

# A Long Duration of Reflux Symptoms is the Predominant Risk Factor for Depression in Vietnamese Patients with Gastroesophageal Reflux Disease

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**Purpose:** Depression is more prevalent in patients with gastroesophageal reflux disease (GERD) than in controls. The disorder can worsen the quality of life of GERD patients and is also associated with poor treatment response. However, there are limited data on its prevalence and risk factors in GERD patients in Southeast Asia. We aimed to assess the prevalence and severity of depression and its associated factors in Vietnamese patients with GERD.

**Patients and methods:** A cross-sectional study was conducted on GERD patients. GERD was defined as troublesome typical reflux symptoms at least twice a week or having endoscopic erosive reflux disease. The revised Beck's Depression Inventory (BDI-IA), which has been locally validated, was used to evaluate depression (BDI-IA < 10: none, 10–18: mild to moderate, 19–29: moderate to severe, and ≥ 30: severe depression). Multiple logistic regression analysis was used to identify independent factors associated with depression.

**Results:** A total of 194 patients were recruited. The mean age was  $44.1 \pm 12.0$  years, and the male-to-female ratio was 1:1.2. The depression rate was 47.9% (mild to moderate: 30.9%, moderate to severe: 16.0%, and severe: 1.0%). In multivariate analysis, sex and duration of reflux symptoms were the only two risk factors for depression. Compared to males, females were more likely to suffer from depression: odds ratio (OR) = 3.941 (95% confidence interval [CI], 1.386–11.205),  $p = 0.010$ . Compared to patients with a duration of reflux symptoms < 1 year, those with a duration of 1–10 years and > 10 years were more likely to suffer from depression with a dose–response: OR = 3.520 (95% CI, 1.057–11.717),  $p = 0.040$ ; and OR = 5.605 (1.046–30.019),  $p = 0.044$ , respectively.

**Conclusion:** Depression was prevalent, and a long duration of reflux symptoms was its predominant risk factor in Vietnamese patients with GERD.

**Keywords:** gastroesophageal reflux disease, depression, prevalence, Vietnam

## Introduction

Gastroesophageal reflux disease (GERD) and depression are major health issues worldwide.<sup>1,2</sup> The two disorders have a bidirectional relationship.<sup>3</sup> Several studies consistently showed that depression was significantly more prevalent in GERD patients than in controls.<sup>4–6</sup> The issue is clinically significant, as depression has been reported to worsen the quality of life (QoL) of GERD patients, even worse than that of patients with other common chronic diseases, such as diabetes, arthritis, and heart failure.<sup>5,7,8</sup> In addition, it is also associated with poor response to proton pump inhibitors, the current best medical treatment for GERD.<sup>9</sup> In GERD patients who are good candidates for antireflux surgery from a physiologic point of view, the surgery can normalize physiologic data. Nevertheless, those with concomitant major depression can improve neither symptoms nor QoL.<sup>10</sup> Therefore, recognizing depression and its risk factors is essential when managing patients with GERD.

The prevalence of GERD in Southeast Asia has been increasing, which is associated with the rapid increase rate of overweight and obesity, a Westernized diet, and the decline in *Helicobacter pylori* in Asian populations.<sup>11,12</sup> The regional population accounts for only 8.8% of the world's population, but more than a quarter of depressed patients worldwide reside in the region.<sup>13</sup> A recent study has demonstrated epidemiological evidence for the relationship between major depression and GERD based on Taiwan biobank data.<sup>14</sup> However, local data on the prevalence and risk factors for depression in GERD patients are limited. This study was conducted to determine the prevalence and associated factors of depression in GERD patients in Vietnam, a Southeast Asian population with a prevalence of depression of 2.45%.<sup>15</sup>

## Methods

### Patients and Study Setting

This study was conducted at the gastroenterology clinic of the University Medical Center in Ho Chi minh City, Vietnam, from September 2019 to April 2020. Outpatients aged  $\geq 18$  years diagnosed with GERD were invited to participate in this study. The criteria for GERD diagnosis were (1) having troublesome heartburn or regurgitation at least twice a week or (2) having objective evidence of GERD on esophagogastroduodenoscopy (ie, reflux esophagitis according to the Los Angeles classification, ulcer or stricture caused by reflux disease, or Barrett's esophagus). The exclusion criteria included (1) prior upper gastrointestinal surgery, (2) having been diagnosed with any type of psychotic disorder and ongoing treatment with psychotropic medicines, or (3) intellectual disability.

This study was approved by the Board of Ethics in Biomedical Research of the University of Medicine and Pharmacy at Ho Chi minh City, Vietnam (numbered 665/HDDD-DHYD, signed on November 15, 2019). The study was performed following the Declaration of Helsinki. All participants were asked to provide written informed consent.

### Data Collection

All participants were asked to complete a structured questionnaire during a face-to-face interview with a physician (BTP). The questionnaire included the demographic information (name, gender, age, height, weight, education level, marital status, and domicile), lifestyle habits (smoking and alcohol drinking), duration with typical reflux symptoms (heartburn or regurgitation), GERD questionnaire (GerdQ) score, atypical reflux symptoms (globus, dysphagia, hoarseness, chronic cough), and the revised Beck Depression Inventory (BDI-IA). Based on smoking status, patients were categorized as current smokers or none/ex-smokers. Those who drank at least one alcohol unit (ie, 14 g of alcohol) per week were considered to have a drinking habit. The duration of typical reflux symptoms was calculated based on the patient's answers to the question:

When did you experience troublesome heartburn or regurgitation for the first time in your life?

During the face-to-face interview, we explained to the patients and emphasized the first time in their life when they realized that reflux symptoms became their health problem.

The GerdQ questionnaire, which has been validated in the Vietnamese population, was used to document the frequency of common upper gastrointestinal symptoms and the impact of reflux symptoms.<sup>16</sup> It is a self-administered and patient-center questionnaire including six items about the frequency of regurgitation, heartburn, upper abdominal pain, nausea, sleep disturbance, and the need for over-the-counter medications to relieve symptoms during the last seven days. The sum score ranged from 0 to 18 points.

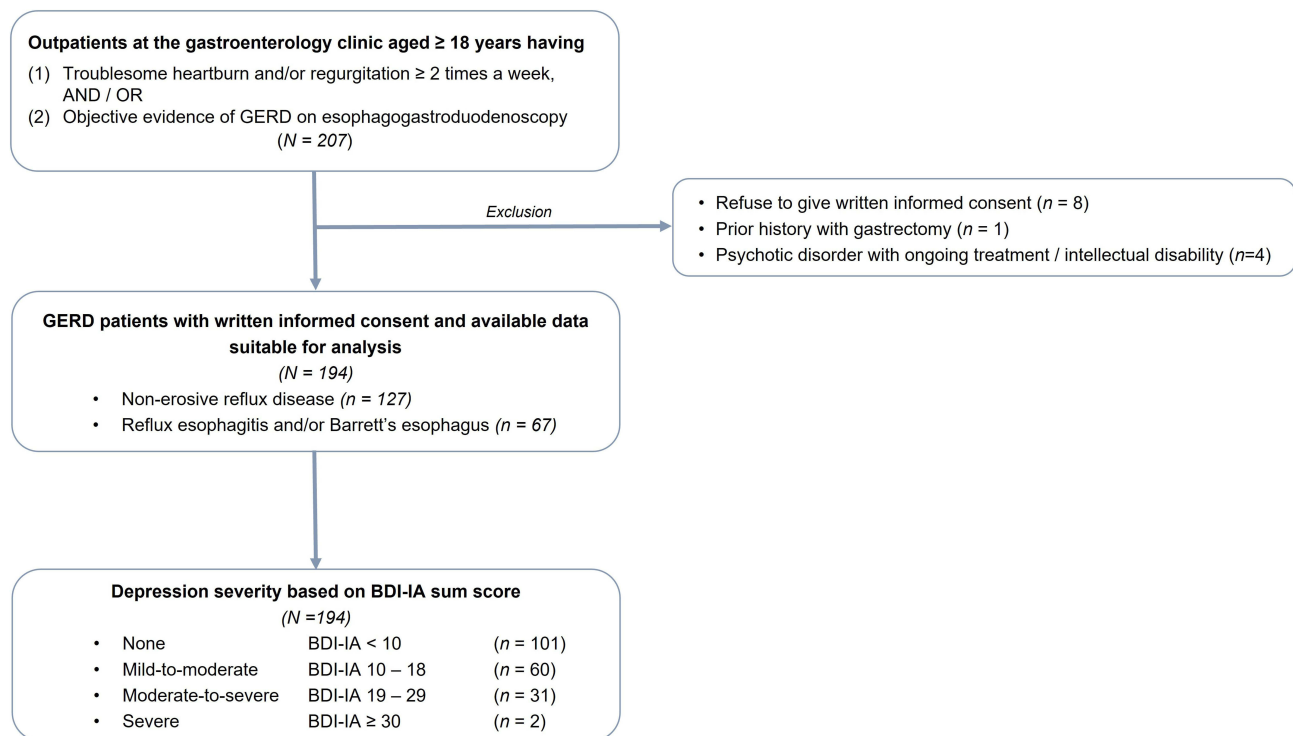
BDI-IA, which was developed during the 1970s and copyrighted in 1978, is a depression screening scale based on the frequency of depression symptoms.<sup>17</sup> This scale has been locally validated and is currently the most used instrument to detect and measure the severity of depression in Vietnam. BDI-IA is a self-report Likert-type scale with twenty-one statements, each of which has four items with scores ranging from 0 to 3 points. The sum score can range from 0 to 63 points. In this study, patients were categorized as having no depressive symptoms (BDI-IA < 10), mild to moderate depressive symptoms (BDI-IA 10–18), moderate to severe depressive symptoms (BDI 19–29), or severe depressive symptoms (BDI-IA  $\geq 30$ ).<sup>18</sup>

The medical records of all participants were assessed for additional information, which included the following:

- GERD phenotype: nonerosive reflux disease (NERD) or erosive reflux disease (ERD). Patients with objective evidence of GERD on esophagogastroduodenoscopy were classified as ERD. Those with typical reflux symptoms at least twice a week but without endoscopic reflux injuries were classified as NERD.
- Coexistent functional gastrointestinal disorders: functional dyspepsia and irritable bowel syndrome.
- *Helicobacter pylori* infection.
- Family history of upper gastrointestinal malignancy.
- Extragastrintestinal comorbidities were also recorded if they satisfied all the following conditions: (1) being listed in the Charlson Comorbidity Index,<sup>19</sup> (2) being listed in the patient's medical record, and (3) manifesting in the patient admission process. The diagnosis of comorbidities was confirmed by screening the medications currently taken or from the patient's medical records. Diseases that were completely recovered were excluded.

## Statistical Analysis

All statistical analyses were carried out with SPSS 23 (SPSS Inc., Chicago, IL). Categorical variables are presented as numbers and percentages and were compared using Pearson's chi-squared test. Continuous variables were tested for normality using the Kolmogorov–Smirnov test. Those with a normal distribution are presented as the mean and standard deviation (SD) and were compared using a *t*-test. Those with a nonnormal distribution are presented as the median (upper and lower quartiles) and were compared using the Mann–Whitney *U*-test (for two groups) or median test (for three groups) as appropriate. Univariate analysis was performed to identify factors associated with the presence of depression. The variables that had *p* values <0.1 in univariate analysis were included in multiple logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for depression. All tests were 2-sided, and a *p* value <0.05 was considered significant.



**Figure 1** Recruitment flowchart of patients in the study.

**Abbreviations:** GERD, Gastroesophageal Reflux Disease; BDI-IA, Revised Beck Depression Inventory (BDI-IA).

## Results

Two hundred and seventeen GERD patients were invited to participate in the study, of whom 194 fulfilled the recruitment criteria (Figure 1). The mean age was  $44.1 \pm 12.0$  years, and the male-to-female ratio was 1:1.2. NERD and ERD accounted for 65.4% (127/194) and 34.5% (67/194) of patients, respectively. The proportion of patients whose BDI-IA scores met the cutoff for depression (ie  $BDI-IA \geq 10$ ) was 47.9% (93/194). The detailed demographic, clinical, and

**Table 1** Demographic, Clinical, and Endoscopic Characteristics of Recruited Patients

Characteristics	Whole Sample	Depression (-)	Depression (+)	p-value
Age (mean $\pm$ SD)	44.1 $\pm$ 12.0 Min: 20, max: 75	42.8 $\pm$ 11.0 Min: 20, max: 74	45.4 $\pm$ 12.9 Min: 20, max: 75	0.095
Sex				
Male, n (%)	85 (44.3%)	55 (54.5)	31 (33.3)	0.004
Female, n (%)	108 (55.7%)	46 (45.5)	62 (66.7)	
Body mass index n (%)				
<18.5	16 (8.2)	6 (6.0)	10 (11.1)	0.621
18.5–22.9	111 (57.3)	57 (57.0)	50 (55.6)	
23–24.9	41 (21.1)	22 (22.0)	19 (21.1)	
25–29.9	26 (13.4)	15 (15.0)	11 (12.2)	
Domicile				
Urban	96 (49.5)	53 (52.5)	43 (46.2)	0.393
Rural	98 (50.5)	48 (47.5)	50 (53.8)	
Education level				
Preliminary	25 (12.9)	12 (11.9)	13 (14.0)	0.441
Secondary school	66 (34.0)	31 (30.7)	35 (37.6)	
High school or higher	103 (53.1)	58 (57.4)	45 (48.4)	
Marital status				
Married	164 (84.5)	87 (86.1)	77 (82.8)	0.121
Divorced	3 (1.5)	0 (0)	3 (3.2)	
Widowed	5 (2.6)	1 (1.0)	4 (4.3)	
Single	22 (11.3)	13 (12.9)	9 (9.7)	
Smoking				
Current smoker	30 (15.5)	18 (17.8)	12 (12.9)	0.428
None/ex-smoker	164 (84.5)	83 (82.2)	81 (87.1)	
Alcohol drinking				
Yes	71 (36.6)	47 (46.5)	24 (25.8)	0.003
No	123 (63.4)	54 (53.5)	69 (74.2)	
Family history of upper gastrointestinal cancer	11 (5.7)	5 (5.0)	6 (6.5)	0.760
Duration with typical reflux symptoms (years) median (IQR)	2 (1, 5)	2 (0.8, 3)	3 (1, 7)	0.008
Chief complaints				
Heartburn	35 (18.0)	21 (21.0)	14 (15.1)	0.432
Regurgitation	90 (46.4)	44 (44.0)	45 (48.4)	
Epigastric pain	28 (14.4)	15 (15.0)	13 (14.0)	
Epigastric burning	11 (5.7)	5 (5.0)	6 (6.5)	
Early satiety	2 (1.0)	0 (0)	2 (2.2)	
Postprandial fullness	13 (6.7)	9 (9.0)	4 (4.3)	
Vomiting or nausea	15 (7.7)	6 (6.0)	9 (9.7)	

(Continued)

**Table 1** (Continued).

Characteristics	Whole Sample	Depression (-)	Depression (+)	p-value
GERDQ score	8 (7, 10)	8 (7, 9)	9 (7, 10)	0.286
Atypical reflux symptoms				
Globus	22 (11.3)	11 (10.9)	11 (11.8)	1.000
Dysphagia	37 (19.1)	22 (21.8)	15 (16.1)	0.432
Hoarseness	22 (11.3)	12 (11.9)	10 (10.8)	0.825
Chronic cough	40 (20.6)	22 (21.8)	18 (19.4)	0.725
Any	81 (41.8)	47 (46.5)	34 (36.6)	0.109
GERD phenotype				
Nonerosive reflux disease	126 (65.0)	60 (59.4)	67 (72.0)	0.071
Reflux esophagitis or Barrett's esophagus	68 (35.0)	41 (40.6)	26 (28.0)	
Coexistent gastrointestinal disorders				
Functional dyspepsia	45 (23.2)	21 (20.8)	24 (25.8)	0.496
Peptic ulcer disease	3 (1.5)	2 (2.0)	1 (1.1)	1.000
Irritable bowel syndrome	6 (3.1)	2 (2.0)	4 (4.3)	0.429
<i>Helicobacter pylori</i> infection	87 (44.8)	40 (39.6)	47 (50.5)	0.149
Extragastrintestinal comorbidities				
Hypertension/chronic heart disease	31 (16.0)	9 (8.9)	22 (23.7)	0.006
Chronic pulmonary disease	5 (2.6)	3 (3.0)	2 (2.2)	1.000
Diabetes mellitus	8 (4.1)	4 (4.0)	4 (4.3)	1.000
Chronic renal failure	4 (2.1)	0 (0)	4 (4.3)	0.051
Chronic liver disease	14 (7.2)	5 (5.0)	9 (9.7)	0.269
Depression				
Yes	93 (47.9)			
Mild to moderate	60 (30.9)			
Moderate to severe	31 (16.0)			
Severe	2 (1.0)			
No	101 (52.1)			

endoscopic characteristics of all patients are presented in Table 1. Compared to the group of patients with BDI-IA scores < 10, the group with BDI-IA scores  $\geq$  10 had a significantly higher proportion of females, a longer duration of reflux symptoms, a higher rate of hypertension/chronic heart disease, and a lower rate of alcohol consumption. However, the two groups had no significant differences in GERD phenotypes or GERDQ scores.

In multivariate analysis, sex and duration of reflux symptoms were the only two independent risk factors for depression (Table 2 and Figure 2). Depression was more prevalent among females than males (OR = 3.941, 95% CI: 1.386–11.205). There was a dose–response between depression and the duration of reflux symptoms. Compared with patients whose duration of reflux symptoms was < 1 year, the ORs for depression among those with a duration from 1 to 10 years and more than 10 years were 3.520 (1.057–11.717),  $p = 0.040$  and 5.605 (1.046–30.019), respectively. The median BDI-IA scores were also significantly higher among females than males [13 (7, 18) vs 6 (3, 14), respectively,  $p < 0.001$ ] and among patients with a longer duration of reflux symptoms [ $> 10$  years: 14 (8, 17), 1–10 years: 9 (4, 16), and < 1 year: 7 (4, 11), respectively,  $p = 0.032$ ] (Figure 3).

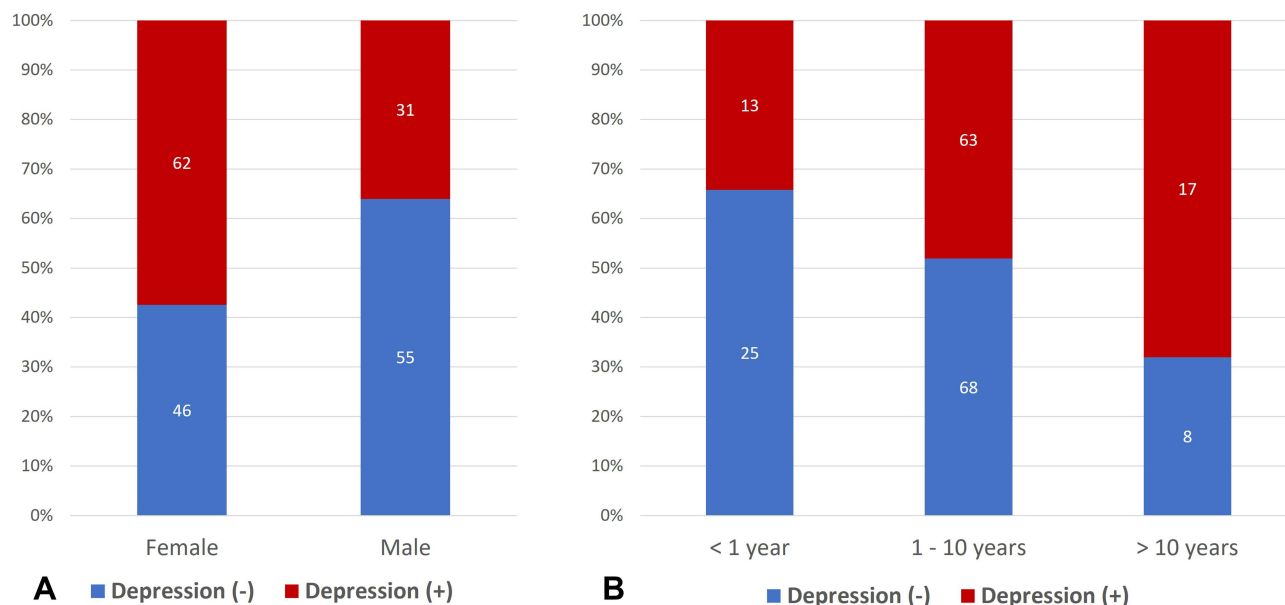
## Discussion

This study shows that depression is quite common in GERD patients in Vietnam. The duration of typical reflux symptoms and female sex were independent risk factors for depression, especially the former demonstrating a dose–response.

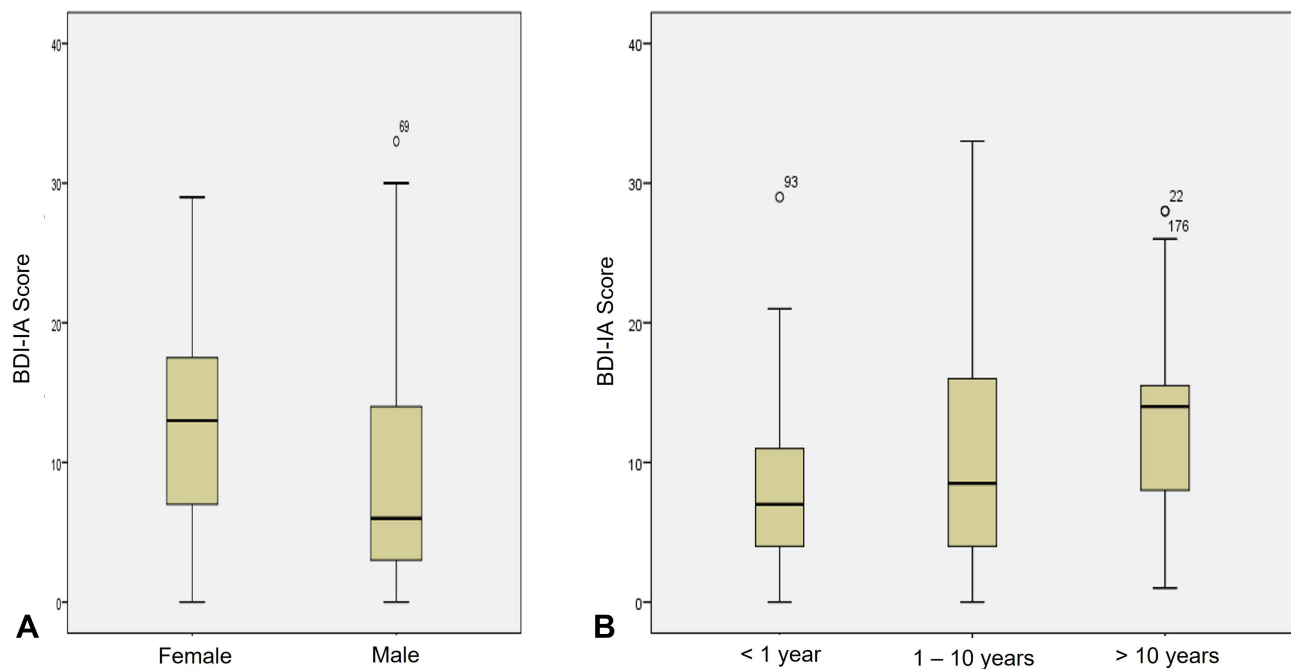
**Table 2** Factors Associated with Depression in Multivariate Analysis

	OR	95% CI	p-value
Age	0	0	0.999
Sex			
Male	1		
Female	3.941	1.386–11.205	0.010
Alcohol drinking			
No	1		
Yes	0.576	0.189–1.757	0.333
Hypertension/chronic heart disease			
No	1		
Yes	1.748	0.526–5.812	0.362
Chronic renal failure			
No	1		
Yes	0	0	0.999
Phenotype of gastroesophageal reflux disease			
Nonerosive reflux disease	1		
Reflux esophagitis/Barrett’s esophagus	0.542	0.212–1.383	0.200
Duration with typical reflux symptoms (years)			
< 1	1		
1–10	3.520	1.057–11.717	0.040
> 10	5.605	1.046–30.019	0.044

There are many similarities in demographic characteristics between this study’s participants and those in previous studies in other populations. The most common age group was from 40 to 50 years, with a female predominance over males.<sup>5,6,20</sup> As the study was conducted at a tertiary hospital, comorbidities were prevalent among participants, especially arterial hypertension and cardiovascular disease. This concurs with the findings of a previous study in the same setting.<sup>21</sup>



**Figure 2** The distribution of depression according to gender (A) and duration of reflux symptoms (B).



**Figure 3** Revised Beck's depression inventory scores (BDI-IA) according to gender (A) and duration of reflux symptoms (B).

The COVID-19 pandemic was associated with increased reflux and depressive symptoms.<sup>22</sup> However, the pandemic situation in southern Vietnam, where the study was conducted, was well controlled during the period this study was carried out. Therefore, we hypothesize that the pandemic would not significantly affect the results of this study.

The reported prevalence of depression in GERD patients significantly varied in previous studies, depending on the studied participants and the diagnostic criteria of depression. Population-based studies tend to report a much lower prevalence than hospital-based studies, as depression is one of the critical factors associated with consolation for reflux symptoms.<sup>23</sup> A large population-based study in Korea showed a higher prevalence of depression diagnosed based on the ICD-10 in the GERD group than in the control group (5.7% vs 3.9%,  $p < 0.001$ ).<sup>3</sup> However, a recent meta-analysis of Chinese patients reported that the prevalence of depression in GERD patients was 37%.<sup>24</sup> This study's main tools used to assess depression were the Self-rating Depression Scale (SDS), Hospital Anxiety and Depression Scale (HADS), and International Classification of Diseases, Ninth Revision, Clinical Modification. Another hospital-based study in Turkey reported a depression rate of 41.3% using the BECK II score with a cutoff of 13.<sup>6</sup> In our study, we chose the Beck IA because it is a diagnostic tool for depression that has been validated and widely used in Vietnam. It has been reported that the two scores displayed a similar pattern of relationships with the same psychosocial characteristics for all practical purposes. However, the mean BDI-IA sum score was approximately 2 points lower than it was for the BDI-II.<sup>25</sup> Overall, depression is prevalent in GERD patients, especially those who seek medical consultation. The slightly higher proportion of depression in our study compared to other hospital-based studies could be partly due to the tertiary setting of the study.

Regarding the risk factors for depression in GERD patients, we found that sex and duration of reflux symptoms were the only two independent risk factors in the multivariate analysis. Being female has been well documented as a risk factor for depression in the general population, and therefore, it is also a risk factor for depression in GERD patients. Salt et al recently reported the results of two meta-analyses representing data from 1,716,195 and 1,922,064 people in over 90 different nations.<sup>26</sup> The study found that all effect sizes for depression were positive among different subgroups. The duration of reflux symptoms was also reported as a risk factor for depression in GERD patients in a previous study in Taiwan.<sup>27</sup> You et al reported that the risk of depression was higher in GERD patients than in controls. The incidence of depression significantly increased in both stratified follow-up durations of  $< 1$  and  $\geq 1$  year. Our study further strengthens this finding, as it demonstrated a dose-response between the duration of reflux symptoms and depression. Interestingly, we found no significant difference in GERDQ scores between the two groups of patients who did or did not meet the



criteria for depression. Therefore, it was not necessarily the reflux symptom severity that differed from depression, but it was the duration of reflux symptoms. In fact, we found that the depression scores were also significantly higher in patients with long experience with reflux symptoms.

In our study, univariate analysis showed that alcohol consumption and arterial hypertension/chronic heart disease were significantly associated with depression ( $p = 0.003$  and  $p = 0.006$ , respectively), and chronic renal failure and NERD were marginally associated with depression ( $p = 0.071$  and  $p = 0.051$ , respectively). These associations in multivariate analysis, however, were not significant. The association between alcohol consumption and depression was negative in univariate analysis (Table 1). Since alcohol drinking is exclusively a habit among Vietnamese men, it must be a confounding factor. Some meta-analyses have reported that the prevalence of depression among patients with arterial hypertension and chronic kidney disease was 26.8% and 21.4%, respectively.<sup>28,29</sup> Some previous studies also investigated the association between the GERD phenotype and depression. Two small studies conducted in China and Turkey on 279 and 158 patients did not find a significant association.<sup>5,6</sup> However, a recent large-scale study in Korea, which included 176 patients with ERD and 1398 patients with NERD, showed that the depression levels according to the mean Beck score in NERD were significantly higher than those in ERD.<sup>4</sup> Due to our study's small sample size, it is impossible to exclude these abovementioned factors of depression in GERD patients in Vietnam. Nevertheless, they were not the predominant risk factors for depression in GERD patients in Vietnam.

Why prolonged GERD is associated with depression is an important question. Disturbances in bidirectional gut-brain communication have been suggested to play an essential role in the complicated underlying pathogenesis, which must be further studied in humans.<sup>30</sup> Recent studies have shown that abnormal microbiota and microbiota-gut-brain dysfunction may also cause depression.<sup>31</sup> The patients' fear that their symptoms represented severe disease was reported as a critical factor that made them seek medical consultation.<sup>23</sup> There is evidence that the gut microbiota can be altered by long-term acid suppression therapy.<sup>32</sup> Further studies on this issue are essential to identify risk factors for depression to shape the consultation and treatment strategy for naïve GERD patients.

This study has some limitations. First, this is a single-center cross-sectional study with a small sample size. Recall and selection bias could not be avoidable, and causal claims about reflux symptoms causing depression could not be made. Second, the tertiary setting of the study may lend itself to patients with more severe psychopathological symptoms, and they may not be generalizable to other populations. Third, we evaluated depressive symptoms using the BDI-IA, which does not fully evaluate all aspects of depression, such as the components in the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV. Fourth, some demographic characteristics, such as social relationships, personal income, or dissatisfaction with the working environment, which may also be associated with depression, were not investigated. Finally, the cross-sectional nature of the study inhibits them from making causal claims about reflux symptoms causing depression.

## Conclusions

In conclusion, depression could be quite common among GERD patients in Vietnam. Female sex and a long duration of reflux symptoms were the two most prominent risk factors for depression in GERD patients. In particular, there was a dose–response phenomenon between the latter and depression. In clinical practice, special attention should be given to evaluating depression in GERD patients, especially in females with a long duration of illness.

## Abbreviations

GERD, Gastroesophageal reflux disease; NERD, Nonerosive reflux disease; ERD, Erosive reflux disease; QoL, Quality of life; BDI-IA, Revised Beck Depression Inventory (BDI-IA).

## Data Sharing Statement

All data generated or analyzed during this study are included in this published article.



## Ethics Approval and Consent to Participate

The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki. This study was approved by the Board of Ethics in Biomedical Research of the University of Medicine and Pharmacy at Ho Chi Minh City, Vietnam (numbered 665/HDDD-DHYD, signed on November 15, 2019). Written informed consent was obtained from all participants and/or their legal guardian(s).

## Consent for Publication

Written informed consent was obtained from all participants and/or their legal guardian(s).

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## Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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## Disclosure

The authors report no conflicts of interest in relation to this work.

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