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Evaluation of the impact of oesophageal reflux disease on muscle fatigue

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Abstract

Gastroesophageal reflux disease (GERD) is a gastrointestinal tract disorder associated with the regurgitation of gastric acid into the esophagus. It can present itself as a non-erosive reflux condition or erosive esophagitis. Our main objective was to evaluate the impact of oesophageal reflux disease on muscle fatigue among patients. The prospective study design was adopted using surveys performed at the South West China Medical University. All patients who were subjected to screening endoscopy at the South West China Medical University were prospectively enrolled in the study. Our study was conducted according to ethical guidelines involving animal and human subjects. Our study used the Epworth Sleepiness Scale (ESS), Hospital Anxiety and Depression Scale (HADS), and the Multidimensional Fatigue Inventory (MFI) questionnaires to perform data collection on the levels of fatigue, depression, daytime hypersomnolence, and anxiety. In the (HADS, Anxiety (β=0.657, p <.001) and Depression (β=2.927, p <.001) exhibited significant positive associations with the predicted fatigue. The Epworth Sleepiness Scale (ESS) showed no significant difference between individuals with and without reflux esophagitis (p=0.787, power=0.071). However, a significant difference was observed based on the presence of GERD symptoms (p=0.003, power=0.789), with higher mean scores for those with GERD symptoms (6.1±3.5) compared to those without (4.9±2.9). In MFI, significant differences were observed between the two groups for General and Physical Fatigue (p=0.040, power=0.823), Mental Fatigue (p=0.002, power=0.767), and MFI Total Score (p=0.002, power=0.981). In conclusion, GERD symptoms exhibited stronger associations with fatigue and daytime sleepiness than endoscopic findings, emphasizing the impact of symptomatic experiences on well-being.

Key Words: GERD, HADS, ESS, MFI, fatigue, esophagus and gastric acid.

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Gastroesophageal Reflux Disease (GERD) is a disorder of the gastrointestinal tract that is associated with the regurgitation of gastric acid into the esophagus.[1] GERD can manifest itself as a non-erosive reflux condition or erosive esophagitis. It has a prevalence of 20% in Western Countries[2] accompanied by an economic burden resulting from direct and indirect costs.[3] El-Serag *et al.*[3] postulated that the reported occurrence of GERD in the United States lies between 18.1% and 27.8%; which could be high because individuals were prone to over-the-counter acid-relieving medications. Nilsson *et al.*[4] suggested that men have a higher prevalence of GERD than women. In contrast. a meta-analysis in 2018 by Eusebi *et al.*[5] observed that the pooled prevalence of GERD signs and symptoms was slightly higher in women compared to men at 16.7% and 15.4%, respectively. Women have a higher potential of developing non-erosive reflux disease while men have a higher chance of developing erosive oesophagitis.[6,7] According to Lottrup *et al.*,[8] the causes of GERD are mainly intrinsic or structural and affect the esophagogastric junction barrier to expose the esophagus to the gastric contents. Fewer studies have established that asymptomatic reflux esophagus occurs in a smaller portion of patients with the majority of patients

experiencing heartburns and regurgitations.[9] Moreover, atypical symptoms, oesophageal and extra—oesophageal symptoms have also been reported. The symptoms of reflux can have severe side effects leading to emotional dysfunctions, disrupted sleep patterns, depression, and anxiety.[10] Maret-Ouda *et al.*[11] postulated that the etiology of GERD is unknown and there is limited information about the development of GERD. Several risk factors have been implicated in the pathogenesis of GERD such as motor abnormalities, impaired lower oesophageal sphincter, and delayed gastric emptying. Hampel *et al.*[12] found that obesity was a risk factor for developing GERD, oesophageal carcinoma, and erosive oesophagitis. Similarly, Malfertheiner *et al.*[13] investigated the risk factors associated with erosive reflux disease in a sample size of more than 6000 individuals and found that the odds ratio for erosive reflux disease was correlated with body mass index. Diamant *et al.*[14] suggested that abnormality in the causal factors of GERD creates a shift in the normal equilibrium. Causal factors such as delayed gastric emptying, physiological and structural adjustments within the gastroesophageal section, transient relaxations in the lower oesophageal sphincter muscles, mechanisms of clearance within the esophagus, ingestion of irritants and negative gastric substances. Fass[15] proposed that endoscopic and histopathological analyses of GERD revealed three phenotypes of non-erosive reflux disease, Barrett esophagus and erosive esophagus. Non-erosive reflux disease is the common phenotype occurring in at least 70% of patients preceded by erosive oesophagitis in at least 30% and 12% experiencing Barett esophagus.[2,15,16] Rieder *et al*.[17] exerted that GERD has a complex pathophysiology involving several factors associated with the secretion of gastric acid, malfunctioning of the antireflux barrier, and defense mechanisms. The interconnections between these factors are not clearly understood; however, previous studies[18] have suggested that these factors are associated with an increased exposure of the oesophageal squamous epithelium to acidic gastric contents such as bile, pepsin, and trypsin.[18] Previous studies[18-20] have found that injury to the mucosal membranes coupled with infiltration of non-specific inflammation around the epithelial cells increases the occurrence of pathological reflux. Furthermore, an endoscopic analysis would reveal mucosal breaks, columnar metaplasia, strictures, and adenocarcinoma. Recently fewer studies[9] have studied the relationship between GERD and fatigue. GERD is usually accompanied by subjective symptoms such as fatigue that is triggered by secondary factors such as organic disorders. Organic disorders include malignant infections, psychological distress, and depressive disorders.[21-23] Additionally, altered sleep patterns from acidic regurgitation exacerbate fatigue.[24,25] Kang *et al.* (2021) adopted and verified the validity of the Multidimensional Fatigue Inventory (MFI) in the Korean population and assessed fatigue among patients. Also, Song *et al.*,[26] found that gender and age have modulating effects on fatigue and GERD among Koreans. Thus, based on the previous studies, the current study seeks to examine the effects of oesophageal reflux disease patients on muscle fatigue. Moreover, we will seek to examine the effects of confounding variables such as psychological disorders, gender, and age that could mediate the effects of fatigue. Lastly, we sought to examine whether fatigue was driven by either endoscopy esophagitis or signs and symptoms of GERD.

Materials and Methods

Ethics

Our study was conducted according to the 2008 Helsinki Declaration on experiments involving animal and human subjects.[27] The study was approved by the Institutional Review Board of South West China Medical University. Informed consent was obtained from all participants before participating in the study. All personal identifiers were removed from the data with participants assured of utmost confidentiality and secure storage of the data obtained.

Research design

The prospective study design was adopted using surveys performed at the South West China Medical University. The study was conducted from September 2021 to September 2023 with data on exposures and various factors being obtained at regular intervals. The study design permits the establishment of temporal relationships between outcomes and exposures and the relationships between these variables.

Eligibility criteria

All patients who were subjected to screening endoscopy at the South West China Medical University were prospectively enrolled in the study. The exclusion criteria involved patients who presented severe comorbidities and had used over-the-counter medications that affected the central nervous system. Furthermore, test results and endoscopy examinations were used to exclude patients presenting signs and symptoms of gastric cancer, duodenal ulcers, and anemia.

Trained endoscopy professionals at the Department of Pathology carried out gastro-duodenoscopy on all patients. The prevalence and degree of reflux oesophagitis were examined and quantified based on the Los Angeles Classification System and any slight changes in the reflux oesophagitis were removed from the study. Lastly, the presence of GERD symptoms was examined and identified by heartburns and regurgitations.

Data collection

Our study used three questionnaires to perform data collection on the levels of fatigue, depression, daytime hypersomnolence, and anxiety. Fatigue measurements can either be one-dimensional or two-dimensional instruments such as the Fatigue Severity Scale (FSS) and the visual analog scale (VAS). The FSS consists of 9 statements designed to rate the severity of fatigue symptoms measured on a 7-point Likert Scale ranging from 1, (disagree) to 7, (agree). The total score is the sum of all numbers recorded in response

to various statements. The Multidimensional Fatigue Inventory (MFI) is an instrument consisting of 20 items subdivided into 5 dimensions general fatigue, reduced motivation, mental fatigue, physical fatigue, and reduced activity. The MFI is a self-report, pencil and paper-based measure that was completed in 10 mins. MFI has a higher level of reliability with consistent validity in assessing fatigue. The Epworth Sleepiness Scale (ESS) was adopted to examine the levels of daytime sleepiness. ESS is a self-administered instrument consisting of 8 statements measured on a 4-point Likert scale from 0 to 3. The 8 statements are based on assessing the usual chances of dozing off or falling asleep while performing different tasks. The scores ranged from 0 to 24 with higher scores showing a higher degree of an individual falling asleep. Scores above 10 show excessive sleepy behavior. Participants took an average of 3 minutes to complete the questionnaire. The Hospital Anxiety and Depression Scale (HADS) was utilized to estimate the levels of anxiety and depression. It is a self-report rating scale consisting of 14 items measured on a 4-point Likert scale ranging from 0 to 3. The instrument is subdivided into two subscales of depression and anxiety each consisting of 7 items. The total score was determined as the sum of all 14 items with higher scores showing high levels of anxiety and depression.

Statistical analysis

Statistical Analyses were performed using GraphPad Prism version 9.5.1 (Chicago, Illinois, United States) at a statistical significance of $p < .05$. Categorical variables were presented using frequencies (percentages) as row and column totals based on chi-square tests. In contrast, continuous variables were presented using measures of central tendency such as mean and standard deviation based on analysis of covariances (ANCOVA). We established correlations between HADS, MFI, and ESS scores based on the Pearson correlation coefficient. Regression analyses were performed to predict the effects of fatigue from age, gender, and HADS scores. Also, a regression analysis was performed to predict the impact of GERD (absent or present) from the independent variables of age, gender, and HADS scores.

Results

Initially, the study consisted of 100 patients. No cases were excluded after the eligibility criteria and 100 cases were examined (see Table 1). The participants reported a mean age of 40.5±5.03 years. Table 1 presents the baseline characteristics of the study population, categorized by the presence or absence of Reflux Esophagitis and GERD Symptoms. The mean age of the participants with and without Reflux Esophagitis was 40.7±10.6 and 40.5±10.0 years, respectively, with no statistically significant difference (p=0.609). Similarly, there was no significant difference in age between those with and without GERD Symptoms, with mean ages of 40.4±9.8 and 40.5±10.2 years, respectively (p=0.836).

Regarding gender distribution, among participants without Reflux Esophagitis, 40.2% were men and 39.8% were women. In the presence of Reflux Esophagitis, the proportion of men increased to 58.9%, and women decreased to 31.1%. These differences were statistically significant (p=0.411). A similar pattern was observed for GERD Symptoms, with significant differences in gender distribution (p=0.621). The Body Mass Index (BMI) showed no significant difference between those with and without Reflux Esophagitis (p=0.260) or GERD Symptoms (p=0.142). The mean BMI for individuals with Reflux Esophagitis was 21.0±7.6, and without it was 21.3±5.1. For those with and without GERD Symptoms, the respective mean BMIs were 21.3±5.9 and 22.2±5.7.

Table 1. *Baseline characteristics of the study population.*

	Reflux Esophagitis (Absent)	Reflux Esophagitis (Present)	Sig. (p-value)	GERD Symptoms (Absent)	GERD Symptoms (Present)	Sig. (p-value)
Age (years)	40.5±10.0	40.7±10.6	0.609	40.5±10.2	40.4±9.8	0.836
Gender			0.411			0.621
Men	37 (40.2)	71 (58.9)		49 (51.5)	59 (64.1)	
Women	57 (39.8)	32 (31.1)		56 (38.5)	33 (35.9)	
BMI (kg/m2)	21.3±5.1	21.0±7.6	0.260	22.2±5.7	21.3±5.9	0.142
WC (cm)	75.1±9.2	75.8±9.2	0.467	75.5±9.3	74.4±8.8	0.174

Note: Mean±SD. Sample size, N (%). GERD, gastroesophageal reflux disease; BMI, body mass index; WC, waist circumference.

Waist circumference (WC) also demonstrated no significant differences between the groups with and without Reflux Esophagitis (p=0.467) or GERD Symptoms (p=0.174). The mean WC for individuals with Reflux Esophagitis was 75.8±9.2, and without it was 75.1±9.2. For those with and without GERD Symptoms, the respective mean WCs were 74.4±8.8 and 75.5±9.3. Smoking status showed significant differences in the distribution of participants with and without GERD Symptoms (p=0.003). Among non-smokers, 37.7% had GERD Symptoms, while among current smokers, 16.1% had GERD Symptoms.

In terms of medical history (see Figure 1), there were no significant differences in the prevalence of hypertension, type 2 diabetes, and dyslipidemia between those with and without Reflux Esophagitis or GERD Symptoms ($p > 0.05$ for all).

In Figure 2, Alcohol consumption did not show significant differences between groups with and without Reflux Esophagitis (p=0.992) or GERD Symptoms (p=0.972). The proportions of individuals consuming alcohol less than once a week and once or more per week.

In Figure 3, smoking status showed significant differences in the distribution of participants with and without GERD Symptoms (p=0.003). Among non-smokers, 37.7% had GERD Symptoms, while among current smokers, 16.1% had GERD Symptoms.

Table 2 presents the results of the Multidimensional Fatigue Inventory (MFI) analysis based on ANCOVA, focusing on reflux esophagitis. The study population is stratified into groups with reflux esophagitis present or absent, as well as those with or without GERD symptoms.

For the dimensions of the MFI related to General and Physical Fatigue, there was no statistically significant difference between individuals with reflux esophagitis present (16.3±4.0) and absent (16.1±3.6) (p=0.434, power=0.076). However, a significant difference was observed when comparing individuals with and without GERD symptoms ($p < 0.001$, power=0.979). Those with GERD symptoms (18.1±4.2) had a higher mean score compared to those without GERD symptoms (15.7±3.5).

In terms of Mental Fatigue (see Figure 4), the analysis showed no significant difference between individuals with and without reflux esophagitis (p=0.764, power=0.060). However, a significant difference was observed between those with and without GERD symptoms ($p < 0.001$, power=0.882), with higher mean scores in the presence of GERD symptoms (14.2±4.1) compared to their absence (13.8±2.5). The dimension of Reduced Activity did not yield a significant difference between individuals with and without reflux esophagitis (p=0.714, power=0.060). Nevertheless, a significant difference was found based on the presence of GERD symptoms (p=0.003, power=0.688), with higher scores for those with GERD symptoms (8.4±1.9) compared to those without (7.5±1.7).

Motivation showed no significant difference between individuals with and without reflux esophagitis (p=0.757, power=0.071). However, a significant difference was observed between those with and without GERD symptoms (p=0.007, power=0.776), with higher mean scores in the presence of GERD symptoms (12.1±2.4) compared to their absence (9.8±2.6). The MFI total score demonstrated no significant difference between individuals with and without reflux esophagitis (p=0.761, power=0.077). Conversely, a significant difference was observed based on the presence of GERD symptoms ($p < 0.001$, power=0.899), with higher mean scores for individuals with GERD symptoms (55.6±12.7) compared to those without (47.6±9.3).

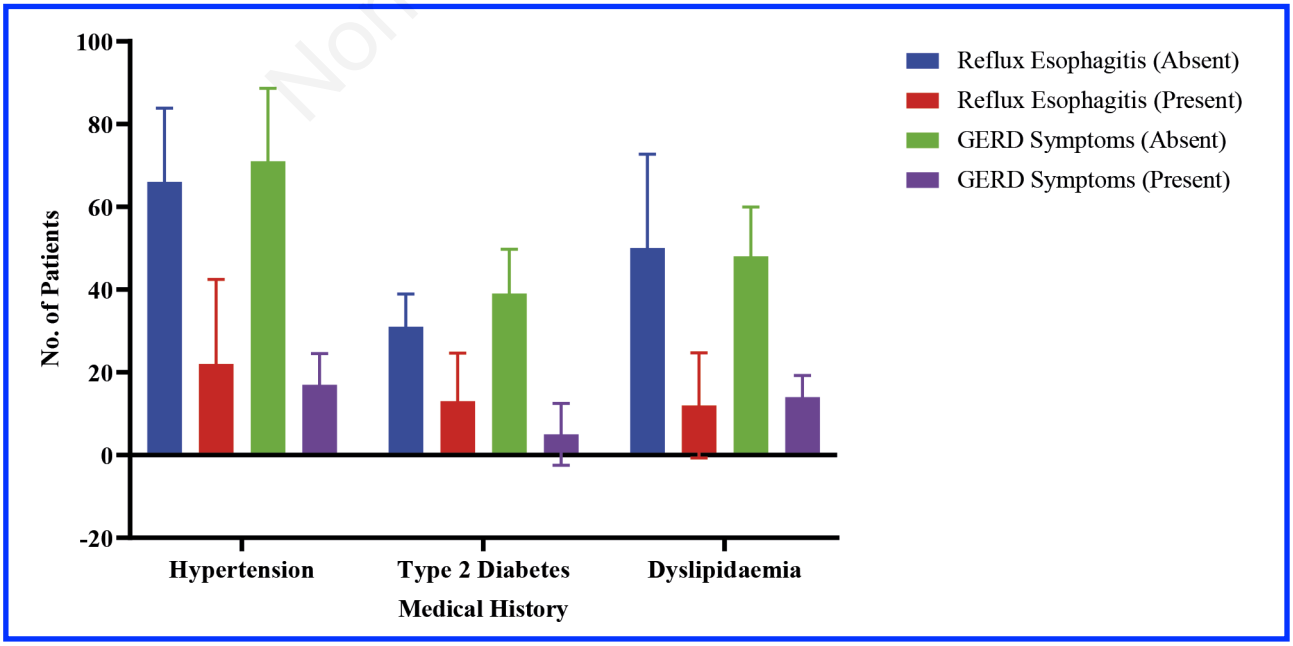

Figure 1. *Medical history of patients with hypertension, type 2 diabetes, and dyslipidaemia.*

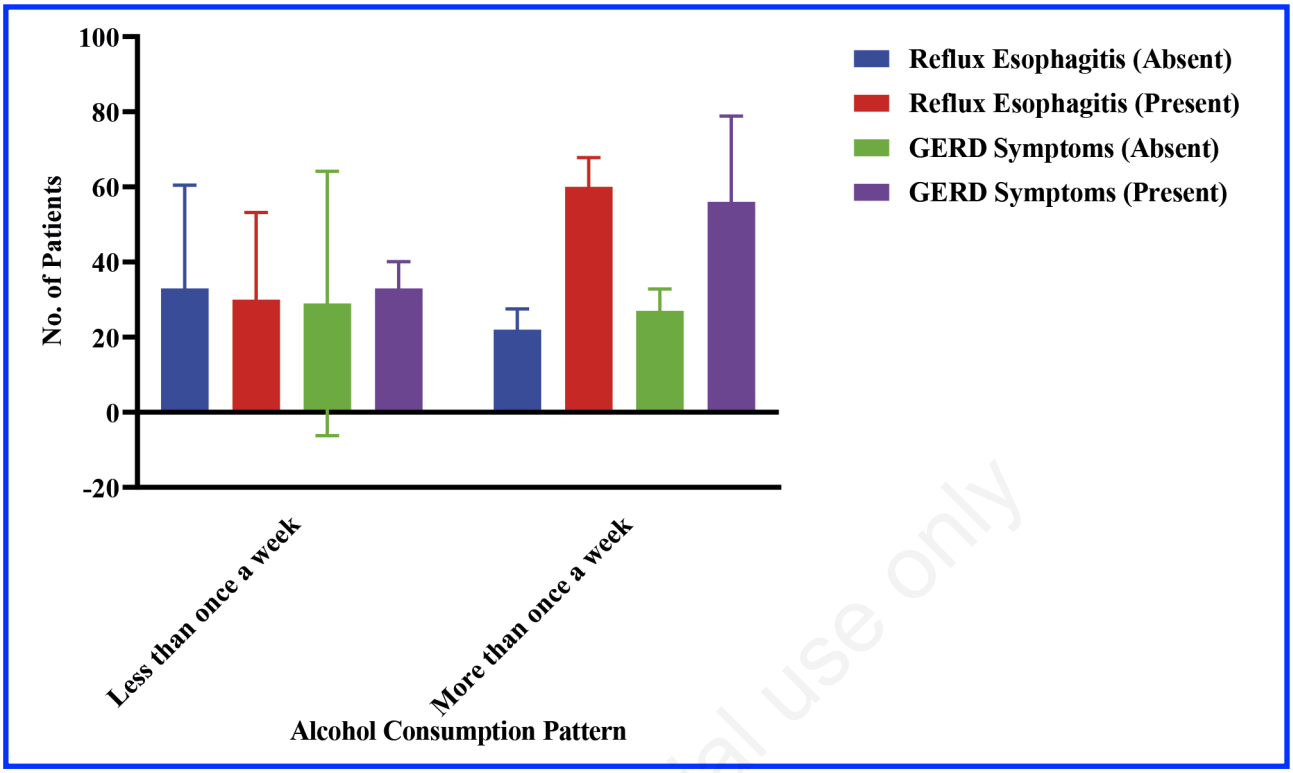

Figure 2. *Alcohol consumption patterns of patients included in the study.*

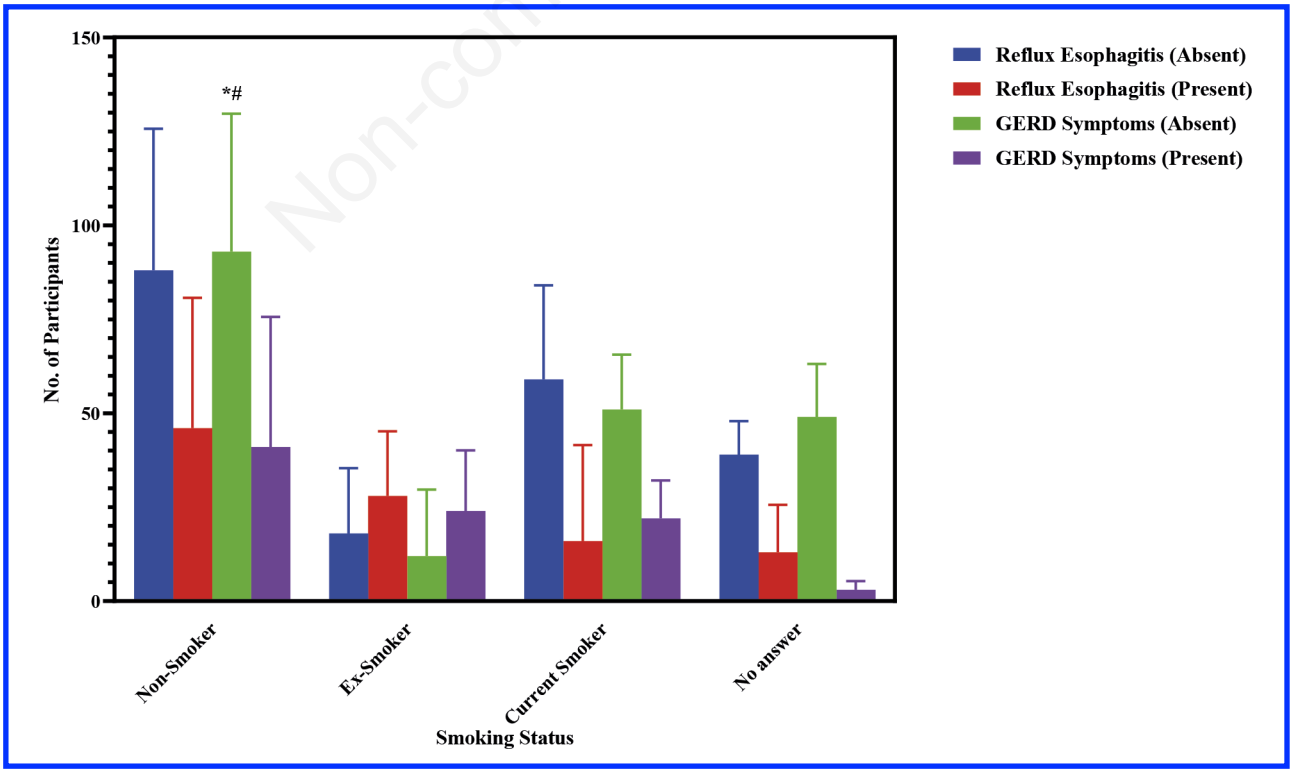

Figure 3. *Smoking characteristics of participants (*p <0.05, #compared to GERD Symptoms (Present).*

The Epworth Sleepiness Scale (ESS) showed no significant difference between individuals with and without reflux esophagitis (p=0.787, power=0.071). However, a significant difference was observed based on the presence of GERD symptoms (p=0.003, power=0.789), with higher mean scores for those with GERD symptoms (6.1±3.5) compared to those without (4.9±2.9).

In the Hospital Anxiety and Depression Scale (HADS), Anxiety showed a marginal difference between individuals with and without reflux esophagitis (p=0.080, power=0.501). A significant difference was observed based on the presence of GERD symptoms (p <0.001, power=0.967), with higher mean scores for individuals with GERD symptoms (5.5±2.3) compared to those without (4.5±3.1). Depression demonstrated no significant difference between individuals with and without reflux esophagitis (p=0.451, power=0.091). However, a significant difference was observed based on the presence of GERD symptoms (p <0.001, power=0.891), with higher mean scores for individuals with GERD symptoms (6.4±4.0) compared to those without (4.8±2.1).

Table 3 provides an analysis of the asymptomatic erosive esophagitis group and the endoscopy-negative reflux disease (ENRD) group based on ANCOVA, with the means and standard deviations presented for each parameter.

In terms of the Multidimensional Fatigue Inventory (MFI), significant differences were observed between the two groups for General and Physical Fatigue (p=0.040, power=0.823), Mental Fatigue (p=0.002, power=0.767), and MFI Total Score (p=0.002, power=0.981). Participants in the ENRD group demonstrated higher mean scores for these dimensions compared to those with asymptomatic erosive esophagitis. For Reduced Activity and Motivation, no statistically significant differences were found between the groups (p=0.078, power=0.457, and p=0.085, power=0.466, respectively). The Epworth Sleepiness Scale (ESS) showed no significant difference between the asymptomatic erosive esophagitis and ENRD groups (p=0.072, power=0.661).

In the Hospital Anxiety and Depression Scale (HADS), while no significant difference was observed for Anxiety between the groups (p=0.352, power=0.253), a significant difference was found for Depression (p=0.002, power=0.985). Participants in the asymptomatic erosive esophagitis group had a higher mean score for Depression compared to those in the ENRD group (see Figure 5).

Table 4 presents the Pearson correlation coefficients between Multidimensional Fatigue Inventory (MFI), Epworth Sleepiness Scale (ESS), and Hospital Anxiety and Depression Scale (HADS) scores. Significant positive correlations were found between MFI dimensions and their respective scores. General and Physical Fatigue exhibited a strong positive correlation with a coefficient of 0.855 (p <0.001), while Mental Fatigue also showed a strong positive correlation with a coefficient of 0.865 (p <0.001). Reduced Activity and Motivation demonstrated positive

***Table 2**. Multidimensional fatigue inventory analysis, reflux esophagitis based on ANCOVA.*

	Reflux Esophagitis (Absent)	Reflux Esophagitis (Present)	Sig.	Statistical Power	GERD Symptoms (Absent)	GERD Symptoms (Present)	Sig.	Statistical Power
MFI								
General and Physical Fatigue	16.1±3.6	16.3±4.0	0.434	0.076	15.7±3.5	18.1±4.2	<0.001	0.979
Mental Fatigue	14.7±2.7	14.7±2.9	0.764	0.060	13.8±2.5	14.2±4.1	<0.001	0.882
Reduced Activity	7.7±4.6	7.7±6.1	0.714	0.060	7.5±1.7	8.4±1.9	0.003	0.688
Motivation	11.2±2.1	11.3±2.7	0.757	0.071	9.8±2.6	12.1±2.4	0.007	0.776
MFI total score	45.7±9.9	55.0±11.5	0.761	0.077	47.6±9.3	55.6±12.7	<0.001	0.899
ESS	5.1±2.1	5.8±2.8	0.787	0.071	4.9±2.9	6.1±3.5	0.003	0.789
HADS								
Anxiety	4.9±3.2	4.8±2.1	0.080	0.501	4.5±3.1	5.5±2.3	<0.001	0.967
Depression	5.7±2.3	5.8±2.6	0.451	0.091	4.8±2.1	6.4±4.0	<0.001	0.891

Note: Mean±SD. Sig. based on ANCOVA. MFI, Multidimensional Fatigue Inventory. ESS, Epworth Sleepiness Scale. HADS, Hospital Anxiety and Depression Scale.

correlations of 0.676 ($p < 0.001$) and 0.739 ($p < 0.001$), respectively.
The correlation between ESS and the MFI dimensions was generally weak. ESS showed a positive correlation with General and Physical Fatigue ($r=0.170$, $p < 0.001$), indicating a mild association. In the realm of HADS scores, both Anxiety and Depression exhibited positive correlations with MFI dimensions. Anxiety showed a correlation coefficient of 0.691 ($p < 0.001$), while Depression demonstrated a correlation coefficient of 0.665 ($p < 0.001$), indicating strong positive associations.
Table 5 presents the results of multiple regression analyses aimed at predicting fatigue from various regressor variables. The beta coefficients (β) and corresponding significance levels (Sig.) are provided for each predictor variable. For Reflux Esophagitis, the beta coefficient is $\beta=-0.496$ with a significance level of 0.881, suggesting no statistically significant association between the presence or absence of Reflux Esophagitis and the predicted fatigue.
In contrast, GERD Symptoms exhibit a beta coefficient of $\beta=3.341$ with a significance level of 0.015, indicating a significant positive association between the presence of GERD Symptoms and the predicted fatigue. This suggests that individuals with GERD Symptoms are expected to experience higher levels of fatigue compared to those without GERD Symptoms. Age, with a beta coefficient of $\beta=0.034$ and a significance level of 0.668, does not show a statistically significant association with the predicted fatigue in this analysis. Gender, on the other hand, demonstrates a significant association with a beta coefficient of $\beta=3.568$ and

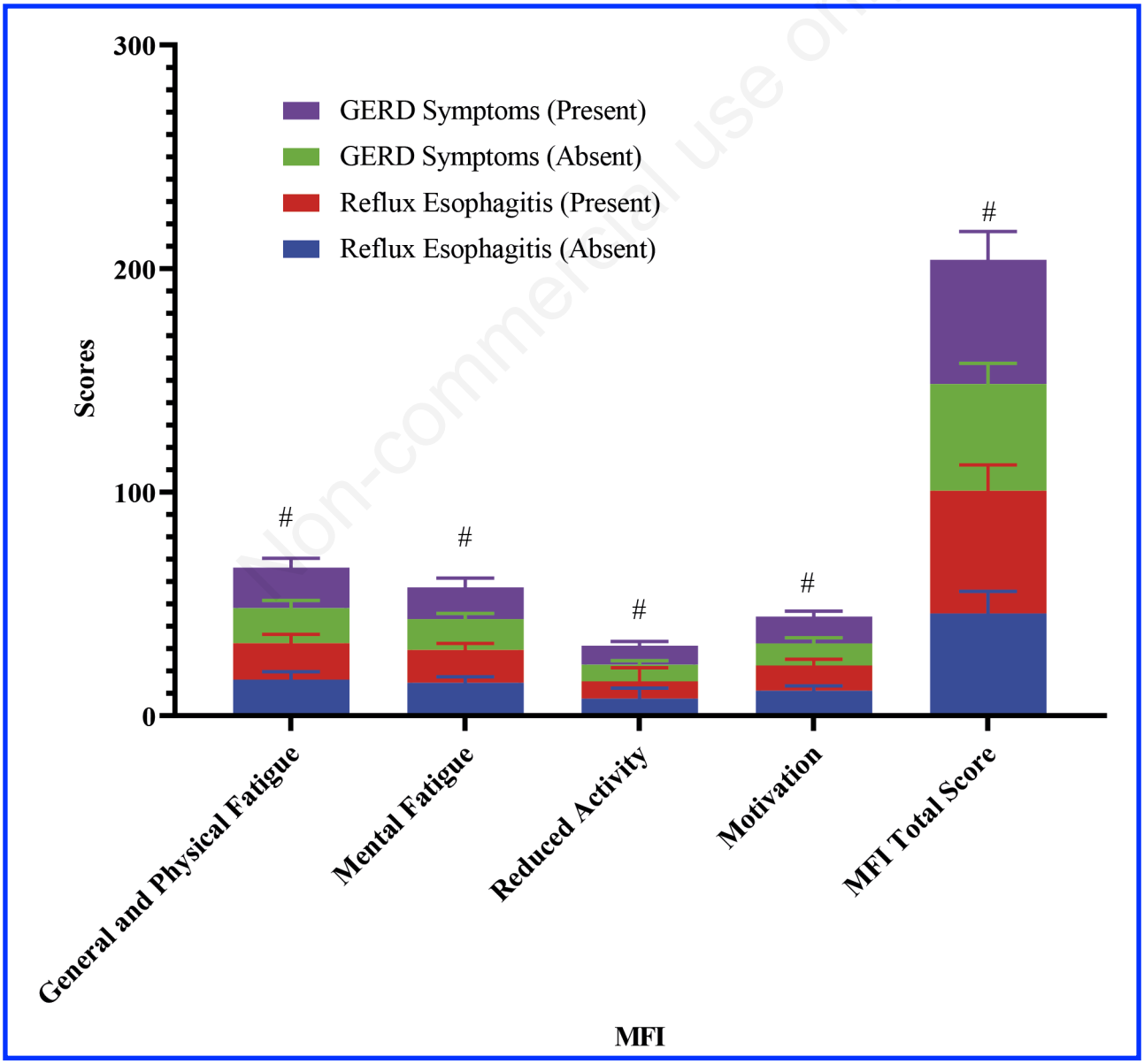

Figure 4. *MFI Scores on various levels of fatigue, activity, and motivation (# implies non-significant differences).*

a significance level of 0.002. This suggests that gender has a notable impact on predicting fatigue, with higher levels expected in one gender compared to the other.
In the Hospital Anxiety and Depression Scale (HADS), both Anxiety and Depression exhibit significant positive associations with the predicted fatigue. The beta coefficient for Anxiety is β=0.657 with a significance level of less than 0.001, and for Depression, the beta coefficient is β=2.927 with a significance level of less than 0.001. These results indicate that higher levels of anxiety and depression, as measured by HADS, are associated with increased predicted fatigue.

Discussion

The study's main findings reveal that the presence of GERD symptoms significantly correlates with heightened levels of fatigue, emphasizing a potential association be-

Table 3. *Analysis of asymptomatic erosive esophagitis group and endoscopy-negative reflux disease (ENRD) groups based on ANCOVA.*

	Asymptomatic Erosive Esophagitis (n=67)	ENRD (n=56)	Sig.	Statistical Power
MFI				
General and Physical Fatigue	15.7±3.4	17.4±3.9	0.040	0.823
Mental Fatigue	14.3±2.4	16.1±2.8	0.002	0.767
Reduced Activity	9.5±5.9	8.3±1.8	0.078	0.457
Motivation	11.0±3.4	10.9±4.4	0.085	0.466
MFI Total Score	47.5±9.8	55.6±12.9	0.002	0.981
ESS	7.0±2.8	6.9±3.6	0.072	0.661

Note: means±SD. ENRD, endoscopy-negative reflux disease. MFI, Multidimensional Fatigue Inventory. ESS, Epworth Sleepiness Scale.

Table 4. *Pearson Correlation between MFI, ESS, and HADS scores.*

	r	Sig.
MFI		
General and Physical Fatigue	0.855	<0.001
Mental Fatigue	0.865	<0.001
Reduced Activity	0.676	<0.001
Motivation	0.739	<0.001
ESS	0.170	<0.001
HADS		
Anxiety	0.691	<0.001
Depression	0.665	<0.001

Note: r, Pearson's correlation analysis.

tween gastrointestinal symptoms and overall well-being. Gender emerges as a notable predictor, with females experiencing greater predicted fatigue than males. Additionally, anxiety and depression, as measured by the HADS scale, demonstrate strong positive associations with fatigue, underscoring the interconnectedness of mental health and fatigue levels. Conversely, the study does not find significant associations between fatigue and the presence or absence of Reflux Esophagitis, age, or the occurrence of asymptomatic erosive esophagitis or endoscopy-negative reflux disease.

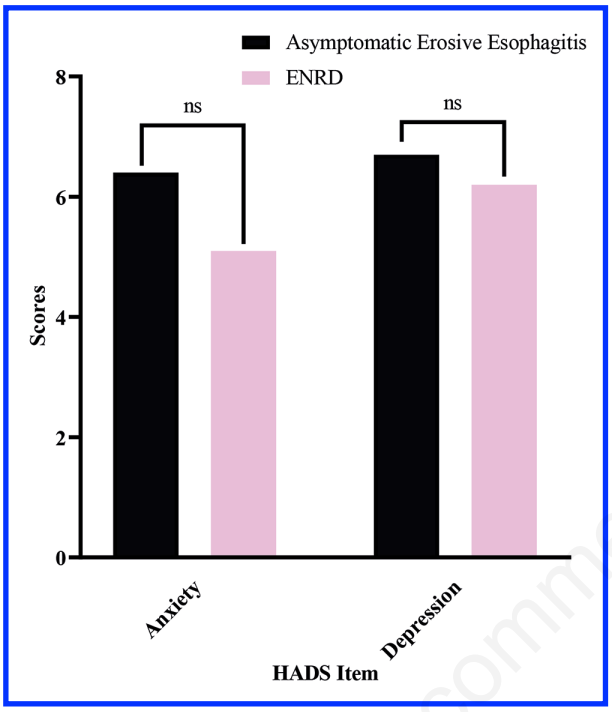

Figure 5. *An ANCOVA to compare HADS scores based on depression and anxiety.*

It is theoretically posited that gastroesophageal reflux disease (GERD) may contribute to fatigue and daytime sleepiness by disrupting sleep through acid regurgitation.[28] In our investigation into the potential link between GERD and fatigue, the study outcomes revealed no significant correlation between fatigue and erosive esophagitis, as measured by the MFI total score and its specific subscales, encompassing general or physical fatigue, mental fatigue, reduced activity, and motivation. Intriguingly, daytime sleepiness was not found to be associated with erosive esophagitis. These findings contrast with epidemiological studies suggesting that individuals experiencing nighttime heartburn may be prone to sleep disorders that subsequently impact daytime performance.[11,29,30] The incongruence prompts a closer examination of the complex interplay between GERD, sleep disturbances, and the subjective experience of fatigue, advocating for further exploration into potential contributing factors such as sleep quality, lifestyle, and dietary habits.

Our findings allude that GERD symptoms, such as acid regurgitation and heartburn, often worsen at night, leading to disrupted sleep. Nighttime awakenings due to GERD can result in poor sleep quality and insufficient rest, contributing to fatigue during the day. Moreover, GERD-related symptoms may prompt individuals to adopt suboptimal sleeping positions or elevate the head of the bed to alleviate discomfort. These adjustments can affect sleep architecture and lead to daytime fatigue.

A systematic review by Jung *et al*.[24] has established an association between gastroesophageal reflux disease (GERD) and sleep disturbance, revealing a bidirectional relationship. While acid regurgitation-induced sleep disruptions may not universally lead to daytime sleepiness, the potential impact of nighttime sleep disturbances on daytime alertness remains evident. Surprisingly, our study

Table 5. *Multiple regression analysis to predict fatigue from regressor variables.*

	β	Sig.
Reflux Esophagitis (absent or present)	−0.496	0.881
GERD Symptoms (absent or present)	3.341	0.015
Age	0.034	0.668
Gender	3.568	0.002
HADS		
Anxiety	0.657	<0.001
Depression	2.927	<0.001

Note: β, Beta coefficient.

did not identify a higher Epworth Sleepiness Scale (ESS) score in individuals with endoscopy-proven erosive esophagitis, challenging the notion that acid contact and regurgitation alone are sufficient to induce daytime sleepiness. This discrepancy suggests that various factors, including psychological influences, contribute to daytime sleepiness. Similarly, the intricate relationship between GERD and fatigue, viewed as a psychophysiological symptom complex, unfolds with nuanced complexity. Previous studies have demonstrated associations between reflux esophagitis and fatigue, highlighting the role of psychosocial stress in influencing reflux severity.[31,32]

The chronic nature of gastroesophageal reflux disease (GERD) can have notable psychological implications, potentially leading to heightened levels of anxiety and stress. These findings align with Gyawali *et al*.[33] who suggested that individuals experiencing GERD symptoms, such as frequent heartburn, regurgitation, and discomfort, may undergo persistent challenges that extend beyond the physical manifestations of the condition. The ongoing discomfort and concern about the recurrence of symptoms, particularly during sleep, can create a cycle of psychological distress. Anxiety, as a common psychological response, may stem from the anticipation of symptom exacerbation or the fear of complications associated with GERD.

Moreover, psychological factors can interact with physiological responses, potentially influencing the perception of symptoms and overall well-being. For instance, heightened stress levels may sensitize individuals to GERD symptoms, making them more noticeable and potentially intensifying the overall impact on psychological and physical health.

The correlation between fatigue and depression was robust, with a notable increase in the prevalence of depression symptoms among individuals experiencing high levels of fatigue. The development of both depression and fatigue involves a multitude of factors, and notably, both conditions are associated with heightened immune system inflammation.[9,34] While previous studies on gastroesophageal reflux disease (GERD) primarily focused on the bidirectional influence of anxiety and depression on patient symptoms,[35,36] our analysis of GERD symptoms revealed a strong association between depression, anxiety, and symptom manifestation, aligning with findings from other studies. In contrast to comparisons based on the presence or absence of endoscopy-proven erosive esophagitis, GERD symptoms such as heartburn and regurgitation demonstrated a correlation with fatigue in both the overall Multidimensional Fatigue Inventory (MFI) scores and specific subscales.

GERD is associated with chronic inflammation in the esophagus.[11] Inflammatory processes can trigger fatigue, and the persistent inflammatory response in GERD may contribute to feelings of tiredness. The immune system's activation during inflammation requires substantial energy resources.[37,39] The body may prioritize these energy resources towards the inflammatory response, diverting them away from other essential processes. This diversion can lead to a general sense of fatigue and tiredness. Inflammatory processes in GERD can result in the release of pro-inflammatory cytokines, signaling molecules that mediate immune responses. Elevated levels of certain cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), have been associated with fatigue.[40] These cytokines can act on the central nervous system, influencing neurotransmitter balance and contributing to feelings of lethargy.

Strengths and limitations

The study has several strengths. The use of the Multidimensional Fatigue Inventory (MFI) provides a comprehensive understanding of fatigue, allowing for a detailed exploration of its various dimensions. The inclusion of psychological factors, such as depression and anxiety, adds depth to the investigation, recognizing the interplay between mental health and GERD symptoms. Lastly, conducting a subgroup analysis of GERD symptoms allowed for a more targeted examination of the relationship between psychological factors, such as depression and anxiety, and the manifestation of symptoms. This enhances the specificity of the study findings. The cross-sectional nature of the study limits the ability to establish causation. Future research with longitudinal designs could offer insights into the temporal relationships between GERD symptoms, psychological factors, and fatigue. Also, reliance on self-reported measures, such as survey responses for GERD symptoms and psychological factors, introduces the potential for recall bias and subjective interpretation.

Conclusions

In conclusion, the study examined the relationship between gastroesophageal reflux disease (GERD), psychological factors, and fatigue. While the chronic nature of GERD was associated with psychological distress, including anxiety and stress, the study did not find a significant correlation between GERD, as confirmed by endoscopy, and fatigue, as measured by the Multidimensional Fatigue Inventory. Notably, GERD symptoms exhibited stronger associations with fatigue and daytime sleepiness than endoscopic findings, emphasizing the impact of symptomatic experiences on well-being. These findings contribute valuable insights into the multifaceted interplay between GERD, psychological factors, and fatigue, shedding light on potential avenues for further research and holistic management strategies for individuals experiencing these health concerns.

Conflict of interest

The authors declare no potential conflict of interest, and all authors confirm accuracy.

Ethics approval and consent to participate

This study was conducted according to the 2008 Helsinki Declaration on experiments involving animal and human subjects. The study was approved by the Institutional Review Board of South West China Medical University. Informed consent was obtained from all participants before participating in the study. All personal identifiers were re-

moved from the data with participants assured of utmost confidentiality and secure storage of the data obtained.

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