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Analysis of Symptoms in Patients with Minimal Change Esophagitis Versus Those with Reflux Esophagitis and Peptic Ulcer

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1. Introduction

According to the 2006 Montreal globally acceptable definition and classification of gastroesophageal reflux disease (GERD), this condition develops when the reflux of gastric contents causes symptoms or complications (Vakil et al., 2006). Because reflux esophagitis is defined as occurring when reflux of gastric acid into the esophagus causes mucosal breaks, erosions and/or ulcers, this condition requires endoscopic diagnosis. Non-erosive reflux disease (NERD) is defined by occurrence of reflux symptoms in patients without any endoscopic mucosal breaks. Thus, NERD includes prominent erythema without clear demarcation or whitish cloudiness of the lower esophageal mucosa obscuring the longitudinal blood vessels, which used to be known as the "discoloring" type of reflux esophagitis in Japan. In the present study, we characterized the symptoms and pathophysiology of patients with minimal change esophagitis (MC esophagitis), who had prominent erythema and whitish cloudiness of the esophageal mucosa.

2. Subjects and methods

The subjects were 347 patients who attended the Gastroenterology Outpatient Department of Gunma University Hospital with symptoms of upper abdominal pain or discomfort. All of them underwent upper gastrointestinal endoscopy to rule out organic disorders. The endoscopic diagnosis was determined by reviewing the endoscopic findings documented for each patient (Table 1). The endoscopists were unaware of the results of the patient questionnaire when they performed endoscopy, and only experienced endoscopists (who had carried out more than 3,000 endoscopic procedures) performed examinations in the present study. The modified Los Angeles (LA) classification was used for endoscopic diagnosis of GERD (Hongo, 2006). This classification employs the term "mucosal break" to describe mucosal lesions of the esophagus, with a mucosal break being defined as an area of slough or erythema that is clearly demarcated from the adjacent normal-looking mucosa. According to the original LA classification, GERD is divided into four grades from A to D. Grade A means one or more mucosal breaks no longer than 5 mm, none of which extends

between the tops of two mucosal folds. Grade B is one or more mucosal breaks>5 mm long, none of which extends between the tops of two mucosal folds. Grade C means mucosal breaks that extend between the tops of two or more mucosal folds, but are not circumferential, while Grade D indicates one or more circumferential mucosal breaks (Armstrong et al., 1996). Before Grade A, we added Grade M (minimal change), which was defined as prominent erythema without clear demarcation or whitish cloudiness of the lower esophageal mucosa obscuring the longitudinal blood vessels (Fig. 1). This corresponds to the so-called "discoloring" type of reflux esophagitis in Japanese terminology. A diagnosis of peptic ulcer (gastric or duodenal ulcer) was made if a lesion with definite plaque was identified. Endoscopic gastritis was classified as erosive (frank erosions), superficial (redness, edema, and adherent mucus in the gastric body), or atrophic (distal migration of the border between the pyloric and fundic glands in the gastric body, as well as clearly visible vessels). When a patient had two or more diagnoses, the following order of priority was employed: GERD, gastric ulcer, duodenal ulcer, gastritis (erosive, superficial, or atrophic), or normal. Patients who were endoscopically normal or had gastroduodenitis were classified into a non-esophagitis and non-ulcer (NE-NU) group. There were 39 patients with MC esophagitis, 85 with GERD (LA grade≥A), 195 in the NE-NU group, and 28 with gastric ulcer or duodenal ulcer (GU+DU).

| | MC esophagitis | GERD | NE-NU | GU + DU |
|-------------------------|----------------|-------------|----------------------------------|-------------|
| | | | (gastritis,duodenitis,or normal) | |
| | (n = 39) | (n = 85) | (n = 195) | (n = 28) |
| Sex (men, women) | 19, 20 | 52, 33 | 81, 114 | 19, 9 |
| Mean age (years)±SD | 59.7 ± 13.1 | 60.9 ± 14.1 | 58.6 ± 14.2 | 55.2 ± 18.9 |
| Endoscopic severity (n) | | | | |
| Grade M | 39 | 0 | 0 | 0 |
| Grade A + B | 0 | 74 | 0 | 0 |
| Grade C + D | 0 | 11 | 0 | 0 |

Table 1. Demographic data of the subjects

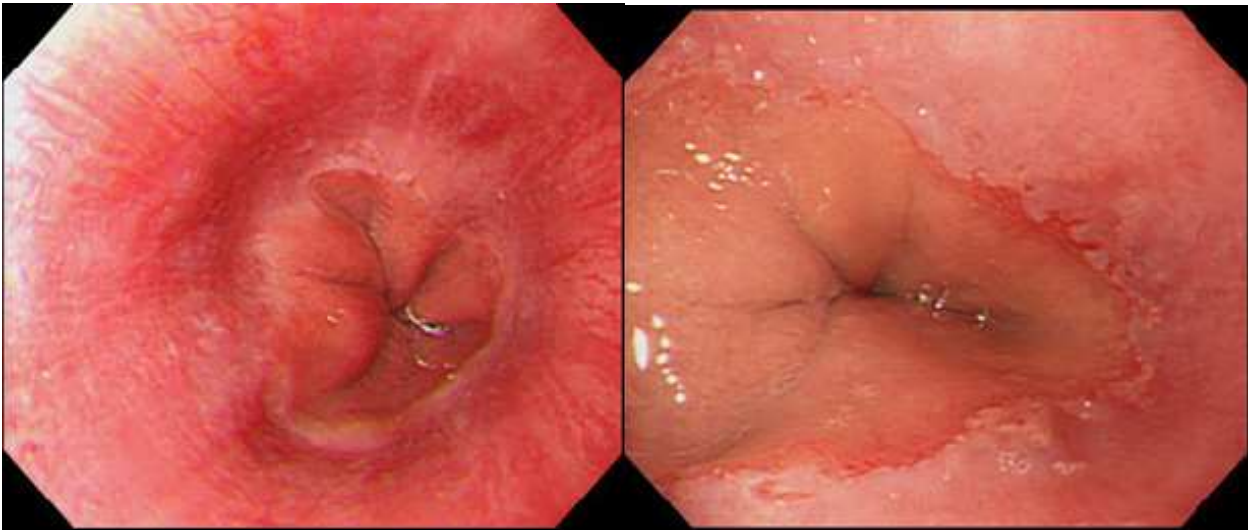


Fig. 1. Minimal change esophagitis. Minimal change esophagitis is endoscopically characterized by prominent erythema that does not show clear demarcation or by whitish cloudiness of the lower esophageal mucosa obscuring the longitudinal blood vessels.

Each subject completed a 37-item self-administered questionnaire that covered gastroesophageal reflux symptoms, dysmotility-like symptoms, ulcer-like symptoms, and psychosomatic symptoms. The questions were randomly arranged and each question could be answered as "yes" or "no") (Table 2). There were 12 questions dealing with gastroesophageal reflux. In particular, heartburn was assessed from multiple perspectives, including the actual symptoms, timing of onset, and influence of posture: "Do you get heartburn?"; "Do you subconsciously rub your chest with your hand?"; "Do you get a stinging sensation in your chest?"; "Do you mainly get heartburn after meals?"; and "Do you get heartburn if you bend forward?". In addition, 10 questions related to dysmotility and 4 questions related to ulcers were used to examine accessory symptoms of GERD. The questions related to dysmotility included: "Does your stomach get bloated?"; "Does your stomach ever feel heavy after meals?"; "Do you feel full right after meals?"; and "Do you get nausea?". The questions relating to ulcer symptoms included: "Do you get pain in the stomach after you eat?"; "Do you get pain in the stomach at night?"; and "Do you get pain when you have an empty stomach?". Furthermore, 11 questions dealt with psychosomatic symptoms, including: "Do you feel sick?", "Are you anxious?" and "Do you feel languid?". Subjects completed the questionnaire prior to endoscopy. An explanation of the questions was not provided, but information was given if a subject had any queries. The frequency of "yes" answers was calculated for each question. The χ^2 test was used to compare data among the MC esophagitis, GERD, and NE-NU groups, with $P<0.05$ being considered statistically significant.

3. Results

Figures 2-5 displays the symptoms in each category that showed significant differences ($p<0.05$ by the χ^2 test) among the four groups (MC esophagitis, GERD, NE-NU, and GU+DU groups).

| Question |
|---|
| <i>Gastroesophageal reflux symptoms</i> |
| Do you get heartburn? |
| Do you subconsciously rub your chest with your hand? |
| Do you cough? |
| Do you get a stinging sensation in your chest? |
| Do you mainly get heartburn after meals? |
| Do you get pain in the throat? |
| Do you get heartburn if you bend forward? |
| Do some things get stuck when you swallow? |
| Do you get heartburn when lying down? |
| Do you feel a burning sensation from the pit of the stomach to the lower chest? |
| Do you get acidic liquid coming up into your mouth? |
| Do you get pain in the chest? |

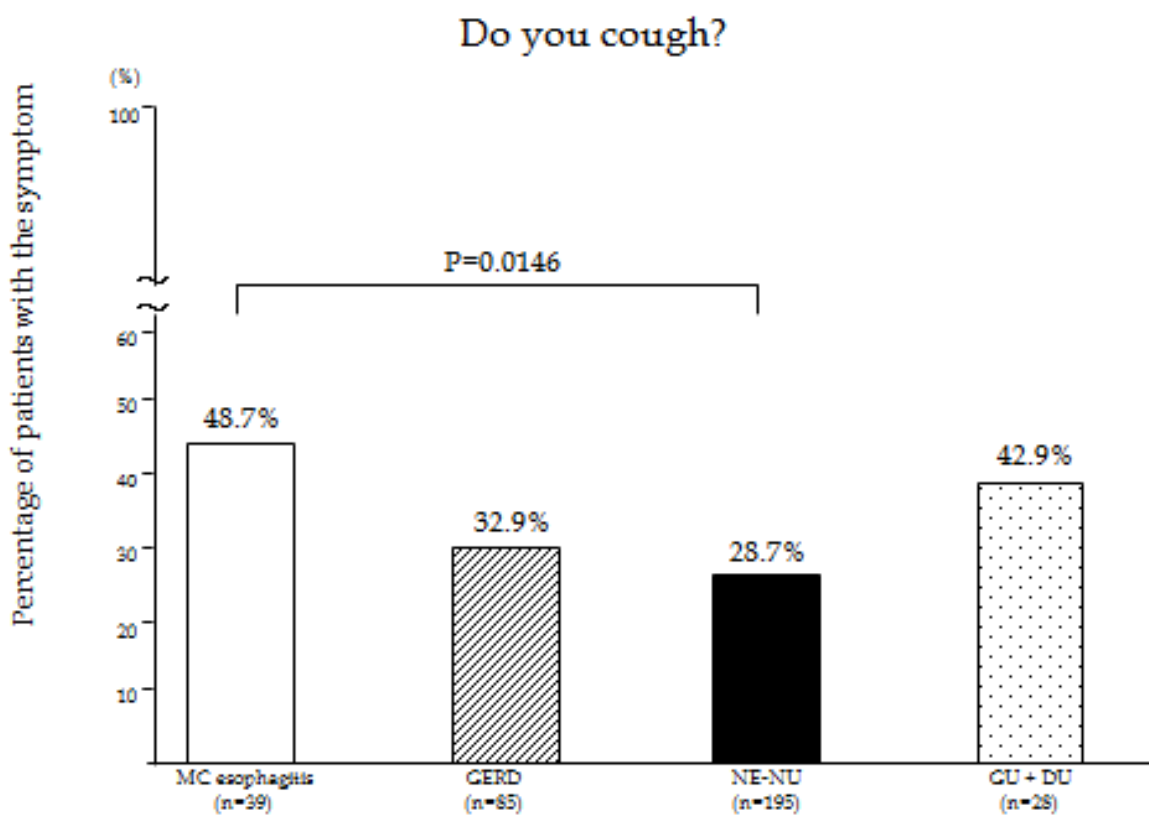
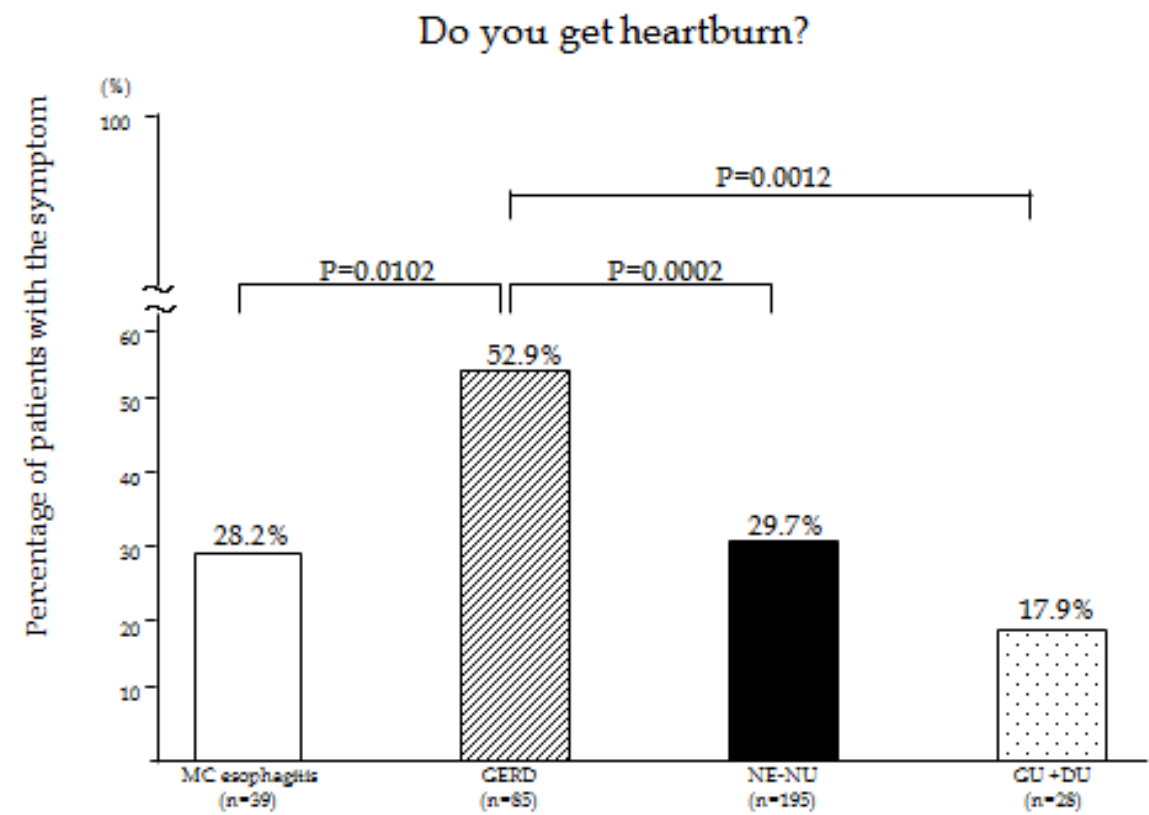
| |
|--|
| <i>Dysmotility-like symptoms</i> |
| Do you get nausea on waking? |
| Does your stomach get bloated? |
| Does your stomach ever feel heavy after meals? |
| Do you feel sick and heavy after fatty meals? |
| Do you feel sick and heavy after you overeat? |
| Do you feel full right after meals? |
| Do you burp a lot? |
| Are you unable to eat immediately after waking in the morning? |
| Do you get nausea? |
| Does your stomach ever feel heavy when it is empty? |

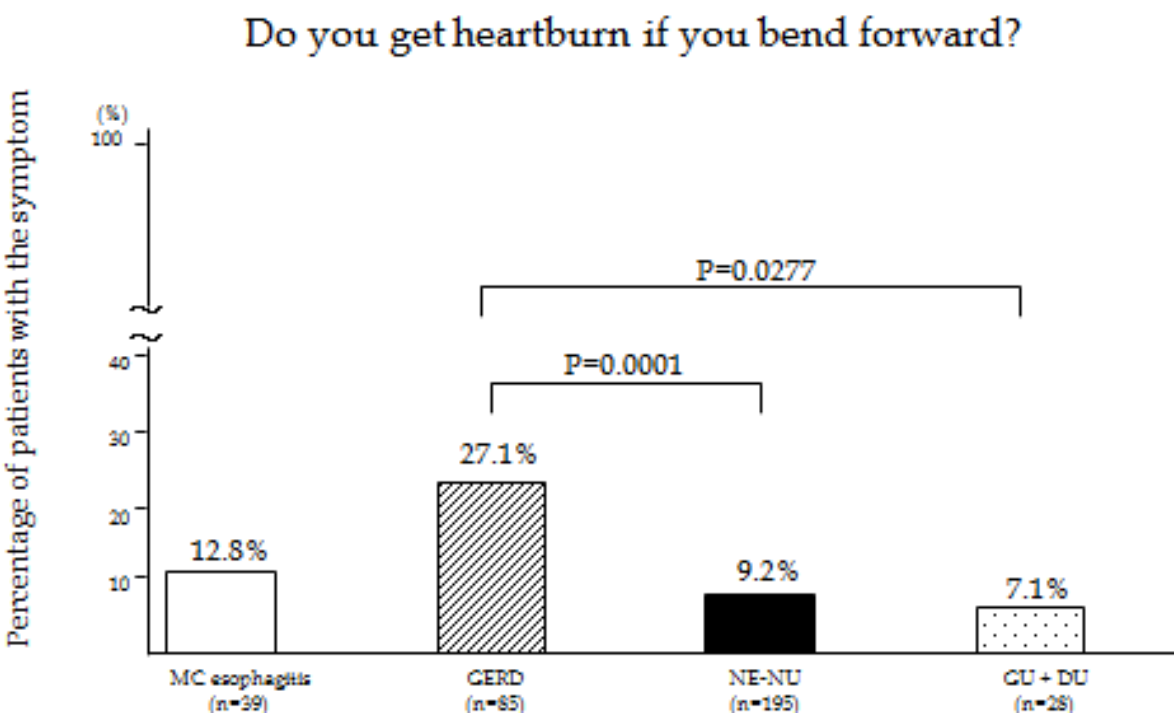
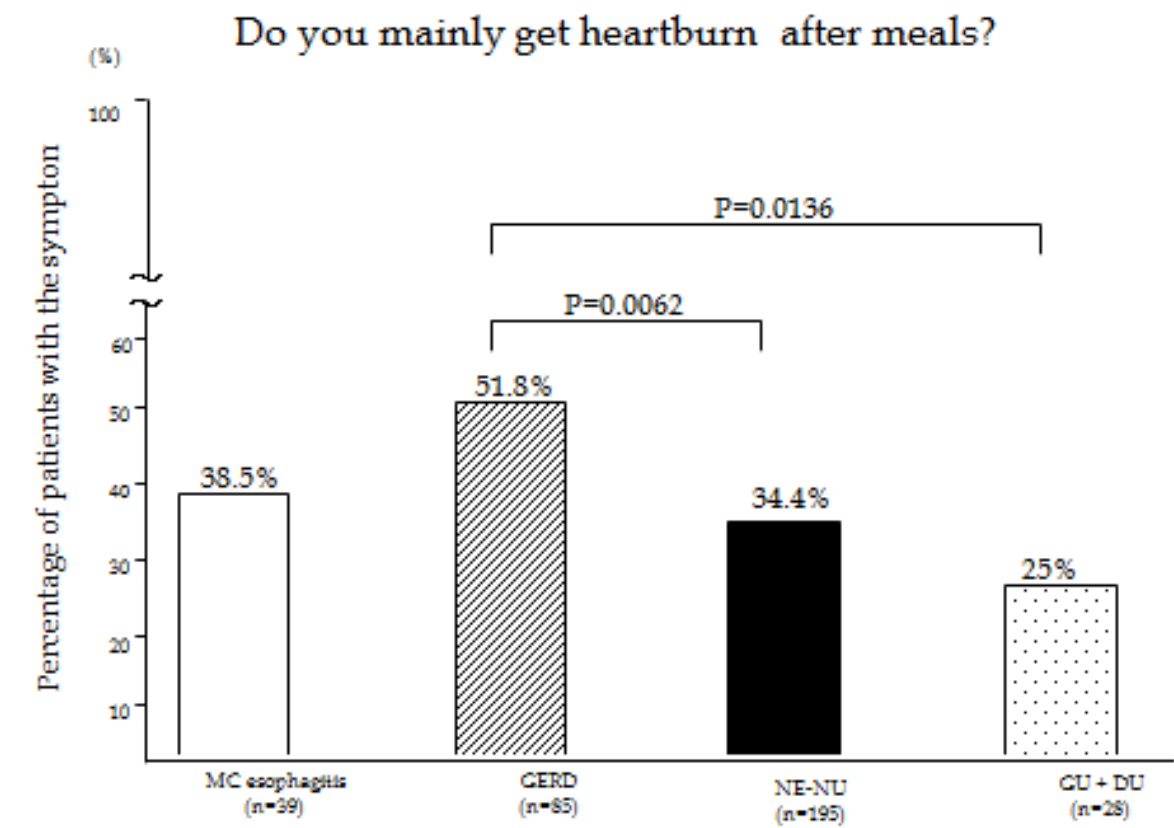
| |
|--|
| <i>Ulcer-like symptoms</i> |
| Do you get pain in the stomach after you eat? |
| Do you have dark feces? |
| Do you get pain in the stomach at night? |
| Do you get pain in the stomach when it is empty? |

| |
|---|
| <i>Psychosomatic symptoms</i> |
| Do you fall asleep unpleasantly? |
| Do you wake up unpleasantly? |
| Do you get frustrated? |
| Do you feel like taking a break? |
| Do you have change in the sense of taste? |
| Have you lost the desire to eat? |
| Do you feel sick? |
| Are you anxious? |
| Are you unable to sleep long enough? |
| Do you easily get tired? |
| Do you feel languid? |

Did you experience any of these symptoms during the previous 2 weeks?
Please circle "yes" or "no".

Table 2. The 37-item questionnaire





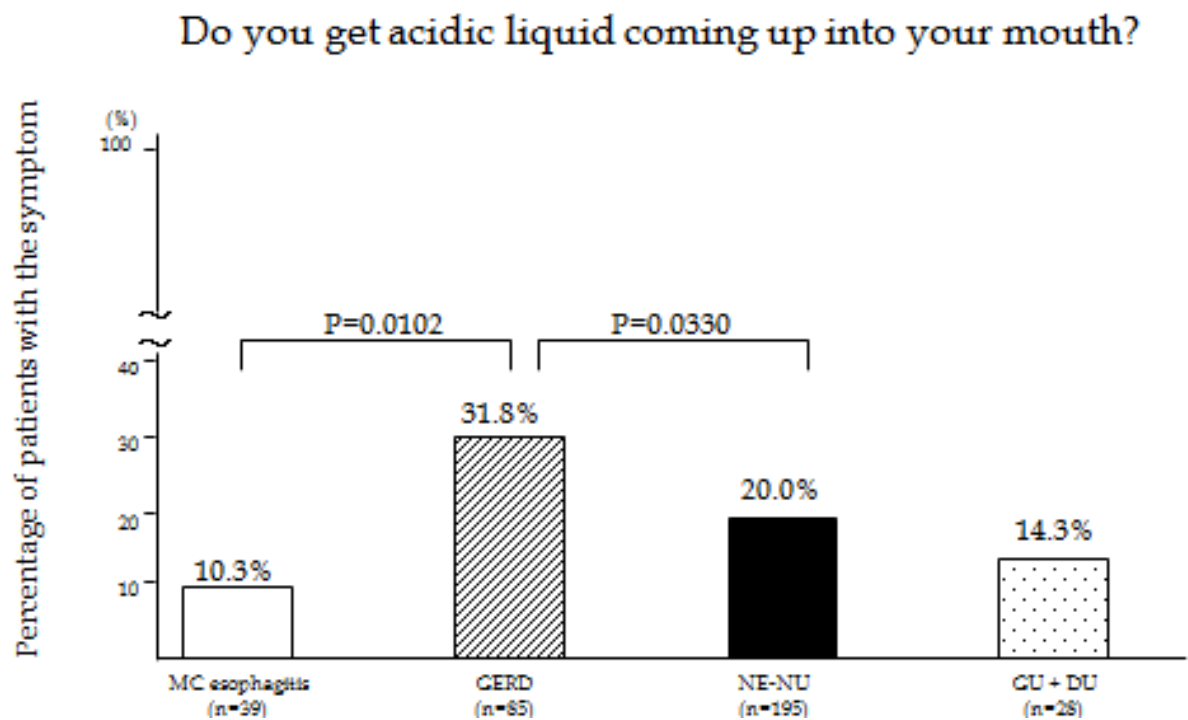
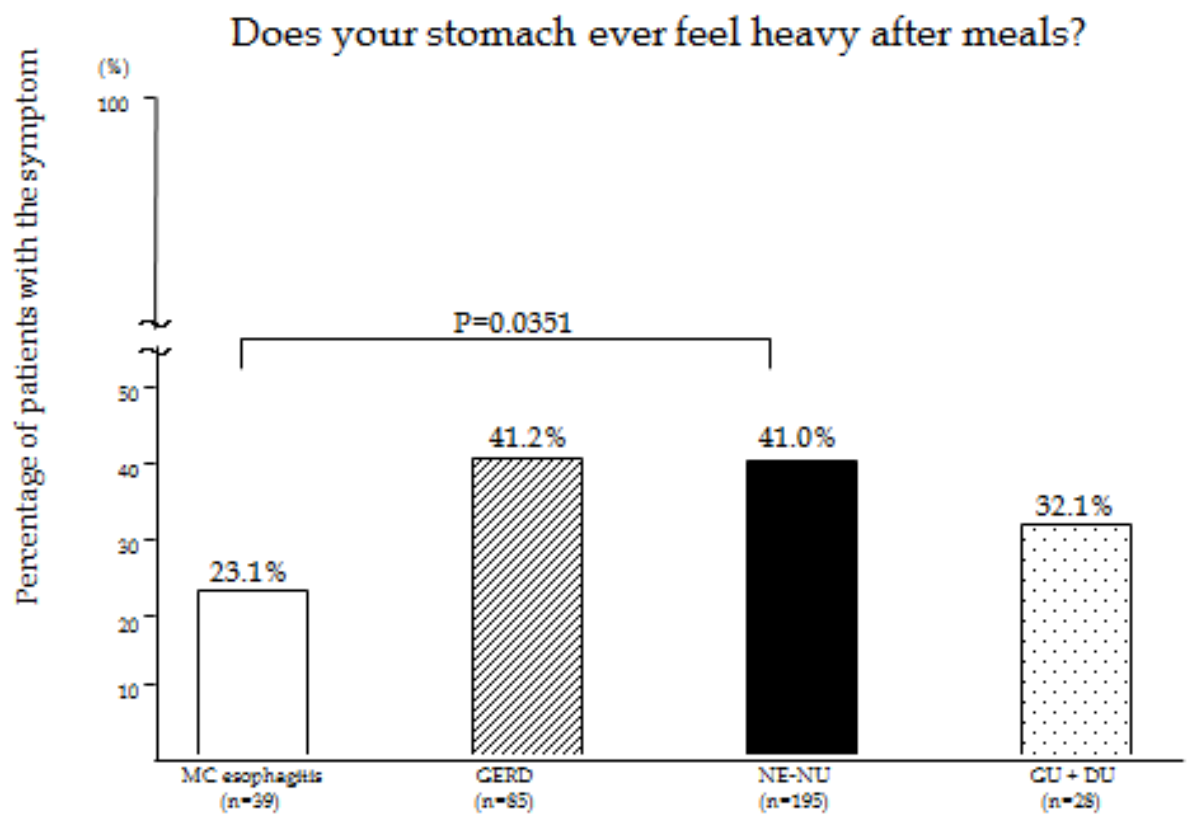


Fig. 2. Gastroesophageal reflux symptoms showing significant differences among the groups Comparison was done among the MC esophagitis, GERD, NE-NU, and GU+DU groups by the χ^2 test.



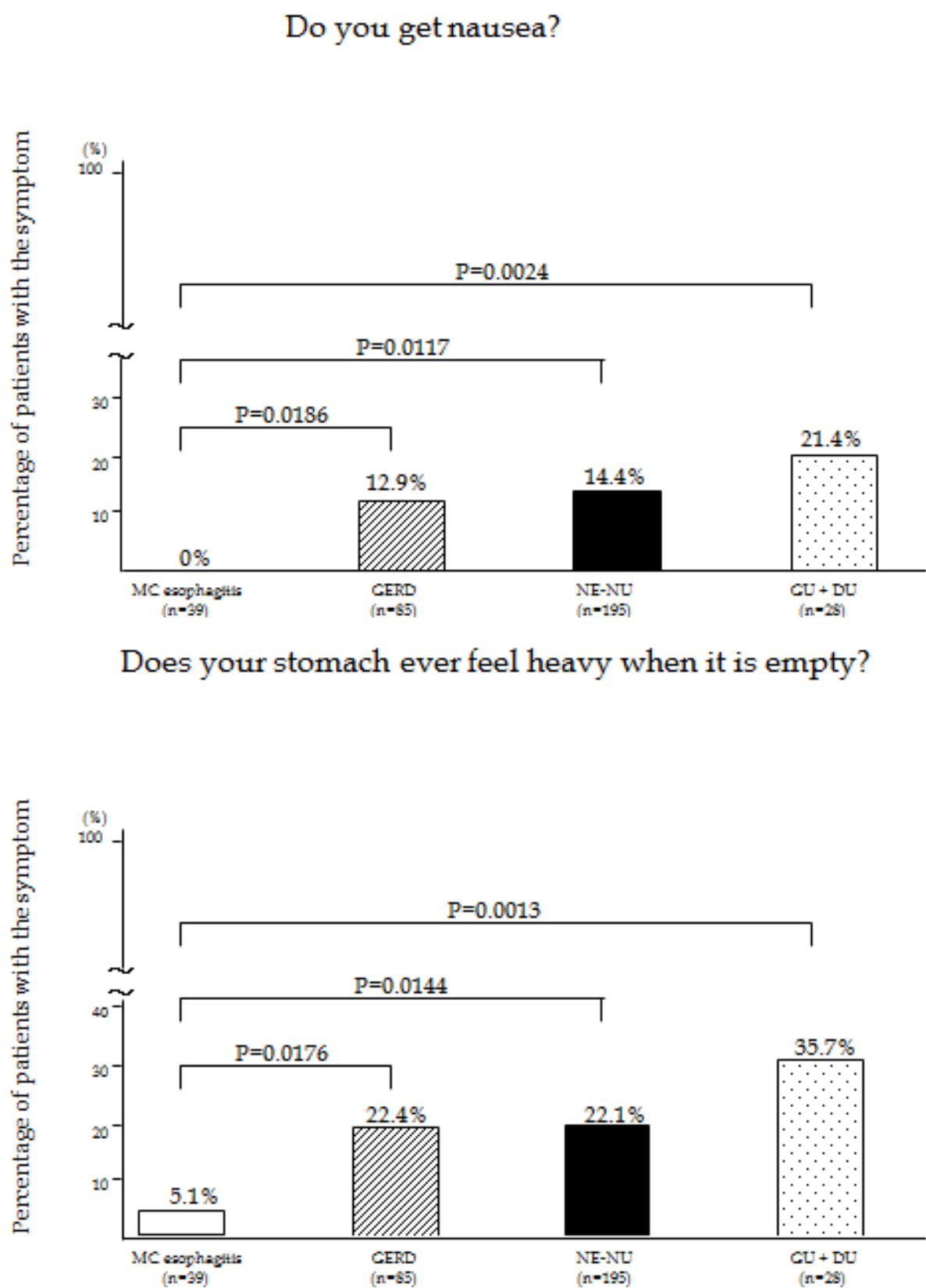


Fig. 3. Dysmotility-like symptoms showing significant differences among the groups
Comparison was done among the MC esophagitis, GERD, NE-NU, and GU+DU groups by the χ^2 test.

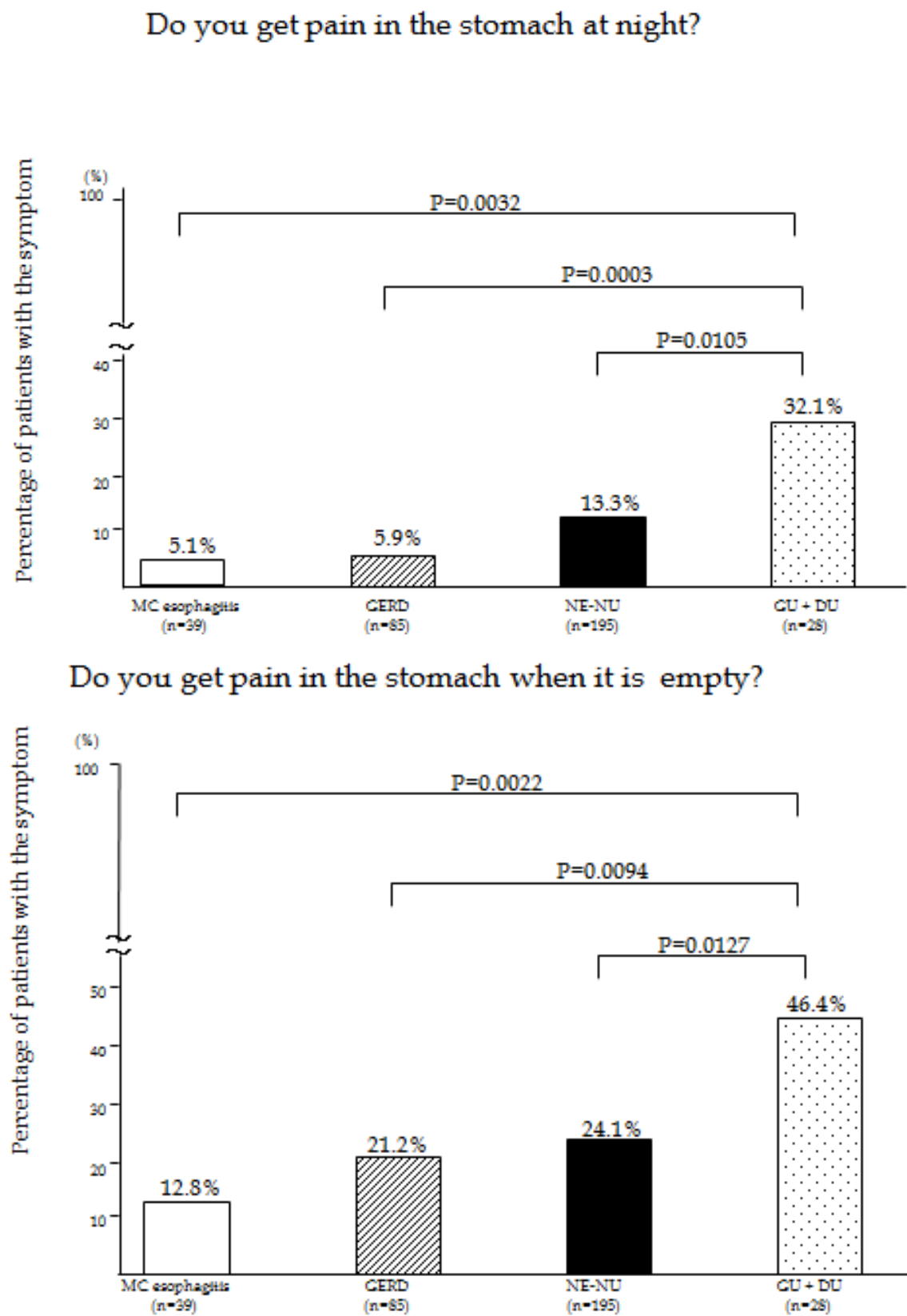
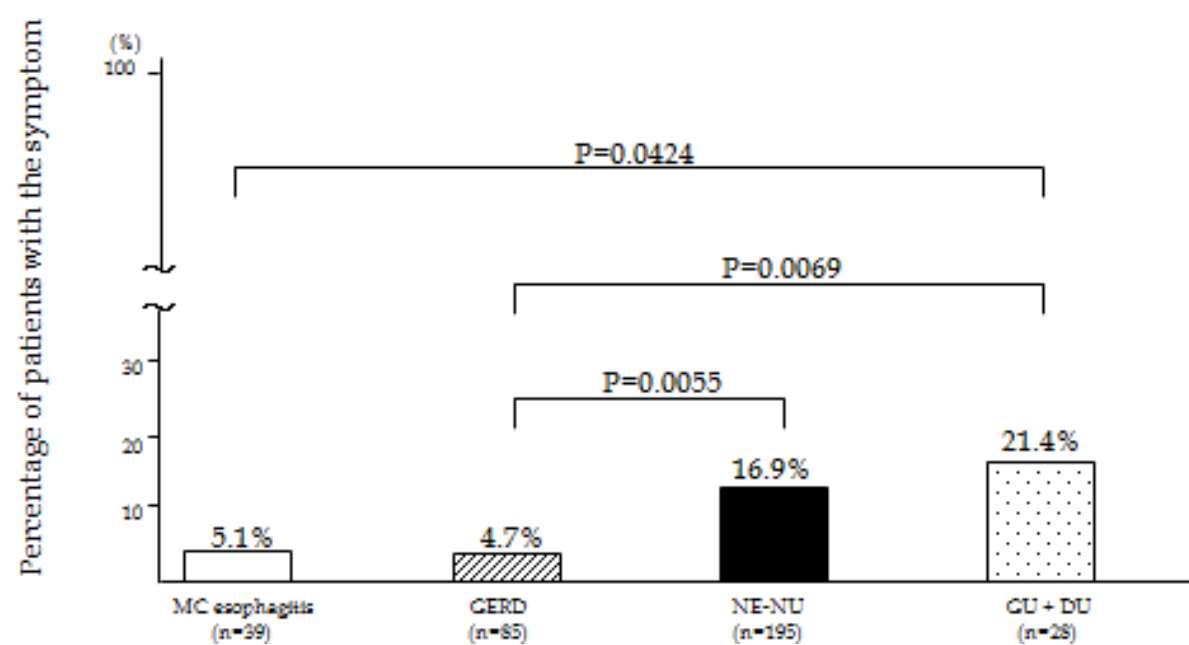
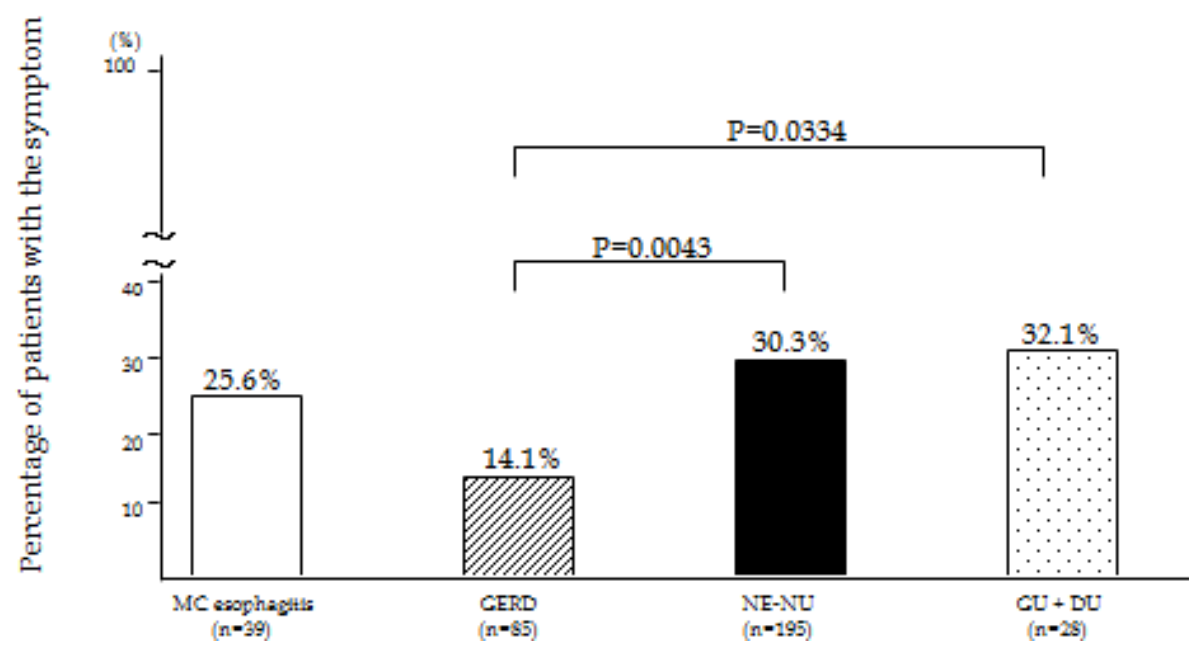


Fig. 4. Ulcer-like symptoms showing significant differences among the groups
Comparison was done among the MC esophagitis, GERD, NE-NU, and GU+DU groups by the χ^2 test.

Do you feel sick?



Are you anxious?



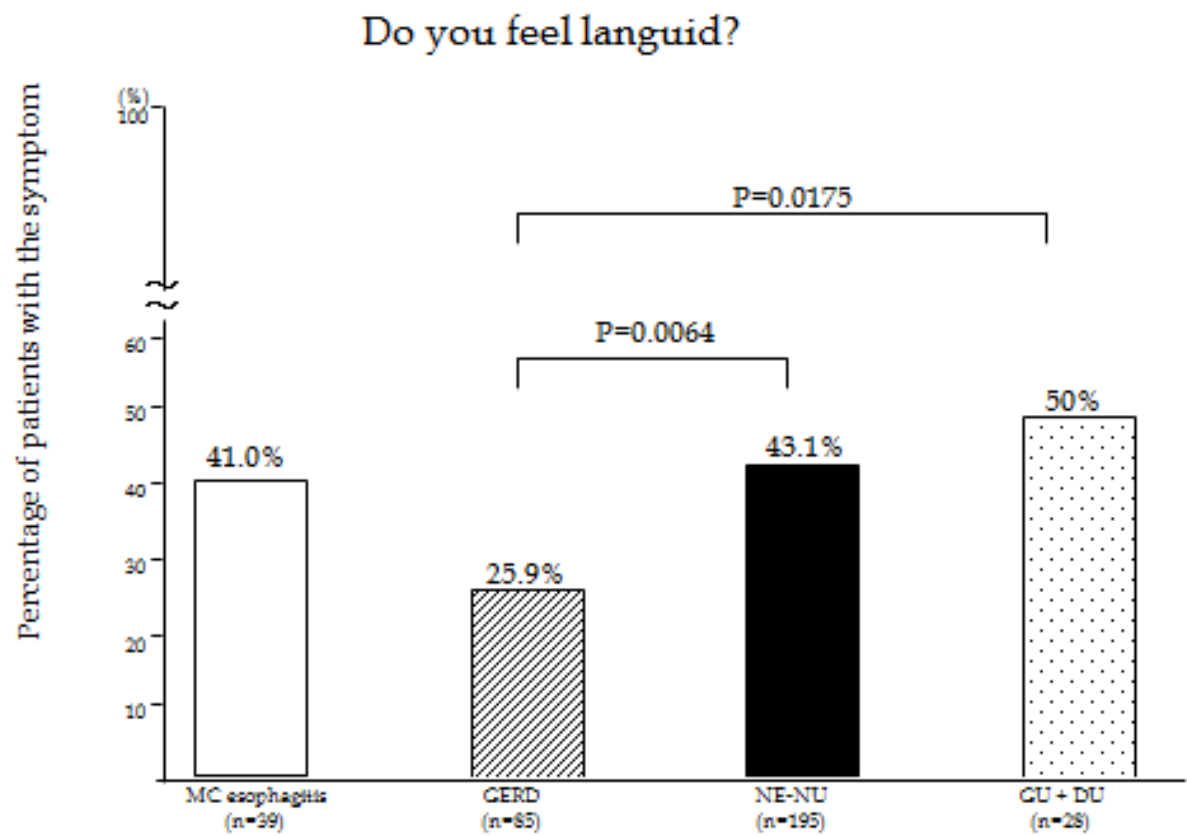


Fig. 5. Psychosomatic symptoms showing significant differences among the groups Comparison was done among the MC esophagitis, GERD, NE-NU, and GU+DU groups by the χ^2 test.

With regard to gastroesophageal reflux symptoms, significant intergroup differences were seen for the following questions (Fig. 2): "Do you get heartburn?", "Do you mainly get heartburn after meals?", "Do you get heartburn if you bend forward?", "Do you get acidic liquid coming up into your mouth?", and "Do you cough?". Heartburn was significantly more frequent in the GERD group (52.9%) than in the MC esophagitis group (28.2%, $P=0.0102$), the NE-NU group (29.7%, $P=0.0002$), or the GU+DU group (17.9%, $P=0.0012$). Cough was significantly more common in the MC esophagitis group (48.7%) than in the NE-NU group (28.7%, $P=0.0146$). Occurrence of heartburn mainly after meals was significantly more frequent in the GERD group (51.8%) than in the NE-NU group (34.4%, $P=0.0062$) or the GU+DU group (25%, $P=0.0136$). Heartburn on bending forward was also significantly more common in the GERD group (27.1%) than in the NE-NU group (9.2%, $P=0.0001$) or the GU+DU group (7.1%, $P=0.0277$). Moreover, acid liquid reflux showed a significantly higher prevalence in the GERD group (31.8%) than in the MC esophagitis group (10.3%, $P=0.0102$) or the NE-NU group (20%, $P=0.0330$). Among dysmotility-like symptoms, significant intergroup differences were noted for the following questions (Fig. 3): "Does your stomach ever feel heavy after meals?", "Do you get nausea?", and "Does your stomach ever feel heavy when it is empty?". In the MC esophagitis group, a heavy stomach after meals was significantly less frequent than in the NE-NU group (23.1% vs. 41%, $P=0.0351$). In addition, nausea was significantly less common in the MC esophagitis group (0%) than in the GERD group (12.9%, $P=0.0186$), the NE-NU group (14.4%, $P=0.0117$), or the GU+DU group (21.4%,

$P=0.0024$). Furthermore, heaviness of an empty stomach was significantly less frequent in the MC esophagitis group (5.1%) than in the GERD group (22.4%, $P=0.0176$), the NE-NU group (22.1%, $P=0.0144$), or the GU+DU group (35.7%, $P=0.0013$). Questions about ulcer-like symptoms showed significant intergroup differences for the following items (Fig. 4): "Do you get pain in the stomach at night?" and "Do you get pain in the stomach when it is empty?". Nocturnal gastralgia was significantly more frequent in the GU+DU group (32.1%) than in the MC esophagitis group (5.1%, $P=0.0032$), the GERD group (5.9%, $P=0.0003$), or the NE-NU group (13.3%, $P=0.0105$). The frequency of gastralgia between meals was significantly higher in the GU+DU group (46.4%) than in the MC esophagitis group (12.8%, $P=0.0022$), the GERD group (21.2%, $P=0.0094$), or the NE-NU group (24.1%, $P=0.0127$). Psychosomatic symptoms showed significant intergroup differences for the following items (Fig. 5): "Do you feel sick?", "Are you anxious?", and "Do you feel languid?". There was a significantly lower frequency of nausea in the GERD group (4.7%) than in the NE-NU group (16.9%, $P=0.0055$) or the GU+DU group (21.4%, $P=0.0069$). Nausea was also significantly less common in the MC esophagitis group (5.1%) than in the GU+DU group (21.4%, $P=0.0424$). The frequency of anxiety was significantly lower in the GERD group (14.1%) than in the NE-NU group (30.3%, $P=0.0043$) or the GU+DU group (32.1%, $P=0.0334$). A languid feeling was also significantly less common in the GERD group (25.9%) than in the NE-NU group (43.1%, $P=0.0064$) or the GU+DU group (50%, $P=0.0175$).

4. Discussion

In Japan, a modified version of the Los Angeles (LA) classification with the addition of Grade N (normal esophageal mucosa) and Grade M (minimal change esophagitis) is widely accepted (Hongo, 2006). In the first report about the original LA classification, seven items related to minimal change were included: (1) localised area(s) of erythema in one or more segment at the mucosal junction, (2) indistinctness or blurring of all or part of the mucosal junction, (3) friability at the mucosal junction, (4) diffuse erythema of the distal esophagus, (5) patchy erythema of the distal esophagus, (6) increased vascularity of the distal esophagus, and (7) edema/accentuation of mucosal folds (Armstrong et al., 1996). Agreement between experienced endoscopists was acceptable to good for recognition of 3 out of 7 items (erythema, Kappa value (K)=0.77; friability, $K=0.55$; and increased vascularity, $K=0.83$). However, agreement between inexperienced endoscopists was poor for recognition of 4 items (blurring, $K=0.22$; friability, $K=0.19$; increased vascularity, $K=0.39$; and edema, $K=0.19$), so the category of minimal change was not adopted. K statistics can be used for interpretation of results as follows. When P_o is the observed proportion of agreement and P_c is the expected (chance) agreement, the equation is obtained: $K = (P_o - P_c) / (1 - P_c)$ ($K=-1$: complete disagreement, $K=0$: chance agreement, $0 < K < 0.4$: poor agreement, $0.4 \leq K < 0.7$: acceptable agreement, $0.7 \leq K < 1$: good, $K=1$: complete agreement). MC esophagitis has been reported to feature prominent erythema without clear demarcation or whitish cloudiness, but the original LA classification does not mention whitish cloudiness. Despite this, MC esophagitis is commonly accepted as part of the spectrum of reflux esophagitis in Japan. In the present study, a 37-item self-administered questionnaire covering questions on gastroesophageal reflux symptoms, dysmotility symptoms, ulcer symptoms and psychosomatic symptoms was used to assess the symptoms of MC esophagitis patients in comparison with GERD patients, NE-NU patients, and GU+DU patients. With regard to gastroesophageal reflux, positive answers to "Do you get heartburn?", "Do you mainly get

heartburn after meals?", "Do you get heartburn if you bend forward?", and "Do you get acidic liquid coming up into your mouth?" were significantly more frequent for GERD patients than for NE-NU patients, while the positive rates were similar for MC esophagitis patients and NE-NU patients. "Do you cough?" was significantly more likely to receive a positive answer from MC esophagitis patients than from NE-NU patients. Thus, "cough" was a characteristic symptom of MC esophagitis compared with NE-NU in the present study. With regard to dysmotility-like symptoms, "Does your stomach ever feel heavy after meals?", "Do you get nausea?" and "Does your stomach ever feel heavy when it is empty?" were significantly more likely to receive positive answers from NE-NU patients than from MC esophagitis patients. These dysmotility-like symptoms were characteristic of NE-NU in the present study. "Nausea" and "heavy stomach" are typical symptoms of functional dyspepsia (FD), suggesting that some NE-NU patients may have FD. This may be the reason why such symptoms were significantly more likely to be positive in the NE-NU group than in the MC esophagitis group. However, it is unclear how closely NE-NU patients conform to the definition of FD established by the Rome III global diagnostic criteria for Functional Gastrointestinal Disorders in 2006 (Galmiche et al., 2006). With regard to ulcer-like symptoms, "Do you get pain in the stomach at night?" and "Do you get pain in the stomach when it is empty?" were significantly more likely to be positive among GU+DU patients than among MC esophagitis patients or NE-NU patients. These ulcer-like symptoms were characteristic of GU+DU patients in the present study, but were uncommon among both MC esophagitis and NE-NU patients. With regard to psychosomatic symptoms, "Do you feel sick?", "Are you anxious?" and "Do you feel languid?" were positive significantly less often in GERD patients than NE-NU patients or GU+DU patients, while positivity for these questions was similar among MC esophagitis and NE-NU patients. Thus, both MC esophagitis and NE-NU patients had similar gastroesophageal reflux symptoms ("heartburn"), ulcer-like symptoms ("pain in the stomach"), and psychosomatic symptoms ("sick", "anxious", and "languid"), although they had differing dysmotility-like symptoms ("nausea" and "heavy stomach"). With regard to the pathophysiology of MC esophagitis, the total number of reflux episodes was greater in MC esophagitis patients compared with normal controls and MC esophagitis was similar to reflux esophagitis (Kusano, 2004). Patients with pathological reflux ($\text{pH} < 4$ for $\geq 4\%$ of the time) were significantly less likely to be in grade N (11.8%) than to have MC esophagitis (57.1%), a finding which suggested the clinical significance of classifying NERD as grade N or MC esophagitis (Joh et al., 2007). According to the 2006 Montreal definition, reflux cough syndrome is an extraesophageal manifestation of GERD (Vakil et al., 2006). In patients with chronic cough and gastroesophageal reflux, esophageal acid reflux leads to a significant increase of cough frequency (Ing et al., 1994), while the pathogenesis of chronic cough and gastroesophageal reflux are associated (Ing et al., 1994). Most of the patients whose chronic cough responds to proton pump inhibitor (PPI) therapy have weakly acidic esophagopharyngeal gas reflux (Kawamura et al., 2011). In this study, the characteristic symptom of MC esophagitis was "cough", indicating that the pathophysiological basis of some of the MC esophagitis is GERD.

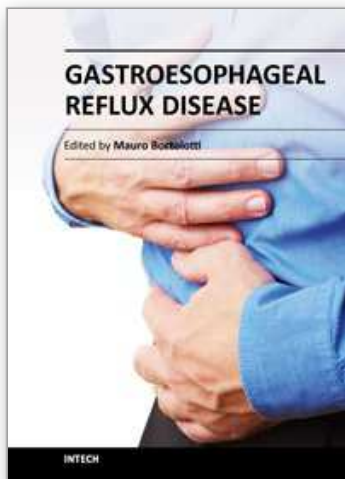
5. Conclusion

Patients with some MC esophagitis can be pathophysiologically classified as having GERD. Therefore, PPI therapy should be tried as their initial treatment, although the symptomatology of **some** MC esophagitis patients is similar to that of NE-NU patients with respect to ulcer-like and psychosomatic symptoms.

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Gastroesophageal reflux disease affects many patients. This disease not only lowers their quality of life, but it also threatens some of them with an underhand risk of cancer. Additionally, it becomes an economic burden for the patients and society. The aim of this book on gastroesophageal reflux disease is to provide advice and guidance to gastroenterologists to help them understand and manage some aspects of this proteiform disease.

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