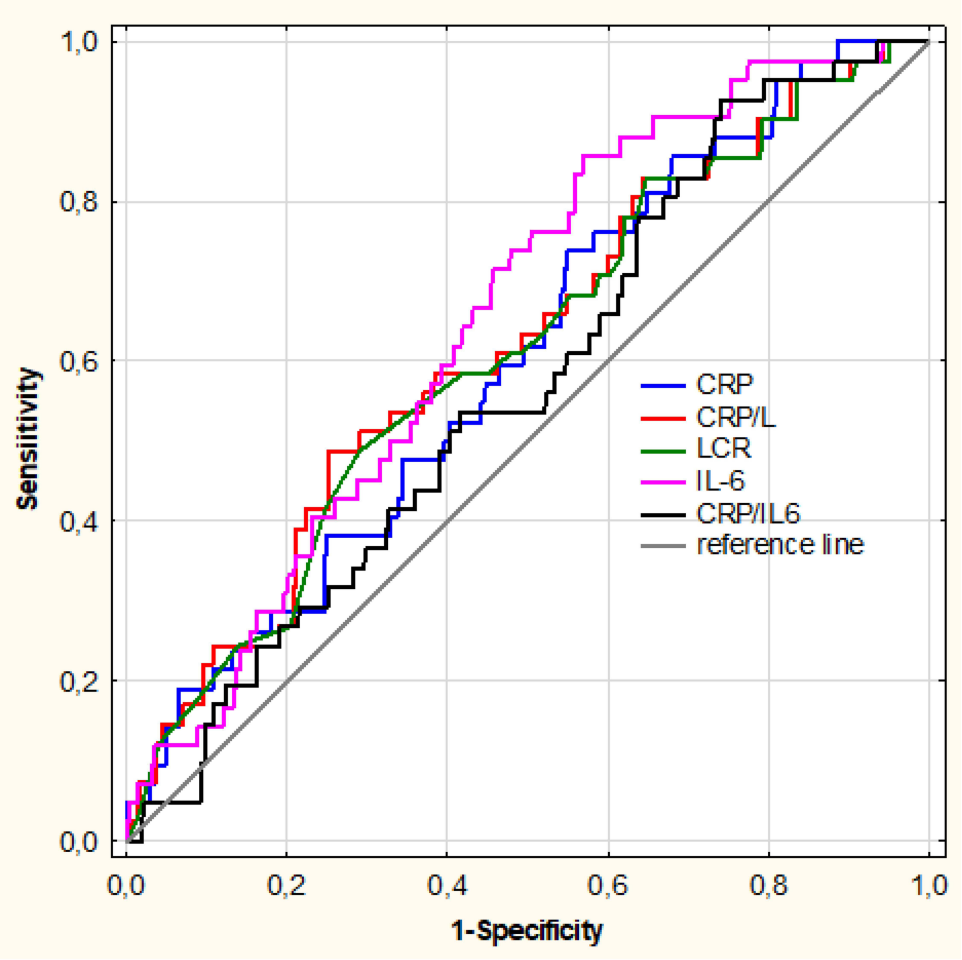

Figure 2 Receiver operating characteristic (ROC) curves of CRP, CRP/L, LCR, IL6, CRP/IL6 in predicting death in patients with COVID-19.

for evaluating disease progression. The results of this study also confirmed the diagnostic value of CRP and IL6 for differentiating between patients with mild and severe COVID-19.[30,31]

According to the literature, IL6 is a good predictor of mortality, in particular in COVID-19 patients with acute respiratory failure.[33,34] Increased counts of Th1 lymphocytes which secrete large amounts of the granulocyte-macrophage colony-stimulating factor (GM-CSF) and interferon-γ (IFN- γ), as well as elevated levels of CD14+ and CD16+ monocytes secreting excessive

Table 6 Areas Under the Curve (AUC) of CRP, CRP/L, LCR, IL6, CRP/IL6 in Predicting Death in Patients with COVID-19

Parameter	AUC	p-value	Cut-Off	Sensitivity	Specificity	95% Confidence Interval
CRP	0.604	0.0178	76.34	0.595	0.537	0.518–0.69
CRP/L	0.619	0.0099	89.816	0.610	0.538	0.529–0.71
LCR	0.612	0.0158	0.009	0.585	0.580	0.521–0.703
IL6	0.652	0.0001	64.9	0.643	0.580	0.573–0.73
CRP/IL6	0.57	0.1087	1.045	0.537	0.537	0.484–0.656

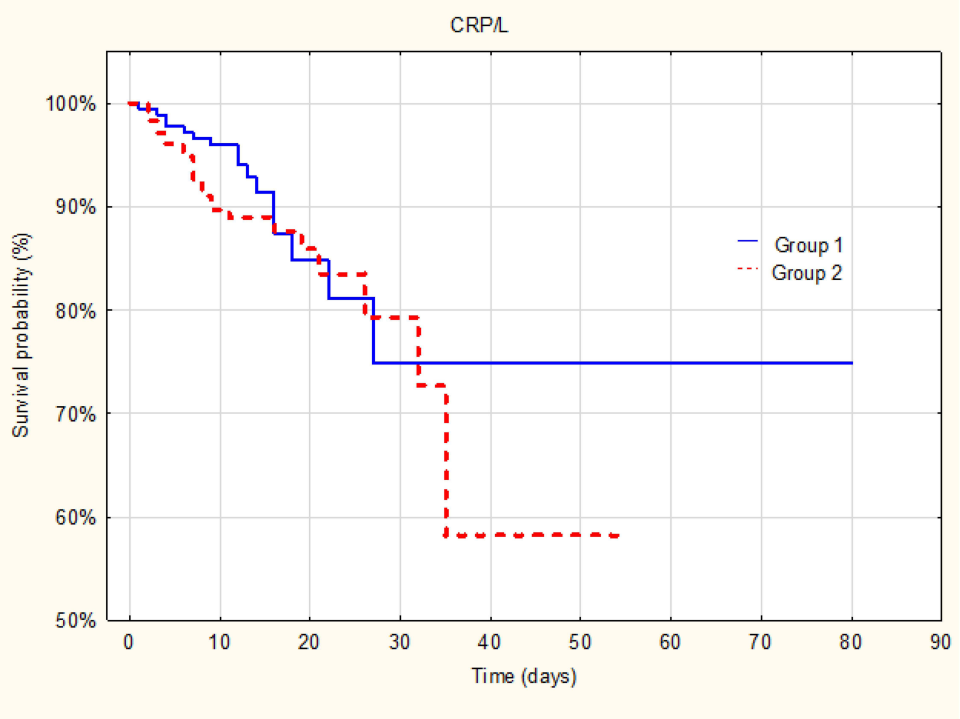

Figure 3 Association of CRP/L with the COVID-19 mortality.

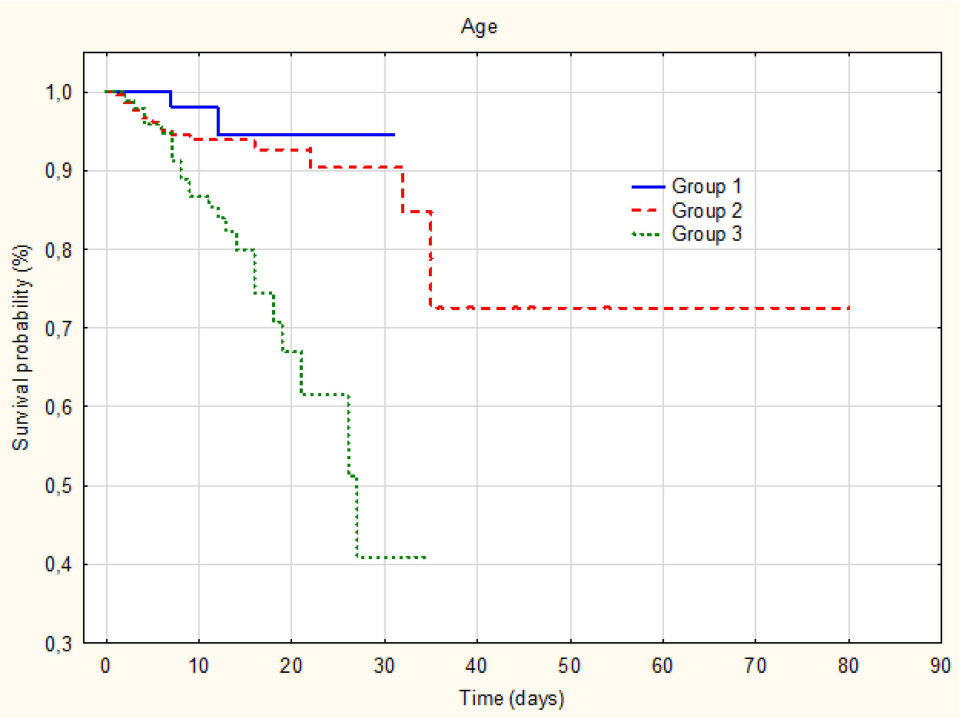

Figure 4 Association of age with the COVID-19 mortality.

Table 7 Association of Inflammatory Biomarkers Results with the COVID-19 Mortality

Variables	HR (95% CI)	*p*
CRP/L	1.001 (1.000–1.002)	0.004
CRP/IL-6	0.8371 (0.0648–1.080)	0.172
Age	1.071 (1.038–1.104)	<0.0001
Diabetes	0.903 (0.588–1.385)	0.639
Hypertension	1.006 (0.490–2.066)	0.985
Obesity	2.627 (0.958–7.204)	0.060
Cardiovascular diseases	1.083 (0.522–2.248)	0.830

quantities of IL6 were observed in patients with severe COVID-19. These cells are associated with a physiological reaction known as the cytokine storm.[35,36] Recent research has demonstrated that the acute respiratory distress syndrome (ARDS) is the main cause of death in patients with COVID-19.[4] A cytokine storm is a systemic inflammatory response which leads to the

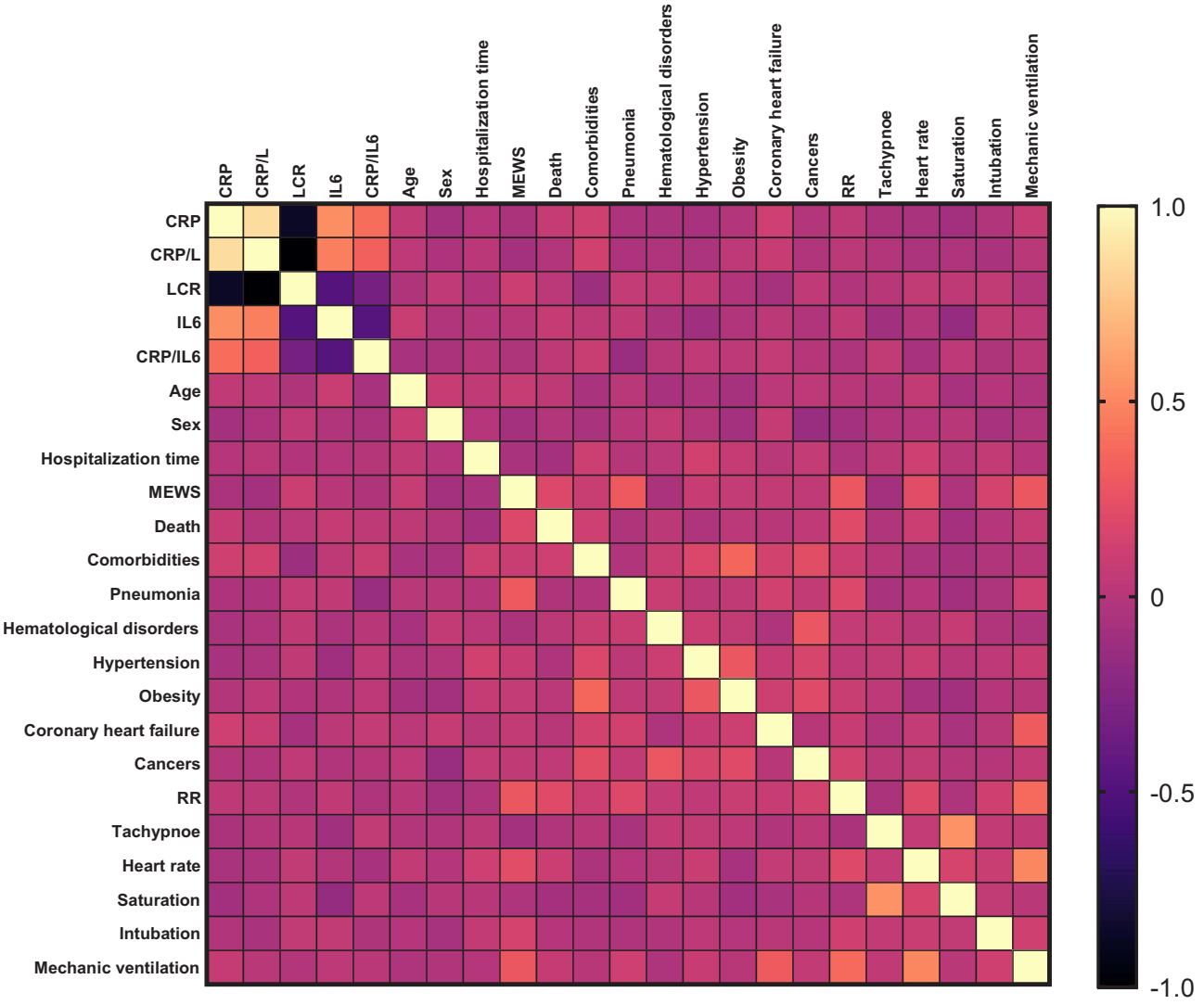

Figure 5 Heat map of correlation chosen inflammatory parameters with clinical parameters.

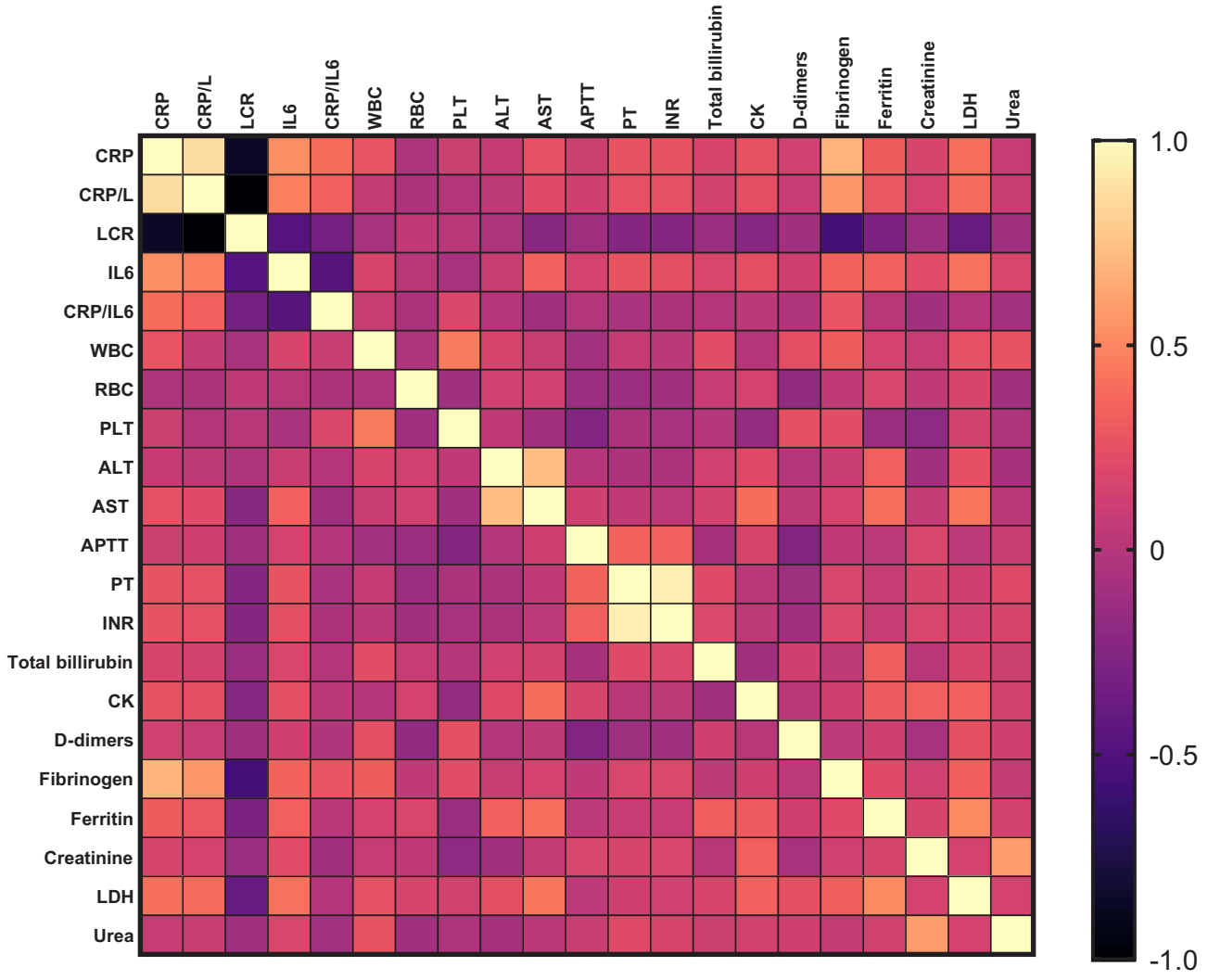

Figure 6 Heat map of correlation chosen inflammatory parameters with laboratory tests results.

overproduction and uncontrolled release of pro-inflammatory cytokines, including IL6, from effector cells in patients infected with SARS-CoV-2.[36] The results of the current study also indicate that IL6 is the most reliable parameter for assessing disease severity and the risk of COVID-19-related death ($p<0.0001$).

According to many researchers, CRP is a good parameter for assessing inflammatory states and the risk of mortality in patients infected with the SARS-CoV-2 virus.[37–39] In the work of Velavan et al,[40] the median concentration of CRP was estimated at 40 mg/l in COVID-19 convalescents and at 125 mg/l in patients who died from COVID-19 complications, which indicates that CRP is a reliable predictor of disease severity and progression. The results of the present study confirm this observation because CRP concentration increased with disease severity assessed based on the MEWS and was a useful indicator for differentiating patients with mild and severe COVID-19 and predicting the risk of mortality.

In this study, CRP/L and LCR differed significantly in their diagnostic value for predicting the severity of SARS-CoV-2 infection according to the MEWS, discriminating between mild and severe disease progression, and predicting the risk of death. Eissa et al[41] also reported that CRP/L could be a useful indicator for assessing the inflammatory status of COVID-19 patients and predicting mortality. In turn, Erdogan et al[23] found that LCR was a reliable predictor for distinguishing between mild and severe cases of COVID-19. Other researchers also remarked that LCR and CRP/L play an important role in diagnosing COVID-19, but none of these studies evaluated the patients' status based on the MEWS.[24–26]

Elevated D-dimer levels and the correlations between this parameter and CRP and IL6 concentrations in patients with severe COVID-19 should also be considered when assessing the diagnostic value of inflammatory markers. According to research, D-dimer values higher than 1 μg/mL increase the risk of death in adult COVID-19 patients with pneumonia.[27,42,43] This parameter was found to be correlated with severe disease progression and mortality. These results suggest that D-dimer could be an early marker of disease progression and a useful tool for guiding treatment in COVID-19 patients.[26] Also the presence of lymphopenia is a useful predictor of COVID-19 severity.[15,44–46] Association between disease severity and lymphopenia is reported in studies. Lymphopenia was more frequent in moderate and severe disease.[44,45,47,48]

Comorbidities undoubtedly influence the progression of COVID-19.[49] In this study, CRP was positively correlated with heart failure and negatively correlated with hypertension in hospitalized COVID-19 patients. Similar relationships were reported by other authors,[50,51] and elevated IL6 levels were also found to be associated with heart disease.[52,53] In the current study, a significant correlation was also noted between the CRP/IL6 ratio and pneumonia in COVID-19 patients. The diagnostic value of IL6 in patients with pneumonia was also recognized by other researchers.[13,54]

The limitation of our study is the fact that it is single-center and retrospective (time between November 2020 to November 2021). We observed more severe course of COVID-19 disease and a higher mortality rate of a higher percentage of patients at the beginning of pandemic than today (2023). However, the SARS-CoV-2 virus is still present and causes the symptomatic disease of varying severity of symptoms. For this reason our study is still current.

Conclusions

The present study demonstrated that CRP, IL6, CRP/IL6, CRP/L, LCR inflammatory markers increase significantly with disease progression assessed based on the MEWS in COVID-19 patients. These parameters can also be useful for assessing the risk of COVID-19 mortality and differentiating between patients with mild and severe disease symptoms. The results of this study can contribute to improvements in diagnosis, treatment, and predictions of disease progression in patients infected with the SARS-CoV-2 virus.

Data Sharing Statement

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

Institutional Review Board Statement

The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Bioethics Committee of Medical University of Bialystok, Poland (Permission number No APK.002.353.2021).

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Disclosure

The authors declare no conflicts of interest in this work.

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