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Original Article

Predictors of Pathological Gastroesophageal Reflux among Emirati Patients with Reflux Symptoms Who Undergo Wireless pH Monitoring

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Abstract

Background: Diagnosis of gastroesophageal reflux disease (GERD) relies on recognizing symptoms of reflux and mucosal changes during esophagogastroduodenoscopy. The desired response to acid suppression therapy is reliable resolution of GERD symptoms; however, these are not always reliable, hence the need for pH testing in unclear cases. Our objective was to identify potential predictors of a high DeMeester score among patients with potential GERD symptoms to identify patients most likely to have pathological GERD.

Methods: We conducted a retrospective case-control study on patients who underwent wireless pH monitoring from January 2020 to April 2022. Cases were patients with a high DeMeester score (more than 14.7), indicating pathological reflux, and controls were those without. We collected clinical and demographic data, including age, sex, body mass index (BMI), smoking status, non-steroidal anti-inflammatory drugs (NSAIDs) use, and presence of atypical symptoms.

Results: 86 patients were enrolled in the study. 46 patients with high DeMeester scores were considered cases, and 40 patients with DeMeester scores less than 14.7 were considered controls. Esophagitis (grade A) was found in 41.1% of the cases and in 22.5% of the control group. In our study, age of more than 50 years compared with age of 20-29 years and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless pH monitoring.

Conclusion: Age above 50 years compared with age between 20-29 years and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless oesophageal pH monitoring. The presence of oesophagitis was approximately four times more likely to be associated with true pathological reflux.

Keywords: Gastroesophageal reflux disease, Epidemiology, Age, DeMeester score, Wireless PH capsule

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Introduction

Gastroesophageal reflux disease (GERD) is a frequent disorder with various symptoms and a high cost of care. Population-based cross-sectional studies carried out globally are the primary source of our current understanding of the epidemiology of GERD.[1-7] Asthma, cough, hoarseness, and chest pain are atypical extra-oesophageal symptoms that people with GERD are more likely to experience.[8,9] These findings, however, are based on research that relied on patient-reported symptoms and their response to acid suppression therapy rather than a confirmed diagnosis of pathological reflux. As a result of this, they are subject to variation because patients perceive their symptoms differently. It is challenging to get a consensus regarding the incidence of true reflux due to the range of clinical symptoms associated with reflux.

According to previous studies, up to 20% of the general population suffers from heartburn and regurgitation at least once a week. Smoking, drinking alcohol, and being overweight are risk factors for GERD. Research has shown that obesity increases the incidence of GERD, particularly in women.[10,12] In general, patients with symptoms of reflux, regardless of the existence of oesophageal inflammation or confirmation of the presence of true pathological reflux, are given the diagnosis of suspected GERD. Heartburn or pyrosis, regurgitation, and, in advanced stages of the disease, dysphagia are suggestive symptoms of GERD; however, symptoms alone, including response to proton pump inhibitors (PPIs), can be unreliable and costly, especially when PPIs are continued long-term without a confirmed diagnosis.

PH monitoring has been used as a diagnostic tool in GERD and is considered the standard for diagnosis of pathological GERD; however, it is a costly and semi-

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invasive test. Recent studies have shown that wireless capsule pH monitoring is better tolerated and interferes less with daily activities as compared with traditional catheter-based pH monitoring. Moreover, prolonged recording time (48 or even 96 hours instead of 24 hours) is possible with wireless pH monitoring.[13]

Materials and Methods

Study Design

We conducted a retrospective case-control study on patients who underwent wireless oesophageal pH monitoring from January 2020 to April 2022 in Sheikh Shakhbout Medical City, Abu Dhabi. Our aim was to study the association between selected predictors/potential risk factors and the presence of a DeMeester score of > 14.7 vs. < 14.7. Cases were patients with a high DeMeester score (> 14.7), indicating pathological reflux and controls were those without. Patients' data were de-identified throughout the data abstraction process to ensure patient privacy.

Participants

All participants were referred for oesophageal pH measurement for various indications, including resistance to acid suppression therapy, typical as well as atypical GERD symptoms, and before GERD correction intervention. Capsule deployment was deferred if upper gastrointestinal (GI) endoscopy showed grade B or C esophagitis. Exclusion criteria were patients with a history of surgery for GERD, patients with inconclusive findings while reporting the study, those with less than 48 hours of pH monitoring data, and patients who were not compliant with the instructions given.

Patients who underwent the 96-hour wireless capsule study had GERD symptoms for more than three months. All patients underwent upper GI endoscopy. Patients were off acid suppression therapy for two weeks before the study.

Before capsule placement, experienced nurses/endoscopy technicians who assisted with the capsule placement did the calibration. During the upper endoscopy, the endoscopic finding of Barrett's esophagus, esophagitis, and hiatus hernia grade were reported if found. The distance between the squamocolumnar junction and the incisors was measured. The pH monitoring capsule was deployed blindly (6 cm above the squamocolumnar junction) using the delivery system guided by the measurements obtained from endoscopy. After wireless capsule placement, all patients remained off PPIs for 2 days and resumed their PPI therapy in the last two days of the study. They were encouraged to be on their usual daily activity and go to work. After verbal instructions, patients were given a patient instruction form to guide them regarding symptom recording. Patients were asked to identify a dominant symptom for symptom analysis. They typically chose one of the following symptoms as their prevalent complaint: heartburn, regurgitation, or chest pain. Patients were instructed to press the symptom indicator button on the pH recorder when experiencing only their one dominant GERD symptom.

Patients returned after 96 hours of capsule placement for the return of the receptor device. Data were downloaded using a standard computer software program (pH Capsule Data Analysis Workstation, Jinshan Science and Technology Co. Ltd, Chongqing, China).[14] The physician made the final review and diagnosis.

Data Collection

Clinical and demographic data including age, sex, body mass index (BMI), nationality, smoking status, non-steroidal anti-inflammatory drugs (NSAIDs) use, presence of atypical symptoms, and history of chronic use of medication affecting lower esophageal sphincter (LES) such as nitro-glycerine, anticholinergics, β-adrenergic agonists, aminophylline, and benzodiazepines[15] were collected retrospectively from patients' electronic records. Endoscopic findings for the presence of Barrett's esophagus, esophagitis, and hiatus hernia were collected. Reports for wireless pH capsules were reviewed, and those with inconclusive results were excluded. According to the average DeMeester score on day one and day 2, the cohort was divided into cases with a score of more than 14.7, indicating pathological reflux, and controls with a score of less than 14.7. The data were stored on a deidentified spreadsheet.

The DeMeester score was chosen for the primary variable as it is the most reproducible of the commonly analyzed pH variables (similar to the percent total time pH < 4) and has an accepted cut-off point of 14.72.[16] Esophagitis grading was made according to LA classification, and hiatus hernia was reported as per Hill grade.

Statistical Analysis

Logistic regression analysis was performed to ascertain the effects of age, sex, BMI, smoking, medications affecting LES, GERD atypical symptoms, Hill grade, esophagitis, and Barrett's esophagus on the likelihood of GERD patients who underwent the study of having a DeMeester score of > 14.7. Based on the Hosmer and Lemeshow test, the logistic regression model was considered to be an excellent fit for the data ($\chi^2 = 26.238$, P value = 0.016). The model explained 35.1% (Nagelkerke R2) of the variance in patients with GERD who underwent the study and had a DeMeester score of > 14.7.[17]

Results

Eighty-six patients were included in the study. All had symptoms over 3 months. 46 patients had DeMeester score of more than 14.7, and the 40 controls had DeMeester score of less than 14.7. Age ranged between 19 and 76 years. BMI ranged from 17.9 to 47 kg/m^2. Women comprised 59%, and 41% were men. Most of the cohort were Emirati (87.2%) and non-smokers (89.5%). 95.3% of the patients were not using NSAIDs regularly. 46.5% presented with atypical GERD symptoms, while 53.5%

presented with typical GERD symptoms. 11 patients (13%) were using medications affecting LES. Endoscopic examination demonstrated esophagitis in 32.6%. Three cases were found to have Barrett's esophagus. 34.9% of the total cohort had no hiatus hernia, while 41.9% had grade 1, 11.6% had grade 2, 7% had grade 3, and 4.7 % had grade 4 hiatus hernia (Table 1).

A comparison of cases and controls also appears in (Table 2). Of note, variables of age, BMI, and presence of esophagitis were significantly different between cases and controls. Unadjusted logistical regression analysis (Table 3) showed that age, BMI, and presence of esophagitis were all associated with a greater likelihood of a high DeMeester score among patients who underwent a wireless oesophageal pH capsule as part of the work-up for GERD. Logistic regression analysis (Table 4) adjusted for age, sex, nationality, and any variable with an effect size of greater than 15% demonstrated that having a high DeMeester score was associated with more than four times the odds of esophagitis ($P=0.02$). The multivariable logistic regression analysis model containing all the variables studied demonstrated that age, BMI, and mild esophagitis were independent predictors of pathological GERD. Patients aged 20-29 years were less likely to have DeMeester score of >14.7 compared with those aged above 50 ($P=0.017$*). BMI 25-29 was also more likely than those with BMI <25 to have GERD ($P=0.026$) with weaker, non-significant trends above BMI 30.

Table 1. Baseline characteristics of all patients

Variables		No. (%)
Age (y)	<20	1 (1.2)
	20-29	30 (34.9)
	30-39	28 (32.6)
	40-49	17 (19.8)
	above 50	10 (11.6)
Gender	Male	35 (40.7)
	Female	51 (59.3)
Nationality	Non-Emirati	11 (12.8)
	Emirati	75 (87.2)
Smoking	No	77 (89.5)
	Yes	9 (10.5)
BMI	18-24	30 (34.9)
	25-29	29 (33.7)
	Above 30	27 (31.4)
Medications affecting LES	No	75 (87.2)
	Yes	11 (12.8)
NSAIDs	No	82 (95.3)
	Yes	4 (4.7)
Standard capsule protocol	No	1 (1.2)
	Yes	85 (98.8)
GERD atypical symptoms	No	46 (53.5)
	Yes	40 (46.5)
Hill grade	Normal	30 (34.9)
	I	36 (41.9)
	II	10 (11.6)
	III	6 (7.0)
	IV	4 (4.7)
Hill grade	normal	30 (34.9)
	I	56 (65.1)
Esophagitis	No	58 (67.4)
	Yes	28 (32.6)
Barrett	No	83 (96.5)
	Yes	3 (3.5)
Symptoms duration	>3 Months	86 (100.0)
Total		86

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.

Discussion

This study showed that patients aged 20-29 years were less likely to have DeMeester score of >14.7 compared with those aged above 50 years. When adjusted against all other variables, the study also showed that higher BMI was associated with pathological reflux. Esophagitis was found more in patients with true reflux, although notably, some patients labeled as having grade A esophagitis had no pathological reflux. The study showed that other parameters studied (some notable surprises) were found to have no significant association with a high DeMeester score.

This case-control study conducted in an Emirati cohort builds on and extends what has been reported in the literature regarding risk factors for GERD. The study showed that only 50% of patients who were referred for pH study were found to have true pathological reflux, as confirmed with a high DeMeester score. This demonstrates the importance of ensuring this diagnosis in such patients, especially if they are going for GERD correction surgery, endoscopic intervention, or having atypical reflux symptoms. Depending only on response to acid suppression is not enough as two other differentials, namely esophageal hypersensitivity and functional dyspepsia, both respond to PPI therapy in the absence of GERD. Most current literature that studied patients with GERD used symptom response to acid suppression for diagnosis. Esophageal pH measurement can be done either by pH capsule or by 24-hour pH catheter. The wireless pH capsule was chosen as patients preferred this type of study while they declined to have a catheter inserted for 24 hours, and both tests were covered by insurance.

We found that higher BMI and being overweight appeared to predict true reflux. Literature showed that an increase in symptoms was more correlated with BMI than with fat distribution (such as the waist-to-hip ratio), which suggests that hormonal factors associated with adiposity may play a more significant role in the pathogenesis of GERD symptoms compared with mechanical factors, at least in women.[18]

The study showed that patients aged 20-29 years were

Table 2. Comparison of characteristics and variables of cases vs. controls

Variables		Demeester score		Test of Sig	*P* value
		Control < 14.7	Cases > 14.7		
Age (y)	< 20	1 (2.5)	0 (0)	F = 11.022	0.026*
	20-29	20 (50)	10 (21.7)		
	30-39	12 (30)	16 (34.8)		
	40-49	5 (12.5)	12 (26.1)		
	Above 50	2 (5)	8 (17.4)		
Gender	Male	13 (32.5)	22 (47.8)	$\chi^2 = 2.082$	0.149
	Female	27 (67.5)	24 (52.2)		
Nationality	Non-Emirati	3 (7.5)	8 (17.4)	$\chi^2 = 1.877$	0.171
	Emirati	37 (92.5)	38 (82.6)		
Smoking	No	34 (85)	43 (93.5)	F = 1.64	0.293
	Yes	6 (15)	3 (6.5)		
BMI	18-24	18 (45)	12 (26.1)	$\chi^2 = 5.015$	0.081
	25-29	9 (22.5)	20 (43.5)		
	Above 30	13(32.5)	14(30.4)		
Medications affecting LES	No	34 (85)	41 (89.1)	$\chi^2 = 0.327$	0.567
	Yes	6 (15)	5 (10.9)		
NSAIDs	No	37 (92.5)	45 (97.8)	F = 1.369	0.334
	Yes	3 (7.5)	1 (2.2)		
Standard capsule protocol	No	1 (2.5)	0 (0)	F = 1.164	0.281
	Yes	39 (97.5)	46 (100)		
GERD atypical symptoms	No	24 (60)	22 (47.8)	$\chi^2 = 1.275$	0.259
	Yes	16 (40)	24 (52.2)		
Hill grade	Normal	16 (40)	14 (30.4)	F = 3.175	0.529
	I	13 (32.5)	23 (50)		
	II	5 (12.5)	5 (10.9)		
	III	4 (10)	2 (4.3)		
	IV	2 (5)	2 (4.3)		
Hill grade	normal	16 (40)	14 (30.4)	$\chi^2 = 0.862$	0.353
	I	24 (60)	32(69.6)		
Esophagitis	no	31 (77.5)	27 (58.7)	$\chi^2 = 3.445$	0.063
	yes	9 (22.5)	19 (41.3)		
Barrett	no	39 (97.5)	44 (95.7)	F = 0.217	0.641
	Yes	1 (2.5)	2 (4.3)		
Symptoms duration	> 3 Months	40 (100)	46 (100)	-	-
Total		40	46		

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs, Sx: Symptoms
F: Fisher's exact test, * Significant.

less likely to have DeMeester score of > 14.7 compared with those aged above 50 years, when adjusted against all other variables. In 2010, Maxwell and colleagues showed that GERD and its associated complications were common in older patients. They concluded that the elderly tended to have fewer symptoms with more severe complications that may be life-threatening. These are important considerations regarding causation, evaluation, and treatment in older patients as compared with younger patients.[19] The possible mechanisms for increased incidence of GERD in the elderly population include weakened and impaired esophageal motility, decreased salivary and bicarbonate secretions, decreased LES pressure with advancing age, diaphragmatic weakness, increased incidence of hiatal hernia, presence of comorbidities such as diabetes and Parkinson disease, and concomitant use of medications such as nitrates, calcium antagonists, theophylline, or antidepressants.[20]

Yamasaki et al also showed that the proportion of patients with GERD using PPIs increased in all age groups, except for the ≥ 70 years group, with the most significant increase being in the 30–39-year age group.[21] On the other hand, in 2018, Yamasaki et al reported that GERD affected a growing number of the adult population and

Table 3. Unadjusted Odds of high DeMeester Score based on Variables Collected

Variables		OR	95% CI		*P* value
			Lower	Upper	
Age (y)	<20 (excluded)	NA	NA	NA	NA
	20-29	0.125	0.022	0.702	0.018*
	30-39	0.333	0.060	1.863	0.211
	40-49	0.600	0.093	3.885	0.592
	above 50 (ref)	-	-	-	-
Gender	Male/Female	0.525	0.218	1.265	0.149
Nationality	Non-Emirati/Emirati	0.385	0.095	1.565	0.171
Smoking	No/Yes	0.395	0.092	1.697	0.293
BMI	18-24 (ref)	-	-	-	
	25-29	3.333	1.139	9.752	0.026*
	Above 30	1.615	0.565	4.618	0.37
Medications affecting LES	No/Yes	0.691	0.194	2.463	0.567
NSAIDs	No/Yes	0.274	0.027	2.746	0.334
Standard capsule protocol	No/Yes	-	-	-	-
GERD atypical symptoms	No/Yes	1.636	0.694	3.856	0.259
Hill grade	Normal/Abnormal	1.524	0.625	3.716	0.353
Esophagitis	No/Yes	2.424	0.941	6.243	0.063
Barrett	No/Yes	1.773	0.155	20.315	0.641
Total		15.633	69.606		4.047

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.
* Significant.

Table 4. Logistic regression (Odds adjusted for age, sex, and any variable with an effect size>5%) of high DeMeester Score based on variables collected)

Variables		OR	95% CI		*P* value
			Lower	Upper	
BMI					0.468
	25-29	0.790	0.198	3.150	0.738
	Above 30	1.870	0.469	7.459	0.375
Gender (female)		2.482	0.691	8.916	0.164
Age					0.124
	less than 20	0.000	0.000	.	1.00
	20-29	0.069	0.008	0.620	0.017*
	30-39	0.178	0.021	1.485	0.111
	40-49	0.324	0.033	3.174	0.333
	Above 50 (ref.)				
Nationality	Non-Emirati/Emirati	0.077	0.005	1.090	0.058
Smoking	No/Yes	2.564	0.340	19.334	0.361
NSAIDs	No/Yes	1.704	0.087	33.461	0.726
Medications affecting LES	No/Yes	3.762	0.414	34.159	0.239
Standard capsule protocol	No/Yes	0.000	0.000	.	1.00
GERD atypical symptoms	No/Yes	0.480	0.155	1.489	0.204
Hill grade	Normal/Abnormal	0.613	0.183	2.055	0.428
Esophagitis	No/Yes	4.384	1.2	15.5	0.022*
Barrett	No/Yes	0.107	0.005	2.407	0.160
Constant		162.593			0.101

BMI: Body mass index, LES: Lower esophageal sphincter, NSAIDs: Non-steroidal anti-inflammatory drugs.
* Significant.

that younger people develop GERD very fast.[22] This study included various age groups and noted a high proportion of younger patients with GERD, especially those aged 30-39 years. Also, in 2018, Gwang and colleagues reported an increasing incidence of GERD in younger patients.[23]

The increased incidence of obesity, decreased prevalence of *Helicobacter pylori* infection, smoking, and heavy alcohol consumption can explain the recent increase in the incidence of GERD in the young age group.[22]

Our study showed that being between 20 and 29 years of age compared with being 50 years of age or older was associated with having a lower Demeester score. While those between the ages of 30-50 also appeared to have a lower likelihood of a high DeMeester score compared with those above the age of 50, this difference was not statistically significant. When we compare our results with the results reported by Khoder et al, we note that in the Emirates (UAE), young populations have higher rates of *H. pylori* infection,[24] and there is overall less consumption of alcohol and tobacco, possibly explaining the lower incidence of pathological reflux in this part of our cohort.

Reflux has been linked to alcohol use and tobacco smoking.[25] Smoking cigarettes likely worsens reflux disease by sharply increasing the frequency of acid reflux episodes. The presence of decreased LES pressure is crucial to the mechanisms of acid reflux during cigarette smoking. Alcohol also lowers LES pressure, much like smoking does. Additionally, it has been shown that alcohol decreases the amplitude of esophageal peristaltic waves, affects acid clearance for roughly 3.5 hours with a considerable acidic shift below pH 3 or 4 when the person is supine and decreases saliva production in healthy individuals.[25]

Despite these physiological effects of smoking and alcohol, we could not conclusively link either substance to GERD. Most likely, the results shown in our study were related to low alcohol and smoking consumption in our cohort.

The current study showed true pathological reflux was associated with four times higher odds of having esophagitis. The LA classification has been used to assess mucosal injury; however, symptoms and endoscopic findings are not always correlated. The intensity and frequency of reflux symptoms are poor predictors of the presence of severe reflux esophagitis.

Previous studies have shown that only one-third of patients with endoscopic LA grade A had GERD symptoms. Endoscopic findings of LA grade B esophagitis had significant inter-observer variability. Therefore, endoscopic LA grades C or D esophagitis, Barrett's esophagus, or peptic stricture are considered confirmatory evidence for GERD in the Lyon consensus. Furthermore, many GI experts consider LA grade B as an indication of definitive GERD needing treatment. Therefore, studies of the natural history and outcome of therapy based on GERD's endoscopic findings are required.[26-29]

The association between LA grade A esophagitis and true reflux in our study is expected and can be attributed to the observation that most of the cohort was using regular acid suppression therapy and stopped two weeks before performing the pH study, which may not be sufficient time to develop endoscopic finding of more severe esophagitis.

Study Limitation

We did not consider the symptoms index from pH capsule results as our aim was to measure true pathological reflux rather than symptom association. Our sample size was overall small.

Conclusion

In conclusion, we have described the epidemiology and clinical characteristics of GERD in the Emirati population. Several factors are associated with the increase in the prevalence of GERD in Emiratis. Increasing age above 50 compared with age between 20-29 and being overweight appeared to be predictors of true pathological reflux among patients with reflux symptoms who underwent wireless pH monitoring. The presence of even grade A esophagitis was associated with true pathological reflux. These data can be further used to guide which patients benefit most from pH testing. Those with either a very high or very low probability of GERD likely do not benefit, as they can be either empirically treated or reassured.

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Authors' Contribution

Conceptualization: Mostafa Ahmed Shehata.
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Competing Interests

The authors declare no conflict of interest related to this work.

Ethical Approval

All the studies were approved by the Institutional Review Board of SSMC, Abu Dhabi.

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