Vol. 30, No. 1, 2026, Pages 135-142

Thi-Qar Medical Journal (TQMJ)

Thi-Qar Medical Journal was established in 2006 and is published by the College of Medicine, University of Thi-Qar, Iraq

ISSN (PRINT): 1992-9218 | ISSN (ONLINE): 3006-4791

www.jmed.utq.edu.iq utjmed@utq.edu.iq

Evaluation of Pentraxin-3 and NADPH oxidase as diagnostic biomarkers in Iraqi Crohn's disease patients: A case-control study

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Received: 25.3.2026

Revised:5.4.2026

Accepted: 13.4.2026

DOI:

10.32792/jmed.2026.30.59

Keywords:

Crohn's disease

pentraxin 3

NADPH oxidase

How to cite

Wafaa Mohammed Ahmed, Ali Abudl Hussein Mahdi, Hamzah Abdulrahman Salman. Evaluation of Pentraxin-3 and NADPH Oxidase as diagnostic biomarkers in Iraqi Crohn's disease Patients: A Case-Control Study. *Thi-Qar Medical Journal (TQMJ)*. 2026: 30 (1): 135-142.

Abstract

Background: Pentraxin-3 (PTX-3) and NADPH oxidase contributed to intestinal inflammation and oxidative stress pathways in Crohn's disease (CD). However, their diagnostic performance in CD patients remains inadequately explored, especially in the Iraqi population**. Aims of the study:** This study aims to assess the serum PTX3 and NADPH oxidase activity in Iraqi CD patients and to determine their diagnostic utility. **Materials and Methods:** A case-control study was conducted at the Al-Yarmouk Teaching Hospital, Baghdad, Iraq. A total of 186 participants with an age range of 19-50 years were enrolled, including 126 CD and 60 healthy controls. PTX-3 concentrations were quantified using an enzyme-linked immunosorbent assay (ELISA), while NADPH oxidase activity was determined using the WST-8 colorimetric assay kit, with absorbance values determined using a microplate reader. **Results:** CD patients exhibited significantly higher levels of PTX-3 (4.5 ± 0.96 ng/mL vs. 2.5 ± 0.53 ng/mL, $p < 0.001$) and NADPH oxidase activity (105.7 ± 35.86 µmol/L vs. 62.8 ± 13.36 µmol/L, $p < 0.001$) compared to controls. PTX-3 showed high diagnostic performance with an area under the curve (AUC) of 0.97. NADPH oxidase also showed good discriminative ability with an AUC of 0.93. Furthermore, the combined biomarker model demonstrated outstanding diagnostic performance with an AUC of 0.99. The correlation analysis between PTX-3 and NADPH oxidase showed no statistically significant correlation ($r = -0.039$, $p = 0.69$). **Conclusion:** This study highlighted the promising role of PTX-3 and NADPH oxidase as non-invasive biomarkers that may aid in the diagnostic evaluation of CD. Future studies are required to validate their clinical applicability.

1.Introduction

Crohn's disease (CD) refers to a chronic inflammatory disorder that represents one of two main types of inflammatory bowel disease (IBD) [1]. It's characterized by persistent, relapsing inflammation that can affect any portion of the gastrointestinal tract from mouth to anus, and the most affected sites are the terminal ileum and colon [2]. Globally, IBD is a global public health problem, with a prevalence continuing to increase and posing a significant challenge to healthcare providers and governments over the past decade [3]. In the Arab world, the incidence of IBD dramatically increases, with an estimated incidence of CD reaching about 1.46 per 100,000 individuals each year, and most of them are diagnosed at

a young age [4]. In Iraq, although epidemiological data on IBD remain restricted, available evidence indicates that the incidence of CD has amplified in recent years [5].

The pathogenesis of CD is multifactorial, arising from complex interactions among genetic susceptibility, environmental stimuli, altered gut microbiota, and dysregulated immune responses [6]. Available evidence indicates that disturbance of innate immune pathways contributes to the intestinal inflammatory response in patients with CD. In addition, previous studies implicated the role of oxidative stress in CD development and progression through excessive production of reactive oxygen species [7,8]. The clinical diagnosis of CD remains challenging, where the current diagnostic methods rely largely on invasive procedures, including endoscopic and histopathological examination. [9]. Therefore, identifying reliable and noninvasive biomarkers that could aid in early disease diagnosis has become a significant research priority.

Pentraxin-3 (PTX-3) is an essential component of the innate immune system and plays a major role in inflammatory response regulation. PTX-3 is an acute-phase protein as a part of the long pentraxin subfamily [10]. It is produced locally at the site of inflammation by different immune cells, which is induced by primary inflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin-1β [11]. Recent research shows that PTX3 dysregulation has a significant role in the development and progression of several autoimmune diseases, including CD, where it reflects intestinal inflammatory activity [12,13].

Similarly, NADPH oxidase is responsible for generating reactive oxygen species (ROS) in various nucleated cells of the human body and is a crucial enzyme complex involved in innate immune response [14]. Regulation of NADPH oxidase activity contributes to intestinal homeostasis. On the other hand, extreme activation of this enzyme stimulates oxidative stress and mucosal injury, which are vital mechanisms in the pathogenesis of IBD, particularly CD [15].

In spite of the role of these biomarkers in intestinal inflammation of CD, there is limited data on the diagnostic value of PTX-3 and NADPH oxidase in CD patients, particularly in the Iraqi population. Therefore, this study aims to assess the serum PTX3 and NADPH oxidase activity in CD patients and to determine their diagnostic utility.

2. Materials and Methods

Research Methods and Subjects:

A case-control study was conducted in the Al-Yarmouk Teaching Hospital Department of Gastroenterology and Hepatology, Baghdad, Iraq, from January to March 2026. A total of 186 participants with an age range of 19-50 years were enrolled, including 126 CD and 60 healthy controls.

Patients were carefully selected based on specific criteria, including only patients confirmed by a specialist gastroenterologist based on standard clinical assessments, endoscopic findings, histopathological examination of biopsy samples, and radiological evaluation. The exclusion criteria included patients with other IBD, such as ulcerative colitis, autoimmune disease, infection of the gastrointestinal tract, and malignancy. In addition, patients are receiving corticosteroids, biological therapy, and other immunosuppression medications.

Sampling and Evaluation of Biomarkers:

Blood samples were obtained from Iraqi patients with CD and healthy individuals. Six milliliters were drawn intravenously and transferred to a gel tube and allowed to stand for approximately 10-15 minutes to clot. After that, serum samples were obtained through centrifugation for 10 minutes at 5000 RPM, all sera were kept at -80°C until ready for use. Shortly before the testing, samples were thawed properly at room temperature.

Pentraxin-3 (PTX-3) concentrations were quantified using a commercially available enzyme-linked immunosorbent assay (ELISA) kit (ELK Biotechnology, China, Cat. No.: ELK3268), while NADPH oxidase activity was determined using the WST-8 colorimetric assay kit (Elabscience, USA, Cat. No.: E-BC-K803-M). Optical density (OD) was determined at a wavelength of 450 nm using a microplate reader (Huma Reader HS, Human GmbH, Germany). All measurements were performed in duplicate, and the concentration of biomarkers was determined using a standard curve. Hemoglobin (Hb) levels were measured using an automated hematological analyzer (Mindray, China).

Statistical Analysis:

All statistical analyses were performed using R version 4.5.1 and RStudio. The Shapiro-Wilk test and Q-Q plots were used to assess the normality of data distribution. Continuous variables were summarized using Mean ± SD and medians (min, max). To compare unpaired groups (CD patients vs. healthy controls), the Mann-Whitney U test (Wilcoxon rank-sum test) was applied for continuous variables, whereas Pearson's chi-squared test for categorical variables. Spearman's rank correlation was used to assess relationships between continuous variables among CD patients. To evaluate the diagnostic performance of biomarkers, the Receiver Operating Characteristic (ROC) curve analysis was employed. The optimal cut-off point for each biomarker was determined using Youden's J statistic. A p value < 0.05 was considered statistically significant.

3. Results

Table 1. presents the demographic characteristics of Crohn's disease (CD) patients and healthy controls. There was no significant difference in age between CD patients and healthy controls (p-value = 0.645), which reflects appropriate age matching between the two groups. In contrast, sex distribution showed a statistically significant difference between males and females (p = 0.015). In the CD group, males constituted 45.2%, and females represented 54.8%, compared with 26.7% males and 73.3% females in the control group.

Table 1. Demographic characteristics of study groups

Characteristic	Healthy Control (N = 60)	CD Patients (N = 126)	p-value*
Age (years)			0.645
Mean ± SD	33.7 ± 7.18	34.2 ± 8.28	
Median (Min, Max)	34.0 (19.00, 49.0)	36.0 (19.00, 49.0)	
Sex			**0.015**
Male	16.0 (26.7%)	57.0 (45.2%)	
Female	44.0 (73.3%)	69.0 (54.8%)	

p-value based on Mann-Whitney U test for age, Chi-squared test for sex.

Table 2. presents the levels of PTX3, NADPH oxidase, and hemoglobin levels among study groups. CD patients had significantly higher levels of PTX-3 compared to the control group (4.5 ± 0.96 vs. 2.5 ± 0.53; p < 0.001), and NADPH oxidase was also shown to be significantly elevated in CD patients compared to the control (105.7 ± 35.86 vs. 62.8 ± 13.36; p < 0.001). In addition, hemoglobin levels were significantly lower in CD patients compared to the control (10.6 ± 1.18 g/dl vs. 12.4 ± 1.38, p < 0.001).

Table 2. Biomarkers and hemoglobin levels among study groups

Biomarker levels	Healthy Control (N=60)	CD Patients (N=126)	p-value*
PTX-3 (ng/mL)			**<0.001**
Mean ± SD	2.5 ± 0.53	4.5 ± 0.96	
Median (Min, Max)	2.4 (1.53, 3.6)	4.4 (2.64, 7.2)	
NADPH oxidase (µmol/L)			**<0.001**
Mean ± SD	62.8 ± 13.36	105.7 ± 35.86	
Median (Min, Max)	62.6 (40.75, 91.3)	96.4 (47.42, 284.7)	
Hb (g/dl)			**<0.001**
Mean ± SD	12.4 ± 1.38	10.6 ± 1.18	
Median (Min, Max)	12.5 (9.60, 14.9)	11.0 (8.00, 13.0)	

*Mann-Whitney U-test for continuous variables

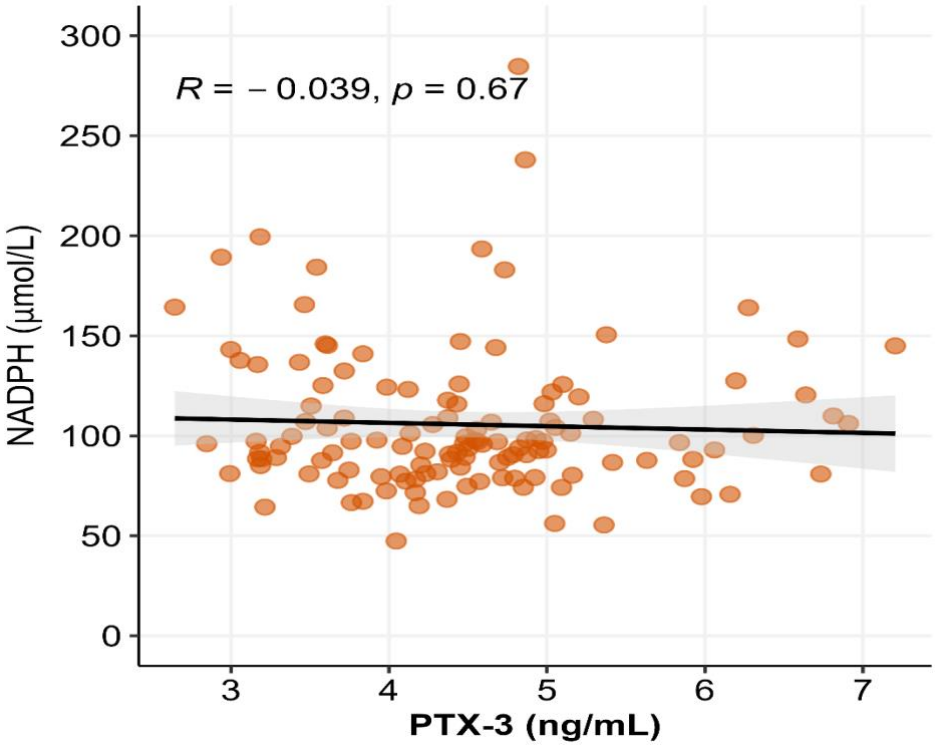

Fig. 1. Correlation between PTX-3 and NADPH oxidase in CD patients (n = 126)

Fig. 1 shows the correlation analysis between PTX-3 and NADPH oxidase, the results indicating no statistically significant correlation between the two biomarkers (r = -0.039, p = 0.69).

Receiver operating characteristic (ROC) analysis was performed to assess the diagnostic accuracy of PTX-3 and NADPH oxidase as markers for Crohn's disease (CD) (Table 3). PTX-3 showed excellent diagnostic performance with an area under the curve (AUC) of 0.97, sensitivity of 0.80, and specificity of 1.00 at the optimal threshold of 3.59.

Similarly, NADPH oxidase showed good discriminative ability with an AUC of 0.93, a sensitivity of 0.91, and a specificity of 0.83 at the optimal threshold of 72.31. The combined biomarker model demonstrated outstanding diagnostic performance with an AUC of 0.99, a sensitivity of 0.97, and a specificity of 1.00, as shown in Fig. 2.

Table 3. ROC test analysis of studies biomarkers with their combined model

Biomarker	Threshold	AUC	Sensitivity	Specificity	Youden-J
PTX-3 (ng/mL)	3.59	0.97	0.80	1.00	0.80
NADPH oxidase (µmol/L)	72.31	0.93	0.91	0.83	0.75
Combined (PTX-3+NADPH)	1.14	0.99	0.97	1.00	0.97

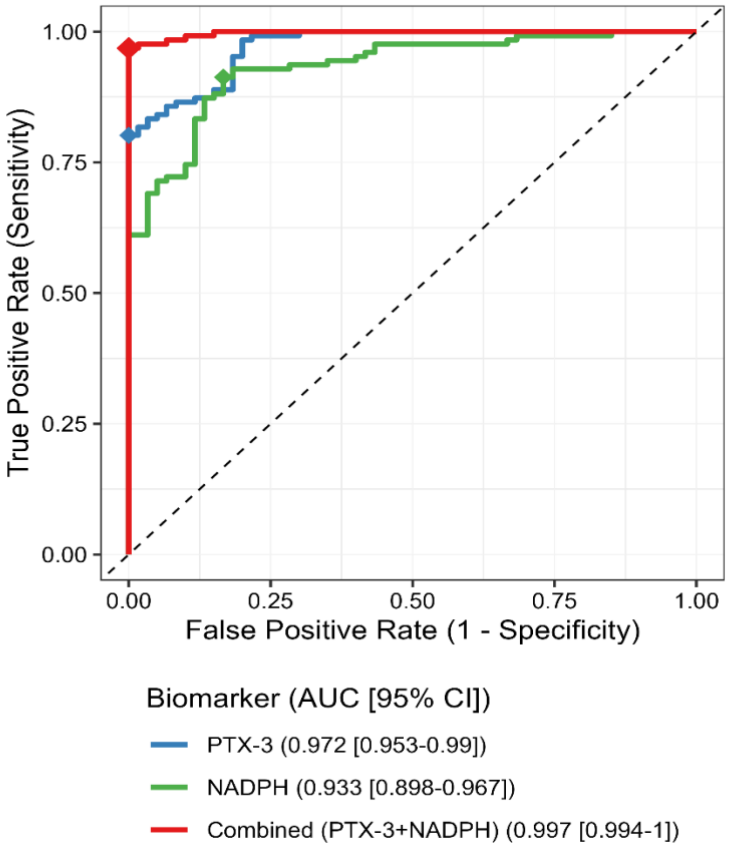

Fig. 2. ROC test for PTX-3, NADPH oxidase, and their combined model

4. Discussion

This study aimed to evaluate the serum PTX3 levels and NADPH oxidase activity in CD patients and assess their diagnostic performance. The findings revealed that PTX-3 levels and NADPH oxidase activity were significantly elevated in CD patients compared to controls, which may suggest enhanced inflammatory activity and oxidative stress in CD patients. ROC curve analysis demonstrated excellent diagnostic performance for both PTX-3 and NADPH oxidase, especially in the combined model.

In this study, the higher PTX-3 levels may reflect local production of PTX-3 at the site of intestinal inflammation in CD, as it is released by infiltrating neutrophils and endothelial cells with inflamed tissue [16]. It's produced in response to inflammatory signals such as TNF-α and IL-1β by mononuclear phagocytic cells, reflecting the local innate immune activation of mucosal inflammation [17]. This finding is consistent with a previous study that reported upregulation of PTX3 in colonic tissue of patients with active CD, indicating that PTX-3 may function as a potential biomarker of intestinal inflammation and be positively associated with disease activity [18]. In the same context, previous research shows that PTX-3 is significantly elevated in CD patients and linked with disease activity score [19].

The current study also revealed that NADPH oxidase activity is significantly raised in CD patients compared to healthy controls, which might be attributed to the recruitment and activation of innate immune cells, particularly macrophages and neutrophils, at the site of intestinal inflammation. Activation of immune cells triggers the NADPH oxidase complex, resulting in an augmented oxidative burst and, as a result, excessive generation of ROS that contributes to oxidative mucosal damage and exacerbation of intestinal inflammation of IBD [20]. This result aligns with a previous study by Hausmann et al., which reported that NADPH oxidase expression is distinctly upregulated in macrophages isolated from the inflamed intestinal mucosa of CD patients compared to normal mucosa, and this elevation promotes oxidative stress and chronic intestinal inflammation [21]. These findings suggest that NADPH oxidase is not only an indicator of oxidative stress but also contributes to sustained inflammation of CD. In addition, Hb levels were significantly lower among CD patients compared to healthy controls. According to the World Health Organization (WHO), anemia in adults is defined as Hb levels <13 g/dl in men or <12 g/dl in nonpregnant women [22]. Based on these criteria, CD patients in our findings suffer from anemia. Consistent with the European Crohn's and Colitis Organization (ECCO) consensus guidelines, reported anemia is one of the most common systemic extraintestinal manifestations of CD patients, mainly due to chronic inflammation, malabsorption, and iron deficiency [23].

On the other hand, the current study showed no significant correlation between PTX-3 and NADPH oxidase levels in patients with CD. Despite the limited studies evaluating these two biomarkers together, particularly in Iraq, the absence of a significant association may suggest that PTX-3 and NADPH oxidase reflect different biological pathways in the pathogenesis of CD, where PTX-3 primarily represents the inflammatory and innate immune activation of CD, whereas NADPH oxidase is mainly related to ROS production and oxidative stress pathways [12,24].

In terms of diagnostic performance, our study found excellent discriminative ability for PTX-3 in distinguishing CD patients from healthy controls. PTX-3 showed an AUC of 0.97, a sensitivity of 0.80, and a specificity of 1.00. Previous evidence has also highlighted the diagnostic potential of PTX-3 in CD. One study reported that PTX-3 showed good performance in distinguishing active CD from remission with an AUC of 0.85 compared with C-reactive protein (CRP), which appeared to have a lower AUC at 0.64 [18]. Another recent study demonstrated that PTX-3 showed good diagnostic performance in identifying fibrotic phenotypes of CD with an AUC of 0.839, indicating PTX-3 is closely associated with intestinal inflammation and disease progression [25].

Furthermore, NADPH oxidase also exhibited strong diagnostic performance in the present study, with an AUC of 0.93, sensitivity of 0.91, and specificity of 0.83. Most previous studies focused on the mechanistic role of NADPH oxidase in oxidative stress and intestinal inflammation rather than its diagnostic performance. To our knowledge, no previous studies from Iraq have evaluated the diagnostic performance of this marker in CD using ROC analysis. Therefore, the present findings provide novel insight into the potential role of this biomarker in diagnosing CD.

The combined model of these two biomarkers further improved the diagnostic performance, achieving an AUC of 0.99 with higher sensitivity and specificity compared with each biomarker alone. These findings may be explained by the complementary biological role of the two biomarkers, PTX-3 reflects inflammatory activity, while NADPH oxidase represents the oxidative stress mechanism of CD. Therefore, the combination of PTX-3 and NADPH oxidase may represent a promising diagnostic strategy for CD.

5. Conclusion

PTX-3 and NADPH oxidase were significantly elevated in patients with CD and demonstrated excellent diagnostic performance in distinguishing CD from healthy controls. The combined assessment of these biomarkers further improved diagnostic accuracy. These observations highlight the promising role of PTX-3 and NADPH oxidase as non-invasive biomarkers that may aid in the diagnostic evaluation of CD.

Ethical Approval

The ethical approval was obtained from the medical ethics committee of Middle Technical University, Baghdad, Iraq (Ref. No.: MEC 167, date 07/01/2026, P.C. NO. 10074). This study was conducted in accordance with the Declaration of Helsinki and with full respect for participants. Written informed consent was obtained from all participants before any sample was taken.

Acknowledgments

The authors gratefully acknowledge the staff of the Gastroenterology and Hepatology Department at Al-Yarmouk Teaching Hospital, Baghdad, Iraq, for their invaluable assistance in patient recruitment and sample collection. The authors are also extending their sincere appreciation to Crohn's disease patients for their cooperation.

Conflict of Interest

The authors declare no conflicts of interest. This study was conducted independently, with no financial support from any commercial entity that could influence the outcomes of the study.

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