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Impact of IL-35 and Presepsin on Immunological, Hematological, and Biochemical Parameters in COVID-19 Patients

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ABSTRACT

Backgrounds: Immune-inflammatory responses appear to play a key role in severe SARS-CoV-2 infections. Interleukin-35 (IL-35) and presepsin (PSN) are inhibitory cytokine and pro-inflammatory interleukin, which play a crucial role in the immune system modulation, respectively. Therefore, the study of IL-35 and PSN interaction with other parameters may be critical for managing patients with COVID-19.

Materials & Methods: A total of 125 severe/critical COVID-19 patients and 60 healthy persons as a control group were enrolled in this work. These patients were admitted to Marjan medical city and Al-Sadeq hospital in Iraq during February to August 2022 and diagnosed as severe cases depending on the SpO_2 percentage according to the guidelines released by the National Health World. Anti- and pro-inflammatory cytokines (IL-35 and PSN) were detected by ELISA technique.

Findings: Presepsin showed a positive correlation with admission to the respiratory care unit (RCU) (r= .022, p= .011). A negative correlation was found between presepsin and C-reactive protein (CRP) (r= .21, p= .018). Both PSN and IL-35 in biochemical tests showed a positive strong effect on glucose levels in COVID-19 patients (r= .234, p= .008 and r= .241, p= .007, respectively). IL-35 had a positive impact on alkaline phosphatase (ALP) (r= .28, p= .002). Hemoglobin (Hb) level showed a positive correlation with presepsin (r= .2, p= .02).

Conclusion: This study confirms the growing evidence showing the direct role of regulatory pro-inflammatory cytokines in the development and control of COVID-19 through the interaction with other parameters.

Keywords: Interleukin-35, COVID-19, Inflammatory cytokine, Presepsin, SARS-CoV-2.

CITATION LINKS

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), was first reported in Wuhan, China in December 2019 [1]. It's the third coronavirus disease that has emerged with zoonotic origin in the last 18 years, following SARS (2002 and 2003) and MERS (Middle East respiratory syndrome; 2012 to present) [2]. SARS and MERS stayed geographically limited, whereas COVID-19 has spread worldwide. The disease could be manifested in a variety of ways, ranging from an asymptomatic illness to severe conditions and even death [3]. Patients with functional immunosuppression, such as the elderly and those with prior respiratory or heart diseases, are at higher risk of this infection and its unfavorable consequences [4]. A series of processes are required for SARS-CoV-2 to enter target cells and release its genomes into host cells. Spike proteins (S) are used by the virus to detect viral transmissibility and tropism. The virus also targets human pulmonary epithelial cells that carry ACE2 (angiotensin converting enzyme-2) receptors on their surfaces. After binding of the S1-RBD (receptor-binding domain) to the ACE2 receptor, host cell-surface proteases like transmembrane serine protease 2 act on a critical cleavage spot on S2 [5]. As a result, the host cell membrane is fused, and the viral infection is infused.

IL-35 reduces inflammatory responses by modulating different cytokines and thereby controlling STAT signaling, unlike IL-12 and IL-23 [6]. As a result, IL-35 could activate STAT1 and STAT4 in T cells and trigger STAT1 and STAT3 in B cells when it binds to IL-35 receptors [7]. IL-35 suppresses the development of monocyte-derived dendritic cells (MoDCs) by activating STAT 1/3 pathways while concurrently suppressing p38 MAPK and NF-κb signaling pathways and reducing pro-inflammatory activities [8].

Interleukin-35 is also thought to be involved in the regulation of autoimmune, inflammatory, and bacterial/viral infectious diseases and malignancies. Recent IL-35 research, along with the development of new methodologies for examining receptors and signal transduction pathways, suggests IL-35 as a potential immunotherapy target [9].

Recently, the soluble CD14 subtype presepsin (PSN) has been suggested as a new biomarker in sepsis patients. Toll-like co-receptor CD14 is a subtype that could recognize a variety of ligands in both Gram-positive and Gram-negative pathogens, including lipids, peptidoglycans, and other surface patterns. The presentation of lipopolysaccharide of Gram-negative bacteria to Toll-like receptors by CD14 is crucial for immune system activation and cytokine production by effector cells. There are two types of CD14: membrane-bound CD14 and soluble CD14. Plasma contains soluble CD14, which is generated by membrane-bound CD14. Soluble CD14 is broken down by proteases in plasma, and 13 kDa N-terminal fragments are produced, which form the soluble CD14 subtype known as PSN [10].

PSN is a new biomarker for sepsis. Numerous studies have demonstrated that PSN helps in the diagnosis of sepsis and may also be helpful in predicting the severity and mortality of the disease. Additionally, according to recent reports, higher PSN levels may serve as a biomarker in the prognostic evaluation of COVID-19 patients [11]. Presepsin and IL-35 as pro-inflammatory and anti-inflammatory cytokines as well as their relationship with other parameters were examined in this study in severe COVID-19 patients.

Objectives: The purpose of this study was to investigate the impact of these immunological indicators (IL-35 and presepsin) on other inflammatory, hematological, and biochemical parameters, which may help better understand how this illness is developed.

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Materials and Methods

Subjects: In this study, a total of 125 severe COVID-19 patients were enrolled, including 56 (44.8%) males and 69 (55.2%) females. All patients were admitted to the COVID-19 ward of Marjan medical city and Al-Sadeq hospital in Iraq. The patients' age ranged from 15 to 90 years. The diagnosis of COVID-19 in each patient was confirmed by SARS-CoV-2-positive RT-PCR. In addition, 60 healthy participants were also included in the control group. Based on the SpO_2 (oxygen saturation) percentage, patients were classified as severe or critical (90%).

Ethical approval: Babylon Health Directorate approved the moral position of this research. Before taking the samples, permission was obtained from the patients and their relatives. In addition to sampling, safety and health precautions were implemented. This study was approved by the Faculty of Medicine, Babylon University, Iraq (19814) in 5/2/2022.

Sample collection and processing: Blood and serum samples were collected from each patient upon admission to the hospital and used to determine IL-35 levels. IL-35 levels were measured using BT LAB Company ELISA kits and a Biotek EL800 automated immunoassay analyzer (BioTek, USA). Using the Architect Ci 8200 automated system, fasting glucose and creatinine levels were measured (Abbott Diagnostics, Lake Forest, IL, USA). Biochemical parameters were detected by reagents, calibrators, and controls depending on the manufacturer's instructions. Anticoagulated blood samples of patients were processed for complete blood count through a hematology auto-analyzer (Minami-Ku Kyoto, Japan).

Data analysis: Data were put into SPSS software (for Windows) Version 26 for statistical analysis (GraphPad Software, San Diego, California, USA). The outcomes were presented as median (25th–75th interquartile range, IQR). Mann–Whitney U test was used to compare two groups. A p value of $< .05$ was taken into account to denote statistical significance. Additionally, Spearman's correlation test was used to explain the connection between serum levels of pro-inflammatory cytokines (PSN and IL-35) and other parameters.

Findings

In the present study, 125 patients with COVID-19 and 60 apparently healthy subjects with matched frequency by gender and age were enrolled. The demographic characteristics of subjects and their laboratory data reported as median (IQR) or number (%) are shown in Table 1. The median age of the patients was 75 years (62-85), the minimum age was 15 years, and the maximum age was 90 years.

Table 1) Demographic characteristics and clinical data of COVID-19 patients

Variables	Units	Median (IQR) or N (%)
Age (years)		75 (62-85)
Gender Males Females		 56 (44.8%) 69 (55.2%)
Creatinine	(µmol/L)	86 (68-143)
D-dimer	(Ng/mL)	1200 (537-2928)
ESR	(mm/hr)	42 (31.5-59.5)
Glucose	(mmol/L)	9.5 (5.9-14.4)
GOT	(IU/L)	34 (28-45)
GPT	(IU/L)	29 (22-41)
LDH	(IU/L)	504 (257-788)
LYM	(20-50 %)	6.4 (4.2-12)
K	(mmol/L)	4.2 (3.8-5.1)
SpO_2	(<94)	82 (78-88)
Total protein	(gm/L)	59 (53.5-65)
Urea	(mmol/L)	11.5 (7.1-17.6)
WBC	(4-11 10^9/L)	15,000 (11570-17490)

ESR: erythrocyte sedimentation rate, GPT: glutamic pyruvic transaminase, GOT: glutamic oxaloacetic transaminase, LDH: lactate dehydrogenase, LYM: lymphocyte, K: potassium, SpO_2: oxygen saturation, WBC: white blood cell

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The correlation between both IL-35 and presepsin with age, gender, SpO_2, diabetes, vaccination, and patient outcome was not significant (p> .05). Presepsin showed a positive correlation with admission to the respiratory care unit (RCU) (r= .022, p= .011), which means that when the presepsin level is high, it may be a predictor of complications in patients such that the patient may require to be admitted to the RCU (Table 2).

Table 2) Impact of IL-35 and presepsin on general characteristics of patients

Variables		Presepsin	IL_35
Age	Cor.	.085	-.175
	Sig.	.343	.052
Gender	Cor.	-.140	-.009
	Sig.	.120	.919
SpO_2	Cor.	.159	.056
	Sig.	.076	.537
Diabetic patients	Cor.	.067	-.158
	Sig.	.455	.078
Vaccination	Cor.	.082	-.098
	Sig.	.363	.275
RCU admission	Cor.	.226*	-.135
	Sig.	.011	.134
CT scan	Cor.	-.061	-.078
	Sig.	.500	.385

SpO_2: oxygen saturation, RCU: respiratory care unite, CT scan: computerized tomography scan

IL-35 and presepsin had no impact on each other (r= -.03, p= .57) as well as on other inflammatory parameters including lactate dehydrogenase (LDH), D dimer, and ferritin (p> .05), except that there was a negative correlation between presepsin and C-reactive protein (CRP) (r= .21, p= .018), which means that presepsin may have a negative direct effect on CRP (Table 3).

Table 3) Impact of IL-35 and presepsin on other inflammatory parameters

Variables		Presepsin	IL_35
LDH	Cor.	-.118	.082
	Sig.	.190	.366
D dimer	Cor.	-.130	.068
	Sig.	.147	.453
Ferritin	Cor.	-.170	-.062
	Sig.	.059	.494
CRP	Cor.	-.211-*	.035
	Sig.	.018	.695
Presepsin	Cor.		-.051
	Sig.		.572
IL 35	Cor.	-.051	
	Sig.	.572	

LDH: lactate dehydrogenase, CRP: C-reactive protein

Both PSN and IL-35 in biochemical tests showed a positive strong effect on glucose levels in COVID-19 patients (r= .234, p= .008 and r= .241, p= .007, respectively) (Figure 1). Also, creatinine was positively correlated with increases in both PSN and IL-35 (r= .17, p= .04 and r= .18, p= .04, respectively) (Figure 2). This finding may predict the impact of these inflammatory parameters on kidney function and suggest them as a contributing factor to the development of acute kidney injury that is responsible for the high mortality rate in patients with COVID-19. Presepsin had a significant negative impact on GPT (glutamic pyruvic transaminase) (r= -.27, p= .002), while a positive correlation was found between IL-35 and ALP (alkaline phosphatase) (r= .28, p= .002). Other biochemical parame-

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ters showed no significant results (Table 4).

Table 4) Impact of IL-35 and presepsin on other biochemical parameters

Variables		Presepsin	IL_35
Glucose	Cor.	.235**	.241**
	Sig.	.008	.007
Urea	Cor.	-.128	-.006
	Sig.	.155	.943
Creatinine	Cor.	.178*	.182*
	Sig.	.047	.043
Na	Cor.	.151	.084
	Sig.	.092	.351
K	Cor.	-.025	-.038
	Sig.	.785	.676
Ca	Cor.	.144	.101
	Sig.	.108	.261
Cl	Cor.	-.006	.106
	Sig.	.950	.240
GPT	Cor.	-.274-**	.015
	Sig.	.002	.871
GOT	Cor.	-.089	-.102
	Sig.	.324	.257
ALP	Cor.	-.171	.281**
	Sig.	.056	.002
T. protein	Cor.	.081	-.052
	Sig.	.367	.561
Albumin	Cor.	.079	.045
	Sig.	.382	.620

Na: sodium, K: potassium, Ca: calcium, CI: chloride, GPT: glutamic pyruvic transaminase, GOT: glutamic oxaloacetic transaminase, ALP: alkaline phosphatase

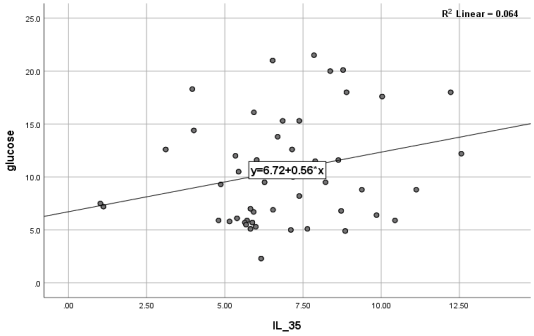

Figure 1) Correlation between IL-35 and glucose level

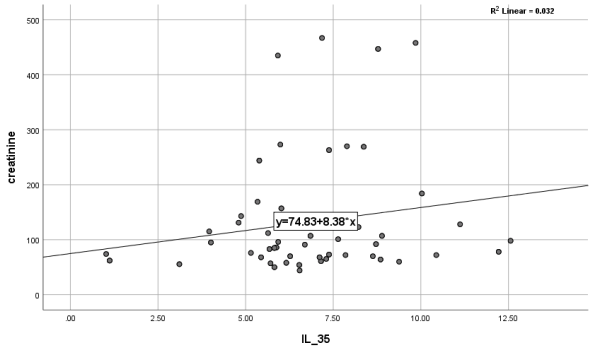

Figure 2) Correlation between IL-35 and creatinine level

Table 5) Impact of IL-35 and presepsin on hematological parameters

Variables		Presepsin	IL_35
ESR	Cor.	-.120	.024
	Sig.	.183	.792
WBC	Cor.	.002	.168
	Sig.	.980	.060
LYM	Cor.	-.019	.082
	Sig.	.838	.360
GRA	Cor.	-.004	.031
	Sig.	.968	.735
PLT	Cor.	.099	.057
	Sig.	.270	.528
Hb	Cor.	.204*	-.085
	Sig.	.023	.344
NLR	Cor.	.023	-.083
	Sig.	.803	.360
PT	Cor.	-.109	.078
	Sig.	.225	.390
PTT	Cor.	.057	.093
	Sig.	.526	.300
INR	Cor.	-.055	-.004
	Sig.	.542	.967

ESR: erythrocyte sedimentation rate, WBC: white blood cell, LYM: lymphocyte, GRA: glucocorticoid-remediable aldosteronism, PLT: platelet count, Hb: hemoglobin, NLR: neutrophil to lymphocyte ratio, PT: prothrombin time, PTT: partial thromboplastin time, INR: international normalized ratio

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Hematological parameters mentioned in Table 5 showed no correlation with IL-35 and PSN, except for hemoglobin (Hb) level which showed a positive correlation with presepsin (r= .2, p= .02), which means that PSN may directly affect the level of Hb in COVID-19 patients.

Discussion

Immunological responses to a viral infection could sometimes be more harmful than the virus itself [12, 13]. As a result, immunopathogenesis must be considered in addition to adaptive immunity in controlling COVID-19. So far, only a few studies have been done on IL-35 and presepsin cytokines, and the functions of these cytokines in combatting viral infection are not yet well understood [14].

Investigations have demonstrated that IL-35 expression is reduced in chronic obstructive pulmonary disease (COPD), a type of chronic bronchitis and emphysema marked by airflow restriction [15]. Furthermore, lower IL-35 levels have been shown to be inversely linked with smoking status, suggesting that IL-35 might be used as a biomarker to predict chronic obstructive pulmonary disease development [16]. According to the findings, IL-35 is an excellent indicator of allergic inflammation and could be utilized as a biomarker [9].

The function of IL-35 during viral infection is poorly understood. According to this study results, patients with seasonal influenza A virus (IAV) had higher levels of IL-35 in their peripheral blood mononuclear cells and throat swabs than healthy people. IAV infection elevated IL-35 mRNA and protein levels in human lung epithelial and primary cells. IAV-induced IL-35 transcription is controlled by NF-B, according to another research. Selective inhibitors of cyclooxygenase-2 (COX-2) and inducible nitric-oxide synthase dramatically reduce IL-35 expression, indicating that they are involved in IL-35 expression [17].

Recently, the soluble CD14 subtype PSN has been suggested as a new biomarker in sepsis patients. Its importance in risk stratification in sepsis patients and in distinguishing between sepsis patients and those advancing to septic shock has been demonstrated in several investigations [18]. According to reports, PSN is involved in the first few steps of the septic process. The soluble CD14 subtype PSN is released into the plasma when an infectious pathogen activates monocytes. Therefore, in the early stages of sepsis, PSN levels in plasma keep rising. It has been postulated that the increase in PSN is caused by the dose-response mechanism of the host-pathogen interaction, which happens in the early stages of pathogen identification, and the PSN level remains raised for several days depending on the severity of the disease. However, not enough studies have yet been done to fully understand and examine the role of PSN in patients with COVID-19 [19]. In this study, COVID-19 patients with severe/critical illnesses had significantly higher PSN levels (almost 3-fold) than COVID-19 patients without such illnesses. In a recent meta-analysis, PSN was shown to have even higher diagnostic accuracy than procalcitonin for identifying mixed-pathogen sepsis in critically sick adult patients [20]. Regular evaluation of PSN in COVID-19 patients may offer useful clinical data to anticipate adverse outcomes and make appropriate clinical and therapeutic decisions [21].

Since *Mycobacterium tuberculosis* (TB) culturing necessitates precise and prolonged culture conditions, culture-based diagnosis of active pulmonary TB is not often available. As a result, an early biomarker to differentiate *M. tuberculosis* from other bacteria is essential for timely diagnosis and effective treatment. PSN may aid in the early differential diagnosis of various respiratory illnesses since PSN has recently been shown to be elevated in active TB patients [22].

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In this research, both PSN and IL-35 in biochemical tests showed a positive strong effect on glucose levels in COVID-19 patients (r= .234, p= .008 and r= .241, p= .007, respectively). Also, creatinine was positively correlated with increases in both PSN and IL-35 (r= .17, p= .04 and r= .18, p= .04, respectively). This finding may predict the impact of these inflammatory parameters on kidney function and suggest them as a contributing factor to the development of acute kidney injury that is responsible for the high mortality rate in patients with COVID-19.

Kidney function affects plasma PSN levels. PSN, as a 13 kDa protein, could be re-absorbed by proximal tubular cells after being filtered by the glomerulus. As a result, plasma PSN levels are affected by any disorder that affects renal filtration function. Recent research has demonstrated that PSN increases with a decrease in glomerular filtration rate, and that plasma PSN levels are correlated with serum creatinine concentrations [23]. Studies have shown that plasma PSN levels in patients not receiving hemodialysis therapy are inversely correlated with glomerular filtration rate, but PSN levels in patients receiving hemodialysis therapy are higher than in patients with severe sepsis and septic shock [22].

Conclusion

By impacting other parameters, IL-35 and presepsin may be useful cytokines to further understand the immunopathogenesis and development of SARS-CoV-2 infection.

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Ethical permissions: The Research Ethics Committee at Babylon University, College of Medicine approved the study (19814 in 5/2/2022).

Conflicts of interests: The authors declare that they have no competing interests.

Authors' contributions: FH collected the data. ZA drafted the manuscript, and edited the paper. FH designed the study, collected the data, and revised the manuscript. All authors read and approved the final manuscript.

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Consent to participate: Written informed consents were obtained from all patients.

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