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THE ROLE OF INFLAMMATORY INDICES IN PREDICTING THE SEVERITY OF COVID-19

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Doi: https://doi.org/10.52340/jecm.2024.05.08

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ანთებითი ინდექსების როლი COVID-19 სიმწვავის პროგნოზირებისთვის

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რეზიუმე

COVID-19-ის გლობალურმა პანდემიამ, რომელიც გამოწვეულია ახალი კორონავირუსით SARS-CoV-2-ით, ჯანმთელობის უპრეცედენტო დაზიანება და მრავალფეროვანი გართულებები გამოიწვია. COVID-19-ის მართვაში მნიშვნელოვანი დაბრკოლება დაავადების გამოვლინებისა და პროგრესირების სწრაფი ცვალებადობა და კომპლექსურობა აღმოჩნდა. ცნობილია, რომ ანთებითი მარკერების (NLR - ნეიტროფილებისა და ლიმფოციტების თანაფარდობა, PLR - თრომბოციტებისა და ლიმფოციტების თანაფარდობა, SII - სისტემური ანთების ინდექსი), დამაჯერებელ და მნიშვნელოვან როლს თამაშობს სხვადასხვა დაავადების (კიბო, ინფექციური და აუტოიმუნური დარღვევები) სიმძიმის, მათ შორის კოვიდ-19-ის პროგნოზირებაში. წინამდებარე რეტროსპექტული კვლევის მიზანი სწორედ ლაბორატორიულად დადასტურებულ 100 კოვიდ-19-ის მქონე პაციენტის ანთებითი მარკერებისა და დაავადების კლინიკური მიმდინარეობის კავშირის შესწავლა გახლდათ საქართველოს პოპულაციაში. პაციენტები დაყოფილ იქნა მსუბუქ, საშუალო და მძიმე კატეგორიებად, კლინიკურ-ლაბოლატორიული პარამეტრებისა და CT ქულის საფუძველზე. ანთებითი მარკერები (NLR, PLR, SII), სხვა ბიომარკერებთან ერთად, გაზომილი და გაანალიზებული იყო სტატიტიკური მეთოდებით. ანალიზის შედეგად გამოვლინდა, რომ C რეაქტიული ცილა, ფერიტინი და ლეიკოციტების რაოდენობა სტატიტიკურად სარწმუნოდ მატულობს მძიმე მიმდინარეობისას. განსაკუთრებით მნიშვნელოვანი სხვაობა დაფიქსირდა NLR, SII მაჩვენებლებში სხვადასხვა სიმძიმის კლინიკური მიმდინარეობისას ($p<0.01$). კვლევის შედეგად დადგინდა, რომ NLR, PLR და SII COVID-19-ის სიმძიმის მნიშვნელოვანი პრედიქტორია და სრულად ასახავს სისტემური ანთებითი პასუხის მასშტაბებს. ამდენად, ამ მარკერების გამოყენება კლინიკურ პრაქტიკაში კლინიკურად პაციენტების დამძიმების მქონე ჯგუფების გამოყოფის საშუალებას მოგვცემს, რაც საბოლოოდ ხელს შეუწყობს პაციენტების ადეკვატურ მკუნალობას და გააუმჯობესებს დაავადების გამოსავალს.

Introduction. The COVID-19 pandemic, caused by SARS-CoV-2, has posed significant health challenges worldwide. One major difficulty in managing COVID-19 is the unpredictable nature of the disease's progression and presentation. This has created an urgent need for reliable methods to predict patient outcomes. In ammatory markers such as the neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), and systemic in ammation index (SII) have been identified as valuable tools in predicting the severity of various diseases, including COVID-19.

Previous studies have demonstrated that these markers can reflect the systemic in ammatory response, which is crucial in viral infections. This study aims to investigate the relationship between these indices and the severity of COVID-19, thereby establishing their potential use in clinical practice.

Since the emergence of SARS-CoV-2, it has been known to trigger a significant in ammatory response, resulting in severe respiratory and systemic complications in some patients. Indices like NLR and PLR have been studied in other respiratory illnesses, such as influenza, where they correlate with

disease severity and mortality. NLR is a recognized marker of systemic in ammation associated with poor outcomes in conditions like cardiovascular diseases and cancer.

PLR is another marker for assessing disease severity and prognosis, particularly in cancer. High PLR levels often indicate an in ammatory response linked to worse outcomes in infectious diseases. SII, calculated from platelet, neutrophil, and lymphocyte counts, offers a comprehensive view of the body's in ammatory state. Although its role in infectious diseases is still under investigation, preliminary studies suggest its utility in predicting infection severity.

COVID-19's immune response involves a significant in ammatory phase, leading to severe complications like acute respiratory distress syndrome (ARDS) and multi-organ failure. Cytokine storms and systemic inflammation drive this response. Various studies have highlighted the importance of systemic inflammatory markers in infectious diseases, including sepsis, cancer, and cardiovascular diseases. In the context of COVID-19, NLR, PLR, and SII may reflect the intensity of the systemic in ammatory response, which correlates with disease severity.

Material and methods. The study was conducted at the Emergency Cardiology Center named after Academician G. Chapidze from 2021 to 2022. Inclusion criteria were patients with cardiovascular disease who had laboratory-confirmed COVID-19 and were hospitalized.

The study included 100 COVID-19 patients with varying severities. Severe cases were identified by symptoms such as dyspnea, respiratory rate >25 breaths per minute, oxygen saturation <92% on room air at rest, or a CT score of 12 or greater (indicating >50% lung damage). A comprehensive panel of laboratory tests was performed, including measurements of blood glucose, alanine aminotransferase, aspartate aminotransferase, creatinine, lactate dehydrogenase, prothrombin time, prothrombin index, international normalized ratio, activated partial thromboplastin time, brinogen concentration, D-dimer, troponin, C-reactive protein, procalcitonin, and ferritin. Electrolytes were also determined. SARS-CoV-2 detection was conducted using PCR from throat and nose swabs.

Statistical analysis. Results were analyzed using modern statistical software. The analysis included calculating averages and standard deviations of studied parameters. Patients were categorized by gender and age into mild, moderate, and severe groups based on symptom severity and CT scores. The critical indices calculated were NLR, PLR, ENR, and SII. Logistic regression was used to determine the association between in ammatory indices and disease severity, while ANOVA compared means among different severity groups.

Results:

Demographics and Baseline Characteristics. The study included 100 patients diagnosed with COVID-19, divided into three groups: mild (n=60), moderate (n=19), and severe (n=21) cases based on clinical symptoms and CT scores.

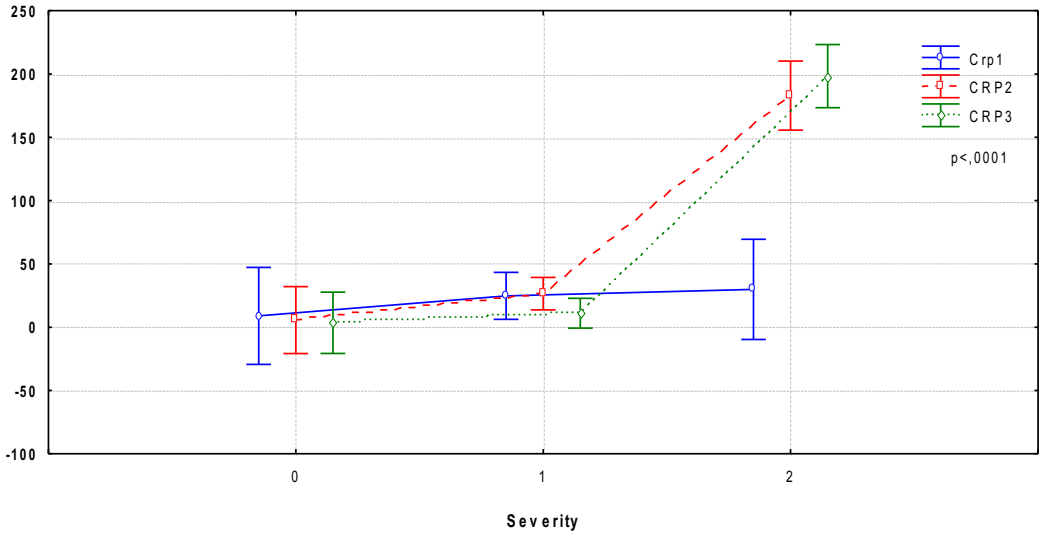
Table 1. Demographics and Baseline Characteristics

	Frequency	Mean	Std. Deviation	Minimum	Maximum
age	19	70.54	12.38	42	93
	60	52.62	18.64	18	82
	21	74.33	12.86	52	91
Hospitalization	19	9.05	3.2	1	16
	60	6.91	2.73	3	19

	Frequency	Mean	Std. Deviation	Minimum	Maximum
	21	18.08	9.18	7	32
CT score	19	10.1	3.76	3	21
	60	5.38	2.19	1	15
	21	13.67	3.65	9	20
procalcitonin	19	0.13	0.15	0.03	1
	60	0.12	0.16	0.03	1
	21	0.13	0.06	0.03	0.2
Fever	19	37.76	0.91	37	40
	60	37.36	0.48	37	38
	21	38	0.95	37	39
saturation	19	92.43	4.34	80	98
	60	93.21	3.54	87	98
	21	88.08	5.37	80	96
Creatinine	19	36.71	79.88	0.5	315
	60	1.07	0.4	0.54	2.02
	21	1.46	1.1	0.76	4.78
ALT	19	28.28	20.59	0.5	98
	60	1357.67	7734.4	7.3	45130
	21	145.08	443.46	0.5	1553
AST	19	29.05	12.9	0.8	56
	60	1351.95	7703.06	11.1	44947
	21	128.14	372.02	0.9	1309
Dimer	19	0.91	0.96	0.14	5.16
	60	0.52	0.46	0.12	2.33
	21	1.17	1.22	0.3	4.8
troponin	19	0.05	0.09	0	0.5
	60	0.05	0.06	0	0.14
	21	0.1	0.12	0	0.38

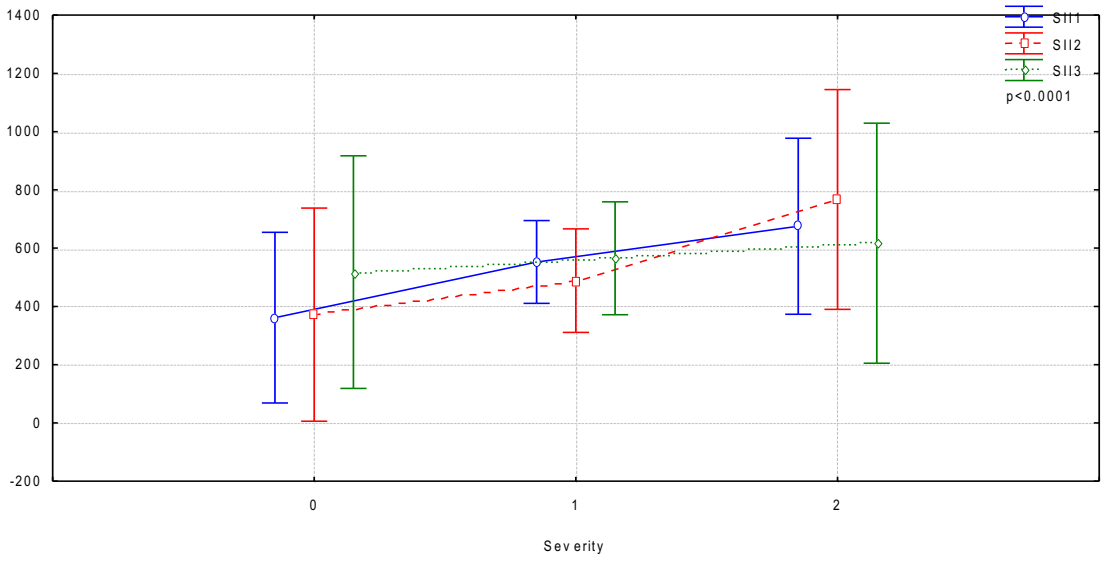
Multiple rounds of testing for in ammatory indices and other biomarkers revealed significant findings across different severity groups. CRP levels were consistently higher in severe cases across three measurement points (CRP1, CRP2, CRP3, $p < 0.01$, Figure 1)

Figure 1. CRP Levels Across COVID-19 Severity



Ferritin levels varied significantly, dramatically higher in severe cases ($p<0.001$). The substantial increase in FERIT3 among severe patients suggests a correlation with heightened in ammatory responses. Total leukocyte counts (Leucocyt1, Leuco2, Leuco3) were notably higher in severe cases, with Leucocyt1 showing statistically solid significance ($p <0.001$). Lymphocyte counts remained stable across groups, while neutrophil counts (Neutro1, Neutro2, Neutro3) and the Neutrophil-to-Lymphocyte Ratio (NLR) were higher in severe cases, indicating more pronounced in ammatory responses (NLR1: $p<0.05$, NLR2: $p< 0.01$). Platelet counts (Plat1, Plat2, Plat3) did not significantly differ across severity groups.

Figure 2. Comparison of Systemic Inflammatory Indices (SII1, SII2, SII3) Across COVID-19 Severity Levels



The systemic inflammatory index (SII) values varied significantly across groups, especially between initial and subsequent measurements (SII1: $p<0.0001$, SII2: $p<0.001$). Fig.2 Saturation levels were significantly lower in severe cases at initial (saturation1: $p<0.01$) and final stages (Satur3: $p = 0.01$), suggesting declining pulmonary function correlating with disease severity. Other markers such as LDH, creatinine, ALT, and AST showed no significant correlation with COVID-19 severity.

Discussion. Elevated NLR in severe cases supports the hypothesis that a higher neutrophil count relative to lymphocytes indicates systemic inflammation and immune system dysregulation. This

dysregulation can exacerbate cytokine storms, which are critical in severe disease states. NLR serves as a simple yet effective biomarker for in ammation.

Consistent and significant CRP levels across various measurement points reinforce its role as an acute-phase reactant. Elevated CRP levels indicate acute in ammatory responses, strongly correlating with COVID-19 severity and potential complications.

These findings have several implications. Integrating these in ammatory indices into routine clinical assessments can significantly enhance the predictive accuracy of COVID-19 severity. This allows healthcare providers to stratify patients based on their risk of severe complications, optimizing resource allocation and improving patient outcomes through targeted therapeutic strategies.

For instance, patients with high SII or NLR could receive more aggressive monitoring and treatment, including early anti-inflammatory therapies or enrollment in clinical trials for novel treatments. Recognizing patterns in CRP elevations can help manage complications before they escalate.

Despite promising results, this study has limitations due to its retrospective nature and limited sample size, which may affect generalizability. The single-center design may not fully capture variability in clinical practices or patient populations. Future research should validate these findings in more extensive multicenter studies with diverse populations to enhance external validity. Prospective studies could provide more insights into these in ammatory indices' dynamics and their causal relationships with COVID-19 outcomes. Investigating the mechanistic pathways through which these indices correlate with the inflammatory response to COVID-19 could reveal new therapeutic targets. Understanding these markers' biological basis may lead to developing more predictive novel biomarkers for disease severity.

Conclusion. This study highlights the significant prognostic value of inflammatory indices, especially SII, in predicting COVID-19 severity. Regular use of these indices in clinical settings provides a practical approach to categorizing patient risk and enhances disease management. By identifying high-risk patients early, clinicians can tailor interventions more effectively, potentially reducing COVID-19's impact on patients and healthcare systems. Healthcare systems should consider the broader incorporation of these biomarkers in clinical assessments. Predictive tools like these will be crucial in combating the disease and improving patient outcomes as the pandemic evolves.

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THE ROLE OF INFLAMMATORY INDICES IN PREDICTING THE SEVERITY OF COVID-19

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SUMMARY

The global pandemic of COVID-19, caused by the novel coronavirus SARS-CoV-2, has resulted in unprecedented health challenges. A significant obstacle in managing COVID-19 is the variability in disease presentation and progression, necessitating the development of reliable methods to predict patient outcomes. It is supposed that inflammatory markers (NL - neutrophil and lymphocyte ratio, PLR - thrombocyte and lymphocyte ratio, SII - systemic inflammation index) can be used to predict different types of disorders (cancer, infectious and autoimmune diseases). The present retrospective study aimed to reveal the relationship between inflammatory markers and the onset and prognosis of disease. Patients (100 hospitalized and PCR-confirmed) were divided into mild, moderate, and severe categories based on control-laboratory parameters and CT scores. Inflammatory markers (NLR, PLR, SII), along with other biomarkers, were measured and analyzed by statistical methods. As a result of the analysis, it was revealed that C-reactive protein, ferritin, and the number of leukocytes statistically significantly increased during the course. The outcomes show that NLR, PLR, and SII are significant predictors of the severity of COVID-19 and fully reflect the systemic in ammatory response ($p<0.01$). Thus, their integration (NLR< PLR< SII) into clinical practice can enhance risk stratification and inform therapeutic decisions, ultimately improving patient outcomes.

Keywords: COVID-19, SARS-CoV-2, neutrophil, lymphocyte, platelet, ratio, SII