ISSN: 2588-4115; Infection Epidemiology and Microbiology. 2025;11(4):331-341 10.52547/iem.11.4.331

Cytokine Profiling and Bacterial Spectrum in Patients with Hospital-Acquired Pneumonia

ARTICLE INFO

Article Type
Original Article

Authors
Shahrazad Ahmed Khalaf, *PhD*[1*]

[1] Department of forensic science , college of science, university of Diyala, Diyala, 32001, Iraq.

** Correspondence*
Department of forensic science , college of science, university of Diyala, Diyala, 32001, Iraq.
E-mail:shahrazadah.kh@uodiyala.edu.iq

How to cite this article
Khalaf Sh.A. Cytokine Profiling and Bacterial Spectrum in Patients with Hospital-Acquired Pneumonia Infection Epidemiology and Microbiology. 2025;11(4): 331-341.

Article History
Received: October 05, 2025
Accepted: December 30, 2025
Published: January 11, 2026

ABSTRACT

Background: This study was aimed to detect bacterial causes of hospital-acquired pneumonia **(**HAP), determine serum levels of IL-6, IL-22, and TGF-β in HAP patients, and compare the levels of these cytokines with those in healthy individuals. Additionally, the study investigated the relationship between cytokine profiles and bacterial species responsible for HAP in Diyala Governorate, Iraq.
Materials & Methods: Samples (blood and sputum) were collected from 150 patients admitted to Baquba Teaching Hospital in Iraq between December 2023 and May 2024. All patients showed clinical signs and symptoms of pneumonia. Sputum samples were cultured on differential media, and only 58 samples displayed bacterial growth. Bacterial species were identified using the Vitek system. In addition, 32 blood samples were obtained from healthy individuals as controls. Serum levels of IL-6, IL-22, and TGF-β were measured in both groups using enzyme-linked immunosorbent assay (ELISA).
Findings: The results revealed that IL-6, IL-22, and TGF-β levels were significantly higher in patients (19.02±1.675 pg/mL, 446.1±3.074 pg/mL, and 14.69±0.191 ng/mL, respectively) compared to healthy controls (7.206±0.274 ng/mL, 365.6±4.265 pg/mL, and 5.88±0.17 ng/mL, respectively). The prevalence of HAP was higher in males. IL-6 and IL-22 levels were significantly higher in males, whereas TGF-β levels were lower compared to females.
Conclusion: Significant differences were observed in IL-6, IL-22, and TGF-β levels among patients and healthy individuals. Understanding the cytokines involved in HAP pathogenesis may contribute to developing targeted therapies and improving clinical outcomes.

Keywords: Hospital-acquired pneumonia, IL-6, IL-22, TGF-β

CITATION LINKS

[1] Quinton LJ, Mizgerd JP. Dynamics of... [2] Martinez R, et al. Factors... [3] Lee KY. Pneumonia... [4] Rendon A, et al. Relevant cytokines... [5] Tanaka T, et al. IL-6 in... [6] Jones SA, Jenkins BJ. Recent... [7] Velazquez-Salinas L, et al. The role of... [8] Wolk K, et al. IL-22 regulates... [9] Sonnenberg GF, et al. Border patrol: Regulation... [10] Aujla SJ, et al. IL-22 mediates... [11] Walton KL, et al. Targeting... [12] Brusselle GG, Joos GF, Bracke KR. New... [13] Worthington JJ, et al. Integrin... [14] Sanjabi S, Oh SA, Li MO. Regulation of... [15] McElvaney OJ, et al. Characterization... [16] Gou X, et al. IL-6 prevents... [17] Meng XM, Nikolic-Paterson... [18] Kalil AC, et al. Management of... [19] Kalanuria AA, Ziai W, Mirski M. Ventilator... [20] Torres A, et al. International... [21] Kabir S, et al. Diagnostic... [22] Zobel K, et al. Interleukin 6... [23] Feng M, et al. Detection of... [24] Zhang Y, Li B, Ning B. Evaluating... [25] Chen W, et al. Evaluation... [26] Yu Q, et al. Combination of... [27] Rose-John S, et al. The role of... [28] Iwase S, et al. Interleukin-6... [29] Takahashi W, et al. Interleukin-6... [30] Younis MY, Altaii HA. Survey... [31] Travaglini KJ, et al. A molecular... [32] Alcorn JF. IL-22 plays... [33] Trevejo-Nunez G, et al. Interleukin-22... [34] Abood RN, et al. IL-22... [35] Yang X, et al. Increased... [36] Zhang K, et al. Current... [37] Hamid RH, AL-Jumaily RM. Immunological... [38] Sakamoto K, et al. IL-22... [39] Saito A, Horie M, Micke P, Nagase T. The role... [40] Willis BC, Borok Z. TGF-β... [41] Travis MA, Sheppard D. TGF-β... [42] Shimbori C, et al. Fibroblast... [43] Wang B, et al. Induction of... [44] Qu Z , et al. Role of... [45] Yoshimura A, et al. Cellular and... [46] McCulloch TR, et al. CIS and TGF-β... [47] Sanjabi S, Oh SA, Li MO. Regulation...

Introduction

Pneumonia caused by bacterial infection remains a major health challenge worldwide, infecting many people and causing mortality each year [1]. Bacteria that invade the lower respiratory tract and trigger a strong immune response include *Staphylococcus aureus* and *Klebsiella pneumoniae* [2]. The most important symptoms of pneumonia that could lead to hospitalization include cough, fever, chest pain, and difficulty breathing [3]. Antibiotic resistance and severe inflammatory responses still complicate treatment, although antibiotics could be used to treat pneumonia [4]. Bacterial pneumonia is caused by bacteria invading the alveoli, leading to local inflammation and disruption of the alveolar-capillary barrier [2]. Bacterial components such as lipopolysaccharides and peptidoglycans could stimulate innate immune system receptors such as TLRs (toll-like receptors), and this stimulus leads to the activation of signaling cascades and the production of cytokines [1].

There are many types of cytokines that play a critical role (such as IL-6) during infections like HAP [5], these cytokines are secreted in response to microbial invasion and tissue injury by a variety of cells, including macrophages, epithelial cells, and endothelial cells [6]. Although IL-6 is critical for initiating protective immune responses, its excessive or prolonged expression could contribute to lung inflammation, alveolar damage, and progression to respiratory failure in severe pneumonia cases [7]. Vascular permeability and leukocyte infiltration could occur through the secretion of pro-inflammatory cytokines such as IL-6 [3]. The secretion of pro-inflammatory cytokines is crucial for eliminating pathogens, but they may damage the alveoli and disturb gas exchange [4]. During bacterial pneumonia, cytokines play an important role in regulating immune responses [1]. Pro-inflammatory cytokines such as IL-6 rapidly recruit neutrophils and macrophages to the site of infection after pathogen recognition [2]. Interleukin-22 (IL-22) plays an important role in maintaining the epithelial barrier, mainly in the lungs [8], it is mostly produced by innate lymphoid cells (ILCs) and Th17 cells in response to bacterial infections in the respiratory tract [9]. IL-22 contributes to host protection through promoting the expression of antimicrobial peptides, limiting excessive inflammation, and enhancing epithelial cell regeneration in HAP [10]. Transforming growth factor-beta (TGF-β) is a main regulatory cytokine that influences both inflammation and tissue repair through pulmonary infections [11]. TGF-β in the lung environment suppresses extreme immune responses while preserving epithelial homeostasis, but this regulation could impair host defenses against invading pathogens [12]. This cytokine is mainly secreted by alveolar macrophages and epithelial cells [13]. Elevated TGF-β levels in HAP have been shown to decrease neutrophil function and bacterial clearance and increase susceptibility to severe infection [14]. TGF-β decreases excessive immune activation and minimizes tissue damage [4].

Interactions between cytokines and immune cells lead to the development and progression of bacterial pneumonia [2]. Excessive production of cytokines, called cytokine storm, leads to lung damage and acute respiratory distress syndrome (ARDS) [1]. The elevated IL-6 and TGF-β levels observed in this study align with mechanisms described in neutrophil- and macrophage-driven cytokine storms during bacterial pneumonia. IL-6 plays the role of an essential amplifier of the acute inflammatory cascade by stimulating neutrophil recruitment and degranulation, thereby sustaining a self-perpetuating inflammatory loop [15]. Activated alveolar macrophages and infiltrating monocyte-

derived macrophages also release large amounts of IL-6 in response to bacterial load and epithelial injury, further exacerbating the cytokine storm [16]. In contrast, TGF-β exhibits a dual context-dependent role: while initially dampening excessive inflammation, sustained TGF-β signaling during prolonged infection contributes to fibrosis, extracellular matrix deposition, and functional immune suppression [17]. Chronic inflammation could result from impaired regulation of bacterial clearance by immune cells [4]. Extensive research is currently underway into therapeutic strategies that modulate cytokine signaling without compromising immune defense [3].

Objectives: This study aimed to detect the bacterial causes of HAP, measure serum levels of IL-6, IL-22, and TGF-β in HAP patients, compare the levels of these cytokines with those in healthy controls, and also compare the levels of these cytokines based on the types of bacteria causing HAP in Diyala Governorate, Iraq.

Materials and Methods

A total of 150 blood samples were collected from both male and female patients admitted to Baqubah Teaching Hospital (Diyala, Iraq) between December 2023 and May 2024. Blood samples (5 mL) were taken under aseptic conditions using sterile disposable syringes. For the control group, blood samples were collected from30 healthy individuals. Each blood sample was transferred into a plain gel tube and allowed to clot for 30 min at 37 ^{0}C. The tubes were then centrifuged at 3000 rpm for 10 minutes to separate the serum, which was stored at - 20 ^{0}C until further analysis. In addition, sputum samples were collected from the same patients in sterile containers and processed within two hours of collection to ensure sample integrity. All sputum samples were cultured on blood agar and MacConkey agar plates and incubated at 37 ^{0}C for 24-48 hours. Bacterial colonies were identified based on their culture and morphological characteristics and then biochemically confirmed using the Vitek2 compact system (bioMerieux, France). Serum levels of IL-6, IL-22, and TGF-β were measured using

Table 1) Frequency of bacterial isolates from sputum (descriptive statistics)

Sample			Total (N=150)	
			No.	%
Positive culture	Gram negative	44 (29.3)	58	38.6
	Gram positive	14 (9.3)		
Negative culture			92	61.3

Table 2) Types of bacterial isolates from sputum culture (descriptive statistics)

Bacterial Isolates		Total (58 Isolates)	
		No.	%
Gram negative bacteria	*Pseudomonas aeruginosa*	22	37.9
	Klebsiella pneumoniae	10	17.2
	Escherichia coli	8	13.7
	Acinetobacter baumannii	4	6.8
Gram positive bacteria	*Staphylococcus aureus*	14	24.13

Table 3) Distribution of patients by gender (descriptive statistics)

Study Groups	N		%
Patients	58	Female 26 (44.82)	64.4
		Male 32 (55.17)	
Controls	32		35.5
Total	90		100

enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions.

Statistical analysis: GraphPad Prism software was used to analyze the data. Quantitative data were expressed as mean± standard deviation (SD).

Comparisons between groups were performed using t-test or one-way ANOVA where appropriate. A *p*-value < .05 was considered statistically significant.

Findings

A total of 150 clinical samples (blood and sputum) were collected from patients admitted to Baquba Teaching Hospital in Diyala. All sputum samples were cultured on differential media to detect bacterial growth. Out of the 150 samples, 58 (38.67%) samples were positive for bacterial growth. This positivity rate might have been influenced by many factors, such as sample quality and prior antibiotic exposure. Among the 58 culture-positive samples, 44 (75.86%) samples contained Gram-negative bacteria, including *Pseudomonas aeruginosa* (n=22, 37.9%), *K. pneumoniae* (n=10, 17.2%), *Escherichia coli* (n=8, 13.7%), and *Acinetobacter baumannii* (n=4, 6.8%). In

Table 4) Serum levels of IL-6, IL-22, and TGF-β1 in the studied groups (independent sample t-test)

Parameter	Patients (Mean ± S.E)	Control (Mean ± S.E)	P Value
IL-6	19.02±1.675	7.206±0.274	< .0001
IL-22	446.1±3.074	365.6±4.265	< .0001
TGF-B	14.69±0.191	5.88±0.17	< .0001

Table 5) Serum levels of IL-6, IL-22, and TGF-β1 by gender (independent samples t-test)

Parameter	Male Patients (Mean ± S.E)	Female Patients (Mean ± S.E)	*P* Value
IL-6	17.94±0.122	20.35±3.757	< .0001
IL-22	450±4.30	440±4.22	< .0001
TGF-B	14.27±0.172	15.22±0.34	< .0001

Table 6) Serum levels of IL-6, IL-22, and TGF-β1 by bacterial type (independent samples t-test)

Type of Bacteria	IL-6	IL-22	TGF-B
Pseudomonasaeruginosa	17.98±0.144	451.2±5.530	14.04±0.213
Klebsiella pneumoniae	17.85±0.237	448.4±6.79	14.77±0.22
Escherichia coli	28.76±12.2	458.8±7.75	14.21±0.765
Acinetobacter baumannii	15.73±0.68	417.0±3.464	15.38±0.832
Staphylococcus aureus	16.87±0.27	437.4±4.121	15.76±0.474
P value	.2359	.0155	.0052

Table 7) Correlation between studied parameters in hospital-acquired pneumonia

	Sex of Patients	Sex of Controls	IL-6 of Patients	IL-6 of Controls	IL-22 of Patients	IL-22 of Controls	TGF-B of Patients	TGF-B of Controls	Type of Bacteria
Sex of patients	1*		- .095		.203		- .329		- .313
Sex of controls		1*	.036	- .296	- .009	- .039	- .361	.206	- .815
IL-6 of patients	- .095	.036	1*	.286	.193	- .162	- .168	.163	.246
IL-6 of controls		- .296	.286	1*	.032	- .085	- .010	.434	.315
IL-22 of patients	.203	- .009	.193	.032	1*	.0371	- .245	- .116	.112
IL-22 of controls		- .039	- .162	- .085	.037	1*	- .147	.126	- .029
TGF-B of patients	- .329	- .361	- .168	- .010	- .245	- .1470	1*	- .353	- .069
TGF-B of controls		.206	.163	.434	- .116	.126	- .353	1*	- .077
Type of bacteria	- .313	- .815	.246	.315	.112	- .029	- .069	- .077	1*

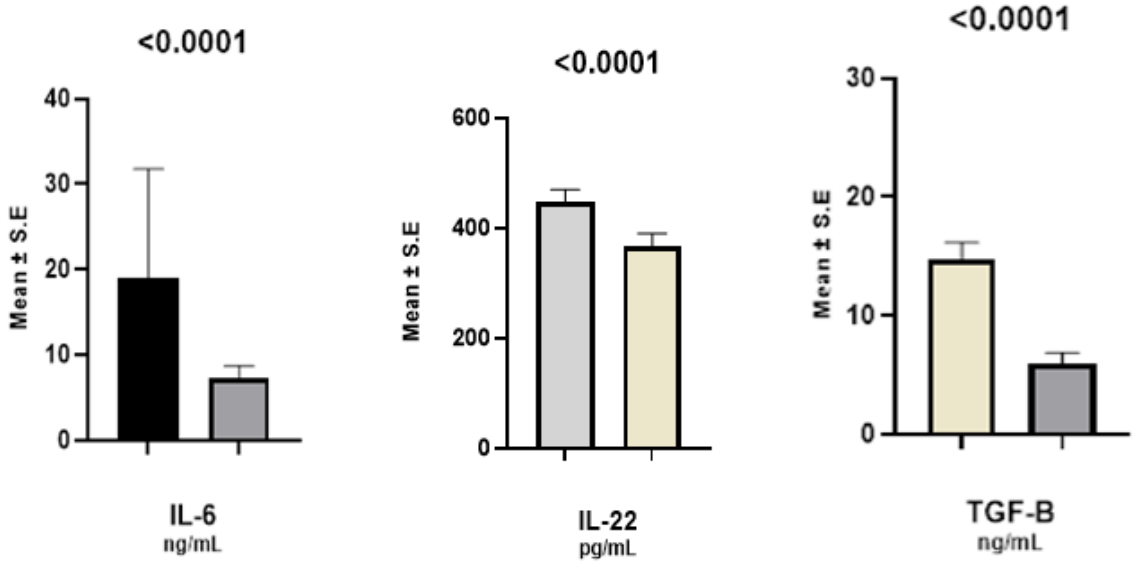

Figure 1) Serum levels of IL-6, IL-22, and TGF-β1 in the studied groups (independent samples t-test)

contrast, 14 (24.13%) samples contained Gram-positive bacteria, mainly *S. aureus* (Tables 1 and 2). These results indicated that Gram-negative bacteria were predominant among HAP cases, with *P. aeruginosa* being the most frequently isolated pathogen. Although Vitek2 is a standardized platform for bacterial identification, the distribution of pathogens isolated in this study, particularly the predominance of *P. aeruginosa* (37.9%) and the detection of only *S. aureus* isolates, differs from global patterns commonly reported for HAP. This difference may be attributed to local hospital ecology and antibiotic stewardship practices.

The distribution of patients by gender

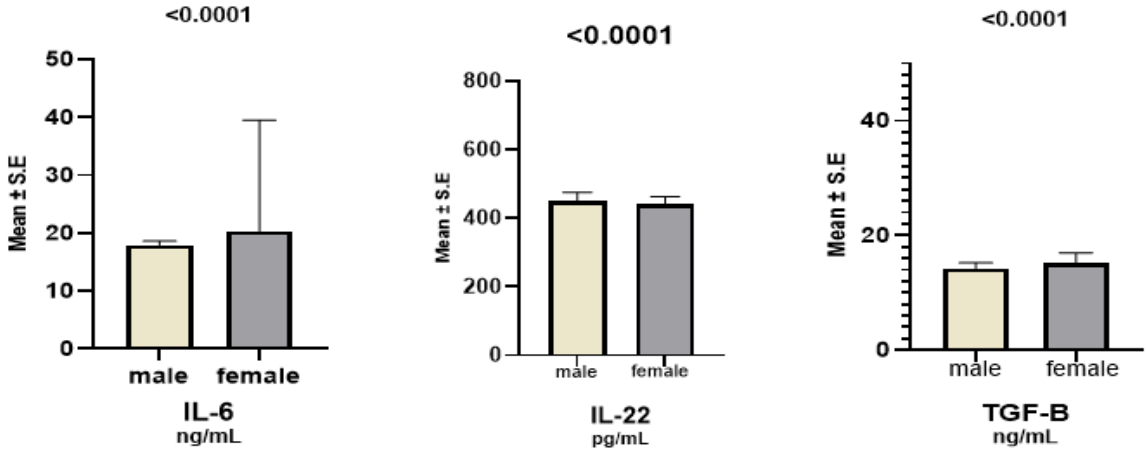

Figure 2) Serum levels of IL-6, IL-22, and TGF-β1 by gender (independent samples t-test)

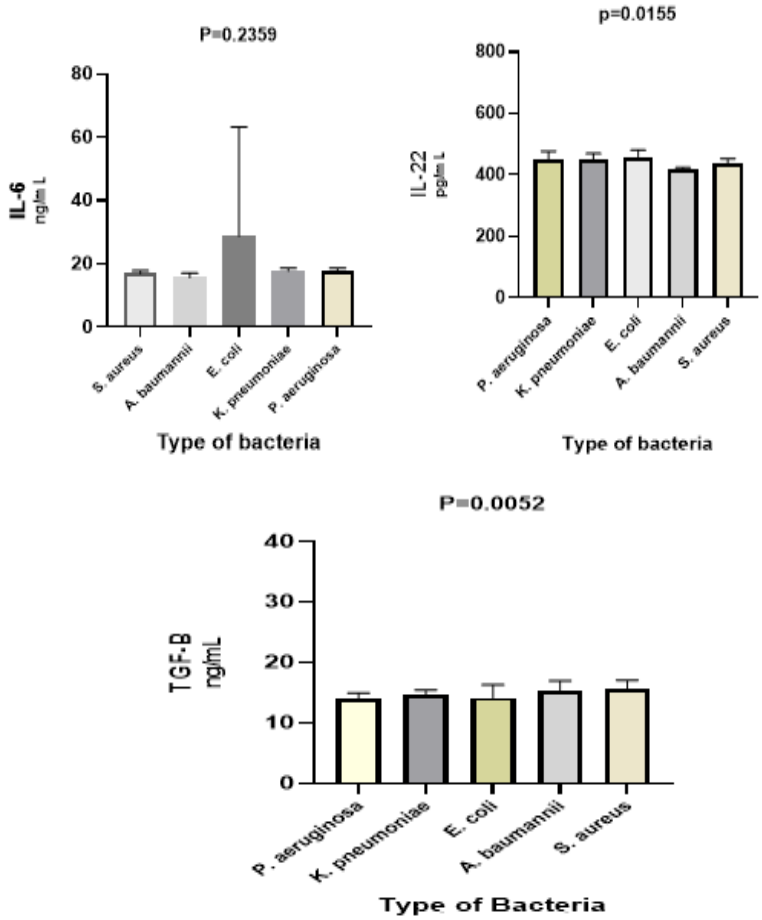

Figure 3) Serum levels of IL-6, IL-22, and TGF-β by bacterial type

showed that the prevalence of the disease was higher among male patients (55.17%) compared to female patients (44.82%) (Table 3). The concentrations of IL-6, IL-22, and TGF-β in the serum of pneumonia patients were higher (19.02±1.675 ng/mL, 446.1±3.074 pg/mL, and 14.69±0.191 ng/mL, respectively) compared to the control

group (7.206±0.274 ng/mL, 365.6±4.265 pg/mL, and 5.88±0.17 ng/mL, respectively) (Table 4, Figure 1).

The gender distribution of IL-6, IL-22, and TGF-β1 levels in the studied groups is shown in Table 5 and Figure 2. The mean concentrations of IL-6, IL-22, and TGF-β1 were higher in male patients (17.94±0.122 ng/mL, 450±4.30 pg/mL, and 14.27±0.172 ng/mL, respectively) compared to the control group (20.35±3.757 ng/mL, 440±4.22 pg/mL, and 15.22±0.34 ng/mL) (Table 5, Figure 2).

The distribution of IL-6, IL-22, and TGF-β1 levels by bacterial type is shown in Table 6 and Figure 3.

The results showed that the correlation between the cytokines IL-6, IL-22, and TGF-β and bacterial causes of hospital-acquired pneumonia was weak and not strong enough to be relied upon to differentiate between the studied groups.

Discussion

Hospital-acquired pneumonia (HAP) remains a major challenge in healthcare settings due to its significant morbidity and mortality rates. In a previous study, the most important finding was the prevalence of Gram-negative bacteria and *S. aureus* as major causes of pneumonia, these bacteria are of great concern due to their increasing resistance to commonly-used antibiotics. Multidrug-resistant bacterial infections lead to worse outcomes, including longer hospital stays and increased mortality rates [19]. There are numerous factors that increase the risk of developing ventilator-associated pneumonia, such as prolonged hospital stay, use of mechanical ventilation, and previous antibiotic use. This type of pneumonia is particularly common among patients receiving mechanical ventilation for long periods of time [20]. Diagnostic challenges play an important role in the management of bronchitis. Previous studies have shown that sputum culture and imaging with traditional diagnostic methods may not always provide conclusive results, leading to delayed or inappropriate treatment [21].

Interleukin-6 (IL-6) is involved in both innate and acquired immune responses and plays a central role in proinflammatory and anti-inflammatory responses through regulating immune and inflammatory responses [22]. This cytokine is produced by many immune cells, such as macrophages and T cells, in response to infection and is also involved in B cell differentiation and T cell activation [4]. This study results are consistent with those of other previous studies indicating increased IL-6 levels in bacterial infections [23]. IL-6 plays an essential role in HAP pathogenesis [24]. Elevated IL-6 levels in HAP patients are associated with disease severity and systemic inflammation [24]. Furthermore, IL-6 has been implicated in immune dysregulation, which could impair bacterial clearance and elevate the risk of secondary infections, particularly in ventilator-associated pneumonia (VAP) [25]. IL-6-guided risk stratification has been proposed as a useful tool for supporting early diagnosis and treatment decisions in nosocomial infections [26]. Previous studies suggest that IL-6 plays a role in promoting protective immune responses and regulating inflammatory pathways [27]. In a study, serum levels of IL-6 were found to be considerably higher in ICU patients with HAP than in non-pneumonia controls, indicating its role in systemic inflammation and disease progression [28]. In another study, clinical severity ratings and length of ICU stay were positively correlated with IL-6 levels in mechanically ventilated HAP patients. These findings imply that this cytokine might be a useful prognostic indicator in hospital environments [29]. A clinical investigation revealed that early IL-6 elevation was associated with worse outcomes and complications such as

sepsis in HAP patients, underscoring the importance of IL-6 monitoring in critical care units [30]. Moreover, a study at Mosul Teaching Hospital revealed that IL-6 levels were significantly higher in HAP patients who were resistant to several antibiotics than in susceptible patients, indicating the connection between pathogen virulence and immune activation [30].

The elevated IL-22 levels observed in our cohort are consistent with its proven role in mucosal immunity and antimicrobial defense [31]. The gender difference in this study is supported by single cell transcriptomic studies indicating that activated neutrophils and lung resident macrophages are involved in IL-22 production during pneumonia [32]. Interleukin-22 plays an important role in mucosal immune responses and tissue protection, particularly in the respiratory system. IL-22 plays an important role in pneumococcal pneumonia and helps suppress the pneumococcal burden in the lungs and extrapulmonary tissues by promoting complement deposition on bacteria, which improves phagocytosis by neutrophils [33]. Recent studies suggest that IL-22 enhances epithelial defense mechanisms by inducing antimicrobial peptides and promoting tissue regeneration, especially in bacterial pneumonia [34]. In murine models of HAP and VAP, IL-22 administration has been shown to reduce bacterial burden and recover survival by strengthening alveolar epithelial barrier integrity [35]. The defensive role of IL-22 has been confirmed in immunocompromised hosts, suggesting its potential as a therapeutic agent for patients at high risk of nosocomial infections [36]. A previous study in Baghdad found that IL-22 was significantly increased in patients with severe pneumonia compared to controls, indicating its protective immunomodulatory role [37]. Increased IL-22 levels in patients with pneumonia caused by multidrug-resistant bacteria were shown in another study [38]. Another research in Iraq examined IL-22 in VAP patients and found that its high levels were associated with disease resolution, supporting its protective function in lung repair and recovery [39].

TGF-β is a cytokine mainly produced by macrophages, regulatory T cells, and epithelial cells. It plays essential roles in fibrosis, immune regulation, and epithelial cell repair. In the lung, this cytokine is crucial for maintaining pulmonary homeostasis by regulating inflammatory responses and promoting tissue remodeling [40]. TGF-β may defend the body against infection by reducing excessive inflammation or contribute to disease pathophysiology by inhibiting immune system function [41].

The high TGF-β levels in HAP patients in the present study may primarily reflect a compensatory strategy aimed at preventing acute lung tissue damage and reducing excessive inflammation. TGF-β plays a dual biological role, and activation of this pathway has been strongly related with pulmonary fibrosis and immune dysregulation. Several previous studies have confirmed that persistent TGF-β signaling promotes fibroblast activation, structural remodeling of the lung parenchyma, extracellular matrix deposition, and long-term functional decline [18]. Higher levels of TGF-β in bronchoalveolar lavage fluid (BALF) are linked to worse outcomes in patients with pneumonia, indicating its dual function in pulmonary immunity [41]. TGF-β is a multipurpose mediator that controls immune responses to lung infections such as HAP by preventing excessive inflammation to maintain tissue integrity. Nevertheless, this inhibition may weaken antimicrobial resistance and increase the persistence of pathogens [42]. Impaired neutrophil recruitment and delayed bacterial clearance have been associated with elevated pulmonary TGF-β levels during bacterial

pneumonia, particularly in nosocomial infections [43]. TGF-β is known to induce epithelial-to-mesenchymal transition (EMT), a process that may worsen the long-term outcomes of HAP or VAP [44]. Despite these negative consequences, TGF-β is essential for reducing inflammation and promoting tissue healing in the latter stages of infection, underscoring its intricate and crucial roles [45]. Therapeutic targeting of TGF-β pathways is under investigation to promote bacterial clearance while reducing lung injury in HAP patients [46]. A clinical study in Baghdad Medical City reported significantly elevated TGF-β levels in ICU patients with HAP compared to non-infected ICU controls [45].

Another study found that increased TGF-β levels were associated with prolonged mechanical ventilation and delayed radiological recovery, underscoring its role in fibrosis and immune suppression during pulmonary infections [46]. Previous studies have shown that TGF-β elevation is part of a compensatory anti-inflammatory response (CARS) that might contribute to immune paralysis in prolonged infections [47].

The present study results also highlight the main gap between therapeutic intervention and cytokine profiling. Although cytokine modulation is suggested as a possible HAP prevention strategy, precise mechanisms are yet difficult to determine. For instance, IL-6 is a desirable target, and IL-6 receptor antagonists, such as tocilizumab, have been evaluated in hyperinflammatory states and cytokine storm syndromes. However, in the setting of severe bacterial pneumonia, any attempt to blunt IL-6–driven inflammation must carefully balance the need to reduce tissue injury against the risk of impairing bacterial clearance.

Study limitations: There are a number of limitations to this study. Important confounding variables that might affect inflammatory responses, such as comorbidities or disease severity, were not taken into consideration.

Conclusion

This study highlights the distinctive cytokine signatures in HAP patients, demonstrating significantly elevated IL-6, IL-22, and TGF-β levels in patients compared with healthy individuals. The intricate interaction between pro-inflammatory and anti-inflammatory reactions determines the severity and course of bacterial pneumonia. Therapeutic manipulation of immune cell function and cytokine activity may lead to better recovery and reduced mortality.

Abbreviations

HAP: Hospital-acquired pneumoni
IL-6:Interleukin-6
IL-22: Interleukin-22
TGF-β: Transforming growth factor-beta
ELISA: Enzyme-linked immunosorbent assay
Th17: T helper 17 cells
ARDS: Acute respiratory distress syndrome
IUC: Intensive care unit
VAP: Ventilator-associated pneumonia

Acknowledgments

Baquba Teaching Hospital in Iraq provided the samples, for which the authors are grateful.

Authors' contributions: The authors worked to design the study, collect samples, analyze data, and write up the results and research process.

Fundings: The authors have not declared.

Conflicts of interests: The authors have not declared.

Ethical approval: The study was approved by ethic committee of Diyala university.

Consent to participate: Informed consent was signed and approved by all participants.

References

1. Quinton LJ, Mizgerd JP. Dynamics of lung defense in pneumonia: Resistance, resilience, and remod-

eling. Ann Rev Physiol. 2015;77(1):407-30.
2. Martinez R, Menéndez R, Reyes S, Polverino E, Cillóniz C, Martínez A, et al. Factors associated with inflammatory cytokine patterns in community-acquired pneumonia. Eur Respir J. 2011;37(2):393-9.
3. Lee KY. Pneumonia, acute respiratory distress syndrome, and early immune-modulator therapy. Int J Mol Sci. 2017;18(2):388.
4. Rendon A, Rendon-Ramirez EJ, Rosas-Taraco AG. Relevant cytokines in the management of community-acquired pneumonia. Curr Infect Dis Rep. 2016;18(3):1-9.
5. Tanaka T, Narazaki M, Kishimoto T. IL-6 in inflammation, immunity, and disease. Cold Spring Harb Perspect Biol. 2014;6(10):a016295.
6. Jones SA, Jenkins BJ. Recent insights into targeting the IL-6 cytokine family in inflammatory diseases and cancer. Nat Rev Immunol. 2018;18(12):773–89.
7. Velazquez-Salinas L, Verdugo-Rodriguez A, Rodriguez LL, Borca MV. The role of interleukin 6 during viral infections. Front Microbiol. 2019;10:1057.
8. Wolk K, Witte E, Wallace E, Döcke WD, Kunz S, Asadullah K, et al. IL-22 regulates the expression of genes responsible for antimicrobial defense, cellular differentiation, and mobility in keratinocytes: A potential role in psoriasis. Eur J Immunol. 2006;36(5):1309-23.
9. Sonnenberg GF, Fouser LA, Artis D. Border patrol: Regulation of immunity, inflammation, and tissue homeostasis at barrier surfaces by IL-22. Nat Immunol. 2011;12(5):383–90.
10. Aujla SJ, Chan YR, Zheng M, Fei M, Askew DJ, Pociask DA, et al. IL-22 mediates mucosal host defense against Gram-negative bacterial pneumonia. Nat Med. 2008;14(3):275–81.
11. Walton KL, Johnson KE, Harrison CA. Targeting TGF-β mediated SMAD signaling for the prevention of fibrosis. Front Pharmacol. 2017;8:461.
12. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. The Lancet. 2011 Sep 10;378(9795):1015-26.
13. Worthington JJ, Kelly A, Smedley C, Bauche D, Campbell S, Marie JC, et al. Integrin αvβ8-mediated TGF-β activation by effector regulatory T cells is essential for suppression of T-cell-mediated inflammation. Immunity. 2015;42(5):903–15.
14. Sanjabi S, Oh SA, Li MO. Regulation of the immune response by TGF-β: from conception to autoimmunity and infection. Cold Spring Harbor perspectives in biology. 2017 Jun 1;9(6):a022236.
15. McElvaney OJ, McEvoy NL, McElvaney OF, Carroll TP, Murphy MP, Dunlea DM, et al. Characterization of the inflammatory response to severe bacterial pneumonia and IL-6–driven cytokine storm. Am J Respir Crit Care Med. 2020;202(6):812–21.
16. Gou X, Xu W, Liu Y, Peng Y, Xu W, Yin Y, et al. IL-6 prevents lung macrophage death and lung inflammation injury by inhibiting GSDME- and GSDMD-mediated pyroptosis during pneumococcal pneumosepsis. Microbiol Spectr. 2022;10(2):e02049-21
17. Meng XM, Nikolic-Paterson DJ, Lan HY. TGF-β: The master regulator of fibrosis and immune suppression. Nat Rev Nephrol. 2016;12(6):325–38.
18. Kalil AC, Metersky ML, Klompas M, Muscedere J, Sweeney DA, Palmer LB, et al. Management of adults with hospital-acquired and ventilator-associated pneumonia: 2016 clinical practice guidelines by the Infectious Diseases Society of America and the American Thoracic Society. Clin Infect Dis. 2016;63(5):e61–111.
19. Kalanuria AA, Ziai W, Mirski M. Ventilator-associated pneumonia in the ICU. Crit Care. 2014;18(2):1-8.
20. Torres A, Niederman MS, Chastre J, Ewig S, Fernandez-Vandellos P, Hanberger H, et al. International ERS/ESICM/ESCMID/ALAT guidelines for the management of hospital-acquired pneumonia and ventilator-associated pneumonia. Eur Respir J. 2017;50(3):1700582.
21. Kabir S, Parash MT, Emran NA, Hossain AT, Shimmi SC. Diagnostic challenges and gene-Xpert utility in detecting Mycobacterium tuberculosis among suspected cases of pulmonary tuberculosis. PLoS One. 2021;16(5):e0251858
22. Zobel K, Martus P, Pletz MW, Ewig S, Prediger M, Welte T, et al. Interleukin 6, lipopolysaccharide-binding protein, and interleukin 10 in the prediction of risk and etiologic patterns in patients with community-acquired pneumonia: Results from the German competence network CAPNETZ. BMC Pulm Med. 2012;12(1):1-10.
23. Feng M, Sun T, Zhao Y, Zhang H. Detection of serum interleukin-6/10/18 levels in sepsis and its clinical significance. J Clin Lab Anal. 2016;30(6):1037-43.
24. Zhang Y, Li B, Ning B. Evaluating IL-6 and IL-10 as rapid diagnostic tools for Gram-negative bacteria and as disease severity predictors in pediatric sepsis patients in the intensive care unit. Front Immunol. 2022 Dec 5;13:1043968.
25. Chen W, Zhong K, Guan Y, Zhang HT, Zhang H, Pan T, et al. Evaluation of the significance of interleukin-6 in the diagnosis of postoperative pneumonia: A prospective study. BMC Cardiovasc Disord. 2022;22(1):306
26. Yu Q, Cen C, Gao M, Yuan H, Liu J. Combination of early Interleukin-6 and-18 levels predicts postoperative nosocomial infection. Front Endocrinol. 2022;13:1019667.

27. Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defense against infections: Immunobiology and clinical implications. Nat Rev Rheumatol. 2017;13(7):399-409.
28. Iwase S, Nakada TA, Hattori N, Takahashi W, Takahashi N, Aizimu T, et al. Interleukin-6 as a diagnostic marker for infection in critically ill patients: A systematic review and meta-analysis. Am J Emerg Med. 2019;37(2):260-5.
29. Takahashi W, Nakada TA, Yazaki M, Oda S. Interleukin-6 levels act as a diagnostic marker for infection and a prognostic marker in patients with organ dysfunction in intensive care units. Shock. 2016;46(3):254-60.
30. Younis MY, Altaii HA. Survey of immunological and bacteriological parameters of septicemia in patients hospitalized in ICU departments of Mosul hospitals. Malays J Microbiol. 2024;20(3):364.
31.Travaglini KJ, Nabhan AN, Penland L, Sinha R, Gillich A, Sit RV, et al. A molecular cell atlas of the human lung from single-cell RNA sequencing. Nature. 2020;587(7835):619–25.
32. Alcorn JF. IL-22 plays a critical role in maintaining epithelial integrity during pulmonary infection. Front Immunol. 2020;11:1160.
33. Trevejo-Nunez G, Elsegeiny W, Aggor FE, Tweedle JL, Kaplan Z, Gandhi P, et al. Interleukin-22 (IL-22) binding protein constrains IL-22 activity, host defense, and oxidative phosphorylation genes during pneumococcal pneumonia. Infect Immun. 2019;87(11):10-128.
34. Abood RN, McHugh KJ, Rich HE, Ortiz MA, Tobin JM, Ramanan K, et al. IL-22-binding protein exacerbates influenza, bacterial super-infection. Mucosal Immunol. 2019;12(5):1231-43
35. Yang X, Weng Q, Hu L, Yang L, Wang X, Xiang X, et al. Increased interleukin-22 levels in lupus nephritis and its association with disease severity: A study in both patients and lupus-like mice model. Clin Exp Rheumatol. 2019;37:400-7.
36. Zhang K, Chen L, Zhu C, Zhang M, Liang C. Current knowledge of Th22 cell and IL-22 functions in infectious diseases. Pathogens. 2023;12(2):176
37. Hamid RH, AL-Jumaily RM. Immunological role of IL-3, IL-22, and some physiological markers in Iraqi patients with chronic kidney disease. Ibn AL-Haitham J Pure Appl Sci. 2024;37(3):42-9.
38. Sakamoto K, Kim YG, Hara H, Kamada N, Caballero-Flores G, Tolosano E, et al. IL-22 controls iron-dependent nutritional immunity against systemic bacterial infections. Sci Immunol. 2017;2(8):eaai8371.
39. Saito A, Horie M, Micke P, Nagase T. The role of TGF-β signaling in lung cancer associated with idiopathic pulmonary fibrosis. Int J Mol Sci. 2018;19(11):3611.
40. Willis BC, Borok Z. TGF-β-induced EMT: Mechanisms and implications for fibrotic lung disease. Am J Physiol Lung Cell Mol Physiol. 2007;293(3):L525–34.
41. Travis MA, Sheppard D. TGF-β activation and function in immunity. Ann Rev Immunol. 2014;32(1):51-82.
42. Shimbori C, Bellaye PS, Xia J, Gauldie J, Ask K, Ramos C, et al. Fibroblast growth factor-1 attenuates TGF-β1-induced lung fibrosis. J Pathol. 2016;240(2):197-210.
43. Wang B, Dileepan T, Briscoe S, Hyland KA, Kang J, Khoruts A, et al. Induction of TGF-β1 and TGF-β1–dependent predominant Th17 differentiation by group A streptococcal infection. Proc Natl Acad Sci. 2010;107(13):5937-42.
44. Qu Z, Guo Z, Chunjuan Y, Guan X, Cheng M, Wang P, et al. Role of toll-like receptors in pulmonary immunity: Mechanisms and therapeutic implications. Front Immunol. 2025;16:1682649.
45. Yoshimura A, Wakabayashi Y, Mori T. Cellular and molecular basis for the regulation of inflammation by TGF-β. J Biochem. 2010;147(6):781-92.
46. McCulloch TR, Rossi GR, Schreuder J, Belz GT, Wells TJ, Souza-Fonseca-Guimaraes F. CIS and TGF-β regulatory pathways influence immunity to bacterial infection. Immunology. 2022;167(1):54-63.
47. Sanjabi S, Oh SA, Li MO. Regulation of the immune response by TGF-β: From conception to autoimmunity and infection. Cold Spring Harb Perspect Biol. 2017;9(6):a022236.