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Clinical and Histopathological Features of Patients with Functional Dyspepsia in Sohag University Hospital.

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Abstract: Background: Functional dyspepsia is considered one of the most common functional gastrointestinal disorders. However functional dyspepsia is not life threatening, it impairs quality of life, has a significant negative impact on work productivity, and increases health care expenses for both the patients and society.
Aim: was to study clinical, and histopathological features of patients with functional dyspepsia according to Rome IV criteria in Sohag University Hospital.
Materials and Methods: A cross-sectional study was conducted among One hundred and twenty consecutive adult patients with functional dyspepsia according to Rome IV criteria. in Sohag University Hospital. All patients subjected to complete physical examination, esophagogastroduodenoscopy, with multiple gastric and duodenal biopsies for histopathological assessment.
Results: 56.5% of laboratory technicians, nursing staff had good knowledge, 65.02% had a positive attitude and 53.81% had bad practice toward HCV patients. Laboratory technicians have better knowledge, more positive attitudes and better practices than nursing staff.
Conclusion: Knowledge, attitudes, the practices about HCV among laboratory technicians, and nursing staff are matters of concern. Educational programs should be formulated to raise their awareness about HCV.
Keywords: Functional dyspepsia, Rome IV, Esophagogastroduodenoscopy, Histopathological assessment.

1 Introduction

Dyspepsia is a prevalent complaint in general practice and gastro intestinal (GI) clinics [1]. Dyspepsia represents up to 5% of all primary care physician visits, and 20-40% of all gastroenterological consultation [2]. Approximately 25% of patients with dyspepsia have an organic cause while up to 75% no obvious cause is detected, and are labeled as having functional dyspepsia [3].

Functional dyspepsia (FD), is considered one of the most common functional GI disorders affecting 5-20% of the population worldwide. However FD is not life threatening, it impairs quality of life, has a significant negative impact on work productivity, and increases health care expenses for both the patients and society (Tally et al., 2015, Tally and Ford, 2015). Rome IV criteria defines FD, as one or more of the following four symptoms during the last 3 months with onset at least 6 months before diagnosis: (1) Bothersome postprandial fullness, (2) Bothersome early satiety, (3) Bothersome epigastric pain, (4) Bothersome epigastric burning, and no evidence of structural disease by Esophagogastroduodenoscopy (EGD), to explain the symptoms [6]. The Rome IV criteria labels patients with bothersome (i.e. severe enough to affect usual activities) epigastric pain and /or burning at least once/ week as epigastric pain syndrome (EPS), while those with bothersome postprandial fullness, and/or early satiety at least 3 days/ week as postprandial distress syndrome [6].

Studies on FD in Sohag governorate are rare, moreover, there are no studies regarding the role of Helicobacter pylori (H. pylori) infection in the causation of FD symptoms and correlation of the histopathological findings with symptomatology of FD. Therefore, this study was conducted to highlight this common health problem.

2 Methodologies

2.1 Ethical Consideration

The study was approved by The Ethical committee of Sohag Faculty of Medicine, Sohag University. The study protocol was adherent to practice guidelines of the World Medical Association Code of Ethics (Declaration of Helsinki). A written informed consent was secured from each participant for participating in the study after

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explanation about the nature of the procedures, possible complications, benefits, and steps of the study.

Study design:

The current study is a cross-sectional study conducted among adult patients with FD according to Rome IV criteria.

Patients:

The studied population was composed of One hundred and twenty (120), consecutive adult patients with FD according to Rome IV criteria in Sohag University Hospital from November 2017 to May 2019.

1. Patients with FD according to Rome IV criteria and older than 18 years old were included in this study. Patients with the following conditions were excluded:

2. Patients with dyspepsia had been investigated previously by radiology, endoscopy or other tests and specific diagnosis established.

3. Patients with positive history of recent treatment with H2 receptor antagonists, proton pump inhibitors, and H. pylori eradication therapy within 4 weeks before being enrolled in the study.

4. Patients with prior upper GIT surgery.

5. Patients with chronic illnesses (Diabetes mellitus, renal, hepatic, Cardiac, thyroid disease, chronic pulmonary disease, Coagulopathy, malignancies).

6. Presence of major psychiatric disorders.

7. Pregnant women.

Methods:

All included patients were subjected to:

1. Detailed history, complete general and systemic examination with special emphasis on the GI manifestations.

2. Body mass index (BMI) calculation.

3. Abdominal ultrasound examination.

4. Laboratory investigations: blood picture, fasting, random blood glucose levels, blood urea, serum creatinine, liver function tests and H. pylori antigen in stool. The stool antigen test for H. pylori is a lateral flow chromatographic immunoassay for qualitative assessment of H. pylori depending on the use of monoclonal antibodies against H. pylori conjugated with colloid gold. The test was performed, as per the manufacturer instructions (On Site H. pylori Ag Rapid Test, CTK Biotech, USA).

5. Endoscopic examination was performed to all included FD patients after overnight fasting for at least 8 hour. EGD was performed using a standard electronic video endoscope (Pentax EG-3440, EG-2985; Tokyo, Japan), under local throat anesthesia with 10% xylocaine spray and light sedation in the left lateral position by the same endoscopist. The esophagus, stomach and duodenum were visualized and mucosal findings noticed. Patients in whom no endoscopic findings, (i.e. had normal mucosal appearance), were found in the esophagus, stomach, duodenal bulb, 2nd portion of the duodenum were enrolled and further evaluated by obtaining multiple biopsies.

6. Biopsy specimens were taken from the following sites according to the Sydney–Houston system for grading gastritis: greater, and lesser curvature of the distal antrum, greater and lesser curvature of the proximal corpus, and lesser curvature at the incisor angularis [7, 8]. Furthermore, multiple patch biopsies from the 1st and 2nd parts of the duodenum were taken. No samples were taken from the lower esophagus as patients with history or symptoms of reflux disease were not included, and this is in accordance with the recommendation of American Gastroenterological Association (AGA) guideline, 2015, that routine biopsy of normal esophagus or gastro esophageal junction (GEJ) in patients with dyspepsia alone would have very low probability of diagnosing esophageal abnormalities or have little impact on clinical management [9].

7. Histopathological examination was performed for all specimens at the Pathology Department, Faculty of Medicine, Sohag University Hospital. The specimens were fixed in 10% formalin, processed using paraffin embedding technique, sectioned at 4 micrometer perpendicular to the mucosal surface and stained with haematoxylin & eosin (H & E) and geimsa stain. All specimens were evaluated for the presence of H. pylori bacilli, mononuclear cells (lymphocytes, plasma cells and histiocytes) as markers of inflammation and polymorph nuclear leucocytes (neutrophils) as markers of

activity. The histopathological parameters were graded using the updated Sydney system to clarify the presence and severity of gastritis or duodenitis (Dixon et al., 1996).

Statistical analysis:

Data entry and analysis were done using SPSS version 24 IBM- Chicago, USA (May 2016).

Data was expressed into phases:

Descriptive: Mean value, Standard Deviation (SD) for quantitative data, frequency and percentage for qualitative data.

Analytic: quantitative data was analyzed using student t-test to compare means of two groups. Mann Whitney test was used in case of non-parametric data. Pearson Chi square was used to compare percentages of qualitative data, and Fisher's Exact test was used for non-parametric data.

For all these tests, the level of significance (P-value) can be explained as:

- Non-significant P > 0.05.
- Significant P < 0.05.
- Highly significant P < 0.001.

Results:

The current included 120 adult patients with FD according to Rome IV criteria, and they were assigned into two groups according to the stool H. pylori antigen.

I- Group I; included 69 (57.5%) patients who were positive for H. pylori stool antigen.

II- Groups II; included 51 (42.5%) patients who were negative stool H. pylori antigen. ***(Figure -1)***.

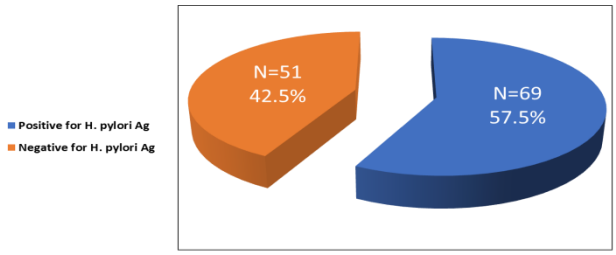

Fig.1: two groups of the studied patients using the stool H. pylori antigen.

As regards the demopghraphic characteritics of the studied patients; the mean age of patients in group 11 was higher significantly than group I (49.61±10.84, and 43.43±11.57 respectively) (p-value = 0.004). 50.7% of group I and 56.9% of group II were females, and there was non-significant statistical difference among both sex. 44 (36.7%) patients out of 120 patients with FD had history of smoking. Group II had more smokers (47.1%) than group I (29%) with significant statistical difference (p-value < 0.05). The mean of BMI was higher in group I than group II (24.97±4.10, and 22.73±2.68 respectively) with high significant statistical difference (p-value < 0.001). As regard BMI categories, 55.1% of group I and 82.4% were normal weight, 33.3% of group I and 15.6% of group II were overweight. Only 11.6% of group I, and 2% of group II were obese with significant statistical difference (p-value = 0.004). ***(Table -1).***

Table 1: Demographic characteristics of both groups of the studied patients.

Item		Group I (N=69) No %	Group II (N=51) No %	Chi square or T test	P value
Age	**Mean ± SD**	43.43±11.57	49.61±10.84	2.966	**0.004 (S)**
Sex	**Male**	34 (49.3%)	22 (43.1%)	0.444	0.505 (NS)
	Female	35 (50.7%)	29 (56.9%)		
Smoking	**Smoker**	20 (29%)	24 (47.1%)	4.125	**0.042 (S)**
	Non-smoker	49 (71%)	27 (52.9%)		
BMI	**Mean ± SD**	24.97±4.10	22.73±2.68	3.393	**< 0.001 (HS)**
	Normal	38 (55.1%)	42 (82.4%)	10.437	**0.004 (S)**
	Overweight	23 (33.3%)	8 (15.6%)		
	Obese	8 (11.6%)	1 (2%)		

Regarding, clinical presentation of the studied patients, table (2) shows that, shows that, in group I, the most common symptom was epigastric pain followed by postprandial fullness, early satiety, nausea, epigastric burning, vomiting, dysphagia and GIT bleeding (71%, 59.4%, 34.8%, 27.5%, 5.8%, 5.8%, 4.3%, and 1.4% respectively). On the other hand, the most common symptom in group II was postprandial fullness followed by early satiety, nausea, epigastric pain, vomiting, GIT bleeding, dysphagia, and epigastric burning (88.2%, 47.1%, 41.2%, 31%, 15.7%, 9.8%, 5.9%, and 2% respectively). There was no significant statistical difference between both groups regarding all symptoms except for each of epigastric pain which higher significantly in group I than group II (p-value < 0.001). Furthermore, postprandial fullness, and GIT bleeding were higher significantly in group II than group I (p-value < 0.001). Regarding family history of GI malignancy, only 7.8% of group II and 1.4% of group I had family history of GI malignancy. There was no significant statistical difference in both groups (p-value = 0.162).

Regarding the clinical subtypes of FD among all the studied patients, the proportion of PDS alone, EPS alone and PDS-EPS overlap was 45.8%, 29.2%, and 25% respectively. In group I, the most common clinical subtype was EPS followed by PDS then PDS-EPS overlap (37.7%, 33.3% and 29% respectively). On the other hand, the most common subtype in group II was PDS followed by PDS-EPS overlap then EPS (62.7%, 19.6% and 17.7% respectively). There was significant statistical difference between both groups regarding EPS which higher significantly in group I than group II (p-value < 0.001), and PDS was higher significantly in group II than group I (p-value < 0.001). ***(Figure-2).***

Table 2: Clinical presentation of both groups of the studied patients

Item	Group I (N=69) No %	Group II (N=51) No %	Chi square	P value
Epigasric pain	49 (71%)	16 (31%)	19.445	**< 0.001 (HS)**
Epigasric burning	4 (5.8%)	1(2%)	1.081	0.393 (NS)
Postprandial Fullness	41(59.4%)	45 (88.2%)	11.991	**< 0.001(HS)**
Early satiety	24 (34.8%)	24 (47.1%)	1.841	0.175 (NS)
Nausea	19 (27.5%)	21 (41.2%)	2.455	0.117 (NS)
Vomiting	4 (5.8%)	8 (15.7%)	3.187	0.074 (NS)
GIT bleeding	1 (1.4%)	5 (9.8%)	5.778	**< 0.001 (HS)**
Dysphagia	3 (4.3%)	3 (5.9%)	0.145	0.698 (NS)
F.H of GI malignancy	1 (1.4%)	4 (7.8%)	3.002	0.162 (NS)

Fig.2: Proportions of clinical subtypes of FD among the studied patients.

As shown in table (3), there was non-significant statistical difference between both groups regarding all laboratory investigations except for hemoglobin level and aspartate aminotransferase (AST), as the mean of hemoglobin level was highly significant in group I than group II (13.25±0.903, 12.63±0.736 respectively) (p-value < 0.001). Furthermore, the mean of AST was significant higher in group I than group II (26.96±6.85, 24.06±7.36 respectively) (p-value = 0.029).

It was founded that 79 (65.8%) patients out of 120 studied patients with FD had histopathological findings. In group I, histopathological findings were found in 61 (88.4%), while in group II, it was found in only 18 (35.3%) patients with high significant statistical difference (p-value < 0.001). ***(Figure-3).***

Table 3: Laboratory data of both groups of the studied patients.

Item		Group I (N=69)	Group II (N=51)	T- test	P-value
WBCs ($x10^3$/mL)	**Mean ± SD**	7.93±1.72	8.08 ± 1.77	0.470	0.640 (NS)
Hemoglobin (g/dL)	**Mean ± SD**	13.2 ± 0.903	12.63 ± 0.736	3.969	**< 0.001(HS)**
Platelet ($x10^3$/mL)	**Mean ± SD**	340.49±38.25	288.76±78.89	1.490	0.139 (NS)
ALT (IU/mL)	**Mean ± SD**	21.01±5.91	21.10±5.95	0.076	0.939 (NS)
AST (IU/mL)	**Mean ± SD**	26.96±6.85	24.06±7.36	2.217	**0.029 (S)**
Bilirubin (mg/dL)	**Mean ± SD**	0.816±0.194	0.796±0.180	0.571	0.569 (NS)
Albumin (mg/dL)	**Mean ± SD**	4.52±0.511	4.70±0.503	1.921	0.067 (NS)
INR	**Mean ± SD**	1.02±0.092	1.02±0.092	0.228	0.820 (NS)
Urea (mg/dL)	**Mean ± SD**	32.67±4.69	31.76±4.10	1.096	0.275 (NS)
Creatinine (mg/dL)	**Mean ± SD**	0.936±0.194	0.949±0.197	0.354	0.724 (NS)
Fasting blood glucose (mg/dL)	**Mean ± SD**	90.90±11.05	91.04±9.76	0.072	0.942 (NS)
Random blood glucose (mg/dL)	**Mean ± SD**	105.91±11.50	104.98±12.57	0.422	0.678 (NS)

ALT: Alanine aminotransferase **AST:** Aspartate aminotransferase

INR: International normalized ratio **WBCs:** White blood cells

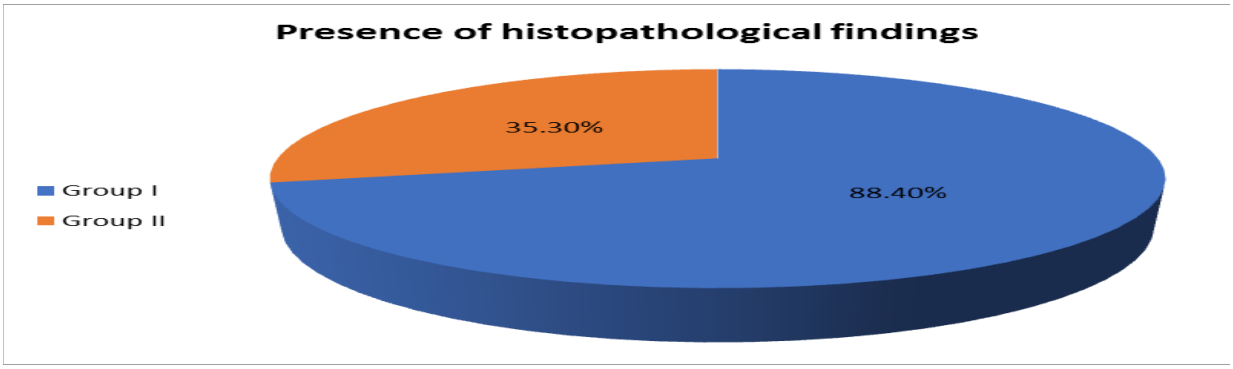

Fig. 3: Percentage of histopathological findings among both groups of the studied patients.

There were various types of histopathological findings seen among the studied patients. Most of group I patients (88.4%%) had histologic evidence of gastritis, while only 35.3% of group II patients had this histologic evidence of gastritis with high significant statistical difference (p-value < 0.001). In group I, mild gastritis was the most common histologic finding (65.2%) characterized by presence of neutrophilic infiltration (72.5%) within the gastric mucosa. On the other hand, in the group II, moderate gastritis was the commonest (19.6%) and neutrophilic infiltration was in only 27.5% with high significant statistical difference (p-value < 0.001). Glandular atrophy was detected in 43.5% of group I, and in only 15.7% of group II with high significant statistical difference (p-value < 0.001). Furthermore, intestinal metaplasia was detected in a minority of patients of both groups (8.7% and 2%, respectively) with non-significant statistical difference (p-value > 0.05). ***(Table-4)***.

In group I, H. pylori bacilli density was detected in 43 (62.3%) out of 69 patients, while it was not detected in 26 (37.7%) patients despite presence of positive stool H. pylori antigen. In group II, H. pylori density was detected in 19 (37.3%) patients despite the stool H. pylori antigen was negative. The degree of H. pylori density was mild in majority of both groups with significant statistical difference (p-value = 0.002). In group I, mild colonization Histologic duodenitis was detected in 68.1% of group I patients, and in only 33.3% of the group II patients was the most common followed by moderate then marked colonization (36.2%, 15.9%, and 10.2% respectively). On the other hand, in group II, mild colonization was the most common followed by moderate (31.4%, and 5.9%, respectively), while marked colonization was not found at all. ***(Table-4)***.

with high significant statistical difference (p-value < 0.001). The histopathological severity of duodenitis was commonly mild in both groups (34.8%, and 19.6% respectively) followed by moderate (27.5%, and 13.7% respectively) and marked duodenitis was found in only 5.8% of group I but not found at all in group II (p-value < 0.001). ***(Table-4)***.

In group I, the prevalence of microscopic duodenitis differ significantly in the presence or absence of gastritis (p-value < 0.001), however, this finding was similar in patients of group II. In group I, microscopic duodenitis was documented in 47 (77%) out of 61 patients with evidence of gastritis, however, it was not present in any patients with normal gastric histopathology. In group II, microscopic duodenitis was documented in 17 (94.4%) out of 18 patients with evidence of gastritis while it was not diagnosed in any patients with normal gastric histopathology (p-value < 0.001). In other words, in patients with functional dyspepsia, microscopic gastritis and duodenitis are completely independent findings in patients of group I, but these two conditions are strongly related to each other in group II patients. ***(Table-5).***

Table 4: Various histopathological lesions among both groups of the studied patients.

Type of histopathological Findings		Group I (N=69) No %	Group II (N=51) No %	Chi square	P value
Gastritis	Marked	5 (7.2%)	1 (2%)	44.018	< 0.001 (HS)
	Moderate	11 (15.9%)	10 (19.6%)		
	Mild	45 (65.2%)	7 (13.7%)		
	None	8 (11.6%)	33 (64.7%)		
Neutrophilic activity	Marked	4 (5.9%)	1 (2%)	26.257	< 0.001 (HS)
	Moderate	7 (10.1%)	5 (9.8%)		
	Mild	39 (56.5%)	8 (15.7%)		
	None	19 (27.5%)	37 (72.5%)		
Glandular atrophy	Marked	3 (4.3%)	1 (2%)	12.680	< 0.001 (HS)
	Moderate	6 (8.8%)	4 (7.8%)		
	Mild	21 (30.4%)	3 (5.9%)		
	None	39 (56.5%)	43 (84.3%)		

Intestinal metaplasia	**Mild**	6 (8.7%)	1(2%)	2.421	0.236 (NS)
	None	63 (91.3%)	50 (98%)		
H. pylori Density	**Marked**	7 (10.2%)	0 (0%)	11.732	**0.002 (S)**
	Moderate	11 (15.9%)	3 (5.9%)		
	Mild	25 (36.2%)	16 (31.4%)		
	None	26 (37.7%)	32 (62.7%)		
(Duodenitis)	**Marked**	4 (5.8%)	0 (0%)	15.524	**<0.001 (HS)**
	Moderate	19 (27.5%)	7 (13.7%)		
	Mild	24 (34.8%)	10 (19.6%)		
	None	22 (31.9%)	34 (66.7%)		

Table 5 : Duodenitis with respect to presence of gastritis among both groups of the studied patients.

Duodenitis	**Gastritis in Group I**		**Gastritis in Group II**	
	Positive	***Negative***	***Positive***	***Negative***
Positive	47 (77%)	0 (0%)	17 (94.4%)	0 (0%)
Negative	14 (23%)	8 (100%)	1 (5.6%)	33 (100%)
Total	61 (100%)	8 (100%)	18 (100%)	33 (100%)
Chi square	19.332		46.750	
P value	**< 0.001 (HS)**		**< 0.001 (HS)**	

The present study showed that; In group I, there was non-significant statistical difference between FD symptoms, presence or absence of histologic gastritis, neutrophilic infiltration, and glandular atrophy except for early satiety, and for epigastric burning as regards presence of histologic duodenitis.

In group II, there was non-significant statistical difference between FD symptoms, presence or absence of histologic gastritis, duodenitis, neutrophilic infiltration and glandular atrophy.

In both groups, there was non-significant statistical difference between FD symptoms and presence or absence of intestinal metaplasia as well as H. pylori bacilli density.

3 Discussion

FD is a common worldwide problem, affecting 5-20% of the population globally, often impacts on quality of life and work productivity [5]. H. pylori infection is a widespread and endemic disease especially in the developing countries [10]. In Egypt, the prevalence reaches up to 90% in adults, in Middle East countries such as Saudi Arabia, Oman, Palestine, Libya, Morocco and Jordan, its prevalence ranges from 60-90%, as documented by World Gastroenterology Organization (WGO) [11]. It has been shown that, the rate of H. pylori is higher in patients with dyspeptic symptoms, and the prevalence of H. pylori in

patients suffering from dyspepsia has been proven to be higher than for the normal population [12].

The aim of this study was to study clinical, laboratory, imaging, endoscopic and histopathological features of patients with FD according to Rome IV criteria in Sohag University Hospitals.

In the present study, stool *H. pylori* antigen test is used for detection of *H. pylori* infection in the studied FD patients due to two main reasons. The first one was to reflect real life scenario that most of the clinicians in our locality usually do as, they usually rely on *stool H. pylori* antigen for detection and diagnosis of *H. pylori* infection. The second one was due to limited availability, and expense of urea breath test (UBT). Similar to the results of this study, ***Konduk et al.***, reported that the overall *H. pylori* infection prevalence was 54.2% (n = 71/131) [13]. Similiary, ***Shrivastava et al***, [14] and ***Mirbagheri et al***, [15] reported that, *H. pylori* infection was found in 67.3% and 65% cases of FD. In contrast to the findings of this study, a prospective study from Korea using standard endoscopy to predict the status of *H. pylori* infection in dyspeptic patients reported lower rates of the prevalence of *H. pylori* (9.4%) of patients with normal vascular patterns [16]. This could be explained by variations in the prevalence of *H. pylori* according to geographic area, age, and socioeconomic status, furthermore, there is a variation in diagnostic methods which may further contribute to different rates of detection [17].

In the present study, the mean age of patients in group 11 was higher significantly than group I (49.61±10.84,and 43.43±11.57 respectively) (p-value = 0.004). 50.7% of group I and 56.9% of group II were females, there was non-signifncant statistical difference among both sex. Similar to the results of this study, ***Konduket et al.,*** eported that**,** the mean of age of the patients was 46.0±16.0 years in both groups [13]. Among all patients, 77 (58.8%) were females and 54 (41.2%) were males in their study. Several studies reported that, the female sex was significantly connected with FD [18, 19]. In a population-based study in Australia, the preponderance of female was statistically higher than in males in most of the FGIDs including FD [19], and a meta-analysis also revealed that the female sex (OR, 1.24; 95% CI, 1.13–1.36) was one of the independent risk factors for uninvestigated dyspepsia [2]. Regarding the relationship between gender, and FD, the differences in sex hormones affect gastric motility and visceral sensitivity. The female hormones, such as estrogen and progesterone, altered gastric emptying [20]. Also in study of ***Mirbagheri et al,*** the mean age of the patients was 39.1 ± 13.6, their study included sixty-five patients (29.9%) were male while 152 (70.1%) were females [15], which is in line with the results of this study. Similar to the results of this study, ***Asfeldt et al,, Alazmi et al., and Okumura et al.,*** reported that, there was no significant statistical difference between males and females [21, 22, 23].

The mean of BMI was higher in group I than group II (24.97±4.10, 22.73±2.68 respectively) with high significant statistical difference (p-value < 0.001). Most of both groups were normal weight (55.1%, 82.4% respectively), 33.3% of group I and 15.6% of group II were overweight. Only 11.6% of group I, and 2% of group II were obese with significant statistical difference (p-value = 0.004). An association BMI and dyspepsia was recognized, some studies reported an association between obesity and dyspeptic symptoms, but subjects with GERD may not have been excluded [24, 25]. A large community based study based on the general practice research database in various regions in the United Kingdom reported a weak association between an increased BMI and dyspepsia (odds ratio "OR" 1.1) among 6913 adult subjects [26]. ***Rocco et al.,*** found no association between BMI and FD, they found instead that subjects with FD, and in particular those with epigastric pain, had a statistically significant reduced BMI [27]. Clinical studies have shown a sizeable and statistically significant association between FD and weight loss, and their result seems to be in line with these data [28].

Regarding smoking, this study revealed that, 44 (36.7%) patients out of 120 patients with FD had history of smoking. Group II had more smokers (47.1%) than group I (29%) with significant statistical difference (p-value = 0.04). ***Gado et al.,*** reported in their study that 32% of patients had history of smoking [29], which is close to the results of this study. The Norway study showed that smoking was a risk factor for FD, but the Swedish study and a study on selected patients did not confirm this [24]. ***Khalifa et al.,*** found that 36 out of one hundred non-ulcer dyspepsia (36%) patients were non-smokers and *H. pylori* negative [30]. However, in this study, we found 29 out of 51 (56.9%) FD patients were non-smokers and stool *H. pylori* negative. This could be explained by there are only limited data from the literature available to show to what degree of the cigarette smoking with *H. pylori* incidence as risk factors in FD patients**.**

Regarding, clinical presentation of the studied patients, in group I, the most common symptom was epigastric pain followed by postprandial fullness, early satiety, nausea, epigastric burning, vomiting, dysphagia and GIT bleeding (71%, 59.4%, 34.8%, 27.5%, 5.8%, 5.8%, 4.3%, and 1.4% respectively). On the other hand, the most common symptom in group II was postprandial fullness followed by early satiety, nausea, epigastric pain, vomiting, GIT bleeding, dysphagia, and epigastric burning (88.2%, 47.1%, 41.2%, 31%, 15.7%, 9.8%, 5.9%, and 2% respectively). There was no significant statistical difference between both groups regarding all symptoms except for each of epigastric pain which higher significantly in group I than group II (p-value < 0.001). Furthermore, postprandial

fullness, and GIT bleeding were higher significantly in group II than group I (p-value < 0.001). Regarding family history of GI malignancy, only 7.8% of group II and 1.4% of group I had family history of GI malignancy. There was no significant statistical difference in both groups (p-value = 0.162). Similar to the results of this study, ***Shrivastava et al.***, ***and Mirbagheri et al.,*** demonstrated that, the epigastric pain was the most common symptoms and significantly associated with *H.pylori* infection (p-value = 0.012), thus favoring its role in dyspepsia symptom generation [14, 15]. Furthermore, this was similar to ***Bazzoli et al.,*** and ***Shimatani et al.,*** who have shown an association between *H. pylori* infection and epigastric pain [31, 32]. On the other hand, ***Sarnelli et al.,*** demonstrated no differences in the clinical presentation of FD patients with or without *H. pylori* infection [33]. In a population study carried out in Asia, the authors detected 20.2% of epigastric pain and only 2.1% of heartburn [34]. This variation that was observed in different countries can suggest a difference in the GI symptoms development pattern between the Eastern and Western populations and different diagnosis instruments used.

Regarding clinical subtypes of FD, the proportion of PDS alone, EPS alone and PDS-EPS overlap was 45.8%, 29.2%, and 25% respectively, among all the studied patients. In group I, the most common clinical subtype of FD was EPS followed by PDS then PDS-EPS overlap (37.7%, 33.3% and 29% respectively). On the other hand, the most common subtype in group II was PDS followed by PDS-EPS overlap then EPS (62.7%, 19.6% and 17.7% respectively). There was significant statistical difference between both groups regarding EPS which higher significantly in group I than group II (p-value < 0.001), and PDS was higher significantly in group II than group I (p-value < 0.001). In adults, some studies have shown good separation of PDS and EPS while others have reported significant overlap of the two subtypes [35]. It appears that separation is better in the general population than in patients who seek medical care [36]. Similar to the results of this study, ***Sung et al.,*** revealed that, the proportion of PDS alone, EPS alone and PDS-EPS overlap was 46.6%, 29.0%, and 24.4%, respectively [37], this was in line with previous studies, that reported that, the proportion of PDS was higher than that of EPS. ***Kim et al.,*** showed that the proportion of PDS, EPS, and PDS-EPS overlap in patients with health checkups was 68.2%, 46.4%, and 14.6%, respectively [38], this explained by, dietary habits affects the results as the participants in the Indian study were mostly vegetarian (97%) [39, 40]. In contrast, the Taiwanese study reported that 71.9% of 491 patients with FD had a PDS subtype and 34.4% had an overlap of EPS and PDS [41]. Whereas the EPS and PDS syndromes can be discriminated better in population-based studies, significant overlap was observed in hospital-based studies [36]. The association of *H. pylori* with FD and its subgroups has been reported with inconsistent results in several observational studies [24, 39, 42]. ***Aro et al.,*** and ***Zagari et al.***, found no significant association of *H. pylori* with FD in Western populations [24, 39]. Of the three trials that showed a benefit of *H. pylori* eradication on FD, there were no significant differences between subgroups ***(Gwee et al., 2009, Mazzoleni et al., 2011)***, [43, 44], by contrast, ***Lan et al. (2011)***, reported a significant effect only in the EPS subgroup [45]. The contradictory results might result from differences in the definitions of subgroups, efficacies of eradication regimens, *H. pylori* infection prevalence and the ethnic groups [42].

In the present study, there was non-significant statistical difference between both groups regarding all laboratory investigations except for hemoglobin level and aspartate aminotransferase (AST), as the mean of hemoglobin level was highly significant in group I than group II (13.25±0.903, 12.63±0.736 respectively) (p-value < 0.001). Furthermore, the mean of AST was significant higher in group I than group II (26.96±6.85, 24.06±7.36 respectively) (p-value = 0.029). ***Konduk et al.,*** reported that there were no differences in blood biochemical parameters of the patients with and without *H. pylori* in terms of hemoglobin, hematocrit, mean corpuscular volume, Fe2+, transferrin saturation, total iron binding capacity, and folic acid levels [13].

In the present study, it was founded that 79 (65.8%) patients out of 120 studied patients with FD had histopathological findings. In group I, histopathological findings were found in 61 (88.4%), while in group II, they were found in only 18 (35.3%) patients with high significant statistical difference (p-value < 0.001). In agreement with the results of this study, ***Singh et al.***, ***Dawod, and Emara***, reported that, the histopathological findings and a high degree of inflammation were observed in 65.7% [40, 46]. Furthermore, this is also in accordance with ***Arruda et al.***, who studied 40 dyspeptic patients (28 women and 12 men) with endoscopically normal stomach and found 72.5% of patients had gastritis by histological examination [47]. ***Garg et al.,*** reported in their studies a lower rate of inflammation in the gastric biopsies (20 and 32% respectively) of dyspeptic cases with a normal endoscopy [48]. This difference may be attributed to difference in the prevalence of *H. pylori* infection which is higher among Egyptian patients. This emphasizes the role of biopsy in examining a case of dyspepsia as the normal endoscopy does not rule out underlying pathology. The relation between *H. pylori* infection and presence of histopathological findings was noted in this study, as *H. pylori* was present in 61 out of 79 patients with histopathological findings, only in 18 out of 41 patients without findings, and the difference was statistically significant (p-value < 0.001), this is matching with ***Dawod, and Emara,*** that noted in their study, *H. pylori* was present in 54 out of 69 patients with histopathological findings, in only 6 out of 36 patients without findings, and the difference was statistically significant (p-value = 0.04) [46].

The present study showed that, various type of histopathological findings were detected among the studied FD patients. Most of group I patients (88.4%%) had histologic evidence of gastritis, while only 35.3% of group II patients had this histologic evidence of gastritis with high significant statistical difference (p-value < 0.001). In group I, mild gastritis was the most common histologic finding (65.2%) characterized by presence of neutrophilic infiltration (72.5%) within the gastric mucosa. On the other hand, in the group II, moderate gastritis was the commonest (19.6%) and neutrophilic infiltration was in only 27.5% with high significant statistical difference (p-value < 0.001). In agreement with the findings of this results, ***Emara et al***., observed that, in the stool *H. pylori* positive group, chronic active gastritis was the most common histologic finding, characterized by neutrophilic infiltration within the gastric mucosa [49]. On the other hand, patients with negative stool *H. pylori* testing showed picture of chronic inactive gastritis (infiltration of the gastric mucosa by plasma cells and lymphocytes). Similiary, ***Dawod and Emara,*** reported that, chronic inflammation was present in 65.7% of patients with FD [46]. Furthermore, ***Singh et al.,*** revealed that**,** chronic inflammation was present in 84 (82.3%) patients with FD on gastric biopsy, and neutrophilic infiltration was seen in 63 (61.7%) patients of non-ulcer dyspepsia on gastric biopsy which was close to the findings of this study [40].

In the present study, glandular atrophy was detected in 43.5% of group I, and in only 15.7% of group II with high significant statistical difference (p-value < 0.001). This was similar to results of the study of ***Nwokediuko and Okafor***, who reported that, glandular atrophy was in 42.7% patients of FD and it was of mild grade in 28.1%, moderate grade in 53.1% and severe grade in 18.7% patients [50]. Similiary, ***Dawod, and Emara***, reported that, glandular atrophy was present in 42.8% of patients with FD [46], however, previous results were less than those reported by ***Singh et al.,*** who found that, glandular atrophy was seen in 10 (9.8%) patients of FD on gastric biopsy and was of mild grade [40]. This difference may be due to including patients with FD and positive H. pylori infection only in their studies. Furthermore, ***Shafii et al.,*** reported that, patients with mild chronic gastritis are less probable to reflect atrophy [51]. Even when extensive biopsy protocols are used, inevitable sampling errors may affect the documentation of the atrophic foci, which are frequently patchy [52].

In the present study, intestinal metaplasia were detected only in a minority of patients of both groups (8.7% and 2%, respectively) with non- significant statistical difference (P value > 0.05).This was similar to results of the study of ***Emara et al.***, who found that advanced stages of gastric mucosal pathology including intestinal metaplasia and dysplasia were detected only in a minority of patients (0.7% and 5.3%, respectively), in absence of statistical difference [49]. Furthermore, ***Singh et al.,*** found that intestinal metaplasia was seen in 4 (3.9%) patients of FD on gastric biopsy and was also of mild grade [40]. Similarly, ***Dawod, and Emara,*** reported that, intestinal metaplasia was present in 5.7% of patients with FD [46].

The present study showed not all patients of group I demonstrated *H. pylori* bacilli in their histopathological examination, as well as not all patients of group II showed absence of *H. pylori* bacilli in histopathological examination. In group I, *H. pylori* bacilli density was not detected or absent in 26 (37.7%) out of 69 patients, while it was detected in 19 (37.3%) out of 51 patients of group II. The degree of *H. pylori* density was mild in majority of both groups with significant statistical difference (p-value = 0.002). In group I, mild colonization was the most common followed by moderate then marked colonization (36.2%, 15.9%, and 10.2% respectively). On the other hand, in group II, mild colonization was the most common followed by moderate (31.4%, and 5.9%, respectively), while marked colonization was not found at all. In agreement with this findings, ***Emara et al.***, observed that**,** not all stool *H. pylori* positive patients (n = 80) showed detectable *H. pylori* bacilli (67 patients, 83.8%) in their histopathological examination [49]. This may point to patchy distribution of the organism and the need for more endoscopic biopsies. The other surprising finding was that despite testing negative for stool *H. pylori* antigen (n = 71) still 34 patients (47.9%) of the group II had the bacilli seen in their histology examination. In a systematic review concerning patients from Middle east regions including Egypt, the prevalence of *H. pylori* density was high in patients with histological features of gastritis [12], results that were also reported from different areas around the world [53, 54], among all patients with histological features of gastritis (N = 146, 96.7%), the prevalence of *H. pylori* (detected in the histology) was 69.2% (N = 101). Furthermore, this was reported by ***Dawod and Emara*** [46], who reported rates of 51.4%, and from other geographic areas emphasizing that, *H. pylori* as the most common and most important cause of gastritis [55, 56].

The detection of *H. pylori* bacilli in patients who initially tested negative for this organism by stool *H. pylori* antigen is an important finding of this study and this raises many questions. The first is regarding the accuracy of *H. pylori* stool antigen as a reliable diagnostic test for *H. pylori* infection. In fact the accuracy of *H. pylori* stool antigen test is affected by many factors. Its efficacy is lower when the stool is unformed or watery, because *H. pylori*-specific antigens in the stool samples are diluted. Temperature (needs lower temperatures) and the interval between stool sample collection and measurement also affect the results [57].

The second is the value of gastric mucosal biopsy in apparently non-inflamed or minimally inflamed gastric

mucosa of dyspeptic patients in absence of gross features as erosions or ulcer. In fact many authors [50, 46], found high prevalence of gastric mucosal inflammation among dyspeptic patients with apparently normal upper endoscopy. The problem of dealing with apparently normal gastric mucosa in dyspeptic patients had been resolved by ***AGA guidelines (2015)*** [9]. They recommended that patients undergoing upper endoscopy for dyspepsia as the sole indication, should be exposed for routine biopsies of the normal-appearing gastric body and antrum for the detection of *H. pylori* infection if the *H. pylori* infection status is unknown whatever the immune status of the patient. They suggested following the 5-biopsy Sydney System with all specimens placed in the same jar [8].

Another important finding of this study is the inability to detect *H. pylori* bacilli in the stained slides from patients with positive stool *H. pylori* antigen. This may be due to several reasons. The first may be the uneven distribution of the infection [58], especially if patients were taking PPI for long period [59]. The second may be non-sufficient four samples policy and the need for more biopsies covering a wide area of gastric mucosa [60, 58], and the ***AGA guideline (2015),*** recommended five biopsy sites including two from the gastric antrum, two from the gastric body and one from the incisura when detection of *H. pylori* is an intent [8, 9, 61]. The third one again is the validity of *H. pylori* stool antigen as a reliable test for diagnosis of *H. pylori* infection. In fact the accuracy of *H. pylori* stool antigen test is comparable to UBT when performed under certain precautions: the usage of monoclonal antibodies rather than polyclonal ones, enzyme immune assay versus immune chromatography, and stoppage of PPIs, antibiotics 2 weeks prior to the test [59]. For patients unable to stop PPIs therapy 2 weeks prior to stool antigen testing, positive test results can be considered as true positive whereas negative results may represent false negatives and should be confirmed with repeat testing 2 weeks after stopping PPIs therapy[59]. However, all patients in this study stopped the use of PPIs and antibiotics 4 weeks in advance we cannot guarantee that all patients were compliant with our instructions, particularly some of them were of low socioeconomic and educational class. Another possible cause for this discrepancy is using geimsa stain in detecting *H. pylori* organisms in the gastric mucosa biopsies, which seem to be less sensitive.

The current study showed that, histologic duodenitis was detected in 68.1% of group I patients, and in only 33.3% of group II patients with high significant statistical difference (p-value < 0.001). The histopathological severity of duodenitis was commonly mild in both groups (34.8%, and 19.6% respectively) followed by moderate (27.5%, and 13.7% respectively) and marked duodenitis was found in only 5.8% of group I but not found at all in group II (p-value < 0.001). In line with this results, ***Basavraj et al.,*** found that, most of the patients had duodenitis (47 out of 60, i.e., 78.4% cases) on histopathology with a predominantly mild grade of inflammation [62]. A similar finding was observed in studies conducted by ***Futagami et al.*** and ***Mirbagheri et al.***, where histological duodenitis was a common finding in cases of FD, especially PI-FD, suggesting that at least some represent part of a spectrum of subclinical peptic disease or PI-FD [63, 14]. This chronic duodenal low-grade inflammation is contributory to persistent dyspeptic symptoms in this subset of cases even after treatment. Several infections such as *H. pylori* infections, as well as other gut infections such as salmonella and shigella have been associated with a subset of FD patients [64]. The results of this study showed that, there is an association between *H. pylori* infection and duodenitis in patients with FD which is similar to results of ***Mirbagheri et al.***, who found in their study that, the presence of *H. pylori* infection and microscopic duodenitis were strongly related to each other [14], a finding that supports the limited evidence in the literature [65, 66]. Furthermore, ***Mirbagheri et al.***, have observed that histological duodenitis is often associated with *H. pylori* (75%-82%) [14], therefore, the presence of *H. pylori i*nfection also increased the severity of duodenitis and the latter resulted in aggravating the symptom severity in FD patients.

In this study, in group I, the prevalence of microscopic duodenitis differ significantly in the presence or absence of gastritis (p-value < 0.001), however, this finding was similar in patients of group II. In group I, microscopic duodenitis was documented in 47 (77%) out of 61 patients with evidence of gastritis, however, it was not present in any patients with normal gastric histopathology. In group II, microscopic duodenitis was documented in 17 (94.4%) out of 18 patients with evidence of gastritis while it was not diagnosed in any patients with normal gastric histopathology (p-value < 0.001). In contrast to our results, ***Mirbagheri et al.***, found that, the prevalence of microscopic duodenitis did not differ significantly in the presence or absence of gastritis (105 (81.4%) out of 129 vs. 15 (88.2%) out of 17 patients, respectively, (p- value = 0.74) [14]. However, this finding was violated in the absence of *H. pylori* infection. This may be explained by the independent nature of microscopic duodenitis from microscopic gastritis in *H. pylori*-infected patients in ***Mirbagheri et al,*** was not proven to be true in non-infected subjects with *H. pylori* [14]. Furthermore, most of the subjects in their study suffering from FD were females (70.1%), with presence of statistical difference while previous studies reported no significant difference between males and females in this regard [21, 22, 23], this is matching with this study. However, complementary studies are needed to confirm or reject this finding.

In the current study, regarding the association between clinical symptoms of FD with respect to presence of histopathological findings among both groups of the study, the findings were, in group I, there was non-significant statistical difference between FD symptoms,

presence or absence of histologic gastritis, neutrophilic infiltration, and glandular atrophy except for early satiety, and epigastric burning as regards presence of histologic duodenitis. On other hand, In group II, there was non-significant statistical difference between FD symptoms, presence or absence of histologic gastritis, duodenitis, neutrophilic infiltration and glandular atrophy. In both groups, there was non-significant statistical difference between FD symptoms and presence or absence of intestinal metaplasia as well as *H. pylori* bacilli density. There are a limited data from the literature available to show the association of FD symptomatology with histopathological findings.

Limitations:

There were some limitations in this study.

1. First, H. pylori infection was confirmed only by the stool H. pylori antigen, however, its sensitivity and specificity are lower than invasive tests.
2. Second, the results of stool antigen test may be influenced by patients compliance.

Conclusion and recommendations:

All physicians dealing with patients with FD should be aware that, All FD patients should be underwent upper endoscopy for dyspepsia, and should be exposed for routine biopsies of the normal-appearing mucosa for histopathological examination, and detection of H. pylori infection.

For FD patients having stool H. pylori negative, further studies are needed to be established the exact cause of symptoms and possible treatment.

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Conflict of interest:

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