



Evaluation of histopathological pattern in patients of chronic diarrhea with normal colonoscopy

Mostafa A M Haridi, Esraa Mansour Omar, Hossam Mahmoud Abdelwahab

¹*Internal Medicine, Assiut University Hospital, Egypt.*

²*Internal Medicine, Assiut University Hospital, Egypt.*

³*Gastroenterology and Hepatology unit, Assiut University Hospital, Egypt.*

Abstract

The wide range of differential diagnoses makes it difficult to diagnose and treat people with chronic diarrhea. A precise diagnosis and suitable treatment follow a thorough examination. To determine the cause of chronic diarrhea, a colonoscopy along with a biopsy is recommended. As a result, patients may experience misdiagnosis or diagnostic delays, which could lead to disease persistence and other adverse consequences. Therefore, quick and precise diagnosis is crucial. The purpose of the study was to determine the frequency of abnormal findings in individuals who had a normal colonoscopy but chronic diarrhea. The current study enrolled 74 patients with chronic diarrhea who underwent a colonoscopy that revealed normal findings. Multiple biopsies were taken from all patients and underwent histopathological evaluation. In addition, demographic and laboratory data were recorded. The main findings of the study were; 1) mean age of patients was 48.72 years with mean body mass index was 25.87 (kg/m²). Out of the studied patients, 63 (85.1%) patients were males, 2) the mean duration of diarrhea was 9.02 weeks with a frequency per day was 5.50 times. A total of 48 (64.8%) patients had normal histopathological findings or nonspecific colitis (NSC). Meanwhile, 16 (21.6%) patients had a picture of microscopic colitis. Lymphoid hyperplasia is present in 5 (6.8%) patients. There were three patients had a picture of eosinophilic gastroenteritis and another two patients had a picture of Crohn's disease. Based on the current study, we concluded that microscopic colitis is fairly common in patients with chronic diarrhea and their colonoscopy was normal. A colonic biopsy is still of high efficacy and great important in the diagnosis of cases with chronic diarrhea and normal colonoscopy. It's recommended to perform such a study on a large number of patients in multiple centers to draw a firm conclusion about such issue.

Keywords: chronic diarrhea, normal colonoscopy, microscopic colitis, nonspecific colitis.

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1. Introduction

Multiple studies have demonstrated that when patients have normal colonoscopies and persistent non-inflammatory diarrhoea, systematic endoscopic biopsies of the colon give good diagnostic results [1,2]. According to data, 10% to 32% of patients with chronic diarrhoea who have never had a diagnosis before can receive a histologic diagnosis following colonoscopy with random biopsy sampling of the terminal ileum, cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, descending colon, sigmoid colon, and rectum. Histopathologic examination can reveal alterations not visible on a routine white-light colonoscopy as well as the extent, location, and depth of the disease-causing chronic diarrhea [2]. The histological findings of microscopic colitis are associated with increased lymphocytic infiltrates with or without collagen fiber growth, and the colonic mucosa

appears almost normal, setting it apart from "classical" inflammatory bowel disease (IBD) [3]. Collagenous colitis (CC) and lymphocytic colitis (LC) are the two main subtypes of microscopic colitis. It frequently causes minimal weight loss and manifests as persistent watery diarrhoea. These forms of colitis also have an entirely of normal endoscopic appearance [4]. The current study attempted to evaluate the frequency of abnormal findings in individuals who had a normal colonoscopy but chronic diarrhoea.

2. Patients and methods

2.1. Study setting & design

At Assiut University Hospital's in Al-Rajhi Liver Hospital, a cross-sectional study was carried out between April 2022 and April 2023.

2.2. Inclusion criteria

Patients with normal colonoscopy results and persistent diarrhoea were eligible to participate in the research. According to one definition, chronic diarrhoea is "the passage of three or more loose or liquid stools per day, or more frequently than is normal for the individual that persisted longer than 28 days." [5].

2.3. Exclusion criteria

Any patient who fit one or more of the criteria listed was excluded; Bloody diarrhoea, histopathologic documentation of inflammatory bowel disease and/or colonoscopy finding of ulcer(s), polyp(s), or mass(es), gastro-intestinal or pancreaticobiliary operations, acute or subacute diarrhoea (less than one month duration), evidence of an infectious cause of diarrhoea such as chronic giardiasis.

2.4. Ethical consideration

The study was authorized by the hospital's ethics committee and carried out in accordance with the Declaration of Helsinki's ethics (ID: 17101862). All participants were told of the study's purpose and provided signed informed consent.

2.5. Sample size calculation

The sample size was calculated using Epi-info version 7 software, based on previously reported frequency of chronic diarrhea in general population that was 20.4% with the following assumptions: confidence limits of 6% and a confidence level =80%, 5% alpha error and 80% power of the study, minimum sample size was 74 patients with chronic diarrhea would be enrolled.

2.6. Methods

Complete history taking and thorough clinical examination, age, gender, place of residence, and drug use history. The stool analysis, full blood count, liver and kidney function tests, c-reactive protein, erythrocyte sedimentation rate and tissue transglutaminase were among the laboratory investigations conducted. Complete colonoscopy (Pentax EPN 3500 videocolonoscopy): Biopsies were taken from every section of the colon and from any locations that were abnormal during the colonoscopy examination. The standard protocols for colonoscopic preparation were followed, including a low-fiber meal the day before the procedure, split-dose bowel preparation using oral high-volume laxatives, and simethicone [6].

2.6.1. Diagnostic criteria of microscopic colitis (MC)

A higher number of chronic inflammatory cells in the lamina propria, surface epithelium degradation, an increase in intraepithelial B lymphocytes, and an increase in mitosis in crypts were among the criteria used for the histological diagnosis of MC. The diagnosis of lymphocytic colitis requires the presence of more than 20 intra-epithelial B lymphocytes per 100 inter-cryptal epithelial cells. To diagnose collagenous colitis, a sub-epithelial collagen band thickness more than 10 μm is necessary [4].

2.6.2. Diagnostic criteria of eosinophilic gastroenteritis (EGE)

According to most publications, the diagnostic standard for mucosal EGE needs to be met if microscopic examination reveals more than 20 eosinophils/HPF in adults [7].

2.6.3. Diagnostic criteria of Crohn's disease (CD)

Cobblestone mucosal appearance, non-continuous distribution of longitudinal ulcers, and longitudinally organized aphthous ulcerations are typical endoscopic findings of CD. Common microscopic characteristics of CD include non-caseating granulomas, localized and patchy chronic inflammation, and focal crypt irregularity [8].

2.6.4. Diagnostic criteria of lymphoid hyperplasia

This contains nodules with diameters typically not greater than 5 mm but ranging in size from 2 to 10 mm. Red macules, elevated papules, or circumferential target lesions (halo sign) can all be signs of colonic lymphoid nodules [9].

2.6.5. Diagnostic criteria of non-specific colitis

Under such circumstances, histological results that did not fit the description of a particular inflammation but were nevertheless higher than expected for a normal or reactive mucosa [10].

2.7. Statistical analysis

The Statistical Package for the Social Sciences – SPSS software version 16 was used. Data expressed as frequency (percentage), and mean (SD). Comparison between continuous data was performed by Student t test while Chi test was used to compare frequency. Level of confidence was kept at 95%, hence, p value was significant if < 0.05 .

3. Results

The demographic data of our results show that patients' mean age was 48.72 years, and their average BMI was 25.87 (kg/m²). Of the patients who were studied, 11 (14.9%) were female and 63 (85.1%) were male (table 1). Criteria of our patients regarding pattern of diarrhea show that mean duration of diarrhea was 9.02 weeks with frequency per day was 5.50 times. It was continuous in 40 (54.1%) patients and intermittent in 34 (45.9%) patients (table 2). Laboratory data of the current study reveal that all data are within normal range. All of those patients had negative antinuclear antibody (table 3). Results of histopathology in patients with normal colonoscopy revealed that a total of 48 (64.8%) patients had normal histopathological findings or nonspecific colitis (NSC). Meanwhile, 16 (21.6%) patients had picture of microscopic colitis. Lymphoid hyperplasia present in 5 (6.8%) patients. There were three patients had picture of eosinophilic gastroenteritis and another two patients had picture of CD (table 4, figure 1). Both groups of patients with normal histopathology/non-specific colitis and those with MC had insignificant differences as regard different characteristics ($p > 0.05$) (table 5).

4. Discussion

Histopathological examination of mucosal biopsy specimens obtained during colonoscopy is very essential in confirming the diagnosis of a large intestinal pathology. In

evidence-based medical practice, confirmation of a diagnosis is crucial to instituting the appropriate treatment protocol for the disease entity [11]. On a colonoscopy, some individuals with persistent diarrhoea do, nevertheless, have normal mucosa. In these situations, repeated biopsies can offer the data needed to make a diagnosis and recommend the best course of action [12]. The current study enrolled 74 patients with chronic diarrhea underwent colonoscopy that revealed normal findings. Multiple biopsies were taken from all patients and underwent histopathological evaluation. The purpose of the study was to determine the incidence of abnormal findings in individuals who had a normal colonoscopy but chronic diarrhoea. The relevant study showed that the mean age of patients was 48.72 years with mean body mass index was 25.87 (kg/m²). Out of the studied patients, most of them were males and the mean duration of diarrhea was 9.02 weeks with frequency per day was 5.50 times. It was continuous in 40 (54.1%) patients and intermittent in 34 (45.9%) patients. Our study revealed that a total of 64.8% patients had normal histopathological findings or nonspecific colitis (NSC). Meanwhile, 21.6% patients had picture of microscopic colitis. Lymphoid hyperplasia present in 6.8% patients. There were three patients had picture of eosinophilic gastroenteritis and another two patients had picture of early CD. So, it concluded that nonspecific colitis and microscopic colitis involve most of our patients. In agreement with the current study, *Kaguyama et al* evaluated 184 patients with chronic diarrhea. The findings of repeated biopsies of the terminal ileum, ascending colon, and rectosigmoid colon were made available, and the authors stated that there were no macroscopic alterations in the mucosa on colonoscopy. In comparison to men (n=62; 33.70%; average age: 39.16±14.65 years), women (n=122; 66.30%) constituted the majority [13]. Another study recruited 86 patients with chronic diarrhea. Up to 48% of patients were 41-60 years old. Majority of patients were females with female to male ratio was 3:2 [14]. Also, *Abdel Monem et al* studied 60 patients with chronic diarrhea. Over half (58.3%) of the patients under study were female, and their ages ranged from 20 to 70 years old, with a mean age of 39.8 years. Among the patients included, there was no family history of chronic diarrhoea or autoimmune illnesses. As many as 53% of patients lived in urban [15]. Our study stated that the most important finding of the current study was that total of 48 (64.8%) patients had normal histopathological findings or nonspecific colitis (NSC). There were three patients had histological data that were consistent with eosinophilic gastroenteritis. Meanwhile, 21.6% patients had picture of microscopic colitis. In agreement with the current study, According to *Karri et al* (2019), 35 (40.7%) of the patients had normal histology. 51 individuals, or 59.3% of the total, exhibited some histologic changes. Nonspecific inflammation was the most frequently reported anomaly, seen in 29 (33.7%) individuals. Furthermore, it was discovered that 12 individuals had lymphocytic colitis, 3 (3.5%) had eosinophilic colitis, and 3 (3.5%) had TB. Four individuals had an inflammatory bowel disease diagnosis (2 with ulcerative colitis, 2.3%), and 2 with Crohn's disease (2.3%) [14]. Also, *Stoicescu et al* study showed that the majority of MC patients were female [16], and the mean age of cases was around 45.9 years (range 22.5 - 76). Similarly, *Larsson et al.* found that women made up 77% of MC

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patients [17]. Nonetheless, *Fumery et al.* found that as people aged, the incidence of MC increased [18]. There were significant differences in the study's findings on the prevalence of MC. The prevalence of MC among patients with chronic watery diarrhoea was found by *Gado et al.* and *Saleh et al.* to be almost 50 percent and 29.5%, respectively [19,20]. In disagreement with the current study, the prevalence of MC was found by *Gomaa et al.* and *Abdelmageed et al.* to be around 10% and 14%, respectively [21,22]. The population features of the included patients and the short sample size might be the cause of this discrepancy. Therefore, extensive multicenter investigations with a broad scope are required to ascertain the true frequency and potential risk factors of MC in Egypt. Another finding in the current study was that lymphoid hyperplasia present in 6.8% patients. In the previous study 39.5% patients with chronic diarrhea and normal colonoscopies had lymphoid hyperplasia [23]. Also, *Hongling et al* found that 25% patients with chronic diarrhea had picture of lymphoid hyperplasia [24]. Variation in the frequency between studies may be secondary to different studied patients, sample size or selection bias. There were two (2.7%) patients who had a picture of CD. In a computerized database of 130 204 patients evaluated for chronic diarrhea; a total of 781(0.60%) patients had CD [25]. Also, in a previously enrolled 86 patients with chronic diarrhea 2.3% patients had CD [26]. Another studied evaluated a total of 142 patients with chronic diarrhea. CD was diagnosed histopathological in 4 (3%) patients [27]. The current investigation found no connection between MC and autoimmune disease history or family history. Additionally, none of the individuals included had celiac disease. Nevertheless, *Stoicescu et al.* identified 6 individuals (40%) as having MC and linked autoimmune conditions such as type 1 diabetes and celiac disease [16]. Since that the majority of this research were carried out in western nations where autoimmune illnesses are very prevalent, the reason for this discrepancy may be attributed to regional, genetic, or demographic variances. The current investigation demonstrated that level of hemoglobin, total leucocytic count, and platelets count was within normal ranges in patients with MC. Furthermore, no statistically significant difference was seen between patients with and without MC in terms of glycosylated haemoglobin, liver function tests, or renal function tests. This was in line with studies by *Gustafsson et al.* and *Larsson et al.* who demonstrated similar outcomes in MC patients [17,28]. Another finding in the current was that there were three patients had histological data that were consistent with eosinophilic gastroenteritis. The study of *Carmona-Sánchez et al* studied 545 patients with chronic diarrhea, a total of 22 (4.01%) patients had eosinophilic gastroenteritis [29]. The lamina propria typically exhibits eosinophilic infiltration that extends to the submucosa and lamina muscularis mucosae in colon biopsies [30]. Eosinophil counts in healthy bowels range from 5 to 35 per high-power field, with higher counts in the right colon. The quantity of eosinophils needed to validate the diagnosis, which still needs the confirmation of significant infiltration in many colon segments, is still up for debate [31]. It is regarded as an uncommon disease. Although the estimated prevalence in the US is 2-3/100,000 people, detection rates have increased recently [32].

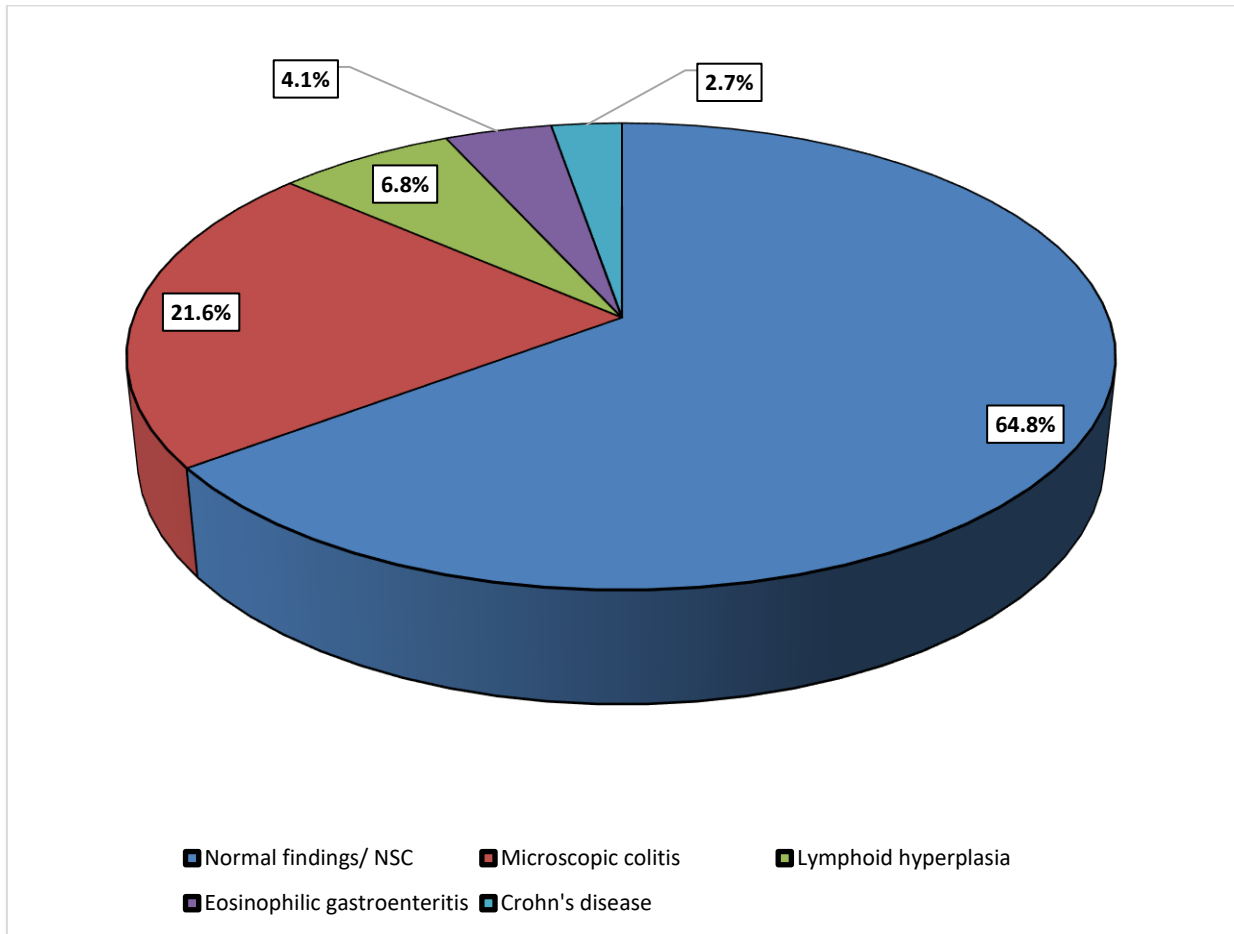


Figure 1: Results of biopsy in patients with normal colonoscopy. NSC: non-specific colitis

Table 1: Baseline characteristics of patients with normal colonoscopy

	N= 74
Age (years)	48.72 ± 6.84
Body mass index	25.87 ± 6.82
Sex	
Male	63 (85.1%)
Female	11 (14.9%)
Residence	
Rural	39 (52.7%)
Urban	35 (47.3%)
Smoking	11 (15.3%)
Occupation	
Worker	62 (83.7%)
Housewife	9 (12.2%)
Employee	3 (4.1%)

Data expressed as frequency (percentage), mean (SD).

Table 2: Characteristics of diarrhea with normal colonoscopy

	N= 74
Duration (weeks)	9.02 ± 2.26
Continuity of diarrhea	
Continuous	40 (54.1%)
Intermittent	34 (45.9%)
Frequency of motion/day	5.50 ± 0.91

Data expressed as frequency (percentage), mean (SD).

Table 3: Laboratory data of patients with normal colonoscopy

	N= 74
Hemoglobin (g/dl)	11.11 ± 2.26
Platelets (10 ³ /ul)	260.44 ± 55.32
Leukocytes (10 ³ /ul)	7.08 ± 1.54
Lymphocytes (10 ³ /ul)	1.07 ± 0.48
Eosinophils (10 ³ /ul)	0.50 ± 0.08
Creatinine (mmol/l)	101.98 ± 12.11
Urea (mmol/l)	12.51 ± 2.98
AST (u/l)	32.67 ± 5.09
ALT (u/l)	30.15 ± 7.80
ALP (u/l)	78.99 ± 21.67
Albumin (g/dl)	3.90 ± 1.11
Proteins (g/dl)	7.89 ± 1.53
Bilirubin (mmol/l)	12.96 ± 3.33
Direct bilirubin (mmol/l)	3.01 ± 0.87
CRP (mg/dl)	4.01 ± 0.38
ESR (ml/hr)	18.09 ± 3.08
Sodium (mmol/l)	133.05 ± 0.09
Potassium (mmol/l)	4.09 ± 0.11
Positive ANA	0

Data expressed as mean (SD). AST: aspartate transaminase; ALT: alanine transaminase; ALP: alkaline phosphatase; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody

Table 4: Results of biopsy in patients with normal colonoscopy

	N= 74
Results of biopsy	
Normal findings/ NSC	48 (64.8%)
Microscopic colitis	16 (21.6%)
Lymphoid hyperplasia	5 (6.8%)
Eosinophilic gastroenteritis	3 (4.1%)
Crohn's disease	2 (2.7%)

Data expressed as frequency (percentage). NSC: non-specific colitis

Table 5: Comparison between patients with normal histopathology and those with MC

	Histopathology		P value
	Normal/ NSC (n= 48)	MC (n= 16)	
Age (years)	47.09 ± 10.56	48.98 ± 6.78	0.90
Body mass index	25.11 ± 6.09	26.01 ± 7.77	0.10
Sex			0.50
Male	38 (79.1%)	13 (81.3%)	
Female	10 (20.9%)	3 (28.7%)	
Residence			0.32
Rural	30 (62.5%)	9 (56.3%)	
Urban	18 (37.5%)	7 (14.6%)	
Smoking	9 (18.8%)	2 (4.2%)	
Duration (weeks)	10.11 ± 2.22	8.88 ± 1.90	0.98
Continuity of diarrhea			0.09
Continuous	30 (62.5%)	8 (50%)	
Intermittent	18 (37.5%)	8 (50%)	
Motion/day	6.01 ± 0.43	5.40 ± 1.01	0.87
Hemoglobin (g/dl)	11.01 ± 2.09	11.89 ± 2.01	0.06
Platelets (10 ³ /ul)	259.59 ± 49.12	265.55 ± 54.32	0.47
Leukocytes (10 ³ /ul)	6.90 ± 1.22	7.18 ± 2.01	0.89
Creatinine (mmol/l)	99.91 ± 10.51	102.22 ± 17.90	0.09
Urea (mmol/l)	10.10 ± 1.53	12.67 ± 3.33	0.58
AST (u/l)	31.31 ± 7.54	34.78 ± 6.66	0.16
ALT (u/l)	30.01 ± 7.53	36.09 ± 5.55	0.08
Albumin (g/dl)	3.88 ± 1.01	3.90 ± 1.01	0.12
CRP (mg/dl)	4.10 ± 0.08	4.09 ± 0.32	0.34
ESR (ml/hr)	18.19 ± 2.19	17.31 ± 2.09	0.18
Sodium (mmol/l)	133 ± 0.03	133.07 ± 0.07	0.09
Potassium (mmol/l)	4.01 ± 0.52	4.11 ± 0.21	0.38

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. MC: microscopic colitis; AST: aspartate transaminase; ALT: alanine transaminase; CRP: c-reactive protein; ESR: erythrocyte sedimentation rate; ANA: antinuclear antibody

Although frequency varies greatly, eosinophilic colitis has been identified from a limited number of biopsies collected from individuals having colonoscopy for the investigation of diarrhoea [33]. Due to the small patient sample size, it was not feasible to determine any potential connections or differences across the various MC subtypes. Due to their small numbers, patients with collagenous and lymphocytic colitis were combined into one group for the purposes of our study. However, more researches are needed to investigate this issue. To conclude chronic diarrhea is common clinical presentation with challenging management, role of endoscopy is of utmost importance, and biopsy with normal colonoscopic appearance could add to diagnosis and early management. microscopic colitis, eosinophilic colitis and early CD were the most obvious findings in this study.

Competing interests

The authors declared that they had no competing interests.

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Declaration

- **Ethics approval and consent to participate:** All study protocols were approved by the institutional review board of the faculty of medicine, Assiut University, Egypt under the IRP number 17101298. Consent has been obtained from the participant patients.
- **Consent for publication:** "Not applicable".
- **Availability of data:** All data used and analyzed during this study are available from the corresponding author on reasonable request.
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- **Authors' contributions:** -
- **DR. Hossam Mahmoud Abdelwahab:** Conceived and designed the analysis, Contributed data and analysis tools.
- **Bishoy Shehata:** Collected data, performed the analysis.
- Prof. Nabila Faiek Amin Mousa: Conceived and designed the analysis, wrote the paper.
- All authors read and approved the final manuscript.
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