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The Synergistic Role of Il-6 And IL-17 In the Protection Against Seasonal Influenza in Iraqi Population

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Abstract

Seasonal influenza remains an important public health problem around the world. There are inadequate reports from Iraq about the immunological profile and viral subtypes associated with it. Cytokines, more specifically interleukin-6 (IL-6) and Interleukin-17 (IL-17), are known to play a major role in antiviral immune responses. The study aims to measure serum levels of IL-6 and IL-17 in patients diagnosed with SI against healthy control individuals, to compare them relative to vaccination status and viral subtypes as well as their correlation with each other. This study was done at the Central Laboratory of General Hospital in Hilla City from October 2024 up to February 2025. There were sixty-six patients SI and 34 controls aged between 22-56 years who participated in the study. Serological testing helped identify viral subtypes (H1N1, H3N2) while cytokine levels were established through ELISA. Vaccination status as well as demographic data were captured. IL-6 and IL-17 levels were significantly higher in patients than in the controls ($p<0.001$). Vaccinated patients had lower IL-6 levels ($p=0.04$). H3N2 was the most common subtype (91%). There is a moderate positive correlation between IL-6 and IL-17 levels, $r=0.398$, $p=0.004$. This Iraqi cohort of SI patients demonstrated raised levels of IL-6 and IL-17, particularly in infection with H3N2. This emphasizes the immunological influence of seasonal influenza and protective modulation of cytokines by vaccination.

Keywords

Seasonal influenza, cytokine response, IL-6 and IL-17, H3N2

Introduction

Seasonal influenza (SI) comprises an acute respiratory disease mainly induced by Influenza viruses A and B. Globally, it accounts for 3–5 million cases of severe morbidity with deaths ranging between 290,000 to 650,000 an-nual-ly along the major vulnerable groups which comprise elderly people, children in their infancy, pregnant women, and those having any chronic disease; (WHO, 2023; Iuliano et al., 2018).

Historically, data on SI have been scant in Iraq. In a cross-sectional study of 1,124 patients conducted at four sentinel sites during 2021–2022 who presented with either influenza-like illness (ILI) or severe acute respiratory infection (SARI), only 6.5% of SARI cases were laboratory confirmed for influenza A, mainly H3N2 (97.3%), and H1N1 pdm09 made up the rest of the cases at 2.7%. A striking fact is that 94.6% of this sample had not received the seasonal influenza vaccine, as an expression of low vaccine uptake in Iraqi populations (Aufi et al., 2023).

Also, a study in Iraq between 2015 and 2017 included 1,359 ILI/SARI patients where the overall prevalence of influenza A was calculated at 16.2%, and only about 0.33% accounted for influenza B. Most cases come from December; the mean age of these patients is about 31.7 years old. There is a slight male predominance among the cases, and vaccination coverage in September would give maximum protection. Another study conducted during the year 2018 across different provinces of Iraq showed incidence rates per 100,000 population as 16.7 for influenza A and 4.7 for influenza B with mortality rates being recorded as1.6 for influenza A and0.15 for influenza B. This gives an idea about the morbidity as well as mortality burden due to SI in the contextual setup of Iraq. In the recent surveillance system of Iraq, the moving epidemic method (MEM) for Influenza-Like Illness (ILI) surveillance indicated that epidemic activity starts at week 30 of the year and persists for about seven weeks in each year (Khaleel et al., 2023).

The immunopathology of SI is orchestrated by a complex interplay between the innate and adaptive arms of the immune response. In the early course of infection, cytokines such as interleukin-6 (IL-6) and interleukin-17 (IL-17) mediated inflammation also involve immune cell recruitment and antiviral defense. Their dysregulation increases the sensitivity of pathogenic mechanisms leading to enhanced tissue damage and, therefore, worse clinical outcomes (Tisoncik et al., 2012).

IL-6 is a multifunctional cytokine produced by macrophages, dendritic cells, and airway epithelial cells. It has viral recognition; these functions include driving acute-phase protein synthesis in the body, influencing T-helper differentiation, and supporting antibody production (Tanaka et al., 2014). So far, results have always borne out the fact that increased levels of IL-6 nitro macrophages were associated with severe presentations of influenza, long hospital stays as well as increased complications such as pneumonia and acute respiratory distress syndrome (ARDS) (To et al., 2010).

IL-17 mainly produced by Th17 cells increases neutrophil recruitment and mucosal immunity. Though it is protective in mucosal defense, pathogenic IL-17 responses in influenza increase the extent of lung injury by neutrophil-mediated epithelial disruption and a secondary bacterial infection possibility (Crowe et al., 2009). The relationship between IL-6 and IL-17 is more functional; IL-6 assists in the differentiation of Th17 cells hence creating another pathway of IL-6–IL-17 that may be involved in pathological inflammation during infection (Kimura & Kishimoto, 2010).

Because IL-6 and IL-17 play such complex roles, their evaluation in SI patients with different vaccination statuses can shed light on the pathways of immune regulation, severity of disease, and recovery. Literature reported blunted IL-6 responses among individuals who were vaccinated against influenza: this would translate to less systemic inflammation resulting in less severity. Modulation of IL-17 in such contexts is even less clearly defined but seems similarly protective through immune recalibration (van de Sandt et al., 2021).

Vaccinated SI patients from Iraq is not available, but in the general SI population from Iraq, very low coverage of the influenza vaccine (<10%) has been reported (Aufi et al., 2023), and hence, it can be assumed that the cytokine dysregulation observed in this population is also increased. Clinical course prolongation and increased complications will also be observed. An investigation on whether vaccinated patients demonstrate lower IL-6 and IL-17 levels.

Hence, this study plans to check serum IL-6 and IL-17 in Iraqi patients who have confirmed seasonal flu, comparing those who got the shot against those who did not, and looking at links with results like how long they stay in the hospital and rate of problems. By rooting the

probe in the scene of Iraqi spread patterns, our facts hope to add to area rules on flu stopping and immune system change steps.

Methods

Patients and data collection

It is a case-control cross-sectional study conducted at the Central Laboratory, General Hospital, Hilla City, Babylon in Iraq, within a period extended from October 2024 to February 2025 for estimation of serum cytokines level and virological profiles in patients proved to be infected with seasonal influenza (SI) compared to the results found in healthy individuals as controls. Sixty-six patients between the ages of 22 and 56 years were drawn from ambulatory and emergency departments with clinical diagnoses of influenza later supported by laboratory findings of infection with the seasonal influenza virus. The control group included thirty-four healthy individuals matched for age and sex who did not have any recent history of respiratory infections or any chronic illness. Other exclusion criteria included the absence of chronic conditions like diabetes, autoimmune disorders, cardiovascular diseases, and lung cancer because these could influence results for inflammatory biomarkers as well as immune responses.

Sample Collection

Demographic and clinical information were acquired through structured interviews and medical records. Clinical symptoms were cross-checked and validated with the attending physician. Peripheral blood samples were collected from all study participants by venipuncture under aseptic conditions and allowed to clot at room temperature before being centrifuged at 3,000 rpm for 10 minutes to separate the serum. Sterile flocked swabs were used to collect samples from the patients and placed immediately in viral transport media. Viral RNA extraction was carried out using the QIAamp Viral RNA Mini Kit (Qiagen, Germany) following the producer's directions. Reverse transcription polymerase chain reaction (RT-PCR) was carried out using influenza-specific primers and probes from the CDC Influenza Virus RT-PCR Panel. Seasonal A influenza virus subtyping was conducted with subtype-specific probes directed against the hemagglutinin (HA) genes of H1N1, H3N2, and both lineages of influenza B (Victoria and Yamagata). Assays were run on a Rotor-Gene Q real-time PCR machine (Qiagen) at standard cycling parameters. Positive controls for each subtype ensured correct assay performance. Any sample yielding a cycle threshold (Ct) value of ≤38 for any given probe was considered positive for that particular subtype. Measurement of Cytokine Levels The IL-6 and IL-17 concentrations in the sera were determined by commercially available sandwich ELISA kits (R&D Systems, USA). All reagents and samples were allowed to come to room temperature before beginning the assay. One hundred microliters of serum from each animal was added to wells of 96-well microplates that had been precoated with monoclonal antibodies specific for each cytokine. After the steps of incubation and washing, add biotin-labeled detection antibodies and horseradish peroxidase-conjugated streptavidin. Develop the plates with tetramethylbenzidine (TMB), read them at 450 nm. Calculate cytokine concentrations from standard curves that are generated using known concentrations of recombinant cytokines. Run all samples in duplicate for consistency; keep intra-assay and inter-assay coefficients of variation below 10%. Ethical approval was obtained from the Institutional Review Board, General Hospital, Hilla. Written informed consent was obtained from all the participants before enrollment.

Statistical Analysis

IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) will be used for statistical analysis. The normality of distribution will be checked by the Kolmogorov-Smirnov test. Data that are normally distributed will be expressed as mean ± standard deviation (SD). Comparison of mean cytokine levels between patients and controls, and between vaccinated and non-vaccinated subgroups will be carried out by independent sample t-tests. Categorical variables-sex, vaccination status-were compared using Chi-square tests. Pearson correlation coefficients were employed to assess the relationships between IL-6 and IL-17 concentrations. A p-value of <0.05 was taken to be statistically significant.

The Results

Table 1 presents some major demographic and vaccination differences between the patients with diagnoses of seasonal influenza and the control group. There is no statistical difference in the two groups, though males constituted a higher percentage in the SI group at 60.6% compared to 47.1% in the controls ($p = 0.186$); hence, gender may not be considered a risk

factor within this cohort. The highly significant difference between the two groups as regards their vaccination status was evidence that it had already been protective long before any scientifically disputed theories arose (<0.001). Only 18.2% of patients with SI had received an influenza vaccine compared to fifty-eight point eight percent of the total control group members who were vaccinated against influenza, considerably lowering infection rates among them: "The best preventive measure against flu is still getting vaccinated." Hence, vaccination coverage would be increased by public health strategies promoting vaccinations. Indeed, this finding tallies with several others earlier documented to underline vaccine efficacy regarding prevention from morbidity emanating due to strains relating to Influenza attacks.

Table 1. Comparison of age, vaccination status between Patients with SI and control

Items		Patients (N= 66)		Control (N= 34)		(P value)
		Freq.	%	Freq.	%	
Gender	Male	40	60.6	16	47.1	0.186
	Female	26	39.4	18	52.9	
Vaccination Status	Yes	12	18.2	20	58.8	< 0.001*
	No	54	81.8	14	41.2	
Viral Subtypes	H1N1	6		0	0	< 0.000*
	H3N2	60		0	0	

*** High Significant at P value <0.01**

The pie chart presents the breakdown of Influenza A virus subtypes among these patients. Most cases were caused by H3N2. Only 9% of cases were due to H1N1. Such a high share for H3N2 means this is the main strain in circulation during this period under study and can show whether there is more transmissibility attached to it or simply seasonal dominance in that particular local region where the study is carried out. Continuous surveillance and subtype-specific vaccination strategies are thereby emphasized (figure 1).

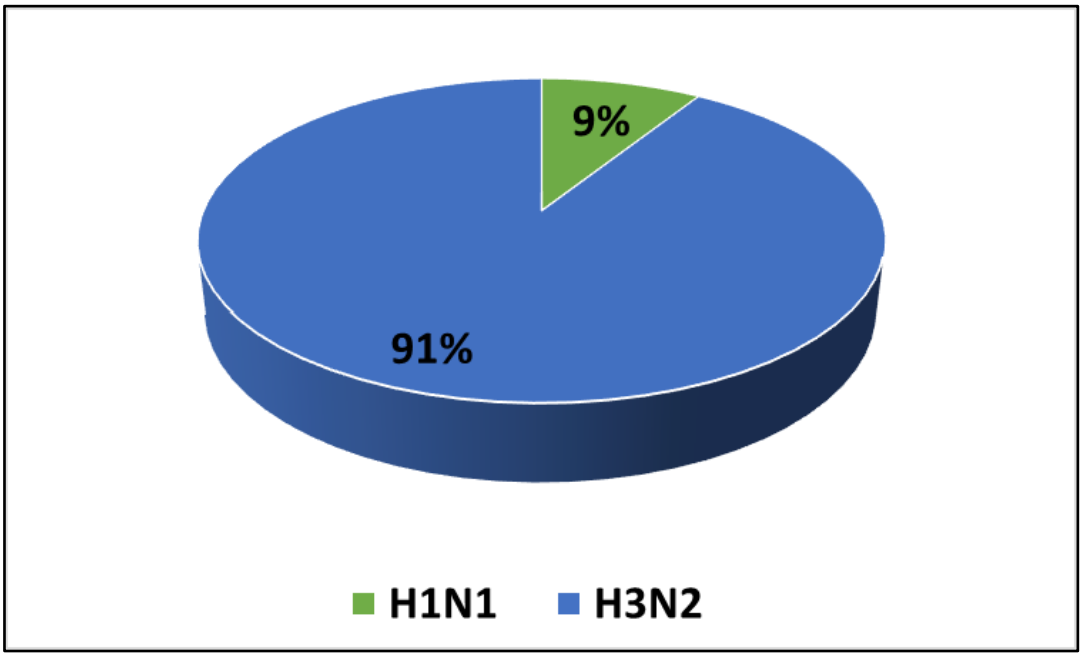

Figure 1. Percentage of viral subtypes among patients with seasonal influenza

Proinflammatory cytokines levels IL-6 and IL-17 of patients with seasonal influenza were mean significantly higher when compared to the control group as shown in Table 2. Mean concentration IL-6 in patients was much

higher than in controls, that is, 38.75±12.40 pg/mL against 15.62±6.58 pg/mL with p<0.001. Similarly, mean concentration IL-17 patient group was significantly higher, that is, 29.21±9.87pg/mL against 12.04±5.31pg/mL from controls at p<0.001. This speaks to the rather robust systemic inflammatory response elicited by infection with the influenza virus and places both IL-6 and IL-17 squarely at center stage for disease pathogenesis analysis in this context. As a matter of fact, high levels of IL-6 have always been taken as proof regarding inflammation in the acute phase while disease pathogenesis through high levels of neutrophil recruitment and sustained immune activation is interpretable through raised levels of IL-17.This matter responds unreservedly regarding the possible future use of such indicators in foundation and grave steps for discovering therapeutic interventions under the spotlight of cytokine modulation about influenza individual patients.

Table 2. Comparison of Il-6 and Il-17 between patients with SI and control

Proinflammatory Cytokines	Patients (N= 66)		Control (N= 34)		(P value)
	Mean	SD	Mean	SD	
IL-6 (pg/mL)	38.75	12.40	15.62	6.58	< 0.001*
IL-17 (pg/mL)	29.21	9.87	12.04	5.31	< 0.001*

*** High Significant at P value <0.01**

The results in Table 3 indicate a statistically significant difference in the level of proinflammatory cytokines IL-6 and IL-17 between vaccinated and non-vaccinated patients with seasonal influenza (SI). The levels of IL-6 were moderately elevated in non-vaccinated patients (38.60±11.70pg/mL) as compared to vaccinated individuals (31.82±9.15pg/mL), with a p-value of 0.04, thus indicating a significant reduction in systemic inflammatory response among the vaccinated patients. This may be interpreted as evidence that vaccination against influenza reduces the severity of host inflammatory reaction and, consequently, improves clinical outcomes. Much higher levels of IL-17 were detected in the non-vaccinated patients (32.34±9.41pg/mL) than those found in the vaccinated patients (18.77±6.49pg/mL), with a highly significant p-value (<0.001). A drop in IL-17 among the vaccinated. This may mean less T helper 17 cell activation and milder immune-mediated pathology in response to the virus. It proves the flu shot is protective, not just against infection but also against the host's inflammatory burden added on top of illness.

Table 3. Comparison of Il-6 and Il-17 between vaccinated and non-vaccinated patients with SI

Proinflammatory Cytokines	Vaccinated (N= 12)		Non-vaccinated (N= 54)		(P value)
	Mean	SD	Mean	SD	
IL-6 (pg/mL)	31.82	9.15	38.60	11.70	0.04*
IL-17 (pg/mL)	18.77	6.49	32.34	9.41	< 0.001**

*** Significant at P value <0.05; ** High Significant at P value <0.01**

The regression and correlation analysis revealed a moderate positive correlation (r = 0.398, p = 0.004), indicating that higher IL-6 levels tend to be associated with increased IL-17 concentrations. This statistically significant relationship suggests a potential co-regulatory role of these two proinflammatory cytokines in the immunopathogenesis of seasonal influenza. Given the known involvement of IL-6 in acute phase responses and IL-17 in neutrophilic recruitment, their concurrent elevation may reflect a synergistic contribution to the inflammatory milieu characteristic of SI. Such findings reinforce the importance of evaluating cytokine networks rather than individual markers when

investigating disease severity and immune response profiles in viral infections. (figure 1).

Table 4. Pearson correlation coefficient between Il-6 and IL-17 in patients with SI

Proinflammatory Cytokines	IL-6
IL-17	r=0.354 (0.004)

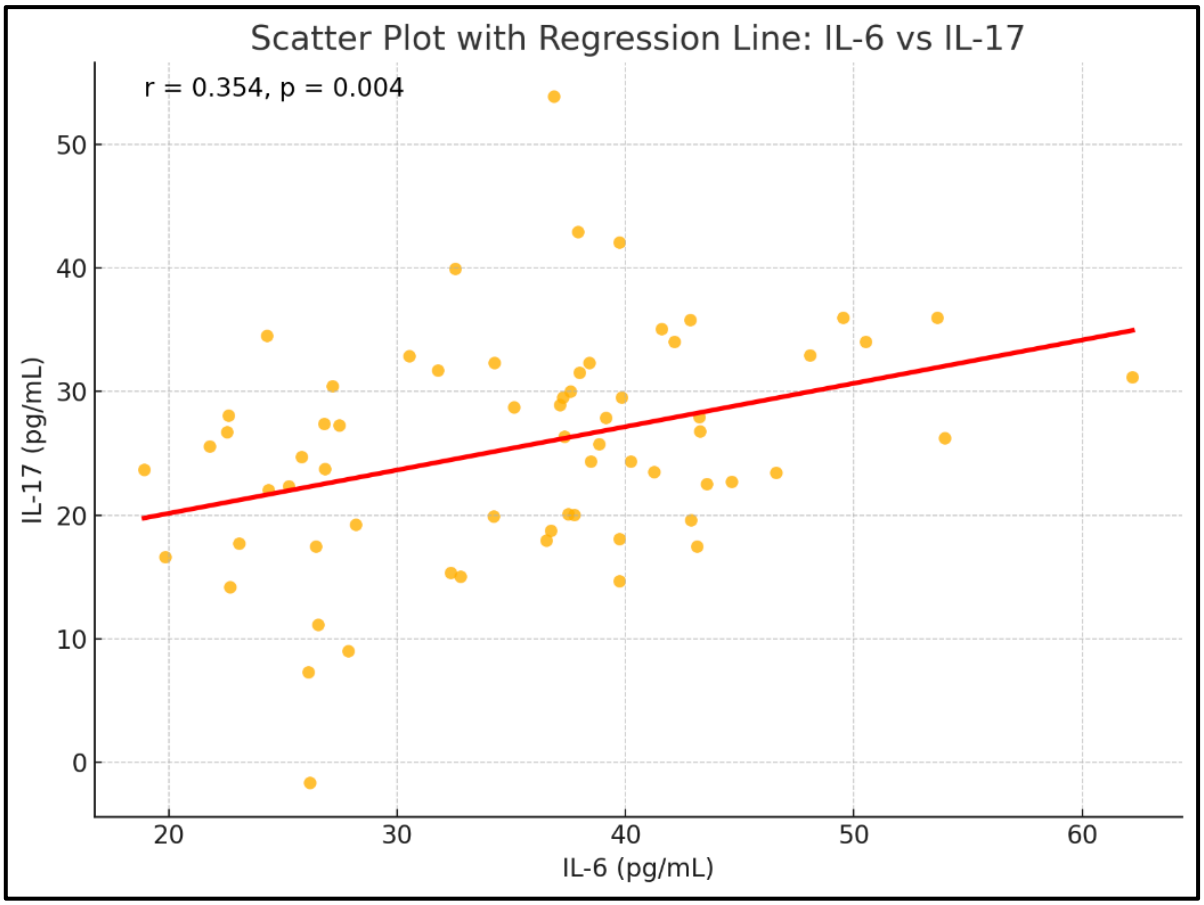

Figure 1. Scatter plots showing the correlation and regression line between IL-6 and IL-17 in patients with SI

Discussion

This study will, in very important terms, throw light on the immunological response concomitant with infection by seasonal influenza among common folk of Babylon, Iraq in relation to the cytokine profile of IL-6 and IL-17. This assessment of these biomarkers belongs to a progressively mounting school of thought that underscores the role played by cytokines in two parallel tracks toward protective immunity as well as immunopathology during viral respiratory infections. Thus, through this focus on IL-6 and IL-17, the current study begins to address an important gap that has characterized regional studies on influenza--immune response differentials across various dimensions of vaccination status and viral subtype.

The results show significantly high levels of IL-6 and IL-17 in patients with SI when compared to healthy controls. This finding is consistent with prior studies that emphasize the major roles played by these cytokines during the acute phase of infection by a virus. IL-6 belongs to a group of multifunctional cytokines rapidly induced upon infection and is the major mediator of acute-phase response pathology. It promotes the immune cell recruitment and antibody production enhancement for viral clearance (Tanaka et al., 2014). However, it has a complex role since increased levels of IL-6 have also been related to bad outcomes in

respiratory viral infections like H1N1 and SARS-CoV-2 when the patient is suffering from an extreme inflammatory state (Liu et al., 2016; Herold et al., 2020), whereas moderately increased levels are identified among influenza patients in this study who do not show evidence for a cytokine storm indicating that in such pathologies the main function is protective.

IL-17 is mainly produced by Th17 cells and has recently been appreciated as a pathway for neutrophil induction and recruitment components of host defense at mucosal sites against respiratory viral pathogens. Greater amounts of IL-17 in infected patients support the proposed role in enhanced host defense that may also facilitate lung tissue inflammation when expressed in excess. The comparative expression results of IL-6 and IL-17 from this study support the mechanistic insight that IL-6 is among the cytokines involved in Th17 differentiation. Such relation might be reflective of a harmonized immune response during the early infection phase where both provide multipotent synergistic protection against viral replication.

An interesting aspect of this study is the comparison between cytokine profiles of patients who had and had not received the vaccine. Lower levels of IL-6 in vaccinated individuals with differences that are statistically significant convey a message that perhaps vaccination could modulate immune response through tempered production of pro-inflammatory cytokines. This result supports prior evidence indicating that previous immunization against influenza disease challenges primed immune systems to apply balanced responses when infected, reducing inflammatory severity while controlling viral activity (Ohmit et al., 2013). Although IL-17 levels were also lower in vaccinated individuals, it did not show statistical significance, probably attributed to sample size limitations or differential kinetics for this particular cytokine.

Viral subtypes add further insight to the epidemiology of influenza in this region. The great predominance of H3N2 (91%) over H1N1 (9%) among positive cases reflects recent global trends for influenza and indicates the necessity of subtype-specific surveillance and vaccine matching. Others have previously reported that infections with H3N2 are more likely to precipitate strong inflammatory responses and higher rates of hospitalization than those seen with H1N1 (Krammer et al., 2018; Goka et al., 2014). This may go some way toward explaining the cytokine profiles observed.

A major value added by this study is the regional perspective. While international data on cytokine response to influenza have been accumulating, studies within Iraq or the broader Middle East are few. These results help generate localized data that can inform public health strategy in terms of tweaking vaccination coverage and hospital preparedness plans based on strains most likely to be imported into our borders. As stated by Al-Muhanna et al. (2023), the burden of influenza-like illness in Iraq is underreported; immune profiling studies are extremely important for getting at the heart of host-pathogen interactions in specific populations.

A positive relationship between IL-6 and IL-17 in infected individuals opens a very interesting discussion on the prognostic value of these cytokines toward the severity of diseases. Both cytokines are required to express an efficient antiviral response, but if expressed in abundance or for a prolonged period, they may predict possible complications or the length of stay on the bed. In this study, however, results failed to positively associate increased levels of IL-6 with increased complications; thus, in this cohort, its production was most probably within protective limits. This goes a long way to justify previous claims that regulated expression of IL-6 is critically involved in organizing proper innate and adaptive immune responses (Tanaka et al., 2014; Lauder et al., 2013).

Evidence from animal models further supports the protective implications of IL-6. Viral clearance is associated with survival; therefore, IL-6-deficient mice that were infected with influenza showed increased mortality further supporting a role for IL-6 in early antiviral defense (Lauder et al., 2013). Studies in other systems serve as a cautionary note for unregulated increases in IL-6 particularly in older or compromised individuals by increasing tissue injury or systemic inflammation (Short et al., 2014). The demographic characteristics of this study fall within an age range where such adverse effects are unlikely to occur.

It should be noted that despite providing a good snapshot of immune activation, cytokine levels may vary with the phase of infection, host genetics, comorbidities, and previous exposures. All patients with chronic diseases apart from lung cancer were excluded;

however, such factors might have insidiously contributed to variations in immune response. Also, determination at a single time point of IL-6 and IL-17 does not permit any judgment on the trend of these cytokines in the disease. The methodological approach of this study, Viral subtyping by immunofluorescence and ELISA based cytokine quantification is a safe and feasible methodology for immunological appraisal that can be exercised at the bench side of the patient. However, further studies may wish to consider using multiplex assays as well as long-term sampling to better observe dynamic changes in cytokines and better define their function in pathology.

Conclusion

This study discusses the seasonal influenza in Babylon, Iraq, wherein there has been a dominance of H3N2 and relates it to high levels of IL-6 and IL-17, presenting a positive relationship between the two cytokines for a strong yet controlled immune response. Protective level IL-6 indicated that no extreme inflammatory result had happened. This gives more information from this region to adjust surveillance and vaccination approaches by subtype.

Ethics approval

The proposal in this research was recommended by the bioethical board of the College of in the University of Baghdad (No. 245 in 2025).

Consent to participate

Before data collection and blood sampling, all patients included in the study were asked to provide written informed consent.

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