Prevalence of Gastro-Esophageal Reflux Disease in Patients with Interstitial Lung Disease: A Case Control Study in Egyptian Patients

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Background and study aims: It is unknown whether the gastro-esophageal reflux disease (GERD) is a cause or consequence of interstitial lung disease (ILD). This study aimed to determine the prevalence of gastro-esophageal reflux disease in patients with interstitial lung disease and to show the correlation between them.

Patients and Methods: From April 2020 to May 2022, we have prospectively analyzed the data of 210 patients with interstitial lung disease who had GERD according to Hull Airway Reflux questionnaire and Los Anglos classification of GERD in upper gastrointestinal (GI) endoscopy and 210 controls without any respiratory disease who performed upper GI endoscopy for any cause. We used binary logistic regression analysis to determine the factors associated with ILD or GERD among the studied participants.

Results: In the study sample, the prevalence of GERD was significant among ILD patients (52.4%) compared to controls (38.6%) (p=0.004).Binary logistic regression analysis revealed that smoking (OR=3.98, 95%CI: 2.44-6.50), GERD (OR=1.59, 95%CI: 1.04-2.46), forced vital capacity (OR=0.95, 95%CI: 0.91-0.99) were the main predictors of ILD, while on analysis of the predictors of GERD, ILD (OR=1.67, 95%CI: 1.10-2.53) and FEF25-75 (OR= 1.06, 95%CI: 1.03-1.09) were the most significant predictors.

Conclusion: The prevalence of GERD in the patients with interstitial lung disease was high and may be an important contributor to the development of interstitial lung diseases .

INTRODUCTION

Interstitial lung disease (ILD) is an umbrella of a large group of respiratory disorders including idiopathic pulmonary fibrosis (IPF), systemic sclerosis (SS), interstitial pneumonia, nonspecific interstitial pneumonitis, hyper-sensitivity pneumonitis, sarcoidosis and asbestosis **[1]**. ILD is characterized by cellular and extracellular infiltrates distal to the

terminal bronchioles or acini causing pulmonary scarring and irreversible lung damage **[2]**. Symptoms of ILD include dyspnea, nonproductive cough, fatigue and weight loss and decreased exercise tolerance **[3]**. Gastroesophageal reflux disease (GERD) develops from reflux of the gastric contents causing troublesome symptoms and/or complications. Classical manifestations of GERD are heartburn and regurgitation "typical symptoms" and a series of extra-esophageal symptoms "atypical symptoms" as chronic cough, laryngitis, asthma, pharyngitis, sinusitis, recurrent otitis media and idiopathic pulmonary fibrosis **[4]**. GERD causal role in ILD has been only speculated and sub-types of ILD that have been associated with GERD with varying degrees of evidence are SS, IPF, obliterative bronchiolitis, and alveolar proteinosis **[5]**. Moreover, GERD in ILD patients was frequently asymptomatic and typical symptoms often didn't allow making a certain diagnosis so, all ILD patients should be screened for GERD as prominent etiological factor of ILD **[6]**. This study aimed to determine the prevalence of gastro-esophageal reflux disease in patients with interstitial lung disease and to show the correlation between them.

PATIENTS AND METHODS

This multi-center prospective case-control study was conducted on 210 patients with interstitial lung disease and 210 controls without any respiratory disease who performed upper GI endoscopy for any cause between April 2020 and May 2022. A well-written informed consent was given by all the participants prior to the initiation of study in routine clinical practice at five highly specialized treatment centers especially concerned with GERD management (Menoufia University Hospitals, National Liver Institute Hospital, Shebin El-Kom Chest Hospital, Shebin Elkom Teaching Hospital and Al-Hussein University hospital). Each patient had an established diagnosis of interstitial lung disease that was confirmed by pulmonologist after preforming pulmonary function tests included {forced vital capacity (FVC), forced expiratory volume in the first second (FEV1) and forced expiratory flow 25–75% (FEF25-75)} and high resolution computed tomography (HRCT) chest in the prone position. All causes of interstitial lung disease as sarcoidosis, pneumoconiosis, hypersensitivity pneumonitis, cryptogenic organizing pneumonitis and idiopathic pulmonary fibrosis were included in this study. All participants answered a Hull Airway Reflux questionnaire (HARQ) with typical symptoms were defined as heartburn, regurgitation, chest pain and atypical symptoms such as cough, dyspnea on exertion, belch, dysphagia, globus sensation, hoarseness of voice and epigastric pain. Also, upper GI endoscopy (Olympus CV240, Tokyo, Japan) was performed to all participants. The diagnosis of GERD was established according to the result of Hull Airway Reflux questionnaire and Los Anglos classification (Grades A, B, C, D) in upper GI endoscopy. In addition, lifestyle factors as smoking status history was taken (smoker, ex-smoker or non-smoker) and body mass index (BMI) was calculated as kg/m2, was defined as underweight when < 18, overweight when ≥25 and < 30, and obese when ≥30.

Statistical analysis:

Analyses were performed using SPSS version 28.0 [SPSS Inc., Chicago, IL, USA]. Shapiro-Wilk test as one of the normality tests was conducted to ascertain the normality of distribution. Independent t test was used for parametric data while Mann-Whitney test was used for non-parametric data. Chi-Squared ($\chi 2$) and Fisher's exact tests were used for qualitative variables. Spearman correlation was applied to assess the strength and direction of association between GERD and pulmonary function tests. Binary logistic regression analyses were performed to detect the independent predictors for ILD and GERD. Multiple comparisons were tested using Holm Bonferroni Sequential Correction: An EXCEL Calculator" © Justin Gaetano, 2013. P-values are statistically significant after this correction.

RESULTS

As regards the demographic characteristics of the studied ILD patients, 114 were males and 96 were females while, their ages ranged from 43-62years (51.18± 9.32). BMI and smoking were significantly higher among ILD patients than controls. Dyspepsia (17.6%, p=0.005), hoarseness of voice (7.1%, p<0.001), persistent vomiting (21.4%, p=0.011) and persistent abdominal pain (21.0%, p<0.001) were the most presenting complaints among ILD patients.

General examination revealed a significantly higher prevalence of eye puffiness (2.9%, p=0.030), fine tremors (6.7%, p<0.001), wheezes (14.3%, p<0.001) and crepitation (16.7%, p<0.001) among ILD patients compared to controls. Local examination presented non-significant findings except hypochondrial tenderness which was the most prominent finding among controls (P=0.033). **(Table 1)**

Laboratory investigations including Albumin (p<0.001), ALT (p=0.011), AST(p=0.005), urea (p=0.003) and creatinine (p=0.005) were significantly increasing among ILD patients. X ray analysis revealed a significantly prominent reticular finding (21.0%, P<0.001), while abdominal U/S presented fatty liver and chronic calcular cholecystitis as the main findings among ILD patents (p=0.010). **(Table 2)**

GERD was significantly presented among ILD patients (52.4%) compared to controls (38.6%) (p=0.004). **(Fig 1)** Pulmonary function tests including FVC, FEV1, and FEF25-75 were significantly decreasing among ILD patients. **(Fig 2)** When ILD patients with and without GERD were compared, the results revealed that FVC and FEF25-75 were significantly decreasing among GERD patients. **(Fig 3).** There was significant negative correlations between stages of GERD and pulmonary function tests, with FVC (rs= - 0.726, 95%CI: [-0.809]- [-0.615] , p<0.001), FEV1(rs= - 0.456, 95%CI: [-0.602]- [-0.282] , p<0.001), FEV1/FVC(rs= -0.429, 95%CI: [-0.579]- [-0.250] , p<0.001) and FEF 25-75(rs= - 0.702, 95%CI: [-0.791]- [-0.583], p<0.001). **(Fig 4)**

Binary logistic regression analyses were conducted to assess the predictors of ILD, and GERD and they revealed that smoking (OR=3.98, 95%CI: 2.44-6.50), GERD] (OR=1.59, 95%CI: 1.04-2.46), FVC (OR=0.95, 95%CI: 0.91-0.99) were the main predictors of ILD, while on analysis of the predictors of GERD, ILD (OR=1.67, 95%CI: 1.10-2.53) and FEF25-75 (OR= 1.06, 95%CI: 1.03-1.09) were the most significant predictors. **(Table 3)**

Table 1: General characteristics, complaint, clinical examination and GERD of the studied ILD patients and controls:

	Groups				Test of sig	P value
	ILD patients (No.=210)		Controls (No.=210)			
	no	%	No	%		
Age (years) (Mean± SD)	**51.18± 9.32**		**50.15± 9.08**		1.14	0.253
BMI (kg/m2) (Mean± SD)	**24.04± 4.92**		**22.52± 3.30**		3.70	<0.001*
Sex						
Male	114	54.3	109	51.9	0.23	0.625
Female	96	45.7	101	48.1		
Smoking						
Smoker	49	23.3	29	13.8	47.21	<0.001*
Ex-smoker	33	15.7	0	0.0		
Non-smoker	128	61.0	181	86.2		
Complaint						
Anemia and/or anorexia	3	1.4	11	5.2	1.91	0.056
Dyspepsia	37	17.6	17	8.1	2.76	0.005*
Hoarseness of voice	15	7.1	0	0.0	3.67	<0.001*
Dysphagia	13	6.2	13	6.2	-	-
Heart burn	25	11.9	29	13.8	0.44	0.662
Halitosis	0	0.0	2	1.0	0.76	0.446
Persistent vomiting	45	21.4	24	11.4	2.54	0.011*
Persistent abdominal pain	44	21.0	85	40.5	4.22	<0.001*
Hematemesis and/or Melena	28	13.4	20	9.6	1.07	0.285
Screening for varices	0	0.0	9	4.3	2.7	0.006*
General Examination						
Eye puffiness	6	2.9	0	0.0	6.08	0.030*[FE]
Pallor	18	8.6	23	11.0	0.67	0.411
Cachexia	12	5.7	7	3.3	1.37	0.240
Fine tremors	14	6.7	0	0.0	14.48	<0.001*
Wheezes	30	14.3	4	1.9	21.63	<0.001*
Crepitations	35	16.7	0	0.0	38.18	<0.001*
Local examination						
Abdominal distension	5	2.4	0	0.0	1.81	0.070
Ascites	5	2.4	6	2.9	0.02	0.987
Hepatosplenomegaly	18	8.6	14	6.7	0.55	0.583
Epigastric tenderness	34	16.2	46	21.9	1.36	0.172
Hypochondrial tenderness	6	2.9	17	8.1	2.12	0.033*
Free	142	67.6	127	60.5	1.41	0.157

*: Significant, BMI Body mass index

Table 2: Laboratory investigations of the studied ILD patients and controls:

	Groups				Test of sig	P value
	ILD (No.=210)		Controls (No.=210)			
	Mean± SD		Mean± SD			
Albumin	4.14± 0.80		4.40± 0.67		3.55	<0.001*
ALT	30(12-452)		28(15-100)		2.55	0.011*
AST	30(12-130)		29(17-78)		2.83	0.005*
Urea	34(10-87)		36(17-98)		2.94	0.003*
Creatinine	1.0(0.5-2.6)		0.9(0.4-3.0)		2.80	0.005*
Hemoglobin	11.84± 1.83		11.99± 2.02		0.80	0.422
Helicobacter Pylori: no, %						
Yes	70	33.3	58	27.6	1.61	0.203
No	140	66.7	152	72.4		
X-ray: no, %						
Reticular	44	21.0	0	0.0	49.14	<0.001*
Non reticular	166	79.0	210	100.0		
Abdominal U/S: no, %						
Fatty liver and CCC	31	14.8	11	5.2	11.41	0.010*
HSM and/or Ascites	21	10.0	19	9.0		
Colonic and/or gastric distention	3	1.4	2	1.0		
Normal	155	73.8	178	84.8		

*Significant

Table 3: Binary logistic regression analysis for factors associated with ILD or GERD among the studied participants:

			95% CI	
Factors associated with ILD	**P value**	**OR**	**Lower**	**Upper**
Smoking	<0.001*	3.98	2.44	6.50
GERD	0.033*	1.59	1.04	2.46
FVC	0.038*	0.95	0.91	0.99
FEV1	0.066	0.98	0.98	1.0
FEF25.75	0.187	1.02	0.99	1.06
			95% CI	
Factors associated with GERD	**P value**	**OR**	**Lower**	**Upper**
FEF25.75	<0.001*	1.06	1.03	1.09
ILD	0.016*	1.67	1.10	2.53
Helicobacter Pylori	0.084	1.49	0.95	2.35
FVC	0.331	0.98	0.94	1.02
FEV1	0.724	0.99	0.99	1.01

*: significant FVC Forced vital capacity, FEV1 Forced expiratory volume, FEF25-75 Forced expiratory flow 25–75%.

Figures Legend

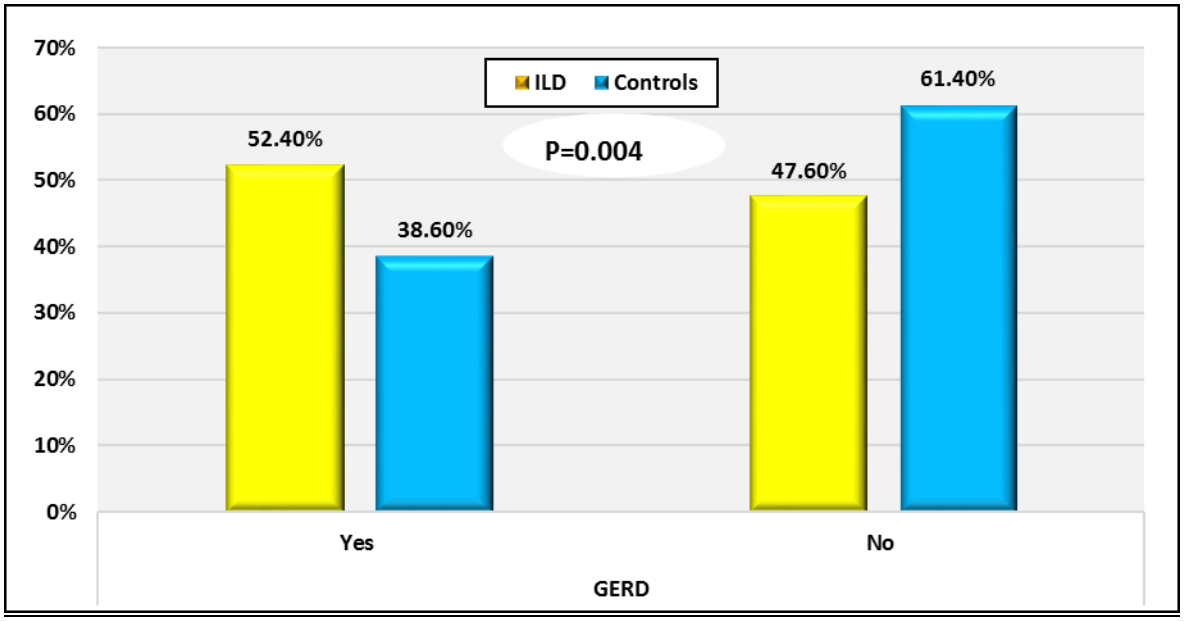

Fig 1: Distribution of GERD among ILD patients and controls

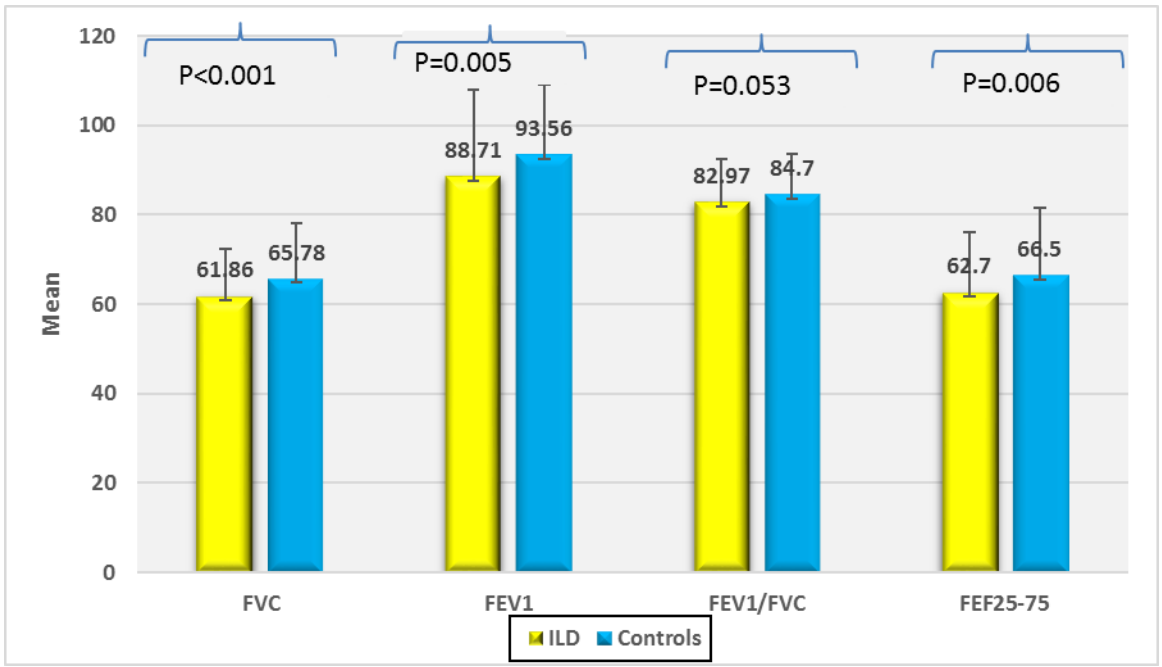

Fig 2: Distribution of Pulmonary function tests regarding ILD patients and controls

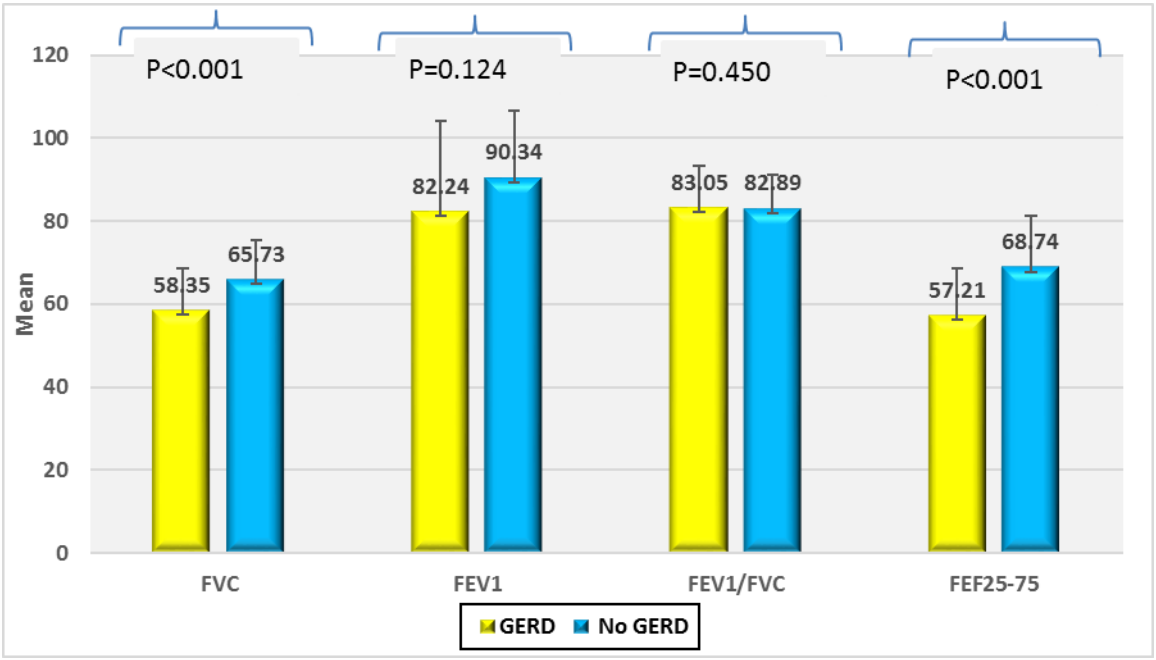

Fig 3: Distribution of Pulmonary function tests regarding patients with and without GERD

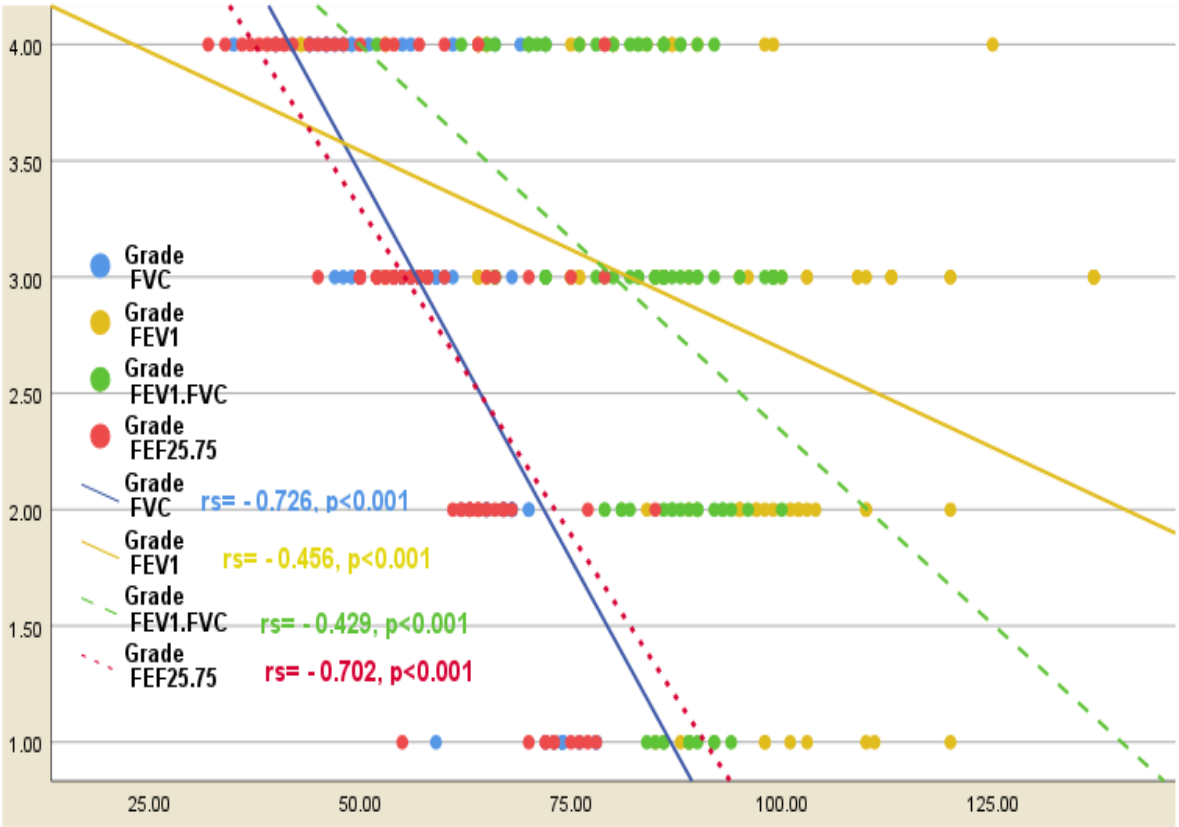

Fig 4: Correlation between stages of GERD and Pulmonary function test

DISCUSSION

For several decades, gastrointestinal specialists have stated that altered pulmonary functions in patients with end stage respiratory disease may cause acid reflux especially, increases in positive intra-abdominal pressure and negative intrathoracic pressure may cause a pressure gradient-favoring reflux **[7]**. Survival analysis demonstrated that identifying the presence of gastro-esophageal symptoms, providing diagnosis of GERD, medication use, and anti-reflux surgery were all collectively associated with longer survival in patients with interstitial lung disease **[8]**. This current study showed that GERD was significantly presented among ILD patients (52.4%) compared to controls (38.6%). The high prevalence of GERD in patients with ILD has been described by previous studies. **Savarino et al. [9]** reported that GERD was significantly increased in patients with IPF compared with patients with other non-IPF ILD and healthy controls. **Qi et al. [10]** reported that frequencies of GERD ranged from 64% to 94% in patients with IPF and ranged from 33% to 50% in patients with non-IPF ILD. Moreover, **Tossier et al. [11]** reported the highest prevalence of GERD among patients with scleroderma ILD compared with patients with IPF (62% vs 46%). Our study had a slightly different design compared with previous studies because we included all causes of ILD either IPF or other non-IPF ILD in one group compared to controls so, the rates of GERD in ILD patients were different from those reported in prior studies. In this study, patients with ILD more frequently were current smokers compared with controls (23.3% vs 13.8%). This result agreed with this obtained by **Rao et al.,** [**12]** who concluded that, inhalation of tobacco smoke is an important risk factor for smoking-related interstitial lung disease. Moreover, **Lederer et al.,** and **Armanios et al. [13,14]** reported that, ILD can be considered as the result of the interaction between tissue damage caused by several agents as smoking, GERD, genetic factors, environmental factors or occupational exposure to harmful substances. In the current study, BMI was significantly higher in ILD group (24.04± 4.92) than controls (22.52± 3.30). These data are consistent with those of a study done by **Comes et al., [15]** to determine the clinical significance of BMI and changes in body weight in ILD and they reported that, BMI was significantly associated with 1-year mortality in ILD therefore, BMI may be useful prognostic indicator of ILD. Tests and methods used for diagnosis of GERD varied among studies **[16, 17]**. In this study we asked about any history of acid reflux symptoms and used the upper gastrointestinal endoscopic findings of reflux esophagitis for diagnosis of GERD according to Los Anglos classification after exclusion of other causes. The results of this study revealed that, the most reported complaints in ILD patients were persistent vomiting, persistent abdominal pain, dyspepsia and hoarseness of voice (21.0%, 21.4%, 17.6%, 7.1%) respectively. These data are in agreement with those obtained by **Soares et al., [18]** who stated that, GERD symptoms were common in patients with ILD. However, a cause-effect relationship had not been well demonstrated and there was still confusion about the diagnostic steps necessary to confirm the presence of GERD and about the role of effective control of GERD in the natural history of ILD. However, these results were different from **Lee et al.** and **Allaix et al. [4,8]** who reported that, GERD is usually clinically silent in ILD patients and heartburn prevalence is significantly lower in ILD-GERD population than in GERD alone. Moreover some studies reported that, GERD symptoms were a less reliable indicator for presence of GERD **[16, 19, 20]**, so we used the Hull Airway Reflux questionnaire for this purpose. **Fahim et al., [21]** also depended on HARQ in diagnosis of GERD and found that, 68% of ILD patients had pathological HARQ scores than controls. **Gao et al.,** [5] also reported that GERD prevalence was 62.3% in their study and typical symptoms were present only in 58.1% of them. Furthermore, **Sweet et al., [22]** reported that, symptoms did not reliably predict the presence of GERD and subsequently were confirmed by pH-metry. Pulmonary function tests including FVC, FEV1, and FEF25-75 were significantly decreasing among ILD patients in our current study. When ILD patients with and without GERD were compared, the results revealed that FVC and FEF25-75 were significantly decreasing among GERD patients. These results were comparable to the previous studies. **Bonacin et al. [23]** demonstrated that, values of FVC and FEF25-75 were significantly lower, and the presence of intrapulmonary shunt was significantly higher in GERD group in comparison with the non-GERD group, and these findings confirmed the correlation between GERD and damaged pulmonary function. Furthermore, these results demonstrated an

additional mechanism in the development of intrapulmonary shunt, as micro-aspiration of the gastric contents causes surfactant damage and microatelectasis of both lungs . So, it is important to perform pulmonary function tests in all GERD patients. In contrast, **Gao et al. [5]** stated that esophageal function parameters in ILD patients presenting with GERD did not correlate with worsened pulmonary function (FVC) and there was no significant correlation between FVC and acid reflux. There was significant negative correlations between stages of GERD and pulmonary function tests in our study. This finding was in agreement with **Troshinsky et al. [24]** who reported that there was no significant correlation between grades of GERD and pulmonary function tests. On the other hand, **Ali et al. [25]** reported that there was significant positive correlation between grades of GERD and FVC, FEV1/FVC and FEF25-75.

The limitations of this current study were that we depended on typical and atypical symptoms of GERD and upper GI endoscopy findings in diagnosis of GERD despite pH-metry or impedance study is the gold standard method for diagnosis of GERD. Moreover, it was difficult to analyze atypical symptoms of GERD due to uncertain relationship between GERD and these symptoms. Some researchers have showed that anti-reflux surgery can improve pulmonary function of GERD patients so further studies are required to determine whether anti-reflux surgery or using PPI might improve the prognosis of ILD patients.

CONCLUSION

Despite not reaching the high rates reported in other studies, the prevalence of GERD was higher in the patients with interstitial lung disease than controls. Moreover, binary logistic regression analyses revealed that smoking, GERD and FVC were the main predictors of ILD, while ILD and FEF25-75 were the most significant predictors of GERD.

List of Abbreviations

BMI Body mass index, GERD Gastro-esophageal reflux disease, GI Gastrointestinal, FVC Forced vital capacity, FEV1 Forced expiratory volume in the first second, FEF 25-75 Forced expiratory flow 25–75%, HRCT High resolution computed tomography, HARQ Hull Airway Reflux questionnaire, ILD Interstitial lung disease, IPF Idiopathic pulmonary fibrosis, SS Systemic sclerosis.

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Conflict of Interest: No any relevant conflicts of interest.

Ethical approval: This study received ethics approval from the local Ethics committee of the Faculty of Medicine, Menoufia university (Approval number:42020Trop).

HIGHLIGHTS

1- The prevalence of GERD was higher in the patients with interstitial lung disease than controls.

2- Smoking, GERD and FVC were the main predictors of interstitial lung disease, while interstitial lung disease and FEF25-75 were the most significant predictors of GERD.

3- It is unknown whether the gastro-esophageal reflux disease (GERD) is a cause or consequence of interstitial lung disease.

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