Predicting factors of recurrence in patients with gastroesophageal reflux disease: a prospective follow-up analysis

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Abstract

Background: Recurrence of gastroesophageal reflux disease (GERD) is common among patients who are no longer receiving proton pump inhibitors (PPIs). This study investigated factors associated with GERD recurrence.

Methods: We included 499 consecutive GERD patients who completed validated reflux and psychological questionnaires before undergoing upper endoscopy. All patients were treated with PPIs and followed up.

Results: Recurrence was observed in 89 (30.4%) of 293 patients during the 1-year follow up. Patients with recurrence had a higher prevalence of diabetes mellitus ($p = 0.037$), higher baseline GERD Questionnaire (GERDQ) scores ($p = 0.002$), and higher Pittsburgh Sleep Quality Index scores ($p = 0.045$). Log-rank analysis showed that a GERDQ score of $\geqslant 8$ was independently associated with an increased recurrence risk ($p = 0.002$). The scores of all psychological questionnaires and health-related quality of life questionnaire worsened more at the end of follow up in patients with recurrence than in those without recurrence. Multivariate analysis revealed that a higher GERDQ score was the only independent risk factor for GERD recurrence ($p = 0.024$). GERD patients who have greater initial symptom burden will have a higher recurrence rate after discontinuing PPIs.

Conclusions: GERD patients with greater initial symptom burden are more likely to have recurrence after discontinuing PPIs. This study highlights the importance of developing a new strategy to prevent GERD recurrence in the management of this common disorder.

Keywords: gastroesophageal reflux disease (GERD), proton pump inhibitors (PPIs), recurrence

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Introduction

Gastroesophageal reflux disease (GERD) is a prevalent gastrointestinal disorder characterized by the abnormal reflux of gastric contents into the esophagus, resulting in troublesome symptoms. GERD negatively affects the quality of life and increases the risk of esophageal adenocarcinoma, leading to a huge economic burden worldwide.[1,2] Evidence suggests that the disease burden of GERD has increased in the last two decades, particularly in North America and East Asia.[3] The reason for this increase is not entirely clear; however, it appears to be correlated with the increasing prevalence of obesity and dietary factors.

The goals of GERD treatment involve a stepwise approach, which includes control of symptoms, healing of esophagitis and prevention of recurrence or complications. Although proton pump inhibitor (PPI) therapy is effective in relieving GERD symptoms, many patients still relapse over time after discontinuing PPIs.[4,5] Therefore, maintenance or long-term PPI therapy is suggested for

patients whose chronic reflux does not resolve by itself and for those with severe erosive esophagitis (EE) and Barrett's esophagus.

Although risk factors for GERD are well known, those for GERD recurrence are not yet fully understood. To date, few studies have investigated risk factors for the disease recurrence in patients with GERD.[6,7] A previous Korean study demonstrated that GERD patients with a shorter dinner-to-bedtime interval had a higher symptom recurrence rate.[7] Another study showed that the presence of regurgitation at baseline is an independent prognostic factor for recurrence.[6] However, whether the baseline symptom burden and the psychological factors of GERD patients can predict the disease recurrence when they are no longer undergoing PPI therapy remains unclear. In addition, the effect of GERD recurrence on psychological profiles has not been studied.

In the present study, we evaluated the recurrence rate of GERD after PPI treatment in a Taiwanese GERD population. In addition, we investigated baseline symptom burden, clinical and psychological factors associated with recurrence, and the effect of GERD relapse on these psychological profiles and health-related quality of life (HRQoL).

Methods

Study design and population
In this prospective, observational study, we enrolled consecutive GERD patients who visited our digestive disease outpatient clinic at Taipei and Hualien Tzu Chi Hospital between March 2016 and December 2017. Patients who presented with typical reflux symptoms of heartburn or regurgitation were recruited. All patients were asked to complete questionnaires before undergoing upper gastrointestinal endoscopy for initial screening. Patients were excluded if they: (i) had undergone any previous gastrointestinal surgery; (ii) had esophageal motility disorder, malignancies, or significant comorbid disease; or (iii) had received aspirin, nonsteroidal anti-inflammatory drugs, PPIs, or histamine-2 receptor antagonists within the past 6 months. After the endoscopic examination, patients with major complications of GERD (including esophageal stricture and Barrett's metaplasia) or peptic ulcers, which

might induce upper gastrointestinal symptoms, were also excluded. Finally, a total of 499 patients were included in this study. All patients provided written informed consent prior to participation in the study. This study protocol was approved by the Ethical Committee of Taipei and Hualien Tzu Chi Hospital, confirming that the study was conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Data collection and questionnaires
At baseline, all patients were personally interviewed by trained professional interviewers. Complete demographic and medical information was obtained, including: age; sex; body mass index (BMI); waist-to-hip ratio; lifestyle factors; medical comorbidities, such as hypertension, diabetes mellitus (DM) and hyperlipidemia; and current and recent medications. Self-administered questionnaires were completed by patients. Questionnaires included the Reflux Disease Questionnaire (RDQ),[8,9] GERD Questionnaire (GERDQ),[10] Reflux Symptom Index (RSI),[11] Pittsburgh Sleep Quality Index (PSQI),[12,13] Taiwanese Depression Questionnaire (TDQ),[14] State–Trait Anxiety Inventory (STAI)[15] and HRQoL questionnaire.[16,17] Screening questions for functional dyspepsia (FD) and irritable bowel syndrome (IBS) were based on the Rome IV diagnostic criteria.[18]

Endoscopic examination
Upper gastrointestinal endoscopy was performed by experienced endoscopists who were blinded to the symptomatic status of patients and the results of the questionnaires. During the examination, the presence of any mucosal injury in the lower esophagus or hiatal hernia was recorded. Patients were classified as having EE or non-EE according to the Los Angeles classification system.[19] After the endoscopic examination, GERD patients were administered PPI therapy for 4 weeks and followed up.

Recurrence definition and assessments
All GERD patients were prospectively reviewed every 4 weeks for up to 16 weeks, and GERD symptoms were assessed at each study visit. Because PPIs are reimbursed by the national insurance company, PPIs were allowed to be prescribed for up to 16 weeks after the initial endoscopic examination.
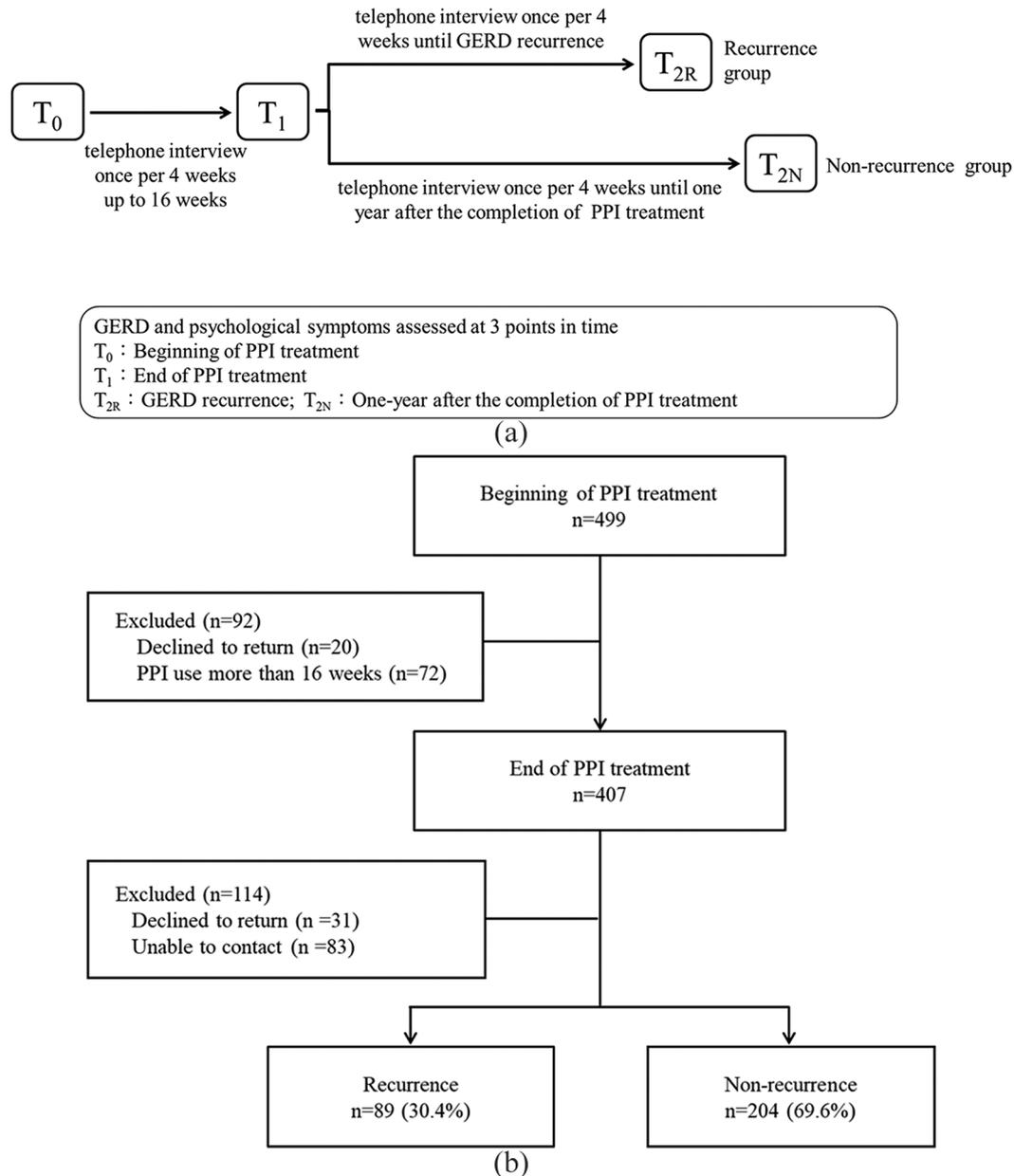
GERD and psychological symptoms assessed at 3 points in time
T_0 : Beginning of PPI treatment
T_1 : End of PPI treatment
T_{2R} : GERD recurrence; T_{2N} : One-year after the completion of PPI treatment

(a)

Beginning of PPI treatment
n=499

Excluded (n=92)
   Declined to return (n=20)
   PPI use more than 16 weeks (n=72)

End of PPI treatment
n=407

Excluded (n=114)
   Declined to return (n =31)
   Unable to contact (n =83)

Recurrence
n=89 (30.4%)

Non-recurrence
n=204 (69.6%)

(b)

Figure 1. (a) Schematic of the study design. (b) Flowchart for patient enrollment.

If patients had incomplete resolution of initial symptoms, then PPIs were prescribed for another 4 weeks. During the follow-up period, after the completion of PPI treatment, phone contact every 4 weeks was conducted by trained professional interviewers to assess GERD symptoms until GERD recurrence. For patients without GERD recurrence, telephone interviews were conducted every 4 weeks for up to 1 year. Recurrence was defined as the recurrence of typical GERD symptoms that required additional medication after complete recovery following initial PPI treatment. The psychological and HRQoL questionnaires were assessed at baseline, end of treatment, and recurrence (or 1 year after the completion of PPI treatment in the nonrecurrence group) to assess the effect of GERD on patients' psychological profiles and HRQoL (Figure 1a). Patients were excluded if they were lost during the follow-up period. Study outcomes were factors associated with GERD recurrence following initial PPI treatment. With such a treatment strategy, all patients

at the end of treatment were assumed to achieve complete symptomatic resolution and be ready for the follow up to examine whether they had symptomatic relapse.

Statistical analysis

Continuous data are expressed as the mean and standard deviation, whereas categorical data are expressed as the number and percentage. Group comparisons were performed using the independent sample *t* test or the chi-squared test, as appropriate. In addition, GERD and psychological symptoms between the two groups were assessed at the end of PPI treatment and the end of follow-up. The Kaplan–Meier recurrence-free survival curves of GERD was assessed by the log-rank test. We performed a Cox regression analysis to determine factors associated with GERD recurrence, calculated the hazard ratio and 95% confidence interval. All analyses were performed using SPSS (Version 21.0. Armonk, NY: IBM Corp) and Stata software 13.0 (StataCorp. 2013. Stata: Release 13. Statistical Software College Station, TX: StataCorp LP).

Results

Characteristics of enrolled patients and recurrence rate of GERD

Of 499 patients, 20 (4.0%) who declined to return to the hospital during the PPI treatment period and 72 (14.4%) who required PPIs for more than 16 weeks were excluded. Of the remaining 407 patients who completed PPI treatment, 114 (28.0%) who were not able to be contacted or declined to return during the 12-month follow up were also excluded. Therefore, a total of 293 patients (156 women and 136 men, median age 48 years) were enrolled in the final analysis. During the 1-year follow-up period, 89 patients had recurrence of GERD symptoms, whereas 204 patients had no recurrence after the completion of PPI treatment. The recurrence rate of GERD in this study was 30.4%. The flowchart for patient enrollment is shown in Figure 1(b).

Comparison of baseline characteristics between GERD recurrence and nonrecurrence groups

Table 1 lists differences in demographics, lifestyle factors, medical comorbidities, and GERD questionnaires between GERD patients with and without recurrence. The recurrence group had a higher prevalence of DM than did the nonrecurrence group ($p = 0.037$). GERD patients with recurrence had a higher GERDQ score at the initial visit than did GERD patients without recurrence (7.5 ± 4.0 *versus* 5.9 ± 4.2, $p = 0.002$). The results of the log-rank test revealed that GERD patients with a GERDQ score of $\geqslant 8$ had a significantly higher incidence of recurrence than did those with a GERDQ score of <8 ($p = 0.002$, Figure 2). No difference was observed in sex, age, BMI, waist-to-hip ratio, smoking status, coffee, alcohol, or tea consumption, medical comorbidities (namely hypertension, hyperlipidemia, FD, and IBS), RDQ, or RSI scores between the groups.

Table 2 shows a comparison of endoscopic findings, PPI treatment profile, and psychological factors between GERD patients with and without recurrence. With regard to psychological factors, the PSQI score was significantly higher in the recurrence group ($p = 0.045$). In other words, patients who had sleep disturbance at the initial visit showed a higher recurrence of GERD than did those who did not. The scores of other psychological questionnaires, namely the TDQ, STAI, and HRQoL, did not show any significant difference. In addition, endoscopic findings (EE, hiatal hernia, and *Helicobacter pylori* infection) and PPI treatment profile (duration of PPI treatment and classes of PPI) did not differ significantly between the groups.

Comparisons of psychological factors and HRQoL at the end of PPI treatment and follow-up between the groups

The scores of psychological questionnaires, namely the PSQI, TDQ, and STAI, as well as the HRQoL questionnaire at the end of PPI treatment did not differ between patients with and without recurrence. However, these scores worsened more at the end of follow up in patients with recurrence than in patients without recurrence (Table 3).

Factors associated with GERD recurrence

To identify independent factors that affect GERD recurrence, a logistic regression analysis was performed and results are listed in Table 4. Although patients with recurrence had a higher prevalence of DM and higher PSQI and GERDQ scores, only

Table 1. Comparisons of demographics, lifestyle factors, medical comorbidities, and GERD questionnaire scores between GERD patients with and without recurrence.

Characteristics	Nonrecurrence (*n* = 204)	Recurrence (*n* = 89)	*p* value
Demographic factors			
Male, *n* (%)	95 (46.6)**C**	41 (46.1)	0.937
Age (years)	48.0 ± 13.4	48.8 ± 13.2	0.628
Body mass index (kg/m^2)	24.3 ± 8.4	24.7 ± 4.2	0.694
Waist-to-hip ratio	0.9 ± 0.1	0.9 ± 0.1	0.140
Lifestyle factors			
Smoking	26 (12.9)	15 (16.9)	0.368
Alcohol drinking	29 (14.4)	9 (10.2)	0.338
Coffee drinking	24 (25.0)	13 (43.3)	0.054
Tea drinking	59 (65.6)	18 (72.0)	0.545
Medical comorbidities			
Irritable bowel syndrome, *n* (%)	51 (25.1)	32 (36.4)	0.051
Functional dyspepsia, *n* (%)	28 (14.0)	20 (23.3)	0.055
Hypertension, *n* (%)	33 (16.2)	15 (16.9)	0.885
Diabetes mellitus, *n* (%)	8 (3.9)	9 (10.1)	**0.037**
Hyperlipidemia, *n* (%)	9 (4.4)	3 (3.4)	1.000
GERD questionnaires			
RDQ score	10.5 ± 8.8	12.4 ± 10.4	0.104
GERDQ score	5.9 ± 4.2	7.5 ± 4.0	**0.002**
RSI score	10.1 ± 7.9	11.3 ± 8.7	0.247

Data are shown as the mean ± standard deviation or the proportion of the characteristic. Bold entries indicate a *p* value less than 0.05.
GERDQ, Gastroesophageal Reflux Disease Questionnaire; RDQ, Reflux Disease Questionnaire; RSI, Reflux Symptom Index.

the GERDQ score (hazard ratio = 1.07, *p* = 0.024) was significantly associated with GERD recurrence after adjustment in the multivariate analysis.

Discussion

Owing to the increasing prevalence of GERD in Asia, efforts to identify clinical characteristics that can predict its recurrence at 1 year after the initial endoscopic examination and PPI treatment are important to formulate optimal treatment strategies and improve clinical management outcomes.

Our study results showed that the overall recurrence rate of GERD was 30.4% at the end of the 1-year follow-up period. In this study, although patients with recurrence had greater sleep disturbance, a higher prevalence of DM, and higher reflux symptomatic burden, as measured using the GERDQ, only the GERDQ score was independently and positively associated with GERD recurrence after adjustment in the multivariate analysis. Specifically, a baseline GERDQ score of ≥8 appeared to be an ideal cutoff point to predict recurrence in our study population within 1 year
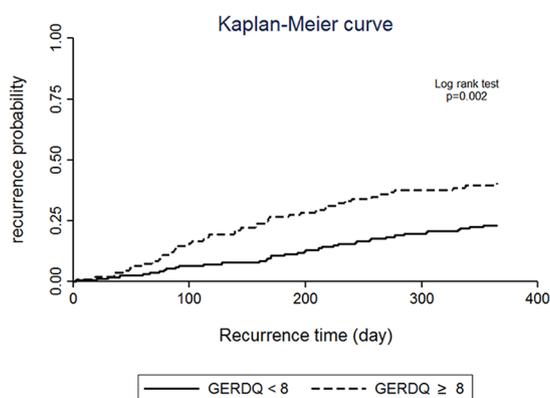
Figure 2. Kaplan–Meier curves showing a significant difference in the cumulative incidence of gastroesophageal reflux disease (GERD) recurrence in patients with a GERD Questionnaire (GERDQ) score of ≥8.

of follow up. Furthermore, despite no difference in any psychological factor between the groups at the end of the treatment, we observed that the scores of the psychological questionnaires and HRQoL questionnaire were higher in the recurrence group than in the nonrecurrence group at the end of follow up or the time of recurrence.

Data regarding GERD recurrence following PPI treatment are limited.[6,7] Studies have demonstrated that 26–48% of GERD patients had recurrence after 4–8 weeks of PPI treatment. In agreement with the result of a study which reported that only initial typical reflux symptoms were independent risk factors for GERD recurrence,[6] our results showed that among many clinical and psychological characteristics, only

Table 2. Comparisons of endoscopic findings, PPI treatment profile, and psychological factors between GERD patients with and without recurrence.

Characteristics	Non-recurrence (n = 204)	Recurrence (n = 89)	p-value
Endoscopic findings			
Erosive esophagitis, n (%)	84 (41.2)	29 (32.6)	0.165
Hiatus hernia, n (%)	5 (2.5)	5 (5.9)	0.158
Helicobacter pylori infection	42 (21.3)	12 (13.5)	0.117
PPI treatment profile			
Duration of PPI treatment, weeks	9.0 ± 5.8	7.8 ± 5.9	0.124
Classes of PPI			0.904
Dexlansoprazole	115 (56.4)	54 (60.7)	
Esomeprazole	23 (11.3)	9 (10.1)	
Omeprazole	12 (5.9)	4 (4.5)	
Rabeprazole	54 (26.5)	22 (24.7)	
Psychological factors			
Sleep disturbance: PSQI score	5.7 ± 3.1	6.6 ± 3.3	**0.045**
Depression: TDQ score	11.2 ± 9.0	13.4 ± 10.0	0.061
Anxiety: STAI score	41.4 ± 8.3	42.7 ± 9.5	0.245
Health related quality of life	10.9 ± 8.9	12.2 ± 9.4	0.281

Data are shown as the mean ± standard deviation or the proportion of the characteristic. Bold entry indicates a p value less than 0.05.
PPI, proton pump inhibitor; PSQI, Pittsburgh Sleep Quality Index; STAI, State–Trait Anxiety Inventory; TDQ, Taiwanese Depression Questionnaire.

Table 3. Comparison of psychological factors and HRQoL at the end of PPI treatment and at the end of follow up between the groups.

Variables	Group	End of PPI treatment (T1)	*p* value	End of follow up[†] (T2)	*p* value
HRQoL	Non-recurrence	2.0 ± 3.5	0.225	2.4 ± 4.2	<**0.001**
	Recurrence	1.5 ± 3.2		9.8 ± 8.2	
PSQI	Non-recurrence	5.1 ± 2.8	0.303	4.3 ± 3.1	**0.003**
	Recurrence	5.6 ± 3.2		5.7 ± 3.0	
TDQ	Non-recurrence	10.3 ± 9.1	0.457	5.6 ± 7.6	**0.002**
	Recurrence	11.3 ± 9.0		9.4 ± 8.5	
STAI	Non-recurrence	40.3 ± 8.8	0.37	36.1 ± 8.8	**0.032**
	Recurrence	41.5 ± 9.0		39.0 ± 8.8	

Data are shown as the mean ± standard deviation. Bold entry indicates a *p* value less than 0.05.
[†]Indicates recurrence date for the recurrence group and 1 year after the end of PPI treatment for the nonrecurrence group.
HRQoL, Health-related quality of life; PPI, proton pump inhibitor; PSQI, Pittsburgh Sleep Quality Index; STAI, State–Trait Anxiety Inventory; TDQ, Taiwanese Depression Questionnaire.

baseline reflux symptom burden, as measured using the GERDQ, could independently predict GERD recurrence within 1 year of follow up. Previous studies have found no association of recurrence with sex, body weight, lifestyle factors, EE, and presence of hiatal hernia,[6,7] which is similar to our findings. In our study, patients with recurrence had a higher prevalence of DM. The explanation for such finding is unclear but may be related to impaired gastric emptying, which is one of the pathological factors leading to GERD[20,21] and not uncommon in patients with DM.

Although the findings of statistical analyses did not show significant differences, we observed a trend of more patients having IBS and FD in the recurrence group. The concomitant presence of IBS and FD was associated with a less favorable PPI response.[22] In addition, a recent pathophysiological study reported that functional heartburn or esophageal hypersensitivity may overlap more frequently with IBS or FD.[23] Therefore, additional studies including more patients are required to confirm the current findings.

A large systematic study evaluated the relationship between endoscopic grading and recurrence and reported that approximately 84% of patients had recurrence within 6 months of follow up after receiving 10 or 20 mg of omeprazole daily for 4–8 weeks.[19] In addition, it indicated that recurrence of GERD were higher in patients with initial EE than in those with non-EE. However, our study results did not reveal any difference in the recurrence rate between the two groups and the overall recurrence rate was lower in our patients. Another study also reported similar findings of a lower recurrence rate and no effects on recurrence based on endoscopic findings.[6] The discrepancy can be attributed to the differences in study design, ethnic factors, and treatment. In our study, patients were allowed to receive PPIs for a longer duration (16 weeks) compared with a previous study in which patients received PPIs for only 4–8 weeks.[19] Therefore, whether a longer duration of PPI use is associated with a lower relapse rate remained unclear; however, such effect appears to be neglected because our data did not show any difference in the duration of PPI use between patients with and without recurrence. In addition, although the classes of PPIs that we used in this study were newer than those used in the previous study,[19] a meta-analysis concluded that the efficacy of newer PPIs is similar to that of omeprazole in terms of symptom control and relapse rates.[24]

The effect of GERD recurrence on psychological factors has not been investigated previously. Our study results showed that all psychological profiles, including anxiety, depression, sleep quality, and

Table 4. Factors associated with GERD recurrence after adjustment in the multivariate analysis.

Characteristics	HR (95% CI)	p value
Female gender	0.97 (0.58–1.61)	0.907
Age	1.02 (0.99–1.03)	0.146
Body mass index	1.01 (0.99–1.04)	0.291
Smoking	1.12 (0.58–2.18)	0.738
Alcohol drinking	0.88 (0.40–1.93)	0.745
Coffee drinking	1.05 (0.51–2.16)	0.897
Tea drinking	0.59 (0.33–1.06)	0.075
GERDQ	1.07 (1.01–1.13)	**0.024**
PSQI	1.03 (0.95–1.12)	0.451
TDQ	1.00 (0.96–1.04)	0.981
STAI	1.01 (0.97–1.05)	0.721
Erosive esophagitis	0.85 (0.51–1.42)	0.529
Hiatus hernia	2.28 (0.91–5.75)	0.080
Duration of PPI treatment	0.97 (0.92–1.01)	0.161
Irritable bowel syndrome	1.59 (0.96–2.61)	0.070
Functional dyspepsia	1.41 (0.81–2.44)	0.228

The Cox proportional hazard model was used. Adjusted for sex, age, body mass index, smoking status, alcohol, coffee, or tea consumption, GERDQ, PSQI, TDQ, and STAI scores, erosive esophagitis, hiatus hernia, duration of PPI treatment, irritable bowel syndrome, and functional dyspepsia. Reference group (ref.) means that category served as the reference group for calculating a hazard ratio. Bold entry indicates a *p* value less than 0.05.
CI, confidence interval; GERD, gastroesophageal reflux disease; GERDQ, Gastroesophageal Reflux Disease Questionnaire; HR, hazard ratio; PPI, proton pump inhibitor; PSQI, Pittsburgh Sleep Quality Index; STAI, State–Trait Anxiety Inventory; TDQ, Taiwanese Depression Questionnaire.

HRQoL, were similar in both patient groups at the end of treatment, but these psychological profiles deteriorated during recurrence compared with their baseline or those without recurrence. Another study also demonstrated the effect of GERD recurrence on HRQoL.[6] This finding indicates that GERD recurrence may affect not only esophageal symptoms but also psychological characteristics.

Earlier studies have suggested multiple risk factors for GERD, including male sex, obesity, cigarette smoking, hiatal hernia and, possibly, absence of *H. pylori*.[25] However, in our study, we did not find sufficient data to support the effect of these factors on GERD recurrence. Although a recent study indicated that a shorter dinner-to-bedtime interval appeared to be an independent risk factor

that can predict GERD recurrence during 12 months of follow up,[7] we did not perform such an investigation in our study. We only found that patients had an initial GERDQ score of ≥8, they were more likely to have disease recurrence compared with those with lower scores. This observation is supported partially by the findings of previous studies.[6,26] Thus, our work may highlight the importance of identifying baseline symptomatic burden to provide more aggressive or continuous therapy and prevent recurrence in such a high-risk population

In this study, a discrepancy was observed between GERDQ and RDQ scores at baseline in the two patient groups. Although both the questionnaires can help diagnose GERD, the GERDQ was

reported to be superior than the RDQ in diagnosing GERD.[27] A study reported that the GERDQ with a cutoff score of 8 had the highest specificity (71.4%) and sensitivity (64.6%), which is proposed as the cutoff score when testing for GERD with a diagnostic accuracy similar to that of a gastroenterologist.[10] Therefore, the discrepancy may reflect potential differences in diagnostic accuracy when applying those questionnaires in clinical practice. Furthermore, the GERDQ may be used to measure the response to treatment over time.[10] Although both the RDQ and GERDQ are validated to be useful for the diagnosis of GERD, it appears that no ideal questionnaire can be used as a standard diagnostic test, supporting the need to use more objective diagnostic tests, such as upper endoscopy and 24-hour esophageal pH-metry.[28]

This study has some limitations that should be addressed. First, the definition of GERD was based on typical symptoms and upper endoscopic findings. Without 24-hour esophageal pH monitoring, it is impossible to identify subtypes of GERD, such as nonerosive reflux disease, esophageal hypersensitivity, or functional heartburn.[29] The recurrence rate may differ among different subgroups. Second, although all patients with symptomatic remission at the end of treatment were evaluated through regular phone calls, it would have been more accurate if they were all assessed using objective questionnaires to confirm the status of disease characteristics at the end of therapy. Finally, we enrolled only consecutive patients from two tertiary hospitals in Taiwan, which might limit the generality of current findings in clinical practice. Additional studies including larger study populations are warranted to confirm our findings.

The current study has some strengths that should be mentioned. First, our data are unique because of the fact that according to the reimbursement requirement from national insurance, all patients have to undergo upper endoscopy in order to be prescribed with PPI therapy for a maximum duration of 16 weeks. Therefore, the recurrence rate measured in this study reflects the real-world experience in accordance with the national guideline in Taiwan based on both clinical symptoms and upper endoscopic findings. Second, our results demonstrated the exacerbation of psychological comorbidities (sleep, depression, and anxiety) owing to GERD recurrence, indicating that psychological disturbance occurs along with GERD recurrence. Third, although the GERDQ is well-established to be useful for the diagnosis of GERD, our study suggests that a baseline GERDQ score of ≥8 also importantly predicts GERD recurrence after the discontinuation of PPIs.

In summary, GERD patients who have greater initial symptom burden will have a higher recurrence rate after discontinuing PPIs. Therefore, it is noteworthy to achieve complete and persistent symptom remission in order to prevent the relapse of GERD, which may also improve relevant psychological distress. This study highlights the importance of developing a new strategy to not only treat GERD, but also prevent its recurrence in the management of this prevalent disease.

Author contribution

WYL and CLC contributed to study concept and design, analysis and interpretation of data, drafting of the manuscript. WCC and SHW contributed to statistical analysis. CHY, TTL, JSH, and MWW contributed to the acquisition of data and research performance. All authors have approved the final version of the manuscript.

Conflict of interest statement

The author(s) declare that there is no conflict of interest.

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References

1. Sandler RS, Everhart JE, Donowitz M, *et al.* The burden of selected digestive diseases in

the United States. *Gastroenterology* 2002; 122: 1500–1511.

2. Tack J, Becher A, Mulligan C, *et al.* Systematic review: the burden of disruptive gastro-oesophageal reflux disease on health-related quality of life. *Aliment Pharmacol Ther* 2012; 35: 1257–1266.

3. El-Serag HB, Sweet S, Winchester CC, *et al.* Update on the epidemiology of gastro-oesophageal reflux disease: a systematic review. *Gut* 2014; 63: 871–880.

4. Katz PO, Gerson LB and Vela MF. Guidelines for the diagnosis and management of gastroesophageal reflux disease. *Am J Gastroenterol* 2013; 108: 308–328; quiz 329.

5. Schindlbeck NE, Klauser AG, Berghammer G, *et al.* Three year follow up of patients with gastrooesophageal reflux disease. *Gut* 1992; 33: 1016–1019.

6. Min YW, Shin YW, Cheon GJ, *et al.* Recurrence and its impact on the health-related quality of life in patients with gastroesophageal reflux disease: a prospective follow-up analysis. *J Neurogastroenterol Motil* 2016; 22: 86–93.

7. Yang JH, Kang HS, Lee SY, *et al.* Recurrence of gastroesophageal reflux disease correlated with a short dinner-to-bedtime interval. *J Gastroenterol Hepatol* 2014; 29: 730–735.

8. Lei WY, Yu HC, Wen SH, *et al.* Predictive factors of silent reflux in subjects with erosive esophagitis. *Dig Liver Dis* 2015; 47: 24–29.

9. Shaw MJ, Talley NJ, Beebe TJ, *et al.* Initial validation of a diagnostic questionnaire for gastroesophageal reflux disease. *Am J Gastroenterol* 2001; 96: 52–57.

10. Jones R, Junghard O, Dent J, *et al.* Development of the GerdQ, a tool for the diagnosis and management of gastro-oesophageal reflux disease in primary care. *Aliment Pharmacol Ther* 2009; 30: 1030–1038.

11. Belafsky PC, Postma GN and Koufman JA. Laryngopharyngeal reflux symptoms improve before changes in physical findings. *Laryngoscope* 2001; 111: 979–981.

12. Buysse DJ, Reynolds CF III, Monk TH, *et al.* The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989; 28: 193–213.

13. Hung HC, Yang YC, Ou HY, *et al.* The association between self-reported sleep quality and metabolic syndrome. *PLoS One* 2013; 8: e54304.

14. Lee Y, Yang MJ, Lai TJ, *et al.* Development of the Taiwanese depression questionnaire. *Chang Gung Med J* 2000; 23: 688–694.

15. Julian LJ. Measures of anxiety: state-trait anxiety inventory (STAI), beck anxiety inventory (BAI), and hospital anxiety and depression scale-anxiety (HADS-A). *Arthritis Care Res (Hoboken)* 2011; 63(Suppl. 11): S467–S472.

16. EuroQol Group. EuroQol—a new facility for the measurement of health-related quality of life. *Health Policy* 1990; 16: 199–208.

17. Rui W, Cheng W, Ma XQ, *et al.* Health-related quality of life in Chinese people: a population-based survey of five cities in China. *Scand J Public Health* 2011; 39: 410–418.

18. Palsson OS, Whitehead WE, van Tilburg MA, *et al.* Rome IV diagnostic questionnaires and tables for investigators and clinicians. *Gastroenterology* 2016; pii: S0016-5085(16)00180-3.

19. Lundell LR, Dent J, Bennett JR, *et al.* Endoscopic assessment of oesophagitis: clinical and functional correlates and further validation of the Los Angeles classification. *Gut* 1999; 45: 172–180.

20. Gyawali CP, Roman S, Bredenoord AJ, *et al.* Classification of esophageal motor findings in gastro-esophageal reflux disease: conclusions from an international consensus group. *Neurogastroenterol Motil* 2017; 29.

21. Horowitz M, Wishart JM, Jones KL, *et al.* Gastric emptying in diabetes: an overview. *Diabet Med* 1996; 13: S16–S22.

22. Wu JC, Lai LH, Chow DK, *et al.* Concomitant irritable bowel syndrome is associated with failure of step-down on-demand proton pump inhibitor treatment in patients with gastro-esophageal reflux disease. *Neurogastroenterol Motil* 2011; 23: 155–160, e131.

23. de Bortoli N, Tolone S, Frazzoni M, *et al.* Gastroesophageal reflux disease, functional dyspepsia and irritable bowel syndrome: common overlapping gastrointestinal disorders. *Ann Gastroenterol* 2018; 31: 639–648.

24. Caro JJ, Salas M and Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole, and pantoprazole compared with omeprazole, ranitidine, and placebo: evidence from randomized clinical trials. *Clin Ther* 2001; 23: 998–1017.

25. Kulig M, Nocon M, Vieth M, *et al.* Risk factors of gastroesophageal reflux disease: methodology

and first epidemiological results of the ProGERD study. *J Clin Epidemiol* 2004; 57: 580–589.

26. Kahrilas PJ, McColl K, Fox M, *et al.* The acid pocket: a target for treatment in reflux disease? *Am J Gastroenterol* 2013; 108: 1058–1064.

27. Siregar GA, Halim S and Sitepu RR. Comparison of endoscopic findings with gastroesophageal reflux disease questionnaires (GerdQ) and reflux disease questionnaire (RDQ) for gastroesophageal

reflux disease in Medan. *Indones J Gastroenterol Hepatol Dig Endosc* 2015; 16: 143–147.

28. Bolier EA, Kessing BF, Smout AJ, *et al.* Systematic review: questionnaires for assessment of gastroesophageal reflux disease. *Dis Esophagus* 2015; 28: 105–120.

29. Gyawali CP, Kahrilas PJ, Savarino E, *et al.* Modern diagnosis of GERD: the Lyon consensus. *Gut* 2018; 67: 1351–1362.