Relationships Between Residual GERD Symptoms and Reflux Esophagitis / Barrett's Esophagus

Hiroya Nakano[1)]

[1)]Graduate School of Public Health, St. Luke's International University, Tokyo, Japan.

Capstone Project Report

Supervisor
Daiki Kobayashi[1,2)]

1)Graduate School of Public Health, St. Luke's International University, Tokyo, Japan.
2)Division of General Internal Medicine, Department of Medicine, St. Luke's International Hospital, Tokyo, Japan

February 8th. 2021

Abstract

Background

Gastroesophageal reflux disease (GERD) symptoms are more common in patients with reflux esophagitis and Barrett's esophagus. Suppression of gastric acid secretion for several weeks cures esophagitis at a high rate, while most of Barrett's esophagus does not disappear. Thus, residual GERD symptoms may persist in patients with Barrett's esophagus, but few studies have actually shown it.

Aim

The purpose of the study was to confirm the relationships between reflux esophagitis, Barrett's esophagus and residual GERD symptoms, and elucidated the causative factors for residual GERD symptoms.

Methods

Retrospectively extracted were patients who complained of GERD symptoms and underwent esophagogastroduodenoscopy and were diagnosed with "reflux esophagitis" or "non-erosive gastroesophageal reflux disease". We investigated the relationships between symptom evaluation after treatment with proton pump inhibitor (PPI) for four weeks or more and the complication status of reflux esophagitis and Barrett's esophagus. In addition, multivariate analysis was used to confirm the relationships between Barrett's esophagus, reflux esophagitis, age, sex, and residual symptoms.

Results

Meeting inclusion criteria for analysis were 79 patients. Symptom evaluation was described in the medical records of 24 patients (30.4%), and the rate of reflux esophagitis was significantly higher in the group in which the symptom evaluation was performed. There were no differences in patient backgrounds between the residual symptom cases and the symptom resolution cases. The presence of Barrett's esophagus and reflux esophagitis tended to increase the odds ratio of residual symptoms. Among the patients whose symptom evaluation was not described in the medical record, 20 patients whose PPI administration period was less than 70 days were regarded as symptom resolution and added to the analysis. There were no differences in patient backgrounds between the residual symptom cases and the symptom resolution cases. The presence of Barrett's esophagus and reflux esophagitis tended to increase the odds ratio of residual symptoms. In a subgroup analysis of those aged 60 years or younger, whose sensory threshold was considered normal, the odds ratio for residual symptoms in Barrett's esophageal cases was 11.2 ($p = 0.047$, 95%CI: [1.00-125.65]), showing a significant difference. The odds ratio was 30.0 ($p = 0.02$, 95%CI: [1.83-399.25]) in patients with both Barrett's esophagus and reflux esophagitis, showing a significant difference.

Conclusion

The risk of residual symptoms increased in patients with Barrett's esophagus and reflux esophagitis. In particular, the increase was remarkable in patients under the age of 60, who were considered to have a normal sensory threshold. Barrett's esophagus was a surrogate marker for refractory GERD, whose symptoms persisted after PPI administration. Large-scale prospective studies using this study as a pilot study are needed to evaluate the relationships between Barrett's esophagus and reflux esophagitis and symptoms.

Introduction

Gastroesophageal reflux disease (GERD) presents with either or both esophageal mucosal injury and reflux symptoms caused by gastric acid or gastric contents reflux (Iwakiri et al., 2016) (Fig. 1). Excessive gastric acid exposure in the esophagus due to acid reflux is a major cause of esophageal mucosal injury and symptoms (Iwakiri et al., 2009; Lundell et al., 1999; Adachi et al., 2001). Typical symptoms of GERD include heartburn and regurgitation. Suppression of gastric acid secretion for several weeks heals most esophagitis, regardless of severity (Ashida et al., 2015). However, the correlation between the severity of reflux esophagitis and GERD symptoms is weak (Fennerty & Johnson, 2006; El-Serag & Johanson, 2002; Okamoto et al., 2003). The residual symptoms persist after healing of esophagitis in many patients (El-Serag et al., 2010), the cause of which has not been completely elucidated. GERD is classified according to the presence or absence of esophagitis, and GERD without esophagitis is called non-erosive gastroesophageal reflux disease (NERD) in a broad sense, and accounts for 60% of GERD in Japan (Fujiwara & Arakawa, 2009). Symptoms may persist after treatment with proton pump inhibitor (PPI) in NERD as well (Nakagawa et al., 2015). The pain threshold of the esophagus has been shown to decrease with age (Yamasaki et al., 2013). It was also reported that the change in sensory threshold with age increased sharply after the age of 60 (Schludermann, 1962).

GERD with reflux esophagitis is also a risk factor for the development and

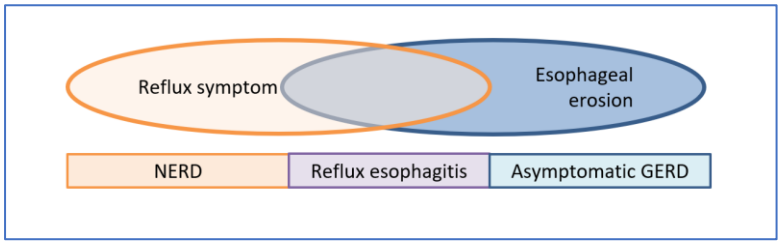
progression of Barrett's esophagus (Ronkainen et al. 2011). Normal esophageal mucosal tissue is histologically composed of squamous epithelium. Exposure to gastric acid causes repeated damage and repair of the esophageal mucosa, continuously replacing squamous epithelium with columnar epithelium from the stomach. Barrett's esophagus is defined as the esophagus with Barrett's mucosa, a columnar epithelium that extends continuously from the stomach to the esophagus, with or without metaplastic columnar epithelium (Japan Esophageal Society, 2015). Barrett's esophagus has abnormal mucosal barrier function (Mullin et al., 2006; Oshima & Miwa, 2017), and is considered a risk factor for esophageal adenocarcinoma. It was reported that the annual incidence of adenocarcinoma in Barrett's esophageal patients is 1.2% in Japan (Matsuhashi et al., 2017), which is considered to be similar to that in Western countries (Hvid-Jensen et al., 2011; Sikkema et al., 2010). Barrett's esophageal patients have a high rate of GERD symptoms (Ronkainen et al., 2005). Barrett's esophageal patients with GERD symptoms were also reported to be at increased risk of adenocarcinoma (Lagergren et al. 1999).

Previous reports have shown that Barrett's esophageal regression by inhibition of gastric acid secretion takes months to years (Peters et al., 1999; Wilkinson et al., 1999). Even if reflux esophagitis is healed by suppressing gastric acid secretion for several weeks, Barrett's esophagus does not disappear in most cases. Thus, it is expected that GERD symptoms may persist in patients with Barrett's esophagus after the treatment. However, few

studies have actually shown it. In this study, we confirmed the relationships between reflux esophagitis and Barrett's esophagus before the administration of PPI and the residual symptoms after treatment in GERD patients.

Figure 1

The Relationship with Reflux Symptoms and Esophageal Erosion



Hypothesis

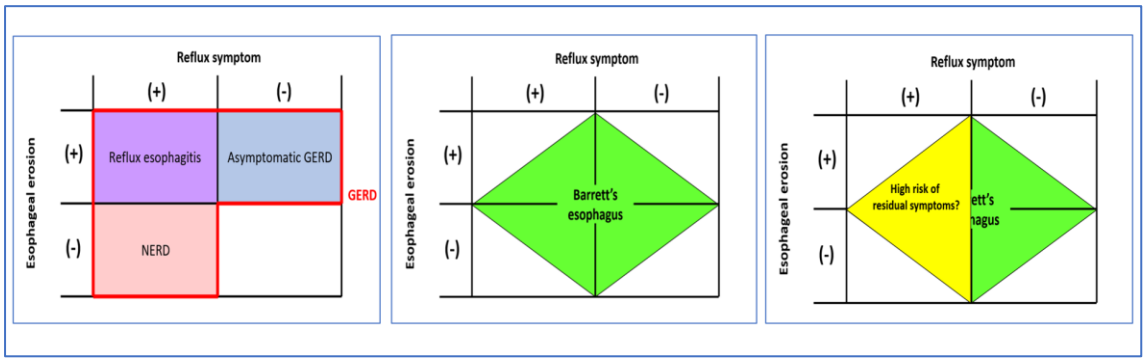
The two hypotheses that we are testing in this study are as follows:

(1) GERD patients with Barrett's esophagus have a higher rate of residual symptoms after treatment;

(2) GERD patients with both Barrett's esophagus and reflux esophagitis have a higher rate of residual symptoms after treatment than patients with either Barrett's esophagus or reflux esophagitis or neither. (See Figure 2.)

Figure 2

Hypothesis: The Risk of Residual Symptoms in Reflux Esophagitis and Barrett's Esophagus



Aim and Objectives

The aim of this study therefore, was to elucidate the causative factors of residual GERD symptoms and to contribute to the construction of a long-term treatment plan considering the improvement of patient's health related quality of life. To achieve this aim we retrospectively examined the relationships between reflux esophagitis, Barrett's esophagus and residual symptoms after treatment by acid secretion inhibitor in GERD patients.

Methods

This was a single-center, retrospective cohort study. We extract patient data of those who had complained of GERD symptoms and underwent esophagogastroduodenoscopy at St. Luke's International Hospital between April 2017 and March 2020, and were diagnosed with "reflux esophagitis" or " non-erosive gastroesophageal reflux disease" for the first time. The symptom evaluation after treatment with PPI for 4 weeks or more was confirmed. In the

subjects, we confirmed the Los Angeles classification that evaluates the severity of esophagitis in esophagogastroduodenoscopy (Armstrong et al., 1996). Furthermore, we extracted from their medical records the presence or absence of Barrett's esophagus at the time of endoscopy of these patients and the presence or absence of symptoms after treatment with PPI.

Exclusion Criteria

We excluded patients who had been treated in the past if they had taken acid secretion inhibitors within the past 3 months. We also excluded patients with reflux symptoms due to factors other than gastric acid and other factors. These factors were:

- Patients with mental illness
- Patients diagnosed with functional heartburn and functional dyspepsia, eosinophil esophagitis, achalasia, gastroduodenal ulcer, esophageal stricture
- History of esophageal, gastric or duodenal surgery
- Patients with gastrointestinal tumor
- Patients judged by the researcher to affect the evaluation of this study.

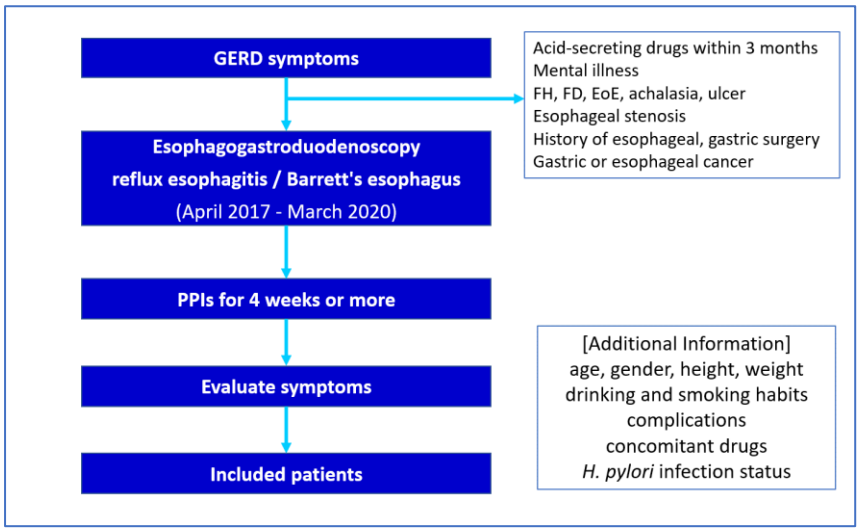
Sociodemographic Data

We also extracted patient information. This included physical data (age, sex, height,

weight), lifestyle (drinking, smoking habits), comorbidities, and *H. pylori* infection status. See Figure 3 for the flow of data extraction.

Figure 3

Flow of Data Extraction



Evaluation Method

Endoscopic findings of the esophagus before treatment were extracted as the presence or absence of reflux esophagitis and Barrett's esophagus. The physician evaluated the residual symptoms based on the patient's complaint. Continuation of drug administration was also used as an index of residual symptoms. The primary endpoints were the rates of residual symptoms after PPI administration for 4 weeks or more with and without reflux esophagitis and Barrett's esophagus before treatment.

For secondary endpoints, multivariate analysis was performed for each of the

following: Barrett's esophagus, reflux esophagitis, sex, drinking habits, smoking habits, and *H. pylori* infection status. We then examined the risk of residual symptoms.

Mullin et al. (2006) reported that the change in sensory threshold with age increased sharply after the age of 60 [16]. Therefore, we extracted and analyzed as a subgroup, those cases who were under 60 years old and who were considered to have a normal sensation.

Statistics

All data were analyzed using EZR (Saitama Medical Center, Jichi Medical University), which was a graphical user interface for R (The R Foundation for Statistical Computing) (Kanda, 2013). Baseline demographic characteristics of patients were compared using t-tests and Fisher exact tests. The odds ratio of residual symptoms with or without esophagus erosion and Barrett's esophagus were evaluated. A multivariate analysis using logistic regression was performed for the factors that influenced the residual symptoms. The significance level was 0.05.

Expected Outcomes

The following results were predicted from this study:

1. Regardless of the presence or absence of reflux esophagitis before treatment, GERD cases with Barrett's esophagus would have a higher residual symptom rate after treatment with

suppression of acid secretion than cases without Barrett's esophagus.

2. Patients with both reflux esophagitis and Barrett's esophagus would have a higher residual rate of symptoms than those with either Barrett's esophagus or reflux esophagitis and those without both.
3. In patients under the age of 60 who were considered to have normal sensory thresholds, the risk of residual symptoms would be higher in patients with Barrett's esophagus or reflux esophagitis than in base-case analysis.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. This study was approved by the Research Ethics Review Committee of St. Luke's International University on April 16, 2020. Since this study used only medical information without intervention for patients, the purpose of the study was disclosed on the website and the opportunity for refusal was guaranteed.

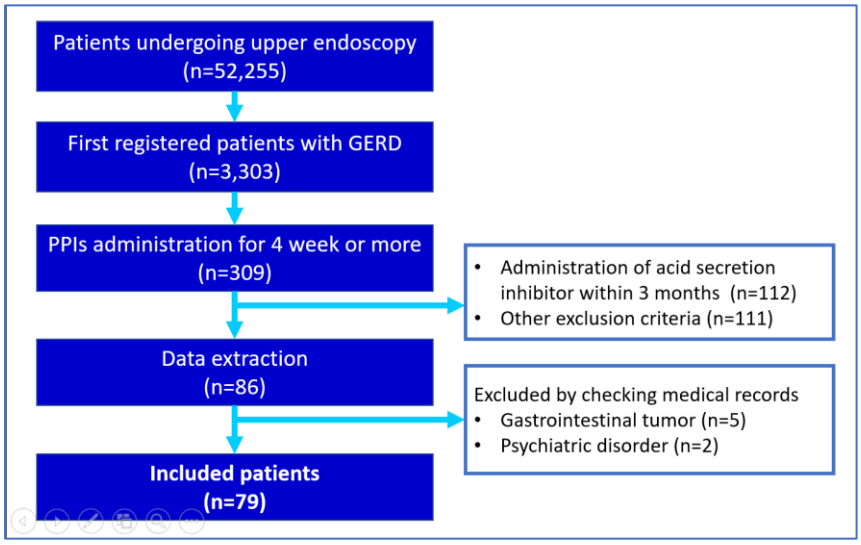
Results

Of the 52,255 patients who underwent esophagogastroduodenoscopy during the period, 3,303 patients were diagnosed as "reflux esophagitis" and "non-erosive gastroesophageal reflux disease". Of those, 309 patients were prescribed PPI for 4 weeks or

more. After excluding 112 patients who received acid secretion inhibitors (PPI) within 3 months before the initial disease name registration and 111 patients who met other exclusion criteria, the remaining 86 patients were further screened by checking their medical records. This resulted in the exclusion of 5 patients with gastrointestinal tumors and 2 with psychiatric disorders. After the exclusions 79 subjects were included in this study (Fig. 4).

Figure 4

Flowchart of Patient Extraction



The symptom evaluation described in the medical record was defined as "Definition 1". However, only 24 of 79 cases (30.4%) had a symptom evaluation described in the medical record. In clinical practice, it was speculated that if the patient complained of symptoms, it would be described in the medical record, and if there were no symptoms and the patient

made no complaints, it would not be described. In general, if symptoms persist, PPI administration is continued. On the other hand, PPI is indicated for "maintenance therapy for reflux esophagitis", and medication may be continued even if the symptoms have disappeared. In addition, the usual interval between hospital visits for patients with chronic diseases is 1 - 2 months. If PPI administration is less than 70 days, it is highly possible that the symptoms have disappeared, but PPI administration would have been continued until the next visit. Therefore, "Definition 2" was set, in which "when the symptom evaluation was unknown in Definition 1, patients, in which PPI administration was less than 70 days, were regarded as symptom resolution". There were 44 cases (55.7%) that corresponded to Definition 2.

The background of 79 patients was as follows: female - 55.7%, mean age - 59.6 years, mean BMI - 23.6, reflux esophagitis - 32.9%, Barrett's esophagus - 22.8%, and drinking habits - 55.8% (Table 1). No differences were found in age, sex, BMI, Barrett's esophagus, drinking habits, or duration of PPI administration in the group with and without symptom assessment. The proportion of reflux esophagitis in the symptom assessment group was significantly higher (Table 2). Sufficient information could not be extracted from the medical records regarding smoking habits and *H. pylori* infection status.

Table 1

Baseline Characteristics (Total Patients)

Baseline characteristics

	N=79	Rate
Sex		
Male	35	44.3%
Female	44	55.7%
Mean age (SD)	59.6 (13.5)	
Mean BMI (SD, n=29)	23.6 (5.7)	
Reflux esophagitis (RE) *LA classification A-D	26	32.9%
Barrett's esophagus (BE)	18	22.8%
RE(+), BE(+)	8	10.1%
RE(+), BE(-)	18	22.8%
RE(-), BE(+)	10	12.7%
RE(-), BE(-)	43	54.4%
Drinking (n=43)	24	55.8%
BMI≧25 (n=29)	8	27.6%

Table 2

Baseline Characteristics (Presence or Absence of Symptom Evaluation)

	Presence of symptom evaluation (n=24)	Absence of symptom evaluation (n=55)	p Value
Age	59.3	59.8	0.89
Male	14 (58.3%)	21 (38.2%)	0.14
BMI	22.6	24.1	0.51
Reflux esophagitis *LA classification A-D	12 (50.0%)	14 (25.5%)	0.04
Barrett's esophagus	7 (29.2%)	11 (20.0%)	0.39
Drinking	7/14 (50.0%)	17/29 (58.6%)	0.75
Days of PPI administration	251.5	261.9	0.87

Definition 1

In the symptom evaluation in Definition 1, there were 12 cases with residual symptoms and there were 12 cases with symptom resolution. There were no differences in patient background between the two groups in age, sex, BMI, reflux esophagitis, Barrett's esophagus, and drinking habits (Table 3). The odds ratio for residual symptoms with reflux esophagitis was 1.00. The odds ratio for residual symptoms with Barrett's esophagus was 3.57 ($p = 0.37$). The odds ratio for residual symptoms in patients with coexisting reflux esophagitis and Barrett's esophagus compared with those with only one or none was 3.67 ($p = 0.59$) (Table 4 - 6). As a result of multivariate logistic regression analysis, the odds ratios were 5.22 for Barrett's esophagus, 0.65 for reflux esophagitis, 1.04 for male, and 1.64 for age, and no significant differences were observed (Table 7). In logistic regression with and without reflux esophagitis (RE) and Barrett's esophagus (BE), the odds ratios were 0.75 for RE (+) BE (-), 2.50 for RE (-) BE (+), 3.75 for RE (+) BE (+), and no significant difference was observed in either case (Fig. 5).

Table 3

Patient Characteristics of the Residual Symptom Group and the Symptom Resolution Group (Definition 1)

	Residual symptoms n=12	Symptom resolution n=12	p Value
Sex			
Male	7 (58.3%)	7 (58.3%)	
Female	5 (41.7%)	5 (41.7%)	1.00
Mean age	61.3	57.4	0.47
Mean BMI (n=4/6)	22.7	22.6	0.96
Reflux esophagitis (RE) *LA classification A-D	6 (50.0%)	6 (50.0%)	1.00
Barrett's esophagus (BE)	5 (41.7%)	2 (16.7%)	0.37
RE(+), BE(+)	3 (25.0%)	1 (8.3%)	
RE(+), BE(-)	3 (25.0%)	5 (41.7%)	
RE(-), BE(+)	2 (16.7%)	1 (8.3%)	
RE(-), BE(-)	4 (33.3%)	5 (41.7%)	
Drinking (n=6/8)	3 (50.0%)	4 (50.0%)	1.00
BMI≧25 (n=4/6)	0 (0%)	3 (50.0%)	0.46

Table 4

Odds Ratio for Residual Symptoms with Reflux Esophagitis (Definition 1, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Reflux esophagitis *LA classification A-D	6	6	12
Non-erosive reflux disease *LA classification N-M	6	6	12
	12	12	24

OR=1.00 (0.20-4.95), p=1.00

T

Table 5

Odds Ratio for Residual Symptoms with Barrett's Esophagus (Definition 1, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Barrett's esophagus	5	2	7
Non-Barrett's esophagus	7	10	17
	12	12	24

OR=3.57 (0.53-23.95), p=0.37

Table 6

Odds Ratio for Residual Symptoms in Patients with Coexisting Reflux Esophagitis and Barrett's Esophagus Compared with Those with Only One or None (Definition 1, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
RE(+) and BE(+)	3	1	4
Non RE(+) and BE(+)	9	11	20
	12	12	24

OR=3.67 (0.32-41.59), p=0.59

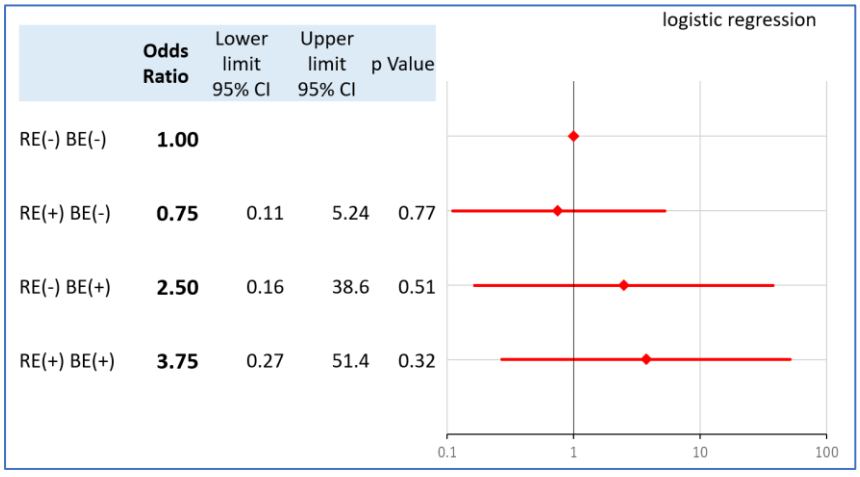
Table 7

Multivariate Analysis for Residual Symptoms (Definition 1, Logistic Regression)

	Odds ratio	95%CI minimum	95%CI maximum	p Value
Barrett's esophagus	5.22	0.06	49.00	0.15
Reflux esophagitis	0.65	0.10	4.27	0.65
Male	1.04	0.96	1.12	0.31
Age	1.64	0.24	11.20	0.62

Figure 5

Odds Ratio for Residual Symptoms with and Without Reflux Esophagitis (RE) and Barrett's Esophagus (BE) (Definition 1, Logistic Regression)



Definition 2

In the symptom evaluation for Definition 2, there were 12 cases with residual symptoms and 32 cases with symptom resolution. No differences were confirmed in patient

background between the two groups in age, sex, body mass index, reflux esophagitis, Barrett's esophagus, and drinking habits (Table 8). The odds ratio for residual symptoms with reflux esophagitis was 1.91 ($p = 0.49$). The odds ratio for residual symptoms with Barrett's esophagus was 1.57 ($p = 0.72$). The odds ratio for residual symptoms in patients with coexisting reflux esophagitis and Barrett's esophagus compared with those with only one or none was 3.22 ($p = 0.32$) (Tables 9 - 11). As a result of multivariate analysis by logistic regression, the odds ratio was 1.57 for Barrett's esophagus, 1.71 for reflux esophagitis, 1.07 for male, and 1.03 for age, and no significant differences between the residual symptom group and the symptom resolution group were observed (Table 12). In logistic regression with and without reflux esophagitis (RE) and Barrett's esophagus (BE), the odds ratios were 1.31 for RE (+) BE (-), 1.00 for RE (-) BE (+), 3.50 for RE (+) BE (+), and no significant difference was observed in either case (Fig. 6).

Table 8

Patients Characteristics of the Residual Symptom Group and the Symptom Resolution Group (Definition 2)

	Residual symptoms n=12	Symptom resolution n=32	p Value
Sex			
Male	7 (58.3%)	12 (37.5%)	
Female	5 (41.7%)	16 (50.0%)	0.74
Mean age	61.3	55.8	0.21
Mean BMI (n=4/12)	22.7	24.9	0.63
Reflux esophagitis (RE) *LA classification A-D	6 (50.0%)	11 (34.4%)	0.49
Barrett's esophagus (BE)	5 (41.7%)	10 (31.3%)	0.72
RE(+), BE(+)	3 (25.0%)	3 (9.4%)	
RE(+), BE(-)	3 (25.0%)	8 (25.0%)	
RE(-), BE(+)	2 (16.7%)	7 (21.9%)	
RE(-), BE(-)	4 (33.3%)	14 (43.8%)	
Drinking (n=6/19)	3 (50.0%)	13 (68.4%)	0.63
BMI≧25 (n=4/12)	0 (0%)	6 (50.0%)	0.23

Table 9

Odds Ratio for Residual Symptoms with Reflux Esophagitis (Definition 2, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Reflux esophagitis *LA classification A-D	6	11	17
Non-erosive reflux disease *LA classification N-M	6	21	27
	12	32	44

OR=1.91 (0.50-7.34), p=0.49

Table 10

Odds ratio for residual symptoms with Barrett's esophagus (Definition 2, Fisher exact tests)

	Residual Symptom	Symptom Resolution	total
Barrett's esophagus	5	10	15
Non-Barrett's esophagus	7	22	29
	12	32	44

OR=1.57 (0.40-6.18), p=0.72

Table 11

Odds Ratio for Residual Symptoms in Patients with Coexisting Reflux Esophagitis and Barrett's Esophagus Compared with Those with Only One or None (Definition 2, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
RE(+) and BE(+)	3	3	6
Non RE(+) and BE(+)	9	29	38
	12	32	44

OR=3.22 (0.55-18.85), p=0.32

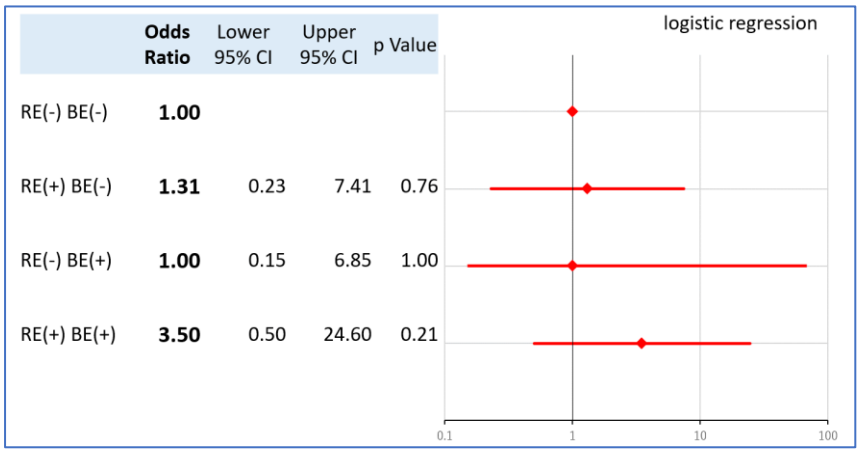
Table 12

Multivariate Analysis for Residual Symptoms (Definition 2, Logistic Regression)

	Odds Ratio	Lower limit 95% CI	Upper limit 95% CI	p Value
Barrett's esophagus	**1.57**	0.39	6.41	0.53
Reflux esophagitis	**1.71**	0.42	6.95	0.45
Male	**1.07**	0.26	4.50	0.92
Age	**1.03**	0.97	1.10	0.28

Figure 6

Odds Ratio for Residual Symptoms with and Without Reflux Esophagitis (RE) and Barrett's Esophagus (BE) (Definition 2, Logistic Regression)



Definition 2 - Subgroup Analysis

A subgroup analysis of Definition 2 was performed for those aged 60 years or younger, who were considered to have had relatively little change in sensory threshold. In a

comparison of 5 patients with residual symptoms and 19 patients with symptom resolution, no differences were shown in age, sex, BMI, reflux esophagitis, or drinking habits. In contrast, the proportion of Barrett's esophagus was significantly higher in the residual symptoms group (Table 13). The odds ratio for residual symptoms with reflux esophagitis was 4.20 ($p = 0.29$). The odds ratio for residual symptoms with Barrett's esophagus was 11.2 ($p = 0.047$), showing a significant difference. The odds ratio for residual symptoms with coexisting reflux esophagitis and Barrett's esophagus was 27.0 ($p = 0.02$), compared with those with only one or none (Tables 14 - 16). As a result of multivariate analysis by logistic regression, the odds ratio was 11.4 for Barrett's esophagus, 3.84 for reflux esophagitis, 1.55 for men, and 0.99 for age, and no significant difference between the residual symptom group and the symptom resolution group was confirmed (Table 17). In logistic regression with and without reflux esophagitis (RE) and Barrett's esophagus (BE), the odds ratios were 2.50 for RE (-) BE (+), and 30.0 for RE (+) BE (+), showing a significant difference in the odds ratio of RE (+) BE (+) (Fig. 7).

Table 13

Patients Characteristics of the Residual Symptom Group and the Symptom Resolution Group (Definition 2 Under the Age of 60)

	Residual symptoms n=5	Symptom resolution n=19	p Value
Sex			
Male	2 (40.0%)	8 (42.1%)	
Female	3 (60.0%)	11 (57.9%)	1.00
Mean age	50.2	47.3	0.49
Mean BMI (n=2/7)	22.3	25.4	0.70
Reflux esophagitis (RE) *LA classification A-D	3 (60.0%)	5 (26.3%)	0.29
Barrett's esophagus (BE)	4 (50.0%)	5 (26.3%)	0.047
RE(+), BE(+)	3 (60.0%)	1 (5.3%)	
RE(+), BE(-)	1 (20.0%)	4 (21.1%)	
RE(-), BE(+)	0 (0.0%)	4 (21.1%)	
RE(-), BE(-)	1 (20.0%)	10 (52.6%)	
Drinking (n=3/12)	3 (100.0%)	8/12 (66.7%)	0.52
BMI≧25 (n=2/7)	0 (0.0%)	3 (28.6)	1.00

Table 14

Odds Ratio for Residual Symptoms with Reflux Esophagitis (Definition 2 Under the Age of 60, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Reflux esophagitis *LA classification A-D	3	5	8
Non-erosive reflux disease *LA classification N-M	2	14	17
	5	19	24

OR=4.20 (0.54-32.96), p=0.29

Note: LA classification – Los Angles classification of endoscopic findings of erosive GERD (LA classification N-M; no mucosal injury, A-D; mucosal injury)

Table 15

Odds Ratio for Residual Symptoms with Barrett's Esophagus (Definition 2 Under the Age Of 60, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Barrett's esophagus	4	5	9
Non-Barrett's esophagus	1	14	15
	5	19	24

OR=11.2 (1.00-125.65), p=0.047

Table 16

Odds Ratio for Residual Symptoms in Patients with Coexisting Reflux Esophagitis and Barrett's Esophagus Compared with Those with Only One or None (Definition 2 Under the Age of 60, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
RE(+) and BE(+)	3	1	4
Non RE(+) and BE(+)	2	18	20
	5	19	24

OR=27.0 (1.83-399.25), p=0.02

Table 17

Multivariate Analysis for Residual Symptoms (Definition 2 Under the Age of 60, Logistic Regression)

	Odds Ratio	Lower limit 95% CI	Upper limit 95% CI	p Value
Barrett's esophagus	**11.40**	0.85	152	0.07
Reflux esophagitis	**3.84**	0.36	40.7	0.26
Male	**1.55**	0.14	17.6	0.72
Age	**0.99**	0.85	1.16	0.92

Figure 7

Odds Ratio for Residual Symptoms with And Without Reflux Esophagitis (RE) and Barrett's Esophagus (BE) (Definition 2 Under the Age of 60, Logistic Regression)

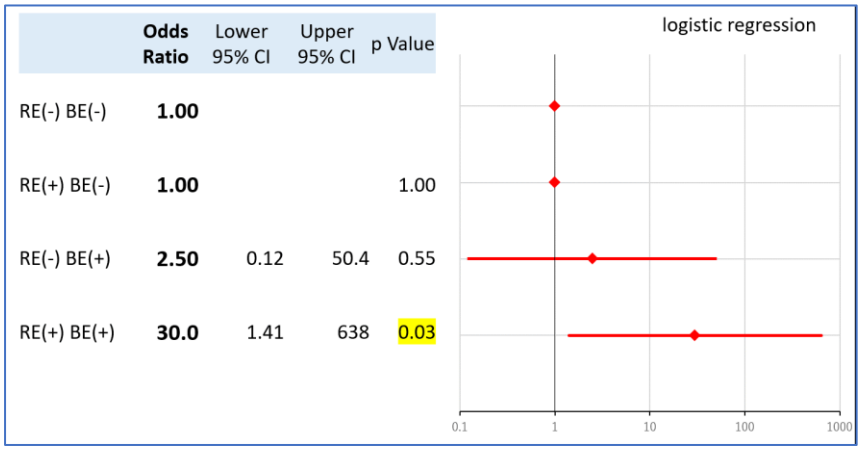
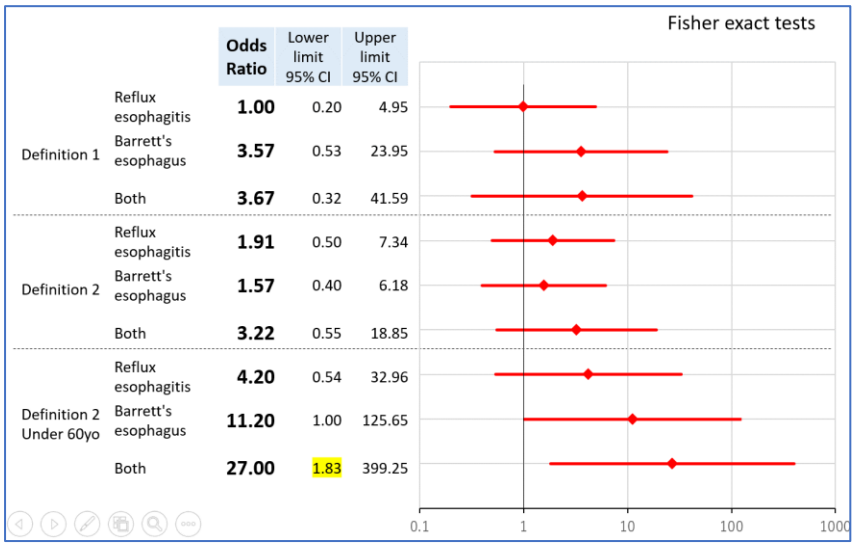


Figure 8

Odds Ratios for Definition 1, Definition 2 and Definition Subanalysis



For the purpose of verification, analyses were conducted for people under 70 years old in Definition 2. The odds ratio for residual symptoms with reflux esophagitis was 2.50 (p = 0.27), whereas the odds ratio for residual symptoms with Barrett's esophagus was 1.60 (p = 0.69). The odds ratio for residual symptoms with coexisting reflux esophagitis and Barrett's esophagus was 4.00 (p = 0.15), compared with patients with either or neither (Tables 18 - 20). As a result of multivariate analysis by logistic regression, the odds ratios were 1.46 for Barrett's esophagus, 2.03 for reflux esophagitis, 1.18 for male, and 1.03 for age; and no significant difference was observed (Table 21).

Table 18

Odds Ratio for Residual Symptoms with Reflux Esophagitis (Definition 2 Under the Age of 70, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Reflux esophagitis *LA classification A-D	5	9	14
Non-erosive reflux disease *LA classification N-M	4	18	22
	9	27	36

OR=2.50 (0.54-11.65), p=0.27

Table 19

Odds Ratio for Residual Symptoms with Barrett's Esophagus (Definition 2 Under the Age of 70, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
Barrett's esophagus	4	9	13
Non-Barrett's esophagus	5	18	23
	9	27	36

OR=1.60 (0.34-7.46), p=0.69

Table 20

Odds Ratio for Residual Symptoms in Patients with Coexisting Reflux Esophagitis and Barrett's Esophagus Compared with Those with Either or None (Definition 2 Under the Age of 70, Fisher Exact Tests)

	Residual Symptom	Symptom Resolution	total
RE(+) and BE(+)	3	3	6
Non RE(+) and BE(+)	6	24	30
	9	27	36

OR=4.00 (0.64-25.02), p=0.15

Table 21

Multivariate Analysis for Residual Symptoms (Definition 2 Under the Age of 70, Logistic Regression)

	Odds Ratio	Lower limit 95% CI	Upper limit 95% CI	p Value
Barrett's esophagus	**1.46**	0.30	7.12	0.63
Reflux esophagitis	**12.03**	0.41	10.00	0.39
Male	**1.18**	0.24	5.76	0.84
Age	**1.03**	0.95	1.13	0.47

Discussion

This study showed that coexisting reflux esophagitis and Barrett's esophagus, tended to be risk factors of residual symptoms. A subgroup analysis of patients under the age of 60 showed that the odds ratio increased from the results of the main analysis, indicating that

Barrett's esophagus was risk factor of residual symptoms and that the risk was further increased with both reflux esophagitis and Barrett's esophagus. The analysis of Definition 1, Definition 2, and Definition 2 for those under the age of 60 showed a similar tendency in that the risk of residual symptoms increased when reflux esophagitis and Barrett's esophagus were combined.

Several studies reported that a weak correlation was found between the severity of subjective symptoms and the endoscopic severity of reflux esophagitis (Fennerty & Johnson, 2006; El-Serag & Johanson, 2002; Okamoto et al., 2003). The presence of reflux esophagitis also tended to increase the risk of residual symptoms in this study, consistent with previously reported results (Fennerty & Johnson, 2006; El-Serag & Johanson, 2002; Okamoto et al., 2003). Other reports showed that there was a weak correlation between the presence or absence of heartburn symptoms and Barrett's esophagus (Lagergren et al., 1999; Kono et al., 2005). Similar to those reports, the main analysis of this study also showed that Barrett's esophagus tended to increase the risk of residual symptoms. In addition, Barrett's esophagus significantly increased the risk of residual symptoms when limited to those less than 60 years of age. The reason for this might be that patients over the age of 60 had worse sensory thresholds and they did not properly evaluate their symptoms.

Hiatal hernia is a risk factor for the development of Barrett's Esophagus (Andrici et al., 2013). In cases with hiatal hernia, the lower esophageal sphincter pressure is diminished

and gastric acid exposure time in the esophagus is prolonged compared with cases without hernia (Emerenziani et al., 2006). Recent reports showed the weak acid reflux at pH 4 - 5 was the main factor associated with reflux symptoms after PPI administration in NERD cases (Abe et al., 2020). Therefore, in the patients with hiatal hernia, the refluxed weak acid into the esophagus tends to stay even after administration of PPI, and the symptoms remain even in patients without esophageal erosion. Therefore, it was assumed that Barrett's esophagus was highly complicated in cases of hiatal hernia, and at the same time, the residual symptom rate was also high. We showed that Barrett's esophagus was a surrogate marker for refractory GERD, whose symptoms persisted with PPI. To our knowledge, this study was the first report to show that patients with both Barrett's esophagus and reflux esophagitis have an increased risk of residual symptoms compared with patients with either or neither in Japan. In a comparison of background factors with and without symptom evaluation in this study, the rate of reflux esophagitis was significantly higher in the group for which symptom evaluation was performed. On the other hand, there was no difference in the proportion of Barrett's esophagus between the groups with and without symptom evaluation. It was assumed that physicians had been paying attention to the symptoms after PPI administration in patients with reflux esophagitis, but not in patients with Barrett's esophagus. This study showed the importance of endoscopic evaluation of not only reflux esophagitis but also Barrett's esophagus in order to predict residual symptoms after treatment. In actual clinical practice,

there are some patients who were diagnosed with GERD by confirming only the symptoms without conducting endoscopic evaluation, and were administered acid secretion inhibitors. In cases that persist having residual symptoms after drug administration, esophagogastroduodenoscopy should be performed to confirm the presence of Barrett's esophagus, which is also a risk factor for esophageal adenocarcinoma.

Limitations

This study includes several limitations. This study was conducted in only one large hospital, where the number of new patients was limited from the viewpoint of primary care in GERD. Therefore, this study included a relatively small number of patients. In addition, due to the characteristics of the study, it was possible that there was a selection bias because the subjects were GERD patients who underwent esophagogastroduodenoscopy.

Symptoms were subjective and were affected by the patient's mental condition and diet of the day (Kimura et al, 2006; Mishima et al., 2005). The symptoms of this study were not evaluated using a specific scale. In addition, it was possible that symptoms evaluation was described in the medical record only when the patient complained of the symptoms. As the endpoint of clinical research, it is desirable to set a hard endpoint that affects the prognosis of life. However, the primary goal of treating GERD, which is not a disease with a poor prognosis, is to control symptoms (Iwakiri et al., 2016). Residual GERD symptoms

reduce labor productivity and health related quality of life (Suzuki et al., 2014). Therefore, the GERD symptoms are a serious problem and were set as the endpoint of this study.

Reflux esophagitis" or "non-erosive gastroesophageal reflux disease" might be conveniently diagnosed for the administration of non-steroidal anti-inflammatory drugs (NSAIDs) or aspirin. In Japan, GERD-related disease names may be given for convenience, especially when prescribing PPI for the purpose of preventing ulcers caused by NSAIDs or aspirin. There is a possibility that patients that were not originally targeted were included in this study. However, NSAIDs and aspirin are frequently administered, especially among the elderly, and the exclusion of patients receiving those drugs did not reflect actual clinical practice.

Conclusion

This study showed that Barrett's esophagus was a surrogate marker for refractory GERD, whose symptoms persisted after PPI administration. Patients with both Barrett's esophagus and reflux esophagitis had an increased risk of residual symptoms. We suggest that esophagogastroduodenoscopy should be performed to confirm Barrett's esophagus if symptoms persist after drug administration. Further prospective studies using this study as a pilot study are needed to evaluate the relationships between Barrett's esophagus, reflux esophagitis and residual symptoms.

Acknowledgements

Hideki Nakajima and Katsuyuki Fukuda provided support in extracting data for this study.

References

Abe, Y., Koike, T., Saito, M., Okata, T., Norita, K., Kikuchi, H., Nakagawa, K., Hatta, W., Asanuma, K., Uno, K., Asano, N., Imatani, A., Shimosegawa, T., & Masamune, A. (2020). Influence of the pH value of refluxate and proximal extent on heartburn perception in patients with proton pump inhibitor-refractory non-erosive reflux disease. *Digestion, 101*(4), 375–381. https://doi.org/10.1159/000500133

Adachi, K., Fuishiro, H., Katsube, T., Yuko, M., Ono, M., Kawamura, A., Rumi, M. A. K., Watanabe, M., & Kinoshita, Y. (2001). Predominant nocturnal acid reflux in patients with Los Angeles grade C and D reflux esophagitis. *Journal Gastroenterology Hepatology, 16*(11), 1191 - 1196. https://doi.org/10.1046/j.1440-1746.2001.02617.x

Armstrong, D., Bennett, J. R., Blum, A. L., Dent, J., De Dombal, F. T., Galmiche, J. P., Lundell, L., Margulies, M., Richter, J. E., Spechler, S. J., Tytgat, G. N., & Wallin, L. (1996). The endoscopic assessment of esophagitis: a progress report on observer

agreement. *Gastroenterology, 111(1), 85 - 92.* https://doi.org/10.1053/gast.1996.v111.pm8698230

Ashida, K., Sakurai, Y., Nishimura, A., Kudou, K., Hiramatsu, N., Umegaki, E., Iwakiri, K. & Chiba, T. (2015). Randomised clinical trial: a dose-ranging study of vonoprazan, a novel potassium-competitive acid blocker, vs. lansoprazole for the treatment of erosive oesophagitis. *Alimentary Pharmacology Therapeutics, 42*(6), 685 - 695. https://doi.org/10.1111/apt.13331

Andrici, J., Tio, M., Cox, M. R., & Eslick, G. D. (2013). Hiatal hernia and the risk of Barrett's esophagus. *Journal Gastroenterology Hepatology, 28*(3), 415 - 431. https://doi.org/10.1111/j.1440-1746.2012.07199.x

El-Serag, H. B., & Johanson, J. F. (2002). Risk factors for the severity of erosive esophagitis in Helicobacter pylori-negative patients with gastroesophageal reflux disease. *Scandinavian Journal Gastroenterology, 37*(8), 899 - 904. https://doi.org/10.1080/003655202760230847

El-Serag, H., Becher, A., & Jones, R. (2010). Systematic review: Persistent reflux symptoms

on proton pump inhibitor therapy in primary care and community studies. *Alimentary Pharmacology Therapeutics, 32*(6), 720 - 737. https://doi.org/10.1111/j.1365-2036.2010.04406.x

Emerenziani, S., Habib, F. I., Ribolsi, M., Caviglia, R., Guarino, M. P. L., Petitti, T., & Cicala M. (2006). Effect of hiatal hernia on proximal oesophageal acid clearance in gastro-oesophageal reflux disease patients. *Alimentary Pharmacology Therapeutics, 23*(6): 751 - 757. https://doi.org/10.1111/j.1365-2036.2006.02816.x

Fennerty, M. B., & Johnson, D. (2006). Heartburn severity does not predict disease severity in patients with erosive esophagitis. *Medscape General Medicine, 8*(2), 6.

Fujiwara, Y., & Arakawa, T. (2009). Epidemiology and clinical characteristics of GERD in the Japanese population. *Journal Gastroenterology, 44*(6), 518 - 534. https://doi.org/10.1007/s00535-009-0047-5

Hvid-Jensen, F., Pedersen, L., Drewes, A. M., Sørensen, H. T., & Funch-Jensen, P. (2011). Incidence of adenocarcinoma among patients with Barrett's esophagus. *New England Journal Medicine, 365*(15), 1375 - 1383.

https://doi.org/10.1056/NEJMoa1103042

Iwakiri, K., Kinoshita, Y., Habu, Y., Oshima, T., Manabe, N., Fujiwara, Y., Nagahara, A., Kawamura, O., Iwakiri, R., Ozawa, S., Ashida, K., Ohara, S., Kashiwagi, H., Adachi, K., Higuchi, K., Miwa, H., Fujimoto, K., Kusano, M., Hoshihara, Y., Kawano, T., Haruma, K., Hongo, M., Sugano, K., Watanabe, M., & Shimosegawa, T. (2016). Evidence-based clinical practice guidelines for gastroesophageal reflux disease 2015. *Journal Gastroenterology, 51*(8), 751 - 767. https://doi.org/10.1007/s00535-016-1227-8

Iwakiri, K., Kawami, N., Sano, H., Tanaka, Y., Umezawa, M., Kotoyori, M., Hoshihara, Y., & Sakamoto, C. (2009). Mechanisms of excessive esophageal acid exposure in patients with reflux esophagitis. *Digestive Diseases Science, 54*(8), 1686 - 1692. https://doi.org/10.1007/s10620-008-0542-1

Japan Esophageal Society 食道癌取扱い規約(第 11 版). 日本食道学会. 金原出版. 2015. Esophageal cancer handling regulations (11th Ed*). Japan Esophageal Society*. Kanahara Publishing.

Kanda, Y. (2013). Investigation of the freely available easy-to-use software 'EZR' for

medical statistics. *Bone Marrow Transplant, 48*(3), 452 – 458. https://doi.org/10.1038/bmt.2012.244

Kimura, Y., Kamiya, T., Senoo, K., Tsuchida, K., Hirano, A., Kojima, H., Yamashita, H., Yamakawa, Y., Nishigaki, N., Ozeki, T., Endo, M., Nakanishi, K., Sando, M., Inagaki, Y., Shikano, M., Mizoshita, T., Kubota, E., Tanida, S., Kataoka, H., Katsumi, K., & Joh, T. (2016). Persistent reflux symptoms cause anxiety, depression, and mental health and sleep disorders in gastroesophageal reflux disease patients. *Journal Clinical Biochemistry Nutrition, 59*(1), 71-77. https://doi.org/10.3164/jcbn.16-9

Kono, T., Kozu, T., Ohara, S., & Kusano, M. (2005). Frequency of Barrett mucosa in Japanese. *Journal of Japanese Endoscopic Society, 47*, 951 - 961. https://doi.org/10.11280/gee1973b.47.951

Lagergren, J., Bergström, R., Lindgren, A., & Nyrén, O. (1999). Symptomatic gastroesophageal reflux as a risk factor for esophageal adenocarcinoma. *New England Journal Medicine, 340*(11), 825 - 831. https://doi.org/10.1056/NEJM199903183401101

Locke, G. R., Zinsmeister, A.R., & Talley, N.J. (2003). Can symptoms predict endoscopic findings in GERD? *Gastrointestinal Endoscopy, 58*(5), 661 - 670. https://doi.org/10.1016/s0016-5107(03)02011-x

Lundell, L. R., Dent, J., Bennett, J. R., Blum, A. L., Armstrong, D., Galmiche, J. P., Johnson, F., Hongo, M., Richter, J. E., Spechler, S. J., Tytgat, G. N., & Wallin, L. (1999). Endoscopic assessment of oesophagitis: Clinical and functional correlates and further validation of the Los Angeles classification. *Gut, 45*(2), 172 - 180. https://doi.org/10.1136/gut.45.2.172

Matsuhashi, N., Sakai, E., Ohata, K., Ishimura, N., Fujsaki, J., Shimizu, T., Iijima, K., Koike, T., Endo, T., Kikuchi, T., Inayoshi, T., Amano, Y., Furuta, T., Hanma, K., & Kinoshita, Y. (2017). Surveillance of patients with long-segment Barrett's esophagus: A multicenter prospective cohort study in Japan. *Journal Gastroenterology Hepatology, 32*(2): 409-414. https://doi.org/10.1111/jgh.13491

Mishima, I., Adachi, K., Arima, N., Amano, K., Takashima, T., Moritani, M., Furuta, K., & Kinoshita Y. (2005). Prevalence of endoscopically negative and positive

gastroesophageal reflux disease in the Japanese. *Scandinavian Journal Gastroenterology, 40*(9), 1005 - 1009. https://doi.org/10.1080/00365520510023260

Mullin, J. M., Valenzano, M. C., Trembeth, S., Allegretti, P. D., Verrecchio, J. J., Schmidt, J. D., Jain, V., Meddings, J. B., Mercogliano, G., & Thornton, J. J. (2006). Transepithelial leak in Barrett's esophagus. *Digestive Diseases and Sciences, 51*(12): 2326-2336. https://doi.org/10.1007/s10620-006-9478-5

Nakagawa, K., Koike, T., Iijima, K., Saito, M., Kikuchi, H., Hatta, W., Ara, N., Uno, K., Asano, N., & Shimosegawa, T. (2015). Characteristics of symptomatic reflux episodes in Japanese proton pump inhibitor-refractory non-erosive reflux disease patients. *World Journal Gastroenterology, 21*(47), 13352 - 13359. https://doi.org/10.3748/wjg.v21.i47.13352

Okamoto, K., Iwakiri, R., Mori, M., Hara, M., Oda, K., Danjo, A., Ootani, A., Sakata, H., & Fujimoto, K. (2003). Clinical symptoms in endoscopic reflux esophagitis: Evaluation in 8031 adult subjects. *Digestive Diseases Science, 48*(12), 2237 -2241. https://doi.org/10.1023/b:ddas.0000007857.15694.15

Oshima, T. & Miwa, H. (2017). Esophageal disease and mucosal barrier dysfunction. *Journal of Hyogo College of Medicine, 42*(1), 57 - 63.

Peters, F. T., Ganesh, S., Kuipers, E. J., Sluiter, W. J., Klinkenberg-Knol, E. C., Lamers, C. B., & Kleibeuker, J. H. (1999). Endoscopic regression of Barrett's oesophagus during omeprazole treatment: A randomised double blind study. *Gut, 45*(4), 489 - 494. https://doi.org/10.1136/gut.45.4.489

Ronkainen, J., Talley, N. J., Storskrubb, T., Johansson, S. E., Lind, T., Vieth, M., Agréus, L., & Aro, P. (2011). Erosive esophagitis is a risk factor for Barrett's esophagus: A community-based endoscopic follow-up study. *American Journal Gastroenterology, 106*(11), 1946 - 1952. https://doi.org/10.1038/ajg.2011.326

Ronkainen, J., Aro, P., Storskrubb, T., Johansson, S. E., Lind, T., Bolling-Sternevald, E., Vieth, M., Stolte, M., Talley, N. J., & Agréus, L. (2005). Prevalence of Barrett's esophagus in the general population: An endoscopic study. *Gastroenterology, 129*(6), 1825 - 1831. https://doi.org/10.1053/j.gastro.2005.08.053

Schludermann, E. (1962). Effects of age on pain sensitivity. *Perceptual Motor Skills, 14*, 296

- 301.

Sikkema, M., de Jonge, P. J., Steyerberg, E. W., & Kuipers, E. J. (2010). Risk of esophageal adenocarcinoma and mortality in patients with Barrett's esophagus: A systematic review and meta-analysis. *Clinical Gastroenterology Hepatology, 8*(3), 235 - 244. https://doi.org/10.1016/j.cgh.2009.10.010

Suzuki, H., Matsuzaki, J., Masaoka, T., & Inadomi, J. M. (2014). Greater loss of productivity among Japanese workers with gastro-esophageal reflux disease (GERD) symptoms that persist vs resolve on medical therapy. *Neurogastroenterology Motility, 26*(6), 764 - 771. https://doi.org/10.1111/nmo.12319

Wilkinson, S. P., Biddlestone, L., Gore, S., Shepherd, N. A. (1999). Regression of columnar-lined (Barrett's) oesophagus with omeprazole 40 mg daily: Results of 5 years of continuous therapy. *Alimentary Pharmacology Therapeutics, 13*(9), 1205 - 1209. https://doi.org/10.1046/j.1365-2036.1999.00593.x

Yamasaki, T., Oshima, T., Tomita, T., Kondo, T., Toyoshima, F., Sakurai, J., Fukui, H., Matsumoto, T., Watari, J., & Miwa, H. (2013). Effect of age and correlation between

esophageal visceral chemosensitivity and mechanosensitivity in healthy Japanese subjects. *Journal Gastroenterology, 48(*3), 360 - 365. https://doi.org/10.1007/s00535-012-0665-1