

Gender differences in both the pathology and surgical outcome of patients with esophageal achalasia

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Abstract

Background Esophageal achalasia is a relatively rare disease that occurs usually in middle-aged patients. The laparoscopic Heller–Dor (LHD) procedure is the gold-standard surgical treatment for esophageal achalasia. There are many studies on the pathology and surgical outcome of esophageal achalasia from various perspectives, but there are no studies on gender differences in both the pathology and surgical outcome.

Aims This study aimed to evaluate gender differences in the surgical outcome with the LHD procedure and in the pathology of esophageal achalasia patients.

Methods The study included 474 LHD-treated patients who were postoperatively followed up for 6 months or more. The patients were divided into 2 groups by gender, to compare the preoperative pathology, surgical outcome, symptom scores before and after LHD, symptom score improvement frequency, and patient satisfaction with the surgery.

Results The study population consisted of 248 male and 226 female, having a mean age of 45.1 years. There were no gender differences in the preoperative pathology, but a significantly lower BMI ($p < 0.0001$) and a smaller esophageal dilation ($p = 0.0061$) were observed in the female group. The frequency and severity of chest pain before the surgery were significantly higher in the female group ($p = 0.0117$ and $p = 0.0103$, respectively), and the improvement in both the frequency and severity of chest

pain was significantly higher in the female group ($p = 0.0005$ and $p = 0.003$, respectively). No differences were identified in the surgical outcomes and postoperative course. The patient satisfaction with the surgery was high in both groups and comparable ($p = 0.6863$).

Conclusions The female patients with esophageal achalasia were characterized by low BMI, less esophageal dilation, and increased frequency and severity of chest pain. LHD improved the chest pain in the female patients, whereas the surgical outcome and satisfaction with the surgery were excellent regardless of gender.

Keywords Achalasia · Gender · Laparoscopy · Surgical outcome · Symptom

Esophageal achalasia is one of the major esophageal motility disorders, and the main symptoms are dysphagia and chest pain caused by the failure of the lower esophageal sphincter [1]. The disease is rare with an incidence of 1 in 0.1 million people [2]. Although the recent use of high-resolution manometry enables evaluation of esophageal motility in detail [3], the pathology of esophageal achalasia has not been fully analyzed. According to previous reports, esophageal achalasia occurs most commonly in middle-aged people and there are no gender differences [4]. In general, endoscopic dilation and surgical procedures achieve effective outcomes [5], and the laparoscopic Heller–Dor (LHD) procedure has been widely used worldwide as the standard surgical treatment for esophageal achalasia [6]. Currently, per-oral endoscopic myotomy (POEM), which is a less invasive treatment than LHD, has been introduced and is becoming a widely used procedure [7]. There are many studies on the pathology and surgical outcome of esophageal achalasia from various perspectives,

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but they were performed with small numbers of patients due to the rarity of the disorder. On the other hand, there are no studies on both the pathology and surgical outcome in terms of the gender differences. This study focused on the gender differences in esophageal achalasia patients and evaluated both the pathology and surgical outcome.

Materials and methods

Patients

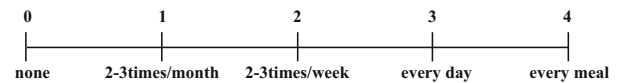
All patients with esophageal achalasia were entered into a prospectively maintained database in our institution. There were 480 patients diagnosed as having achalasia by both esophagography and esophageal manometry who had LHD as the initial surgical treatment between August 1994 and October 2014. Of these patients 474 were included in this study, with the following patients excluded: 4 with laparotomy, 1 with thoracoscopic surgery, and 1 with hand-assisted laparoscopic surgery (HALS).

Methods

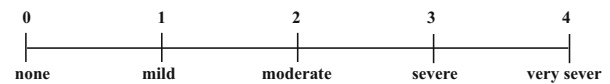
The patients were divided into 2 groups by gender to compare the preoperative pathology, surgical outcome, intraoperative blood loss, intraoperative complications, postoperative course, symptom scores before and after the LHD procedure, and patient satisfaction with the surgery. Contrast examination of the gastrointestinal tract, timed barium esophagogram (TBE) [8], and esophageal manometry were performed to evaluate the pathology. The type of esophageal dilation, maximum dilation diameter, and severity of the dilation were evaluated in accordance with Descriptive Rules for Achalasia of the Esophagus in Japan. TBE was performed for the esophageal clearance assessment and used to calculate the complete clearance of barium at 1, 2, and 5 min. The lower esophageal sphincter pressure (LESP) and the lower esophageal sphincter (LES) relaxation were calculated by esophageal manometry. A questionnaire covering 4 symptoms, including dysphagia, vomiting, chest pain, and heartburn, was completed by the patients before and at 3 months after the surgery using a five-point rating system as previously reported [9]. In general, patients are hard to discriminate between heartburn and chest pain. We performed questionnaire by ourselves to solve this problem. The patients answered on the frequency of the symptoms using the following criteria: 0 designated to no symptoms, 1 to 2 to 3 times in a month, 2 to 2 to 3 times in a week, 3 to every day, and 4 to during every meal. The severity of the symptoms was established using the following criteria: 0 designated to no symptoms, 1 to mild, 2 to

Table 1 Scoring system of each symptom

【Frequency】



【Severity】



moderate, 3 to severe, and 4 to very severe symptoms (Table 1). The improvement score for the frequency and severity was calculated by the following method: The postoperative scores (b) were subtracted from the preoperative scores (a) and divided by the preoperative scores (a) $[(a - b)/a \times 100]$, to evaluate each symptom. The patient satisfaction with the surgery was also evaluated using a five-point rating system (1 designated to very unsatisfied, 2 to unsatisfied, 3 to neither satisfied nor dissatisfied, 4 to satisfied, and 5 to very satisfied) [10].

Statistical analysis

The median and interquartile range of each test result were provided. Either the Chi-square test or Fisher's exact test was used to compare categorical variables between the groups, and the Mann–Whitney's *U* test was used to compare continuous variables between the groups. A $p < 0.05$ was considered statistically significant. STATA 12.1 (Stata Corp., TX, USA) was used for the statistical analysis.

Results

Background of the patients

The study population consisted of 248 male and 226 female, with a mean age of 45.1 years. Although no gender differences were observed in the preoperative pathology in terms of age, duration of illness, preoperative body weight loss, or history of balloon dilation between the two groups, the BMI was significantly lower in the female group ($p < 0.0001$). Furthermore, although no differences in the LESP and LES relaxation and in the type of esophageal dilation between the two groups, the female group had significantly lower maximum dilation diameter of the esophagus and milder severity of dilation was significantly

Table 2 Patients' background

| | Male (<i>n</i> = 248) | Female (<i>n</i> = 226) | <i>p</i> |
|-------------------------------------|------------------------|--------------------------|----------|
| Age (years) | 43 (33, 56) | 44 (32, 59) | 0.7936 |
| BMI (kg/m ²) | 21 (19.3, 22.9) | 19.5 (18.1, 21.7) | <0.0001 |
| Body weight loss (%) | 101/232 (43.5) | 98/218 (45.0) | 0.762 |
| Length of symptoms (months) | 48 (24, 120) | 60 (24, 120) | 0.3198 |
| Pre-op. dilation(%) | 60 (24.2) | 49 (21.7) | 0.516 |
| LESP (mmHg) | 46.1 (32.4, 56.1) | 41.5 (31, 52.5) | 0.4075 |
| LES relaxation (%) | 55.7 (35.75, 73.6) | 50.7 (30.8, 76) | 0.8399 |
| Morphologic type (St/Sg/unknown) | 196/46/6 | 191/29/6 | 0.09 |
| Degree of dilatation | 2 (2, 3) | 2 (2, 2) | 0.0061 |
| Maximum width of the esophagus (mm) | 55.6 ± 16.0 | 49.7 ± 13.9 | 0.0002 |

BMI body mass index, LES lower esophageal sphincter, St straight type, Sg sigmoid type

milder in the female group ($p = 0.0002$ and $p = 0.0061$, respectively) (Table 2). The complete clearance of barium in both the male and female groups, assessed at 1, 2, and 5 min by TBE, was 44.8 % (82/183) and 54.1 % (93/172), 58.2 % (107/184) and 63.4 % (109/172), and 66.3 % (122/184) and 70.9 % (122/172), respectively, and there were no differences between the two groups ($p = 0.081$, $p = 0.314$ and $p = 0.348$, respectively).

Preoperative symptom score

The preoperative symptom scores of the frequency and severity of chest pain were significantly greater in the female group ($p = 0.0117$, $p = 0.0103$, respectively), but there were no differences in the other symptoms, including dysphagia, vomiting, and heartburn, between the two groups (Fig. 1A–D).

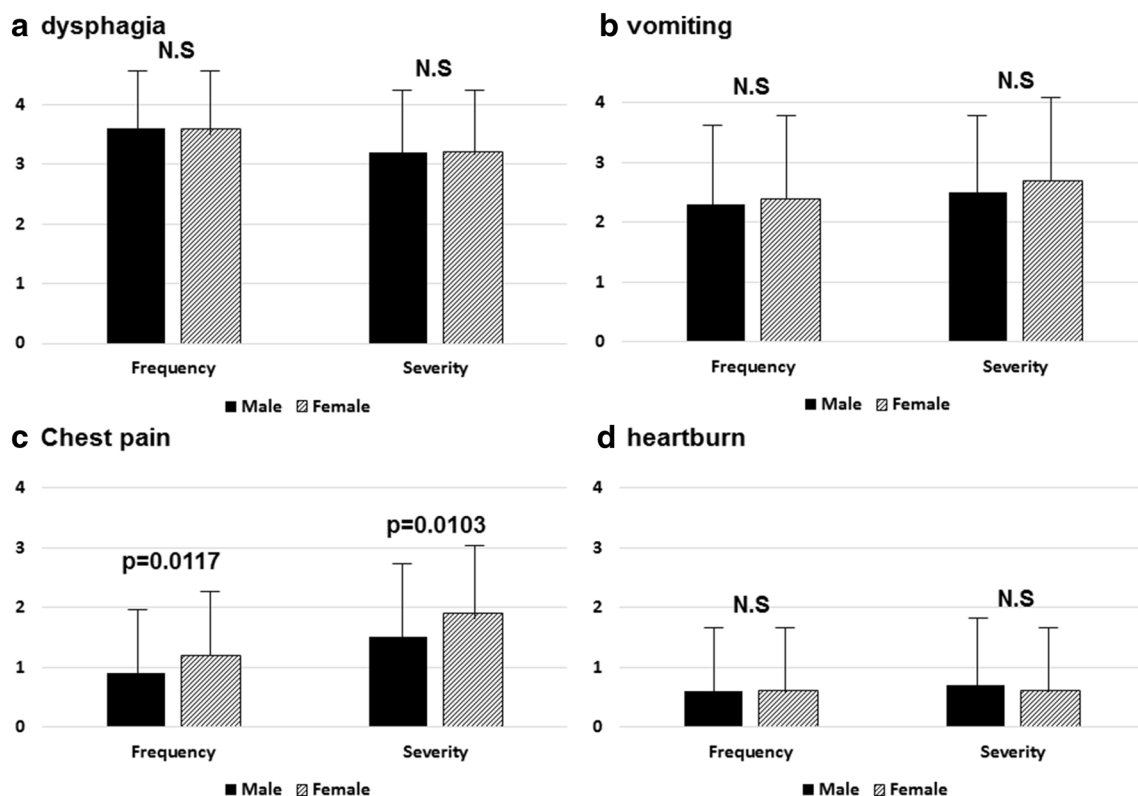


Fig. 1 The preoperative questionnaire shows the scores for the symptoms, including **A** dysphagia, **B** vomiting, **C** chest pain, and **D** heartburn. There were no gender differences in the scores for

dysphagia, vomiting, and heartburn, while the frequency and severity of chest pain were significantly higher in the female group ($p = 0.0117$ and $p = 0.0103$, respectively)

Table 3 Surgical outcome and postoperative course

| | Male (<i>n</i> = 248) | Female (<i>n</i> = 226) | <i>p</i> |
|--------------------------------------|------------------------|--------------------------|----------|
| Operative time (minutes) | 172 (145, 205) | 170 (140, 205) | 0.4263 |
| Blood loss >200 ml (%) | 7 (2.8) | 2 (0.9) | 0.123 |
| Mucosal perforation (%) | 37 (14.9) | 33 (14.6) | 0.922 |
| Start of diet intake (days) | 2 (2, 2) | 2 (2, 2) | 0.433 |
| Post-op hospital stay (days) | 4 (4, 6) | 4 (4, 6) | 0.7967 |
| Occurrence of reflux esophagitis (%) | 22 (8.9) | 18 (8.0) | 0.723 |
| Administration of antacid (%) | 36 (14.5) | 31 (13.7) | 0.803 |
| Post-op dilation (%) | 4 (1.6) | 1 (0.4) | 0.213 |
| Redo operation (%) | 2 (0.8) | 5 (2.2) | 0.205 |

Surgical outcomes

As for the surgical outcomes, no statistical differences were identified in the operating time, the rate of intraoperative blood loss ≥ 200 ml, and the incidence of intraoperative mucosal injury between the two groups (Table 3).

Postoperative symptom scores and patient satisfaction

The improvement in the frequency and severity of the preoperative symptoms, including dysphagia, vomiting, chest pain, and heartburn, in both the male and female

groups was 91.0 % (273/300) and 95.3 % (286/300), 94.2 % (242/257) and 94.2 % (242/257), 77.8 % (147/189) and 82.5 % (156/189), and 85.2 % (69/81) and 88.9 % (72/81), respectively. The above-mentioned symptoms were significantly improved in both groups after the surgery, and there were no differences in the scores between the two groups (Fig. 2A–D). The improvement of the symptom scores indicated that the frequency and severity of chest pain were significantly better in the female group ($p = 0.0005$, $p = 0.003$, respectively), which indicated that the improvement effect was greater in the female group. However, there were no gender differences in the improvement in the scores of the other 3 symptoms, i.e.,

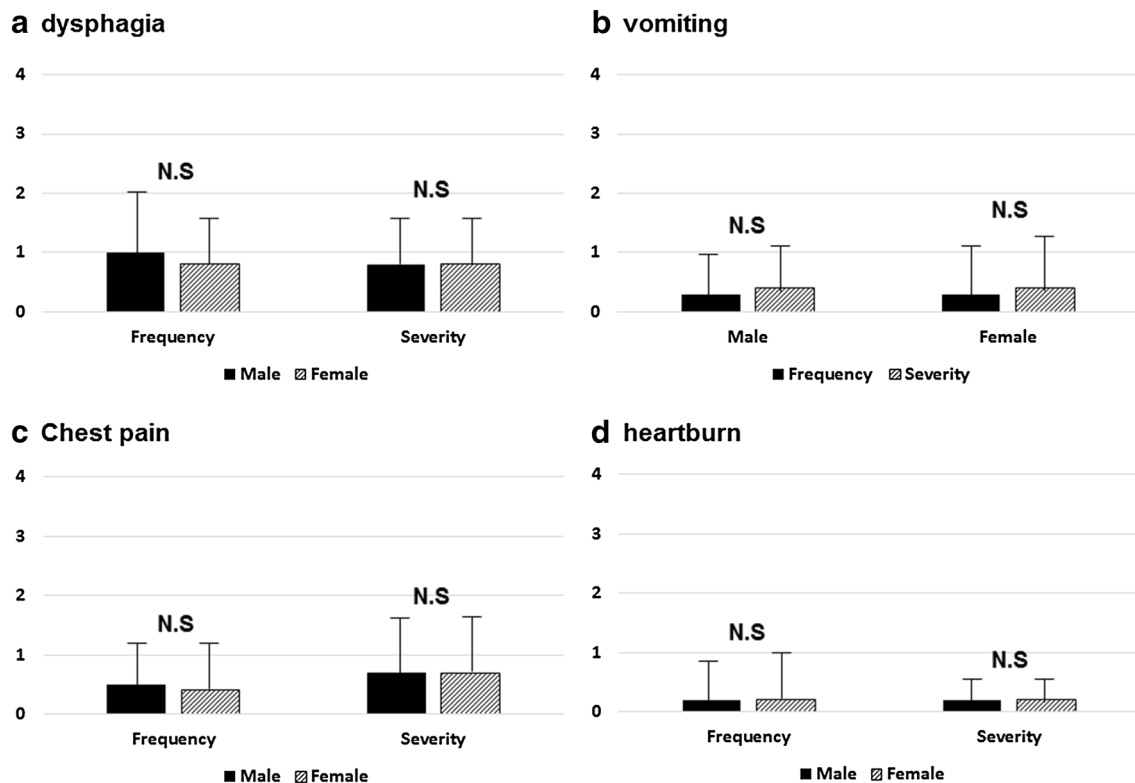


Fig. 2 The postoperative questionnaire shows the scores of the symptoms, including **A** dysphagia, **B** vomiting, **C** chest pain, and **D** heartburn. There were no gender differences in all 4 symptoms, and the scores were similar between the groups

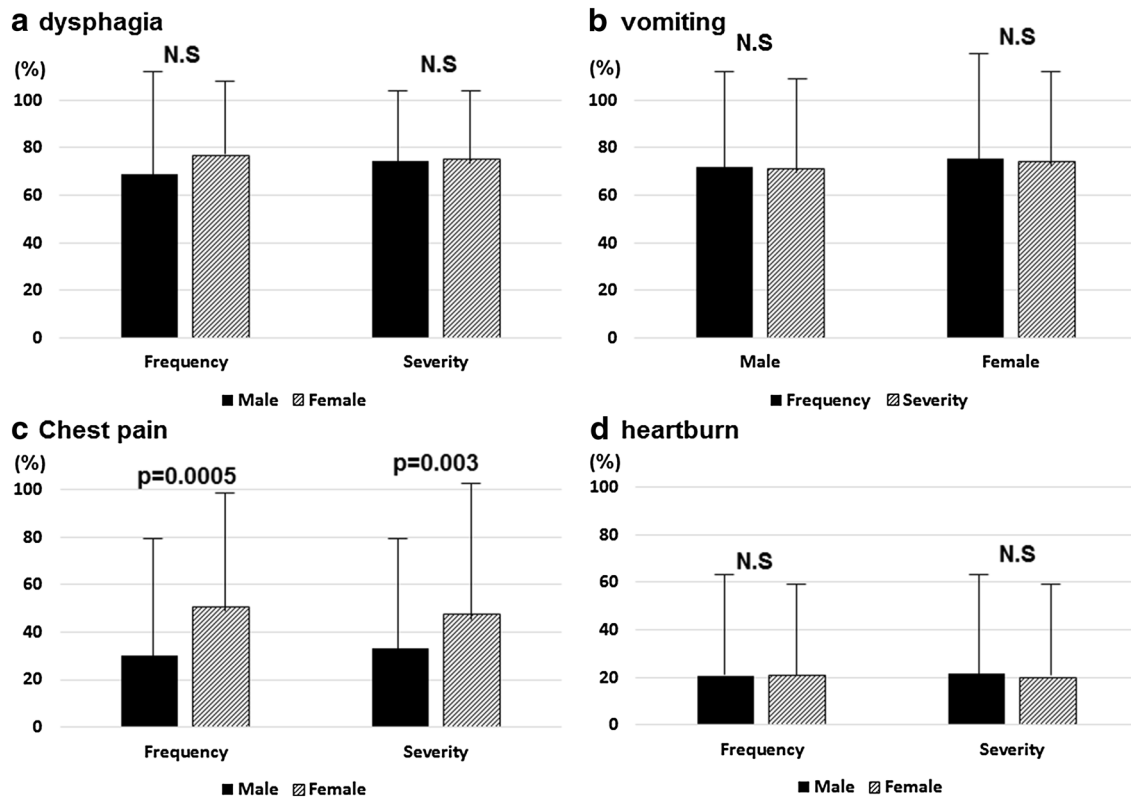


Fig. 3 The improvement in dysphagia (A), vomiting (B), chest pain (C), and heartburn (D) is shown. The frequency and severity of chest pain alone improved after the surgery ($p = 0.005$ and $p = 0.003$, respectively)

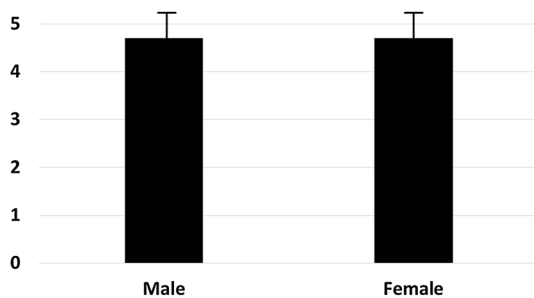


Fig. 4 The patient satisfaction with the surgery was high in both groups, and there was no gender difference

dysphagia, vomiting, and heartburn, between the two groups (Fig. 3A–D). The patient satisfaction with the surgery was high and similar in both groups ($p = 0.6863$) (Fig. 4).

Postoperative course

There were no differences in the duration of the postoperative hospital stay, incidence of postoperative reflux esophagitis, and postoperative oral administration of gastric secretion inhibitors between the two groups. Furthermore, no statistical differences were observed in the need for

balloon dilation or retreatment due to persistence of dysphagia after the surgery between the two groups (Table 3).

Discussion

Esophageal achalasia is a benign esophageal disease, which was first reported in 1915 by Hertz et al. [11]. There have been many studies on the pathology and surgical outcome of esophageal achalasia, but they were performed with small numbers of patients due to the rarity of the disorder, and the pathology has not been elucidated. Although the reports of the disease from high volume centers have increased [12, 13], many aspects of the disease remain to be clarified.

Some reports had demonstrated gender differences in that the pathology and surgical outcome of gastroesophageal reflux disease (GERD) [14, 15]. On the other hand, there are no reports on the gender differences in both the pathology and surgical outcome of esophageal achalasia which has a much lower incidence than that of GERD. We have previously conducted various studies on both the pathology and surgical outcome of esophageal achalasia [16–19].

Although a significantly lower BMI and smaller esophageal dilation were observed in the female group, there were no differences in many other factors between the two

groups, which suggested that the disease pathology and surgical outcome might not vary by gender and that the data on both BMI and esophageal dilation might be due to the difference in body size between males and females.

The studies on the association of gender with the surgical outcome of laparoscopic fundoplication for GERD revealed that acid reflux was milder in the female patients than that in the male patients [20] and started at the early stage of mild GERD [15, 21]. For that reason, the male gender has been considered to be one of the factors predicting excellent outcome of laparoscopic fundoplication for GERD [22]. Our study on esophageal achalasia found that the chest pain score was significantly greater in the female group than that in the male group. A mechanism of chest pain associated with esophageal achalasia has not been elucidated, but stimulation by esophageal contraction and expansion has been suspected to be the cause [23]. Like in GERD patients, greater esophageal sensitivity in female patients with achalasia may lead to the higher chest pain score. In this study, the symptom score improvement by the LHD procedure has been used to evaluate the gender differences in symptom improvement detail, and the frequency and severity of chest pain alone were significantly improved in the female group. The higher scores of chest pain before surgery in the female group might be one of the factors contributing to the better improvement in scores, but it is also clear that the successful LHD procedure contributes greatly to the score improvement. The score improvement in chest pain was not considered high at approximately 50 %, possibly due to the lack of chest pain in many patients before the surgery. However, such patients became aware of mild chest pain after the surgery. The score improvement in the patients who had chest pain before the surgery was approximately 80 %, which indicated that the surgery significantly improved chest pain. As the surgery relieved lower esophageal obstruction and expansion of the esophageal wall, the symptom was immediately improved in the female patients, who generally have high esophageal sensitivity.

On the other hand, there were no differences between the groups in overall surgical outcomes, postoperative course, and patient satisfaction, and LHD yielded excellent outcome regardless of gender.

There were some limitations in this study. It took approximately 20 years from 1994 to 2014 to collect a sufficient number of patients for this study. However, we have used the same surgical technique for a long time in our department as previously reported, and therefore, we believe that the surgical outcomes were rather consistent during the study period. Another limitation in this study is that the majority of the subjects were Japanese. In order to establish the findings of this study, multicenter studies in a

larger population consisting of different races should be performed in the future.

Conclusion

The characteristics of female patients with achalasia were lower BMI, smaller esophageal dilation, and higher frequency and severity of chest pain as compared to the male patients. The LHD procedure yielded excellent outcomes regardless of gender, while greater improvement for chest pain is achieved in the female patients as compared to the male patients.

Disclosures Drs. Tsuboi, Omura, Yano, Hoshino, Yamamoto, Akimoto, Masuda, Kashiwagi, and Yanaga have no conflicts of interest or financial ties to disclose.

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