RESEARCH PAPER

A Comparative Assessment of Interleukin-8 in Influenza, COVID-19, and Asthma Cases

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Abstract

Background: Emerging respiratory viruses are major health threats due to their potential to cause massive outbreaks. Infection with seasonal influenza, or COVID-19, Asthma may lead to respiratory failure may be due to local immune dysregulation like Cytokine storms are viewed as the driving force behind morbidity, such as interleukin 8 (IL-8), a pro-inflammatory cytokine that plays a role in neutrophil activation and has been linked to the pathogenesis and progression of these diseases.

Methods: cohort study, conducted at the University of Diyala from 11/2023 to 6/2024. A total of 120 cases have been participated in our study, divided into 4 groups (healthy control, COVID-19, Seasonal flue, and Asthma patients). IL-8 concentration was measured by using ELISA kit ELK-Biotechnology kit /CHINA.

Results: A male-to-female ratio of 71.6:28.3% and 63.3% of participants were over 40 years. IL-8 levels were highest in COVID-19 (598.80 pg/mL), followed by asthma (494.92 pg/mL) and influenza (362.99 pg/mL), with healthy individuals lowest (68.10 pg/mL). IL-8 distribution varied, with COVID-19 and asthma showing broader variability and higher correlations.

Conclusion: Interleukin-8 (IL-8) exhibits varying sensitivity and specificity across respiratory conditions, with limited utility as a standalone biomarker for influenza and COVID-19, high specificity but low sensitivity for asthma, and potential clinical value when considered alongside other biomarkers within the broader context of disease pathogenesis.

Keywords: Interleukin-8, COVID-19, Asthma, Influenza, Cytokine.

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Introduction

Acute respiratory illnesses (ARIs) pose a significant global health burden, with influenza, coronavirus disease 2019 (COVID-19), and asthma being three prevalent conditions (1). Each of them has distinct features, but they all participate in a common underlying matter, which is inflammation, which is known as a consistent immune response to any injury or infection and plays a vital role in the disease's pathogenesis. (2). However, excessive inflammation may contribute to worsening disease severity in addition to tissue damage. Interleukin-8 (IL-8), a robust chemoattractant as well as an activator of neutrophils, is an inflammatory mediator implicated in several respiratory illnesses. IL-8's role in the case of influenza, asthma, and COVID-19 may supply valuable insights into disease mechanisms and potentially guide the development of novel therapeutic strategies. (3).

Influenza is a highly infectious respiratory sickness caused by influenza viruses, its symptoms characterized by a sudden onset of sore throat, fever, cough, muscle aches, and fatigue (4). In case of viral infection, it will trigger an inflammatory response, where IL-8 plays a distinguished role in recruiting neutrophils, which are a type of white blood cell, to the site of infection. While neutrophil infiltration is essential for viral removal, excessive neutrophil activation may cause tissue damage and make complications such as pneumonia (5). Studies found that there was an elevation of IL-8 levels in the airways of influenza patients, which is correlating with disease severity. Furthermore, they found a genetic polymorphism for the IL-8 gene is associated with susceptibility to influenza and the development of complications (6).

Like influenza, COVID-19, which is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is another extremely intense respiratory illness. COVID-19 could appear with huge symptoms, involving fever, shortness of breath, cough, loss of taste or smell, fatigue, and in severe cases, pneumonia and

acute respiratory distress syndrome (ARDS) (7). The lineament for severe SARS-CoV-2 is a hyperinflammatory state, known as a "cytokine storm," due to excessive production of pro-inflammatory cytokines, one of them being IL-8, causing lung damage and organ failure. Studies suggest that COVID-19 infection disrupts the normal regulation of IL-8, leading to its sustained and uncontrolled production. Moreover, the high levels of IL-8 could be correlated with disease severity and mortality in COVID-19 patients (8).

Asthma, a chronic inflammatory disorder of the airways, is characterized by shortness of breath, recurrent episodes of wheezing, cough, and chest tightness. The exact cause of asthma remains unknown; several factors, like environmental irritants, allergens, and viral infections, are known to trigger airway inflammation (9). IL-8 is linked in asthma development by fostering airway hyperresponsiveness, a defining trait in which airways become extremely sensitive to stimuli and constrict rapidly. According to studies, asthmatics have higher levels of IL-8 in their airways both during acute exacerbations and in stable conditions. Furthermore, variations in the IL-8 gene have been related to asthma susceptibility and illness severity (10).

There are possible connections between COVID-19, influenza, and asthma. Viral infections, such as influenza and SARS-CoV-2, may trigger asthma exacerbations. Furthermore, asthma patients are more susceptible to severe SARS-CoV-2 or influenza infections due to airway inflammation. Investigating the role of IL-8 in these interactions may provide interesting insights into preventing and managing these co-morbidities (11).

The study aims to compare and assess the levels of Interleukin-8 (IL-8) in patients with influenza, COVID-19, and asthma and identify differences in IL-8 expression across these respiratory diseases.

3 . Materials and Methods

Before starting the sample collection, ethical approval for sample collection was obtained from the Research Ethics Committee of the College of Medicine/University of Diyala. Informed consent was obtained from all participants after explaining the procedures for taking blood samples from each participant according to the principles of the Declaration of Helsinki, Nuremberg Code and others.

Specimens were collected for the time period from November 2023 to June 2024, as (120) blood specimens were collected from patient, 30 from patient with Influenza, 30 from patient with COVID-19, 30 from patient with asthma, and 30 specimens of apparently healthy people as a control group. Thier ages between (20-60) frm both sexes. All of them have not suffering from any type of chronic or acute diseases.

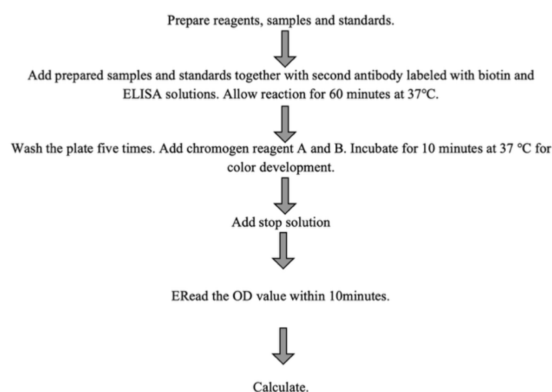
The specimens were collected by drawing venous blood, as (3 ml) of blood was withdrawn by using plastic medical syringes, then The sera were separated by the central device for (10) minutes at a rate of (1000g).

The concentration of IL-8 has been measured by using enzyme-linked immunosorbent assay ELISA using ELK-Biotechnology kit /China with Sensitivity: 6.7 pg/mL.

The data were input and analyzed using the Statistical Package for the Social Sciences (SPSS) version 26 and STATISTICA version 9 software. Descriptive statistics included frequency distribution tables, counts, and percentages for qualitative data, while quantitative data were summarized using the mean, standard deviation, and range.

To assess significant differences between study groups (cases and controls), an unpaired t-test, one-way ANOVA, and Chi-square test were applied for quantitative and categorical variables, respectively. Additionally, the Pearson correlation test was utilized to examine relationships among biochemical and immunological markers of pro-inflammatory and anti-inflammatory parameters within the study groups. Statistical significance was established at a P-value < 0.05 throughout the analysis.

Summary



Make concentration of standards the abscissa and OD value the ordinate.Draw the standard curve on the graph

paper (Appendix A). According to the OD value of the sample, locate its corresponding concentration (which is the concentration of the sample); or calculate the linear regression equation of the standard curve according to the standard concentration and the OD value. Then substitute with the OD value of the sample to calculate its concentration.

Assay range：5 ng/L→1000 ng/L.

Sensitivity：2.51 ng/L.

4-Results

The male/female ratio was 71.6:28.3 %. According to age, the age ratio was demonstrated to be 36.7% under 40 years and 63.3% more than 40 years Table 1.

Table 1: Comparative anthropometric features of participants calculated by chi-square test.

			Groups				**Total N=120**
			Patients N=90			**Healthy N=30**	
			Influenza N=30	**COVID-19 N=30**	**Asthma N=30**		
Sex	**Males**	N	22	19	25	20	86
		%	73.3 %	63.3 %	83.3%	66.6 %	71.6%
	Females	N	8	11	5	10	34
		%	26.7 %	36.7 %	16.7%	33.4 %	28.3%
Age	**≤40**	N	9	7	15	13	44
		%	30%	23.3 %	50 %	43.3%	36.7
	> 40	N	21	23	15	17	76
		%	70%	76.7 %	50 %	56.7%	63.3%

The current study found that IL-8 levels varied depending on the disease compared to healthy individuals. IL-8 levels were highest in COVID-19 patients (598.80 pg/mL, SD = 144.77), followed by asthma patients (494.92 pg/mL, SD = 122.11) and seasonal influenza patients (362.99 pg/mL, SD = 94.97), with healthy individuals showing the lowest levels (68.10 pg/mL, SD = 23.86) figure 1.

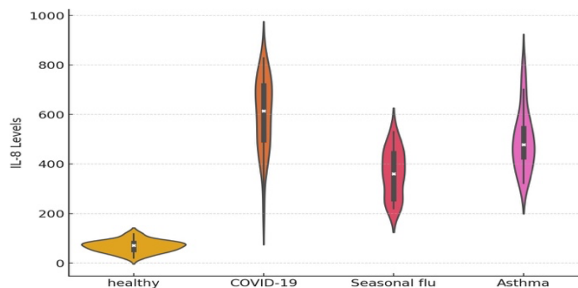


Figure 1: the levels of IL-8 in Healthy, COVID-19, asthma, and seasonal influenza

According to Ross Curve, interleukin-8 exhibits a sensitivity of 40% and a specificity of 83% in patients with influenza. In individuals diagnosed with COVID-19, interleukin-8 sensitivity reaches 100%, while specificity is recorded at 58%. Additionally, in patients with asthma, the sensitivity and specificity values are 20% and 100%, respectively, as illustrated in Table (2).

Table 2: ROC curve, sensitivity, and specificity of variables under study

Variables	**AUC**	**Std. Error[a]**	***P* value**	**Sensitivity %**	**Specificity %**
IL-8 (Flu)	***0.525***	***0.134***	***> 0.05***	***40 %***	***83 %***
IL-8 (Covid)	***0.842***	***0.084***	***< 0.01***	***100 %***	***58 %***
IL-8 (Asthma)	***0.483***	***0.123***	***> 0.05***	***20 %***	***100 %***

In terms of frequency, the relative frequency of IL-8 for each category was presented. Healthy individuals had low and uniformly distributed levels within the range of 20-120. COVID-19 patients exhibited high frequency in levels ranging from 400-800. IL-8 levels in seasonal influenza patients were concentrated between 200-500 with lower frequency of higher levels. On the other hand, asthma patients showed a wide distribution ranging from 300-800, reflecting the variability in disease severity figure 2.

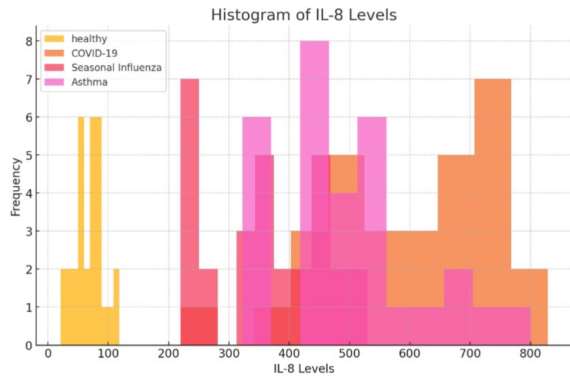


Figure 2: frequency distribution of IL-8 in Healthy, COVID-19, asthma, and seasonal influenza.

In terms of pairwise relationships between all categories, there was significant dispersion between asthma and COVID-19 patients, showing a relatively higher correlation compared to other relationships. There was no clear pattern of relationship between healthy individuals and other categories due to the significantly lower IL-8 levels. Some pairs showed scattered clusters, reflecting variability in immune responses figure 3.

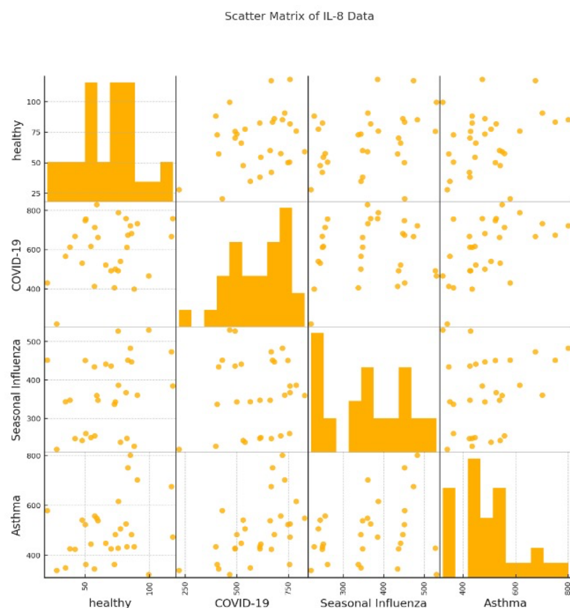


Figure 3: pairwise relationships between Healthy, COVID-19, asthma, and seasonal influenza.

In terms of Pearson correlation coefficients between each pair of categories, the highest correlation was observed between COVID-19 and asthma patients (0.53). Healthy individuals showed low correlation with all other categories. The correlation between COVID-19 and seasonal influenza was low (0.09), as in the figure 4.

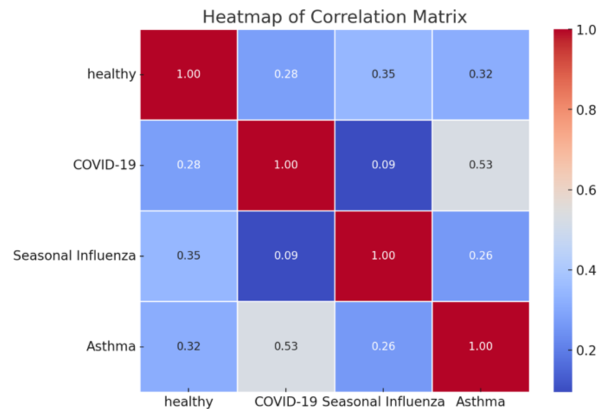


Figure 4: Pearson correlation coefficients between Healthy, COVID-19, asthma, and seasonal influenza.

Discussion

The study involved 120 individuals, including 90 patients who were equally divided into four groups: COVID-19, seasonal influenza, asthma, and healthy controls.

The highest proportion of participants was male in all disease groups, while the highest proportion was in the asthma group (83.3%). According to age, the study showed that most of the study participants were patients over the age of 40, with the exception of asthma patients who had a more balanced age distribution. While the healthy group was distributed towards older age groups, but to a lesser extent.

The results of the current study reflect the demographic composition of people with these diseases and can therefore be used to understand the demographic factors associated with their prevalence. For example, the high proportion of males in asthma cases may be related to genetic or environmental factors that affect their immune response. Also, the high proportion of patients over the age of 40 may indicate the role of aging in increasing the inflammatory response.

The sensitivity of IL-8 at 40% and specificity at 83% in influenza patients indicate a moderate diagnostic utility of IL-8 as a biomarker for detecting influenza infection. This finding is consistent with previous research highlighting the crucial role of IL-8 in the immune response to influenza while suggesting that IL-8 alone may not serve as a highly sensitive biomarker (13).

IL-8 is one of the chemokines that assist the induction of neutrophils and other immune cells to the site of infection, sharing the major inflammatory response to reduce viral replication and clear infected cells (14).

Studies have shown increasing the level of IL-8 in the respiratory secretions and serum of patients with influenza, especially in the case of the acute phase of infection (15). However, others indicated that IL-8 may not be the most sensitive biomarker for detection for influenza. Alternate biomarkers, like interleukin-6 (IL-6), interferons (IFNs), and C-reactive protein (CRP), could be giving a higher sensitivity in diagnosing influenza or predicting disease severity (16).

The current study found that there was a significant variation in the levels of IL-8 between groups. The highest levels were recorded in COVID-19 cases, asthma, and seasonal influenza cases, respectively, compared with the lowest levels in healthy cases. The high IL-8 levels in COVID-19 patients may be due to its major role in the "cytokine storm" in which IL-8 is involved in the exacerbation of acute respiratory symptoms (17). In contrast, in asthma, IL-8 contributes to persistent airway inflammation and rises during exacerbation episodes. These findings show that the shared inflammatory mechanism of COVID-19 and asthma may be related to neutrophil recruitment to the respiratory tract via IL-8, which explains the similarity in their levels.

IL-8 levels were relatively lower in the seasonal influenza group, reflecting the various intensities of the immune response compared to COVID-19. This can be related to several factors like vaccination status, strain, and individual immune response (18).

When Pearson correlation analysis was used, the strongest link was found between COVID-19 and asthma patients ($r = 0.53$). This showed that the levels of IL-8 in these two groups were somewhat linearly related.

Although these two diseases are different, but both are related with significant inflammatory responses. This finding is in line with what other research has found: people with asthma may be more likely to get acute viral illnesses like COVID-19, which make the inflammation process worse (19). Healthy people, on the other hand, didn't clearly connect with any of the disease groups because their IL-8 levels were low and their responses didn't change much.

The data dispersion analysis and the diversity in immune response, the results showed that there is a distinaction of the distribution of IL-8 between groups. Where COVID-19 patients had high levels within the range of 400-800 pg/mL, while in seasonal influenza patients were between 200-500 pg/mL with a lower frequency of higher values. While Asthma patients showed a wide distribution ranging between 300-800 pg/mL, reflecting the variation in disease severity. This dispersion could be due to non-homogeneous immune responses in each group but might be affected by several factors like the general health of the cases, the possibility of comorbidities, and the nature of the inflammatory response. For instance, the level of IL-8 in influenza patients could be different depending on the virus strain and vaccination, while the difference in asthma patients can be related to the severity of the condition and the frequency of exacerbations.

Due to data results, it can be considered that IL-8 is a biomarker of inflammatory response because of its higher levels in patients with inflammatory respiratory diseases compared to healthy people. On the other hand, the study showed that there are significant differences in IL-8 levels between different diseases, which may contribute to understanding the role of this cytokine in the mechanisms of inflammation and disease progression.

Conclusion

In conclusion, interleukin-8 (IL-8) demonstrates varying degrees of sensitivity and specificity across different respiratory conditions. While its performance as a standalone biomarker for influenza and COVID-19 may be limited due to moderate sensitivity and specificity, respectively, considering IL-8 within the broader context of disease pathogenesis and in conjunction with other biomarkers could enhance its clinical utility for diagnosing and managing these infections. Conversely, IL-8 exhibits excellent specificity but low sensitivity in identifying asthma patients, highlighting the challenges of relying on IL-8 alone for asthma diagnosis. Understanding the complex inflammatory pathways and phenotypic heterogeneity of asthma is essential for interpreting IL-8's diagnostic performance and identifying complementary biomarkers to improve accuracy in asthma diagnosis and management.

Ethics

Ethical approval for this study was obtained from the Ethical Review Board of the Diyala University ,Baqubah, Iraq /

Conflict of interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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