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Evaluation of Serum Amyloid A Levels and Some Inflammatory Biomarkers in Patients with Severe Inflammatory Bowel Disease

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Abstract: Crohn's disease and ulcerative colitis is a chronic inflammatory disorder characterized by variability in activity and severity. Identifying accurate biomarkers remains a major challenge to improve diagnosis and monitoring of the disease. The aims of this study were to study the level of serum amyloid A protein towards inflammatory bowel disease severity. To compare the level of serum amyloid A protein with other biomarkers such as cytosolic phospholipase A2, myeloperoxidase, and presepsin; Also to evaluate the sensitivity and specificity of these biomarkers. The study involved 135 participants, distributed into 40 patients with Crohn's disease and 35 patients with ulcerative colitis, in addition to a comparison group of 60 healthy controls. Amyloid A, cytosolic phospholipase A2, myeloperoxidase, and presepsin concentrations were measured for all contributors. Disease activity was evaluated by measures calculated specifically for Crohn's disease and ulcerative colitis. In addition, a receiver operating characteristic curve analysis was used to evaluate the efficacy of the biomarkers by assessing their sensibility and particularity rates of these indicators. The results of the study revealed a significant increase in amyloid A levels in IBD patients compared to healthy individuals, with statistically significant differences It also showed a strong positive correlation among amyloid A and the severity of disease activity indices. Statistical analysis confirmed that amyloid A levels had the highest discriminatory ability to differentiate between patients and the control group, indicating that it may be the most perfect biomarker for assessing disease status. Amyloid A protein has high specificity and sensibility in distinguishing between patients with IBD and healthy individuals, as well as in differentiating between patients with Crohn's disease and ulcerative colitis, indicating that it may be the most accurate candidate for diagnosing inflammatory bowel diseases.

Keywords: Crohn's disease, Ulcerative colitis, Amyloid A, Myeloperoxidase, Cytosolic Phospholipase A2, presepsin.

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Introduction

Inflammatory bowel disease remains a chronic flaming condition in digestive tract, with two chief forms Crohn's disease and ulcerative colitis. Inflammatory bowel disease can happen at any time, but maximum often appears in late teenage years and initial adulthood (1). Inflammatory bowel disease (IBD) is caused by a disruption of the normal internal barrier, this barrier plays an important role in protecting the intestines from pathogens and harmful substances (2). When it is disrupted, the intestinal walls become more permeable, allowing foreign substances (such as bacteria or food components) to enter the inner tissues. As a result, the immune system overreacts abnormally.

Instead of just attacking risky mediators, the immune system turns to targeting the intestine cells themselves, causing prolonged infection (3, 4). The occurrence of inflammatory bowel disease has been rising rapidly over the past twenty years, particularly in emerging manufacturing areas. The number of cases is expected to continue to rise globally in the coming years, posing a significant challenge to both affected individuals and healthcare organizations global (5, 6).

Crohn's disease is a condition that can affect any part of the gastrointestinal, from the mouth to the anus, and often causes deep inflammation that extends through several layers of organ walls (7, 8).

Ulcerative colitis it is limited to the colon and rectum and mainly affects the superficial layer of the wall. Ulcerative colitis -related inflammation is concentrated in the colon and rectum , where it mainly touches the apparent layer of the walls of these organs (9, 10). Patients experience a decrease in their feature of life due to the persistence of their symptoms, in adding to the psychological and communal effects causing from the limitations forced by these diseases (11, 12).

Despite the remarkable advances in the health ground, there is still an urgent necessity for accurate biomarkers that help in quick diagnosis of IBD. This study targets to evaluate the effectiveness of amyloid A, cytosolic phospholipase A2, myeloperoxidase, and presepsin as potential applicants for use as biomarkers for this purpose.

Amyloid A is a protein secreted by the liver in reply to infection and is portion of the group of proteins associated with the acute response. Elevated levels of it are often a sign of inflammation, whether acute or chronic (13, 14). In both, Crohn's disease and ulcerative colitis the body products big quantities of amyloid A in reply to prolonged infection (15).

Cytosolic phospholipase A2 (cytosolic PLA2) is a basic enzyme in prolonged inflammatory replies, playing a prominent part in the development of IBD-related inflammation. Elevated concentrations in blood may be reflected disease activity or progression (16).

Myeloperoxidase (MPO) is an enzyme found mostly in white blood cells, particularly neutrophils and some other types of immune cells, and acting a vital role in regulating immune and inflammatory replies (17).

Presepsin is a protein that is the solvable form of CD14, and acts as a receptor create on the external of immune cells (18). It is secreted into the bloodstream as part of the body's response when exposed to germs or infection (19).

The Harvey-Bradshaw Index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI) are practical and easy-to-use tools for assessing the severity of disease activity based on clinical symptoms (20). The use of surrogate biomarkers such as SAA, MPO, and cytosolic PLA2 becomes necessary when a more accurate assessment of disease activity or rapid response to treatment is needed, these biomarkers provide important additional and alternative information, especially in cases where C-reactive protein (CRP) is limited; CRP remains useful as a general biomarker of systemic inflammation but does not specify the site of inflammation. C-reactive protein levels may be normal in some patients with ulcerative colitis (UC) despite significant disease activity (21). C-reactive protein is more sensitive in patients with Crohn's disease (CD), but

may be less accurate in patients with localized inflammation (22). Fecal calprotectin is sometimes abandoned in favor of serum parameters because collecting a stool sample can be inconvenient for patients, leading to refusal or delay of the procedure. Fecal calprotectin is also not always available in all laboratories, and may be expensive compared to serological tests (23).

This study aims to assess the levels of blood biomarkers including amyloid A, presepsin, cytosolic phospholipase A2, and myeloperoxidase in patients with inflammatory bowel disease, both Crohn's disease and ulcerative colitis and compare them with the levels of these biomarkers in healthy individuals, and to assess the correlation between these biomarkers and the severity of disease activity using the Harvey-Bradshaw Index (HBI) and the Simple Clinical Colitis Activity Index (SCCAI). In addition, the sensitivity and specificity of these biomarkers were analyzed using the receiver operating characteristic (ROC) curve to determine their accuracy as diagnostic and evaluative tools. **Subjects and methods**

Seventy five Iraqi patients with IBD (35 male and 40 female) and sixty control (28 male and 32 female) attended to Gastrointestinal Department, Gastroenterology and Hepatology Teaching Hospital and Baghdad Teaching Hospital, Medical City Complex; from January 2024 to September 2024. The range patients' age from 17-59 years who enrolled in the study. Formal consent was obtained from all patients and healthy subjects included in the study. All studied patients were subjected to the following; clinical assessment by full history taking (age, sex, residence, occupation, special habits, medications, operations). The time of diagnosis was determined by medical records of the patients. Patients with comorbidities that may be a confounding factor were excluded, such as cardiovascular diseases, other chronic inflammatory diseases (such as rheumatoid arthritis and pneumonia), cancer, acute liver disease, and bacterial or viral infection, and renal failure. The patient group was compared with a healthy group: people without chronic or immune diseases, and used as a control group. The patients were then divided into a group of Crohn's patients and a group of ulcerative colitis patients. The Simple Clinical Colitis Activity Index (SCCAI) was used to measure the activity of ulcerative colitis and Use of the Harvey-Bradshaw Index (HBI) for Crohn's disease activity.

Methods

Serum amyloid A (SAA) and cytosolic phospholipase A2 levels were measured by (Wuhan Feiyue Biotechnology Company, China) enzyme linked immunosorbent assay (ELISA) kit. Presepsin level was measured by (ELK Biotechnology company, USA) ELISA kit. Serum MPO activity was measured using the method described by Klebanoff and Clark (24). The Harvey-Bradshaw Index (HBI) was calculated to assess the severity of Crohn's disease through five criteria (general condition, abdominal pain, frequency of bowel movements, presence of complications, rectal bleeding). Scores are added for each component (0–16), where ≥17 consider severe disease (25). Simple Clinical Colitis Activity Index (SCCAI) was calculated to assess the severity of ulcerative colitis based on five criteria (frequency of bowel movements, rectal bleeding, nocturnal symptoms, general fatigue, and abdominal pain). Scores are added for each component (0–19+), where ≥12 consider severe disease (26).

Statistical analysis

Data were presented as mean ± standard deviation. Statistical analysis included the use of unpaired samples t-test to analyze differences between groups, as well as Pearson correlation analysis to assess relationships between variables. A P-value of ≤ 0.05 was considered to indicate statistically significant differences. To assess the performance diagnosis of a serum amyloid A (SAA) and other biochemical parameters in predicting inflammatory bowel disease activity (including Crohn's disease and ulcerative colitis), receiver operating characteristic curves analysis have been used. All analyses were performed using SPSS version 27.0.

Results and discussion

In present study results of comparison of biomarkers between patients and healthy controls appeared a significant increase ($p \leq 0.05$) in the concentration of amyloid A, presepsin, cytosolic phospholipase A2, and myeloperoxidase in patients with inflammatory bowel disease compared to healthy controls as shown in table 1. An increase in these four biomarkers indicates inflammation related with IBD, underlining the possible of these biomarkers as diagnostic tools. Amyloid A in particular has been shown to have high sensibility and particularity, making it an effective means of evaluating the efficacy of IBD. Healthy persons tend to maintain low amyloid A levels. Although, through the acute phase reply, the liver produces amyloid A protein dramatically, causing serum amyloid A concentrations to rise during the first day of the response. This is tailed by a noticeable decrease in amyloid A levels after this phase is over (27). This result is reliable with a prior study that found that SAA is among the most responsive and sensible proteins during the severe phase of inflammatory bowel disease, compared to other proteins associated with this phase (28).

Table (1): Comparison of biomarkers between all patients and control.

Biomarker	Groups	N	Mean± SD	P value
Amyloid A (ng/mL)	control	60	2.97 ± 2.66	0.001
	patient	75	9.10 ± 2.01	
Phospholipase A2 (ng/mL)	control	60	0.46 ± 0.14	0.001
	patient	75	1.09 ± 0.87	
Myeloperoxidase (U/L)	control	60	17.31± 17.82	0.004
	patient	75	61.30 ± 113.62	
Presepsin (ng/mL)	control	60	0.17±0.05	0.001
	patient	75	0.81±0.77	

p- value ≤ 0.05 considered significant.

Results of comparing Crohn's disease patients with healthy people appeared a significant increase ($p \leq 0.05$) in the concentration of amyloid A, presepsin, cytosolic phospholipase A2, and myeloperoxidase in Crohn's disease patients compared to healthy controls as shown in table 2. The protein amyloid A produce by the liver is elevated through the acute phase reply, and its concentrations can be readily monitored in sera samples using laboratory examination procedures. Amyloid A levels may represent a valuable further biomarker to help evaluate inflammation and observer the acute phase reply (26, 29). Research shows that serum amyloid A levels rise sharply through the acute phase reply, then gradually decline to normal. However, in chronic inflammation, these levels continue determinedly elevated, making serum amyloid A an important biomarker for evaluating long-term inflammatory activity(30, 31).

Table (2): Comparison of biomarkers between patients with crohn's disease and control.

Biomarker	Groups	N	Mean± SD	P value
Amyloid A (ng/mL)	control	60	2.97 ± 2.66	0.001
	CD	40	10.20 ±1.64	
Phospholipase A2 (ng/mL)	control	60	0.46 ± 0.14	0.001
	CD	40	1.19± 0.93	
Myeloperoxidase (U/L)	control	60	17.31± 17.82	0.033
	CD	40	58.52±146.07	
Presepsin (ng/mL)	control	60	0.17±0.05	0.001
	CD	40	1.14±0.82	

p- value ≤ 0.05 considered significant. CD: Crohn's disease.

Patients with ulcerative colitis (UC) had similar results to those with Crohn's disease when compared with healthy controls, where the levels of amyloid A, presepsin, cytosolic phospholipase A2, and myeloperoxidase were significantly higher when compared to healthy controls as shown in table 3. In a study of ulcerative colitis patients, the most common clinical symptoms were diarrhea (40%), stomach discomfort (80%), bloody stools (36%), and weight loss (60%), it revealed that amyloid A levels were significantly higher in active patients compared to other groups (32). Serum amyloid A can be used for prediction of remission in patients with ulcerative colitis. It has been considered as a viable alternative as a biomarker for predicting mucosal healing in ulcerative colitis (28, 33). Amyloid A plays an important part in enhancing the barrier function of the intestinal epithelium, stimulating the action or process of T cell differentiating, and enhancing phagocytosis of microbes (15). Given the close association among amyloid A levels and intestinal infections, several clinical studies have suggested that it could be used as a biomarker for diagnosing the IBD, assessing its activity, and predicting its prognosis (34, 35).

Table (3): Comparison of biomarkers between patients with ulcerative colitis and control.

Biomarker	Groups	N	Mean± SD	P value
Amyloid A (ng/mL)	control	60	2.97 ± 2.66	0.000
	UC	35	7.85 ±1.63	
Phospholipase A2 (ng/mL)	control	60	0.46 ± 0.14	0.000
	UC	35	0.97± 0.78	
Myeloperoxidase (U/L)	control	60	17.31± 17.82	0.000
	UC	35	64.46±60.03	
Presepsin (ng/mL)	control	60	0.17±0.05	0.000
	UC	35	0.45±0.52	

p- value ≤ 0.05 considered significant. UC: ulcerative colitis.

In the current study when comparing biomarker results between Crohn's and ulcerative colitis patients the results appeared a significant increase ($p \leq 0.05$) in the concentration of amyloid A and presepsin in Crohn's disease patients compared to ulcerative disease patients. A slight increase in cytosolic PLA2 levels was observed in Crohn's disease patients compared to ulcerative colitis patients, but this increase did not reach the level of statistical significance ($p > 0.05$). In contrast, myeloperoxidase levels were slightly high in UC patients than in CD patients, but without statistical significance ($p > 0.05$) as shown in table 4. The current findings suggest differences in inflammatory patterns between Crohn's disease and ulcerative colitis. The significantly higher levels of amyloid A and preseptin in Crohn's disease may reflect

more severe inflammatory activity in this type of disease compared to ulcers.

The current results suggest differences in inflammatory patterns between Crohn's disease and ulcerative colitis. The significant elevated of serum amyloid A and presepsin in Crohn's disease patients may reflect a more severe and extensive inflammatory response that may be related to the disease's effect on the deeper layers of the intestine. Although cytosolic PLA2 levels were slightly elevated in Crohn's disease patients, the lack of statistical significance suggests that this biomarker may not be sensitive in distinguishing between the two types. The slightly elevated myeloperoxidase levels in ulcerative colitis patients may be related to different inflammatory pathways associated with this type, but it was not sufficient to constitute a statistically significant difference (36). The slight and insignificant differences in cytosolic phospholipase A2 and myeloperoxidase may be due to similarities in the superficial inflammatory processes common to the two species.

Table (4): Comparison of biomarkers between patients with Crohn's disease and ulcerative colitis.

Biomarker	Groups	N	Mean± SD	P value
Amyloid A (ng/mL)	CD	40	10.20 ± 1.64	0.000
	UC	35	7.85 ±1.63	
Phospholipase A2 (ng/mL)	CD	40	1.19 ± 0.93	0.293
	UC	35	0.97± 0.78	
Myeloperoxidase (U/L)	CD	40	58.53 ±146.07	0.823
	UC	35	64.46±60.03	
Presepsin (ng/mL)	CD	40	1.14 ± 0.82	0.000
	UC	35	0.45±0.52	
Index (HBI & SCCAI)	CD	40	17.23 ± 2.13	0.000
	UC	35	12.17± 2.11	

p- value ≤ 0.05 considered significant. HBI: Harvey Bradshaw Index, SCCAI: Simple Clinical Colitis Activity Index. CD: Crohn's disease. UC: ulcerative colitis.

In the present study, the results of correlation between disease activity index and biomarkers showed a significant positive correlation ($p \leq 0.05$) between disease activity index and amyloid A level in both CD and UC as shown in table 5, suggests its role as a sensitive biomarker of inflammatory activity. Previous studies have shown a strong correlation between amyloid A levels and the endoscopic activity of intestinal inflammation (37 ,28). Studies have shown a significant positive correlation between amyloid A and ulcerative colitis activity index (33, 38). These findings are consistent with another study that demonstrated a strong positive correlation between mucosal inflammation and amyloid A levels in ulcerative colitis patients, and amyloid A levels were found to accurately reflect the degree of mucosal inflammation (28). Furthermore, amyloid A concentrations showed a Spearman correlation of 0.42 with the Crohn's disease activity index. Serum amyloid A concentration was tenfold higher in Crohn's disease patients with clinical activity compared to patients in clinical remission (39).

In the current study, there was a non-significant positive correlation ($p > 0.05$) between disease activity index and levels of presepsin, cytosolic PLA2, and MPO in Crohn's disease patients. In UC patients, a significant positive correlation was observed between disease activity index and levels of

cytosolic phospholipase A2 and myeloperoxidase, while the correlation was non-significant with presepsin as shown in table 5. The correlation between indicators (cytosolic phospholipase A2, myeloperoxidase, and presepsin) and the disease activity index indicate that the effect of these indicators varies according to the type of IBD, as some correlations were significant only in ulcerative colitis patients.

Table (5): Correlation between biomarkers and disease severity index (HBI & SCCAI).

Biomarker	Index	N	r	P value
Amyloid A (ng/mL)	HBI	40	0.553	0.001**
	SCCAI	35	0.398	0.018*
Phospholipase A2 (ng/mL)	HBI	40	0.285	0.075
	SCCAI	35	0.416	0.013*
Myeloperoxidase (U/L)	HBI	40	0.251	0.118
	SCCAI	35	0.362	0.032*
Presepsin (ng/mL)	HBI	40	0.233	0.147
	SCCAI	35	0.291	0.090

**** correlation is significant at 0.01, * correlation is significant at 0.05.**
HBI: Harvey Bradshaw Index, SCCAI: Simple Clinical Colitis Activity Index.

In the present research in Future Operating Characteristic (ROC) Curve Analysis as shown in table 6, the results between patients and healthy people when comparing four parameters (amyloid A, cytosolic phospholipase A2, myeloperoxidase, and presepsin) between patients (both CD and UC) and healthy controls, amyloid A showed the best performance, achieving the highest sensitivity and specificity (AUC: 0.948) compared to the rest of the parameters as shown in figure 1.

The results between healthy people and Crohn's disease patients were amyloid A showed the best sensitivity and specificity (AUC: 0.982); while some parameters such as cytosolic phospholipase A2 and myeloperoxidase were less efficient as shown in figure 2. And the result between healthy people and ulcerative colitis patients was amyloid A also showed the highest sensitivity and specificity (AUC: 0.908) in distinguishing ulcerative colitis patients from healthy controls as shown in figure 3. Among patients with CD and UC when comparing the four parameters between CD and UC patients, amyloid A had the best sensitivity and specificity (AUC: 0.898), indicating its high ability to differentiate between the two types as shown in figure 4. In receiver operative characteristic curve, serum amyloid A levels showed superior discriminatory ability for assessing the complex endoscopic activity of IBD, the area under the operating curve of amyloid A values was 0.75, indicating its high accuracy (34). In addition, studies have suggested that amyloid A levels may be an important predictive factor for predicting results of inflammatory bowel disease, like relapses and treatment response (39, 40). A study of 41 patients with clinically Advanced Crohn's disease showed that amyloid A concentrations greater than 5.9 μg/dL were associated with a faster relapse (39). However, amyloid A showed higher sensitivity than C-reactive protein in predicting active infection, amyloid A was capable of recognize approximately half of patients who had active inflammation even when C-reactive protein values were normal (31, 41). This suggests the potential power of amyloid A in assessing mucosal inflammation, particularly in the group patients who do not appearance C-reactive protein response throughout the

disease. Measuring amyloid A concentrations may help in adjusting treatment plans, assessing the need for endoscopy, and determining the interval for future visits (42).

Serum amyloid A can be used as an effective tool in IBD management, contributing to diagnosis, assessment of disease activity level, and prognosis of disease course. In addition, it can help improve treatment decisions and explore new treatment options, contributing to more efficient IBD management (15). Also in the present results show that amyloid A has the highest sensitivity and specificity among all biomarkers, making it an excellent diagnostic tool for differentiating patients from healthy controls or between different types of IBD. Another study showed that amyloid A levels < 5.8 μg/dL were able to differentiate mucositis from mucosal healing with at a sensibility of 0.722 and a particularity of 0.850. These results suggest that amyloid A may be a very good biomarker for prognosticate mucosal healing in IBD patients in clinical remission (28, 43).

In the current study the good performance of cytosolic phospholipase A2 and myeloperoxidase reinforces their value as adjuvants, while the intermediate performance of presepsin suggests the need for further study to determine its role. These biomarkers, especially amyloid A, can be used in the early assessment and differentiation of IBD patients from healthy controls. Given the low cost of measuring serum amyloid A levels and the speed on the same day results, more medical places could take on this approaches. This could reduce the money burdens on patients and improve the efficiency of diagnosis and care.

Table (6): Sensitivity and specificity values of biomarkers extracted from receiver operating characteristic (ROC) curve.

All patients vs. Control				
Parameter	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**
Amyloid A (ng/mL)	0.948	84 %	87 %	7.060
Phospholipase A2 (ng/mL)	0.809	76 %	78 %	0.536
Myeloperoxidase (U/L)	0.771	68 %	80 %	23.600
Presepsin (ng/mL)	0.706	60 %	77 %	0.189
Crohn's vs. Control				
Parameter	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**
Amyloid A (ng/mL)	0.982	92 %	93 %	8.057
Phospholipase A2 (ng/mL)	0.857	83 %	92 %	0.636
Myeloperoxidase (U/L)	0.733	63 %	80 %	23.600
Presepsin (ng/mL)	0.825	70 %	77 %	0.189
Ulcerative colitis vs Control				
Parameter	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**
Amyloid A (ng/mL)	0.908	83 %	83 %	6.380

Phospholipase A2 (ng/mL)	0.755	71 %	75 %	0.508
Myeloperoxidase (U/L)	0.815	74 %	80 %	23.600
Presepsin (ng/mL)	0.571	51 %	58 %	0.169
Crohn's vs Ulcerative colitis				
Parameter	**AUC**	**Sensitivity**	**Specificity**	**Cut-off value**
Amyloid A (ng/mL)	0.898	80 %	83 %	9.345
Phospholipase A2 (ng/mL)	0.618	60 %	63 %	0.865
Myeloperoxidase (U/L)	0.585	57 %	60 %	42.480
Presepsin (ng/mL)	0.756	69 %	74 %	0.410

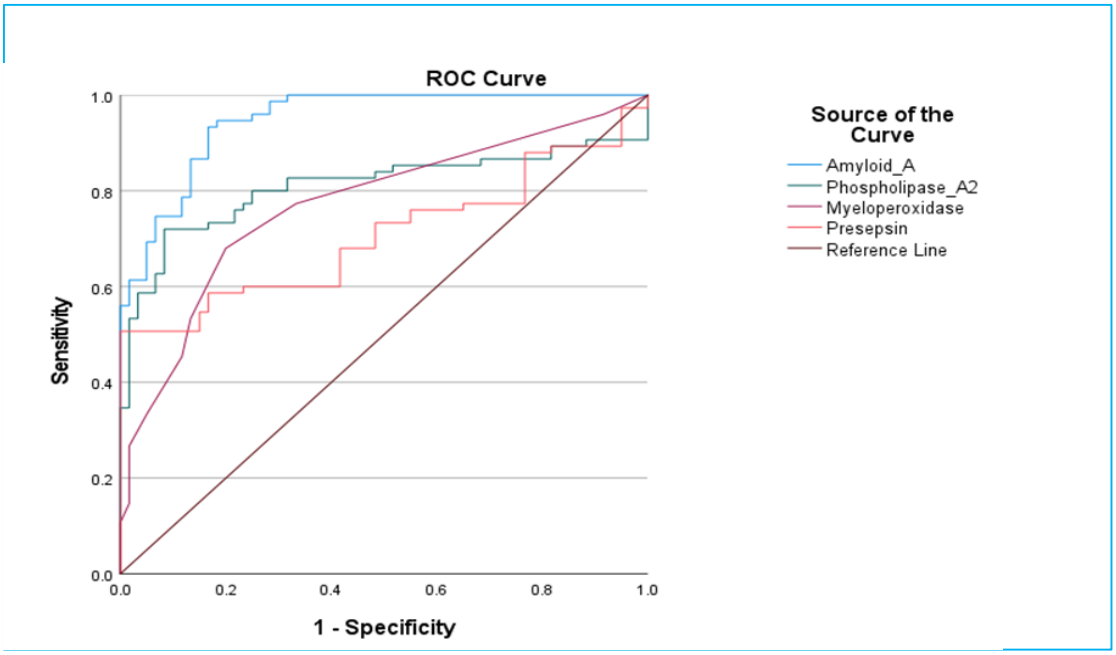

Figure (1): ROC analysis for biomarkers (amyloid A, phospholipase A2, myeloperoxidase, and presepsin) between patients and healthy people.

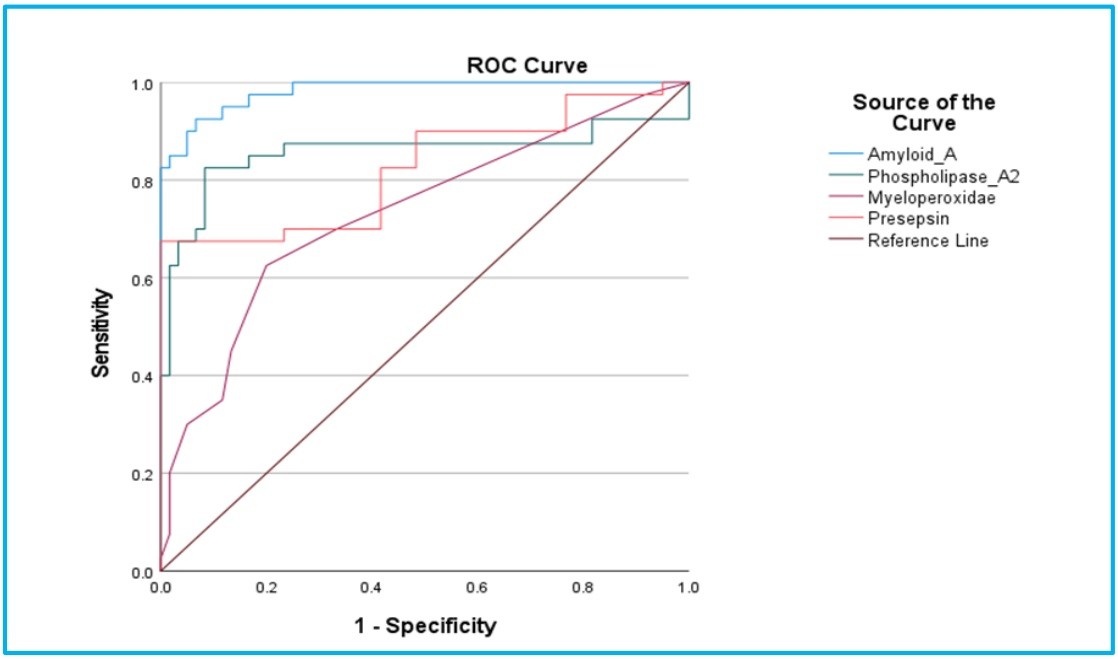

Figure (2): ROC analysis for biomarkers (amyloid A, phospholipase A2, myeloperoxidase, and presepsin) between healthy people and Crohn's patients.

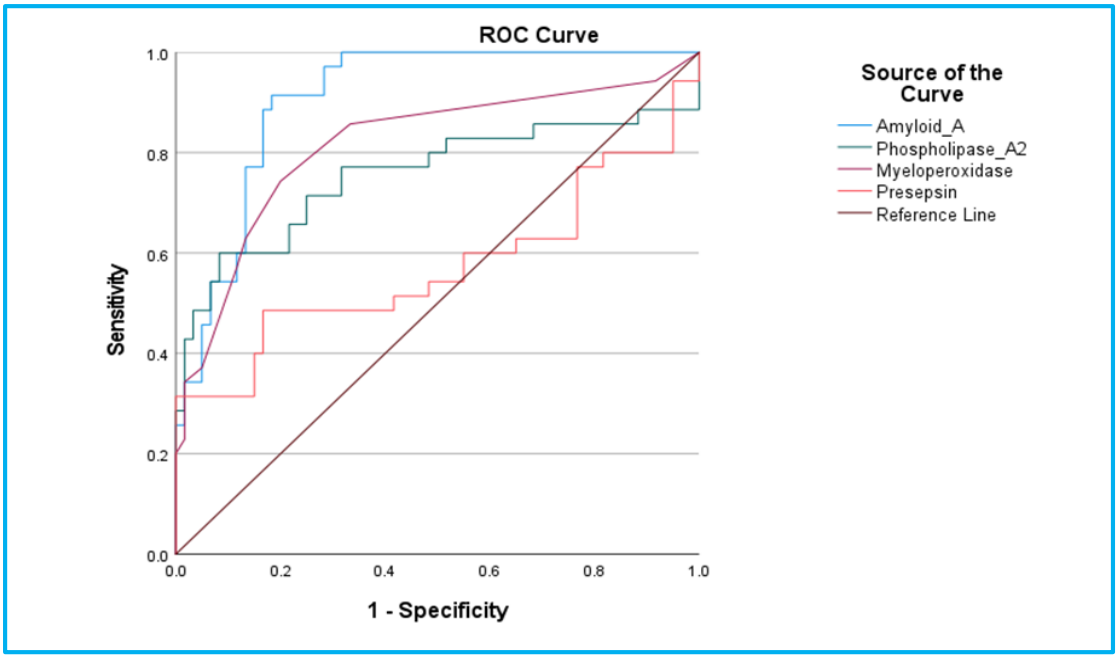

Figure (3): ROC analysis for biomarkers (amyloid A, phospholipase A2, myeloperoxidase, and presepsin) between healthy people and ulcerative colitis patients.

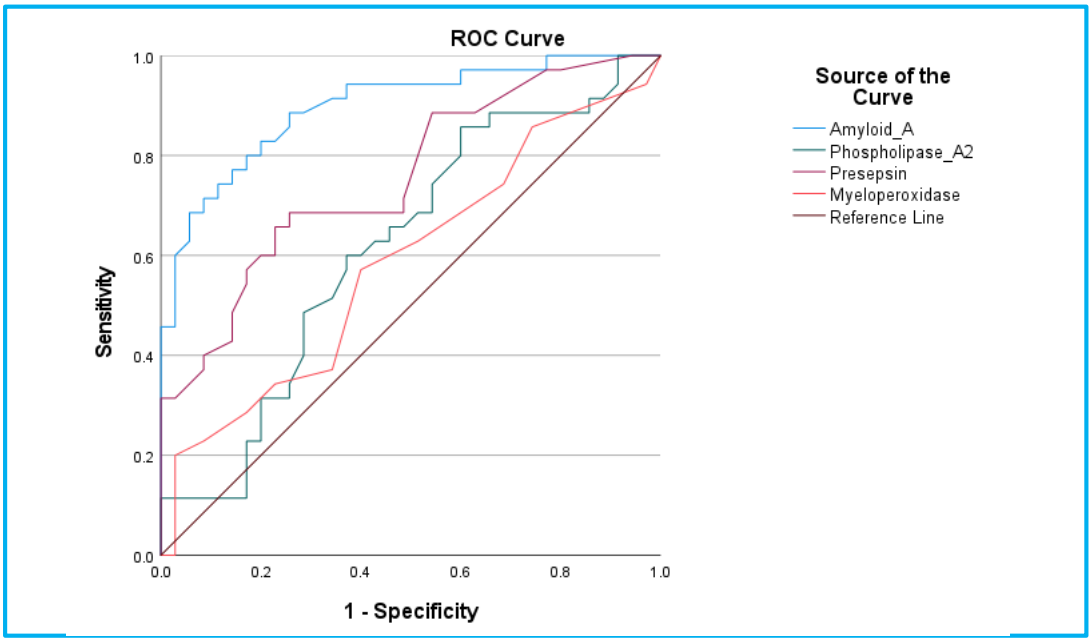

Figure (4): ROC analysis for biomarkers (amyloid A, phospholipase A2, myeloperoxidase, and presepsin) between patients with Crohn's disease and ulcerative colitis.

Conclusion

Amyloid A could serve as a biomarker in diagnostic and evaluative value in IBD patients, as it a significant positive correlates with disease activity severity indicators according to the Harvey-Bradshaw Index and Simple Clinical Colitis Activity Index in Crohn's disease and ulcerative colitis patients, respectively, and have got to high specificity and sensibility in distinguishing between patients and healthy controls, indicating that it may be the most accurate candidate for diagnosing IBD.

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