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ORIGINAL ARTICLE

Clinical and high-resolution manometry of 801 patients with esophageal dysmotility, including achalasia, in relation to age

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Author contribution: Uday C Ghoshal contributed to study concept, design, data analysis, and writing the paper. Akshay Kulkarni contributed to collection of the data. Vivek V Shirol and Anshuman Elhence helped in data collection and critical input in the paper writing. Bushra Fatima, Anand Prakash Agrahari, and Asha Misra performing the esophageal manometry and helped during the data collection. All the authors read and approved the final version of the paper. Uday C Ghoshal and Akshay Kulkarni contributed equally to the work and are joint first authors of the paper.

Abstract

Background and Aim: Spectrum of esophageal motility disorders may differ according to age, but studies on this are scanty, contradictory, and included small number of patients. Accordingly, we retrospectively analyzed data of a large sample of patients to study the spectrum of esophageal motility disorders in relation to age, and to evaluate the clinical profile and high-resolution manometry parameters and achalasia subtypes according to Chicago IV criteria.
Methods: Of 909 patients evaluated by high-resolution water perfusion or solid-state manometry during a 3-year period, data on 801 were finally analyzed.
Results: Achalasia cardia was the commonest motility disorder of esophagus in this large study and type II was the commonest subtype. There was no difference in clinical and manometry parameters among elderly patients as compared to younger patients with achalasia. Type I achalasia patients less often had chest pain and tended to have nocturnal coughing spells more often, and patients with achalasia experiencing chest pain tended to have higher distal contractile integral (DCI) than those not having pain irrespective of age.
Conclusion: The clinical and high-resolution manometry parameters among young and elderly patients with esophageal motility disorders are quite comparable. However, these differed in relation to achalasia subtypes and symptoms. Type I achalasia patients less often had chest pain and those experiencing chest pain tended to have higher DCI values than those not having pain irrespective of age.

Introduction

Several disorders of esophageal motility pose considerable diagnostic and therapeutic challenges to the clinicians.[1–4] Moreover, the pathophysiology of these disorders is quite complex and may even change with the age and the duration of the disease.[5–10] Achalasia is the most common disorder of esophageal motility presenting with dysphagia.[11] Achalasia was subdivided into vigorous and classic subtypes previously based on the contraction amplitude in the body of the esophagus.[11] Currently, achalasia has been subclassified into type I, II, and III based on the distal contractile integral (DCI, the current matrix of esophageal contraction amplitude) and its distribution across the length of the esophageal muscles (either panesophageal or segmental pressurization) as per Chicago classification.[2] Some data suggest that these subtypes of achalasia may change over time from type III to type I and also non-achalasia motility disorders may evolve to achalasia.[5,9,10,12–14] However, the data on this issue are scanty.

The relationship between age, clinical features, and manometric patterns of esophageal motility disorders, including achalasia are scanty and contradictory.[15–18] Moreover, most of the available studies are based on conventional manometry and the older subtypes of achalasia (classic and vigorous) without the

use of the current matrices as defined by Chicago classification such as DCI, and integrated relaxation pressure (IRP); moreover, most of the earlier studies were undertaken on a small number of patients.[15–17] Accordingly, we undertook a retrospective analysis of the prospectively maintained data of a large cohort of patients with esophageal motility disorders with the following aims: (i) to study the spectrum of esophageal motility disorders in elderly and younger patients, and (ii) to evaluate the clinical profile and high-resolution manometry parameters and achalasia subtypes according to Chicago IV criteria among patients with achalasia cardia.

Methods

Prospectively maintained data of consecutive patients referred to a Gastrointestinal Pathophysiology and Motility Laboratory in a teaching university hospital in northern India for evaluation of clinically suspected esophageal motility disorders during a 3-year period (January 2017 to September 2020) were retrospectively analyzed. Demographic, clinical, and laboratory data were recorded in a questionnaire from the case files, electronic medical records, and Gastrointestinal Pathophysiology and Motility Laboratory records. Patients with incomplete records and those in whom a prior intervention was done for the treatment of the esophageal motility disorders were excluded. The study was performed in a manner to conform with the Helsinki Declaration of 1975, as revised in 2000 and 2008, concerning the human rights. Waiver from the Institute Ethics Committee was obtained (IEC code: 2023-78-DM-130).

Esophageal manometry. High-resolution manometry (HRM) was performed either with a solid-state system with 36 sensors (SandHill Scientific, Colorado, USA) or a 16-channel water perfusion system (developed by Dr. Geoff Hebbard, Melbourne, Australia). In each HRM, the patient was asked to take 10 wet swallows of 5 mL each in supine position, while a transnasal catheter recorded the findings. The HRM was performed according to standard technique. HRM tracings were analyzed using Bioview Analysis software (Sandhill Scientific Ltd. Milwaukee, USA) for tracing obtained from solid-state system and Trace 1.3.3 software (developed by Dr. Geoff Hebbard from Royal Melbourne Hospital, Melbourne, Australia) for tracings obtained from water perfusion system. Esophageal motility disorders were classified based on Chicago classification version 4.[2]

Statistical analysis. Data were checked for distribution using Shapiro–Wilk test. Categorical variables were presented as proportion and intergroup comparison of these data was performed by Chi-squared test with Yates' correction, as applicable or Fisher's exact test. Continuous parametric and nonparametric data were presented as mean, SD, median, and interquartile range (IQR), respectively. Comparison of parametric and nonparametric data of two groups was done by unpaired *t* and Mann–Whitney *U* tests, respectively. Such data of more than two groups were compared using one-way analysis of variance (ANOVA) and post hoc Schiffe test or Krushkal–Wallis *H* test based on the distribution. Correlation between two continuous variables was performed using Pearson's correlation method. *P* values of less than 0.05 were considered significant in all types of analysis. Statistical analysis was performed by R, EpiCalc, and R Studio software (R Development Core Team, Vienna, Austria), and MedCalc version 14 (Warandeberg 3, 1000 Brussels, Belgium), Orange (Bioinformatics Lab at University of Ljubljana, Slovenia), and Origin, version 9.8.5.201 (OriginLab Corporation, Northampton, MA, USA).

Results

Of the 909 patients initially screened for inclusion into the study, 108 were excluded due to either prior intervention ($n = 107$) and incomplete records ($n = 1$). Of the 801 patients (age 39.6 ± 15.0-years, 446 [55%] male) finally included in the analysis, solid-state and water-perfusion manometry studies were performed in 310 (38.7%) and 491 (61.3%), respectively. The diagnoses in these 801 patients included achalasia (450, 56%), ineffective esophageal motility disorders (120, 15.0% six of whom had scleroderma), esophagogastric junction outflow obstruction (27, 3.4%), diffuse esophageal spasm (8, 1%), absent contractility (5, 0.6%), and hypercontractile esophagus (1, 0.1%). A total of 190 (23.7%) patients had normal high-resolution esophageal manometry (Fig. 1). Demographic, clinical parameters and the diagnoses on high-resolution manometry in the age groups below and equal to or above 60 years are shown in Table 1.

The symptoms reported by 450 patients with achalasia included dysphagia (442, 98%), chest pain (223, 49.7%), regurgitation (331, 73.7%), weight loss (244, 54.3%), and nocturnal cough (59, 13%). Median Eckardt's score was 7 (range 2 to 11). The duration of symptoms reported by the patients was 30.8 ± 32.1 months.

Of the 450 patients with achalasia, one was excluded from some of the further analysis due to incomplete records. Among 449 achalasia patients, esophageal manometry was done using solid-state and water-perfusion system using 189 (42%) and 260 (58%) patients, respectively. Of them (age 38.6 ± 14.4-years, 252 [56%] male), 103 (22.9%) had type I, 312 (69.5%) had type II, 30 (6.7%) had type III, and four (0.9%) had variant achalasia (Fig. 1). For the purpose of all the analysis, the patients with variant achalasia were included with type III achalasia group.

Relationship between the clinical and manometry parameters in relation to age. Table 2 shows the demographic, clinical, and manometry parameters of the two age groups of achalasia patients. As seen from Table 2, there was no difference in clinical and manometry parameters among elderly patients as compared to younger patients with achalasia except for the achalsia subtype among the two subgroups.

Relationship between achalasia subtypes, symptoms, and manometry parameters. Table 3 presents the data on demographic, clinical, and manometry parameters of different subtypes of achalasia. As shown in Table 3, patients with type I achalasia less often had chest pain and tended to have nocturnal coughing spells more often. On HRM, LES pressure and DCI were lower among patients with type I than the other subtypes of achalasia. As shown in Figure 2, patients with

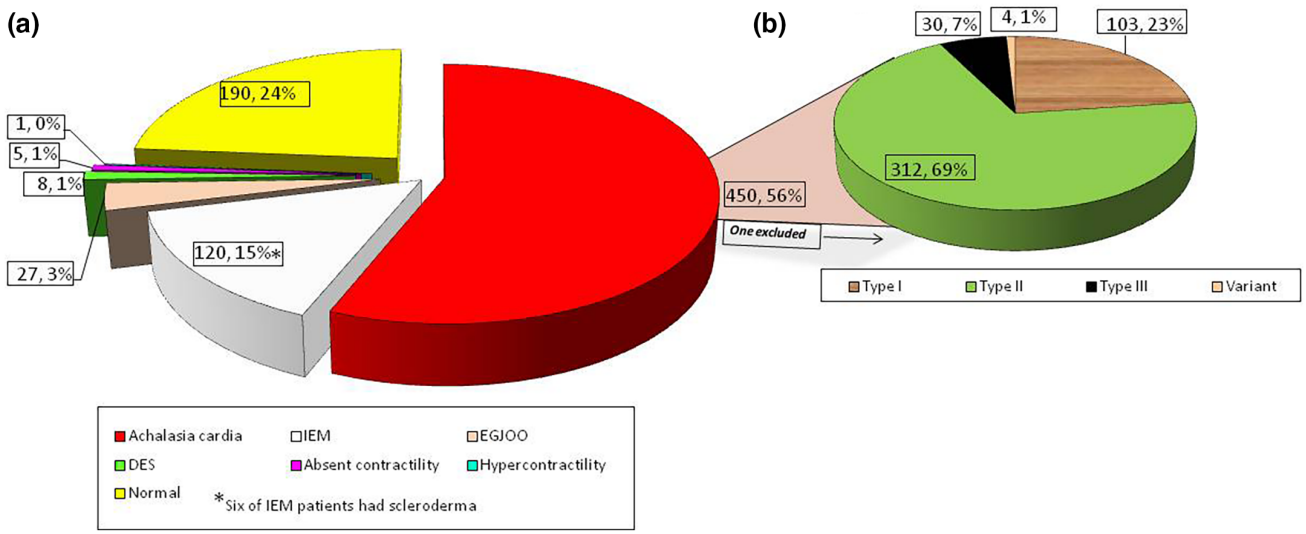

Figure 1 Showing spectrum of esophageal motility disorders on high-resolution manometry (a); and subtypes of achalasia cardia (b). DES, diffuse esophageal spasm; EGJOO, esophago-gastric outflow obstruction; IEM, ineffective esophageal motility; PSS progressive systemic sclerosis.

achalasia cardia experiencing chest pain tended to have higher DCI than those not having pain irrespective of age.

Relationship between age, symptoms, and manometry parameters among achalasia patients. Tables 2 and 4 present the data on demographic, clinical, and manometry parameters of achalasia patients in relation to age. As shown in Table 2, the clinical and manometry parameters were comparable between younger (<60 years) and older patients with achalasia, though the subtypes of the disease did differ in relation to age. Table 4 shows that the subtypes of achalasia rather than the age group were associated with the variation in the clinical and manometry parameters.

Table 1 Demographic, clinical, and laboratory characteristics of the patients with esophageal motility disorders in the two age groups

Parameters	Age <60-years ($n = 706$)	Age ≥60-years ($n = 95$)	*P* values
Gender (male)	385 (54.5%)	57 (60%)	0.37
Dysphagia (yes)	537 (76.1)	74 (77.9)	0.79
Chest pain (yes)	225 (31.9)	32 (33.7)	0.811
Regurgitation (yes)	440 (62.3)	56 (58.9)	0.601
Weight loss (yes)	228 (32.3)	27 (28.4)	0.52
Heartburn (yes)	104 (14.7)	11 (11.6)	0.505
Nocturnal cough (yes)	83 (11.8)	11 (11.6)	1
Eckardt score (median, IQR)	7 (6, 8)	7 (6, 8)	0.438
IRP (median, IQR)	21 (9, 33)	17 (9, 29.5)	0.323
Resting LES pressure (median, IQR)	22 (9.3, 37)	25 (4.9, 42)	0.891
DCI (median, IQR)	717.2 (245.1, 1760)	738 (288.5, 2130.2)	0.372
Diagnosis on HRM			
Type I achalasia	94 (13.3)	9 (9.5)	
Type II achalasia	284 (40.2)	29 (30.5)	
Type III achalasia	25 (3.5)	5 (5.3)	
Variant achalasia	4 (0.6)	0 (0)	
DES	4 (0.6)	4 (4.2)	0.01
EGJOO	23 (3.3)	4 (4.2)	
IEM	100 (14.2)	20 (21.0)	
Hypercontractile esophagus	0 (0)	1 (1.1)	
Absent contractility	5 (0.7)	0 (0)	
Normal	167 (23.7)	23 (24.2)	

DCI, distal contractile integral; DES, diffuse esophageal spasm; EGJOO, esophago-gastric outflow obstruction; IEM, ineffective esophageal motility; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

Table 2 Demographic, clinical, and laboratory characteristics of the patients with achalasia in the two age groups

Parameters	Age <60-years ($n = 404$)	Age ≥60-years ($n = 45$)	*P* values
Gender (male)	223 (55.2%)	28 (62.2%)	0.45
Dysphagia (yes)	398 (98.5)	43 (95.6)	0.187
Chest pain (yes)	195 (48.3)	28 (62.2)	0.105
Regurgitation (yes)	296 (73.3)	35 (77.8)	0.636
Weight loss (yes)	218 (54)	26 (57.8)	0.741
Heartburn (yes)	2 (0.5)	0 (0)	1
Nocturnal cough (yes)	53 (13.1)	6 (13.3)	1
Duration of symptoms (months; median, IQR)	18 (12, 36)	36 (8.2, 96)	0.131
Eckardt score (median, IQR)	7 (6, 8)	6 (5, 7.5)	0.07
IRP (median, IQR)	31 (23, 44)	29.5 (22.8, 41.5)	0.777
Resting LESP (median, IQR)	31.2 (17, 46)	30.2 (12.6, 51)	0.974
DCI (median, IQR)	744 (176, 2815.2)	653 (139, 2124.9)	0.919
Types of achalasia			
Type I	94 (23.3%)	9 (20%)	0.004
Type II	285 (70.5%)	27 (60%)	
Type III and variant	25 (6.2%)	9 (20%)	

DCI, distal contractile integral; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

Discussion

The current study on a large number of patients showed that, (i) achalasia is the commonest motility disorders among patients referred for esophageal manometry in a tertiary referral laboratory, (ii) type II achalasia is the commonest type, (iii) achalasia subtypes did differ in relation to age, (iv) type I achalasia patients less often had chest pain and tended to have nocturnal coughing spells more often, (v) patients with achalasia experiencing chest pain tended to have higher DCI than those not having pain irrespective of age, and (vi) subtypes of achalasia rather than the age group was associated with the variation in the clinical and manometry parameters.

There are scanty data on spectrum of esophageal motility disorders using high-resolution manometry.[11,19,20] In an earlier study from our centre at Lucknow, India using conventional manometry on 250 patients, 193 (77%) had achalasia cardia, 86% of whom had classic achalasia (which is similar to type I achalasia according to current Chicago classification).[11] Twenty (8%) of them had other esophageal motility disorders in this study (11 [4.4%] diffuse esophageal spasm, and 9 [3.6%] hypertensive lower esophageal sphincter); the other 37 (15%) had normal esophageal manometry.[11] In another study from Ludhiana, India on 401 patients, 217 of whom had dysphagia, 157 retrosternal discomfort and 27 regurgitation, underwent high-resolution water-perfusion manometry.[19] 44%, 26%, 7% and 19% of dysphagia patients had ineffective esophageal motility, achalasia cardia, diffuse esophageal spasm and normal manometry, respectively.[19] 43%, 6%, 6%, 4.5% and 42% patients with retrosternal discomfort had ineffective esophageal motility, achalasia cardia, diffuse esophageal spasm and normal manometry, respectively.[19] In a large study from USA on 397 patients, achalasia was the commonest motility disorder in 305 (77%) patients.[20] Current study is perhaps the largest study

Table 3 Demographic, clinical, and manometry parameters of different subtypes of achalasia

Parameters	Type 1 ($n = 103$)	Type 2 ($n = 312$)	Type 3 and variant ($n = 34$)	*P* value
Age (years, median, IQR)	35 (27.5, 47)	36 (28, 49)	36.5 (24.2, 50)	0.895
Gender (male)	54 (52.4)	178 (57.1)	19 (55.9)	0.715
Symptoms				
Dysphagia	101 (98.1)	307 (98.4)	33 (97.1)	0.589
Chest pain	21 (20.4)	177 (56.7)	25 (73.5)	<0.001
Regurgitation	73 (70.9)	231 (74)	27 (79.4)	0.602
Weight loss	50 (48.5)	182 (58.3)	12 (35.3)	0.015
Eckardt score (median, IQR)	7 (6, 8)	7 (6, 8)	6 (5, 7)	0.098
Nocturnal coughing spells	18 (17.5)	40 (12.8)	1 (2.9)	0.09
Duration of symptoms (months, median, IQR)	18 (12, 36)	24 (12, 36)	12 (6, 24)	0.139
Manometry parameters				
Resting LES pressure (mmHg, median, IQR)	16 (6.6, 30.7)	34 (23, 49)	33 (18.9, 51.5)	<0.001
IRP (mmHg, median, IQR)	30 (22, 38)	32 (24, 46)	28 (22, 39)	0.01
DCI (mmHg Cm S, median, IQR)	1 (0, 36)	1160.5 (522, 3641.2)	1043.5 (425, 2078.6)	<0.001

DCI, distal contractile integral; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

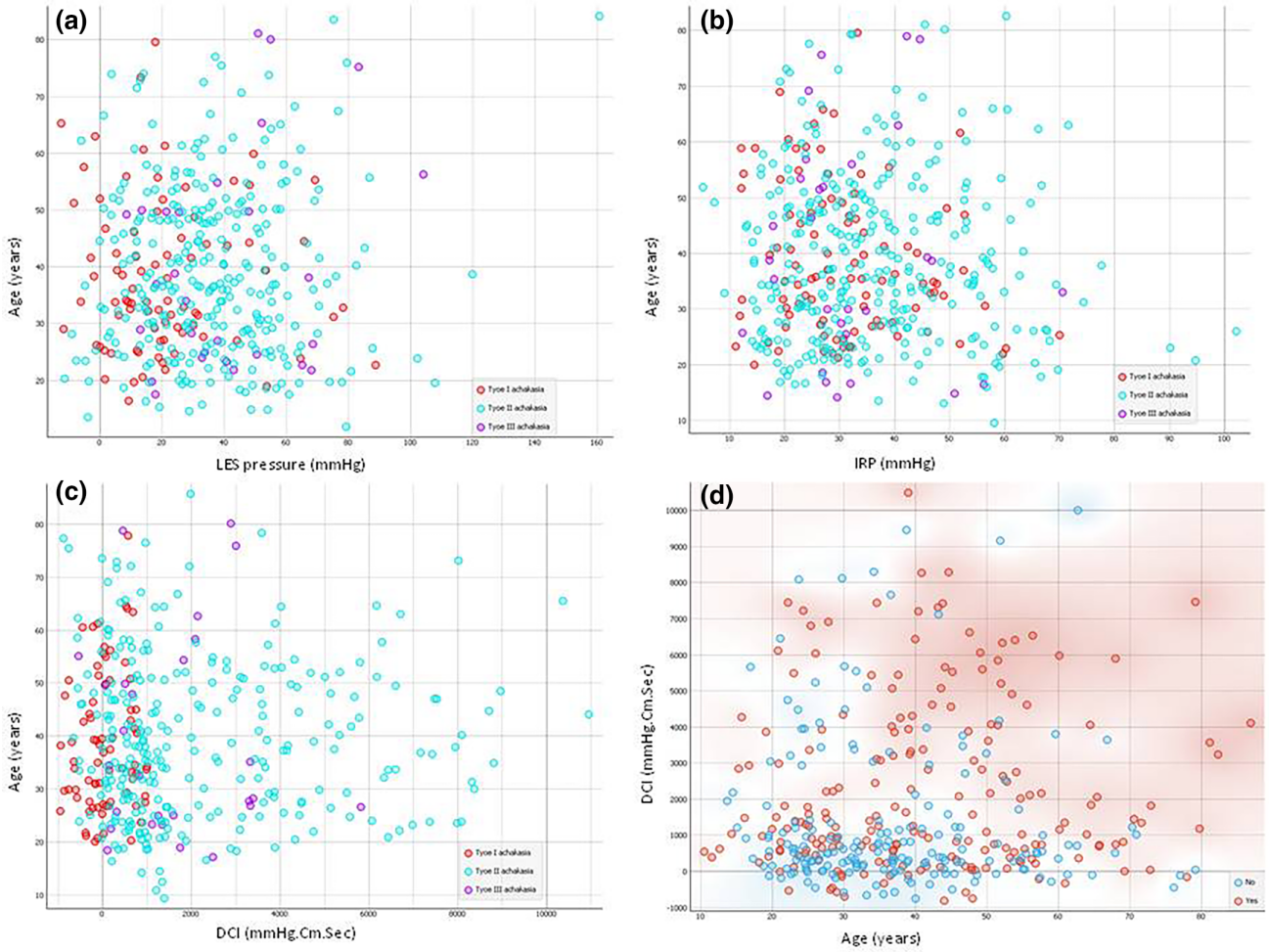

Figure 2 Relationship between high-resolution esophageal manometry parameters and age in relation to achalasia subtypes and presence or absence of chest pain. Relationship between age and lower esophageal sphincter (LES) pressure (a), integrated relxation pressure (IRP, b), distal contractile integral (DCI, c) in relation to achalasia subtypes are shown. (d) Relationship between age and DCI in relation to presence and absence of chest pain.

of esophageal motility disorders showing that achalasia is the commonest type of esophageal motility disorder among patients undergoing esophageal manometry study in a tertiary referral laboratory and type II achalasia is the commonest subtype.

Based on the pathogenesis, type I achalasia is more advanced disease associated with esophageal dilation, decompensation and failure of muscular contraction.[5] Accordingly, we hypothesized that older patients with achalasia, expectedly having greater duration of the disease, will differ in disease subtypes and manometry parameters than the younger patients. Type II achalasia tended to be commoner and type III and variant subtypes less common among younger patients than older people in our study (Table 2). Based on the disease pathogenesis,[5] type III may be considered to be the initial stage of achalasia and hence, commoner in younger patients, but in our study, it was more common in the elderly. This finding is difficult to explain. However, since duration of the disease was comparable among younger and elderly patients with achalasia (Table 2), the hypothesis of pathogenesis of different subtypes of achalasia is not contradicted by the findings of our study.[5] Moreover, despite a large sample size, patients with type III and variant achalasia subtypes were small in number raising a possibility of statistical error. There was no correlation between age and esophageal motility indices such as DCI, LES pressure, and IRP (Fig. 2). Data on relationship between age and achalasia subtypes and their manometry parameters are scanty in the World literature. In a Korean study on 103 achalasia patients, older age group patients (>60-years) with classic achalasia had higher basal LES pressure than the younger age group.[15] In Taiwanese study on 49 achalasia patients, older patients (>65-years) more often had higher basal LES pressure.[16] In an old study from USA, Clouse *et al.* compared clinical and manometry parameters of 13 elderly (≥70-years) and 79 younger patients with achalasia.[17] Elderly patients had chest pain in lesser frequency and severity than the younger patients.[17] Though the basal LES pressure was comparable in the two groups, post-deglutitive residual LES pressure was

Table 4 Demographic, clinical, and manometry parameters among young (<60 years) and elderly (≥60 years) patients with achalasia cardia categorized according to subtypes.

	≥60-years (n = 41)				<60-years (n = 409)			
	Type I (n = 9)	Type II (n = 27)	Type III/variant (n = 5)	P values	Type I (n = 94)	Type II (n = 286)	Type III/variant (n = 29)	P values
Symptoms								
Dysphagia	8 (88.9%)	27 (100%)	5 (100%)	0.34	93 (98.9%)	281 (98.3%)	28 (96.6%)	0.61
Chest pain	1 (11.1%)	20 (74.1%)	4 (80%)	0.002	20 (21.3%)	157 (55.1%)	21 (72.4%)	<0.001
Regurgitation	5 (55.6%)	24 (88.9%)	4 (80%)	0.086	68 (72.3%)	207 (72.6%)	23 (79.3%)	0.73
Weight loss	5 (55.6%)	19 (70.4%)	0 (0%)	0.015	45 (47.9%)	163 (57.2%)	12 (41.4%)	0.10
Nocturnal coughing spells	1 (11.1%)	5 (18.5%)	0 (0%)	0.82	17 (18.1%)	35 (12.3%)	1 (3.4%)	0.09
Manometry parameters								
Resting LES pressure (mmHg, median, IQR)	6 (4.2–24.6)	36.5 (24–51.8)	51.5 (49.2–56)	0.006	16.4 (7–31.4)	34 (23–48.1)	30 (17.1–45.5)	<0.001
IRP (mmHg, mean ± SD for ≥60-years, median, IQR for <60-years age group)	25 (6.7)	38.4 (15.1)	35 (10.4)	0.044	30 (22.2–40.8)	32 (24–45.5)	27 (22–32.8)	0.023
DCI (mmHg Cm S, median, IQR)	3 (1–211.5)	1147.2 (433.5–3198)	2004.2 (1569–2189.2)	0.003	1 (0–31)	1137.5 (518.5–3665.1)	913.5 (368.2–1641.8)	<0.001

DCI, distal contractile integral; IQR, interquartile range; IRP, integrated relaxation pressure; LES, lower esophageal sphincter.

lower in the older patients.[17] Another study from Mexico, comparing clinical and manometry parameters of 36 elderly (>60-years) and 123 younger patients with achalasia showed lesser frequency of chest pain in elderly patients.[18] However, basal LES pressure, residual LES pressure or the amplitude of the esophageal body contractions were comparable in the two age groups.[18] In another study from USA on 121 patients (73 ≥ 65 year in age), the authors found aperistalsis of obscure origin was commoner in elderly.[21] Our study on a large number of patients, however, did not show any difference in frequency of chest pain among older and younger patients with achalasia raising a possibility of type I statistical error in the former two studies due to relatively smaller sample size.[17,18] Our data suggest that chest pain is related to the subtype of achalasia with type II disease with greater esophageal muscular contractile vigor having chest pain more often than type I disease. Our findings showing patients with achalasia experiencing chest pain tending to have higher DCI than those not having pain irrespective of age, is quite expected. It has been quite well-documented that pain of esophageal motility disorders results from esophageal muscle spasm and type I achalasia patients with low esophageal contraction amplitude resulting from muscle atrophy are less likely to have chest pain.[22] Our data on a large number of patients showing subtypes of achalasia rather than the age group determining the variation in the clinical and manometry parameters may explain some of the contradictory observations in the earlier studies on small sample of patients.

The strengths of the present study include large sample size that mitigated the limitation of inadequate power of most of the earlier studies on this issue, and use of high-resolution rather than conventional manometry. The findings of our study on a large number of patients might suggest that variations in esophageal manometry parameters in some of the earlier studies[15–17] in relation to age, including a small number of patients, might be related to difference in subtypes of achalasia in different age groups rather than a true effect of age. The limitations include inclusion of patients from a single tertiary type referral center setting of the study, and retrospective analysis of the data. Despite these limitations, this study overcomes most of the limitations of all the earlier studies on this issue.

In conclusion, the current study on a large number of patients showed achalasia, particularly type II, to be the commonest motility disorder among patients referred for esophageal manometry in a tertiary referral laboratory. There was no difference in clinical and manometry parameters among elderly (≥60 years) and younger patients with achalasia except for difference in subtypes of disease with younger patients having type II and less often type III and variant subtypes. Type I achalasia patients less often had chest pain but more often had weight loss, and tended to have nocturnal coughing spells more often. Patients with achalasia experiencing chest pain tended to have higher DCI than those not having pain irrespective of age.

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