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Predictive Role of Immunological Markers sCD14-ST and Interleukin-6 in Assessing Severity and Recovery Outcomes in COVID-19 Patients

Zahra'a Abdul AL-Aziz Yousif [*,1], Jabbar S. Hassan[2], Ghaith H. Hameed[3]
[1] *Ibn Sina University of Medical and Pharmaceutical Sciences, Baghdad, Iraq.*
[2] *Microbiology Department, College of Medicine, Al-Nahrain University, Baghdad, Iraq.*
[3] *MRCP Respiratory Medicine, Imamein Kadhimein, Medical City Baghdad, Iraq.*

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Abstract

The soluble cluster of differentiation CD14 subtype (sCD14-ST) acts as a cofactor, increasing pattern recognition receptor (PRR) activity through some infections. Interleukin-6 (IL-6) has a critical clinical role in infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing a cytokine storm that eventually leads to acute respiratory distress syndrome (ARDS). During the coronavirus disease 2019 (COVID-19) pandemic, various investigations found that IL-6 and sCD14-ST are predictive biomarkers for disease prognosis and severity. This study strives to investigate the immunological role of IL-6 and sCD14-ST in predicting COVID-19 outcomes. A case-control study involving 180 participants was divided into three groups: a severe group (with a particular focus on intensive care unit (ICU) patients), a mild-moderate group, with 60 patients, and a control group consisting of 60 healthy participants. ELISA was utilized to quantify IL-6 and sCD14-ST. The results exhibited a statistically significant increase (*p-value* ≤0.001) in median serum levels of IL-6 and sCD14-ST among patient groups compared to the control group. The Spearman correlation demonstrates a positive and substantial association between patient indicators. According to the findings, high levels of IL-6 and sCD14-ST associated with COVID-19 severity could be used as predictive markers for disease progression, particularly in ICU patients. In contrast, the low levels of these biomarkers in both control and mild-moderate infections may reflect inflammation resolution and infection recovery.

Keywords: COVID-19. IL-6, sCD-14ST, sandwich ELISA, SARS-CoV-2

الدور التنبئي للعلامات المناعية البرسبسين و الانترلوكين-6 في تقييم شدة المرض ونتائج الشفاء لدى مرضى كوفيد-19

زهراء عبد العزيز يوسف[1]، جبار سلمان حسان[2] و غيث حامد حميد
[1] جامعة ابن سينا للعلوم الطبية والصيدلانية، بغداد ، العراق.
[2] فرع الاحياء المجهرية، كلية الطب، جامعة النهرين، بغداد، العراق.
[3] مدينة الاماميين الكاظميين الطبية، مستشفى الكاظمية، بغداد ، العراق.

*Email: Zahraa.altaie@ibnsina.edu.iq

الخلاصة

تعمل مجموعة التمايز القابلة للذوبان من النوع الفرعي (البرسبسين) كعامل مساعد يعزز نشاط المستقبل الخاص بتميز الاجسام الغريبة أثناء مجموعة متنوعة من الألتهابات . ويلعب الانترلوكين-6 دوراً حاسماً من خلال عاصفة السايتوكين المحرضة التي تؤدي في النهاية الى متلازمة الضائقة التنفسية الحادة. خلال جائحة كوفيد-19 ، وجدت دراسات مختلفة أن انترلوكين-6 والبرسبسين يعملان كمؤشران حيويان للتنبؤ بتشخيص المرض وشدته، تسعى هذه الدراسة الى أستكشاف الدور المناعي لانترلوكين -6 والبرسبسين في التنبؤ بنتائج كوفيد-19.اجريت هذه الدراسة على 180 فردا مشاركاً، تم تقسيمهم الى ثلاث مجموعات: مجموعة الأصابة الشديدة (مع التركيز بشكل عام على مرضى وحدة العناية المركزة)، ومجموعة الاصابة الخفيفة الى المتوسطة، كلاهما ضم 60 مريضاً . وايضاً هناك مجموعة السيطرة وتضم 60 فرداً مشاركاً سليماً. تم استخدام اختبار فحص الأنزيم المناعي المرتبط للكشف الكمي عن الانترلوكين-6 والبرسبسين . كشفت النتائج عن مستوى عالي الدلالة الأحصائية (0.001) للانترلوكين-6 والبرسبسين بين مجوعات المرضى مقارنة مع مجموعة السيطرة. ويكشف اختبار الأرتباط سبيرمان عن ارتباط ايجابي بين مشؤشرات المرضى. وفقاً لنتائج هذه الدراسة يمكن استخدام المستوى المرتفع من انترلوكين-6 والبرسبسين المرتبطة بشدة عدوى كوفيد-19 كعلامة تنبؤية لتقدم المرض، خاصة في مرضى وحدة العناية المركزة، في حين أن المستوى المنخفض لهذه العلامات الحيوية في كل من مجموعة السيطرة والخفيفة الى المتوسطة يعكس شفاء الألتهاب والتعافي من العدوى .

1. Introduction

Coronavirus disease 2019 (COVID-19) is a disease that first appeared in Wuhan, China, in December 2019, and quickly spread throughout the world before being declared a global pandemic by the World Health Organization. The causal agent of this infectious disease is known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is a unique beta coronavirus strain. Although most COVID-19 cases are asymptomatic or mild. However, about 20% of infections develop pneumonia along with fatigue, fever, and cough, which may progress to multiple organ failure in critical cases [1]. Different components of cellular and humoral immune responses play a critical role in COVID-19 infection [2]. The most important immune-pathological effect is the cytokine storm, particularly the role of interleukin-6 (IL-6). It is defined as a multifunctional mediator of inflammation and plays a significant role in COVID-19 by inducing a cytokine storm, which ultimately leads to acute respiratory distress syndrome (ARDS) [3]. Clinical studies show a positive correlation between this marker and disease severity and mortality [4]. The main source of IL-6 is lymphocytes and macrophages in response to pathogens and for controlling different viral infections [5]. High levels of IL-6 can inhibit the cytotoxicity of natural killer cells by affecting granzyme B and perforin activity, which may promote cytokine release syndrome through the induction of cytolytic dysfunction [6].

On the other hand, the soluble cluster of differentiation CD14 subtype (sCD14-ST) serves as a cofactor that enhances Pattern Recognition Receptor (PRR) activity during a variety of infections [7]. During infections, activation signals of the pro-inflammatory marker sCD14-ST are released into circulation. Various studies indicate that sCD14-ST is one of the important biomarkers for determining the severity of different infectious diseases and mortality [8]. sCD14-ST serves as a predictive biomarker to detect risk stratification and prognosis in COVID-19 patients with sepsis and pneumonia. It helps differentiate patients who will stay for extended periods in the hospital and patients with severe or early stages of infection [9].

Due to the pathophysiological cascade of IL-6 during COVID-19 infection, which can be summarized as follows: SARS-CoV-2 infection activates innate immune responses, then

activated macrophages and epithelial cells release high levels of IL-6, which causes the development of Systemic Inflammatory Response Syndrome (SIRS). Endothelial dysfunction leads to increased vascular permeability. Finally, coagulation cascade stimulation causes thrombosis and ARDS development. Furthermore, predictions for specific outcomes include respiratory failure and multi-organ dysfunction syndrome, requirement for mechanical ventilation, thrombotic complications, ICU stay duration, and risk of mortality. On the other hand, regarding sCD14-ST's pathogenic role, it causes monocyte-macrophage activation pathway, increased pathogen recognition receptor signalling, enhanced pro-inflammatory cytokine production, and excessive inflammation that can cause tissue damage. It correlates with lung injury severity and serves as a predictor for sepsis-like illness in COVID-19, pneumonia severity, need for oxygen supplementation, risk of additional bacterial infections, and recovery time and hospital discharge. Therefore, this study aims to explore the immunological role of IL-6 and sCD14-ST as predictive biomarkers for COVID-19 outcomes and disease severity.

Materials and Methods

Populations and study design

During the fourth COVID-19 wave, a case-control study was conducted with 180 participants. Of the 120 individuals who presented with COVID-19 symptoms, it was verified using reverse transcriptase real-time polymerase chain reaction (RT-PCR) from nasopharyngeal swabs. The cases were divided into two groups depending on COVID-19 severity, according to Iraqi Ministry of Health recommendations [10], which included; 60 cases in the mild-moderate group, (Mild illness: includes patients who have a positive PCR test result and have symptoms or indications of COVID-19, such as a high temperature, cough, sore throat, fatigue, headache, pain in the muscles, nausea, vomiting, diarrhea, loss of taste and smell, but no shortness of breath, breathing difficulties or atypical scans of the chest. Moderate illness: refers to patients who suffer from lower respiratory disease, an oxygen saturation (SpO_2) of ≥94% on room air, and various COVID-19 symptoms, and 60 cases in the severe category (defined as having a SpO_2 level below 93% and requiring oxygen supplementation or ventilator examination, along with COVID-19 symptoms). All patient samples were collected from two hospitals in Baghdad: Imamein Kadhimein Medical City and Dar AL-Salam, which served as Baghdad's main quarantine facility. Additionally, 60 healthy individuals served as a control group, with negative RT-PCR test results from nasopharyngeal swabs. The sample collection took place over a five-month period, from January to May 2021. Demographic variables, clinical characteristics, and laboratory results of biochemical and hematological parameters were collected from hospital registries for each patient who participated in this study, including PCR test results, computed tomography (CT) scan values, and complete blood count (CBC), C- reactive protein (CRP), D-dimer, and ferritin test results.

Blood specimen collection and processing

Venous blood specimens (5 mL) were collected from severe patients within the first 3-10 days of admission, as well as from the mild-moderate and control groups. The sCD14-ST and IL-6 levels in serum samples were measured using the ELISA technique (Sun Long/China).

Inclusion criteria

Cases of severe, moderate, and mild illnesses, who tested positive for RT-PCR and had to stay in a hospital for numerous days (three to ten), and patients with chronic conditions, including patients with various comorbidities such as diabetes mellitus, hypertension, cardiovascular disease, chronic kidney disease, and obesity, as well as smokers with unhealthy lifestyles that

could independently affect cytokine levels. The control group consisted of individuals who tested negative for COVID-19 using RT-PCR.

Exclusion criteria

included individuals who had been hospitalized for over 14 days, those lacking or insufficient medical information, patients with concurrent bacterial, fungal, or other viral co-infections as confirmed by laboratory testing and clinical assessment.

Statistical Analysis

The information collected for the current investigation was examined with the Statistical Package for the Social Sciences (SPSS, version 25, Chicago). To assess data normality, the Shapiro-Wilk test was used, and it was found that non-normally distributed data was displayed as median, while normally distributed data was shown as mean. The chi-squared test for category variables was reported as both numbers and percentages. The Spearman correlation test was used to detect significant correlation relationships between variables in patient groups, and the Mann-Whitney test, a non-parametric test, was performed to determine the significant effect of markers; a *p-value* less than 0.05 was deemed statistically significant.

Results

Patients with severe infections had a greater median age (64 years) compared to those with mild-moderate infections (35 years) or control individuals (34 years), with a highly significant effect ($p<0.001$). On the other hand, 47 (39.2%) of the patients in the study were male, while 73 (60.8%) were female. In the severe group, there were 38 females compared to 35 in the mild/moderate group, and 25 males were in the mild/moderate group compared to 22 in the severe group, with no statistically significant difference detected (*p-value* 0.638). The control group consisted of 20 males (33.3%) and 40 females (66.7%). The highest prevalence of patients was observed in their sixth and seventh decades of life (>71 years). There was a highly statistically significant difference *(p-value* ≤0.001) in the median serum levels of these markers between patient groups and the control group. The median IL-6 level in the control group (11.00 pg/ml) versus mild-moderate and severe groups, respectively (39.38 and 148.23 pg/ml). The sCD14-ST median level in the control group was (761.9 ng/ml), lower than in the patient groups, mild-moderate and severe, respectively (3589 and 4865 ng/ml), as shown in Table 1.

Table 1: Serum level of sCD-14ST and IL-6 in study populations

Parameter	Control	Mild-Moderate	Severe	*P-value*
IL-6 (pg/ml)				
Median (5th-95th percentile)	11.00 (3.62-24.70)	39.38 (27.77-72.02)	148.23 (61.00-262.35)	<0.001**
sCD-14ST (ng/ml)				
Median (5th-95th percentile)	761.9 (620.8-938.3)	3589 (3221-3811)	4865 (4628-5681)	<0.001**

**: highly statistically significant Spearman correlation reveals a positive, significant correlation between IL-6 and sCD-14ST in both patient groups, with a *p-value* ≤0.05. As shown in Table 2.

Table 2: Spearman correlation between IL-6 and sCD-14ST among patient groups

Variable	IL-6 (Mild /moderate group)	
sCD-14ST	r	*P- value*
	0.388**	0.002
	IL-6 (severe group)	
	r	*P- value*
	0.978**	0.001

**correlation is significant at level 0.001

In the mild-moderate group, Spearman's correlation results reveal that IL-6 significantly correlates with all biochemical parameters (which were obtained from hospital registries for each patient who participated in this study), including CRP (r=0.538, p=0.004), ferritin (r=0.143, p=0.007), and D-dimer (r=0.182, p=0.036). The sCD14-ST marker also showed significant correlation with all biochemical parameters: CRP (r=0.328, p=0.022), ferritin (r=0.413, p=0.011), and D-dimer (r=0.331, p=0.012). Among hematological parameters, the results reveal no statistically significant correlation with these markers, as shown in Table 3.

Table 3: Correlation between severity markers with laboratory tests in the mild-moderate group

Variables	IL-6		sCD-14 ST	
	r	***p-value***	**r**	***p-value***
CRP (mg/L)	0.538 **	0.004	0.328*	0.022
Ferritin (ng/ml)	0.143**	0.007	0.413*	0.011
D-dimer (ng/ml)	0.182*	0.036	0.331*	0.012
Lymphocyte %	0.072	0.587 NS	0.057	0.667 NS
Monocyte %	0.104	0.434 NS	0.113	0.396 NS
Neutrophil %	0.272	0.136 NS	0.058	0.659 NS
N/ L	-0.108	0.413 NS	0.122	0.351 NS

NS: non-significant, *: significant at level 0.01, **: is significant at the level 0.001

Among the severe group, correlation test results reveal that IL-6 and sCD14-ST have significant correlations with most hematological and biochemical parameters, as shown in Table 4.

Table 4. Correlation between severity markers and laboratory tests in the severe group

Variables	IL-6		sCD-14 ST	
	r	***p. value***	**r**	***p. value***
CRP (mg/L)	0.606*	0.016	0.463**	0.004
Ferritin (ng/ml)	0.775*	0.038	0.863*	0.023
D-dimer (ng/ml)	0.786**	0.001	0.764**	0.002
Lymphocyte %	-0.257**	0.005	-0.503**	0.001
Monocyte %	-0.216**	0.007	-0.197	0.032*
Neutrophil%	-0.151	0.250 NS	-0.138	0.293 NS
N/L	-0.034	0.798 NS	-0.037	0.777 NS

NS: Non-significant, *: significant at the level 0.01, **: is significant at the level 0.001

Discussion

Before discussing the results, there were several obstacles to our study, including the challenge of collecting medical clinical data for the greatest number of participants due to the

medical quarantine rules enforced by most isolation hospitals, in addition to the fact that this study comprised just patients from a limited number of hospitals in the capital Baghdad, with a total of 180 individuals participating.

Regarding the use of IL-6 as a COVID-19 biomarker, although there are some strengths, including a strong link between disease severity and mortality, well-established involvement in cytokine storm pathogenesis, commercially accessible standardized assays, and potential therapeutic targets (sarilumab and tocilizumab), there are some limitations about this marker, including being a non-specific inflammatory marker (highly elevated in various diseases), half-life issues affecting measurement timing, variability across assay platforms, cost considerations for routine clinical applications, and limited prognostic value in mild cases. Furthermore, regarding the sCD14-ST marker, although there are some strengths, including being more specific for bacterial/severe viral sepsis, earlier elevation compared to traditional markers, correlation with monocyte-macrophage activation, and potential for severity stratification, there are some limitations about this marker, including limited availability in many clinical settings, higher cost compared to conventional markers, less extensive validation in COVID-19 compared to bacterial sepsis, potential interference from renal function, and limited data on therapeutic implications.

COVID-19 is a serious public health issue with high morbidity and fatality rates. Several studies have found that severe COVID-19 is connected with higher age; however, the current study found that COVID-19 has a much greater impact on individuals over the age of 60. These results are consistent with prior research [11]. This finding may be due to the progression of age-related complications, such as cardiovascular and additional chronic disorders, and diabetes. Given the probability of severity, pre-existing disorders like obesity, smoking, and other unhealthy behaviors are more common in the elderly [12]. During the COVID-19 pandemic, different biomarkers were recommended as predictive and prognostic tools in COVID-19 patients. sCD14-ST is considered one of the most important biomarkers, as it has improved diagnosis and severity detection. Furthermore, sCD14-ST emerges as an important first step in host identification of viral infection and host-derived products in the lungs. This makes this marker a therapeutic target to block numerous inflammatory responses to SARS-CoV-2, providing a viable therapeutic method to attenuate the detrimental host response in severely ill COVID-19 patients [13]. sCD14-ST is found on monocytes and macrophages and serves as an excellent biomarker for monocyte-macrophage activity [14]. For this reason, the elevated level, along with other inflammatory markers, illustrates the positive correlation between immunopathology and monocyte-macrophage activation in severe COVID-19 cases [15]. The resulting study by [16] reveals that monocyte-macrophage activation correlates with severe COVID-19 cases and can act as attractive cells in a cytokine storm.

Regarding IL-6, the current results are consistent with both Iraqi and international studies [17, 18]. This can be explained by the fact that during COVID-19 infection, activation of both innate and adaptive immune responses occurs, leading to the production of various cytokines, particularly IL-6. As well, SARS-CoV-2 infects the lungs and causes injury to them, which can explain why IL-6 is elevated in severe patients who are admitted to ICU and need oxygen supplementation [19]. Additionally, COVID-19 triggers a hyper-inflammatory state, leading to the massive production of pleiotropic cytokines, particularly IL-6, by lung-resident cells, including circulating immune cells and macrophages [19]. The study by Guirao *et al*., shows that the level of IL-6 is closely associated with disease severity and mortality, pulmonary inflammation, severe lung injuries, and the need for mechanical ventilation [20]. Yang *et al.,*

reported that IL-6 is considered a spark for cytokine storm and might be used as an independent factor to predict disease progression [21].

The Spearman positive correlation between IL-6 and sCD14-ST in both mild-moderate and severe groups can be attributed to sCD14-ST acting as a type of acute phase protein produced by hepatocytes, which act as the major source of acute phase proteins (APP), which are regulated by IL-6. The findings of our study align with prior research conducted by Kocyigit *et al.,* [22], which demonstrated a notable positive correlation between these markers in individuals with COVID-19. Additionally, our results further support the relationship between COVID-19 infections and increased levels of sCD14-ST, resembling the connection observed in bacterial sepsis. Furthermore, this association is accompanied by excessive immune system activation, leading to the overproduction of IL-6 in these patients.

The results of this study, as revealed by Spearman correlation, demonstrate a positive and significant correlation between IL-6 and sCD14-ST, as well as biochemical parameters in the mild-moderate group, while the significant correlation between these markers and hematological parameters occurs only in the severe group. These results agree with different studies in Iraq and worldwide [23- 25] and can be attributed to the various inflammatory markers, particularly D-dimer, CRP, ferritin, IL-6, which are being elevated during COVID-19 infection and correlated with worse disease outcomes [26, 27]. In COVID-19, IL-6 is superior to CRP along with other inflammatory indicators for predicting respiratory failure [28, 29]. Also, IL-6 release causes the induction of CRP production. Likewise, another study found a significant correlation between IL-6 and CRP, lymphocytes, and monocytes; this was attributed to elevated CRP levels in severe cases, resulting from hepatocyte release induced by IL-6 [30]. The positive correlation between cytokines and chemokines and lymphocytes in severe cases may occur due to the production of pro-inflammatory cytokines and chemokines, causing the induction of lymphocyte apoptosis [31]. Meanwhile, a study by Sayah *et al.,* found that IL-6 was positively correlated with CRP, NLR, and neutrophil count but negatively associated with lymphocyte count [32]. The authors attributed this discrepancy to the treatment effects on hematological parameters and IL-6 levels, particularly noting that corticosteroids were administered to approximately 14% of severe COVID-19 cases, which might affect the levels of pro-inflammatory cytokines, particularly IL-6.

In addition, this study reported a positive correlation between sCD14-ST and lymphocyte and biochemical parameters, which agrees with the study by Assal *et al.,* [33]. COVID-19 patients are more vulnerable to ARDS and other lower respiratory infections, which are marked by the migration of lymphocytes and neutrophils to the lungs and the release of pro-inflammatory cytokines. Likewise, the current study results agree with Fukada *et al.,* [34], who reported a positive correlation between CRP and sCD14-ST, whereas sCD14-ST increased immediately after CRP elevation in moderate to severe COVID-19, which illustrates the finding that sCD14-ST correlates with lung damage. Variations in methods, timing of marker estimation, sample collection, and treatment received during infection may explain discrepancies between studies.

Finally, the clinical significance and implications of these markers include the early detection of people at risk for serious illness development, optimizing ICU bed allocation and resource utilization, providing guidance on early intervention options, and reducing healthcare system strain. Additionally, quantification of these marker levels aids in treatment decision-making, selecting patients for anti-inflammatory medications (e.g., corticosteroids, IL-6 inhibitors), timing therapeutic interventions, monitoring treatment response, and identifying patients who need closer monitoring. Furthermore, these findings have implications for public

health, including improved pandemic preparedness through better prognostic tools, resource allocation amid healthcare system pressure, the development of standardized care regimens to reduce mortality through early intervention, shorter hospital stays due to better risk stratification, and the avoidance of unnecessary procedures for low-risk patients.

Conclusion

The study reveals that high levels of IL-6 and sCD14-ST are significantly correlated with COVID-19 severity and could be utilized as predictors of illness development, particularly in ICU patients. However, low levels of these biomarkers in both control and mild-moderate cases may reflect inflammation resolution and infection recovery. Additional studies are recommended to incorporate these markers into COVID-19 patient treatment guidelines to mitigate the impact of cytokine storm, which contributes to disease severity.

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Conflicts of Interest:

Conflicts of Interest: None of the authors present any conflicts of interest.

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Ethics Statements:

The Iraqi Ministry of Health and the Institutional Review Board of Al-Nahrain University, College of Medicine, both approved of this experiment's ethical standards, NO: 20211058.

Author’s contribution

The authors verified their contribution to the research paper in this order: Contributed to methods, handling of resources, collection of data, and official analysis. Zahra’a Abdul AL Aziz Yousif and Jabbar S. Hassan planned and oversaw the original data draft, while Ghaith Hamid Hameed did the investigation and prepared the document. All authors assessed the results and approved the final version of the text.

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