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Longitudinal Impact of IL-6 on Cardiovascular Outcomes in COVID-19 Patients: Comparative Analysis During Hospitalization and at Six-Month Follow-Up

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ABSTRACT

Background: The COVID-19 pandemic has underscored the interconnection between infectious diseases and cardiovascular health, revealing a significant increase in acute coronary syndrome (ACS) and other cardiovascular complications among those severely affected by the virus. Recent studies have indicated that the systemic inflammation triggered by COVID-19, mainly through cytokines such as interleukin-6 (IL-6), is critical in exacerbating these complications. IL-6 mediates the acute inflammatory response and influences long-term cardiovascular outcomes. Understanding these mechanisms is crucial for managing the long-term health of COVID-19 survivors, especially in regions like Georgia, where cardiovascular diseases are prevalent.

Objectives: This study aims to elucidate the predictive role of IL-6 in long-term cardiovascular outcomes post-COVID-19, explicitly focusing on the development of acute coronary syndrome. By comparing IL-6 levels in patients with and without ACS during their hospitalization and following up six months post-recovery, the research seeks to identify patterns that could guide more effective clinical interventions and long-term patient management strategies. Additionally, the study investigates whether elevated IL-6 levels during acute COVID-19 are associated with increased cardiovascular risk, helping to shape targeted approaches for patient care and recovery.

Methods: Conducted at the Chapidze Heart Hospital in Tbilisi, Georgia, this retrospective cohort study included 100 RT-PCR-confirmed COVID-19 patients aged 40 to 80. IL-6 levels were measured thrice upon hospitalization, within one week post-hospitalization, and before discharge. Patients were monitored for six months to assess the development of ACS. Statistical analyses included Mann-Whitney U tests for between-group comparisons and repeated measures ANOVA for longitudinal analysis.

Results: Our findings indicate significant differences in IL-6 levels between the ACS and non-ACS groups during hospitalization, with elevated levels persistently associated with worse cardiovascular outcomes. Six months post-recovery, patients in the ACS group continued to exhibit higher IL-6 levels, suggesting a sustained inflammatory response. Additionally, ischemic patients demonstrated more severe clinical features, such as more extended hospital stays and higher rates of thrombotic events. Despite these trends, the high variability in IL-6 and other inflammatory markers like ferritin and leukocyte counts underscored the complex nature of their relationship with ACS development.

Conclusions: Elevated IL-6 levels during and following hospitalization indicate a higher risk of developing ACS, underscoring the importance of monitoring inflammatory markers for long-term cardiovascular risk assessment. However, the variability in these markers highlights the need for a comprehensive approach to patient evaluation, incorporating multiple biomarkers and clinical data to effectively stratify and manage risk in post-COVID-19 patients. These results emphasize the dynamic interplay of inflammation and cardiovascular disease in COVID-19 recovery and call for further research into targeted interventions to mitigate these risks.

Keywords: Acute coronary syndrome; cardiovascular outcomes; COVID-19; Inflammatory biomarkers; interleukin-6.

BACKGROUND

Acute coronary syndrome (ACS), myocardial injury, cardiac arrest, and pulmonary thromboembolism have been extensively documented among patients with severe manifestations of COVID-19 and are associated with poor clinical outcomes.[1,2] Myocardial injury has been observed in approximately 20–30% of hospitalized COVID-19 patients, particularly those presenting with electrocardiographic features indicative of ST-segment elevation myocardial infarction (STEMI).[3] The primary therapeutic approach for diagnosing and managing ACS is restoring coronary blood flow via percutaneous coronary intervention (PCI). However, this intervention risks post-procedural heart failure with reduced ejection fraction (HFrEF).[4] Recent observations have emphasized that COVID-19 patients can often operate in a state of high systemic inflammation, marked by the exaggerated release of proinflammatory cytokines, including notably heightened levels of interleukin-6 (IL-6), IL-8, and tumor necrosis factor-alpha (TNF-α). These cytokines lead to life-threatening complications.[5,6] High levels of IL-6 correlate with severe progression of COVID-19 and aggravation of the viral infection at the cellular level.[7]

Furthermore, COVID-19-induced systemic inflammation has been implicated in myocardial injury, with C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and creatinine being the primary biomarkers of this

process.[8] Previous studies conducted by Moccia et al. have demonstrated that among COVID-19 patients, IL-6 levels are significantly elevated in non-survivors, and higher rates of acute cardiac injury and acute heart failure are associated with increased IL-6 concentrations, underscoring IL-6 as a pivotal mediator of myocardial injury in this population.[9] The present study investigates post-recovery COVID-19 patients with persistently elevated IL-6 levels in Georgia, a European region with an exceptionally high prevalence of cardiovascular diseases, including ACS. The primary objective was to elucidate the pathophysiological progression leading to ACS, given previous findings that link IL-6 to an elevated risk of atherosclerosis.

The study aims to identify risk factors associated with clinical outcomes (disposition, intensive care needed, mortality) by comparing hospitalized patients with and without HF. Comprehending the interplay is crucial for optimizing patient care, especially in cohorts at higher risk of worse outcomes. The purpose of this research also focuses on reviewing the specific events that make COVID-19 a risk in HF patients, such as systemic inflammation, myocardial injury, and decompensated cardiac function.[8]

METHODS

The study was conducted at the Chapidze Heart Hospital in Tbilisi, Georgia. It included 100 patients aged between 40 and 80 years who exhibited symptoms of COVID-19 and had a diagnosis confirmed by RT-PCR. The inclusion criteria were laboratory-confirmed COVID-19 infection and hospitalization. Disease severity was classified based on symptoms, respiratory rate, oxygen saturation, and CT scores indicative of lung damage. The Ethics Commission of Tbilisi State Medical University approved the study, which adheres to the Declaration of Helsinki. Informed consent was obtained from all participants.

Cytokine and Other Clinical Laboratory Parameters

Serum interleukin-6 (IL-6) levels were measured using an electrochemiluminescence immunoassay with a Roche Cobas e411 analyzer (Hoffmann-La Roche Ltd, Switzerland). The detection limits for IL-6 ranged from 1.5 pg/ml to 5000 pg/ml without pre-dilution. IL-6 levels were assessed at three-time points: upon hospitalization, within 1-week post-hospitalization, and before discharge. A comprehensive set of laboratory tests was also performed, including measurements of alanine aminotransferase, aspartate aminotransferase, creatinine, lactate dehydrogenase, prothrombin time, PI prothrombin index, international normalized ratio, activated partial thromboplastin time, fibrinogen concentration, D-dimer, troponin, C-reactive protein, procalcitonin, ferritin, and complete blood count (CBC). These tests utilized state-of-the-art equipment, ensuring high reliability and accuracy.

Statistical analyses were conducted using STATISTICA software (Statsoft, Inc., USA). The analysis included several stages: Preliminary descriptive statistics (mean±SD) and Stratification of patients by gender and age. The Kolmogorov-Smirnov and Lilliefors tests assessed the normal distribution of cytokine levels. Given the skewed distribution of these data, biochemical markers were log-transformed to correct for non-normality before further analysis. Any outlier values (≥4 SD) were excluded from subsequent analyses. Differences in cytokine levels between male and female groups were analyzed using the Mann-Whitney U test. Two-way repeated measures ANOVA was employed to assess differences over time, with a p-value of ≤0.05 considered statistically significant. Long-term Follow-up: After recovery, a six-month follow-up was conducted for patients with elevated IL-6 and other inflammatory markers during their hospital stay. This phase aimed to observe the development of acute coronary syndrome (ACS) in this high-risk group, enhancing our understanding of the long-term cardiovascular consequences of COVID-19.

RESULTS

The analysis revealed significant differences in several key parameters between ischemic and nonischemic patients. Ischemic patients had a more extended hospital stay (10.78±6.9 days) compared to nonischemic patients (8.47±4.38 days), with borderline statistical significance (p=0.050). This suggests that ischemic patients may experience more complications or require prolonged medical intervention. The CT score, representing lung involvement, was higher in ischemic patients (9.58±4.9) than in nonischemic patients (8.00±3.83), though this difference was not statistically significant (p=0.0989). IL-6 levels were consistently higher in ischemic patients at all three-time points, with a statistically significant difference at the second measurement (p=0.0421), indicating a heightened inflammatory response in ischemic patients. Despite the elevation of CRP levels in ischemic patients, no significant difference was observed across time points. Ferritin levels were also increased in ischemic patients, though not to a statistically significant extent. Leukocyte counts were significantly higher in ischemic patients at the first (p=0.0026) and second (p= 0.0310) time

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points, suggesting an early and more intense inflammatory response in this group. Oxygen saturation was consistently lower in ischemic patients, with statistically significant differences at the second (p=0.0383) and third (p=0.0011) time points, suggesting more pronounced hypoxia. At the second measurement, D-dimer levels were also significantly higher in ischemic patients (p = 0.0031), indicating increased thrombotic activity (Tab.1).

TABLE 1. Comparative analysis of clinical and laboratory parameters in ischemic and nonischemic patient cohorts

Parameters	Mean ± SD		p
	non-ischemic	Ischemic	
Hospitalization (days)	8.47±4.38	10.78±6,9	0.050
CT score	8.00±3.83	9.58±4,9	0.0989
Interleukin 6[1]	27.7±33.50	31.42±41,9	0.6208
Interleukin 6[2]	89.91±303.96	336.34±742,0	0.0421
Interleukin 6[3]	124.74±736.67	505.00±1782,1	0.2038
C-reactive protein[1]	38.07±50.46	33.65±42,0	0.6697
C-reactive protein[2]	28.83±34.82	37.15±67,6	0.4838
C-reactive protein[3]	14.02±30.03	26.46±65,5	0.2578
Ferritin[1]	281.08±280.46	353.75±343,1	0.2862
Ferritin[2]	334.73±338.06	392.25±294,0	0.4694
Ferritin[3]	416.16±588.21	885.80±1868,9	0.1104
White blood cells[1]	5.66±1.91	7.63±3,8	0.0026
White blood cells[2]	7.38±4.51	10.00±5,8	0.0310
White blood cells[3]	9.63±4.83	11.10±5,9	0.2446
Platelets[1]	198.20±53.80	213.39±70,4	0.2626
Platelets[2]	227.18±66.21	224.68±78,2	0.8816
Platelets[3]	266.83±89.93	249.86±108,2	0.4641
Lympocytes[1]	26.55±13.74	31.10±15,0	0.1510
Lympocytes[2]	30.55±18.10	28.41±18,0	0.6186
Lympocytes[3]	27.85±14.77	23.12±18,4	0.2223
Fever[1]	37.46±0.58	37.86±1,0	0.0197
Fever[2]	37.50±0.84	37.92±1,2	0.0584
Fever[3]	36.39±0.79	36.97±1,3	0.0127
Oxygens saturation[1]	92.73±4.85	91.14±3,7	0.1363
Oxygens saturation[2]	93.51±4.14	91.54±3,6	0.0383
Oxygens saturation[3]	95.86±2.60	91.56±8,4	0.0011
Neutrophils[1]	57.24±21.86	51.32±21,1	0.2145
Neutrophils[2]	52.18±23.11	53.32±23,4	0.8371
Neutrophils[3]	56.17±21.02	58.12±24,3	0.7139
Lactatehydrogenase	349.44±170.61	313.39±83,7	0.2463
Creatinine	1.11±0.66	38.75±81,6	0.0017
Alanine aminotransferase	58.73±218.93	28.55±15,4	0.4122
Aspratat aminotransferase	55.65±183.38	28.17±12,9	0.3728
D-imer[1]	0.66±0.53	0.98±1,2	0.1202
D-imer[2]	0.78±0.98	1.78±2,0	0.0031
D-imer[3]	1.04±1.68	1.60±3,7	0.3677
Troponin[1]	0.05±0.06	0.06±0,1	0.8459
Troponin[2]	2.96±1.44	3.61±3,2	0.205

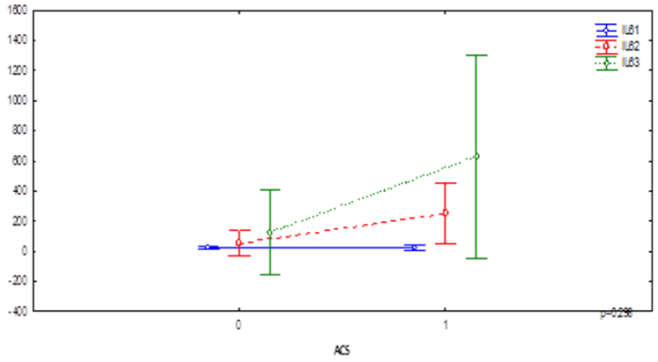
The follow-up analysis revealed notable differences in inflammatory and hematological parameters between patients who developed acute coronary syndrome (ACS-1) after six months and those who did not (ACS-0) (Tab.2).

TABLE 2. A comparative analysis of inflammatory and hematological parameters between patients who developed acute coronary syndrome (ACS-1) after 6 months and those without ACS (ACS-0)

Parameters	Mean ± SD	
	non-ischemic	Ischemic
Interleukin 6[1]	468.38+1086.48	87.00+258.66
Interleukin 6[2]	206.63+608.50	80.25+207.93
Interleukin 6[3]	560.27+664.90	264.14+1272.92
Ferritin[1]	276.57+209.68	341.15+339.28
Ferritin[2]	249.52+239.38	391.67+343.19
Ferritin[3]	261.80+229.54	701.29+1407.52
Neutrophil-to-lymphocyte ratio[1]	2.02+0.54	2.56+1.48
Neutrophil-to-lymphocyte ratio[2]	2.25+1.25	2.36+1.27
Neutrophil-to-lymphocyte ratio[3]	2.05+0.99	2.38+1.13
Platelet-to-lymphocyte ratio[1]	127.87+46.07	135.49+55.17
Platelet-to-lymphocyte ratio[2]	167.51+57.77	134.27+54.48
Platelet-to-lymphocyte ratio[3]	137.12+69.97	143.44+66.01
Systemic inflammatory index[1]	423.53+169.17	507.80+338.12
Systemic inflammatory index[2]	607.92+463.56	529.56+372.08
Systemic inflammatory index[3]	493.74+269.34	618.30+402.70

IL-6 levels were consistently higher in ACS-1 patients across all three time points (IL6_1: 468.38 ± 1086.48, IL6_2: 206.63 ± 608.51, IL6_3: 560.27 ± 664.90) compared to ACS-0 patients (IL6_1: 87.00 ± 258.60, IL6_2: 80.25 ± 207.93, IL6_3: 264.14 ± 1272.90) (Fig.1).

TABLE 2. Comparison of IL-6 levels in patients with and without acute coronary syndrome (ACS) at 6-month follow-up after COVID-19



However, despite this trend, the differences in IL-6 levels did not reach statistical significance, likely due to the high standard deviation values indicating large variability among individual patients.

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Ferritin levels were unexpectedly higher in ACS-0 patients at all three time points (Ferritin1: 341.15±339.20, Ferritin2: 391.67±343.10, Ferritin3: 701.29±407.52) compared to ACS-1 patients (Ferritin1: 276.57±209.68, Ferritin2: 249.52±239.38, Ferritin3: 261.80±229.54). This suggests a different inflammatory or iron metabolism profile in non-ACS patients. The neutrophil-to-lymphocyte ratio (NLR) values were relatively similar between the two groups, with ACS-0 patients showing slightly higher values at some time points (NLR1: 2.56±1.40, NLR2: 2.22±1.45, NLR3: 2.28±1.13) compared to ACS-1 patients (NLR1: 2.02±0.54, NLR2: 2.36±1.27, NLR3: 2.38±1.13).

The platelet-to-lymphocyte ratio (PLR) also showed no significant differences, with values fluctuating between the two groups. Systemic inflammatory index (SII) trends were inconsistent, with ACS-0 patients having higher SII values at the first and third-time points (SII1: 507.80±338.10, SII3: 618.30±402.71) compared to ACS-1 patients (SII1: 423.53±69.17, SII3: 493.74±269.34). In contrast, ACS-1 patients had a higher SII at the second time point (SII2: 607.92±463.56) than ACS-0 patients (SII2: 529.56±372.00).

DISCUSSION

The observed differences between ischemic and nonischemic patients can be attributed to several pathophysiological mechanisms. The prolonged hospitalization in ischemic patients may be due to a more severe disease course, necessitating extended medical management and supportive care. The trend toward higher CT scores in ischemic patients suggests greater pulmonary involvement, aligning with the known association between ischemia and extensive lung injury in conditions like COVID-19 and other systemic inflammatory diseases.[11,12] Significantly elevated IL-6 levels in ischemic patients highlight the role of systemic inflammation in ischemic pathology. IL-6 is a proinflammatory cytokine linked to endothelial dysfunction, vascular inflammation, and thrombogenesis.[13,14] Elevated IL-6 in ischemic patients may contribute to worsening endothelial injury, increased vascular permeability, and subsequent complications such as hypoxia and multi-organ dysfunction.[15,16] The lack of significant differences in CRP and ferritin suggests that while ischemic patients exhibit an exaggerated inflammatory response, these markers may not fully capture the severity of the ischemic condition.[17] Higher leukocyte counts in ischemic patients, particularly at the first two time points, reflect an early and heightened immune response.[18,19] This compensatory mechanism could counteract ischemia-induced tissue injury and oxidative stress.[20] However, persistent leukocytosis may contribute to further vascular damage and increased thrombotic risk.[21] The increased frequency and severity of fever in ischemic patients align with the inflammatory burden associated with ischemia, where excessive immune activation leads to a systemic febrile response.[22] Lower oxygen saturation observed in ischemic patients is a critical finding. Ischemic conditions often lead to impaired oxygen delivery and utilization at the tissue level.[23] This, combined with possible microvascular thrombosis and endothelial dysfunction, may exacerbate hypoxemia, leading to worse clinical outcomes. Significantly higher creatinine levels in ischemic patients indicate renal involvement, which could be secondary to hypoperfusion, increased systemic inflammation, or direct ischemic injury to the kidneys.[24] Elevated D-dimer levels in ischemic patients indicate hypercoagulable states. D-dimer is a biomarker of reduced fibrinolysis and increased thrombotic activity, and its elevation indicates an increase in clot formation and breakdown. Patients with ischemia also may have a higher thrombotic load, resulting in a greater propensity for thromboembolic phenomena, increasing hypoxia, and contributing to multi-organ failure.

Follow-up data indicates that continuation of inflammation, as indicated by increased levels of IL-6, may be an important factor in the progression of ACS. IL-6 is a proinflammatory cytokine with pleiotropic functions that contributes to atherosclerosis development by inducing endothelial dysfunction (which facilitates vascular inflammation and plaque destabilization.[25,26] In healthy subjects and patients with established coronary artery disease, higher levels of proinflammatory interleukin-6 (IL-6) have been linked to a higher risk of cardiovascular events.[27,28] However, in this study, the absence of statistical significance regarding IL-6 levels in ACS-1 versus ACS-0 patients is likely because large standard deviations indicate a high inter-individual variability. This variability could also be due to genetic differences, concurrent conditions, and inflammatory reactions.[29]

Higher ferritin was an unexpected finding in the ACS-0 group, as elevated ferritin is associated with increased inflammation and an adverse cardiovascular risk profile.[30,31] An explanation could be that ACS-0 patients carried chronic inflammatory diseases unrelated to atherosclerosis or disorders of iron metabolism that resulted in increased ferritin.[32] Conversely, lower ferritin levels in ACS-1 patients may indicate iron demand due to continuous myocardial injury or acute ischemic events.[33] Neither group significantly differed

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in the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR). However, these markers, while related to systemic inflammation and cardiovascular risk based on previous studies, did not discriminate well in this cohort, indicating they have limited value in predicting the development of ACS.[34,35] This conclusion emphasizes the complexity of the inflammatory processes involved in atherosclerosis and the importance of a multipronged approach to risk stratification. The contradictory trends regarding the SII between ACS-1 and ACS-0 patients also reinforce that inflammation is dynamic. It should be noted that inflammatory markers are affected by numerous dynamic factors, such as infections, stress, and metabolic status, and therefore are subject to temporal fluctuations.[36] As a result, a single-point measurement of one or more inflammatory markers may not reflect a person's chronic inflammatory state or predict a subsequent cardiovascular event.[37,38]

Reiteratively, patients with elevated IL-6 levels experienced a chronic inflammatory state and subsequently an increased risk of ACS; however, due to the high variability demonstrated in this study, IL-6 cannot serve independently as a prognostic marker of ACS. Thus, data about ferritin levels is surprising. Also, the fact that we rarely observe differences in NLR, PLR, and SII in these groups poses the question of whether applying one biomarker is sufficient to stratify risk accurately. Thus, an assessment that relies on various biomarkers, clinical evaluation, and imaging studies is needed to identify individuals at high risk for ACS.[38,39] The innovation of bespoke therapeutic approaches that selectively modulate inflammatory pathways and thus potentially curb acute coronary syndromes requires further exploration of the pathophysiologic interrelations between inflammatory markers.

CONCLUSIONS

Proinflammatory status is an important mechanism in both ischemic and nonischemic patients, displaying particular significance in the upsurge of IL-6, leukocytes, and clotting disturbance. Ischemic patients had a more extended hospital stay, higher inflammatory markers, lower oxygen saturation, and higher thrombotic activity than nonischemic patients, suggesting a more severe clinical course. Additional data suggested that sustained instead of rebound inflammation (assessed by IL-6 levels) might be the driving factor for acute coronary syndrome. However, the variation seen in these mediators, primarily IL-6, indicates that inflammation does not, by itself, explain disease evolution.

These findings highlight the complexity of the inflammatory pathways in cardiovascular diseases and reinforce the need to consider the multifactorial nature of the park's Stratification of risk. Moreover, the absence of significant differences in borderline parameters, such as ferritin, NLR, PLR, and SII, suggests that no single biomarker effectively predicts ACS progression. A holistic perfusion assessment considering various biomarkers, clinical features, and imaging studies is critical to determining high-risk patients.

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