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Original Article

Development of Dilated Esophagus, Sigmoid Esophagus, and Esophageal Diverticulum in Patients With Achalasia: Japan Achalasia Multicenter Study

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Background/Aims
Patients with achalasia-related esophageal motility disorders (AEMDs) frequently present with dilated and sigmoid esophagus, and develop esophageal diverticulum (ED), although the prevalence and patients characteristics require further elucidation.

Methods
We conducted a multicenter cohort study of 3707 patients with AEMDs from 14 facilities in Japan. Esophagography on 3682 patients were analyzed.

Results
Straight (n = 2798), sigmoid (n = 684), and advanced sigmoid esophagus (n = 200) were diagnosed. Multivariate analysis revealed that long disease duration, advanced age, obesity, and type I achalasia correlate positively, whereas severe symptoms and integrated relaxation pressure correlate negatively with development of sigmoid esophagus. In contrast, Grade II dilation (3.5-6.0 cm) was the most common (52.9%), while grade III dilation (≥ 6 cm) was rare (5.0%). We found early onset, male, obesity, and type I achalasia correlated positively, while advanced age correlated negatively with esophageal dilation. Dilated and sigmoid esophagus were found mostly in types I and II achalasia, but typically not found in spastic disorders. The prevalence of ED was low (n = 63, 1.7%), and non-dilated esophagus and advanced age correlated with ED development. Patients with right-sided ED (n = 35) had a long disease duration (P = 0.005) with low integrated relaxation pressure values (P = 0.008) compared with patients with left-sided ED (n = 22). Patients with multiple EDs (n = 6) had lower symptom severity than patients with a single ED (P = 0.022).

Conclusions
The etiologies of dilated esophagus, sigmoid esophagus, and ED are considered multifactorial and different. Early diagnosis and optimal treatment of AEMDs are necessary to prevent these conditions.
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Key Words
Eckardt score; Epiphrenic diverticulum; High-resolution manometry; Integrated relaxation pressure; Megaesophagus

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Introduction

Achalasia is a primary esophageal motility disorder (EMD); its etiology is the degeneration of Auerbach's plexus, which results in failure of relaxation of the lower esophageal sphincter (LES) and absence of normal esophageal peristalsis.[1,2] Thus, the natural course of achalasia often involves dilated and sigmoid esophagus; hence, radiological assessment, including esophagography, plays an important role in the diagnosis of achalasia.[3,4] However, the prevalence of disease natural course with regard to dilated and sigmoid esophagus and the clinical factors associated with dilated and sigmoid esophagus require further elucidation. Furthermore, our previous study highlights the discrepancies between dilated and sigmoid esophagus.[5]

It was also reported that esophageal diverticulum (ED) is a common complication of achalasia-related EMDs.[6-8] Similar to esophagography findings such as dilated and sigmoid esophagus, the prevalence of ED in patients with achalasia-related EMDs has not been thoroughly investigated. One of the main reasons for this situation is that the incidence of ED is low; therefore, a large sample size of patients with achalasia-related EMDs is needed for statistical power analysis.

Achalasia is rare and has an incidence rate of 1.0/100 000 persons per year;[9,10] hence, the number of patients with achalasia in a single facility is usually small. Therefore, to investigate esophagography findings such as dilated esophagus, sigmoid esophagus, and ED, we conducted a multicenter study involving high-volume centers in Japan.

Materials and Methods

Patients

This study was conducted at 14 high-volume EMD centers in Japan. Patients with EMDs diagnosed using standard methods, such as high-resolution manometry (HRM), esophagography, and gastroscopy, and treated between 2010 and 2020 were enrolled in this study. From these patients, we analyzed the patients with achalasia-related EMDs such as achalasia and esophagogastric junction outflow obstruction (EGJOO), major disorders of peristalsis such as jackhammer esophagus (JE) and distal esophageal spasm (DES), and unclassified spastic disorders.

This study was part of a more extensive retrospective clinical study of patients with EMDs, including achalasia. The study was approved by the ethics committees of all the participating institutions (Supplementary Material), and it was conducted in accordance with the principles stipulated in the Declaration of Helsinki. Informed consent (in the form of an opt-out system on a website) was obtained from the patients. All the authors had access to the study data, and each author reviewed and approved the final manuscript.

Data Collection

A study-specific spreadsheet was created to collect validated case data from each hospital. The survey items included the following: age at onset and diagnosis of EMD, duration of symptoms, sex, body mass index (BMI), Eckardt score, HRM diagnosis, type of achalasia, and degree of esophageal dilation. If esophagography revealed ED in a patient, the side of the ED (right, left, or multiple lesions) was also investigated. To prevent data omission or entry error and to minimize missing values, we used the multiple-choice rules in Excel to input categorical variables (eg, type of achalasia: straight, sigmoid [S1], advanced sigmoid [S2], or unknown) and free input for continuous variables. The Excel spreadsheet was filled using data retrieved from electronic medical records and was then sent to a representative's facility. The representative checked for omissions and errors in the input values of the data sent from each hospital. Data that needed correction were communicated to input physician(s) of each hospital using detailed comments.

Variables

Symptom severity was evaluated using the Eckardt score.[11] The Eckardt score is the sum of the respective 3-point scores for dysphagia, regurgitation, chest pain, and weight loss. The higher the score, the more severe the symptoms of achalasia-related EMDs

(maximum score = 12), and the lower the score, the milder the symptoms (minimum score = 0). HRM diagnosis was based on the Chicago classification criteria version 3.0.[12] To assess deglutitive LES relaxation, integrated relaxation pressure (IRP) was measured, and IRP ≥ 26 mmHg on Starlet (Starmedical Ltd, Tokyo, Japan) was considered high IRP, which indicates incomplete LES relaxation.[13] IRP values obtained using several HRM systems were converted to the Starlet criteria using a previously reported formula.[14,15] Type of achalasia on esophagography was classified as straight esophagus, sigmoid esophagus (S1), or advanced sigmoid esophagus (S2). S2 was subclassified when the esophageal angle < 90° (Supplementary Fig. 1). Based on the diameter of the esophageal lumen observed during esophagography, the degree of esophageal dilation was classified as grade I (< 3.5 cm), grade II (3.5-6.0 cm), or grade III (> 6 cm) (Supplementary Fig. 2).[16]

Statistical Methods

Pearson's chi-squared test or Fisher's exact test was used to compare categorical data, while Mann-Whitney *U* test was used to compare continuous data. To determine associations between dilated esophagus, sigmoid esophagus, and ED development, we used univariate and multivariate logistic regression models and computed the odds ratio (OR) and 95% confidence interval (CI). Factors with $P < 0.05$ in the univariate analysis were included in the multivariate analysis. All statistical analyses were performed using SAS statistical software (version 9.4; SAS Institute, Cary, NC, USA). All reported *P*-values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 3707 patients with achalasia-related EMDs were enrolled in this study (Supplementary Fig. 3). Findings on radiography, including esophagography, were made in 3682 of the 3707 patients, and these findings were analyzed in study 1. In study 1, 3411 patients with achalasia, 115 patients with EGJOO, 65 patients with DES, 68 patients with JE, and 23 patients with unclassified spastic disorders were included. Furthermore, 63 patients with ED (1.7%) were identified from among the patients who underwent esophagography. To investigate the characteristics of patients with ED, a case-control study of 63 patients with ED and 3619 without ED (study 2) was conducted.

Natural Course and Risk Factors of Sigmoid Esophagus

The characteristics of patients with straight esophagus (n = 2798), sigmoid esophagus (n = 684), and advanced sigmoid esophagus (n = 200) are summarized in Table 1. Statistically sig-

Table 1. Characteristics of Patients With Straight, Sigmoid, and Advanced Sigmoid Esophagus (n = 3682)

Variables	Straight (n = 2798)	Sigmoid (n = 684)	*P*-value[a]	Advanced sigmoid (n = 200)	*P*-value[b]	*P*-value[c]
Age at onset (yr)	40 (28, 55)	42 (29, 61)	0.005	39 (27, 59)	0.984	0.174
Age at onset < 40 yr	1358 (48.5%)	311 (45.5%)	0.163	102 (51.0%)	0.548	0.194
Duration of symptoms (mo)	49.0 (22.0, 121.0)	109.5 (40.8, 222.5)	< 0.001	181.5 (63.3, 325.8)	< 0.001	< 0.001
Duration of symptoms ≥ 10 yr	734 (26.2%)	309 (45.2%)	< 0.001	122 (61.0%)	< 0.001	< 0.001
Age at diagnosis (yr)	48.0 (37.0, 64.0)	58.0 (44.0, 72.0)	< 0.001	62.5 (49.0, 71.0)	< 0.001	0.036
Age at diagnosis ≥ 65 yr	679 (24.3%)	266 (38.9%)	< 0.001	89 (44.5%)	< 0.001	0.164
Sex (men)	1393 (49.8%)	353 (51.6%)	0.417	112 (56.0%)	0.104	0.296
Body mass index (kg/m^2)	20.7 (18.6, 23.3)	21.6 (19.2, 24.2)	< 0.001	21.5 (18.6, 24.2)	0.082	0.321
Body mass index ≥ 25 kg/m^2	416 (14.9%)	139 (20.4%)	<0.001	39 (19.5%)	0.097	0.842
Eckardt score	6 (4-8)	5 (4-7)	< 0.001	5 (4-7)	< 0.001	0.243
Eckardt score ≥ 7	1118 (41.4%)	209 (32.1%)	0.014	62 (32.1%)	0.014	0.930
Type I achalasia on HRM[d]	1146 (51.9%)	330 (67.8%)	< 0.001	65 (83.3%)	< 0.001	0.005
IRP on HRM[e]	28.1 (19.0, 39.0)	22.2 (15.2, 33.5)	< 0.001	17.0 (12.9, 25.9)	< 0.001	0.007
IRP ≥ 26 mmHg on HRM[e]	1409 (57.5%)	209 (41.1%)	< 0.001	21 (26.9%)	< 0.001	0.018

[a]*P*-value was calculated between straight esophagus and sigmoid esophagus.
[b]*P*-value was calculated between straight esophagus and advanced sigmoid esophagus.
[c]*P*-value was calculated between sigmoid esophagus and advanced sigmoid esophagus.
[d]Type I achalasia was analyzed in patients with type I, type II, and type III achalasia on high-resolution manometry (HRM).
[e]Integrated relaxation pressure (IRP) was measured in patients who underwent HRM for diagnosis (n = 3037).
Number of missing values: 2 for body mass index and 128 for Eckardt score.

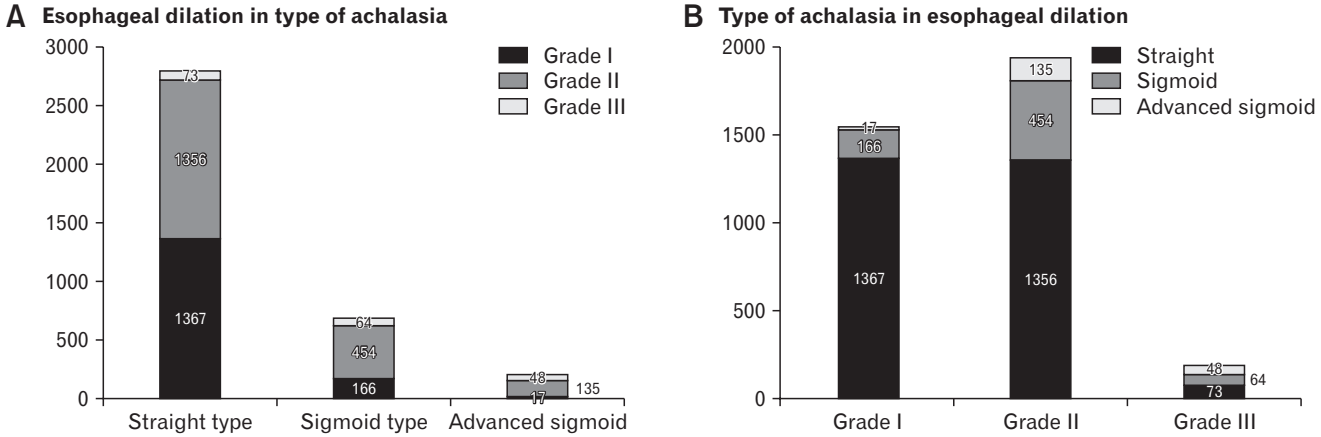

Figure 1. Prevalence of esophagography findings. (A) Esophageal dilation (grades I to III) in straight, sigmoid, and advanced sigmoid esophagus. The rates of sigmoid esophagus (n = 684; 18.6%) and advanced sigmoid esophagus (n = 200; 5.4%) are lower than the rate of straight esophagus (n = 2796; 76.0%). More than half the patients with straight-type achalasia had dilated esophagus (n = 1429; 51.1%). (B) Type of achalasia (straight, sigmoid, and advanced sigmoid) in patients with grades I to III esophageal dilation. Grade II dilation is more common than grade I dilation (n = 1945; 52.9% vs n = 1550; 42.1%), and grade III dilation is rare (n = 185, 5.0%). Sigmoid-type achalasia is more common than straight-type achalasia in patients with grade III esophageal dilation (n = 112; 60.5% vs n = 73; 39.5%).

nificant differences in age at onset, duration of symptoms, age at diagnosis, BMI, Eckardt score, type I achalasia on HRM, and IRP values were observed between patients with sigmoid esophagus and patients with straight esophagus. Duration of symptoms, age at diagnosis, type I achalasia, and IRP values showed consistent statistical significance in the natural course from straight esophagus to advanced sigmoid esophagus. Multivariate analysis revealed that duration of symptoms ≥ 10 years (OR, 1.980 [95% CI, 1.610-2.430]), age at diagnosis ≥ 65 years (OR, 2.460 [95% CI, 2.000-3.020]), BMI ≥ 25 kg/m^2 (OR, 1.550 [95% CI, 1.200-2.000]), and type I achalasia (OR, 1.780 [95% CI, 1.430-2.210]) correlated positively with development of sigmoid esophagus, while Eckardt score ≥ 7 (OR, 0.754 [95% CI, 0.609-0.934]) and IRP ≥ 26 (OR, 0.620 [95% CI, 0.502-0.766]) correlated negatively with development of sigmoid esophagus (Supplementary Table 1). Furthermore, esophageal dilation in the types of esophagus was compared (Fig. 1A). Statistically significant differences in the prevalence of dilated esophagus (grades II and III) were observed between the 3 groups (all values of P were < 0.001). More than half of the patients with straight esophagus had dilated esophagus (n = 1429; 51.1%), and the prevalence of dilated esophagus was higher in patients with sigmoid esophagus (n = 518; 75.7%), and in patients with advanced sigmoid esophagus (n = 183; 91.5%).

Natural Course and Risk Factors of Dilated Esophagus

The characteristics of patients with grade I (n = 1550), grade II (n = 1945), and grade III (n = 185) esophageal dilation are summarized in Table 2. Grade II was the most common degree of esophageal dilation (52.9%), and grade III esophageal dilation was rare (5.0%). Statistically significant differences in age at onset, duration of symptoms, age at diagnosis, male sex, BMI, Eckardt score, and type I achalasia on HRM were observed between patients with grade II esophageal dilation and patients with grade I esophageal dilation. Male sex, BMI, and type I achalasia on HRM showed consistent statistical significance in the natural course from grade I to grade III esophageal dilation. Multivariate analysis revealed that age at onset < 40 years (OR, 1.320 [95% CI, 1.100-1.590]), male sex (OR, 1.630 [95% CI, 1.390-1.900]), BMI ≥ 25 kg/m^2 (OR, 1.460 [95% CI, 1.160-1.840]), and type I achalasia (OR, 1.990 [95% CI, 1.690-2.350]) correlated positively with development of dilated esophagus, while age at diagnosis ≥ 65 years (OR, 0.706 [95% CI, 0.578-0.863]) correlated negatively with development of dilated esophagus (Supplementary Table 2).

Types of esophagus per each grade of esophageal dilation was compared in Figure 1B. The prevalence of sigmoid (including advanced sigmoid) esophagus was less than that of straight esophagus in patients with grade I (n = 183; 11.8%) and grade II (n = 589; 30.2%) esophageal dilation. In contrast, the prevalence of sigmoid

Table 2. Characteristics of Patients With Non-dilated (Grade I) Esophagus and Dilated (Grade II and III) Esophagus (n = 3680)

Variables	Grade I (n = 1550)	Grade II (n = 1945)	*P*-value[a]	Grade III (n = 185)	*P*-value[b]	*P*-value[c]
Age at onset (yr)	44 (31, 62)	38 (27, 52)	< 0.001	38 (26, 45)	< 0.001	0.064
Age at onset < 40 yr	626 (40.4%)	1039 (53.4%)	< 0.001	106 (57.3%)	< 0.001	0.350
Duration of symptoms (mo)	48 (21, 122)	66 (26, 160)	< 0.001	86 (31, 235)	< 0.001	0.079
Duration of symptoms ≥ 10 yr	436 (28.1%)	654 (33.6%)	< 0.001	75 (40.5%)	< 0.001	0.062
Age at diagnosis (yr)	54 (40, 70)	49 (37, 64)	< 0.001	48 (39, 58)	< 0.001	0.327
Age at diagnosis ≥ 65 yr	537 (34.6%)	468 (24.1%)	< 0.001	28 (15.1%)	< 0.001	0.006
Sex (men)	676 (43.6%)	1048 (53.9%)	< 0.001	133 (71.9%)	< 0.001	< 0.001
Body mass index (kg/m^2)	20.6 (18.4, 23.1)	21.2 (18.9, 23.7)	< 0.001	22.4 (19.1, 25.4)	< 0.001	0.002
Body mass index ≥ 25 kg/m^2	202 (13.0%)	338 (17.4%)	< 0.001	54 (29.2%)	< 0.001	<0.001
Eckardt score	6 (4,7)	6 (4, 8)	0.001	6 (4, 8)	0.150	0.898
Eckardt score ≥ 7	545 (36.7%)	761 (40.2%)	0.042	82 (46.1%)	0.019	0.151
Type I achalasia on HRM[d]	520 (45.5%)	942 (61.8%)	< 0.001	79 (74.5%)	< 0.001	0.009
IRP on HRM[e]	27.3 (18.0, 38.4)	26.8 (17.8, 38.0)	0.412	25.2 (17.0, 36.5)	0.243	0.408
IRP ≥ 26 mmHg on HRM[e]	751 (55.5%)	836 (53.1%)	0.206	52 (47.3%)	0.115	0.274

[a]*P*-value was calculated between grade I and grade II.
[b]*P*-value was calculated between grade I and grade III.
[c]*P*-value was calculated between grade II and grade III.
[d]Type I achalasia was analyzed in patients with type I, type II, and type III achalasia on high-resolution manometry (HRM).
[e]Integrated relaxation pressure (IRP) was measured in patients who underwent HRM for diagnosis (n = 3035).
Number of missing values: 2 for body mass index and 128 for Eckardt score.
The esophagography findings of 2 patients were excluded due to inadequate measurement of esophageal dilation.

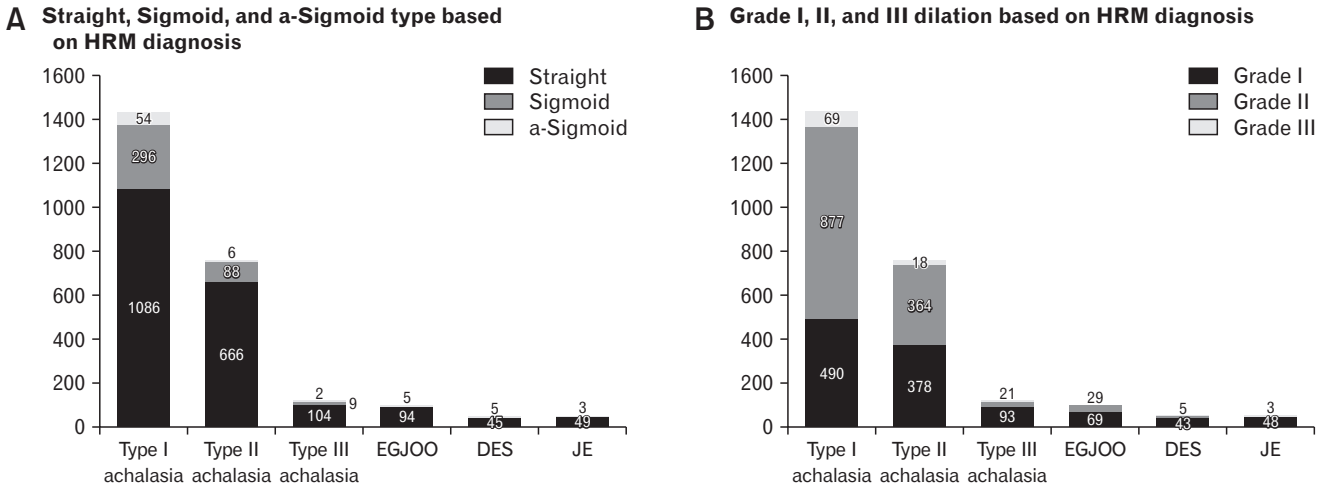

Figure 2. Correlation between esophagography and high-resolution manometry (HRM) findings. (A) Straight, sigmoid, and advanced sigmoid esophagus based on diagnosis using HRM. (A) Straight, sigmoid, and advanced sigmoid esophagus based on diagnosis using high-resolution manometry (HRM). A total of 2512 patients diagnosed using Starlet HRM and esophagography are analyzed. Sigmoid esophagus and advanced sigmoid esophagus are found mostly in patients with type I or type II achalasia ($P < 0.001$). (B) Grades I, II, and III esophageal dilation based on diagnosis using HRM. In total, 2510 patients who underwent Starlet HRM and esophagography are analyzed. Grades II and III esophageal dilation are found mostly in patients with type I or type II achalasia ($P < 0.001$).

(including advanced sigmoid) esophagus was greater than that of straight esophagus in patients with grade III esophageal dilation (n = 112; 60.5%).

Sigmoid and Dilated Esophagus Are Common in Type I and II Achalasia on High-resolution Manometry

The prevalence of straight esophagus, sigmoid esophagus, and advanced sigmoid esophagus were compared in cases with HRM diagnosis (Fig. 2A). Sigmoid esophagus and advanced sigmoid

Table 3. Characteristics of Patients With Esophageal Diverticulum (n = 63) in Achalasia-related Esophageal Motility Disorders (n = 3682)

Variables	Cases of esophageal diverticulum (n = 63)	Controls (n = 3619)[a]	*P*-value
Age at onset (yr)	59 (40, 66.5)	40 (28, 56.0)	< 0.001
Age at onset < 40 yr	15 (23.8%)	1756 (48.5%)	< 0.001
Duration of symptoms (mo)	105.5 (66.8, 191.5)	64.5 (20.8, 186.0)	0.219
Duration of symptoms ≥ 10 yr	24 (38.1%)	1141 (31.5%)	0.330
Age at diagnosis (yr)	70 (56.5, 75.0)	50 (38.0, 66.0)	< 0.001
Age at diagnosis ≥ 65 yr	39 (61.9%)	995 (27.5%)	< 0.001
Sex (men)	40 (63.5%)	1818 (50.2%)	0.050
Body mass index (kg/m^2)	20.8 (18.1, 23.6)	20.9 (18.7, 23.6)	0.933
Body mass index ≥ 25 kg/m^2	14 (22.2%)	580 (16.0%)	0.250
Eckardt score	5 (3.8, 6.3)	6 (4.0, 8.0)	0.004
Eckardt score ≥ 7	15 (25.0%)	1374 (39.3%)	0.034
Type I achalasia on HRM[b]	12 (35.3%)	1529 (55.8%)	0.026
IRP on HRM	23.8 (15.5, 34.9)	27.1 (17.9, 38.0)	0.100
IRP ≥ 26 mmHg on HRM	26 (44.8%)	1613 (54.1%)	0.202
Sigmoid-type achalasia[c]	13 (20.6%)	871 (24.1%)	0.629
Grade of esophageal dilation ≥ II	18 (29.0%)	2112 (58.4%)	< 0.001

[a]Controls were defined as patients without esophageal diverticulum on esophagography.
[b]Type I achalasia was analyzed in patients with type I, type II, and type III achalasia on high-resolution manometry (HRM).
[c]Sigmoid-type achalasia includes advanced sigmoid-type achalasia.
IRP, integrated relaxation pressure.
Number of missing values: 2 for body mass index and 128 for Eckardt score.
The esophagography findings of 2 patients were excluded due to inadequate measurement of esophageal dilation.

Table 4. Factors Associated With Incidence of Esophageal Diverticulum in Patients With Achalasia (n = 63)

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age at onset < 40 yr	0.332 (0.185-0.594)	< 0.001	1.320 (0.527-3.310)	0.553
Duration of symptoms ≥ 10 yr	1.330 (0.799-2.230)	0.270		
Age at diagnosis ≥ 65 yr	4.240 (2.540-7.090)	< 0.001	5.670 (2.320-13.90)	< 0.001
Sex (men)	1.720 (1.030-2.880)	0.040	1.550 (0.758-3.160)	0.230
Body mass index ≥ 25 kg/m^2	1.490 (0.819-2.720)	0.191		
Body mass index < 18.5 kg/m^2	1.460 (0.845-2.510)	0.176		
Eckardt score ≥ 7	0.516 (0.287-0.930)	0.028	0.708 (0.323-1.550)	0.388
Type I achalasia on HRM[a]	0.432 (0.213-0.876)	0.020	0.517 (0.244-1.110)	0.086
IRP ≥ 26 mmHg on HRM	0.691 (0.410-1.170)	0.166		
Sigmoid-type achalasia	1.020 (0.496-2.100)	0.954		
Grade of esophageal dilation ≥ II	0.282 (0.142-0.558)	< 0.001	0.397 (0.183-0.864)	0.020

[a]Type I achalasia on high-resolution manometry (HRM) was analyzed in patients with type I, type II, and type III achalasia.
IRP, integrated relaxation pressure.

esophagus were mostly observed in patients with type I or type II achalasia, and they were rarely observed in patients with type III achalasia, EGJOO, DES, or JE ($P < 0.001$). The prevalence of grades I, II, and III esophageal dilation were also compared in cases with HRM diagnosis, and grades II and III dilation were observed only in patients with type I or type II achalasia ($P < 0.001$) (Fig. 2B).

Esophageal Diverticulum Is Observed in Elderly Patients With Non-dilated Esophagus

The characteristics of patients with ED (n = 63) are shown in Table 3. Age at onset, age at diagnosis, Eckardt score, type I achalasia on HRM, and grade of esophageal dilation ≥ II were found to be factors associated with ED development. Multivariate analysis revealed that age at diagnosis ≥ 65 years correlated positively with ED development (OR, 5.670 [95% CI, 2.32-13.90]), while grade of esophageal dilation ≥ II correlated negatively with ED development (OR, 0.397 [95% CI, 0.183-0.864]) (Table 4).

Assessment of the 63 patients with ED revealed that ED was right-sided, left-sided, and multiple in 35, 22, and 6 patients, respectively (Table 5). All patients with multiple lesions had right-sided and left-sided EDs (Supplementary Fig. 4). Duration of symptoms was longer and IRP was lower in patients with right-sided ED than in patients with left-sided ED ($P = 0.042$ and $P = 0.008$, respectively). Patients with multiple EDs had lower Eckardt scores than patients with a single ED ($P = 0.022$).

Discussion

This large-scale multicenter study of achalasia-related EMDs revealed that development of sigmoid esophagus is associated with long disease history, advanced age at diagnosis, obesity, low symptom severity, type I achalasia, and low IRP values. On the other hand, early onset, low age at diagnosis, male sex, obesity, and type I achalasia were found to be associated with the development of dilated esophagus. It was also found that grade II esophageal dilation is common, while grade III esophageal dilation and advanced sigmoid esophagus are rare. ED was observed in 1.7% of patients, and it was found to be associated with advanced age at diagnosis and non-dilated esophagus. Further, this study clarified the difference in etiology between right-sided, left-sided, and multiple EDs.

This is the first study to report detailed characteristics of patients with sigmoid esophagus and patients with advanced sigmoid esophagus. The prevalence of straight, sigmoid, and advanced sigmoid esophagus decreased gradually, and the rate of dilated esophagus increased in sigmoid and advanced sigmoid esophagus by degrees, indicating that the development of sigmoid esophagus and advanced sigmoid esophagus rather reflects disease progression. Multivariate analysis of factors such as long disease duration and advanced age at diagnosis supports the hypothesis. Low IRP values and type I achalasia diagnosed using HRM were also shown to be statistically significant factors. Type I achalasia is reported to represent progression from type II achalasia[17,18] meaning that type I has a longer disease duration, even though available published data and the bulk of clinical experience do not suggest progression from

Table 5. Characteristics of Patients With Right-side, Left-side, and Multiple Esophageal Diverticulum

Variables	Right side (n = 35)	Left side (n = 22)	*P*-value[a]	Both sides, multiple (n = 6)	*P*-value[b]
Age at onset (yr)	61.0 (35.0, 69.0)	56.5 (46.8, 65.0)	0.902	59.0 (40.0, 67.0)	0.925
Duration of symptoms (mo)	120 (60.0, 364.0)	93.5 (24.3, 124.3)	0.042	40.5 (21.8, 93.8)	0.182
Age at diagnosis (yr)	73.0 (62.0, 78.5)	65.5 (52.3, 71.0)	0.064	60.5 (55.3, 71.0)	0.460
Sex (men)	26 (74.3%)	11 (50.0%)	0.113	3 (50.0%)	0.660
Body mass index (kg/m^2)	21.9 (18.0, 23.3)	20.2 (17.9, 23.6)	0.575	23.9 (22.7, 25.4)	0.085
Eckardt score	5.0 (4.0, 7.0)	5.0 (4.0, 6.0)	0.885	3.0 (2.3, 3.0)	0.022
Type I achalasia on HRM[c]	7 (46.7%)	5 (29.4%)	0.467	0 (0.0%)	1.000
IRP on HRM (mmHg)	16.4 (13.0, 26.2)	28.5 (23.0, 35.7)	0.008	41.0 (26.1, 50.1)	0.090
Sigmoid-type achalasia[d]	5 (27.8%)	5 (26.3%)	1.000	2 (33.3%)	0.595
Grade of esophageal dilation ≥ II	5 (27.8%)	7 (36.8%)	0.728	1 (16.7%)	0.662

[a]*P*-value was calculated between patients with right-side esophageal diverticulum and patients with left-side esophageal diverticulum.
[b]*P*-value was calculated between patients with a single esophageal diverticulum and patients with multiple esophageal diverticula.
[c]Type I achalasia was analyzed in patients with type I, type II, and type III achalasia on high-resolution manometry (HRM).
[d]Sigmoid-type achalasia includes advanced sigmoid-type achalasia.
IRP, integrated relaxation pressure.

type III achalasia to type I or II achalasia.[19] Low IRP values with impaired LES distensibility have been observed relatively more in cases of type I achalasia than in other types.[20] Likewise, type I achalasia reflected low IRP values in sigmoid esophagus in the present study. Symptom severity decreased in patients with sigmoid esophagus, indicating that sigmoid esophagus can pool the liquid and food in the esophagus despite that a straight esophagus regurgitates additional food and liquid instead of pooling them. This finding may be related to increased obesity in patients with sigmoid esophagus.

Esophageal dilation (grade II and grade III) has not been analyzed using a large-scale database. The results of this study clearly show that dilated esophagus is common, even though grade III esophageal dilation is rare. Multivariate analysis revealed differences in early onset, male sex and age at diagnosis between patients with esophageal dilation (grades II and III) and patients with sigmoid esophagus. Our study results may indicate that excessive ingestion of food or drink causes esophageal dilation, especially in young and middle-aged men. Hence, we can predict achalasia onset based on esophagography findings of sigmoid and dilated esophagus together even though a patient's recollection of achalasia onset may not be entirely accurate. Furthermore, there is no consensus on the definition of megaesophagus in patients with achalasia;[21] we found in our study that the proportion of patients with advanced sigmoid esophagus and grade III esophageal dilation together is 1.3%, which may match the rate of megaesophagus.

Our HRM-based analysis revealed that sigmoid and dilated esophagus occurred mostly in patients with type I or type II achalasia. Although we do not have a definitive explanation for this finding, types I and II achalasia can be differentiated from other achalasia-related EMDs pathologically.[2,17,18]

In this study, 63 out of 3682 patients with achalasia-related EMDs (1.7%) had ED. Right-side ED was common, and multiple ED was not rare; these findings are comparable to those of a previous study.[22] The etiologies of right-sided ED and left-sided ED remain unknown. In general, the right side of the esophagus is considered more susceptible to ED development than the left side of the esophagus due to the relative weakness of mediastinal structures.[22] On the other hand, spontaneous rupture of the esophagus (Boerhaave syndrome) usually (in 90% of cases) occurs in the lower third and in the left lateral aspect of the esophagus, and it is believed to be caused by anatomical weakness at the point and a rapid rise in intraluminal pressure in the distal esophagus.[23] The interplay between structural vulnerability and intraluminal pressure in the esophagus may explain the differences between right-sided, left-sided, and multiple EDs. Disease progression to multiple EDs had inverse correlation with the symptom severity, suggesting that they can pool the additional liquid and food in the esophagus rather than single EDs.

We recognize some limitations in this study. First, this is a cross-sectional study, and to identify causal relationships in cases of dilated esophagus, sigmoid esophagus, and ED, it is necessary to follow the natural courses of these pathological conditions. However, following the natural course is problematic because symptomatic patients need to receive optimal treatment. Second, the study has a retrospective design, and there were missing values of some baseline characteristics (eg, BMI and Eckardt score), which constitutes a potential source of bias. However, the proportion of missing values was small and can be compensated for by the large-scale database. Considering the retrospective design of our study, the detailed technique of esophagography may not have been completely unified across all institutions; thus subsequent prospective study using a unified technique and interpretation is necessary to further elucidate the etiology of achalasia.[24]

In conclusion, we provide useful clinical data on dilated esophagus, sigmoid esophagus, and ED in patients with achalasia-related EMDs. The etiologies of these pathological conditions are considered different and multifactorial.

Supplementary Materials

Note: To access the supplementary material, tables, and figures mentioned in this article, visit the online version of *Journal of Neurogastroenterology and Motility* at http://www.jnmjournal.org/, and at https://doi.org/10.5056/jnm21188.

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