Association between fibromyalgia syndrome and peptic ulcer disease development

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Abstract

Purpose
The correlation of fibromyalgia syndrome (FMS) with peptic ulcer disease (PUD) is unclear. We therefore conducted a cohort study to investigate whether FMS is correlated with an increased risk of PUD.

Methods
In this study, we established an FMS cohort comprising 26068 patients aged more than 20 years who were diagnosed with FMS from 2000 to 2011. Furthermore, we established a control cohort by randomly choosing 104269 people without FMS who were matched to the FMS patients by gender, age, and index year. All patients were free of PUD at the baseline. Cox proportional hazard regressions were performed to compute the hazard ratio of PUD after adjustment for demographic characteristics and comorbidities.

Results
The prevalence of comorbidities was significantly higher in the FMS patients than in the controls. The incidence of PUD was 29.8 and 19.4 per 1000 person-years in the FMS and control cohorts, respectively. In addition, the FMS cohort exhibited a 1.40-fold higher risk of PUD (95% confidence interval = 1.35–1.45) compared with the control cohort. After control for confounding factors, the medications (selective serotonin reuptake inhibitors, serotonin–norepinephrine reuptake inhibitors, and antidepressants) taken by the FMS patients did not increase the risk of PUD.

Conclusion
FMS patients exhibit a higher risk of PUD than that of patients without FMS.
Introduction

Currently, fibromyalgia syndrome (FMS) is a complex condition affecting patients and can represent a diagnostic challenge for physicians. It is characterized as a pain processing disorder with several distinct secondary symptoms and is associated with low quality of life. [1–4] With the multitude of conditions contributing to FMS development, the exact cause of the disorder is unclear. However, it has been hypothesized that FMS is caused by an extensive list of factors, ranging from persistent inflammation and immunologic and muscular abnormalities to triggering [5] and maintenance factors. [6–9]

Approximately 50% of FMS patients often exhibit other illnesses, such as gastroesophageal reflux disease (GERD), irritable bowel syndrome, and other gastrointestinal disorders. [10–12] Among these illnesses, food sensitivities are an essential determinant of inflammation that might be associated to FMS pain. This pain and inflammation can be provoked by particular foods, such as preservatives, eggs, and gluten; however, the food causing FMS symptoms differs from person to person. Until now, few studies have demonstrated which specific foods are connected to FMS pain. [13–15] Moreover, recent studies have revealed that the severity of small intestinal bacterial outgrowth (SIBO) is correlated with FMS patients’ level of pain, indicating the significance of SIBO in FMS. [16,17] Furthermore, some researchers believe that FMS and gastrointestinal disorders occur in conjunction because their drivers—inflammation in the brain and gut or bacterial outgrowth in the intestines—are similar. [18]

The Helicobacter pylori bacterium is typically the causative agent of peptic ulcers, which are sores in the gastric lining, esophagus, or duodenum. These ulcers can also be attributed to the consistent use of nonsteroidal anti-inflammatory drugs (NSAIDs). Various classes of drugs, which often include NSAIDs, are utilized for treating FMS. However, despite their widespread use, results have shown their ineffectiveness in relieving FMS pain. [19] Therefore, physicians currently prescribe drugs that affect the central nervous system, [19,20] targeting the origins of pain reception and slowly eliminating the use of NSAIDs in FMS treatment.

Some physicians believe that stress [21] may play a role in the activity of the gut through its effect on hormones and nerves [22,23], although the link is yet to be confirmed. To the best of our knowledge, the epidemiological evidence for the association of FMS with the risk of PUD is still insufficient. Therefore, in this population-based study, we investigated the relationship between FMS and PUD development.

Methods

Data source

The National Health Insurance (NHI) program in Taiwan is a single-payer universal insurance program implemented on March 1, 1995, and the NHI program covers approximately 99% of the Taiwanese population. [24] The National Health Insurance Administration has authorized the National Health Research Institutes (NHRI) to create an encrypted, secondary database—the National Health Insurance Research Database (NHIRD)—for research purposes. In this study, we analyzed the Longitudinal Health Insurance Database 2000 (LHID2000), which constitutes a subdataset of the NHIRD. The details of the LHID2000 are provided in previous studies. [25,26] Diagnoses were classified according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes.

Data availability statement

The dataset used in this study is held by the Taiwan Ministry of Health and Welfare (MOHW). The Ministry of Health and Welfare must approve our application to access this data. Any
A researcher interested in accessing this dataset can submit an application form to the Ministry of Health and Welfare requesting access. Please contact the staff of MOHW (Email: stcarol-wu@mohw.gov.tw) for further assistance. Taiwan Ministry of Health and Welfare Address: No.488, Sec. 6, Zhongxiao E. Rd., Nangang Dist., Taipei City 115, Taiwan (R.O.C.). Phone: +886-2-8590-6848. All relevant data are within the paper.

Ethics statement
The NHIRD encrypts patient personal information to ensure patient privacy, and researchers are provided with anonymous identification numbers associated with the relevant claims information, including sex, date of birth, medical services received, and prescriptions. Therefore, patient consent is not required to access the NHIRD. This study was approved to fulfill the condition for exemption by the Institutional Review Board (IRB) of China Medical University (CMUH104-REC2-115-CR1). The IRB also specifically waived the consent requirement.

Study population
This study was assessed on the risk of PUD between the individual with and without FMS. FMS, characterized by widespread musculoskeletal pain and multiple tender points, was diagnosed by rheumatologists, neurologists, psychologists, physiatrists, and pain specialists with clinical accuracy, according to the American College of Rheumatology Criteria for the Classification of Fibromyalgia. Patients aged ≥20 years who were diagnosed with FMS (ICD-9-CM code 729.1) more than three times within 3 months were included in the FMS cohort. The index date was defined as the first diagnosis date of FMS. To establish a control cohort, patients without FMS were randomly selected and matched to the FMS patients at a 4:1 ratio by age group (every 5-year span), sex, and index date. The exclusion criteria were a history of PUD (ICD-9-CM codes 531–533) before the index date and missing information.

Outcome
The outcome of interest was a new diagnosis of PUD from 2000 to 2011. Both the FMS and control cohorts were monitored until diagnosis of PUD or until the patients were censored because of withdrawal from the NHI program or the end of 2011.

Comorbidities and medications
To evaluate the potential risk and to control for confounding factors, we included the comorbidities and medications of each patient, namely hyperlipidemia (ICD-9-CM code 272), diabetes (ICD-9-CM code 250), liver cirrhosis (ICD-9-CM codes 571.2, 571.5, and 571.6), alcohol-related illness (ICD-9-CM codes 291, 303, 305, 571.0, 571.1, 571.2, 571.3, 790.3, A215, and V11.3), hypertension (ICD-9-CM codes 401–405), depression (ICD-9-CM codes 296.2, 296.3, 300.4, and 311), anxiety (ICD-9-CM code 300.0), sleep disorder (ICD-9-CM code 307.4 and 780.5), stroke (ICD-9-CM codes 430–438), H. pylori infection (ICD-9-CM code 041.86), GERD (ICD-9-CM codes 530.11 and 530.81), and proton pump inhibitor (PPI) and NSAID use. Furthermore, we assessed whether FMS medications, including amitriptyline, fluoxetine, duloxetine, milnacipran, moclomide, tponsitron, pramipexole, and pregabalin, play a role in PUD outcomes.

Statistical analysis
The chi-square test was used for analyzing categorical variables, and the Student’s t test was used for analyzing continuous variables. The cumulative incidence of PUD in the FMS and
control cohorts was explored using the Kaplan–Meier method, and the differences were determined using log-rank tests. The incidence density rates were calculated by dividing the number of PUD events by the total follow-up years (per 1st000 person-years). The incidence density rates of PUD for each risk factor and stratified by age, sex, comorbidity, and medications in the both cohorts were calculated. Univariable and multivariable Cox proportional hazard regression models were used to determine the risk factors for PUD, denoted as a hazard ratio (HR) with a 95% confidence interval (CI). Stratified analysis of PUD risk by age, sex, comorbidities and medications was also estimated by the Cox models. The multivariable models included all statistically significant risk factors identified in the univariable model. Data management and analyses were performed using SAS 9.4 software (SAS Institute, Cary, NC, USA). A two-tailed $P$ value $< 0.05$ was considered significant.

**Results**

A total of 26068 FMS patients and 104269 controls were included in this study (Table 1). Most patients were aged $\leq 49$ years (53.8%) and were women (54.6%). The mean ages of the FMS and control cohorts were 49.5 ± 16.0 and 49.0 ± 16.3 years, respectively. The comorbidities of hyperlipidemia, diabetes, liver cirrhosis, alcohol-related illness, hypertension, depression, anxiety, sleep disorder, stroke, and GERD and NSAID use were more prevalent in the FMS cohort.

| Variable                | Non-FM cohort | FM cohort | $p$-value |
|-------------------------|---------------|-----------|-----------|
| **Age, year**           |               |           |           |
| $\leq 49$               | 56100(53.8)   | 14025(53.8)| 0.99      |
| 50–64                   | 28020(26.9)   | 7005(26.9) |           |
| 65+                     | 20149(19.3)   | 5038(19.3) |           |
| Mean±SD$^T$             | 49.0(16.3)    | 49.5(16.0) | $<0.001$  |
| **Sex**                 |               |           |           |
| Female                  | 56972(54.6)   | 14243(54.6)| 0.99      |
| Male                    | 47297(45.4)   | 11825(45.4)|           |
| **Comorbidity**         |               |           |           |
| Hyperlipidemia          | 14314(13.7)   | 4900(18.8) | $<0.001$  |
| Diabetes                | 6838(6.56)    | 2159(8.28) | $<0.001$  |
| Liver cirrhosis         | 468(0.45)     | 150(0.58)  | 0.008     |
| Alcohol-related illness | 2148(2.06)    | 714(2.74)  | $<0.001$  |
| Hypertension            | 24322(23.3)   | 7673(29.4) | $<0.001$  |
| Depression              | 2561(2.46)    | 1064(4.08) | $<0.001$  |
| Anxiety                 | 3695(3.54)    | 1624(6.23) | $<0.001$  |
| Sleep disorder          | 12290(11.8)   | 5072(19.5) | $<0.001$  |
| Stroke                  | 2633(2.53)    | 874(3.35)  | $<0.001$  |
| Gastroesophageal reflux disorder | 439(0.42) | 168(0.64) | $<0.001$  |
| H. pylori infection     | 42(0.04)      | 11(0.04)   | 0.89      |
| **Medication**          |               |           |           |
| NSAID                   | 42400(40.7)   | 14738(56.5)| $<0.001$  |

Chi-square test;

$^T$: t test

NSAID, nonsteroidal anti-inflammatory drug

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than in the control cohort. The average follow-up durations were 5.59 and 5.87 years in the FMS and control FMS cohorts, respectively. As shown in Fig 1, the cumulative incidence of PUD was higher in the FMS cohort than in the control cohort (log-rank test $P < 0.001$).

The incidence density rate of PUD was 29.8 per 1000 person-years in the FMS cohort, which was significantly higher than that in the control cohort (19.4 per 1000 person-years; Table 2). The FMS cohort exhibited a 1.40-fold higher risk of PUD compared with the control cohort (95% CI = 1.35–1.45). Compared with patients aged ≤49 years, the risk of PUD was 1.58- and 1.96-fold higher in those aged 50–64 years and ≥65 years (95% CI = 1.52–1.64 and 1.88–2.05, respectively). The risk of PUD was higher in patients with the comorbidities of hyperlipidemia [adjusted HR (aHR) = 1.22, 95% CI = 1.17–1.27], liver cirrhosis (aHR = 1.76, 95% CI = 1.48–2.09), hypertension (aHR = 1.24, 95% CI = 1.19–1.29), depression (aHR = 1.19, 95% CI = 1.09–1.29), anxiety (aHR = 1.15, 95% CI = 1.10–1.20), and sleep disorder (aHR = 1.15, 95% CI = 1.10–1.20). The aHR of PUD development was high in patients taking NSAIDs (aHR = 1.28, 95% CI = 1.24–1.33).

Table 3 shows a comparison of PUD incidence and the Cox model-measured hazards ratio between the patients with FMS and those without FMS after stratification by age, sex, comorbidity, and medications. Regardless of stratification, the risk of PUD was higher in the FMS patients than in the controls.

Table 4 displays the results of an analysis of the effects of FMS medications on the risk of PUD compared with the control cohort. FMS patients who did not receive medications exhibited a significantly 1.48-fold higher risk of PUD (95% CI = 1.42–1.53) compared with the
Table 2. Incidence and risk factors for peptic ulcer disease.

| Variable                        | Event | PY     | Rate\(^a\) | Crude HR (95% CI) | Adjusted HR\(^b\) (95% CI) |
|---------------------------------|-------|--------|------------|-------------------|--------------------------|
| **Fibromyalgia**                |       |        |            |                   |                          |
| Non-FM cohort                   | 11879 | 612540 | 19.4       | 1.00              | 1.00                     |
| FM cohort                       | 4337  | 145634 | 29.8       | 1.53(1.48, 1.58)*** | 1.40(1.35, 1.45)***       |
| **Age, year**                   |       |        |            |                   |                          |
| ≤ 49                            | 6258  | 435894 | 14.4       | 1.00              | 1.00                     |
| 50–64                           | 5309  | 198789 | 26.7       | 1.84(1.77, 1.91)*** | 1.58(1.52, 1.64)***       |
| 65+                             | 4649  | 123491 | 37.7       | 2.54(2.44, 2.63)*** | 1.96(1.88, 2.05)***       |
| **Sex**                         |       |        |            |                   |                          |
| Female                          | 9287  | 426012 | 21.8       | 1.00              | 1.00                     |
| Male                            | 6929  | 332162 | 20.9       | 1.06(1.02, 1.09)*** | 1.02(0.98, 1.05)          |
| **Comorbidity**                 |       |        |            |                   |                          |
| **Hyperlipidemia**              |       |        |            |                   |                          |
| No                              | 12600 | 659721 | 19.1       | 1.00              | 1.00                     |
| Yes                             | 3616  | 98453  | 36.7       | 1.88(1.81, 1.95)*** | 1.22(1.17, 1.27)***       |
| **Diabetes**                    |       |        |            |                   |                          |
| No                              | 14707 | 715952 | 20.5       | 1.00              | 1.00                     |
| Yes                             | 1509  | 42222  | 35.7       | 1.68(1.59, 1.77)*** | 1.00(0.94, 1.06)          |
| **Liver cirrhosis**             |       |        |            |                   |                          |
| No                              | 16088 | 755855 | 21.3       | 1.00              | 1.00                     |
| Yes                             | 128   | 2319   | 55.2       | 2.43(2.04, 2.89)*** | 1.76(1.48, 2.09)***       |
| **Alcohol-related illness**     |       |        |            |                   |                          |
| No                              | 15895 | 746747 | 21.3       | 1.00              | 1.00                     |
| Yes                             | 321   | 11427  | 28.1       | 1.24(1.11, 1.38)*** | 1.06(0.95, 1.19)          |
| **Hypertension**                |       |        |            |                   |                          |
| No                              | 10280 | 592447 | 17.4       | 1.00              | 1.00                     |
| Yes                             | 5936  | 165727 | 35.8       | 2.02(1.96, 2.09)*** | 1.24(1.19, 1.29)***       |
| **Depression**                  |       |        |            |                   |                          |
| No                              | 15610 | 741182 | 21.1       | 1.00              | 1.00                     |
| Yes                             | 606   | 16992  | 35.7       | 1.63(1.51, 1.77)*** | 1.19(1.09, 1.29)***       |
| **Anxiety**                     |       |        |            |                   |                          |
| No                              | 15325 | 734729 | 20.9       | 1.00              | 1.00                     |
| Yes                             | 891   | 23445  | 38.0       | 1.73(1.62, 1.85)*** | 1.15(1.10, 1.20)***       |
| **Sleep disorder**              |       |        |            |                   |                          |
| No                              | 13513 | 676459 | 20.0       | 1.00              | 1.00                     |
| Yes                             | 2703  | 81716  | 33.1       | 1.59(1.52, 1.65)*** | 1.15(1.10, 1.20)***       |
| **Stroke**                      |       |        |            |                   |                          |
| No                              | 15665 | 743843 | 21.1       | 1.00              | 1.00                     |
| Yes                             | 551   | 14331  | 38.5       | 1.72(1.58, 1.87)*** | 0.97(0.89, 1.06)          |
| **Gastroesophageal reflux disorder** |   |     |   |   |                           |
| No                              | 16157 | 756844 | 21.4       | 1.00              | 1.00                     |
| Yes                             | 59    | 1330   | 44.4       | 1.75(1.35, 2.25)*** | 1.16(0.90, 1.51)          |
| **H. pylori infection**         |       |        |            |                   |                          |
| No                              | 16215 | 758066 | 21.4       | 1.00              | 1.00                     |
| Yes                             | 1     | 108    | 9.25       | 0.36(0.05, 2.53)   | -                        |
| **Medication**                  |       |        |            |                   |                          |
| **NSAID**                       |       |        |            |                   |                          |
| No                              | 7853  | 472003 | 16.6       | 1.00              | 1.00                     |

(Continued)
controls. Patients receiving meclobemide, fluoxetine, tropisetron, duloxetine, or milnacipran exhibited a significantly 1.64-fold higher risk of PUD (95% CI = 1.28–2.10) compared with the controls. FMS patients who received pregabalin, amitriptyline, or pramipexole exhibited a significantly 1.55-fold higher risk of PUD (95% CI = 1.22–1.97) compared with the controls.

Discussion

This is the first study that showed the long-term risk of PUD in FMS patients by using a population-based database. Through the primary findings, our hypothesis that FMS patients have an elevated risk of PUD is proven true. At the end of the follow-up period, the cumulative frequency of PUD was higher in the FMS cohort than in the control cohort (Fig 1). The incidence density rates of PUD were 29.8 and 19.4 per 1000 person-years in the FMS and control cohort, respectively.

Table 2. Incidence of peptic ulcer disease by age, sex, comorbidity, and medications and Cox model-measured hazard ratio for patients with fibromyalgia syndrome compared those without fibromyalgia syndrome.

| Variable   | Event | PY  | Rate# | Crude HR (95% CI) | Adjusted HR† (95% CI) |
|------------|-------|-----|-------|------------------|----------------------|
| Yes        | 8363  | 286171 | 29.2 | 1.69(1.64, 1.74)*** | 1.28(1.24, 1.33)***  |

PY, person-years; 
Rate#, incidence rate, per 1000 person-years; crude HR, relative hazard ratio; 
adjusted HR†: multivariable analysis including age; sex; comorbidities of hyperlipidemia, diabetes, liver cirrhosis, alcohol-related illness, hypertension, depression, anxiety, sleep disorder, stroke, and gastroesophageal reflux disorder; and NSAID use. 
***P < 0.001

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Table 3. Incidence of peptic ulcer disease by age, sex, comorbidity, and medications and Cox model-measured hazard ratio for patients with fibromyalgia syndrome compared those without fibromyalgia syndrome.

| Variables   | Non-FM cohort | FM cohort |
|-------------|---------------|-----------|
|             | Event | PY  | Rate# | Event | PY  | Rate# | Crude HR (95% CI) | Adjusted HR† (95% CI) |
| Age, years  |       |     |       |       |     |       |                  |                      |
| < 49        | 4423  | 351605 | 12.6 | 1835  | 84290 | 21.8 | 1.72(1.63, 1.82)*** | 1.52(1.44, 1.61)*** |
| 50–64       | 3947  | 161146 | 24.5 | 1362  | 37643 | 36.2 | 1.47(1.38, 1.56)*** | 1.32(1.24, 1.40)*** |
| 65+         | 3509  | 99789 | 35.2 | 1140  | 23702 | 48.1 | 1.36(1.27, 1.45)*** | 1.30(1.22, 1.39)*** |
| Sex         |       |     |       |       |     |       |                  |                      |
| Female      | 6825  | 344075 | 19.8 | 2462  | 81937 | 30.1 | 1.51(1.44, 1.58)*** | 1.37(1.31, 1.44)*** |
| Male        | 5054  | 268465 | 18.8 | 1875  | 63697 | 29.4 | 1.56(1.48, 1.64)*** | 1.45(1.37, 1.53)*** |
| Comorbidity†|       |     |       |       |     |       |                  |                      |
| No          | 5608  | 408359 | 13.7 | 1621  | 77476 | 20.9 | 1.5291.44, 1.61)*** | 1.48(1.40, 1.56)*** |
| Yes         | 6271  | 204181 | 30.7 | 2716  | 68158 | 39.9 | 1.30(1.24, 1.36)*** | 1.33(1.27, 1.39)*** |
| Medication  |       |     |       |       |     |       |                  |                      |
| NSAID       |       |     |       |       |     |       |                  |                      |
| No          | 6195  | 402114 | 15.4 | 1658  | 69890 | 23.7 | 1.53(1.45, 1.62)*** | 1.50(1.42, 1.59)*** |
| Yes         | 5684  | 210426 | 27.0 | 2679  | 75745 | 35.4 | 1.32(1.26, 1.39)*** | 1.33(1.27, 1.39)*** |

PY, person-years; 
Rate#, incidence rate, per 1000 person-years; crude HR, relative hazard ratio; 
adjusted HR†: multivariable analysis including age; sex; comorbidities of hyperlipidemia, diabetes, liver cirrhosis, alcohol-related illness, hypertension, depression, anxiety, sleep disorder, and stroke; and NSAID use. 
Comorbidity†: Patients with any one of the comorbidities of hyperlipidemia, diabetes, liver cirrhosis, alcohol-related illness, hypertension, depression, anxiety, sleep disorder, and stroke. 
***P < 0.001

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cohorts, respectively. Moreover, the FMS cohort exhibited a 1.40-fold higher risk of PUD (95% CI = 1.35–1.45) compared with the control cohort (Table 2).

The prevalence rate of comorbidities was also compared between the FMS and control cohorts, as shown in Table 1. Comorbidities such as hyperlipidemia, diabetes, liver cirrhosis, hypertension, depression, anxiety, sleep disorder, stroke, and GERD and PPI and NSAID use were more common in the FMS cohort than in the control cohort. Although not a primary concern of the current study, certain illnesses are expected to be more prevalent in the FMS cohort. [2,28] Because FMS is a complex condition that is likely multifactorial, both internal and external factors may be triggers for PUD development. [28–32]

The mechanisms underlying the association of FMS with an increased risk of PUD are unclear. However, many patients reported an intestinal infection as the initial symptom of FMS; therefore, current and past infection with common intestinal pathogens (i.e., H. pylori) might induce PUD development in FMS patients. [16,17,33] In addition, gut infection, gut inflammation, medications, stress, and trauma can induce PUD development and damage the mucosal barrier of the gastrointestinal epithelium, [34–36] which allows unshielded molecules to enter the bloodstream (known as leaky gut syndrome). The leaky gut causes systemic inflammation and triggers immune responses, leading to a wide array of diseases, including FMS. [34–36]

The risk of PUD in FMS patients receiving medications and those not receiving medications was 1.59-fold (95% CI = 1.34–1.89) and 1.48-fold (95% CI = 1.42–1.53) higher than that in the controls. Drugs that affect serotonin levels (fluoxetine, tropisetron, duloxetine, mocllobemide, and milnacipran) were shown to increase the risk of gastrointestinal problems by other investigators [37–41], but they did not exert more adverse effects than those of other medications (pregabalin, amitriptyline, and pramipexole) in our study (aHR = 1.64 and 1.55, respectively). Our findings show that the listed drugs may not be the cause of ulcers (Table 4).

Increasing evidence has shown that bioenergetics and mitochondrial function are impaired in FMS [42–44] and PUD [45–47] patients. Although it is unclear whether oxidative stress is a common pathway of PUD and FMS, recent studies have shown that oxidative stress can cause the pathophysiological mechanisms that culminate in the symptoms of PUD and FMS.

This study has some limitations. First, the data extracted from the NHIRD represent only the incidents at discharge; discrepancies between medical treatments and patient diagnoses cannot be directly verified. Second, our study did not assess the severity of FMS and PUD;
therefore, we cannot for certain state how the FMS severity affects the subsequent risk of PUD. Moreover, the evidence in this study may be restricted to Taiwan, because it was obtained using the claims data in the NHIRD for feasibility and practicality. Finally, the patients’ diet, exposure to smoking and alcohol, and psychological factors are not available in the NHI dataset; therefore, these factors could not be estimated when determining the PUD risk.

**Conclusion**

In this study, we demonstrated that FMS contributes to an elevated risk of PUD. FMS patients had a high prevalence of comorbidities, and the drugs identified that relieve psychosomatic symptoms in FMS did not increase the likelihood of ulcers. The mechanisms underlying the link between FMS and PUD are still unclear. Additional studies are required to clarify the underlying mechanisms.

**Supporting information**

S1 STROBE Checklist. Checklist of items that should be included in reports of observational studies.

(DOC)

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**Author Contributions**

**Conceptualization:** KAW CHT.

**Data curation:** KAW JCW CLL CHT.

**Formal analysis:** KAW JCW CLL CHT.

**Funding acquisition:** CHT.

**Investigation:** CLL CHT.

**Methodology:** CLL CHT.

**Project administration:** CHT.

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**Visualization:** KAW JCW CLL CHT.
Writing – original draft: KAW JCW CLL CHT.
Writing – review & editing: KAW JCW CLL CHT.

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