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Immunological changes associated with post-surgical gram-negative bacterial infections

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Abstract
Objective: Post-surgical bacterial infections provoke immune responses mediated by various cytokines. This study aimed to assess immunological changes by measuring serum levels of IL-2, IL-7, IL-10, and IL-17 in post-surgical patients with bacterial infections and comparing them with non-infected post-surgical patients and healthy controls.
Methods: In this prospective, single-centre investigation, we analysed serum cytokine levels across three distinct groups: (1) patients with post-surgical bacterial infections, primarily involving *Klebsiella pneumoniae*; (2) non-infected post-surgical patients (surgical controls); and (3) healthy individuals (baseline controls). Serum cytokine levels were measured using ELISA. Statistical analysis was performed using one-way ANOVA to identify group differences, and ROC curve analysis was used to evaluate diagnostic performance.
Results: Serum analysis revealed significantly elevated levels of all measured cytokines in post-surgical patients with bacterial infections compared to surgical controls and healthy individuals ($p < 0.001$). IL-2 levels reached 363.6 ± 38.5 pg/mL in infected patients, compared to 225.8 ± 24.5 pg/mL in non-infected post-surgical patients and 151.6 ± 24.4 pg/mL in healthy controls. Similarly, IL-7, IL-10, and IL-17 levels were substantially higher in infected individuals. ROC analysis showed excellent diagnostic accuracy, with IL-2 and IL-10 demonstrating an AUC of 1.000.
Conclusion: Post-surgical bacterial infections lead to clear immunological changes. Cytokine profiling, particularly that of IL-2 and IL-10, could serve as a biomarker for early detection and better treatment of these infections. These observations indicate that IL-2 and IL-10 could potentially act as reliable biomarkers for the early detection and ongoing assessment of infections following surgery.

Keywords: Post-surgical infections, Klebsiella pneumoniae, Cytokines, IL-2, IL-7, IL-10, IL-17, Immune response, Surgical site infection (SSI), Biomarkers

Plain English Summary

Post-surgical bacterial infections, especially those caused by a common bacterium (*Klebsiella pneumoniae*), can delay recovery and increase patient illness from diseases. This study aimed to assess immunological changes by measuring serum levels of several chemical agents in the immune system (cytokines) in post-surgical patients with bacterial infections and comparing them with non-infected post-surgical patients and healthy controls. The study included three groups: (1) patients with post-surgical bacterial infections, primarily involving *Klebsiella pneumoniae*; (2) non-infected post-surgical patients (surgical controls); and (3) healthy individuals (baseline controls). Serum analysis revealed significantly elevated levels of all measured cytokines in post-surgical patients with bacterial infections compared to

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surgical controls and healthy individuals. Post-surgical bacterial infections lead to clear immunological changes.

Introduction

Surgical site infections (SSIs) are a major problem in the current era of healthcare, especially in patients who have undergone invasive surgical procedures. SSIs constitute an epidemic concerning nosocomial infections throughout the world (1). Irrespective of the advances in surgical practices and preoperative antisepsis and antibiotic prophylaxis, SSIs remain a significant and widespread concern, particularly in immunocompromised patients (2).

Gram-negative bacteria, including Klebsiella pneumoniae, are predominant pathogens in SSIs, with some K. pneumoniae strains being highly aggressive and multidrug-resistant (3). This bacterium is a common isolate from post-surgical wounds and is typified by an impressive collection of virulence determinants. These are its thick polysaccharide capsule that evades phagocytosis, robust biofilm formation, which promotes chronic colonisation, adhesins such as fimH, giving urease production and endotoxins like lipopolysaccharide that trigger high inflammatory responses (4, 5, 6). Furthermore, the magA gene was reported to correlate with hypermucoviscosity, improving protection for bacteria and the virulence of host tissues (7).

Gram-negative bacteria, especially Klebsiella pneumoniae, are becoming more commonly recognised for their role in surgical site infections (SSIs). Some strains are now hypervirulent and resistant to multiple drugs, which has been observed in various hospitals. These strains can cause serious health problems and high death rates, particularly in patients with weakened immune systems or those who have recently had surgery (3). Their strong ability to cause disease and resist treatment makes typical antibiotics less effective. Because of this, finding infections early is important. Using immune system markers, like cytokines, could be a helpful way to diagnose these infections sooner.

Innate and adaptive mechanisms mediate the host response to bacterial invasion. One of the most important players in this defence is cytokines, tiny protein messages that pass from cell to cell, controlling inflammation, immune cell differentiation and tissue repair. Pro-inflammatory cytokines, such as IL-2 and IL-17, are critical for priming and recruiting T-cells and neutrophils to the infection site to promote bacterial clearance (8, 9, 10). By contrast, the anti-inflammatory cytokines, like IL-10, are immunoregulators that attenuate tissue injury resulting from excessive inflammation (11, 12). IL-7 also exerts a vital duality as a T-cell survival factor and immune homeostatic factor during immunological stress, such as operation trauma and infection (13).

Cytokine profiling has evolved into a useful diagnostic and prognostic tool for analysing immune responses during infectious and inflammatory processes. With regards to the postoperative bacterial infection, determination of individual cytokine value may assist physicians in discriminating patients with or without the infection, monitoring disease courses, and performing early therapeutic intervention (14). The importance of the knowledge of these immunological alterations is particularly relevant in the recent context of rising antibiotic-resistant pathogens such as K. pneumoniae, which constitute significant challenges in the treatment and are responsible for a higher morbidity and mortality in surgical patients (3, 15).

The current study thus investigated the serum concentrations of some cytokines, IL2, IL7, IL10, and IL17, in these patients. These results may shed more light on the immune mechanisms of SSIs and indicate some biomarkers for early diagnosis and targeted immunomodulation. While previous investigations have frequently concentrated on individual cytokines to understand immune responses related to surgical stress or infections, such focused approaches might overlook the complexity of immune dysregulation. This research aims to address that limitation by examining a comprehensive panel of cytokines, specifically IL-2, IL-7, IL-10, and IL-17, thereby providing a more complete view of the energetic interactions between pro-inflammatory and regulatory immune mechanisms during post-surgical bacterial infections. The cytokines IL-2, IL-7, IL-10, and IL-17 were carefully selected for their unique and complementary roles within the immune system. IL-2 is essential for the activation and proliferation of T-cells, while IL-7 primarily supports the survival and maintenance of lymphocytes. IL-10 is a key regulator that suppresses excessive inflammatory responses, and IL-17 is instrumental in recruiting neutrophils and defending mucosal surfaces. Collectively, these cytokines provide a comprehensive perspective on immune activation and regulation, considering post-surgical immune responses.

Materials and Methods

Study Groups

The study encompassed three distinct groups: 1) post-surgical patients with confirmed bacterial infections, primarily caused by *Klebsiella pneumoniae*; 2) post-surgical patients without infections (surgical controls); and 3) Healthy individuals (baseline controls).

The inclusion criteria for the post-surgical infection group comprised adult patients aged between 18 and 70 years who displayed signs of surgical site infection (SSI) within seven days following surgery. Confirmation of infection was achieved through microbiological analysis, specifically by isolating Klebsiella pneumoniae from wound swabs. The surgical control group, representing non-infected patients, consisted of individuals who underwent similar surgical procedures within the same timeframe, up to seven days post-operation, without any clinical or microbiological evidence of infection. Healthy controls were selected to match the age and sex of the infected group and had no recent surgical history or signs of widespread inflammation. Exclusion criteria uniformly applied across all groups included immunocompromised states such as HIV infection or chemotherapy, autoimmune diseases, chronic inflammatory conditions, or ongoing widespread infections unrelated to the surgical procedure.

Sample collection and serum preparation:

Five mL of venous blood was aseptically withdrawn from each participant using sterile syringes into plain tubes and left to coagulate at ambient temperatures. Coagulated samples were then centrifuged speed of 1000–2000 × g for 10 minutes, and serum was isolated. The serum was aliquoted into labelled microtubes that were stored at –80°C until the time of immunological analysis.

Bacterial isolation and identification:

Surgical wounds suspected of being infected were sampled using sterile swabs. The swabs were inoculated onto MacConkey agar and blood agar plates before incubating the plates aerobically at 37°C for 24 to 48 hours. Mucoid colonies were identified using Gram staining and several conventional biochemical tests, including lactose fermentation, citrate utilisation, urease production, and indole formation, consistent with Klebsiella pneumoniae. Conclusively, the isolated strains were subjected to VITEK® 2 Compact bioMérieux, France, for susceptibility testing and further biochemical identification.

Cytokine quantification (ELISA):

Interleukins IL-2, IL-7, IL-10, and IL-17 assay in serum samples was quantified using commercially available ELISA kits, such as those from R&D Systems or Abcam, following the manufacturer's procedure. The calibrated microplate reader finally read the absorbance at 495 nm, and the cytokine values obtained were interpolated using standard curves plotted from standard dilutions. Serum concentrations of IL-2, IL-7, IL-10, and IL-17 were quantified employing commercially available ELISA kits supplied by R&D Systems (USA) and Abcam (UK). Each sample was analysed in duplicate, following the protocols provided by the manufacturers. The assays demonstrated intra-assay coefficients of variation (CV) below 8% and inter-assay CVs under 10%, emphasising the reliability and reproducibility of the measurements.

Statistical Analysis

Using G*Power 3.1, we calculated the required sample size based on an estimated effect size of 0.40 and a power of 80%. This analysis indicated that 21 participants per group would be sufficient. However, our actual sample size of 30 per group exceeds this minimum requirement, ensuring adequate statistical power. The presented data are represented as mean value and their standard deviations.

We checked if the data followed a normal distribution using the Shapiro-Wilk test, and we looked at the variance with Levene's test. Since everything looked good and the assumptions were met, we went ahead with a one-way ANOVA to compare the groups. After that, we did some pairwise comparisons with Bonferroni correction to make sure we didn't get false positives from testing multiple times. To assess the diagnostic performance for each cytokine, a Receiver Operating Characteristic curve was computed. In this test, the calculation of the area under the curve, sensitivity, and specificity was assessed. When a p-value was less than 0.05, the results were significant.

Results

The study population comprised 90 individuals divided into three groups: 30 post-surgical patients with confirmed infections, 30 post-surgical patients without infection serving as controls, and 30 healthy volunteers.

Cytokine responses in post-surgical patients serve as critical indicators for understanding immune reactions to surgical interventions and associated complications. The current study demonstrated notable changes in the serum levels of IL-2, IL-7,

IL-10, and IL-17 among post-surgical patients, both infected and non-infected, when compared to healthy individuals. These findings are highly relevant for analysing immune mechanisms and identifying factors contributing to infection development or therapeutic success in surgical care settings.

As shown in Table 1, the mean serum level of IL-2 was 363.6 ± 38.5 pg/mL in post-surgical infected patients, compared to 225.8 ± 24.5 pg/mL in post-surgical non-infected patients and 151.6 ± 24.4 pg/mL in healthy controls. IL-2 levels were significantly higher in both patient groups compared to healthy controls and markedly elevated in infected patients versus non-infected surgical patients (P = 0.000), as also illustrated in Figure 1.

Table 1: Assessment of Cytokine Levels in Patients and Healthy Controls

Groups	Interleukin levels			
	IL-2	IL-7	IL-10	IL-17
Post-surgery infection	363.6 ± 38.5^{A}	197.7 ± 24.7^{A}	691.5 ± 49.6^{A}	113.9 ± 12.8^{A}
	261.2 – 469.1	129.93 – 275.18	561.5 – 865.6	119.1– 139.9
Post-surgery without infection	225.8 ± 24.5^{B}	116.5 ± 15.3^{B}	517.9 ± 33.2^{B}	78.6 ± 2.9^{B}
	112.4-339.2	78.9-172.5	399.8-685.9	77.1-80.4
Control	151.6 ± 24.4^{C}	90.14 ± 16.6^{B}	229.3 ± 26.1^{C}	35.83 ± 6.6^{C}
	68.2 – 232.6	9.84 – 152.70	115.8 – 370.2	24.7 – 149.7
p-value	0.001**	0.001**	0.001**	0.001**
	†	†	†	†

*Different superscript letters (A, B, C) within each row indicate statistically significant differences (p ≤ 0.05) by one-way ANOVA; SD: standard deviation; †: one-way ANOVA; **: p ≤ 0.05.*

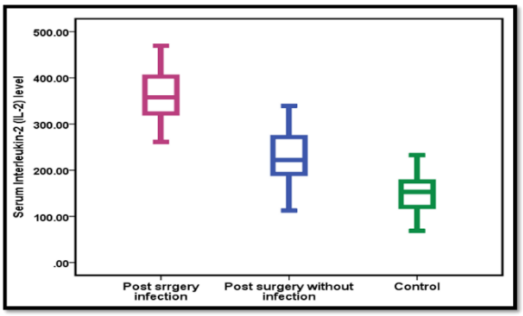

Figure 1: Mean IL-2 Level in Patients and Control *Groups*

Figure 2 shows a significant elevation in IL-7 serum levels in post-surgical infected patients (197.7 ± 24.7 pg/mL), compared to both non-infected post-surgical patients (116.5 ± 15.3 pg/mL) and healthy controls (90.14 ± 16.6 pg/mL) (p = 0.001). However, the difference between non-infected post-surgical patients and healthy controls was not significant (p > 0.05), as illustrated in Figure 2.

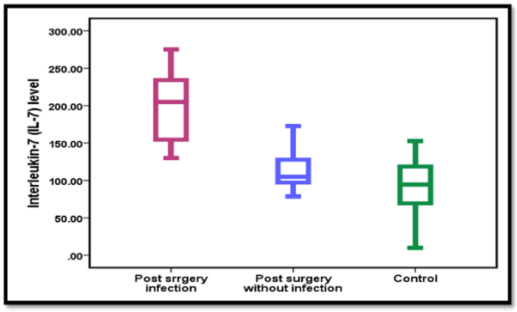

Figure 2: Mean IL-7 Level in Patients and Control Groups

IL-17 enhances cell migration, chemokine expression, and invasive potential, in addition to promoting metalloproteinase secretion, which damages cartilage and mediates angiogenesis.

Moreover, IL-10 produced by regulatory B10 cells was shown to ameliorate arthritis by inhibiting Th17 responses, as illustrated in Figures 3 and 4.

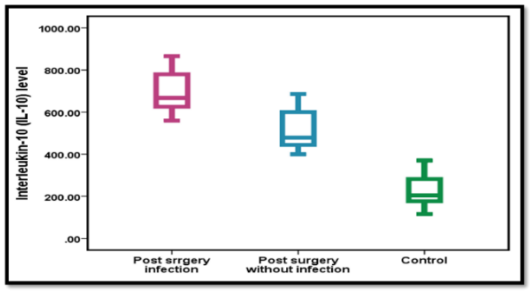

Figure 3: Mean IL-10 Level in Patients and Control Groups

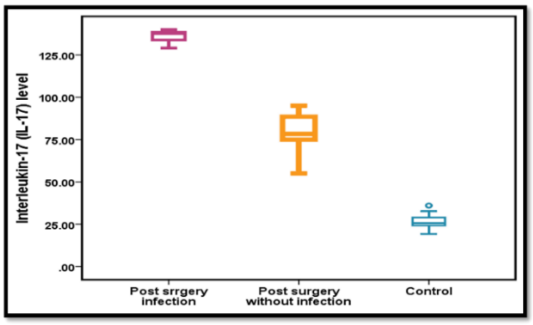

Figure 4: Mean IL-17 Level in Patients and Control Groups

Cytokine Levels by Age Group

The levels of immunological markers (IL-2, IL-7, IL-10, and IL-17) were analysed according to age groups in both patient categories. The results are presented as mean ± standard deviation in Table 2.

Statistical comparisons revealed no significant differences in the concentrations of IL-2, IL-7, IL-10, and IL-17 among patients across different age groups in either the infected or non-infected post-surgical groups.

Table 2: Frequency Distribution of Cytokine Levels by Age Groups in Post-Surgical Infection Patients

Age groups	IL-2 levels	IL-7 levels	IL-10 levels	IL-17 levels
Post-surgery infection patients				
11-20 years	303.8 ± 17.6	174.2 ± 23.6	652.3 ± 34.4	133.9 ± 11.1
20-30 years	375.4 ± 28.1	219.2 ± 23.3	667.9 ± 44.9	137.1 ± 8.5
31-40 years	378.9 ± 29.6	162.5 ± 11.1	720.5 ± 36.5	134.5 ± 8.9
41-50 years	332.4 ± 30.5	196.3 ± 22.9	730.1 ± 43.5	135.7 ± 9.3
51-60 years	394.1 ± 30.4	208.3 ± 25.7	734.7 ± 42.6	135.5 ± 12.4
61-70 years	380.2 ± 20.1	196.5 ± 26.6	649.5 ± 30.5	136.9 ± 12.1
p-value	0.151	0.761	0.736	0.816
Post-surgery, without infection, patients				
20-30 years	212.4 ± 25.3	109.2 ± 15.6	544.9 ± 30.7	72.8 ± 7.8
31-40 years	228.9 ± 26.8	117.9 ± 17.6	498.9 ± 29.7	82.1 ± 10.3
41-50 years	222.4 ± 24.4	117.3 ± 17.4	446.6 ± 29.1	79.8 ± 8.4
51-60 years	245.5 ± 20.1	131.1 ± 16.2	444.9 ± 13.9	75.5 ± 5.9
p-value	0.855	0.861	0.206	0.553

SD: standard deviation; †: Independent T test; **: significant at $P < 0.05$

Parameters Performance Regarding Sensitivity and Specificity Using ROC Curve Analysis

Tables 3 and 4 and Figures 5 and 6 present the results of ROC (Receiver Operating Characteristic) curve analysis for IL-2, IL-7, IL-10, and IL-17 levels. IL-2 demonstrated an AUC (Area Under the Curve) of 1.000 (P = 0.001), indicating excellent diagnostic accuracy for post-surgical infection at a cutoff value above 246.77 pg/mL with sensitivity and specificity both at 100.0%. For IL-7, the AUC was 0.985 (P = 0.001), identifying post-surgical infection at a cutoff value above 130.15 pg/mL, with a sensitivity of 95.0% and specificity of 90.0%. IL-10 also showed an AUC of 1.000 (P = 0.001), with a cutoff value of 465.87 pg/mL and perfect diagnostic performance (sensitivity = 100.0%, specificity = 100.0%). Additionally, IL-17 demonstrated an AUC of 0.950 (P = 0.001) at a cutoff above 130.44 pg/mL, with both sensitivity and specificity at 95.0%, as shown in Table 3.

Table 3: ROC Curve Analysis for Evaluating Marker Performance in Post-Surgical Infection Patients

Characteristic	AUC	p-value	Cut off value	Sensitivity	Specificity
IL-2	1.000	< 0.001	> 246.77	100.0%	100.0%
IL-7	0.985	< 0.001	> 130.15	95.0%	90.0%
IL-10	1.000	< 0.001	> 465.87	100.0%	100.0%
IL-17	0.950	< 0.001	> 130.44	95.0%	95.0%

95% Confidence interval, AUC: Area under the curve

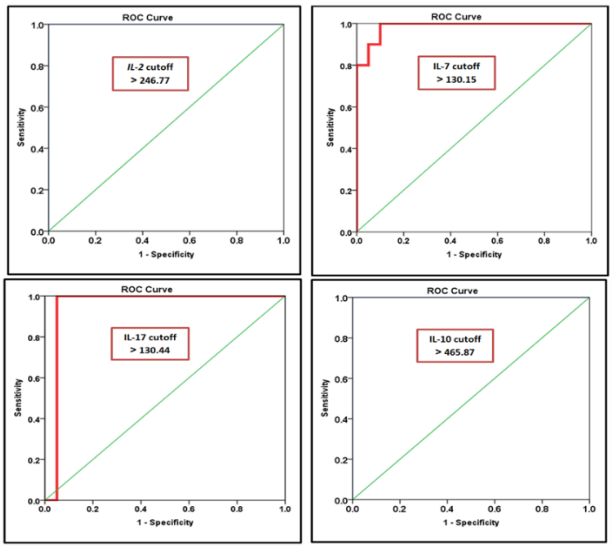

Figure 5: ROC Curve Analysis of Immunological Markers in Post-Surgical Infection Patients to Determine Potential Diagnostic Cut-off Values

Table 4: ROC Curve Analysis for Evaluating Marker Performance in Post-Surgical Non-Infected Patients

Characteristic	AUC	p-value	Cut off value	Sensitivity	Specificity
IL-2	0.883	< 0.001	> 179.4	85.0%	85.0%
IL-7	0.702	0.004	> 103.14	75.0%	70.0%
IL-10	1.000	< 0.001	> 384.9	100.0%	100.0%
IL-17	1.000	< 0.001	> 45.5	100.0%	100.0%

95% Confidence interval, AUC: Area under the curve

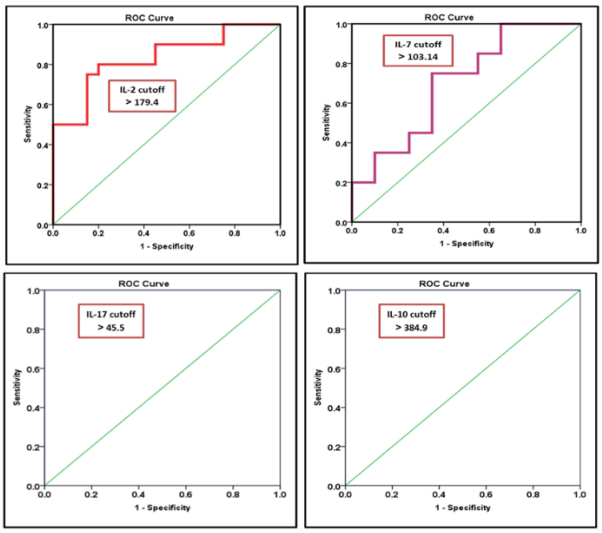

Figure 6: ROC Curve Analysis of Immunological Markers in the Post-Surgical Non-Infected Phase to Determine Potential Diagnostic Cut-off Values

Correlation Between Immunological Parameters

Table 5 presents the correlations among various immunological markers. The current results reveal a significant positive correlation between IL-2 and IL-7 (r = 0.461, p = 0.011), IL-2 and IL-17 (r = 0.300, p = 0.033), and IL-7 and IL-17 (r = 0.558, p = 0.001) in post-surgical infected patients.

Table 5: Correlations between Immunological Parameters in Post-Surgical Infection Patients

Parameters		IL-2	IL-7	IL-10	IL-17
IL-2	r	1			
	P				
IL-7	r	0.461	1		
	P	0.011*			
IL-10	r	0.251	0.227	1	
	P	0.087	0.101		
IL-17	r	0.300	0.558	0.119	
	P	0.033*	0.001*	0.618	1

r: Pearson correlation coefficient

Additionally, in non-infected post-surgical patients, there was also a significant positive correlation between IL-2 and IL-7 (r = 0.335, p = 0.031), as well as between IL-2 and IL-17 (r = 0.483, p = 0.009) (Table 6). These findings suggest a coordinated immune response involving both pro-inflammatory and regulatory cytokines in both infected and non-infected surgical cases.

Table 6: Correlations Between Immunological Parameters in Post-Surgical Non-Infected Patients

Parameters		IL-2	IL-7	IL-10	IL-17
IL-2	r	1			
	P				
IL-7	r	0.335	1		
	P	0.031*			
IL-10	r	0.200	0.133	1	
	P	0.398	0.576		
IL-17	r	0.483	0.065	0.173	
	P	0.009*	0.787	0.467	1

Logistic Regression Correlations Between Immunological Parameters in the Patient Group

Figure 7 illustrates the logistic regression analysis between serum IL-2 and IL-7 levels in the patient group. The results demonstrated a positive relationship between the two variables, with a coefficient of determination (R^2) of 0.1943.

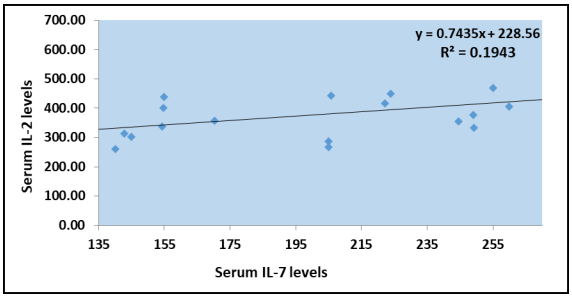

Figure 7: 2D Logistic Scatter plot for IL-2 and IL-7 in the patients

Logistic Regression between IL-2 and IL-10 Levels in Patients

The logistic regression of serum concentrations of IL-2 and IL-10 of the patient group is given in Figure 8. There was only a very poor relationship between the two, as indicated by a coefficient of determination (R^2) of 0.0328. Thus, only about 3.28% of the variation in IL-2 levels is attributable to the variation in IL-10 levels.

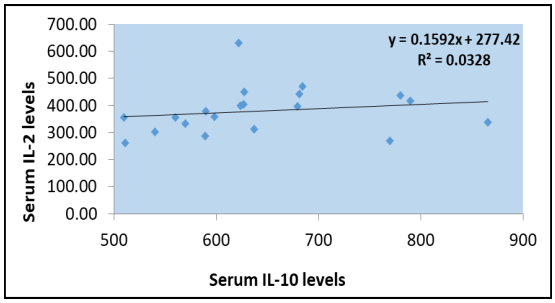

Figure 8: Logistic Scatter Plot of IL-2 and IL-10 in patients

Logistic Regression Analyses of IL-2 and IL-17 Levels in Patients

Figure 9 shows the logistic regression analysis of serum IL-2 and IL-17. The coefficient of determination (R^2) was 0.092, yet it is a positive weak relationship. This indicates that approximately 9.2% of the variance in IL-2 levels can be accounted for by changes in IL-17 levels. IL-17 is a Th17-derived pro-inflammatory cytokine, and IL-2 is involved in the activation of these cells

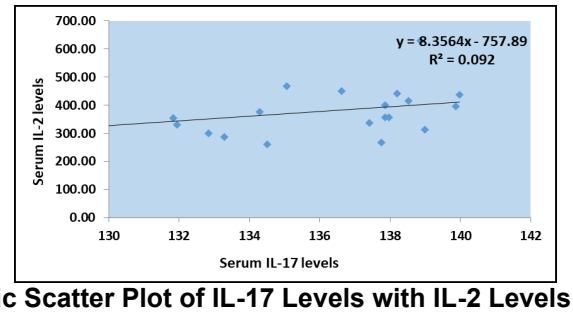

Figure 9: Logistic Scatter Plot of IL-17 Levels with IL-2 Levels among Patients

Logistic Regression of IL-7 and IL-10 Levels in Patients

The logistic regression analysis of the association of IL-7 and IL-10 serum concentrations is shown in Figure 10. We found a low to moderate positive relationship with R-squared (R^2) of 0.1536. This would mean that about 15.36% of the variability in IL-7 can be explained by variations in IL-10. Such

an association indicates a potential combinatorial regulation between the anti-inflammatory IL-10 and the T-cell proliferation/survival factor IL-7.

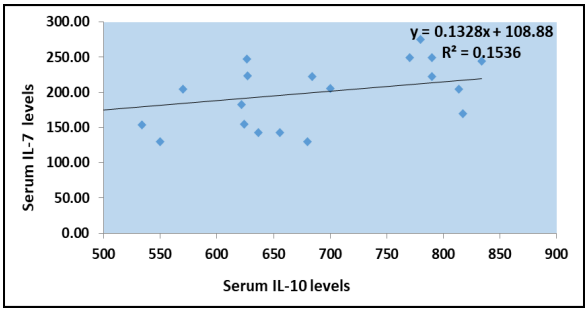

Figure 10: Logistic Scatter Plot of IL-7 and IL-10 Levels among Patients

Logistic Regression Analysis between IL-7 and IL-17 Levels in Patients

Figure 11 illustrates the logistic regression analysis of the relationship between serum levels of IL-7 and IL-17 in the patient group. The results demonstrated a moderate positive correlation, with a coefficient of determination (R^2) of 0.2039.

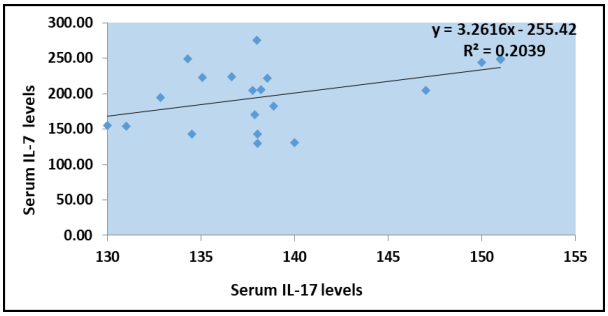

Figure 11: Logistic Scatter Plot of IL-7 and IL-17 Levels among Patients

Logistic Regression Analysis Between IL-10 and IL-17 Levels in Patients

Figure 12 displays the logistic regression analysis of the relationship between IL-10 and IL-17 serum levels. The results revealed a very weak positive correlation, with a coefficient of determination (R^2) of 0.0439. This indicates that only about 4.39% of the variation in IL-10 levels can be explained by changes in IL-17 levels.

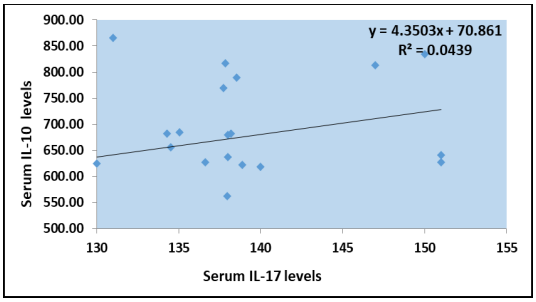

Figure 12: Logistic Scatter Plot of IL-10 and IL-17 Levels among Patients

Discussion

Cytokines play a central role in regulating physiological processes such as cytoskeletal organisation, stem cell differentiation and proliferation, tissue regeneration, wound healing, and the coordination of innate and adaptive immune responses (16). They mediate humoral and cellular immunity, regulate immune cell trafficking and tissue remodelling, and influence local inflammatory environments. Although cytokines are often present in low or undetectable concentrations under normal conditions, their

levels rise rapidly in response to infection or inflammation (17, 18).

IL-2 is a cytokine involved in immune signalling pathways, influencing various essential immune functions. It modulates the activation and differentiation of immune cells, particularly CD4+ and CD8+ T-cells, and may impact wound healing as well (19). The significantly elevated IL-2 levels observed in infected post-surgical patients align with findings by Muhammad et al. (2023), who reported IL-2 as a crucial mediator in T-cell activation in response to infections (20). This increase suggests that surgical stress combined with infection enhances immune activation through IL-2 upregulation. In addition, the remarkably distinct folds in IL-2 levels between infected and non-infected postsurgical patients indicated that IL-2 was a valuable marker in helping diagnose infection in surgical patients. Yan et al. (2021) also emphasised the predictive role of IL-2 in critically ill patients and found an independent association between high levels of IL-2 and 28-day mortality (21).

IL-2 stimulates T-cell proliferation, maturation, and commitment to activated phenotypes, as well as a direct effect on the local immune environment and reactivity (22). The surgical trauma can cause tissue injury and abrogation of microbial exposition that results in either exaggerated innate host immunity or immune suppression and imbalance of the adaptive immune system, which leads to a high susceptibility to severe complications, such as SIRS, sepsis, and MODS (23). Nevertheless, some publications suggest that high concentrations of IL-2 are not always a parameter related to the disease severity, being influenced by the surgical procedure (24). For instance, Handayani et al. (2023) reported higher IL-2 levels in non-infectious inflammatory diseases, like our findings, and Risan et al. (2012) in cases of rheumatoid arthritis. This indicates that IL-2 is involved in more general intracellular defence against infections and autoimmune diseases (25, 26). IL-2 is not a marker, but a central element of adaptive immunity.

Recent studies confirmed its role in stimulating CD8+ cytotoxic T-cell activity, which is vital for pathogen clearance (9). Therefore, elevated IL-2 levels in infected post-surgical patients may reflect ongoing immune conflict with pathogens and offer insight into infection severity and therapeutic outcomes (21).

IL-7 is an important cytokine involved in immune regulation, particularly in the survival and maintenance of T-cells. The elevated levels of IL-7 observed in infected patients suggest that the immune system increases T-cell availability as a defence mechanism. This finding is consistent with a study by Bartlett et al. (2016), which reported elevated IL-7 levels in chronic wound environments, especially following stressors like surgery (27).

Infection-related IL-7 elevation may reflect enhanced T-cell proliferation and survival during immune stress, a notion supported by Gao et al. (2023), who observed that IL-7 levels correlate with T-cell recovery in immunocompromised 8conditions (28). However, overproduction of IL-7 has been linked to dysregulated T-cell activation and potential autoimmunity, as demonstrated by Lin et al. (2021) (29).

Interestingly, the lack of significant differences between non-infected surgical patients and healthy controls implies that IL-7 elevation may be specific to infectious complications rather than surgery alone. This supports previous findings by Bartlett et al. (2016), who found that IL-7 was significantly higher in patients with postoperative complications than in those undergoing uneventful recovery [27].

IL-7 is recognised for its proliferative effects on both B and T lymphocytes. A deficiency in IL-7 can lead to arrested development of immature immune cells (30). Multiple studies have confirmed that human T-cells require IL-7 for survival, clonal expansion, and T-cell receptor gene rearrangement (13). IL-7 promotes T-cell survival by increasing the expression of anti-apoptotic proteins such as Mcl-1 and Bcl-2, which inhibit the mitochondrial apoptosis pathway (31).

Furthermore, Bartlett et al. (2016) reported increased IL-7 expression during chronic wound healing, supporting its role in the inflammatory phase of tissue repair. Surgical stress may affect cytokine dynamics, influenced by factors such as procedure complexity, operation duration, and volume of blood transfusion (32).

The study also revealed marked elevations in the serum levels of IL-10 and IL-17 among post-surgical infected patients. IL-10, an anti-inflammatory cytokine, reached levels of 691.5 ± 49.6 pg/mL, while IL-17, a pro-inflammatory cytokine, was observed at 113.9 ± 12.8 pg/mL. This simultaneous increase reflects the dual nature of immune responses, where both pro- and anti-inflammatory pathways were activated to regulate inflammation and defend against pathogens (33). These findings differ from those reported by Gatea (2022), who documented a reduction in IL-10 levels among diabetic foot patients when compared to healthy controls.

IL-10 plays a crucial role in suppressing excessive inflammation and preventing tissue damage during immune responses. Its elevation in infected post-

surgical patients suggests a protective mechanism aimed at controlling the inflammation triggered by surgical trauma and subsequent infection [12]. IL-10 is known to enhance wound healing by modulating macrophage activity and promoting extracellular matrix formation, including collagen synthesis (34). However, persistent overexpression may impair monocyte function and lead to post-surgical immune paralysis, increasing susceptibility to sepsis (35). Our result aligns with the findings of Al-Dulaimi (2017), who observed elevated IL-10 levels in infected patients compared to healthy individuals. IL-10 is central to the regulation of inflammation and immune responses and plays a defensive role against microbial invasion (36, 37). Nonetheless, an aberrant regulation of IL-10 may predispose to infections and autoimmune diseases (38). It also helps to normalise leukocyte and neutrophil counts during immune reconstitution (39). The results in the present work agree with those of Carlin et al. (2023) (38).

IL-10 is a two-sided coin. It is a strong anti-inflammatory and immunosuppressing agent on the one hand and may have (under some conditions) immune modulating properties on the other hand (40, 41). The diverse origins, target cell types, release timing, and site of action make it as immune suppressive as immune stimulating (42). IL-17 is a pro-inflammatory cytokine essential for the recruitment of neutrophils and other leukocytes at sites of infection. The high significance level for IL-10 and IL-17 (P = 0.000) levels' differences among patients could indicate crosstalk between pro-inflammatory and anti-inflammatory responses in post-operative infections [10]. Although IL-10 is beneficial in that it can facilitate the pausing of injury to tissues, the excessive amounts of IL-10 may also promote inefficient immune clearance, thereby being likely to help the progression of the infection (43). These diverging roles highlight the dual function of IL-10 in immune regulation following surgery.

Ahmed et al. (2018) reported that serum IL-17 was increased significantly in polytrauma patients and was associated with higher sepsis risk; thus, IL-17 levels could be applied as a useful predictive biomarker in traumatic-stress patients (44). Positive correlation between IL-17 and IL-10 (r = 0.228, p = 0.022) was also observed in their (45) study, and both predictors were independent of sepsis risk. Increased IL-17 was associated with a 3.2-fold greater risk for sepsis and was also significantly higher in patients who died within 28 days after ICU admission. Similarly, Zhang et al. (2011) (46) showed that IL-17 was overexpressed in patients compared to controls.

Age-Related Analysis of Cytokine Levels

The current study showed no significant differences in cytokine levels across various age groups, a finding that contrasts with previous studies suggesting that age may influence cytokine production and immune responses (47). The absence of variation in this study may indicate that the surgical procedure and the resulting immune response override age-related immune influences. It is well documented that ageing is associated with a decline in immune function, often referred to as immunosenescence, which can affect cytokine production (48).

However, the results suggest that acute surgical stress may induce a sufficiently robust immune response that mitigates age-related variations in cytokine levels. This observation contrasts with studies such as that of Weiskopf et al. (2016), who reported altered cytokine responses in elderly patients following surgical stress, potentially affecting recovery outcomes (49). These findings highlight the need to design postoperative care strategies that consider age-related differences in immune responses. The results also contradict the findings of Mamdoh (2023), who reported elevated IL-17 levels in diabetic foot patients, particularly within the 45–54 and 55–64 age groups. Prior research has shown that ageing of the immune system may promote the development of various conditions through chronic inflammation, particularly involving interleukin signalling (50). Increased IL-17A levels have been associated with numerous autoimmune and chronic inflammatory diseases, such as diabetes mellitus (51).

Future studies should explore the interactions between age, surgical stress, and cytokine responses to better understand how these factors influence postoperative outcomes, especially given the growing population of elderly patients undergoing surgery.

Despite the well-recognised impact of immunosenescence on immune responsiveness in older individuals, our findings did not reveal major variation in cytokine levels associated with age. This may be due to the intense and immediate immune activation triggered by surgical trauma and infection, which temporarily supersedes baseline age-related immune alterations. Besides, the limited postoperative timeframe and standardised management protocols across patients likely contributed to minimising age-related differences.

Diagnostic Value of Cytokines Based on ROC Curve Analysis

All other post-surgical infection diagnoses were determined based on the ROC curve calculations of IL-2 and IL-10. An AUC (Area Under the Curve) value of 1.000 for IL-2 and IL-10 was observed, that were also reflected in perfect sensitivity as well as specificity. It indicated that these cytokines might be considered as potential effective biomarkers in the clinic (52). These results agree with other reports, which indicated the value of cytokines as diagnostic tools with increased levels of IL-2 in several infectious aetiologies, which is a good marker to monitor post-operative infections (53). The ROC-defined cutoff values for IL-2 and IL-10 show remarkable sensitivity and specificity, emphasising their potential utility as tools in clinical decision-making. These thresholds could assist the early detection of infection risks in patients following surgery, enabling prompt initiation of antimicrobial therapy and potentially decreasing complication rates and hospital stays. The perfect AUC values (1.000) observed for IL-2 and IL-10 merit cautious interpretation. While these results indicate excellent diagnostic potential, they may be influenced by the limited sample size and absence of external validation. Such conditions can result in overfitting or an overestimation of biomarker effectiveness. Larger, multicentre studies involving diverse patient populations are essential to validate these diagnostic thresholds

Yan et al. (2021) suggested a type of cell balance and immune equilibrium, with IL-2 serving as the centre of regulation, and reported the diagnostic value of IL-2 as 0.822. But a dysregulated multiplication of cytokines can destroy this action, causing inflammation and tissue damage (21). Yan et al also observed that the predictive power of IL-2 might be subject to different disease and treatment types. Qu et al. (2019) reported that IL-10 had high diagnostic accuracy in patients with rheumatoid arthritis, pulmonary parenchymal lesions, and that it was superior to IL-2 in some circumstances because of its immunosuppressive characteristics. In addition, the sensitivity of IL-17, a strong pro-inflammatory cytokine, was found to be high, which was related to disease progression, indicating it as a possible marker, both for diagnostic purposes and therapeutic strategy. They found that the combination of IL-10 with IL-17 had higher sensitivity for diagnosis and clinical reference of rheumatoid arthritis (54).

Zhang et al. (2022) (55) found that the combined AUC of IL-10 and IL-17 for sepsis patients was 0.951 (91.67% sensitivity and 96.30% specificity). Another study by Qu et al. (2019) reported that in patients with rheumatoid arthritis, the AUC for IL-10 was 0.671 and for IL-17 0.856 (54, 56). Furthermore, these high AUCs suggest that IL-10 is a central inflammatory response indicator, especially in infection control. IL-7 also had good diagnostic performance (AUC 0.985), consistent with our previous observations of the potential clinical utility of cytokines as diagnostic markers. This, meanwhile, is in line with Zhang et al. (2019) with an AUC of 0.860 for IL-10 (57). The simultaneous increase in IL-10 and IL-17 emphasises a complex immune response: an initial pro-inflammatory effort driven by IL-17 to eliminate pathogens, paired with regulatory mechanisms mediated by IL-10 to limit tissue damage. While this energy initially benefits immune defence, enhanced IL-10 levels could potentially hinder microbial clearance if excessive, possibly leading to persistence of infection or immune paralysis, and increasing the risk of sepsis. In this context, IL-10 elevation functions as both a protective response and a potential detriment if dysregulated.

However, some studies warn about using cytokine levels as the only diagnostic tool, as they may be modified by several factors, including comorbidities and surgical intervention (58). The early identification of infection through cytokine monitoring can improve patient management and outcome, and therefore, the clinical value of these biomarkers must be further examined. These results are significant for clinical application, especially postoperative management. High pro-inflammatory cytokines, such as IL-2 and IL-17, may be used as a sign of infection, which, in turn, helps physicians to take immediate steps and treat before any complications. Moreover, IL-10 levels might be a tool to evaluate the efficacy of anti-inflammatory treatment. For instance, therapeutic transfer of IL-10 or IL-7 would improve recovery and diminish the rate of infection (36).

Cytokine profiling might revolutionise postoperative surveillance by allowing personalised treatment strategies matching individual immune profiles. By gaining insights into the immunological constellation of the postoperative period, to be able to manage and improve the patients treated in the postoperative setting.

In summary, the cytokine profiles in this study indicate that immune activity following surgery is complex. Increased IL-2, IL-7, IL-10, and IL-17 levels show a strong activation of the immune system to surgical stress and a possible infection. These findings contribute not only to our knowledge of cytokine kinetics in surgically treated patients but also to preparations for new studies

focusing on the use of these biomarkers to manage the care of these patients.

High IL-17 levels may augment clearance of pathogens; however, they may also lead to tissue destruction in the absence of IL-10 regulation. This intricate balance and dilemma emphasise the importance of therapeutic approaches to modulate cytokine activity for the promotion of an adequate recovery and to prevent fibrotic complications (59). Sun et al. (2023) (58)., IL-17 has a dual role as being either destructive or protective in the immune system. Although recent advances have linked IL-17 to various infectious and autoimmune diseases, it also contributes to host defence and physiological balance. Future studies should focus on longitudinal tracking of cytokine levels in post-surgical patients to evaluate their predictive value for infection and recovery. Additionally, exploring targeted therapies that adjust cytokine responses could provide new avenues to improve outcomes in this patient population.

Interpretation of Cytokine Correlations and Immune Implications

These correlations suggest that T helper cells actively mediate the immune responses during the post-surgical period. The observed relationship between IL-2 and IL-7 indicates that IL-2 may enhance IL-7 receptor expression on T cells, thereby facilitating their survival and proliferation (59). Additionally, the significant association between IL-7 and IL-17 supports the notion that T helper cells orchestrate the inflammatory response in post-surgical infections. As T cells proliferate in response to IL-2, they begin producing IL-17, which in turn activates additional immune pathways to combat infection (60).

This result is consistent with the observation of Kim et al. (2021), who showed that IL-2 and IL-7 are not competitive in T-cell stimulation but rather synergistic and a “power couple” for most immunotherapies (as checkpoint inhibitors) (61). Like previous research by Al-Rawi et al. (2022) (62). Directed against interleukins identified that high levels of IL-17 might be linked to resistance to treatment, disease severity, or certain clinical phenotypes, as observed by Zwicky et al. (2019) (63). Such cytokine interplays emphasise the importance of understanding immune dynamics in personalised cancer therapeutic approaches for the post-surgical patient.

However, not all studies agree on the roles of these cytokines. Some researchers have observed that while IL-2 promotes T-cell activation, its excessive production may lead to dysregulation of T-cell subsets, potentially suppressing the overall immune response (64). This complexity necessitates further investigation to clarify the specific roles and interactions of these cytokines, especially in the context of recovery from surgery and infection. Sun et al. (2023) reported that IL-17 is produced in response to many infections; however, other studies have suggested that dysregulated IL-17 and other Th17 cytokines may contribute to the pathogenesis of various disorders (58). Overproduction of IL-17 has been implicated in numerous human inflammatory and autoimmune diseases, including psoriasis, arthritis, and inflammatory bowel disease (65). The moderate correlation observed between IL-7 and IL-17 likely indicates their shared involvement in T-cell-mediated immune responses, especially regarding the activation and survival of Th17 cells. Conversely, the weak link between IL-7 and IL-10 may reflect their roles in separate immune pathways. IL-7 primarily influences T-cell subsets, whereas IL-10 is mainly produced by regulatory B cells and macrophages to inhibit inflammation. These findings emphasise the specificity and distinct interactions of cytokines within different immune cell lineages.

Logistic Regression: Correlations between Immunological Parameters in the Patient Group

The results demonstrated a positive relationship between the two variables, with a coefficient of determination (R^2) of 0.1943. This suggests that approximately 19.4% of the variation in IL-2 levels can be explained by changes in IL-7 levels. This outcome suggests regulatory synergy between these two cytokines, supporting the likelihood that they participate in a shared inflammatory or immunological signalling pathway in patients. This finding agrees with the study by Kim et al. (2021), which highlighted the complementary roles of IL-2 and IL-7 in enhancing T-cell responses in cancer immunotherapy, positioning them as ideal partners in various immune-modulating strategies, including checkpoint blockade therapy (61). Moreover, Malek (2008) underlined that IL-2 is essential for T-cell proliferation and immune response as another evidence for functional redundancy between IL-2 and IL-7 in the control of immune cell homeostasis (64).

Logistic Regression between IL-2 and IL-10 Levels in Patients

There was only a very poor relationship between the two, as indicated by a coefficient of determination (R^2) of 0.0328. Thus, only about 3.28% of the variation in IL-2 levels is attributable to the variation in IL-10 levels. This weak

association between the two cytokines indicates that the association between them is weak and may not be significant in the study group. This coincides with the conclusion of Carlini et al. (2023), which sheds light on the multi-faceted function of IL-10 in the control of inflammation and immune homeostasis (36). Furthermore, Mosser and Zhang (2008) highlighted that the bioeffects of IL-10 are very context-dependent, and are the result of its varied cellular sources, target cells, and temporal and spatial expression, each mechanism governing different signalling cascades with opposite effects on immune suppression/activation (65).

Logistic Regression Analyses of IL-2 and IL-17 Levels in Patients

The coefficient of determination (R^2) was 0.092, yet it is a positive weak relationship. This indicates that approximately 9.2% of the variance in IL-2 levels can be accounted for by changes in IL-17 levels. IL-17 is a Th17-derived pro-inflammatory cytokine, and IL-2 is involved in the activation of these cells. The low correlation found in the present study may indicate a restricted or indirect effect of IL-17 on levels of IL-2, with, for example, infection or other immune stimuli affecting both cytokines.

Wallner et al. The connection between IL-2 and IL-17 was described to be important - it was reported in (2017) that the relationship observed could be very important for understanding the influence of drugs on cytokine networks. In addition, a therapeutic biomarker, cytokines, could be used in conjunction with related therapeutic cytokines in a diagnostic panel to increase the accuracy of the diagnosis and clinical management (66).

Logistic Regression of IL-7 and IL-10 Levels in Patients

We found a low to moderate positive relationship with R-squared (R^2) of 0.1536. This would mean that about 15.36% of the variability in IL-7 can be explained by variations in IL-10. Such an association indicates a potential combinatorial regulation between the anti-inflammatory IL-10 and the T-cell proliferation/survival factor IL-7. This relationship might relate to IL-10 signalling affecting or augmenting pathways that regulate IL-7 action in an inflammatory setting, or suggest crosstalk between anti-inflammatory and immune-supportive processes in post-surgical patients.

Logistic Regression Analysis Between IL-7 and IL-17 Levels in Patients

The results demonstrated a moderate positive correlation, with a coefficient of determination (R^2) of 0.2039. This means that approximately 20.39% of the variation in IL-7 levels can be explained by changes in IL-17 levels. This finding suggests a clear regulatory interaction between IL-7 and IL-17, where IL-7 may support the survival and expansion of T cells, including Th17 cells that produce IL-17. This functional link likely accounts for the observed moderate correlation, reflecting the cooperative role of these cytokines in sustaining immune responses during inflammation.

Logistic Regression Analysis Between IL-10 and IL-17 Levels in Patients

The results revealed a very weak positive correlation, with a coefficient of determination (R^2) of 0.0439. This indicates that only about 4.39% of the variation in IL-10 levels can be explained by changes in IL-17 levels. Given the distinct immunological roles of these cytokines—IL-10 as an anti-inflammatory mediator and IL-17 as a pro-inflammatory mediator—this weak correlation is scientifically plausible. It suggests that the regulation of each cytokine likely occurs through largely independent pathways within the inflammatory environment. However, Elvira et al. (2020) reported a moderate positive correlation between IL-10 and IL-17 in certain pathological conditions, suggesting the possibility of regulatory interaction between the two cytokines under specific disease contexts (67).

Study limitations

Although our overall sample size was statistically adequate, the division into multiple age groups resulted in smaller subgroup numbers, which may have limited our capacity to detect age-specific variations in cytokine levels. Future research with larger, age-stratified cohorts is necessary to explore immune differences associated with age more comprehensively. Besides, the cross-sectional design of this study restricts our ability to analyse cytokine fluctuations throughout the postoperative timeline. Longitudinal sampling would be essential to understand cytokine kinetics, peak response periods, and markers of resolution. Furthermore, factors such as comorbidities, including diabetes, hypertension, or obesity, along with variations in surgical procedure type, duration, and preoperative inflammatory status, were not specifically controlled and could have influenced cytokine profiles. Future investigations should consider stratified analyses or adjusting for these clinical variables.

Conclusions

This study highlights the significant immunological alterations in post-surgical patients with bacterial infections, particularly in IL-2, IL-7, IL-10, and IL-17 levels. The findings confirm that surgical stress and secondary infections elicit complex immune responses involving pro-inflammatory and anti-inflammatory cytokines. The consistently elevated levels of IL-2 and IL-17 in infected patients reflect an activated inflammatory response, likely driven by T helper cell activity, especially Th17 subsets. Simultaneously, the upregulation of IL-10 suggests a compensatory anti-inflammatory mechanism aimed at regulating immune overactivation. IL-7 levels were also markedly increased, supporting its role in T-cell survival and proliferation under immune stress.

ROC curve analysis revealed exceptional diagnostic performance for IL-2, IL-10, and IL-7, with IL-2 and IL-10 achieving perfect AUC values (1.000), positioning them as strong candidates for early infection detection biomarkers in post-surgical patients. Correlation and regression analyses demonstrated varying degrees of association among the cytokines, with moderate relationships between IL-7 and IL-17, and weaker or minimal correlations between IL-10 and other cytokines. These findings indicate that while certain cytokines may act in coordinated pathways, others function independently in the immune regulatory network. Collectively, these results emphasise the diagnostic and possibly prognostic value of cytokine profiling in surgical settings. Integrating cytokine-based monitoring into routine postoperative care could support timely clinical interventions, improve infection control, and facilitate personalised immunomodulatory strategies. Further research is recommended to validate these biomarkers in larger cohorts and explore their therapeutic potential.

Based on our current knowledge, this appears to be the first investigation to identify that measuring IL-2 and IL-10 simultaneously can be highly precise dual biomarkers for detecting infections following surgery. The perfect AUC scores emphasise their major role in capturing both the pro-inflammatory and regulatory aspects of the immune response to bacterial infections. Employing this dual-marker strategy offers promising potential for enhancing biomarker-based diagnostics within clinical surgical environments. The strong diagnostic performance of IL-2 and IL-10 as dual biomarkers emphasises their potential integration into point-of-care testing platforms for swift detection of surgical site infections. Such approaches could assist swift clinical decision-making, enable prompt antimicrobial therapy, and potentially decrease the rates of postoperative complications and hospital readmission. Future efforts should focus on developing portable assays for cytokine detection, making routine postoperative monitoring more accessible and efficient.

List of abbreviations

AUC: Area Under the Curve
ROC Receiver Operating Characteristic
SSIs: Surgical site infections

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of the Department of Biology, College of Education, University of Al-Qadisiyah, Iraq (Approval No **:** 33 – 15/1/2025).

Consent for Publication

All the authors gave consent for the publication of the work under the Creative Commons Attribution Non-Commercial 4.0 license.

Availability of Data

Data for this work is available from the authors and may be provided upon reasonable request.

Conflicts of Interest

None.

Funding

None.

Authors' contributions

DMA: Conceived and designed the study, performed microbiological and immunological analyses, and contributed to data interpretation and manuscript drafting.
JET: Supervised the research activities, assisted in experimental design, and contributed to the critical revision of the manuscript.
HAN: Co-supervised the study, carried out statistical analysis, and participated in manuscript preparation and final approval.

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