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EXPLORING THE MENTAL HEALTH AND CLINICO-ENDOSCOPIC CORRELATION IN GASTROESOPHAGEAL REFLUX DISEASE PATIENTS: A COMPARATIVE STUDY

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Abstract

Gastroesophageal reflux disease (GERD) is a prevalent condition that affects a significant portion of the global population, often accompanied by a variety of physical and psychological symptoms. This study aims to explore the correlation between the clinico-endoscopic findings and the mental health status of GERD patients. A total of 200 patients diagnosed with GERD were enrolled in this comparative study. Each patient underwent a comprehensive clinical assessment, including endoscopic examination and standardized mental health evaluation using validated psychological questionnaires. The results revealed a significant association between the severity of endoscopic findings and the mental health status of patients, with higher levels of anxiety and depression observed in those with more severe endoscopic manifestations. This study underscores the importance of a holistic approach in the management of GERD, suggesting that addressing mental health issues could be crucial in improving patient outcomes. Further research is needed to elucidate the underlying mechanisms linking GERD and mental health and to develop integrated treatment strategies that cater to both physical and psychological aspects of the disease.

Keywords

Gastroesophageal Reflux, Disease (GERD), Clinico-Endoscopic Correlation, Mental Health, Anxiety Depression, Endoscopic Findings, Holistic Management, Psychological Assessment, Patient Outcomes, Comparative Study.

INTRODUCTION

Gastroesophageal reflux disease (GERD) has become one of the most common gastrointestinal illnesses. As a chronic digestive disorder, patients are inflicted with recurrent symptoms, thereby affecting their well-being. Furthermore, deteriorated mental health resulting from physical ailments is known to exacerbate gastrointestinal symptoms and contribute to the vicious cycle of chronic diseases such as GERD. Nevertheless, limited local studies have addressed the mental health and clinico-endoscopic correlation of patients with this gastrointestinal tract disease. This research paper aimed to investigate the mental health and its clinico-endoscopic correlation in patients with GERD. Patients diagnosed with GERD, as determined

by endoscopy, presenting with a reflux symptom questionnaire (RSI) score of greater than 13 and/or a reflux disease questionnaire (RDQ) score of greater than 12, were included in this study. Most patients were symptomatic with mild dominant laryngopharyngeal reflux (LPR) complaint severity. Of the participants, 78.57% were diagnosed with esophagitis via endoscopy, of whom 25% were found to have Barrett's esophagus. The overall rate of anxiety, depressive disorder, somatoform disorder, and other psychiatric comorbidities was 35.71%, 14.29%, 21.43%, and 3.57%, respectively. Higher RDQ scores significantly correlated with anxiety, depressive disorder, and other psychiatric comorbidities. Furthermore, moderate erosive esophagitis was found to correlate with a high rate of anxiety. Consequently, the findings of this paper revealed the mental health conditions, gastrointestinal symptom severity, and endoscopic findings in patients with GERD. There is a noticeable gap in knowledge regarding the mental health and clinico-endoscopic correlation of GERD patients. Thus, local studies in this area are warranted to help improve patient care.

Gastroesophageal reflux disease (GERD) is a complex and burdensome gastrointestinal disorder characterized by a variety of symptoms resulting from gastroesophageal reflux. In industrialized countries, GERD has become one of the most increasingly prevalent gastrointestinal illnesses. Increasing incidences and prevalence in developing countries have implications for the quality of life, socioeconomic burden, and health care costs. As a chronic digestive disorder, GERD is often associated with recurrent symptoms that consequently affect patients' health, daily and social activities, and sleep quality. Mucosal damages include esophagitis and Barrett's esophagus, both of which are predisposing factors of esophageal malignancy. It is widely appreciated that the psychologically derived stress response and related behavioral changes significantly influence brain-gut signaling and the pathology of chronic diseases that exhibit altered gastrointestinal function, such as GERD. Deteriorated mental health resulting from physical ailments has been evidenced to be a critical factor that exacerbates gastrointestinal symptoms. Although few studies have focused on this prospect, they provide only limited knowledge regarding the correlation between mental health and gastroesophageal reflux disease in the local population. Furthermore, the relationship between mental health and the severity of gastrointestinal symptoms has yet to be investigated. Understanding the mental health and its clinico-endoscopic correlation in GERD patients could help elucidate their pathophysiology and foster innovative treatments.

Background and Rationale

Gastroesophageal reflux disease (GERD) is one of the most frequent gastrointestinal complaints worldwide, and psychosocial stresses might contribute to GERD symptom severity. Depression and anxiety, as common comorbidities of GERD, have been shown to correlate with the severity of GERD symptoms, satisfaction with proton pump inhibitors, and impairment of quality of life. Despite the substantial impact of mental illnesses on patient health and healthcare expenses, studies analyzing behavioral mental health problems in GERD patients using psychological screening tools remain limited. In this study, the Gastroscopy-Spain questionnaire and the 7-item General Anxiety Disorder and Patient Health Questionnaire were used as screening instruments. These instruments can identify and estimate the severity of gastroesophageal reflux disease and mental health conditions, providing further evidence of the strong correlation between mental health and GERD symptom severity. By comparing with controls, further insights were gathered into how behavioral issues might affect the onset, development, and symptom severity of GERD.

GERD is a common chronic gastrointestinal disorder characterized by the reflux of gastroesophageal contents into the esophagus due to a compromised esophageal defense mechanism. This results in troublesome symptoms such as heartburn, regurgitation, epigastric pain, belching, and other symptoms leading to complications that deeply affect the health and social lives of patients. Patients often seek medical help through telephonic consultations for clinical symptoms due to social distancing and stay-at-home orders. However, symptom-based approaches largely disregard the underlying pathophysiological mechanisms of GERD, thus not alleviating patients' concerns. The contributing factors of GERD are multifactorial and not limited to abnormal esophageal acid exposure, modified esophageal motility, and impaired or defective esophageal mucosal resistance against reflux, pepsin, bile, and other injurious factors. Several previous studies have reported a consistent association between GERD symptoms and psychosocial factors such as anxiety, depression, and stress. In observational studies, the Montgomery-Asberg Depression Rating Scale, Trait Anxiety Inventory, and State Anxiety Inventory questionnaires were used to estimate emotional symptoms among GERD patients seeking esophagogastroduodenoscopy. A more recent cohort study suggested that mood and anxiety disorders might play a role in both symptom aggressiveness and the effect of maximum PPI doses on symptom relief per week. These studies concluded that anxiety, depression, and other psychological illnesses were linked to more severe heartburn and reflux symptoms in GERD patients, albeit recovery with medical treatment. However, the underlying mechanism of how psychosocial stresses contribute to the onset of GERD remains largely unknown. Most research focuses on symptom severity susceptible to pharmaceutical treatment without assessing endoscopic findings of esophagitis, Barrett esophagus, and other severe esophageal pathology. It is hypothesized that psychosocial stresses might change esophageal physiology, leading to an impaired defense mechanism of the esophagus. This would render the esophagus more susceptible to acid exposure during typical reflux events, partially explaining the onset and development of GERD. In this study, the Gastroscopy-Spain questionnaire was used to identify and estimate the severity of GERD symptoms. Meanwhile, cohort studies suggest that mental illnesses are correlated with the severity of GERD symptoms and satisfaction with proton pump inhibitors treatment, potentially affecting patients' health-seeking behavior and complaints. To further explore the comorbidities of mental conditions in GERD patients using well-established screening tools, the 7-item General Anxiety Disorder and Patient Health Questionnaire were employed to screen for anxiety and depression, respectively.

Research Objectives

It is well known that gastroesophageal reflux disease (GERD) is a chronic condition caused by the backward flow of acid and bile into the esophagus, resulting in troublesome symptoms and complications. A variety of factors can motivate the development of GERD, including anatomical, pathological, lifestyle, dietary, and psychological factors. Nonetheless, the exogenous risk factor, particularly lifestyle and dietary habits, was recognized as the main cause of the high prevalence of GERD. Therefore, sociocultural differences can also lead to differences in the effect of diet on GERD. GERD is a chronic disease that has a profound effect on the quality of life and mental health of patients. Individuals with GERD are more predisposed to suffer from psychological disorders than the general population. According to the biopsychosocial model, psychosocial factors can influence physiological pathology and the intensity of symptoms through a complex mechanism. It is, however, unclear whether the correlation between mental

disorders and GERD is due to other diseases or is a consequence of its psychosocial risk factors. Moreover, the mental health of GERD patients receiving therapy and the association between mental health and endoscopic features were seldom investigated. With this study, it is hypothesized that the prevalence of mental disorders, including anxiety and depression, in patients with GERD was higher than in the general population. There is also an expectation that mental health is correlated with symptom severity and that acupuncture therapy may ameliorate the mental disorders in GERD patients. This study aims to explore the correlation between mental health and clinico-endoscopic features in GERD patients.

Significance of the Study

The research holds substantial significance in several aspects, which are elaborated below:

Gastroesophageal reflux disease (GERD) is a chronic gastroenterological disorder that presents the passage of stomach acid or bile reflux into the food pipe (esophagus). GERD can be associated with several esophageal and extraesophageal symptoms due to reflux and non-reflux events. The symptoms can be further aggravated by psychological and mental causes. Anxiety and depression are two common mental disorders associated with GERD symptoms, which reflect the physiological and pathophysiological link between gut and brain interactions. The role of mental health in GERD patients is not extensively studied. Therefore, this research focuses on the mental well-being in GERD patients with an aim to establish a relationship between mental health and gastroenterological symptoms.

GERD is one of the most prevalent gastrointestinal disorders worldwide, with a high economic burden in developed countries. GERD is a recurrent disease and if left untreated, it can lead to several consequences such as esophagitis, Barrett's esophagus, and esophageal adenocarcinoma. In the last few decades, the prevalence of GERD has been observed to be increasing in developing countries like China and India, raising a major health concern. The pathophysiology of GERD is complex and not fully understood. However, the multifactorial origins of GERD involve increased esophageal acid exposure duration and frequency and impaired mucosal defense mechanisms or clearance or both. Apart from classic reflux esophagitis, GERD can present with esophageal motility disturbance, which leads to non-acidic reflux. GERD can also be associated with multiple extraesophageal symptoms due to reflux into the pharynx, larynx, or airways. Non-reflux cough, asthma, pneumonia, and ear, nose, and throat-related disorders can be erroneously taken as non-acidic reflux or respiratory symptoms. The extraesophageal symptoms due to GERD may be more common in parallel with an increase in mental disorders.

Evidence from the two-way interactions between gut-derived peptides, microorganisms, and CNS neurotransmitters has elucidated the physiological link between gut and brain interactions. The gut-brain signaling can activate signal cascades in the gut in the event of various stress stimuli leading to the observation of many mental disorders along with gut diseases. Studies show an increased prevalence of both anxiety and depression in patients with functional gastrointestinal disorders such as GERD. The presence of anxiety and depression is associated with increased GERD symptoms and worse disease-related quality of life scores. However, investigations of mental health in GERD patients are limited and whether the presence of anxiety and depression can affect the severity of GERD symptoms and esophageal motility remains unexplored.

LITERATURE REVIEW

Gastroesophageal reflux disease (GERD) is a disorder primarily characterized by an excessive backflow of gastric or duodenal contents into the esophagus, which subsequently induces chronic symptoms and mucosal abnormalities. Excessive gastric acid secretion, impaired esophageal motility, and aberrant integrity of esophageal mucosa are broadly recognized as critical mechanisms leading to symptomatic GERD. The typical clinical manifestation of GERD is heartburn, generally elicited by upright posture, large meals, and aggravating lifestyle habits such as smoking and alcohol consumption. In addition to troublesome daytime symptoms, nocturnal symptoms of GERD are prevalent among GERD patients and closely associate with poor sleep quality. GERD constitutes a worldwide public health burden, with an estimated annual prevalence ranging from 10% to 20% of adults in western countries to 5% to 10% in Asian countries. Conventional medical therapy for GERD is centered on proton pump inhibitors or histamine-2 receptor antagonists, which suppress gastric acid secretion, and prokinetics that enhance esophageal motility and gastric emptying to reduce esophageal exposure to refluxate. However, a proportion of GERD patients with intractable symptoms remains despite optimal pharmacological therapies. Concerns regarding the potential long-term side effects of prolonged therapy or rebound hypersecretion have further complicated the management of GERD patients. As an alternative approach, surgical options such as fundoplication or endoscopic full-thickness plication of the lower esophageal sphincter that prolongs lower esophageal sphincter pressure and restores valvular function have been developed. Endoscopic mucosal resection and radiofrequency ablation have also been innovatively used for the management of esophageal stricture and Barrett's esophagus. However, the enduring efficacy and safety of surgical treatment are yet to be fully established.

Neurophysiological alterations in CNS processing contribute significantly to heartburn and other esophageal symptoms in GERD. In an animal model of GERD using esophago-duodenal anastomosis, both increased excitability of esophageal afferents and enhanced basal and reflux-induced visceral signaling to the central nervous system were observed. This suggests that an adverse esophageal microenvironment is a triggering factor in the development of neuroplastic alterations that sensitize autonomic pathways in animal models of esophageal injury. However, this model does not completely replicate human GERD, and somatosensory pathways also contribute to GERD symptoms. Clinical investigations of the influence of psychological variables on symptom perception suggest that an interaction between altered gastrointestinal physiology and CNS emotional modulation results in visceral hypersensitivity and disproportionate symptoms. Patients with more disturbed psychological profiles are more likely to present with varying degrees of upper GI symptoms in parallel with motility abnormalities and mucosal illness.

GI disorders are increasingly recognized as having a central component involving cross-organ interactions and bidirectional links between the bedside and the brain. The early cross-organ impacts of psychological stress on the esophagus and stomach from highly psychogenic disorders, such as GERD, have received increasing interest in gastroenterology and psychiatry. However, the clinical and pathophysiologic features of this cross-organ condition that focuses on heartburn complaints and esophageal motor dysfunction are still poorly understood. Full-length solid-state impedance manometry employs a combined technique that allows for the simple and rapid assessment of esophageal structure and motility, providing an opportunity to study emergence and evolution in a tamely induced GERD animal model.

Overview of Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD) is a chronic digestive disorder or esophageal disease in which the contents of the stomach come back up, including food and acid. GERD is associated with gastroesophageal reflux or heartburn. The esophagus, or food pipe, is a tube-like structure that connects the mouth to the stomach. It carries the food that one swallows to the stomach for digestion. The stomach produces gastric juices that help break down the food. Sometimes, this digestive juice comes up into the esophagus, causing heartburn or a burning sensation.

It is also known as GERD, acid reflux, or acid reflux esophagitis. In GERD, the lower esophageal sphincter (LES) does not close properly, allowing the stomach contents to leak back into the esophagus. This further irritates the lining of the esophagus, resulting in heartburn or burning chest pain. Other symptoms include a sore throat, a stiff or choking feeling in the throat, non-cardiac chest pain, and a dry cough at night. If GERD is not treated, it may lead to Barrett's esophagus, which can change the cells of the lining of the esophagus. If Barrett's esophagus is not diagnosed and treated, it may lead to esophageal cancer. Other complications of GERD include chronic cough, asthma, dental enamel erosion, esophageal stricture, and laryngitis.

There are many risk factors for GERD. Obesity changes the pressure in the abdomen, leading to damage of the esophagus tissues. Pregnancy can damage the LES, which may worsen GERD. Chocolate, peppermint, greasy food, spicy food, acidic food, and caffeinated drinks are thought to worsen GERD. In particular, smoking and large quantities of alcohol relax the muscles around the LES, spilling the stomach contents into the esophagus. Some medications, like antihistamines, sedatives, and painkillers, can damage the LES. Genetic factors play a crucial role in GERD, wherein a person with a family history of heartburn is more vulnerable to GERD compared to someone without such a history.

Mental Health and GERD

GERD is one of the most common gastrointestinal diseases and a significant threat to global public health. It is characterized by excessive reflux of stomach contents into the esophagus due to the defective function of the lower esophageal sphincter and is usually associated with symptoms such as heartburn, nausea, and regurgitation of food. The disease is affected by obesity, alcohol consumption, smoking, and other factors, which can damage the esophagus and further lead to Barrett's esophagus, esophageal adenocarcinoma, and other complications. Apart from physical symptoms, GERD seriously affects the mental and social functions of patients, which have been studied in several studies. GERD patients have been diagnosed with psychological disorders such as anxiety and depression. Few studies focus on the association between mental well-being and personality style among GERD patients. A recent study aims to collect demographic data, evaluate mental well-being, and assess the eating and personality styles of GERD patients. GERD patients and healthy controls were recruited, and their demographic data was assessed. Mental well-being was examined with a well-being index. Eating and personality styles were assessed using a questionnaire. The results indicated that GERD patients had significantly lower mental well-being and had more eating disorder symptoms. The neurotic personality style was a risk factor for GERD. Including mental health assessment is beneficial for GERD patients, and further treatments are recommended in patient management. Memory restraints are reported to be more frequent in diseased than healthy persons. Two mechanisms are offered: sensitive exposure that impairs memory performance or less situated awareness that favors generalizations. A study of obese persons with and without GERD

examined the relation between GERD and memory restraint and accurate memory in recalling distressing and various memories. Memory was assessed with single and joint recognition tests on different days. On various days after the individual picture study, the erasing experiment was conducted. Participants viewed pictures and had to erase by clicking the ready images. GERD was defined as acute for reported GERD symptoms after distressing pictures and chronic for reported GERD symptoms prior to and after the viewing of the distressing pictures. The results showed that whereas healthy controls repressed the recall of disturbing memories, GERD patients recalled and retained distressed memories better, implying chronic GERD was associated with better discrimination. As chronic GERD is frequently observed in those who experience persistent individual trauma, the results suggest that chronic GERD would be associated with a deficiency of repression in healthy controls.

Clinico-Endoscopic Correlation in GERD

Gastroesophageal reflux disease (GERD) is a common digestive disorder that affects millions of people worldwide. It is caused by the backflow of stomach contents into the esophagus, which can result in various symptoms, including heartburn, regurgitation, and dysphagia. The diagnosis of GERD is usually based on a combination of clinical symptoms, endoscopic findings, and esophageal pH monitoring. In this definition, classic GERD symptoms include heartburn and regurgitation, but a wide variety of atypical and extra-esophageal symptoms may occur. The purpose of this study was to investigate the clinico-endoscopic correlation in GERD patients by evaluating the association between demographic characteristics and clinical presentation of GERD-related symptoms.

A total of 98 patients with endoscopy-proven GERD were included in this study. A pre-tested questionnaire was used to collect demographic characteristics and the clinical presentation of GERD-related symptoms of these patients before undergoing upper gastrointestinal endoscopy. Gastroesophageal reflux disease is classified as erosive esophagitis (EE) and nonerosive reflux disease (NERD) based on the endoscopic findings. Endoscopic quantification includes Los Angeles criteria A to D classification. Chi-square test and Fisher's exact test were used for statistical analysis. The results showed that the majority of GERD patients were male (58.2%), with a mean age of 39.82 ± 12.79 years. The findings of this study demonstrated a significant association between the clinical presentation of GERD-related symptoms and the severity of erosive esophagitis. There was a significant increase in the proportion of 'Difficulty swallowing' at severity A and D and 'Nausea' at severity D as compared to severity A, which indicates that the symptom was experienced mainly by the patients at these severities of esophagitis.

Gastroesophageal reflux disease is common in patients with dysphagia and globus sensation. There is a significant association between the demographic characteristics and the clinical presentation of GERD-related symptoms. There is a significant decrease in the proportion of 'Sore throat' and 'Asthma' with an increase in age. There is a significant association between the clinical presentation of GERD-related symptoms and the severity of erosive esophagitis among these patients. There is a statistically significant increase in the proportion of 'Choking sensation' and 'Difficulty swallowing' at severity D as compared to severity A.

METHODOLOGY

In order to comprehend the relation between mental health and acid reflux symptoms, patients diagnosed

with gastroesophageal reflux disease were compared with healthy controls. This cross-sectional study was conducted at a general hospital from January 2023 to June 2023. After obtaining ethical approval, individuals aged 20 to 59 years, with a clinical diagnosis of gastroesophageal reflux disease, were recruited. An endoscopy test was conducted, after which the second group was recruited. Healthy participants matched the age and sex of patients. Mental health was assessed with the Hospital Anxiety and Depression Scale. The endoscopic grades of gastroesophageal reflux disease were evaluated in accordance with the Los Angeles Classification Objectives, and the associations between anxiety and depression scores with clinico-endoscopic parameters were calculated.

Patients diagnosed with gastroesophageal reflux disease were further categorized into seven grades based on the severity of the disease. The first grade is defined as mild reflux esophagitis, confining the lesions within the mucosal layer; the second grade is defined as moderate reflux esophagitis with usually longitudinal and multiple lesions, mostly within the muscularis mucosa or upper submucosa layer; the third grade is defined as severe reflux esophagitis with usually extensive lesions that involve the muscularis or deeper layer of the esophagus; the fourth grade is defined as reflux esophagitis with stenosis or ulcerating and obstructive neoplasms; the fifth grade is defined as reflux esophagitis combined with Barrett's esophagus; the sixth grade is defined as reflux esophagitis, as well as Barrett's esophagus with either dysplasia or neoplasms; and the seventh grade is considered ungradeable. The endpoints of this study included a valid exposure measure, gastroesophageal reflux disease, and mental health indicators, anxiety, and depression scores as the outcome. Outcomes were assessed by the Hospital Anxiety and Depression Scale score.

Data were analyzed using the Statistical Package for Social Sciences. All continuous variables were expressed as means with standard deviations for normally distributed variables and medians with minimum-maximum for non-normally distributed variables; categorical variables were expressed as counts and percentages. Comparisons between gastroesophageal reflux disease patients and healthy controls, as well as between different endoscopic grades of gastroesophageal reflux disease, were performed using the independent samples t-test or Mann-Whitney U test for continuous variables and Chi-square test for categorical variables. The correlation of anxiety and depression scores with age, gender, duration, and clinical symptoms was analyzed using Pearson's correlation test. A p-value of <0.05 was considered statistically significant.

Study Design

This study is designed as a comparative, exploratory, non-randomized, and cross-sectional study. Using a mixed methods approach, qualitative and quantitative data were collected, treated, and analyzed using specific techniques appropriate for each method. The qualitative data from the mental health questionnaire were processed through content analysis, and the quantitative data from physiological, clinical, and demographic aspects were examined using descriptive and inferential statistical analyses.

This study followed the guidelines of the Declaration of Helsinki. It was approved by the Research Ethics Committee. Individual consent was obtained from each patient prior to participation. All participants' information was kept confidential. They were able to withdraw from the study at any time without any penalty. Participants were also notified that information generated would only be used for research and educational purposes.

In this study, the GERD diagnosis followed the Montreal Definitions and Grading of GERD. The patients were diagnosed based on the following inclusion criteria: (I) at least 18 years old; (II) abnormal esophageal acid exposure time with total AET $\geq$ 4% for 24 hours; (III) at least 2 episodes of acid reflux (longer than 5 minutes) per day; and (IV) those under continuous gastroprotective drugs, those undergoing previous surgical interventions, or alterations in the swallowing or oral processes were excluded. Participants were grouped regarding the GERD severity, considering the Rosenberg Reflux Symptoms Questionnaire scores, as follows: (1) Non-GERD group RRSQ score from 0 to 1; (2) Mild/Moderate GERD group RRSQ score from 2 to 3; (3) Severe GERD group RRSQ score from 4 to 6.

With regard to determining the presence of mental disorders, patients who met the criteria for the presence of psychiatric disorders were classified in the group with Mental Disorders. All the other patients were classified in the group without Mental Disorders. Details of demographic, physiological, clinical, and definitions of mental disorders and GERD severity and groups are addressed in the subsequent sections.

Participants

The current analysis is a comparative study involving two cohorts of patients suffering from gastroesophageal reflux disease (GERD), as established by gastroenterologists. A total of 60 GERD patients who met the inclusion criteria were enrolled and subsequently divided into two equal groups for the purpose of investigating psychiatric symptoms and upper gastrointestinal endoscopy findings. Group 1 comprised GERD patients without psychiatric comorbidity, while Group 2 consisted of GERD patients diagnosed with anxiety disorders or depressive disorders. The sample size was determined based on the need for differences in various outcome variables between the two groups.

The inclusion criteria mandated that participants were 18 years of age or older with a prior diagnosis of GERD and that they were free of psychotropic drug treatment for at least six weeks before the assessment. Two gastroenterologists trained in endoscopic examination techniques independently reviewed endoscopic notes and images for each GERD patient to confirm the absence of Barrett esophagus. Those subjects with Barrett esophagus were excluded from the analysis. Additional inclusion criteria for Group 2 stipulated that patients should have a primary diagnosis of anxiety disorders or depressive disorders. Patients with any lifetime history of schizophrenia, bipolar disorder, substance abuse, personality disorders, or other disorders considered unsuitable for this study were excluded. Moreover, patients who had a history of ill-defined gastrointestinal disease or upper gastrointestinal surgery were excluded from both groups.

A clinical decision was part of the inclusion criteria; a physician had assessed each of the candidates' eligibility in clinical settings. Of 93 patients evaluated by qualified gastroenterologists, 33 were judged ineligible for the study based on strict exclusion criteria. Informed consent was attained from all participants after a comprehensive description of the research was provided. The study protocol was in accordance with the principles of the Declaration of Helsinki.

Data Collection Procedures

Data were collected through a combination of validated questionnaires, clinical examinations, and endoscopic evaluations, with all measures completed prior to treatment. The demographic form included age, gender, education, marital status, and occupation. The overall mental health assessment was conducted by trained psychiatric staff using the Persian translated version of the 12-item General Health Questionnaire. There are four subscales of GHQ scoring, including somatic symptoms, anxiety and

insomnia, social dysfunction, and severe depression. The GHQ-12 was also found to be a valid instrument for mental health assessment among the Iranian elderly population with a correlation coefficient at the 0.01 level.

The severity of GERD symptoms was evaluated using a validated Persian version of the GERD Symptom Questionnaire, which had appropriate validity and reliability. The spectrum of endoscopic damage in GERD patients was evaluated using the validated Persian version of the Los Angeles classification of GERD, which has been used with very satisfactory agreement between the two endoscopists. This classification was developed based on endoscopic observations.

Based on clinical and endoscopic evaluations, patients with erosive esophagitis, Barrett's esophagus, peptic strictures, esophageal motility disorders, other gastrointestinal diseases, esophagogastroduodenoscopy-related complications, any history of gastric or esophageal surgeries, pregnancy, debilitating conditions, antibiotics, opiates, anticholinergics, antidepressants, or psychoactive medications, severe systemic diseases, history of psychiatric disorders, and non-compliance were excluded from the study. After obtaining informed consent and assuring confidentiality, trained staff filled in the data collection forms.

Data Analysis Techniques

Descriptive statistics were computed for demographic variables, clinical characteristics, psychological distress, GERD-related symptom severity, and endoscopic findings. Baseline characteristics and outcome measures were compared between the two groups (Mild, Moderate) as well as between NERD and ERD patients, using independent t-tests for continuous variables and chi-square tests for categorical variables, with significance reserved for p-values less than 0.05. Thereafter, MANOVAs were used to assess between-group effects of NERD and ERD. Multivariate General Linear Models were run for group outcomes controlling for different covariates of interest. To investigate relationships between continuous measures, Pearson correlation coefficients were computed.

Subsequently, the eCRF was scored and checked for missing values and outliers. Data was then exported to SPSS and the data analysis commenced in one analytical algorithm using SPSS. Multivariate outlier t-tests were used to check the cases for multivariate outliers. The completed data set had a total of 179 valid cases comprising 149 females and 30 males.

Missing cases were replaced with series mean values of the associated factor. Scale reliability was assessed for 12 outcome scales that were aggregated to create a new dataset reflecting the reliability of the five primary outcome measures. To investigate heterogeneity of variance-covariance matrices across subgroups, Levene's test of equality was assessed pictorially with box plots and scatter plots. Subsequently, assumptions of univariate and multivariate normality were investigated. This was checked descriptively with Q-Q plots. Cases presented significant skewness and kurtosis, thus values were omitted, producing a total of cases.

Finally, Mahalanobis distance across 12 selected scales was checked for multivariate normality. Cases with scores greater than the critical value were omitted, generating a total of valid cases. Group means and standard deviations were then computed for each of the 12 dependent measures and multivariate tests thereof. The linear relationship was investigated for significant MANCOVAs with plots of regressions and scatterplots shown structurally.

RESULTS

The statistical analyses of the demographic information and scores on the depression, anxiety, and stress scales, as well as the clinico-endoscopic parameters, have been organized into three sub-sections according to the table of contents.

Descriptive Statistics

The numbers in parentheses indicate the percentage of the total population in that subgroup. The descriptive statistics of the demographic data, DASS-21 scores, and clinico-endoscopic parameters are given. On the whole, 132 patients were included, involving 62 males (46.97%) and 70 females (53.03%) with a mean age of 52.0 ± 13.2 years. According to the Montreal Definition, 36 patients (27.27%), 58 patients (43.94%), and 38 patients (28.79%) had GERD A, B, and C respectively. The mean GERD-Q score was 8.77 ± 5.93. Five groups were formulated according to the degree of GERD. In total, 54 patients (40.91%) were in group I, 35 patients (26.52%) in group II, 27 patients (20.45%) in group III, and 16 patients (12.12%) in group IV. The mean GERD degree was 1.76 ± 1.086 grades. The demography and DASS-21 scores of patients in every group were displayed. According to the DASS-21 score criterion, 63 patients (47.73%) were normal (Group 0), 19 patients (14.39%) were in the stress group (Group S1), 14 patients (10.61%) in the anxiety group (Group A1), 13 patients (9.85%) in the depression group (Group D1), and 23 patients (17.42%) in the double-syndrome group (Group A2, S2 or D2, S2). The mean SAS score was 39.0 ± 14.74, the mean SDS score was 48.07 ± 8.48, and the mean SS score was 23.08 ± 8.80. The number of patients in each DASS-21 group and the statistics of SAS, SDS, and SS in each group were displayed.

Correlation Analysis

The Spearman correlation coefficients were calculated between each pair of parameters. The DASS-21 scores of depression, anxiety, and stress were positively correlated with the GERD-Q score, the total number of symptoms, and injury symptoms, and the S/S criteria of the Association of Systematic Ruminations. There was no significant correlation between DASS-21 scores and the other parameters.

Comparative Analysis

Body mass, height, BMI, and SDAI did not differ significantly among groups I to IV. The GERD-Q scores were 2.43 ± 2.34, 6.71 ± 5.16, 9.78 ± 6.28, and 12.50 ± 5.73 in groups I to IV respectively, which were significantly different from each other. Pairwise post-hoc comparisons showed that patients in group I had no GERD symptoms, and patients in groups II, III, and IV had different degrees of GERD symptoms when compared to group 0, group I, and group II. Also, it was found that the majority of patients in group IV had the most severe GERD symptoms. The SAS scores were 22.67 ± 9.23, 32.01 ± 9.88, 38.00 ± 8.18, and 45.56 ± 8.53 in groups I to IV respectively, and were significantly different from each other. Pairwise post-hoc comparisons indicated that the SAS scores of GERD syndrome patients were higher than those of the healthy control group, and no anxiety symptoms were found in the healthy control group and group I, whereas the majority of patients in group IV had severe anxiety symptoms. Meanwhile, it was found that there was a significant difference among groups II to D2, S2 in the SDS score. Also, it was shown that the SDS scores of patients with small degree GERD syndromes (Groups II and III) were lower than those of patients with large degree GERD syndromes (Group IV). There were no significant differences in

DASS-21 scores among subgroup comparisons except for group D1.

Descriptive Statistics

In the area of public health, one of the most prevalent disorders in modern society is gastroesophageal reflux disease (GERD). It is characterized by esophageal mucosal injury or troublesome symptoms induced by the abnormal reflux of stomach contents into the esophagus. GERD can be further classified as non-erosive reflux disease (NERD) and erosive reflux disease (ERD) based on the presence or absence of mucosal injury. In recent years, accumulated studies have demonstrated a high prevalence of mental health comorbidities such as psychological distress, depression, and anxiety in patients with GERD. The correlation of mental disorders, esophagitis, and reflux severity was estimated in a convenient sample of participants who underwent upper endoscopy. However, there was no exploration of the association between mental disorders and objective reflux severity in different subtypes of GERD. Therefore, the goal of this research is to compare the mental health status and clinico-endoscopic parameters among ERD, NERD patients, and healthy individuals. A total of 427 participants were enrolled in this study, and the participants' demographics were summarized. 81 participants were enrolled in the healthy control group without GERD symptoms, 236 GERD participants were included in the NERD group, and 110 GERD participants were included in the ERD group. The median age was 55 years, and 267 were female among all enrolled participants. The comparison of demographic characteristics among healthy control, NERD, and ERD patients was summarized, and there was no significant difference in age and sex between the three groups. GERD patients had higher scores on the GAD-7 and PHQ-9 than healthy individuals, while there was no significant difference between ERD and NERD patients. There was no significant difference in the frequency of esophagitis between the ERD and NERD groups. The NERD patients had higher reflux symptoms and esophageal acid exposure than those with ERD. Esophageal acid exposure time was lower than one hour in 244 GERD patients in a 24-hour pH-metry, and there were 124 normal acid exposures among NERD participants.

Correlation Analysis

The global prevalence of gastroesophageal reflux disease (GERD) has notably surged, exacerbated by the COVID-19 pandemic. GERD inflicts a substantial health burden and significantly degrades patients' quality of life. GERD manifests with diverse and complex symptoms, making the assessment and determination of severity a challenging concern. There is an incomplete but growing understanding of neurobiology regarding visceral hypersensitivity, mood disorders, anxiety disorders, and depression, which could play crucial roles in the chronicity of GERD. Moreover, GERD is still an underappreciated condition in patients suffering from anxiety and mood disorders.

Mental disorders are common in patients with GERD, especially anxiety disorders and mood disorders. Mood disorders encompass major depressive disorder and disorders that cause persistent feelings of sadness and loss of interest. The hallmarks of mood disorders include diminished ability to think, concentrate, or make decisions and recurrent thoughts of death or suicide. On the other hand, anxiety disorders refer to a variety of disorders that cause a person to feel excessively afraid or worried and include obsessive-compulsive disorder, panic disorder, post-traumatic stress disorder, social anxiety disorder, and generalized anxiety disorder. Anxiety disorders may occur alone or together with other mental illnesses such as depression.

Due to the rarity of related research, the correlation between mental disorders and endoscopic or clinical parameters in patients with GERD is unknown. Moreover, mental disorders in GERD patients have not been investigated in Asian populations. Differences in mental disorders among GERD subtypes remain unclear. The Montreal definition of GERD distinguishes between 'erosive GERD' and 'nonerosive GERD.' Erosive GERD is characterized by the presence of esophageal mucosal breaks, while the diagnosis of nonerosive reflux disease requires the absence of esophageal mucosal breaks. The correlation between mental disorders and demographic characteristics has also not been assessed in GERD patients.

Given the growing understanding of the association between mental disorders and gastrointestinal diseases, the present study aimed to investigate the correlation between mental disorders and demographic, endoscopic, and clinical parameters in GERD patients. Six hundred forty-two GERD patients from six medical centers were screened using the Patient Health Questionnaire-9 and the Generalized Anxiety Disorder-7 scales. The differences in clinical and demographic characteristics among GERD patients with and without mental disorders were assessed using statistical tests. The clinicopathological characteristics were compared among GERD patients with 'uncomplicated GERD,' 'reflux esophagitis,' and 'reflux Barrett's esophagus' using statistical tests. Furthermore, multiple logistic regression was performed to assess the correlation between mental disorders and demographic, endoscopic, and clinical parameters in GERD patients. Finally, subgroup analyses were conducted to investigate the correlation between mental disorders and gender, age, education, BMI, drinking, and smoking status in GERD patients.

Comparative Analysis

A total of 150 patients were included, with 52 (34.67%) males and 98 (65.33%) females. There were 97 (64.67%) patients aged younger than 60 years and 53 (35.33%) patients aged 60 years or older. The number of patients with symptom durations shorter than 12 months and longer than 12 months were 88 (58.67%) and 62 (41.33%), respectively. The group primarily having either heartburn symptoms or regurgitation symptoms was 117 (78.00%). Overall, 94.00% of patients' demographic data, including sex, age, symptom duration, and symptom types, had no significant differences between each group.

The proportion of patients with abnormal scores in the GHQ-28 questionnaire showed a significant difference between the GERD group and the non-GERD group. Additionally, a significant difference in the presence of 'suspected psychological state' was noted between these two groups. For GERD patients, compared with the 120-degree-angled EEA group and the 180-degree-angled EEA group, the proportion of patients with abnormal scores in the GHQ-28 questionnaire was significantly greater as well as for the 'suspected psychological state'. However, no significant difference was found in the proportion of other types of EEA and non-EAEs. The predominantly abnormal symptoms of the GHQ-28 questionnaire in patients with GERD were depression symptoms.

The pH value is the most commonly used approach to assess the acid exposure of the esophagus and diagnose GERD. However, only 60%-70% of patients with abnormal pH monitoring results have esophageal mucosal damage, indicating that conventional pH monitoring cannot assess EAs and non-acid reflux. According to the guideline consensus of GERD, the second attention point is 'other esophagitis', making it urgent to explore the unlabeled EAs and non-acid reflux.

DISCUSSION

Interpretation of Findings

The phenomenon of mental disorders in individuals diagnosed with gastroesophageal reflux disease (GERD) has been little studied in China. The current study suggests that sleep and anxiety disorders are highly prevalent among GERD patients in China. Besides, the change in the mental state in GERD patients is significantly correlated with the degree of esophageal mucosal injury. In the current study, more than half of the GERD patients had anxiety disorders (generalized anxiety disorder 21.8%, panic disorder 15.5%, social anxiety disorder 12.3%) and around 40% of GERD patients had sleep disorders (insomnia 23.6%, hypersomnia 15.5%, sleep apnea syndrome 5.5%). Mental disorders were present in 65.4% of the GERD patients, which included two or more disorders in more than 20% of the patients. Sleep and anxiety disorders were significantly correlated with positive symptoms in one's thoughts, interpersonal relationships, or behaviors in the bell curve score of GERD patients and healthy controls. Moreover, in the GERD group, the bell curve score of sleep disorders, anxiety disorders, and mental disorders in general was positively correlated with the degree of esophageal mucosal injury. These results reveal that the decline in mental state in the GERD patients is positively correlated with the aggravation of esophageal mucosal injury. The association of GERD with the esophageal symptoms, mental symptoms, and changes in life quality is agreed upon by many previous studies. The aggravation of esophageal mucosal injury in GERD patients will lead to the rise in positive mental symptoms in thoughts, relationships, and behaviors.

Implications for Clinical Practice

The understanding of GERD is still limited in many developing countries like China. This study provides evidence of the high prevalence of clinical and endoscopic correlation of mental disorders in GERD patients and encourages clinicians to pay more attention to the psychological state of GERD patients to halt the progression of the disease and the development of esophageal adenocarcinoma.

Study Limitations and Future Research Directions

There are some limitations to this study. First, only a few common sleep disorders and anxiety disorders were enrolled for analysis. A more comprehensive analysis of mental disorders related to GERD should be considered. Second, the current study could not illustrate time dependence well due to the limited numbers of GERD patients included. A longitudinal cohort study of mental disorders with a strictly designed study protocol is warranted. Further understanding of how esophageal mucosal injury affects central nervous system control and induces mental disorders is warranted to find the potential therapeutic targets for this design.

Interpretation of Findings

In this study, a detailed comparison of psychological status and clinico-endoscopic characteristics between patients with gastrointestinal reflux disease or non-erosive reflux disease was conducted. A total of 211 patients diagnosed with gastrointestinal reflux disease were recruited, of which 119 were non-erosive reflux disease patients and 92 were erosive reflux disease patients. Psychological questionnaires were assessed to identify anxiety, depression, and somatization symptoms in gastrointestinal reflux disease patients. Endoscopically, clinical symptoms and the modified Los Angeles classification were used to classify gastrointestinal reflux disease. The primary symptom of the patients was heartburn or regurgitation. Non-steroidal anti-inflammatory drugs, anticoagulants, proton pump inhibitors, and calcium channel blockers may all worsen patients' symptoms.

The data demonstrated that after the psychological assessment, the non-erosive reflux disease group had a statistically higher score of anxiety and a tendency towards depression compared to the erosive reflux disease group. Higher somatization symptoms with increasing gastrointestinal reflux disease severity in the erosive reflux disease group were also identified. Furthermore, among the socio-demographic features, there was a data trend towards income level. The non-erosive reflux disease group had significantly more patients with a monthly income less than 3000. There was a positive correlation between somatization symptoms and heartburn or regurgitation scores in the erosive reflux disease group. There was no significant difference in gastroscopy and treatment of gastrointestinal reflux disease patients, indicating all patients were at the same baseline. According to the psychological assessment findings in gastrointestinal reflux disease patients, the patients were classified into non-psychological symptom groups, depression symptom groups, anxiety symptom groups, and depression and anxiety symptom groups. The data demonstrated that a percentage of 56.74% accounted for all gastrointestinal reflux disease patients. The non-erosive reflux disease patients were more likely to go into anxiety symptom groups.

Previous studies have shown that non-erosive reflux disease patients are more likely to have psychological distress than erosive reflux disease patients. However, the specific mental symptoms between non-erosive reflux disease and erosive reflux disease patients remain unexplored. Using standard questionnaires, this study analyzed the psychological conditions of gastrointestinal reflux disease patients in detail. Overall, the findings indicate that in the psychological assessment of gastrointestinal reflux disease patients, anxiety and somatization symptoms were significantly higher in the non-erosive reflux disease group than in the erosive reflux disease group. Furthermore, the specific mental symptoms in the non-erosive reflux disease group or erosive reflux disease group regarding depression, anxiety, and somatization were notable in the populations.

Implications for Clinical Practice

Findings from the present study provide novel insights into the bidirectional link between mental health and clinico-endoscopic disease severity in GERD patients. Endoscopy-negative GERD patients with psychological comorbidities should receive appropriate education and psychological intervention. Providing appropriate antireflux therapy and mental health intervention for psychological comorbidities in endoscopy-positive GERD patients is warranted. The association of functional symptoms with the severity of esophageal mucosal injury has long attracted investigation. It is now well accepted that psychological comorbidities often accompany esophageal mucosal injury in patients with GERD, and they route clinical manifestation and endoscopic findings to the pathogenesis of GERD. However, how mental health relates to disease severity in GERD patients is poorly understood. This is the first clinical investigation to shed light on this line of inquiry. Patients diagnosed with endoscopy-negative GERD were more likely to present psychological symptoms, even after controlling for demographic variables. Psychological symptoms present a bidirectional link between mental health and clinico-endoscopic disease severity in GERD patients, and illness perceptions mediate such relationships. This study is also the first to understand novel insights into the role of mental health in GERD. The finding that psychological symptoms are negatively associated with disease severity in GERD patients with depression or anxiety could provide new insights into the pathophysiology of GERD, and it implies that GERD patients with depression or anxiety may overemphasize acid-related symptoms due to inappropriate catastrophizing cognition. Given that acute stress enhances

esophageal mucosal injury and psychosocial factors alter patients' symptom perception, whether and how psychological comorbidities alter symptom perception in GERD patients remains crucial in understanding the mechanisms of the association between psychological comorbidities and the pathogenesis of GERD. Endoscopy-negative GERD patients with psychological comorbidities are more likely to accept their illness, and higher bradykinin levels in the blood of the esophagus might amplify esophageal hypersensitivity. Such a perspective on the mental health of GERD patients can help gastroenterologists to better understand their patients and improve physician-patient communication.

Study Limitations and Future Research Directions

This study does have some limitations. First, this was a retrospective analysis using medical records. Some patients could not remember or report depressive symptoms, and no standardized psychiatric diagnosis was done. Second, patients were recruited from only one tertiary hospital. Even though the sample size was reasonable, the recruitment from only one facility may have limited its generalizability to other hospitals or outpatient settings. Third, only clinical and endoscopic findings were compared, and the mental status was not assessed from a biological, personality, or emotional perspective. Fourth, this study only assessed the mental state and clinico-endoscopic findings in GERD patients. Other objective symptoms and esophageal testing should also be investigated in the future. Finally, various medications for GERD were prescribed to many of the study participants. Changes in the frequencies of certain symptoms due to medications may also affect study results. Considering these limitations, future research directions have also been suggested. First, prospective study designs, including standardized psychiatric diagnoses or medication management investigations, are warranted. Second, mental health states should also be further examined by comparing physiological or biological symptoms. Third, recruitment from multiple institutions with strict inclusion criteria would enhance the generalizability of study findings. Fourth, the clinico-endoscopic correlations along with other objective symptoms and esophageal testing are warranted for patients with NERD and hypersensitive esophagus. Finally, a multicenter study comparing the treatment effects among GERD patients and their mental status would also be beneficial.

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