Rzeszów University Press 2025
ISSN 2544-1361 (online)
doi: 10.15584/ejcem.2025.4.1

http://www.ejcem.ur.edu.pl
European Journal of Clinical and Experimental Medicine
Eur J Clin Exp Med 2025; 23 (4): 828–834

ORIGINAL PAPER

Dipeptidyl peptidase-4 dysregulation and inflammatory cytokines as dual biomarkers in ulcerative colitis – a case-control study

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ABSTRACT

Introduction and aim. Ulcerative colitis (UC) is a chronic inflammatory bowel disease (IBD) characterized by immune dysregulation and mucosal inflammation. Current UC biomarkers lack specificity, underscoring the need for novel diagnostic tools. Dipeptidyl peptidase-4 (DPP-4), a serine protease implicated in immune modulation and inflammation, and interleukin-7 (IL-7), a cytokine linked to mucosal immune dysregulation, may serve as dual biomarkers. This study aimed to evaluate the diagnostic utility of serum levels of DPP-4, C-reactive protein (CRP), and IL-7 to differentiate UC patients with UC from healthy individuals.

Material and methods. This research conducted a case-control study involving 130 individuals, 65 diagnosed with UC and 65 apparently healthy individuals serving as the control group. Blood samples were obtained to measure DPP-4, IL-7, insulin and C-reactive protein levels.

Results. The study demonstrated a significantly higher level of inflammatory markers compared to the healthy controls with a significantly higher CRP (23.38±17.76 vs. 2.38±0.89 mg/dL, p<0.001) and IL-7 concentrations (62.39±19.7 vs. 22.86±4.73 ng/L, p<0.001). and lower level of DPP-4 activity (1.33±0.19 vs. 2.37±0.35 U/L, p<0.001). ROC curve analysis revealed the excellent diagnostic performance of DPP-4 and IL-7 in identifying UC.

Conclusion. Reduced serum DPP-4 levels and elevated levels of inflammatory markers (CRP and IL-7) highlight their utility as dual biomarkers for the diagnosis and monitoring of UC disease. DPP-4 expression is inversely correlated with inflammation. These biomarkers demonstrate diagnostic potential for UC; however, longitudinal studies are needed to assess their role in monitoring disease progression and response to treatment.

Keywords. dipeptidyl peptidase-4, inflammatory bowel disease, ulcerative colitis

Introduction

Inflammatory bowel disease (IBD), which includes ulcerative colitis (UC) and Crohn's disease (CD), is caused by chronic intestinal inflammation. These two primary idiopathic conditions differ in their anatomical distribution patterns and the depth of intestinal wall involvement. UC, unlike CD, is characterized by continuous mucosal inflammation confined to the colon.[1] By contrast, CD can affect any part of the gastrointestinal tract and often involves transmural inflammation. Phenotypically, Crohn's is classified using the Vienna and Montreal systems, which categorize patients based on age at diagnosis, disease location, and behavioral manifestations (inflammatory, stricturing, or penetrating).[2] In contrast, UC characteristically involves continuous and symmetric inflammation limited to the colonic mucosa and submucosa, with a sharp demarcation between affected and normal tissues.[3] UC typically begins in the

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Received: 21.04.2025 / Revised: 20.05.2025 / Accepted: 5.06.2025 / Published: 30.12.2025

Hamid HH, Shaker BM, Almamory AJ. Dipeptidyl peptidase-4 dysregulation and inflammatory cytokines as dual biomarkers in ulcerative colitis – a case-control study. *Eur J Clin Exp Med.* 2025;23(4):828–834. doi: 10.15584/ejcem.2025.4.1.

rectum and may remain localized (ulcerative proctitis) or extend proximally. The Montreal classification classifies UC as proctitis (E1) with rectal involvement, left-sided colitis (E2) when the disease extends distally to the splenic flexure, and extensive colitis/pancolitis (E3) when the inflammation extends proximally to the splenic flexure.[4]

UC is characterized by chronic inflammation and ulceration of the colon and rectum, with patients typically experiencing gradual-onset symptoms, such as bloody diarrhea that persists for weeks. Although exact etiopathogenesis remains unclear, UC arises from a complex interplay of immune dysfunction, genetic predisposition, and environmental triggers.[5] As a chronic disease with significant morbidity, UC cannot be cured, increasing the risk of colorectal cancer.[6] UC represents a major global health challenge, with an estimated worldwide prevalence of 5 million by 2023. Incidence rates continue to rise in industrialized and developing nations.[7] Canada exemplifies this trend, reporting one of the highest global UC incidence rates at 17.5 / 100,000 person years, alongside an overall inflammatory bowel disease (IBD) of 825 per 100,000 individuals.[8] The United States mirrors this trend, with the prevalence of UC reaching 238 per 100,000 and incidence rates between 19.2–20.2 per 100,000.[9] The European UC epidemiology exhibits bifurcated trends. Northern Europe has the highest incidence (24.3 per 100,000) and prevalence (505 per 100,000).7 In the Middle East, the incidence ranges from 1.37 to 5.0 per 100,000 people, with Saudi Arabia and Qatar showing an annual increase since 2010.[9]

In addition to epidemiological trends, dysregulation of immune mediators such as interleukin-7 (IL-7) has emerged as a key focus, IL-7 is a 25-kDa hematopoietic growth factor produced by stromal cells in the bone marrow, thymus and epithelial cells and plays a crucial role in lymphocyte development and homeostasis.[10] IL-7 signals through a heterodimeric receptor comprising IL-7Rα and a common gamma chain, activating the JAK/STAT and PI3K/Akt pathways to regulate cell survival via modulation of anti-apoptotic factors (Bcl-2, Bcl-xL, and Mcl-1) and pro-apoptotic factors.[11] Compelling evidence demonstrates a significant connection between IL-7 and UC, with IL-7 transgenic mice developing chronic colitis that mimics human UC pathology.[12] Systemic, rather than intestinal, IL-7 has been shown to be essential for colitis persistence.[13] Notably, increased IL-7R expression in the colonic mucosa of UC patients correlates with disease activity and non-responsiveness to anti-TNF therapy, with IL-7 influencing the gut-homing specificity of T cells through α4β7 integrin regulation.[14]

Dipeptidyl peptidase-4 (DPP-4), classified under EC 3.4.14, is a member of the serine peptidase family. DPP was classified into nine categories.[15] In particular, proteins and DPP-4, also known as CD26, are responsible for the degradation of peptides that contain proline or alanine at the penultimate position, an exopeptidase located on the surface of cells.[16] DPP-4 regulates bioactive peptides by cleaving the N-terminal dipeptides from substrates with proline or alanine at the penultimate position.[17] DPP-4 is widely expressed in several organs and cell types, and contributes to immunological control, glucose balance, inflammation, and cancer development. DPP-4 is widely expressed in the gastrointestinal tract, liver, lungs, and kidneys.[18] DPP-4 exerts a variety of pleiotropic effects through enzymatic and non-enzymatic mechanisms when interacting with extracellular matrix proteins.[19] In terms of enzyme activity, DPP-4 cleaved peptides with proline or alanine as second amino acid (NH-Xaa-Pro) were cleaved at the NH2-terminus by DPP-4. The preference for proline was the strongest, followed by a gradually decreased preference for alanine and glycine.[20] DPP-4 has been shown to interact with several proteins in a variety of biological processes, including sodium-hydrogen exchanger 3 (NHE3), mannose-6-phosphatase, insulin-like growth factor II (IGF II), collagen, fibronectin, caveolin I and CD45 tyrosine phosphatase.[21]

DPP-4 plays a complex and controversial role in UC by affecting immune modulation and regulation of incretin. It influences T cell activation and cytokine levels, a protease that has far-reaching effects on endocrine pathways is DPP-4, which is essential to regulate the bioactivity of peptide hormones produced in the gastrointestinal tract.[22] Preventing DPP-4 from breaking down gut hormones helps increase hormone production in the pancreas and improves food processing after meals. This effectively lowers blood sugar levels in individuals with type 2 diabetes.[23]

Aim

The present study was designed to assess the diagnostic potential of serum DPP-4, CRP, and IL-7 as a panel of combined biomarkers to distinguish patients with UC from healthy subjects and to explore their pathophysiological crosstalk in UC-related immune dysregulation and mucosal inflammation. By combining biomarker performance analysis with mechanistic exploration, this study aimed to evaluate the diagnostic utility of serum levels of DPP-4, C-reactive protein (CRP) and IL-7 levels in differentiating patients with UC from healthy individuals.

Material and methods

The present case-control study was conducted at Marjan Medical City Hospital within the Babylon Governorate to investigate factors associated with UC. A

total of 65 patients diagnosed with UC by a gastroenterologist were enrolled based on clinical presentation, endoscopic findings and histopathological examination were enrolled, along with 65 age- and sex-matched healthy controls (HC) recruited from adult volunteers aged 18 to 60 years, consisting of apparently healthy individuals who were selected based on clinical evaluation by a physician. Participants had no prior history or current symptoms suggestive of inflammatory bowel disease, including UC, and had no gastrointestinal complaints at the time of inclusion. Patients were excluded from both groups in the event of active smoking, alcohol consumption, diabetes mellitus, pregnancy or lactation, concomitant chronic diseases, autoimmune disorders, or recent use of antibiotics/probiotics within 3 months before enrollment. The control group. Control group selection was performed to ensure a similar age (±2 years) and sex as the UC cohort. The study protocol was approved by (IRB: 95 -25/11/2024). All cases that did not meet the inclusion criteria or meet the exclusion parameters were systematically excluded using a two-stage evaluation process of evaluation by gastroenterologists and laboratory confirmation. No disease severity stratification (for example, using the Mayo score) was performed, which may have limited the interpretation of biomarker variations in disease stages.

Sample collection

Each participant was given a blood sample (5 mL) drawn from their veins and the patient's sample was rapidly collected. Blood was gradually dispensed into a gel tube (CHAORAN Vacuum, Lot. no. 20231001), coagulated at room temperature for 10-15 min and centrifuged at 3000×g for 10 min. After collection, serum was stored at -40°C for subsequent analysis of DPP-4, insulin, fasting blood sugar (FBS) and C-reactive protein (CRP) levels. Serum levels of DPP-4, Interleukin-7 (IL-7), and insulin were measured using the following ELISA kits provided by (BT LAB, Shanghai, China): DPP-4 ELISA Kit (Cat. No. E0912Hu), Insulin ELISA kit (Cat.No.BTB-E0010Hu), and IL-7 ELISA Kit (Cat. No. E1948Hu). CRP concentrations were analyzed using the ichromaTM fluorescent immunoassay (FIA) platform (Boditech Med- Korea) following the manufacturer's instructions. Calibration curves for each biomarker using kit-provided standards. Quality control procedures included the use of blanks, internal controls, and strict adherence to protocol guidelines. The absorbance for the ELISA assays was measured using a spectrophotometer (Biotech Instruments (USA), and serum fasting blood sugar levels were evaluated using a Simi auto spectrophotometer (Mindray BA-88A, Mindray Bio-Medical, Shenzhen, China).

Statistical analysis

Statistical analyses (SPSS version 25, IBM, Armonk, NY, USA). Both percentages and frequencies were used to illustrate variable groupings. Continuous factors are presented as (mean±standard deviation). The mean values of the two groups were compared using an independent sample t-test. We used a paired t-test to analyze the averages of the two sets of readings.

Results

The average difference between the healthy group and patients with UC, along with the association among the different patient parameters, and the findings of a cohort of 65 patients, with ages ranging from 18 to 60 years, according to demographic data. The findings did not show statistically significant age differences, with the mean age of patients being 31.26±9.35, compared to HCs at 28.98±6.33, with a (p=0.107). Indicated that the change in BMI was not statistically significant, with a (p=0.450) The mean for the healthy group were 23.39±1.17, but for UC patients, the mean was 23.21±1.52. The sex distribution of the analyzed groups included 65 patients with UC, including 26 males (40%) and 39 females (60%), corresponding to controls. As shown in Table 1 comparing biochemical variables, UC patients demonstrated a significantly higher level of inflammatory markers compared to the HCs with a significantly higher CRP (23.38±17.76 vs. 2.38±0.89 mg/dL, p<0.001) and a lower level of the DPP-4 activity (in U/L) (1.33±0.19 vs. 2.37±0.35, p<0.001) and significantly higher levels were determined for IL-7 concentrations (62.39±19.7 vs. 22.86±4.73 ng/L, p<0.001), whereas metabolic parameters such as FBS (90.66±9.88 vs. 95.20±10.90 mg/dL, p=0.014), levels of the insulin (5.49±0.77 vs. 5.36±0.60 mIU/L, p=0.292^NS^) and HOMA-IR (1.21±0.17 vs. 1.25±0.14, p=0.238) were comparable.

Table 1. Comparative analysis of biochemical parameters in patients with ulcerative colitis and healthy controls

Variable	Patients (Mean±SD) (n=65)	Control (Mean±SD) (n=65)	p
FBS (mg/dL)	90.66±9.88	95.20±10.90	0.014
Insulin level (mIU/L)	5.49±0.77	5.36±0.60	0.292
HOMA-IR	1.21±0.17	1.25±0.14	0.238
CRP level (mg/dL)	23.38±17.76	2.38±0.89	<0.001
Interleukin-7 (ng/L)	62.39±19.7	22.86±4.73	<0.001
DPP-4 (U/L)	1.33±0.19	2.37±0.35	<0.001

Table 2 shows that the analysis of the ROC curve for DPP-4 in patients with UC indicated good diagnostic accuracy, with a cut-off value of ≤1.85 U/L for DPP-4 presenting high sensitivity (98%) and specificity (92%) and an overall accuracy of 90%. The AUC was 99% (p35.18 ng / L) and showed perfect sensitivity, specificity, PPV and NPV (100% each), with a accuracy of 100% and an AUC of 100% (p<0.001).

Table 2. ROC curve analysis for DPP-4 in UC patients*

Biomarkers	Cut-off value	Sens %	Spec%	PPV	NPV	Accuracy	AUC%	p
DPP-4 (U/L)	≤ 1.85	98	92	93	98	90	99	<0.001
Interleukin-7 ((ng/L)	> 35.18	100	100	100	100	1.0	100	<0.001

* Sens – sensitivity, Spec – specificity, PPV – positive predictive value, NPV – negative predictive value, AUC – area under the curve

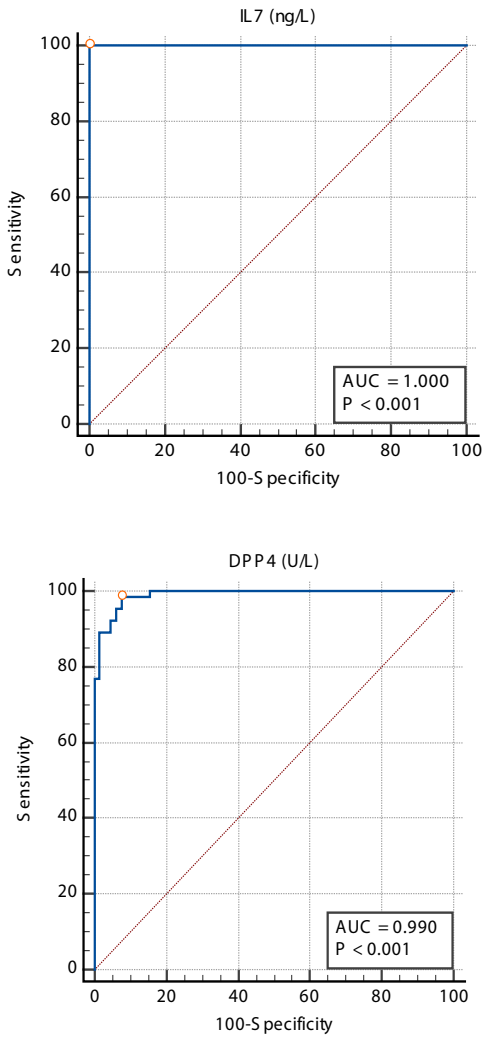

Fig. 1. ROC curve analysis of DPP-4 and interleukin-7

A strong positive correlation was observed between CRP and IL-7 (r=0.872, p<0.0001), whereas both CRP and IL-7 were significantly negatively correlated with DPP-4 (r=-0.533 and r=-0.624, respectively; both p<0.0001). IL-7 showed a weak negative association with HOMA-IR (r=-0.279, p=0.0244). These results highlight notable interactions between the inflammatory markers (CRP and IL-7).

Discussion

UC is often associated with comorbid systemic conditions and environmental factors and involves chronic inflammation of the immune system. Lifestyle factors, such as smoking, obesity, and poor eating habits, may also contribute to the initiation and progression of UC.[24] This study demonstrated that patients with UC had significantly higher CRP levels than those in the control group. This elevation in CRP levels is indicative of its involvement in inflammatory processes and serves as a prognostic marker for the disease. These results are consistent with those of previous studies by Henriksen et al., who reported that CRP levels are frequently used in the follow-up of patients with IBD. Furthermore, CRP levels at diagnosis are correlated with the extent of the disease in patients with UC.[25] CRP is an acute phase reactant that has been identified as a key indicator of IBD. CRP activates the complement cascade, promotes the production of pro-inflammatory cytokines, and assists in the elimination of microbial infections.[26]

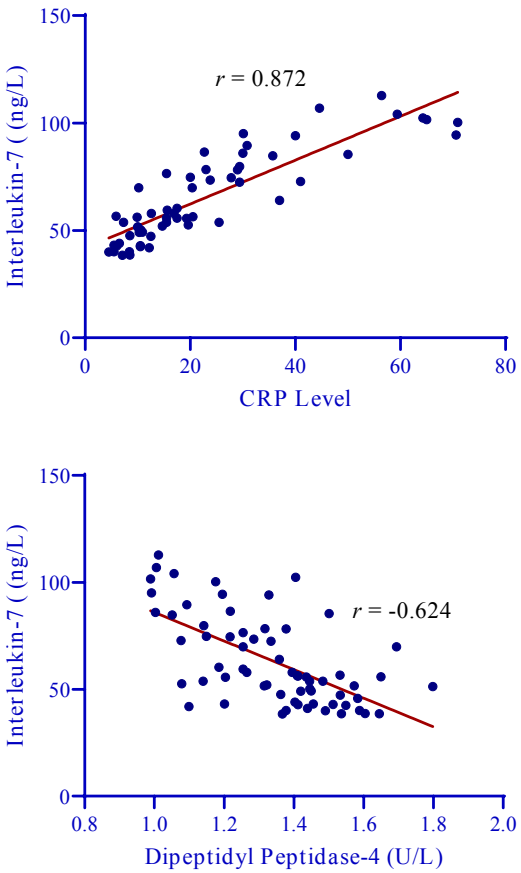

Fig. 2. Correlation charts for IL-7 and different biomarkers

The current study showed significantly higher levels of IL-7 in patients with UC than in HC. The IL-7 signaling pathway has emerged as a critical regulator of mucosal immunity in UC, with increasing evidence linking aberrant IL-7 activity with disease pathogenesis.[27] Belarif et al. demonstrated disrupted IL-7 signaling in UC, with elevated transcripts of the IL-7 receptor pathway observed in inflamed colon tissues of patients with se-

vere UC not responsive to standard therapies, as shown in an analysis of 500 patients with IBD and 100 controls.[14] Barata et al. further demonstrated that patients with UC exhibit elevated systemic and mucosal levels of IL-7 and its receptor subunit IL-7Rα, underscoring the complexity of IL-7 signaling dynamics in different stages of disease stages and tissue compartments. This overexpression was correlated with persistent colonic inflammation and dysregulated immune responses, suggesting a critical role for dysregulation of the IL-7 pathway in UC pathogenesis.[28] The mechanistic role of IL-7 in UC involves complex immune regulation. Studies have revealed that IL7 expression is strongly inversely correlated with regulatory T cell signatures or the regulatory T cell-to-effector T cell ratio in colon tissues of patients with UC before anti-TNF therapy. This suggests that elevated IL-7 signaling may contribute to UC pathogenesis by disrupting immune tolerance mechanisms.[29]

Unlike IL-7, serum DPP-4 levels were significantly reduced in patients with UC compared to those with those in HCs, corroborating the findings of recent studies. Abrahami et al. reported that patients with IBD exhibit lower serum DPP-4 concentrations than healthy individuals, with an inverse correlation between DPP-4 levels and clinical disease activity.[30] While the inverse correlation between serum DPP-4 levels and inflammation suggests a possible role for DPP-4 in disease progression, the causal relationship between reduced DPP-4 levels and inflammation or active disease remains unresolved.[31] In UC, dysregulation of DPP-4-mediated adenosine signaling may exacerbate mucosal inflammation, as adenosine typically attenuates T cell activation.[32] Paradoxically, while circulating DPP-4 levels decrease during active disease, mucosal DPP-4 activity increases, indicating distinct roles in systemic circulation versus localized mucosal inflammation. The apparent contradiction between DPP-4 biomarker behavior (lower levels in active disease) and the enzyme expression patterns in patients showed compartment-specific alterations. While circulating DPP-4 levels decrease during active disease, mucosal DPP-4 activity increases, suggesting a tissue-specific role in inflammation. This dichotomy underscores the involvement of the DPP-4 complex in the pathophysiology of UC, acting as both a biomarker of systemic immune status and a local mediator of gut inflammation.[33] Perry et al. further demonstrated an inverse correlation between serum DPP-4 levels and IBD activity, with lower levels corresponding to higher clinical and endoscopic disease severities.[34] This dichotomy underscores the dual role as a systemic biomarker and a local modulator of gut inflammation.

ROC curve analysis in this study demonstrated that DPP-4 exhibits excellent diagnostic performance with high sensitivity and moderate specificity at a defined cutoff point, underscoring its diagnostic reliability. Lopez et al. evaluated serum DPP-4 levels in patients with IBD, compared active disease to remission, and assessed treatment outcomes. The results revealed significantly lower DPP-4 levels in patients with active IBD than in those in remission and in HCs. DPP-4 effectively distinguished disease activity from remission and predicted the need for escalation of treatment. In particular, higher levels of DPP-4 were observed in patients who responded to biological therapy, and this association was more pronounced in patients with UC than in those with CD. The strongest correlation emerged for UC, underscoring its potential utility in the management of this IBD.[35]

Emerging evidence identifies fecal DPP-4 (fDPP-4) as a novel noninvasive biomarker, with cohort studies reporting significantly lower median levels of fDPP-4 in active UC compared to remission, with a statistically significant difference. Fecal DPP-4 also showed greater accuracy than fecal calprotectin in differentiating endoscopic disease activity. Mechanically, decreased systemic DPP-4 levels during active inflammation may reflect the enzymatic utilization by the inflamed tissues. Immunohistochemical analyses further supported this hypothesis, revealing prominent DPP-4 staining in mucosal biopsies, especially within regenerating epithelial regions and areas infiltrated by lymphocytes.[36]

Study limitations and strengths

The strengths of this study include its structured case–control design with matched controls, which improves internal validity. Their model achieved high diagnostic accuracy and offered insight into potential disease mechanisms, due to the inclusion of diverse biomarkers and comprehensive statistical methods. However, it has limitations, including a small sample size and recruitment from a single center, which may limit its representativeness. The exclusion of comorbidities may limit real-world relevance, and the cross-sectional design restricts causal conclusions. Another limitation is the lack of long-term follow-up data. Notwithstanding these limitations, our findings highlight the diagnostic potential of these biomarkers.

Conclusion

The present findings demonstrate a significant reduction in serum DPP-4 levels and an elevation of inflammatory markers (CRP and IL-7) in patients with UC compared to HC. The inverse correlation between DPP-4 and inflammation underscores its dual utility as a biomarker for the diagnosis and monitoring of UC. ROC analysis confirmed the strong diagnostic accuracy, emphasizing its clinical relevance. Elevated CRP and IL-7 levels are associated with immune dysregulation and mucosal inflammation, reinforcing their role in the pathogenesis of UC. Future studies should incorporate disease stratifica-

tion (eg active vs. remission and treatment response) to refine the clinical utility of these biomarkers.

Acknowledgements

The authors express their sincere appreciation to the College of Medicine at the University of Babylon for their unwavering support. We are also profoundly grateful to the participants who actively contributed to this study and provided invaluable collaboration. Furthermore, we acknowledge the dedication of the esteemed staff members of the Merjan Medical City Hospital in Babylon for their commitment and assistance. Finally, we recognize the significant contributions of all individuals involved in this research.

Declarations

Funding

No funding was received for this work.

Author contributions

Conceptualization, H.H.H. and B.M.S.; Methodology, H.H.H.; Software, H.H.H.; Validation, H.H.H., B.M.S. and A.J.A.; Formal Analysis, H.H.H.; Investigation, H.H.H.; Resources, H.H.H.; Data Curation, H.H.H.; Writing – Original Draft Preparation, H.H.H.; Writing – Review & Editing, H.H.H.; Visualization, H.H.H.; Supervision, B.M.S.; Project Administration, B.M.S.; Funding Acquisition, H.H.H.

Conflicts of interest

The author declare that they have no competing interests.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request and pending approval by the College of Science guidelines of the Biomedical Research Ethics Committee.

Ethics approval

A college of medicine at the University of Babylon and hospital ethics committee examined and approved the study protocol, subject information, and authorization form by document number [IRB: 95 -25/11/2024].

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