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Value of esophagogastroduodenoscopy in assessment of chronic kidney disease patients with iron deficiency anemia without gastrointestinal symptoms

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Abstract:

Background: Iron deficiency anemia is one of the most important etiological factors for anemia in chronic kidney disease patients. Iron deficiency anemia in adults is commonly caused by upper gastrointestinal bleeding. However, the epidemiology of gastrointestinal lesions in patients with chronic kidney disease remains questionable. Aim: to assess the presence of potential upper gastrointestinal disorders in asymptomatic patients with chronic kidney disease and assess the risk factors contributing to the most prevalent endoscopic findings.

Methods: This randomized controlled trial involved 81 patients categorized into two groups according to the estimated glomerular filtration rate. History taking, examination, laboratory investigations, and esophagogastroduodenoscopy were performed on all participants from May 2021 to November 2021.

Results: The most common endoscopic findings were chronic gastritis, *helicobacter pylori*, and erosive gastritis. Risk factors associated with helicobacter pylori gastritis included higher serum creatinine and lower transferrin saturation. Risk factors for erosive gastritis included older age, higher serum creatinine, lower hemoglobin, and lower serum iron.

Conclusion: Endoscopic gastrointestinal lesions are common in asymptomatic chronic kidney disease patients with iron deficiency anemia. The severity of renal disease increased the prevalence of severe gastrointestinal lesions.

Keywords: Occult bleeding; Fecal occult blood test; Duodenal Ulcer; Stomach Ulcer.

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Introduction

Anemia is a prevalent complication of renal disease, and its magnitude intensifies with the reduction of the glomerular filtration rate [1]. The primary reason for this complication is the decreased synthesis of erythropoietin. Additional etiological factors include insufficient hematopoietic nutrients, such as iron, folate, and cobalamin, digestive system losses, hemolysis, bone marrow dysfunction, and erythropoietin resistance [2]. Meanwhile, Iron deficiency anemia (IDA) is a prevalent and essential etiological factor for this condition among patients who have chronic kidney disease (CKD). IDA is attributable to either actual or functional iron insufficiency, often linked to underlying inflammation [3]. However, the epidemiology of gastrointestinal disorders in Arab patients with CKD and IDA remains questionable. Some investigators revealed that almost all CKD patients experienced these disorders, whereas other researchers stated that CKD patients had the exact prevalence of gastrointestinal diseases as the general population [4]. Thus, this work's primary objectives were to assess potential gastrointestinal disorders in patients with CKD and iron deficiency anemia who do not have gastrointestinal symptoms and determine the risk factors contributing to the most prevalent endoscopic findings.

Methods

This randomized controlled trial was conducted at the outpatient clinic of the Internal Medicine Department of Zagazig University Hospital from May to November 2021. All study participants signed consent before sharing in the study. We followed the Helsinki Declaration ethical guidelines. The protocol was approved by the Institutional Review Board of the Ethical Committee of Zagazig University (ZU-IRB #9145). We included patients older than 18 with a history of CKD stages 1-5 and iron deficiency anemia without gastrointestinal symptoms. Iron deficiency anemia was considered present if hemoglobin was less than 13 g/dL in men and 12 g/dL in women and transferrin saturation was less than 20% [5].

As 135 CKD patients with a confirmed diagnosis of iron deficiency anemia attended the outpatient clinic of the Internal Medicine Department of our hospital within six months, and the prevalence of iron deficiency anemia in patients with CKD is 15.4% [6]; therefore, the sample size was calculated to be 81 patients with using OpenEpi software with confidence level 95% and power of study 80%.

Patients with a history of gastrointestinal symptoms (especially hematemesis and melena), active bleeding in the last year, active infection, malignancy, hemolytic anemia, advanced liver disease, folate deficiency, and cobalamin deficiency were ruled out from the study. Additionally, patients with a history of Helicobacter pylori eradication therapy were excluded.

The patients were classified according to the estimated glomerular filtration rate (eGFR) as follows:

1. Group 1 included 48 patients with an eGFR $\geq$ 60 ml/min/1.73 m^2. There were 31 males and 17 females.

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2. Group 2 included 33 patients with an eGFR < 60 ml/min/1.73 m^2. There were 23 males and ten females.

All enrollees performed the following procedures: medical history taking, medical examination, and routine laboratory investigations. Routine investigations included a complete blood picture, test for occult blood in stool, serum creatinine, blood urea, estimated glomerular filtration rate (eGFR) using the Modification of Diet in Renal Disease (MDRD) formula, liver function tests, coagulation profile, lipid profile, iron indices, erythrocyte sedimentation rate (ESR) and abdominal ultrasound. All patients underwent esophagogastroduodenoscopy (EGD) with routine testing for helicobacter pylori (H. pylori) infection using the Campylobacter-like organism (CLO) test. Biopsy and histopathological examinations were done if any suspicious pathology was detected during EGD.

Statistical analysis

Data analysis was performed using SPSS (Statistical Package for the Social Sciences) version 28. Categorical variables were described using their absolute frequencies. We then used Chi-square and Monte Carlo tests to compare them. We used Kolmogorov-Smirnov and Levene tests to verify the assumptions of normality and homogeneity of variances for parametric tests. The Mann-Whitney test (for non-normally distributed data) and the independent sample t-test (for normally distributed data) were used to compare quantitative data between the two groups. We used the Spearman rank correlation coefficient to assess the strength and association of the correlation between two continuous variables. The level of statistical significance was set at $p \leq 0.05$. A highly significant difference was present at $p \leq 0.001$.

Results

This study included 81 patients with CKD. The baseline data of the patients studied is presented in Tab1. About 43% of patients had positive fecal occult blood testing (FOBT) (Tab1).

Tab1. ***Baseline data of the studied patients.***

Parameter	**N=81**	**%**
Age (year):		
Mean ± SD.	62.78 ± 12.16	
Range	34 – 82	
Male sex	54	66.7%
Comorbidities:		
Hypertension	54	66.7%
Diabetes	42	51.9%
IHD	18	22.2%
Drugs:		
Aspirin	25	30.9%
NSAIDs	37	45.7%
Clopidogrel	15	18.5%
Oral anticoagulants	4	4.9%

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Steroid	10	12.3%
CKD stages:		
Stages 1- 2	48	59.3%
Stage 3A	22	27.2%
Stage 3B	1	1.2%
Stage 4	6	7.4%
Stage 5	4	4.9%
Positive FOBT:	35	43.2%

(SD): Standard deviation, (IHD): Ischemic heart disease, (NSAIDs): Non-steroidal anti-inflammatory drugs, (CKD): Chronic kidney disease, (FOBT): Fecal occult blood test.

The patients in group 2 were older than those in group 1. Group 2 also had a higher prevalence of diabetes mellitus and a history of intake of non-steroidal anti-inflammatory drugs (NSAIDs). In addition, hemoglobin, total serum protein, serum albumin, and alanine transaminase (ALT) levels were lower in group 2 than in group 1. In contrast, serum creatinine, blood urea, and ESR were higher in group 2 than in group 1 (Table 2). Statistically, no significant relationships were observed between CKD severity and EGD results for the esophagus and duodenum. However, there was a statistically significant relationship between CKD severity and EGD results for the stomach, with 12.1% of patients with severe CKD having large gastric ulcers (Table 3).

Tab 2. ***Comparison between the studied groups regarding baseline data.***

Parameter	**Group 1 (n=48)**	**Group 2 (n=33)**	*p*-value
Male sex	31 (64.5%)	23 (69.7%)	0.631
Age (years)	60.23 ± 12.78	66.48 ± 10.29	0.017*
Body mass index (kg/m^2)	25.9 ± 5.0	25.68 ± 4.51	0.836
Hypertension	29 (60.4%)	25 (75.8%)	0.15
Diabetes	17 (35.4%)	25 (75.8%)	<0.001**
Ischemic heart disease	11 (22.9%)	7 (21.2%)	0.856
Aspirin	18 (37.5%)	7 (21.2%)	0.119
NSAIDs	28 (58.3%)	9 (27.3%)	0.006*
Clopidogrel	8 (16.7%)	7 (21.2%)	0.605
Oral anticoagulants	1 (2.1%)	3 (9.1%)	0.299
Steroid	5 (10.4%)	5 (15.2%)	0.524
Creatinine (mg/dL)	0.86 (0.69 – 2)	1.5 (0.98 – 10.17)	<0.001**
Urea (mg/dL)	30.4 (16.8 – 89)	46.7 (22.2 – 139.49)	<0.001**
Hemoglobin (g/dL)	9.66 ± 1.1	8.9 ± 1.4	0.008*
WBCs (x10^3/mm^3)	5.99 (3 – 29)	6.2 (3.21 – 25.5)	0.474
Platelet (x10^3/mm^3)	263.75 ± 66.02	306.42±119.8	0.077
Albumin (g/dL)	4.26 ± 0.43	3.9 ± 0.31	<0.001**
Alanine transaminase (IU/L)	15.7 (6.3 – 92)	12.2 (5 – 27)	<0.001**
Ferritin (ng/mL)	70 (7 – 1392)	100 (6.48 – 1210)	0.402
Transferrin saturation (%)	12 (5.2 – 10)	13 (3.43 – 24)	0.307
Serum iron (µg/dL)	52.8 (17.42 –430)	38 (13.8–136.8)	0.059

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Total cholesterol (mg/dL)	160.5 (100 – 242)	157 (88.9 – 280)	0.788
LDL (mg/dL)	100.25 (46 – 176)	100 (36.35 – 210)	0.554
HDL (mg/dL)	42.3 (17.4 – 77.3)	46.89 (28 – 77)	0.561
ESR (mm/hr)	24 (6 – 95)	35 (6 – 85)	0.014*
Positive FOBT	15 (31.3%)	20 (60.6%)	0.009*

(*): Statistically significant, (**): Highly effective, (NSAIDs): Non-steroidal anti-inflammatory drugs, (WBCs): White blood cells, (LDL): Low-density lipoproteins, (HDL): High-density lipoprotein, (ESR): Erythrocyte sedimentation rate, (FOBT): Fecal occult blood test.

Tab 3. Comparison between the studied groups regarding endoscopic data.

Parameter	Group 1 (n=48)	Group 2 (n=33)	*p*-value
Esophagus:			
Normal	44 (91.7%)	33 (100%)	0.37
Esophagitis	4 (8.3%)	0 (0%)	
Stomach:			
Normal	11 (22.9%)	2 (6.1%)	
Chronic gastritis	19 (39.6%)	11 (33.3%)	
Small gastric ulcer	2 (4.2%)	0 (0%)	0.012*
Large gastric ulcer	0 (0%)	4 (12.1%)	
H. pylori gastritis	9 (18.7%)	10 (30.3%)	
Erosive gastritis	7 (14.6%)	4 (12.1%)	
Malignancy	0 (0%)	2 (6.1%)	
Duodenum:			
Normal	47 (97.9%)	31 (93.9%)	0.136
Duodenitis	1 (2.1%)	0 (0%)	
Large duodenal ulcer	0 (0%)	2 (6.1%)	

Data is represented by n (%). (*): Statistically significant, (H. pylori): Helicobacter pylori.

There was a statistically significant relationship between *H. pylori* gastritis and serum creatinine, transferrin saturation, and advanced stages of CKD. Specifically, serum creatinine was higher, and transferrin saturation was lower in patients with *H. pylori* gastritis. Additionally, 21% of patients with H. pylori gastritis had advanced CKD. There was no statistically significant relationship between *H. pylori* gastritis and other parameters (Table 4). Fig.1 shows the relationship between serum creatinine levels and H. pylori gastritis (p=0.012).

Tab 4. Risk factors associated with Helicobacter pylori gastritis.

Parameter	**H pylori Gastritis**		*p*-value
	Absent (n=13)	**Present (n=19)**	
Male sex	9 (69.2%)	14 (73.7%)	0.763
Age (years)	56.54 ± 11.27	60.89 ± 16.67	0.385
Body mass index (kg/m^2)	24.77 ± 4.25	26.89 ± 5.71	0.263
Hypertension	7 (53.8%)	16 (84.2%)	0.109
Diabetes	5 (38.5%)	12 (63.2%)	0.169

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Aspirin	4 (30.8%)	1 (5.3%)	0.132
NSAID	6 (46.2%)	5 (26.3%)	0.283
Clopidogrel	5 (38.5%)	0 (0%)	0.006*
Oral anticoagulants	0 (0%)	0 (0%)	>0.999
Steroid	1 (7.7%)	2 (10.5%)	>0.999
FOBT	5 (38.5%)	8 (42.1%)	0.837
Creatinine (mg/dL)	0.85 (0.76 – 1.6)	1.11 (0.76 – 12)	0.012*
Urea (mg/dL)	33.5 (19.8 – 73)	33.45 (22.2 – 74.5)	0.659
Hemoglobin (g/dL)	9.46 ± 0.89	9.92 ± 1.04	0.207
Ferritin (ng/mL)	99 (10.9 – 280)	156 (13 – 1210)	0.139
Transferrin saturation (%)	18 (10 – 20)	10 (8 – 20)	0.021*
Serum iron (µg/dL)	36.86 (26 – 72.6)	56 (14.69–430)	0.129
CKD:			
Stage 2	11 (84.6%)	9 (47.4%)	
Stage 3A	2 (15.4%)	6 (31.6%)	
Stage 3B	0 (0%)	0 (0%)	0.034*
Stage 4	0 (0%)	2 (10.5%)	
Stage 5	0 (0%)	2 (10.5%)	

(*): Statistically significant, (**): Statistically highly significant, (NSAIDs): Non-steroidal anti-inflammatory drugs, (FOBT): Fecal occult blood test, (CKD): Chronic kidney disease.

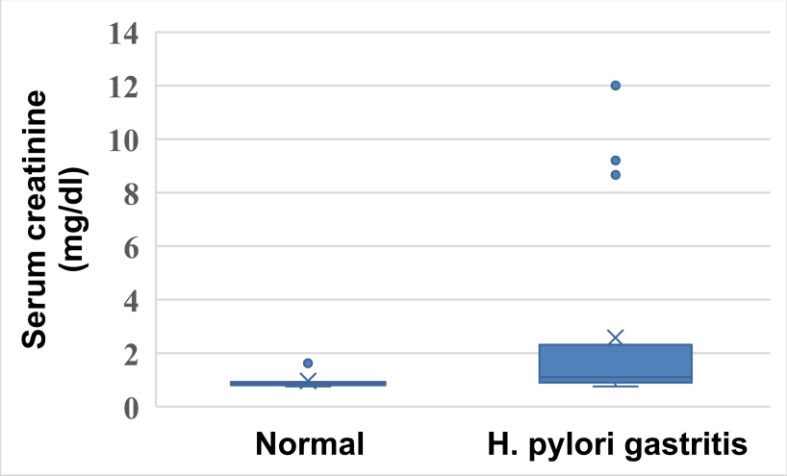

Fig 1. Boxplot showing the relationship between serum creatinine and H. pylori gastritis (p=0.012).

There was a statistically significant relationship between the presence of erosive gastritis and age, serum creatinine, hemoglobin, serum iron, and advanced stages of CKD. Hemoglobin and serum iron levels were lower in the erosive gastritis group than in the non-erosive gastritis group. There was no significant relationship between erosive gastritis and other parameters (Table 5). Fig.2 shows the relationship between serum creatinine levels and erosive gastritis (p=0.009).

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Table 5. ***Risk factors related to erosive gastritis.***

Parameter	Erosive gastritis		*p*-value
	Absent (n=13)	Present (n=11)	
Male sex	9 (69.2%)	4 (36.4%)	0.107
Age (years)	56.54 ± 11.27	65.64 ± 3.47	0.015*
Body mass index (kg/m^2)	24.77 ± 4.25	23.41 ± 3.61	0.412
Hypertension	7 (53.8%)	9 (81.8%)	0.211
Diabetes	5 (38.5%)	5 (45.5%)	0.729
Aspirin	4 (30.8%)	5 (45.5%)	0.675
NSAIDs	6 (46.2%)	7 (63.6%)	0.392
Clopidogrel	5 (38.5%)	1 (9.1%)	0.166
Oral anticoagulants	0 (0%)	3 (27.3%)	0.082
Steroid	1 (7.7%)	2 (18.2%)	0.576
FOBT	5 (38.5%)	8 (72.7%)	0.093
Creatinine (mg/dL)	0.85 (0.76 – 1.63)	1.45 (0.79 – 10.17)	0.009*
Urea (mg/dL)	33.5 (19.8 – 73.27)	40.2 (16.8 – 140.9)	0.258
Hemoglobin (g/dL)	9.46 ± 0.89	7.89 ± 1.13	0.002*
Ferritin (ng/mL)	99 (10.9 – 280)	14.5 (7 – 1392)	0.839
Transferrin saturation (%)	10 (8 – 20)	9 (5.2 – 23)	0.308
Serum iron (µg/dL)	36.9 (26.25 – 72.6)	25.1 (17.42–44.68)	0.002*
CKD:			
Stage 2	11 (84.6%)	7 (63.6%)	
Stage 3A	2 (15.4%)	0 (0%)	
Stage 3B	0 (0%)	0 (0%)	0.042*
Stage 4	0 (0%)	2 (18.2%)	
Stage 5	0 (0%)	2 (18.2%)	

(*): Statistically significant, (**): Statistically highly significant, (NSAIDs): Non-steroidal anti-inflammatory drugs, (FOBT): Fecal occult blood test, (CKD): Chronic kidney disease.

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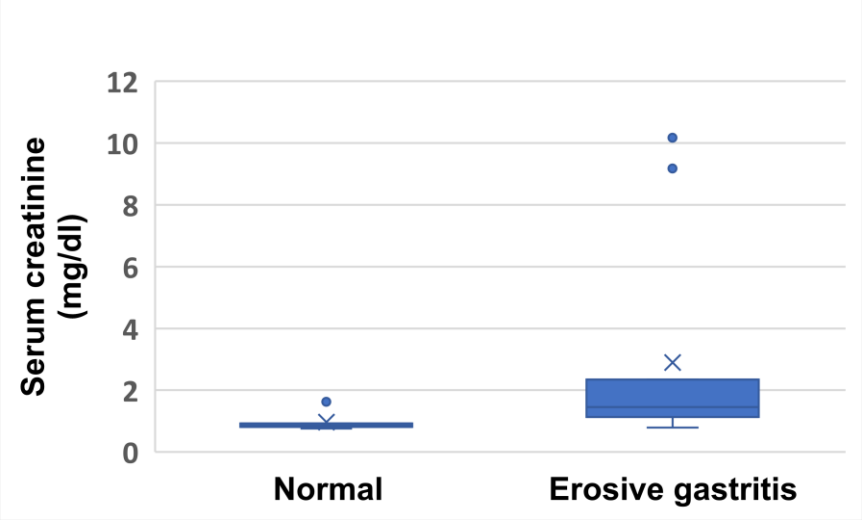

Fig 2. Boxplot showing the relationship between serum creatinine and erosive gastritis (p=0.009).

Discussion

In this study, we evaluated the presence of upper gastrointestinal lesions in CKD patients with IDA using EGD, followed by biopsy and histopathological examination. The current study revealed a high prevalence of upper gastrointestinal lesions in asymptomatic CKD patients with IDA. We did not depend on fecal occult blood testing results as they have low diagnostic value in evaluating causes of IDA with CKD [7].

Chronic gastritis, *H. pylori gastritis*, and erosive gastritis were the most frequently identified lesions, with prevalences of 37.04%, 23.46%, and 13.58%, respectively. According to our results, the stomach was the most frequent lesion site. This is like previous studies that ascertained that gastric lesions were the most frequent lesion in CKD patients, such as in the Odhaib et al. study [8], which found atrophic gastritis in 24% of cases and peptic ulcer in 20% of cases and Usta et al. [9], who reported gastritis in 62.3%, and erosive gastritis in 38.7% of cases. This can be explained by the fact that the kidneys play an essential role in the metabolism of gastrin hormone, which tends to increase in CKD, causing relaxation of the pyloric sphincter and irritation of the gastric mucosa by bile [10]. Furthermore, CKD patients suffer from accumulated uremic toxins, infection by H. pylori, and dysregulated gastrointestinal motility [11].

Additionally, patients in group 2 (CKD stages 3-5) had a higher prevalence of gastric lesions than in group 1 (CKD stages 1-2), and peptic ulcers were more abundant in group 2. Patients in group 2 exhibited a higher occurrence of gastric lesions due to their increased consumption of NSAIDs, which could exacerbate gastric lesions [12]. Furthermore, ESR levels were notably elevated in group 2, indicating an active inflammatory state that contributes to the development of transmural inflammation in the mucous membranes of the digestive system [13].

In this study, about 23.46 % of asymptomatic patients with IDA and CKD had confirmed H. pylori gastritis. After analyzing the risk factors associated with H. pylori gastritis, we discovered that higher serum creatinine levels and CKD stages 4-5 were linked to H. pylori gastritis. This

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finding corresponds with the findings of Wang et al. [14]. This connection is attributed to the lower levels of tight junction proteins (zonula occludens-1, occludin, and claudin-1) in CKD patients, which disrupt the integrity of the mucosal barrier, enabling a higher influx of H. pylori organisms into the epithelial cells [15]. Additional risk factors associated with H. pylori gastritis included low transferrin saturation, which aligns with the results reported by Demerdash et al. [16] in a previous study. Generally, low transferrin saturation and iron deficiency may serve as risk factors for H. pylori infection and as consequences of H. pylori infection. Patients experiencing iron deficiency and low transferrin saturation often exhibit a weakened immunological response to invading organisms, particularly in T-cell immunity [17]. Furthermore, experimental animals with iron deficiency displayed more virulent H. pylori strains with increased synthesis and activity of the cag type IV secretion system. This, in turn, led to gastritis and an elevated risk of developing gastric carcinoma [18].

In this study, approximately 13.6% of asymptomatic patients with both IDA and CKD were confirmed to have erosive gastritis. A prior study by Thomas et al. [19] similarly identified erosive gastritis as the most prevalent observation among CKD patients. Risk factors linked to erosive gastritis include older age, elevated serum creatinine levels, reduced hemoglobin levels, decreased serum iron levels, and advanced stages of CKD (as stages 4 and 5 each constituted 18.2% of the erosive gastritis group).

Conclusion

Endoscopic gastrointestinal lesions are common in asymptomatic CKD patients with IDA. This study's most frequent pathological findings were chronic gastritis, H. pylori gastritis, and erosive gastritis. Finally, the severity of CKD increased the prevalence of severe gastrointestinal lesions, and large gastric and duodenal ulcers occurred in 4.9% and 2.5% of patients with eGFR < 60 ml/min/1.73 m^2, respectively.

Footnotes.

Peer-Reviewers: Tamer Goda (assistant professor of internal medicine), Bassam Mansour Salama (Assistant professor of tropical medicine), Samah Soliman (Assistant professor of tropical medicine).

E- Editor: Salem Youssef Mohamed, Osama Ahmed Khalil, Mohamed Hassan Ali Emara.

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Ethics Approval and Consent to Participate: All procedures followed were by the ethical standards of the responsible committee on human experimentation (Institutional Review Board (IRB)" (ZU-IRB #9145) of Zagazig University and with the Helsinki Declaration of 1964 and later versions.

Trial registration number ClinicalTrials.gov NCT05240677, date of registration: 2 February 2022.

Consent for publication: All patients included in this research gave written informed permission to publish the data contained within this study.

Availability of data and materials: The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions

The study was conceptualized and designed by Walid Ahmed Ragab Abdelhamid and Mahmoud Ahmed Sharafeddin. Walid Ahmed Ragab Abdelhamid, Said Abdel Baky Gad, and Mahmoud Ahmed Sharafeddin collected and compiled data. Mahmoud Ahmed Sharafeddin conducted the statistical analysis, while Walid Ahmed Ragab Abdelhamid drafted the manuscript. Said Abdel Baky Gad and Mahmoud Ahmed Sharafeddin provided significant intellectual input throughout the project, contributing to comments and revisions. All authors reviewed and approved the final manuscript.

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