Original Article

Subtype of Achalasia and Integrated Relaxation Pressure Measured Using the Starlet High-resolution Manometry System: A Multicenter Study in Japan

Tetsuya Tatsuta,[1] Hiroki Sato,[2,3]* Yusuke Fujiyoshi,[4] Hirofumi Abe,[5] Akio Shiwaku,[6] Junya Shiota,[7] Chiaki Sato,[8] Masaki Ominami,[9] Yoshitaka Hata,[10] Hisashi Fukuda,[11] Ryo Ogawa,[12] Jun Nakamura,[13] Yuichiro Ikebuchi,[14] Hiroshi Yokomichi,[15] Shinsaku Fukuda,[1] and Haruhiro Inoue[4]

[1]Department of Gastroenterology and Hematology, Hirosaki University Graduate School of Medicine, Aomori, Japan; [2]Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Niigata, Japan; [3]Division of Allergy and Immunology, Cincinnati Children's Hospital Medical Center, OH, USA; [4]Digestive Diseases Center, Showa University Koto-Toyosu Hospital, Tokyo, Japan; [5]Department of Gastroenterology, Kobe University Hospital, Kobe, Japan; [6]Department of Gastroenterological Surgery, Fukuoka University Faculty of Medicine, Fukuoka, Japan; [7]Department of Gastroenterology and Hepatology, Nagasaki University Hospital, Nagasaki, Japan; [8]Division of Advanced Surgical Science and Technology, Tohoku University School of Medicine, Sendai, Japan; [9]Department of Gastroenterology, Osaka City University Graduate School of Medicine, Osaka, Japan; [10]Department of Medicine and Bioregulatory Science, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan; [11]Division of Gastroenterology, Department of Medicine, Jichi Medical University, Shimotsuke, Japan; [12]Department of Gastroenterology, Faculty of Medicine, Oita University, Oita, Japan; [13]Department of Endoscopy, Fukushima Medical University Hospital, Fukushima, Japan; [14]Division of Gastroenterology and Nephrology, Department of Multidisciplinary Internal Medicine Tottori University Faculty of Medicine, Yonago, Japan; and [15]Department of Health Sciences, University of Yamanashi, Yamanashi, Japan

Background/Aims
ManoScan and Sandhill high-resolution manometry (HRM) systems are used worldwide; however, the diagnosis of achalasia on the Starlet HRM system is not fully characterized. Furthermore, the impact of calcium channel blockers and nitrites in treating achalasia has not been investigated using HRM. Management of recurrent cases is a priority issue, although few studies have examined patient characteristics.

Methods
We conducted a multicenter, large-scale database analysis. First, the diagnosis of treatment-naive achalasia in each HRM system was investigated. Next, patient characteristics were compared between type I-III achalasia, and the impact of patient characteristics, including calcium channel blocker and nitrite use for integrated relaxation pressure (IRP) values, were analyzed. Finally, patient characteristics with recurrent achalasia were elucidated.

Results
The frequency of type I achalasia with Starlet was significantly higher than that with ManoScan and Sandhill HRM systems. In achalasia, multivariate analysis identified male sex, advanced age, long disease duration, obesity, type I achalasia, and sigmoid type as risk factors related to normal IRP values (< 26 mmHg). Calcium channel blockers and nitrites use had no significant impact on the IRP values, although achalasia symptoms were indicated to be alleviated. In recurrent cases, the IRP value was significantly lower, and advanced age, long disease duration, and sigmoid type were more common than in treatment-naive patients.

Conclusions
We should cautiously interpret the type of achalasia and IRP values in the Starlet HRM system. Symptoms of recurrent cases are related to disease progression rather than IRP values, which should be considered in decision making.
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Key Words
Calcium channel blockers; Esophageal achalasia; Manometry; Nitrites; Risk factors

*Correspondence: Hiroki Sato, MD, PhD

Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, 757-1, Asahimachidori, Chuo-ku, Niigata City, Niigata 951-8510, Japan

Tel: +81-25-223-2207, Fax: +81-25-223-0776, E-mail: pyloki-sato@med.niigata-u.ac.jp

Introduction

Achalasia is a well-known esophageal motility disorder (EMD) characterized by the degeneration of the Auerbach plexus.[1] Recently, high-resolution manometry (HRM) was developed,[2,3] and achalasia was clearly defined as an EMD with impaired lower esophageal sphincter (LES) relaxation and no normal esophageal peristalsis.[4] Using the ManoScan HRM system, the Chicago classification categorizes achalasia into 3 subgroups based on the type of esophageal contraction: type I, 100% failed peristalsis; type II, pan-pressurization; and type III, spastic contraction (Supplementary Fig. 1).[4] ManoScan and Sandhill HRM systems are used worldwide,[5] and patients' characteristics between type I, II, and III achalasia have been clarified in Western countries using these systems.[6,7]

In the Starlet HRM system, mainly used in Japan, the cutoff points of several parameters have been reported in healthy volunteers.[8,9] Integrated relaxation pressure (IRP) is the most important parameter in HRM findings for evaluating LES relaxation, and IRP values of Starlet were reported to have different cutoff points from ManoScan.[8] However, limited information is available about the difference in IRP values between Starlet and others in patients with achalasia.

In Japan, data on the characteristics of patients with type I, II, and III achalasia are scarce,[10] and relevant data should be evaluated using the Starlet HRM system to establish a diagnosis and treatment strategy. Achalasia is typically diagnosed with high IRP values in HRM systems.[6] In contrast, data of achalasia patients with normal IRP values have been reported.[11,12] Clarifying the characteristics of normal IRP values in achalasia on Starlet is an urgent issue because they are difficult to diagnose. Further, calcium channel blockers and nitrites are commonly used for comorbidities such as hypertension and cardiovascular disease. Although previous reports have shown their efficacies to treat achalasia as they are expected to lower the LES pressure,[13,14] there is no recent investigation of the impact of these drugs using HRM.

Similar to treatment-naive cases, the management of recurrent cases is a priority issue, although few studies have examined patient characteristics, including HRM findings. In achalasia, therapeutic efficacy is not perfect, with balloon dilation (BD) having an efficacy of 56.8-90.0%[1,15-17] and Heller myotomy (HM) having an efficacy of 77.6-95.0%.[1,16-18]

Achalasia is a rare disease with an incidence of 1.0 per 100 000 person-years.[19,20] Thus, a single-center study cannot provide a statistically significant number of cases. Therefore, we planned a multicenter study involving high-volume centers in Japan to study a large number of cases. In this study, using the database, achalasia subtypes in each HRM system were investigated. Next, patient characteristics, including IRP values and the impact of medication with calcium channel blocker and nitrite, were analyzed in achalasia. Finally, the characteristics of patients with recurrent achalasia were elucidated.

Materials and Methods

Patients

This study was conducted at 13 high-volume centers as part of a more retrospective cohort study of EMD cases, including achalasia (Japan Achalasia multicenter study; JAMS).[21,22] The study protocol was approved by the ethics committee of the respective institutions (Supplementary Table 1). In JAMS, EMD cases diagnosed using standard methods, including HRM, esophagography, and esophagogastroscopy, and treated between 2010 and 2020 were recruited. Among them, cases of achalasia diagnosed using HRM were analyzed in this study.

This study was conducted according to the tenets set in the Declaration of Helsinki. Informed consent was obtained in the form of an opt-out system on the website. All authors had access to the study data and reviewed and approved the final manuscript.

Data Collection and Variables

A multicenter, large-scale database of patients with EMDs was created. The survey items included the following: age at onset and diagnosis of EMDs, duration of symptoms, sex, body mass index (BMI), Eckardt score, HRM diagnosis, IRP values, calcium

channel blocker use, nitrite use, esophageal dilation, and type of achalasia. In general, calcium channel blocker and nitrite are used for hypertension and coronary artery disease; therefore, their uses were considered regardless of the purpose. HRM was performed under continuous calcium channel blocker and nitrite use.

The Eckardt score, calculated as the sum of the respective 3-point scores for dysphagia, regurgitation, chest pain, and weight loss, was used to assess symptom severity.[18] A higher score reflects more severe symptoms of achalasia (maximum: 12), whereas a lower score indicates milder symptoms (minimum: 0). The HRM diagnosis was based on the Chicago classification version 3.0.[4] To assess deglutitive LES relaxation, IRP was measured as the lowest 4-second cumulative pressure values that occurred during a 10-second post-deglutition time window in the electronically generated e-sleeve signal through the anatomic zone defining the esophagogastric junction.[23] On Starlet (Starmedical Ltd, Tokyo, Japan), IRP of $\geq$ 26 mmHg was defined as a high IRP value indicating incomplete LES relaxation.[9] IRP values between several HRM systems were converted to Starlet criteria, following the formula previously reported.[9,11,24] The diagnosis of achalasia with normal IRP was made comprehensively using the typical findings of esophagogra-

phy as bird-beak appearance with the retention of contrast medium and endoscopy as the appearance of rosette-like esophageal folds.[25] The degree of esophageal dilation was classified as grade I ($<$ 3.5 cm), grade II (3.5-6.0 cm), or grade III ($\geq$ 6.0 cm) according to the diameter of the esophageal lumen on esophagography.[26] The type of achalasia was defined as straight or sigmoid. Sigmoid-type achalasia was classified based on esophageal flexion (α) findings (α $<$ 135°).[26]

Study 1: Analysis of the Risk Factors Associated With Integrated Relaxation Pressure Value

A total of 3583 patients with achalasia-related EMDs were registered at 13 hospitals. First, to clarify the difference in achalasia diagnosis between Starlet, ManoScan, and Sandhill HRM systems, 2109 treatment-naive achalasia patients were selected, excluding 649 patients diagnosed using esophagography and endoscopy only and 579 patients with prior treatment. The frequencies of type I, II, and III achalasia were compared between HRM systems. We used propensity score matching method to confirm the validity of this analysis. Propensity scores were calculated using logistic regression analysis. Sex and age were used as matching factors.
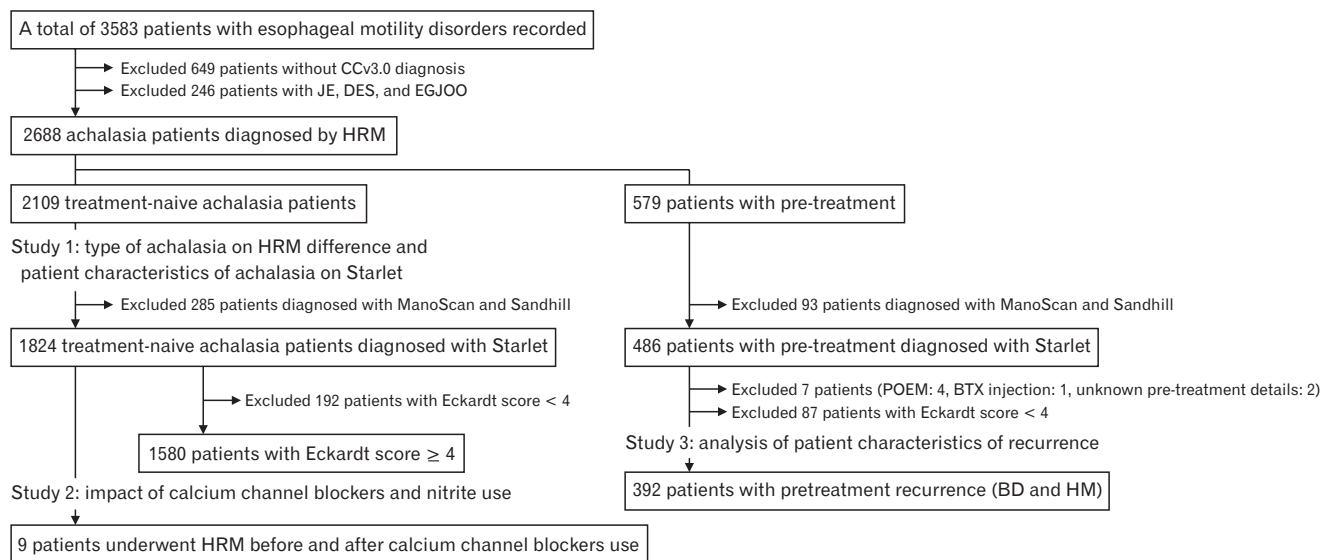
Figure. Study flowchart. A total of 3583 patients with esophageal motility disorders (EMDs) were registered in 13 hospitals. Study 1 was performed in 2109 patients to clarify the differences in achalasia diagnoses between Starlet, ManoScan, and Sandhill high-resolution manometry (HRM) systems. Furthermore, to analyze the characteristics of patients with type I, II, and III achalasia diagnosed using HRM, a total of 1824 treatment-naive patients with achalasia diagnosed using Starlet HRM were selected. Study 2 was performed to investigate the impact of calcium channel blocker and nitrate use. Nine patients underwent HRM before and after medication. Study 3 was performed to clarify the etiology of symptom recurrence, and 392 patients with Eckardt score $\geq$ 4 after achalasia interventions (344 cases with balloon dilation [BD] and 48 cases with Heller myotomy [HM]) were selected; among treatment-naive patients recruited in Study 1, patients with Eckardt score $\geq$ 4 were assigned to the control group. CCv3.0, Chicago classification version 3.0; JE, Jackhammer esophagus; DES, Distal esophageal spasm; EGJOO, Esophagogastric junction outflow obstruction; POEM, peroral endoscopic myotomy; BTX, botulinum toxin.

Second, to analyze the characteristics of patients with type I, II, and III achalasia diagnosed using Starlet HRM, a total of 1824 treatment-naive achalasia patients diagnosed using Starlet HRM were selected. We compared patient characteristics including sex, age at onset, age at diagnosis, disease duration, Eckardt score, BMI, IRP values, calcium channel blocker use, nitrite use, esophageal dilation, and type of achalasia between type I-III achalasia. A flowchart of the study is shown in Figure.

Study 2: Impact of Calcium Channel Blocker and Nitrate Use for Integrated Relaxation Pressure Value

Using this database, we examined the impact of calcium channel blocker use and nitrate use on IRP values and severity of symptoms in treatment-naive patients with achalasia. Further, patients who received these medications and underwent HRM before and after the treatment were retrieved. Change of IRP values and severity of symptoms, and incidence of adverse events were investigated.

Study 3: Analysis of the Risk Factors Associated With Recurrence After Achalasia Intervention

To clarify the etiology of symptom recurrence, 392 patients with Eckardt scores of ≥ 4 after achalasia interventions (344 patients with BD and 48 patients with HM) were selected from 579 patients who underwent pretreatment. We defined these patients as recurrent cases in this study. Among treatment-naive patients recruited in Study 1, patients with Eckardt scores of ≥ 4 were assigned to the control group. Patient characteristics and findings of achalasia including IRP values were compared between recurrent cases and controls.

Statistical Methods

Continuous values (age, duration of symptom, BMI, and IRP) were treated as categorical variables according to common cut-off points to facilitate interpretation. Categorical values were compared using Pearson's χ^2 test and Fisher's exact test, whereas comparisons of 2 groups with correspondence were assessed using the Wilcoxon

signed-rank test. Univariate and multivariate logistic regression models were used to determine the risk factors associated with normal IRP values, and odds ratios (ORs) and 95% confidence intervals (CIs) were computed. In multivariate analysis, we included factors with P-values of < 0.05 in the univariate analysis. In Study 3, we analyzed the correlation between severity of dysphagia and IRP values using Spearman's rank correlation coefficient.

All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[27] All reported P-values were 2-sided, and P-values of < 0.05 was considered statistically significant.

Results

Discrepancies in Achalasia Diagnosis Among the High-resolution Manometry Systems

The frequency of type I, II, and III achalasia was significantly different between Starlet, ManoScan, and Sandhill HRM systems (Table 1). The prevalence of type I achalasia was significantly higher in the Starlet group (1073/1824, 58.8%) than in the ManoScan and Sandhill groups (37/285, 13.0%) ($P < 0.001$), whereas the rate of type II achalasia was significantly lower in the Starlet group (663/1824, 36.3%) than in the ManoScan and Sandhill groups (218/285, 76.5%) ($P < 0.001$). Similarly, the rate of type III achalasia in the Starlet group (88/1824, 4.8%) was significantly lower than that in the ManoScan and Sandhill groups (30/285, 10.5%) ($P < 0.001$). In contrast, ManoScan and Sandhill HRM systems did not significantly differ in type I, II, and III achalasia diagnoses.

Propensity score matching yielded 285 matched pairs. The frequency of achalasia was significantly different among these HRM systems even after matching patients' background including sex and age (Table 2).

Table 1. Comparison of High-resolution Manometry Diagnosis Between the Starlet and Other High-resolution Manometry Systems in Treatment-naive Achalasia Patients (N = 2109)

Subtype of achalasia	Starlet (n = 1824)	ManoScan and Sandhill (n = 285)	P-value	ManoScan (n = 60)	Sandhill (n = 225)	P-value (Starlet vs ManoScan)	P-value (Starlet vs Sandhill)	P-value (ManoScan vs Sandhill)
Type I achalasia	1073 (58.8%)	37 (13.0%)	< 0.001	6 (10.0%)	31 (13.8%)	< 0.001	< 0.001	0.522
Type II achalasia	663 (36.3%)	218 (76.5%)	< 0.001	47 (78.3%)	171 (76.0%)	< 0.001	< 0.001	0.864
Type III achalasia	88 (4.8%)	30 (10.5%)	< 0.001	7 (11.7%)	23 (10.2%)	0.029	0.003	0.813

Table 2. Comparison of High-resolution Manometry Diagnosis Between the Starlet and Other High-resolution Manometry Systems Before and After Propensity Score Matching

Variables	Before matching			After matching		
	Starlet (n = 1824)	ManoScan and Sandhill (n = 285)	P-value	Starlet (n = 285)	ManoScan and Sandhill (n = 285)	P-value
Type I achalasia	1073 (58.8%)	37 (13.0%)	< 0.001	215 (75.4%)	37 (13.0%)	< 0.001
Type II achalasia	663 (36.3%)	218 (76.5%)	< 0.001	59 (20.7%)	218 (76.5%)	< 0.001
Type III achalasia	88 (4.8%)	30 (10.5%)	< 0.001	11 (3.9%)	30 (10.5%)	0.003
Sex (male)	919 (50.4%)	124 (43.5%)	0.035	140 (49.1%)	124 (43.5%)	0.208
Age at diagnosis (mean [SD])	49.7 (17.0)	52.0 (18.5)	0.036	54.1 (17.5)	52.0 (18.5)	0.173

Table 3. Characteristics of Treatment-naive Achalasia Patients Diagnosed Using the Starlet High-resolution Manometry System (n = 1824)

Variables	Type I (n = 1073)	Type II (n = 663)	Type III (n = 88)	P (Type I vs II)	P (Type I vs III)	P (Type II vs III)
Sex (male)	540 (50.3%)	330 (49.8%)	49 (55.7%)	0.843	0.375	0.309
Age at onset (≥ 40 yr)	538 (50.1%)	339 (51.1%)	69 (78.4%)	0.693	< 0.001	< 0.001
Age at diagnosis (≥ 65 yr)	231 (21.5%)	125 (18.9%)	51 (58.0%)	0.199	< 0.001	< 0.001
Disease duration (≥ 10 yr)	283 (26.4%)	145 (21.9%)	22 (25.0%)	0.039	0.900	0.497
Eckardt score (≥ 4)[a]	937 (89.9%)	575 (89.4%)	68 (78.2%)	0.742	0.002	0.004
Dysphagia	1033 (99.1%)	633 (98.4%)	87 (100.0%)	0.236	1.000	0.617
Regurgitation	945 (90.7%)	583 (90.7%)	74 (85.1%)	> 0.999	0.092	0.125
Chest pain	682 (65.5%)	452 (70.3%)	48 (55.2%)	0.042	0.062	0.007
Weight loss	656 (63.0%)	384 (59.7%)	42 (48.3%)	0.197	0.008	0.049
BMI (≥ 25 kg/m^2)	152 (14.2%)	102 (15.4%)	16 (18.2%)	0.485	0.343	0.532
IRP (< 26 mmHg)	572 (53.3%)	193 (29.1%)	31 (35.2%)	< 0.001	0.001	0.264
Calcium channel blocker use[a]	63 (12.5%)	24 (9.8%)	12 (23.1%)	0.331	0.052	0.017
Nitrite use[a]	14 (2.8%)	7 (2.9%)	1 (1.9%)	> 0.999	>0.999	> 0.999
Esophageal dilation (≥ II)	708 (66.0%)	331 (49.9%)	15 (17.0%)	< 0.001[a]	< 0.001	< 0.001
Type of achalasia (sigmoid)	227 (21.2%)	72 (10.9%)	9 (10.2%)	< 0.001[a]	0.013	> 0.999

[a]Missing values of Eckardt score: 52. Calcium channel blocker use and nitrite use are analyzed in 798 and 796 patients, respectively. Esophageal dilation: the grade of esophageal dilation based on maximum transverse diameter (d) using barium esophagogram. Grade I: d < 3.5 cm, grade II: 3.5 cm ≤ d < 6.0 cm, grade III: d ≥ 6.0 cm.
BMI, body mass index; IRP, integrated relaxation pressure.

Difficult-to-Diagnose Achalasia With a Normal Integrated Relaxation Pressure Value on the Starlet High-resolution Manometry System

Using the Starlet HRM system, 1824 treatment-naive achalasia patients were diagnosed, and patient characteristics between type I, II, and III achalasia were compared (Table 3). The sex ratio did not differ significantly between type I, II, and III achalasia. On the other hand, age at onset and diagnosis was significantly higher in type III achalasia than in type I and II achalasia (P < 0.001). The rate of chest pain was significantly higher in type II (452/663, 70.3%) than in type I (682/1,073, 65.5%; P = 0.042) and type III achalasia (48/88, 55.2%; P = 0.007). In addition, the rate

of normal IRP values was significantly higher in type I achalasia (572/1073, 53.3%) than in type II (193/663, 29.1%) (P < 0.001) and type III (31/88, 35.2%) (P = 0.001).

Next, the characteristics of patients and findings of achalasia with normal (< 26 mmHg) and elevated IRP values (≥ 26 mmHg) were compared, as shown in Table 4. Statistical differences were observed in sex (P = 0.042), age at onset ≥ 40 years (P = 0.002), age at diagnosis ≥ 65 years (P = 0.009), disease duration ≥ 10 years (P < 0.001), Eckardt score ≥ 4 (P = 0.045), BMI ≥ 25 kg/m^2 (P = 0.002), type I achalasia (P < 0.001), esophageal dilation ≥ II (P = 0.002), and sigmoid achalasia (P < 0.001). Calcium channel blocker and nitrate use were not significantly different between groups with normal and elevated IRP values.

Risk factors associated with normal IRP values ($<$ 26 mmHg) are shown in Table 5. In the univariate analysis, statistical differences were observed in sex ($P = 0.038$), age at onset $\geq$ 40 years ($P = 0.002$), age at diagnosis $\geq$ 65 years ($P = 0.008$), disease duration $\geq$ 10 years ($P < 0.001$), Eckardt score ($P = 0.045$), BMI $\geq$ 25 kg/m^2 ($P = 0.002$), type I achalasia ($P < 0.001$), esophageal dilation $\geq$ II ($P = 0.002$), and sigmoid achalasia ($P < 0.001$). In the multivariate analysis, male sex (OR, 1.270; 95% CI, 1.040-1.550),

age at onset $\geq$ 40 years (OR, 1.530; 95% CI, 1.220-1.920), disease duration $\geq$ 10 years (OR, 1.880; 95% CI, 1.480-2.380), BMI $\geq$ 25 kg/m^2 (OR, 1.430; 95% CI, 1.080-1.890), type I achalasia (OR, 2.710; 95% CI, 2.200-3.340), and sigmoid achalasia (OR, 1.570; 95% CI, 1.200-2.070) were identified as risk factors for normal IRP values ($<$ 26 mmHg).

Efficacy of Calcium Channel Blockers for Relaxing the Lower Esophageal Sphincter Could Not Be Determined With High-resolution Manometry

Nine patients received calcium channel blockers for achalasia and also conducted HRM examination before and after treatment in our cohort (Table 6). Due to adverse events, including nausea, vertigo, and headache, 2 patients could not continue with the medication (defined as failure). The other 7 cases received medication therapy for a median of 38 days (range 25-125 days). After treatment, achalasia symptoms were ameliorated in 4 cases but did not change in 3 cases. In case 2, due to the tight LES even after calcium channel blocker administration, the catheter did not pass through the LES. There was no significant difference between IRP values before and after administration in 6 cases (median IRP value; before administration 30.1 mmHg [20.6-34.5], after 28.8 mmHg [21.6-35.9]; $P = 0.063$).

We compared the Eckardt score between the calcium channel blocker group (n = 87), nitrite group (n = 12), and the treatment-naive group without these medications (n = 671) (Supplementary Table 2). Total Eckardt scores did not differ significantly between these groups. On the other hand, the prevalence of regurgitation

Table 4. Characteristics of Treatment-naive Achalasia Patients With Normal and Above the Cutoff Integrated Relaxation Pressure Values

Variables	IRP < 26 mmHg	IRP ≥ 26 mmHg	P-value
Sex (male)	423 (53.1%)	496 (48.2%)	0.042
Age at onset (≥ 40 yr)	446 (56.0%)	500 (48.6%)	0.002
Age at diagnosis (≥ 65 yr)	201 (25.3%)	206 (20.0%)	0.009
Disease duration (≥ 10 yr)	246 (30.9%)	204 (19.8%)	< 0.001
Eckardt score (≥ 4)	675 (84.8%)	905 (88.0%)	0.045
BMI (≥ 25 kg/m^2)	141 (17.7%)	129 (12.5%)	0.002
Type I achalasia	557 (72.1%)	484 (48.5%)	< 0.001
Calcium channel blocker use	39 (12.6%)	60 (12.5%)	>0.999
Nitrite use	6 (1.9%)	16 (3.3%)	0.276
Esophageal dilation (≥ II)	492 (61.8%)	562 (54.7%)	0.002
Type of achalasia (sigmoid)	182 (22.9%)	126 (12.3%)	< 0.001

Missing values of Eckardt score: 52. Calcium channel blocker use and nitrite use are analyzed in 798 patients and 796 patients, respectively. Esophageal dilation: the grade of esophageal dilation based on maximum transverse diameter (d) using barium esophagogram. Grade I: d < 3.5 cm, grade II: 3.5 cm ≤ d < 6.0 cm, grade III: d ≥ 6.0 cm.
IRP, integrated relaxation pressure; BMI, body mass index.
Data are presented as n (%).

Table 5. Risk Factors Associated With Normal Integrated Relaxation Pressure ($<$ 26 mmHg) in Treatment-naive Achalasia Patients

Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Sex (male)	1.220 (1.010-1.460)	0.038	1.270 (1.040-1.550)	0.020
Age at onset (≥ 40 yr)	1.350 (1.120-1.620)	0.002	1.530 (1.220-1.920)	< 0.001
Age at diagnosis (≥ 65 yr)	1.350 (1.080-1.6800)	0.008	0.980 (0.748-1.280)	0.886
Disease duration (≥ 10 yr)	1.810 (1.460-2.240)	< 0.001	1.880 (1.480-2.380)	< 0.001
Eckardt score ≥ 4	0.758 (0.579-0.993)	0.045	0.753 (0.546-1.040)	0.084
BMI (≥ 25 kg/m^2)	1.500 (1.160-1.940)	0.002	1.430 (1.080-1.890)	0.012
Type I achalasia	2.690 (2.210-3.270)	< 0.001	2.710 (2.200-3.340)	< 0.001
Calcium channel blocker use	0.987 (0.641-1.520)	0.951		
Nitrite use	1.750 (0.675-4.510)	0.250		
Esophageal dilation (≥ II)	1.340 (1.110-1.620)	0.002	1.060 (0.860-1.310)	0.569
Type of achalasia (sigmoid)	2.120 (1.650-2.720)	< 0.001	1.570 (1.200-2.070)	0.001

Esophageal dilation: the grade of esophageal dilation based on maximum transverse diameter (d) using barium esophagogram. Grade I: d < 3.5 cm, grade II: 3.5 cm ≤ d < 6.0 cm, grade III: d ≥ 6.0 cm.
BMI, body mass index.

Table 6. Analysis of the Efficacy of Calcium Channel Blockers for Integrated Relaxation Pressure Values on High-resolution Manometry

Case	Sex	Age (yr)	Type of achalasia	IRP mmHg (before administration)	Medication (dosage, mg/day)	Adverse events	Symptoms (after)	IRP mmHg (after administration)
Case 1	Female	40	Type II	33.4	Nifedipine (10)	Nausea, vertigo	No change	35.5 (failure)
Case 2	Male	39	Type I	32.1	Nifedipine (10)		No change	Unmeasurable
Case 3	Female	50	Type I	20.6	Nifedipine (20)		No change	28.3
Case 4	Female	52	Type I	24.3	Nifedipine (10)		Improved	34.7
Case 5	Female	46	Type I	34.5	Nifedipine (10)		Improved	35.9
Case 6	Male	37	Type II	30.7	Nifedipine (10)	Nausea, headache		(Failure)
Case 7	Male	49	Type II	29.4	Nifedipine (20)		Improved	28.8
Case 8	Female	46	Type II	23.2	Diltiazem (60)		Improved	24.2
Case 9	Male	72	Type I	25.1	Diltiazem (90)		No change	26.6

Integrated relaxation pressure (IRP) values have no significant difference on calcium channel blocker use ($P = 0.063$, Wilcoxon signed-rank test).
Failure: in 2 cases, due to adverse events, including nausea, vertigo, and headache, these patients could not continue the medication therapy. Unmeasurable, due to the tight lower esophageal sphincter (LES) even after the medication therapy, the catheter did not pass through the LES.
IRP, integrated relaxation pressure.

Table 7. Comparison of Patients' Characteristics Between Recurrent and Treatment-naive Achalasia Patients[a]

Variables	Failure of BD (n = 344)	Failure of HM (n = 48)	Treatment-naive (n = 1580)	P (BD vs HM)	P (BD vs naive)	P (HM vs naive)
Sex (male)	163 (47.4%)	24 (50.0%)	800 (50.6%)	0.760	0.285	1.000
Age at onset ($\geq$ 40 yr)	163 (47.4%)	8 (16.7%)	792 (50.1%)	< 0.001	0.372	< 0.001
Age at presentation ($\geq$ 65 yr)	90 (26.2%)	19 (39.6%)	324 (20.5%)	0.059	0.025	0.003
Disease duration ($\geq$ 10 yr)	145 (42.2%)	43 (89.6%)	369 (23.4%)	< 0.001	< 0.001	< 0.001
BMI ($\geq$ 25 kg/m^2)	55 (16.0%)	10 (20.8%)	236 (14.9%)	0.408	0.619	0.303
Type I achalasia	245 (71.2%)	39 (81.2%)	937 (59.3%)	0.169	< 0.001	0.002
IRP (< 26 mmHg)	228 (66.3%)	40 (83.3%)	675 (42.7%)	0.020	< 0.001	< 0.001
Calcium channel blocker use	26 (19.3%)	4 (22.2%)	81 (11.7%)	0.756	0.024	0.256
Nitrite use	6 (4.4%)	0 (0.0%)	20 (2.9%)	1.000	0.415	1.000
Esophageal dilation ($\geq$ II)	214 (62.2%)	28 (58.3%)	945 (59.8%)	0.636	0.430	0.882
Type of achalasia (sigmoid)	91 (26.5%)	20 (41.7%)	263 (16.6%)	0.039	< 0.001	< 0.001

[a]Recurrent cases are defined as patients having Eckardt score $\geq$ 4 after achalasia interventions, and patient characteristics are compared between these patients and treatment-naive patients having Eckardt score $\geq$ 4.
Esophageal dilation: the grade of esophageal dilation based on maximum transverse diameter (d) using barium esophagogram. Grade I: d < 3.5 cm, grade II: 3.5 cm $\leq$ d < 6.0 cm, grade III: d $\geq$ 6.0 cm. Calcium channel blocker use and nitrite use are analyzed in 845 patients and 841 patients, respectively.
BD, balloon dilatation; HM, Heller myotomy; BMI, body mass index; IRP, integrated relaxation pressure.

and chest pain were significantly lower in the group with calcium channel blockers than in the medication-free group ($P = 0.013$ and $P = 0.005$, respectively).

Etiology of Symptoms Are Different in Recurrent Achalasia Cases Compared With Treatment-naive Cases

Patient characteristics between 392 cases of recurrent achalasia and 1580 treatment-naive achalasia cases were compared in Table 7. The IRP value was significantly lower in recurrent cases after BD and HM than in treatment-naive patients ($P < 0.001$ and P < 0.001, respectively). The rate of disease duration $\geq$ 10 years and sigmoid achalasia was significantly higher in recurrent cases after BD and HM than in treatment-naive patients ($P < 0.001$ and $P < 0.001$, respectively).

The correlations between severity of dysphagia and IRP values in treatment-naive patients and cases after HM and BD are shown in Supplementary Figure 2. Although there was a significant positive correlation between IRP value and dysphagia in each group, the value of the correlation coefficient was small less than 0.2 (Treatment-naive cases; $r = 0.068$, $P = 0.004$. Cases after HM and BD; $r = 0.180$, $P < 0.001$).

Discussion

This large-scale multicenter study revealed that the frequency of type I, II, and III achalasia in the Starlet HRM system was significantly different from that of the ManoScan and Sandhill systems. In the Starlet HRM system, normal IRP values were not rare, even in treatment-naive achalasia patients. Therefore, multivariate analysis for the normal IRP value was conducted, and male sex, late-onset, long disease duration, obesity, type I achalasia, and sigmoid type were determined as risk factors. Further, our cohort showed no evidence of the efficacy of calcium channel blocker and nitrite use in reducing the IRP values. In recurrent achalasia patients, advanced age, long disease duration, and sigmoid achalasia were characteristic.

The ManoScan HRM system has a catheter with solid-state sensors spaced at 1-cm intervals (Given Imaging, Ltd, Yoqneam, Israel); each sensor of the catheter has 12 circumferential sensors. The pressure is detected by individual sensors, and the mean pressure is recorded as a representative value.[8,28] In contrast, the Starlet HRM system using a Unisensor catheter (Unisensor AG, Attikon, Switzerland) also has solid-state sensors spaced at 1-cm intervals, although the sensor is unidirectional and covered by circumferential soft membranes with fluid inside. The pressure acts on the membrane and is transferred to the fluid so that the sensors perceive the average luminal pressure.[29] Such structural differences may cause the difference in the diagnosis of achalasia.

Previous studies using a pneumohydraulic perfusion manometry system and ManoScan HRM system have shown that type II is the most prevalent achalasia type.[6,8] In contrast, our results showed that type I achalasia was the most frequent in Starlet. Using ManoScan, the treatment success rates of BD and HM were higher in type II achalasia patients than in type I or type III achalasia patients.[6,7] Conversely, type III achalasia patients were less likely to respond to therapies, including BD and HM, than type I patients.[6] However, our findings suggest that these results may not be the same for achalasia patients diagnosed using the Starlet HRM system because the frequency of type I, II, and III achalasia was significantly different from that of other HRM systems. Our results suggest that, on the Starlet HRM system, more patients with type I achalasia can be successfully treated.

Rohof et al[7] showed no significant differences in sex and age between type I, II, and III achalasia. In contrast, in our study, age at onset and diagnosis were significantly higher in type III achalasia than in type I and type II achalasia. It has been reported that chest

pain is more common in type II achalasia and that normal IRP values are more common in type I achalasia.[6] Our findings are consistent with this previous report, although the ratio of normal IRP values was significantly higher with the Starlet in our study. A previous study showed that the rate of achalasia with normal IRP diagnosed using ManoScan was 5.2%.[12] In our study, 43.6% of treatment-naive achalasia patients had normal IRP values. It is difficult to diagnose achalasia with normal IRP values;[30] therefore, to find the patient characteristics and findings of achalasia with normal IRP value is important. Male sex, late-onset, long disease duration, obesity, type I achalasia, and sigmoid type were identified as risk factors for achalasia with normal IRP in our study. Kim et al[31] reported that patients with normal IRP were older than those with elevated IRP using the Sandhill HRM system, supporting the determined risk factors in our study such as late-onset and long disease duration. Type I achalasia was reported to be the most common subtype in a group with normal IRP using the ManoScan and Starlet system.[13,30] Eckardt scores in patients with normal IRP were low or were not significantly different.[30,31] BMI values were reported to have no significant difference between the normal and high IRP groups,[31] however, our result indicates that obesity-related increased abdominal pressure reduce the LES pressure. Esophagogram recording video and timed barium esophagography may be useful in the diagnosis of these cases with normal IRP values.[30,32] Additionally, the use of impedance planimetry (EndoFLIP) has been recommended to assess achalasia with normal IRP.[32]

Our large-scale database analysis and case series of HRM before and after the medication showed no significant difference in IRP values between patients on calcium channel blockers or nitrites and those not on these drugs. In contrast, regurgitation and chest pain were slightly but significantly lower in patients who used calcium channel blockers than those who did not. Further, some patients experienced alleviation of symptoms after calcium channel blocker administration. We hypothesize that the effect of calcium channel blockers is not dependent on lowering the IRP values in HRM.

Refractory cases with BD were reported to be younger and have high LES pressure after treatment[17,33,34] that is possibly related with the high LES pressure before the treatment and failure of treatment procedure. In contrast, patients with long disease duration, sigmoid type, and low LES pressure were at risk of refractory cases with HM.[35] Our analysis shows that long disease duration and sigmoid type are characteristics of refractory cases with BD and HM. These findings are similar to the previous study above mentioned. Moreover, late onset is a risk factor for recurrence in our results, unlike previous findings. In addition, there were slight

correlations between dysphagia and the IRP values. These findings suggest that other factors may be involved in treatment recurrence instead of failure to relax LES. Additional treatment may be performed for recurrent cases with high IRP after BD or HM. On the other hand, we should consider decision-making for patients with low IRP after BD or HM instead of additional interventions because their recurrent symptoms are related with other factors such as disease progression.

There are several limitations to this study. First, although the HRM diagnosis was performed only by expert doctors in each facility, some discrepancies in HRM diagnosis might be present. Second, the patient's recollection of the age of onset and disease duration may not have been entirely accurate, and any potential misrepresentations may have affected our findings and interpretations. Third, the proportion of cohort studies related to calcium channel blockers was not large enough. Further large-scale prospective studies are necessary to determine the natural course of achalasia and arrive at a definitive conclusion regarding the efficacy of calcium channel blockers.

In conclusion, we should cautiously interpret the type of achalasia and IRP values in the Starlet HRM system for decision-making. Our findings indicate that calcium channel blockers may alleviate symptoms, although not by reducing IRP values. Recurrent cases of achalasia have different patient characteristics, and the best strategy should be determined based on this.

Supplementary Materials

Note: To access the supplementary 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/jnm21254.

Author contributions: Conception and design of study: Tetsuya Tatsuta and Hiroki Sato; acquisition of data: Yusuke Fujiyoshi, Hirofumi Abe, Akio Shiwaku, Junya Shiota, Chiaki Sato, Masaki Ominami, Yoshitaka Hata, Hisashi Fukuda, Ryo Ogawa, Jun Nakamura, and Yuichiro Ikebuchi; drafting the manuscript: Tetsuya Tatsuta and Hiroki Sato; and revising the manuscript critically for important intellectual content: Hiroshi Yokomichi, Shinsaku Fukuda, and Haruhiro Inoue.

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