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ORIGINAL RESEARCH

The association between peptic ulcer disease and depression risk: The role of serotonin as a diagnostic biomarker in a case-control study

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Running title: Abbas et al. Serotonin in peptic ulcer disease

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ABSTRACT

Aim: To evaluate serum serotonin levels in patients with peptic ulcer disease (PUD) and assess its potential as a biomarker associated with depressive symptoms in patients with PUD.

Methods: This case-control study included 50 adult male patients with endoscopically confirmed PUD and 50 apparently healthy male controls. Serum serotonin levels were measured using enzyme-linked immunosorbent assay (ELISA). Depression was diagnosed by a psychologist and assessed using the Patient Health Questionnaire-9 (PHQ-9). Statistical analyses included the Mann-Whitney U test, chi-square test, multivariate logistic regression, and receiver operating characteristic (ROC) curve analysis.

Results: Patients with PUD had higher PHQ-9 scores than controls, with a median score of 13.5 (7.0-16.6) versus 4.0 (2.0-8.0) ($p<0.001$). Serum serotonin levels were lower in patients with PUD than in controls, with a median of 530.086 (435.7-592.8) pg/mL versus 1008.763 (874.89-1120.43) pg/mL ($p<0.001$). In the adjusted model, lower serotonin levels remained independently associated with comorbid PUD-depression status (OR=0.992; 95% CI 0.988-0.996; $p<0.001$). ROC analysis showed high diagnostic performance for serotonin in the full sample (AUC=0.920; 95% CI 0.870-0.970; cut-off 803.131 pg/mL; sensitivity 85.0%; specificity 100%).

Conclusion: Serum serotonin levels were lower in male patients with PUD and depressive symptoms than in healthy controls. Serotonin may have diagnostic value as a biomarker associated with depressive symptoms in patients with PUD, but longitudinal studies including women and PUD patients without depression are required.

Keywords: depression; peptic ulcer disease; serotonin

INTRODUCTION

Peptic ulcer disease (PUD) is a common gastrointestinal disorder characterized by mucosal defects in the stomach or duodenum that extend through the muscularis mucosae. It develops when the balance between aggressive factors, such as gastric acid, Helicobacter pylori infection, non-steroidal anti-inflammatory drugs (NSAIDs), and alcohol exposure, and mucosal protective mechanisms is disrupted. Untreated or severe disease may lead to bleeding, perforation, obstruction, and impaired quality of life (1). Depression is a common chronic mental health disorder characterized by persistent low mood, loss of interest, fatigue, impaired concentration, and reduced daily functioning (2).

The relationship between PUD and depression is clinically relevant because gastrointestinal symptoms, chronic pain, sleep disturbance, and inflammatory responses may contribute to depressive symptoms, while depression may affect gastrointestinal function, health behaviour, medication use, and disease perception. This bidirectional psychophysiological relationship may complicate diagnosis and management in patients with PUD.

Serotonin, or 5-hydroxytryptamine (5-HT), is a key neurotransmitter and signalling molecule, with most peripheral serotonin produced in the gastrointestinal tract by enterochromaffin cells. Serotonin contributes to intestinal motility, visceral signalling, and mood regulation (3). Altered serotonin metabolism has been implicated in depression and may also be relevant in gastrointestinal disease through changes in gut microbiota, tryptophan metabolism, inflammation, and gut-brain axis signalling (4,5). However, the diagnostic value of circulating serotonin in patients with PUD and depressive symptoms remains insufficiently defined.

The aim of this study was to evaluate serum serotonin levels in patients with PUD and depressive symptoms and to assess its potential as a diagnostic biomarker for depression in this disease context.

MATERIAL AND METHODS

Patients and study design

Between October and December 2025, a case-control study including 100 adult male participants was conducted at the Kerbala Centre for Gastrointestinal and Liver Diseases, Kerbala, Iraq. The study included 50 patients with endoscopically confirmed PUD diagnosed by a gastroenterologist and 50 apparently healthy male controls without gastrointestinal symptoms or known gastrointestinal tract disorders.

The minimum required sample size was determined using the a priori power analysis module in IBM SPSS Statistics, version 27. The calculation was based on an independent-samples t-test designed to detect a moderate-to-large effect size (Cohen's d=0.6) in serum serotonin levels between groups, with α=0.05 and 80% power for a two-sided test. The minimum sample size was estimated at 45 participants per group. To improve robustness and allow for potential missing data, 100 participants were recruited.

Inclusion criteria were adult male sex and endoscopically confirmed PUD. Exclusion criteria were incomplete data, age <18 years, female sex, malignant tumours or severe atypical hyperplasia confirmed by endoscopic pathology, surgery involving the stomach, oesophagus, or duodenum within the preceding three months, other gastrointestinal diseases such as Crohn's disease, ulcerative colitis, or coeliac disease, and autoimmune disorders. The study protocol was approved by the Medical Ethics Committee of the College of Applied Medical Sciences at Karbala University, Iraq (Ref. No.: CLAMSKU/19; 4 October 2025).

Methods

Peptic ulcer disease was diagnosed using Olympus endoscopy (EVIS EXERA III, Olympus Medical Systems, Tokyo, Japan). Demographic and socioeconomic variables included age, marital status, education, family income, employment status, and work-related difficulties.

Health and behavioural variables included body mass index (BMI), physical activity, family history of depression, NSAID use, and current antidepressant or mood stabiliser prescriptions.

Depression was diagnosed clinically by a psychologist, and the Patient Health Questionnaire-9 (PHQ-9) was used to assess symptom severity. The PHQ-9 includes nine items scored on a 4-point Likert scale from 0 (not at all) to 3 (nearly every day). The total score ranges from 0 to 27 and classifies depression severity as none/minimal (0-4), mild (5-9), moderate (10-14), moderately severe (15-19), or severe (20-27). A score of 10 or higher indicates clinically relevant depressive symptoms (8). To prevent observer bias, the psychologist was completely blinded to the participants' group allocation (case or control status). Furthermore, blinding to the biochemical results was inherently guaranteed, as the measurement of serum serotonin and other biomarkers was conducted collectively only after the clinical and psychological evaluations for all 100 participants had been fully completed.

From each participant, 5 mL of venous blood was collected by venipuncture into a gel tube for serum extraction. Each sample was assigned a unique identification number and centrifuged at 4000 rpm for 15 minutes using an NL-2000 centrifuge (NewLezhen, Shanghai, China). Serum was stored at -20 °C until serotonin measurement. BMI was calculated as weight (kg)/height (m)² (9).

Serum serotonin levels were measured using enzyme-linked immunosorbent assay (ELISA) kits in 96- and 48-well formats from ELK Biotechnology (Sugar Land, TX, USA). The assay was performed according to the sandwich ELISA principle. Optical density was measured at 450 nm using a Human Reader spectrophotometer (HUMAN Diagnostics, Wiesbaden, Germany) (10).

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics, version 27.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was used to assess data distribution. Because continuous data were not normally distributed, values were reported as medians with interquartile ranges (IQRs). Median differences with 95% confidence intervals (CIs) were estimated using the Hodges-Lehmann estimator. Categorical variables were reported as numbers and percentages. Between-group comparisons were performed using the Mann-Whitney U test, chi-square test, or Fisher's exact test, as appropriate. Multivariate logistic regression was used to estimate odds ratios (ORs) while adjusting for potential confounders. The dependent variable was defined as the binary case status (1 = comorbid PUD and depression, 0 = healthy controls). The primary independent variable was the serum serotonin level, while age, employment status, work difficulty, educational level, and marital status were entered into the model as sociodemographic covariates. Receiver operating characteristic (ROC) curve analysis was used to evaluate the diagnostic performance of serum serotonin. Two analyses were performed: State A compared patients with PUD and depression with controls without active depressive symptoms, whereas State B compared patients with PUD and depression with the entire control group. The Youden index was used to determine the optimal cut-off. Statistical significance was set at $p<0.05$.

RESULTS

Patients with PUD were less often employed, 21 (42%) versus 31 (62%) controls ($p<0.05$), and more often reported work difficulties, 12 (24%) versus 1 (2%) ($p<0.001$). Family income was comparable, with middle income in 39 (78%) patients and 42 (84%) controls ($p=0.487$). Education and marital status differed significantly: high education was less frequent in patients, 13 (26%) versus 48 (96%), while marriage was more frequent, 43 (86%) versus 26 (52%) (both $p<0.001$). NSAID use was higher in patients, 32 (64%) versus 5 (10%)

(p=0.002), whereas family history of depression and physical activity did not differ significantly. Depression severity was greater in patients with PUD: no depression was recorded in 0 (0%) patients versus 17 (34%) controls, while moderate to severe depression was present in 36 (72%) patients versus 5 (10%) controls (p<0.001) (Table 1).

Serum serotonin levels were lower in patients with PUD than in controls (median 530.086 (435.7-592.8) pg/mL versus 1008.763 (874.89-1120.43) pg/mL; p<0.001), with an estimated median difference of 496.048 pg/mL (95% CI 418.435-569.365). Patients were older than controls (median 49.5 (35.75-63) years versus 29 (25.75-38.25) years; p<0.001), with an estimated median difference of -18 years (95% CI -25 to -12). PHQ-9 scores were higher in patients than in controls (median 13.5 (7.0-16.6) versus 4.0 (2.0-8.0); p<0.001), with an estimated median difference of -8 points (95% CI -10 to -5). BMI did not differ significantly between groups (p=0.285) (Table 2).

To account for differences in sociodemographic variables between groups, multivariate logistic regression was performed. The model evaluated the association between serum serotonin levels and the clinical outcome after adjustment for age, employment status, work difficulty, education level, physical activity, and marital status. Serum serotonin remained independently associated with the comorbid PUD-depression status (OR=0.992; 95% CI 0.988-0.996; p<0.001; B coefficient=-0.008), indicating that lower serotonin levels were associated with higher odds of having this comorbid condition (Table 3).

Table 4 and Figure 1 present the diagnostic performance of serum serotonin using ROC curve analyses. In State A, which excluded controls with active depressive symptoms, serotonin showed an AUC of 0.999 (SE<0.001; p<0.001). At the optimal cut-off of 791.911 pg/mL, sensitivity, specificity, and overall accuracy were all 100%. In State B, which included the full control group, serotonin showed an AUC of 0.920 (95% CI 0.870-0.970; SE=0.03;

p<0.001). The optimal cut-off was 803.131 pg/mL, with sensitivity of 85.0%, specificity of 100%, and accuracy of 92.5%.

DISCUSSION

This study showed that male patients with PUD had substantially lower serum serotonin levels and higher PHQ-9 scores than apparently healthy controls. Serum serotonin demonstrated high diagnostic performance in ROC analysis, although interpretation is limited by the case-control design, group differences, and the absence of a PUD group without depressive symptoms.

A plausible explanation for lower serotonin levels in patients with PUD and depressive symptoms is disruption of gut-brain axis signalling. Serotonin precursors may be influenced by gut microbiota through tryptophan metabolism, and altered microbial composition may reduce 5-HT synthesis (11). Depression may also affect serotonergic signalling through changes in neurogenesis and pre- and postsynaptic serotonin receptors, contributing to low mood (12).

The bidirectional relationship between PUD and depression may also involve chronic symptoms, pain, sleep disturbance, anxiety, inflammation, and behavioural changes. Previous longitudinal evidence has suggested a reciprocal association between depression and peptic ulcer disease (13). In the present study, no patient with PUD was free of depressive symptoms, which supports a strong clinical overlap but also limits the ability to distinguish whether serotonin is associated with PUD, depression, or their combined presentation.

Patients with PUD may experience depressive symptoms because of pain, discomfort, fatigue, appetite loss, and chronic stress. These factors may influence tryptophan hydroxylase activity and serotonin synthesis (14). Reduced serotonin levels may also reflect mucosal injury, altered enterochromaffin cell function, or microbiota changes associated with gastric acidity and

Helicobacter pylori-related mechanisms (5,15). However, these mechanisms were not directly measured in this study and should be interpreted as hypotheses.

The ROC results suggest that serotonin may have diagnostic utility in this cohort. However, the near-perfect performance in State A probably reflects comparison of extreme clinical phenotypes after excluding controls with active depressive symptoms. The more clinically relevant analysis is State B, which included the full control group and still showed high discrimination. Similar high diagnostic accuracy has been reported for platelet serotonin in untreated patients with depression (16), although direct comparison is limited by differences in study population, sample type, and reference standard.

No participants reported current antidepressant or mood stabiliser use, including selective serotonin reuptake inhibitors (SSRIs). Therefore, medication-related interference with serum serotonin measurement is unlikely in this cohort. Nevertheless, future studies should systematically record antidepressant exposure, other serotonergic medications, dietary factors, and inflammatory markers.

The clinical relevance of evaluating depression in patients with PUD lies in the possibility that psychological symptoms may remain unrecognised when patients present primarily with gastrointestinal complaints. Integrating psychological screening into gastroenterology practice may help identify patients requiring further mental health assessment (17).

NSAID use was more frequent among patients than controls. This finding is consistent with the established role of NSAIDs in ulcer pathogenesis through cyclooxygenase inhibition and reduced prostaglandin-mediated mucosal protection (18). The relationship between NSAID use, inflammation, prostaglandin E2, indoleamine 2,3-dioxygenase activation, and serotonin metabolism is biologically plausible but complex and was not directly tested in this study (19).

Age differed substantially between groups, with patients being older than controls. Although some studies suggest that whole-blood serotonin levels may not be primarily driven by ageing, age-related changes in receptors and compensatory enterochromaffin cell responses have been described (20,21). Because age differed between groups, residual confounding remains possible despite adjustment.

This study has several limitations. The sample size was relatively small and included only adult male participants, which limits generalisability to women and broader clinical populations. The study was conducted at a single centre, and all patients with PUD had depressive symptoms, so the design cannot determine whether lower serotonin is specific to depression among patients with PUD or reflects PUD case status more broadly. The control group differed from the patient group in age, education, employment, marital status, and NSAID use, which may have introduced residual confounding. Clinical mechanisms of serotonin depletion, including Helicobacter pylori status, inflammatory markers, microbiota composition, and tryptophan metabolism, were not directly assessed. The cross-sectional case-control design does not allow causal inference; therefore, longitudinal studies including PUD patients with and without depression are required to determine predictive value and clinical utility.

Serum serotonin levels were lower in male patients with PUD and depressive symptoms than in apparently healthy controls. Serotonin showed high diagnostic performance in this case-control cohort and may be useful as a biomarker of depressive symptoms in patients with PUD. However, because all PUD patients had depressive symptoms and the study was cross-sectional, these findings should be validated in larger longitudinal studies including women, PUD patients without depression, and clinically matched control groups.

CONCLUSION

Serum serotonin levels were lower in male patients with PUD and depressive symptoms than in apparently healthy controls. Serotonin showed high diagnostic performance in this case-control cohort and may be useful as a biomarker of depressive symptoms in patients with PUD. However, because all PUD patients had depressive symptoms and the study was cross-sectional, these findings should be validated in larger longitudinal studies including women, PUD patients without depression, and clinically matched control groups.

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Conflicts of interest: None to declare.

Author contributions (CRediT): Conceptualization—S.F.K., A.C.Y.; Methodology—S.F.K., A.C.Y.; Validation—S.F.K., A.C.Y.; Formal analysis—A.C.Y.; Investigation—S.F.K.; Resources—S.F.K.; Data curation—A.C.Y.; Writing – original draft—S.F.K.; Writing – review and editing—S.F.K., A.C.Y.; Visualization—A.C.Y.; Supervision—A.C.Y.; Project administration—S.F.K.; Funding acquisition—S.F.K., A.C.Y.

Ethics statement: The study protocol was approved by the Medical Ethics Committee of the College of Applied Medical Sciences at Karbala University, Iraq (Ref. No.: CLAMSKU/19; 4 October 2025). All procedures were conducted in accordance with relevant national and international ethical guidelines and the Declaration of Helsinki.

Data availability statement: The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

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TABLES AND FIGURES

Table 1. Classification and distribution of subjects according to demographic characteristics

Parameters	Indicators	PUD (N=50)	Control (N=50)	p
		N (%)		
Work status	Employment	21 (42)	31 (62)	<0.05
	Unemployment	29 (58)	19 (38)	
Difficult at work	Yes	12 (24)	1 (2)	<0.001
	No	38 (76)	49 (98)	
Family income	Low	5 (10)	2 (4)	0.487
	Middle	39 (78)	42 (84)	
	High	6 (12)	6 (12)	
Education level	Illiterate	7 (14)	0 (0)	<0.001
	Primary	18 (36)	1 (2)	
	Middle	12 (24)	1 (2)	
	High	13 (26)	48 (96)	
Marital status	Unmarried	7 (14)	24 (48)	<0.001
	Married	43 (86)	26 (52)	
NSAIDs usage	Yes	32 (64)	5 (10)	0.002
	No	18 (36)	45 (90)	
Family history of depression	Yes	3 (6)	1 (2)	0.297
	No	47 (94)	49 (98)	
Psychological counselling	Yes	0 (0)	0 (0)	N/A
	No	50 (100)	50 (100)	
Antidepressant/mood stabiliser drug use	Yes	0 (0)	0 (0)	N/A
	No	50 (100)	50 (100)	
Physical activity	No activity	37 (74)	44 (88)	0.341
	Once per week	4 (8)	2 (4)	
	Twice per week	3 (6)	1 (2)	
	Three times per week	6 (12)	3 (6)	
Depression classes	No depression	0 (0)	17 (34)	<0.001
	Minimal depression	6 (12)	19 (38)	
	Mild depression	8 (16)	9 (18)	
	Moderate depression	19 (38)	5 (10)	
	Moderate-severe depression	15 (30)	0 (0)	
	Severe depression	2 (4)	0 (0)	

PUD, peptic ulcer disease; N/A, not applicable; NSAIDs, non-steroidal anti-inflammatory drugs.

Table 2. Comparison of biochemical, demographic, and clinical characteristics between study groups

Biomarker	PUD Group (N=50)	Control Group (N=50)	p
	Median (IQR)		
Serotonin (pg/mL)	530.086 (435.7-592.8)	1008.763 (874.89-1120.43)	<0.001
BMI (kg/m²)	24.73 (22.52-29.45)	26.37 (23.49-30.34)	0.285
Age (years)	49.5 (35.75-63)	29 (25.75-38.25)	<0.001
PHQ-9	13.50 (7-16.6)	4.0 (2-8)	<0.001

IQR, interquartile range; BMI, body mass index; PHQ-9, Patient Health Questionnaire-9.

Table 3. Multivariate logistic regression analysis of factors associated with the clinical outcome

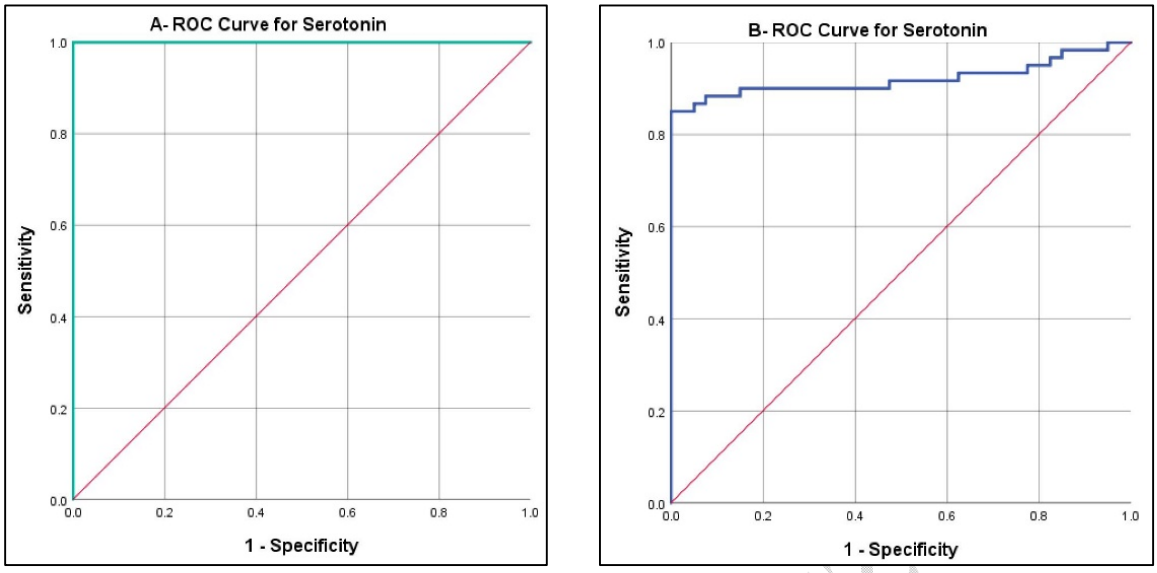
Parameters	OR (95% CI)	p
Serotonin (pg/mL)	0.992 (0.988- 0.996)	<0.001
Age (years)	0.482 (0.083- 2.788)	0.692
Employment status (Employed vs. Unemployed)	1.852 (0.488-7.019)	0.365
Work difficulty (Yes vs. No)	0.464 (0.40- 5.383)	0.539
Marital status (Married vs. Unmarried)	0.702 (0.183- 2.693)	0.606
Educational level (Higher vs. Basic education)	1.843 (0.366- 9.285)	0.459

OR, odds ratio; CI, confidence interval.

Table 4. Receiver operating characteristic (ROC) curve results for serum serotonin

Metrics		Serotonin	
		State A*	State B**
Standard error		< 0.001	0.03
Asymptotic significance		< 0.001	< 0.001
Asymptotic 95% CI	Lower bound	0.985	0.861
	Upper bound	1.000	0.980
Cut-off point (pg/mL)		791.911	803.131
AUC		0.999	0.920
Sensitivity		100 %	85%
Specificity		100%	100%
Accuracy		100%	92.5%

*, AUC calculated against filtered controls (excluding active depression control cases); **, AUC calculated against the total control group (unfiltered/general population).



A **B**

Figure 1. Receiver operating characteristic (ROC) curve analysis for serum serotonin. A - filtered controls excluding active depression control cases. B - unfiltered total control group.