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Evaluation of The Effect of CXCL9 Levels on Liver Function in Gastrointestinal and Respiratory infections Patients.

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ABSTRACT
Background: CXCL9, a chemokine stimulated by gamma interferon, is crucial in immunological responses by promoting leukocyte recruitment. **Aim:** This study investigates the correlation between blood CXCL9 levels and liver function tests in patients with particular respiratory and gastrointestinal diseases, considering potential confounding variables. **Methods:** A cross-sectional study was performed in Salah AL-Din governorate, Iraq, from December 15, 2023, to July 25, 2024. 320 isolates were obtained from patients diagnosed with asthma, COPD, pneumonia, bronchitis, inflammatory bowel disease, and gastroenteritis disease, ranging in age from 20 to 70 years at the Tikrit Teaching Hospital, the Public Health Laboratory and the Respiratory Chest and Respiratory Diseases consulting clinics. An investigation was conducted on the concentrations of CXCL9 in correlation with many liver enzymes, including alkaline phosphatase (ALP), gamma-glutamyl transferase (GGT), glutamic oxaloacetic transaminase (GOT), glutamic pyruvic transaminase (GPT), and total serum bilirubin (TSB). **Results:** The research identified a statistically significant correlation between CXCL9 levels and GGT, particularly in those with respiratory dysfunction. GGT levels exhibited considerable variation between males and females, with a statistically significant disparity between the two groups. The results indicate that elevated levels of CXCL9 may be associated with liver dysfunction, particularly in those with respiratory conditions. This study highlights the potential of CXCL9 as a biomarker for hepatic health and its role in inflammatory processes affecting liver function. Future studies should elucidate how CXCL9 affects liver function and explore its therapeutic potential. Body Mass Index (BMI) data could assist in minimising bias in the findings, enhancing our knowledge of the biology of liver illness and facilitating the development of targeted treatments for liver-related problems in afflicted patients.

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INTRODUCTION

HUMAN C-X-C MOTIF CHEMOKINE 9(CXCL9), or monokine produced by gamma interferon (MIG), is crucial for liver function, especially for hepatic inflammation and immunological response. CXCL9 is a chemokine mostly stimulated by interferon-gamma (IFN-γ) and has a role in the recruitment of immune cells, including cytotoxic T lymphocytes (CTLs), natural killer (NK) cells, and macrophages to inflammatory areas. In hepatic disorders, CXCL9 is increased and facilitates the migration of leukocytes into the liver, potentially aggravating hepatic inflammation and damage. This chemokine is recognized as a crucial factor in the aetiology of chronic hepatitis B (CHB), with its increased levels correlating with liver damage indicators such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The interaction between CXCL9 and its receptor, CXCR3, is essential for the immune cell-mediated response in the liver, affecting the advancement of liver disorders and the possibilities for treatments [1,2].

The liver, a vital organ with a strong immune response, is crucial in removing infections, producing acute-phase proteins, and regulating the immune response. Its vulnerability to bacteria and their byproducts can impact its functioning [3,4]. CXCL9 indirectly affects liver function by affecting the stomach and respiratory mucosa. CXCL9 reduces bacteria entry, protecting the liver from infection [5,6].

The study of CXCL9's role in liver function is crucial for understanding the factors influencing its health and improving strategies for managing liver diseases. The increasing prevalence of conditions like NAFLD and viral hepatitis necessitates research on liver pathology mechanisms. CXCL9, a key mediator in immune responses, could be a biomarker for disease progression or severity. Investigating its signalling pathways can identify therapeutic targets to enhance liver function or mitigate damage. This article contributes to the growing literature on the immune system's role in liver health, potentially paving the way for innovative treatments promoting liver repair and regeneration.

Therefore, the objective of this study is to investigate the influence of CXCL9, a chemokine suppressed by gamma interferon, on the liver function of patients with respiratory and gastrointestinal diseases.

MATERIAL

STUDY DESIGN

A cross-sectional study was carried out from 15th December 2023 to 25th July 2024. A total of 320 microbial isolates of 160 patients (70 + 90) with gastrointestinal infection and respiratory tract infections, respectively were collected from the Tikrit Teaching Hospital, the Public Health Laboratory and the Respiratory Chest and Respiratory Diseases consulting clinics in Salah AL-Din governorate, Iraq. The age of patients ranges between (20–70) years. Out of the 140 blood samples collected from patients were obtained from 70 patients diagnosed with gastrointestinal disorders, 180 blood samples were gathered from 90 patients diagnosed with respiratory system disorders.

HUMAN CXC-CHEMOKINE LIGAND 9, CXCL9 ELISA KIT (QUALITATIVE): CATALOGUE NUMBER: SL3346HU-

The ELISA is a qualitative enzyme immunoassay technique that uses a pre-coated microplate with an antibody specific to CXCL9. The sample is numbered in sequence, and samples are added to the microplate wells. Horseradish Peroxidase (HRP)-conjugated antibody is added to each well, forming an antibody-antigen-enzyme labelled antibody complex. The TMB

substrate solution is added to each well, and only wells containing CXCL9 and HRP conjugated antibodies appear blue. The optical density (OD) is measured spectrophotometrically at 450 nm, and the qualitative determination of CXCL9 is determined by comparing it with the CUTOFF value.

Negative Judgment: If OD value < CUTOFF, the sample is considered Human CXCL9 negative.

Positive Judgment: If OD value ≥ CUTOFF, the sample is considered Human CXCL9 positive.

LIVER FUNCTION TESTING

The liver function parameters were conducted in Tikrit Central University Laboratories using a Chemistry Analyzer System (Geno. TEK; USA). The analysis was carried out according to the instructions of the Italian company GISSE.

STATISTICAL ANALYSIS

The data was gathered, analyzed, and shown using the statistical software IBM-SPSS version 27 and Microsoft Office Excel 2010 [7]. The data was presented in pie diagrams and charts.

ETHICAL APPROVAL CONSIDERATIONS

The study was approved by the Ethics Committee of Tikrit University of Medicine. All individuals provided informed permission before their involvement in the research. The research was done in compliance with the Declaration of Helsinki, prioritizing the rights and welfare of the participants throughout the study procedure.

RESULTS

ASSOCIATION BETWEEN CXCL9 IN PATIENTS WITH LIVER ENZYMES

The mean, standard deviation (SD), range, and p-value for the correlation between CXCL9 levels and several liver function tests in patients with gastrointestinal and respiratory disorders are shown in (Table 1). The statistical analysis at a significance level of 0.05 indicated that the *P-values* for ALP, GGT, GOT, GPT, and TSB were 0.754, 0.019, 0.712, 0.672, and 0.136, respectively. The obtained p-value of 0.019 for GGT indicates a statistically significant association with CXCL9.

ASSOCIATION BETWEEN CXCL9 IN PATIENTS (MALE AND FEMALE) WITH LIVER ENZYMES

The study demonstrated a statistically significant difference in CXCL9 levels across distinct sex and disease groups (R and G) at a significance level of 0.05. Specifically, in the GGT group, the *p-value* was 0.050 (Table 2).

ASSOCIATION BETWEEN CXCL9 IN PATIENTS WITH LIVER ENZYMES ACCORDING NORMAL AND ABNORMAL LEVELS

The data in (Table 3) illustrates the correlation between liver enzyme abnormalities, CXCL9 levels, and various patient categories at the 0.05 level. No significant correlations were seen between increased levels of CXCL9 and abnormalities in ALP, GOT, GPT, and TSB. The study revealed a statistically significant association (*P. value*=0.004) between CXCL9 levels and GGT abnormalities, primarily in the Respiratory groups.

THE CORRELATION ANALYSIS OF THE PATIENTS WITH GASTROINTESTINAL DISEASES REGARDING CXCL9

Upon analyzing the gastrointestinal illnesses group using liver enzymes, at 0.05, and 0.001 levels a very significant positive connection was found between GOT and GPT (r: 0.821 $P<0.001$). The statistical significance of $p<0.001$ indicates that there are substantial differences in the levels of GOT and GPT. Furthermore, there is a direct association between them, meaning that a rise in the concentration of GOT in the blood is associated with an increase in the concentration of GPT, and vice versa. There

is no statistically significant association seen between other liver enzymes. The data shown in (Table 4) demonstrate a positive connection, as seen in (Figure 1).

THE CORRELATION ANALYSIS OF THE PATIENTS WITH RESPIRATORY DISEASES REGARDING CXCL9

Upon analyzing the respiratory illnesses group in connection to liver enzymes, it was shown that there exists a statistically significant at 0.05, 0.001 levels, positive, and robust link between GPT and the respiratory disorders (r: 0.721 and $p<0.001$). Statistically significant results indicate a modest positive connection (r: 0.544, $P<0.05$) between GOT and TSB in the respiratory disorders related to CXCL9. However, no link was detected between other liver enzymes. The findings shown in (Table 5) demonstrate the positive association seen in (Figures 2 and 3).

DISCUSSION

ASSOCIATION BETWEEN CXCL9 IN PATIENTS WITH LIVER ENZYMES

Table 1 presents the results of the study, which shed light on the association between the levels of the chemokine CXCL9 and a variety of liver function tests in patients with respiratory and gastrointestinal diseases. The fundamental finding is the statistically significant difference (*p-value* = 0.019) in the association between GGT and CXCL9 levels between the two disease groups. In particular, the mean GGT level in the respiratory disease group (27.44 ± 20.69) was considerably higher than the gastrointestinal disease group (14.57 ± 5.36). This finding is especially intriguing because GGT is a biomarker frequently employed to evaluate liver function and identify liver diseases [8].

A variety of hepatic conditions, such as alcoholic liver disease, non-alcoholic fatty liver disease, and viral hepatitis, are frequently associated with elevated GGT levels [9]. The observed association between CXCL9 and GGT levels in the respiratory disease group is by prior research that has examined the role of CXCL9 in liver pathologies. Patel et al. [10] revealed that CXCL9 levels were substantially elevated in patients with chronic hepatitis C and were positively correlated with GGT. They stated that nine markers (levels of ALT, GGT, hyaluronic acid, intracellular adhesion molecule 1, IL-4, CXCL10, CXCL9, and vascular cell adhesion molecule 1) were associated with a change in the histologic activity index (*P values* ranging from .000 to .049) were associated with a change in the fibrosis stage (*P values* ranging from .001 to .042).

ASSOCIATION BETWEEN CXCL9 IN PATIENTS (MALE AND FEMALE) WITH LIVER ENZYMES

The findings presented in Table 2 are intriguing in terms of the correlation between CXCL9 levels and various liver enzymes, particularly in the context of sex and disease groups (respiratory and gastrointestinal). A statistically significant difference (*p-value* = 0.050) in the GGT levels of the four groups (R-male, R-female, G-male, and G-female) is the primary observation.

This finding was before the research documented sex-specific variations in the association between liver function parameters and CXCL9. The study conducted by Xiao et al. [11] revealed a stronger correlation between CXCL9 and GGT in male patients diagnosed with chronic hepatitis C compared to female patients. The authors proposed that this sex-specific difference may be associated with the potential influence of sex hormones on the regulation of CXCL9 and liver enzymes. Estrogen has been demonstrated to influence the expression and functionality of numerous chemokines, such as CXCL9, which may account for the observed disparities between males and females [12].

ASSOCIATION BETWEEN CXCL9 IN PATIENTS WITH LIVER ENZYMES ACCORDING NORMAL AND ABNORMAL LEVELS

The results provided in Table 3 offer additional insight into the relationship between CXCL9 levels and a variety of liver enzyme abnormalities in patients with respiratory and gastrointestinal conditions. The most significant finding in this table is the statistically significant association (*p-value*=0.004) between GGT abnormalities and CXCL9 levels, particularly in the respiratory disease group. According to the data, 15.8% of patients in the respiratory group had abnormal GGT levels, while none in the gastrointestinal group exhibited GGT abnormalities. This indicates that the increased levels of CXCL9, as shown in the earlier study (Table 3), maybe more strongly linked to variations in GGT in respiratory disorders rather than gastrointestinal disorders.

This observation is consistent with the results of Cao et al. [13], which have documented a more robust association between liver enzyme disturbances in patients with respiratory diseases and CXCL9. Sanhueza et al. [14] showed that CXCL9 levels were substantially elevated in patients with chronic obstructive pulmonary disease (COPD) and were associated with elevated GGT levels. The authors suggested that the elevated CXCL9 in COPD may contribute to the development of liver injury and dysfunction, potentially through mechanisms involving inflammation and oxidative stress. Hirschfield et al. [15] conducted a study that showed that CXCL9 levels were elevated in patients with idiopathic pulmonary fibrosis and were correlated with the severity of liver enzyme abnormalities, particularly GGT. The authors proposed that the elevated CXCL9 in pulmonary fibrosis may serve as a marker of concurrent liver involvement, which is indicative of the systemic nature of the disease.

Correlation between serum levels CXCL-9 and liver function tests, specifically GOT and TSB, in patients with RTI. The results indicated that there was no statistically significant correlation between CXCL-9 and either GOT or TSB levels. This suggests that CXCL-9 may not have a direct impact on these specific liver enzymes in the context of respiratory infections. The absence of a substantial correlation between CXCL-9 and GOT or TSB levels in this study implies that CXCL-9 may not directly affect the activity of these specific enzymes during RTI.

A potential function in the inflammatory response has been suggested by Hachem et al. [16], who reported elevated CXCL-9 levels in patients with pneumonia. Nevertheless, the precise relationship between CXCL-9 and liver enzymes, specifically GOT and TSB, in RTI has not been thoroughly examined.

Table 1. Association between CXCL9 and liver enzymes in gastrointestinal and respiratory tract patients.

Liver Function	**CXCL9**				***P. value***
	Respiratory		**Gastrointestinal**		
	Mean± SD	**Range**	**Mean± SD**	**Range**	
ALP	176.67±55.09	218.00	184.10±85.51	361.00	0.754
GGT	27.44±20.69	73.00	14.57±5.36	21.00	0.019
GOT	20.94±8.83	34.00	22.71±18.42	93.00	0.712
GPT	18.06±17.74	92.00	15.38±14.39	84.00	0.672
TSB	0.80±0.51	1.83	0.57±0.45	1.45	0.136

Abbreviations: CXCL9: Human C-X-C Motif Chemokine 9, ALP: Alkaline Phosphatase, GGT: Gamma-Glutamyl Transferase, GOT: glutamic oxaloacetic transaminase, GPT: glutamic pyruvic transaminase, TSB: Total Serum Bilirubin.

Table 2. Association between CXCL9 and liver enzymes according to gender.

CXCL9		**N**	**Mean**	**SD**	***P. value***
ALP	R-Male	10	171.10	66.607	0.971
	R-Female	8	183.63	39.572	
	G-Male	10	181.90	89.181	
	G-Female	11	186.09	86.361	
GGT	R-Male	10	30.20 A	25.789	0.050
	R-Female	8	24.00 A B	12.649	
	G-Male	10	15.20 B	7.068	
	G-Female	11	14.00 B	3.435	
GOT	R-Male	10	18.30	8.970	0.636
	R-Female	8	24.25	7.960	
	G-Male	10	25.90	25.588	
	G-Female	11	19.82	8.364	
GPT	R-Male	10	19.60	27.155	0.953
	R-Female	8	16.13	9.448	
	G-Male	10	16.10	25.009	
	G-Female	11	14.73	10.622	
TSB	R-Male	10	0.7050	0.57175	0.346
	R-Female	8	0.9175	0.43791	
	G-Male	10	0.5050	0.50163	
	G-Female	11	0.6200	0.40561	

Different letters denote a significance of less than 0.05.

Table 3. Comparative CXCL9 levels in patients with a liver enzyme in normal and abnormal values.

Liver functions		**CXCL9**				***P. value***
		Respiratory		**Gastrointestinal**		
		No.	**%**	**No.**	**%**	
ALP Categories	Normal	16	88.9	15	71.4	0.768
	Abnormal	2	11.1	6	28.6	
GGT Categories	Normal	15	84.2	21	100.0	0.004
	Abnormal	3	15.8	0	.0	
GOT Categories	Normal	17	94.7	20	95.2	0.911
	Abnormal	1	5.3	1	4.8	
GPT Categories	Normal	16	88.9	19	90.5	0.871
	Abnormal	2	11.1	2	9.5	
TSB categories	Normal	13	73.6	14	66.6	0.510
	Abnormal	5	26.4	7	33.4	

Table 4. Relation between liver enzymes in gastrointestinal patients and CXCL9 values.

Correlations (G- CXCL9)						
		ALP	**GGT**	**GOT**	**GPT**	**TSB**
ALP	r	1	.234	-.029	-.221	.394
	P. value		.308	.901	.336	.077
GGT	R		1	.340	.299	.253
	P. value			.131	.188	.269
GOT	r			1	**0.821****	-.142
	P. value				**<0.001**	.540
GPT	r				1	.038
	P. value					.872
TSB	r					1
	P. value					

Table 5. Relation between liver enzymes in respiratory patients and CXCL9 values.

Correlations (R- CXCL9)						
		ALP	**GGT**	**GOT**	**GPT**	**TSB**
ALP	r	1	.105	.116	.264	-.046
	P. value		.677	.648	.290	.856
GGT	r		1	-.088	**0.721****	.210
	P. value			.729	**0.001**	.402
GOT	r			1	-.132	**0.544***
	P. value				.601	**0.020**
GPT	r				1	.232
	P. value					.354
TSB	r					1
	P. value					

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

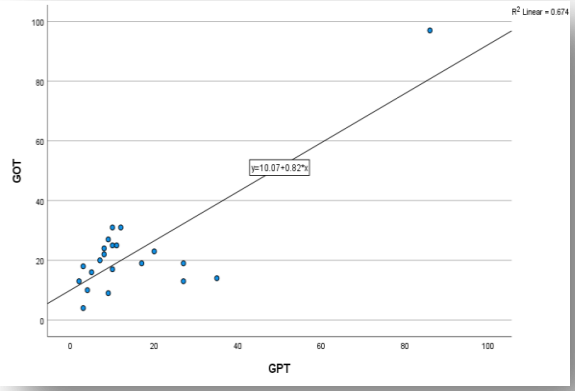

Figure 1. Linear positive correlation between GPT and GOT in patients with gastrointestinal disease.

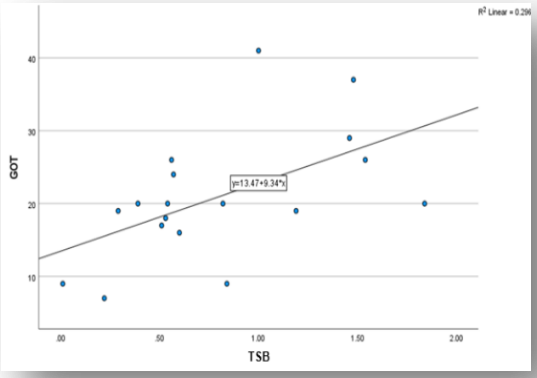

Figure 2. Linear positive correlation between GGT and GPT in patients with respiratory disease.

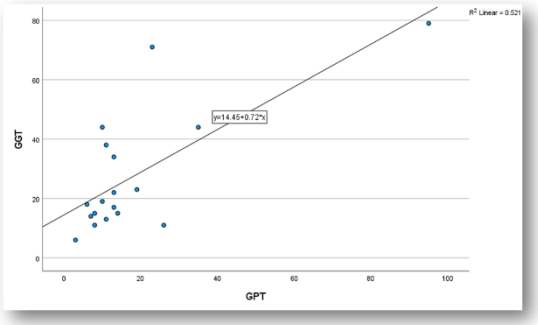

Figure 3. Linear positive correlation between TSB and GOT in patients with respiratory disease.

CONCLUSION

The findings of this research highlight the strong correlation between CXCL9 levels and liver function, especially in those with respiratory and gastrointestinal disorders. The results demonstrate a significant association between higher levels of CXCL9 and higher levels of GGT, indicating that CXCL9 might be a promising predictive indicator for liver disease. Females have greater susceptibility and responsiveness to cytokines and liver enzymes. Observed gender disparities in GGT levels underscore the intricate nature of the connection between CXCL9 and liver function, suggesting that sex-specific variables may impact this link. A comprehensive understanding of the processes that underlie this association is of utmost importance, as it has the potential to provide valuable insights into the pathophysiology of liver illnesses, especially in those afflicted with chronic respiratory disorders.

Future studies should focus on clarifying the mechanisms by which CXCL9 affects liver function and examining its possible therapeutic consequences. Through intensive study of the function of CXCL9 in liver health, we may deepen our knowledge of its usefulness in clinical environments and devise specific approaches for controlling liver-related problems in afflicted individuals. In the realm of liver function and illness, CXCL9 offers a promising field of investigation.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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AUTHOR CONTRIBUTION

Rafal Khalil Farhan: Conceptualization, methodology, data collection, statistical analysis, and manuscript writing.
Saja Khudhur Jamal: Supervision, project administration, critical review, and final approval of the manuscript.

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