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Alimentary Tract

Diagnostic delay in achalasia

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ABSTRACT

Background: Achalasia is a rare disorder characterized by impaired esophageal motility and symptoms like dysphagia, regurgitation, chest pain, and weight loss. A timely diagnosis is crucial to adequately manage this condition.
Aims: This study aimed to assess the diagnostic delay from symptom onset to a definite diagnosis of achalasia, and to identify associated factors.
Methods: This retrospective, single-center study included patients diagnosed with achalasia between January 2013 and September 2023. Demographic data, symptoms, manometric, endoscopic, and radiological findings were collected. We also considered socio-economic deprivation. Early diagnosis was defined as occurring within 12 months of symptom onset, while late diagnosis was defined as occurring more than 12 months.
Results: We included 278 patients (142 males, median age 58 years). Dysphagia was the most common symptom (96 %), followed by regurgitation (70.1 %). The median diagnostic delay was 24 months (IQR 12–72, range 0–720), with 213 patients (76.6 %) experiencing late diagnosis. Early diagnosis was more common in patients with weight loss (63.1% *vs.* 42.0 %, $p = 0.003$). Lower material deprivation correlated with shorter diagnostic delay (24 months, IQR 10–60 vs. 60 months, IQR 18–300, $p = 0.001$).
Conclusions: Achalasia diagnosis is often delayed. Weight loss along with socio-economic factors, influence the timeliness of diagnosis. Improving awareness of disease and relevance of initial symptoms may facilitate earlier diagnosis and treatment.

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1. Introduction

Achalasia is a rare esophageal motility disorder which is characterized by the failure of the lower esophageal sphincter (LES) to relax and the absence of peristalsis in the esophagus [1]. Achalasia manifests through a constellation of symptoms including dysphagia, regurgitation of undigested food, chest pain, and unintended weight loss. These symptoms significantly impair quality of life and can lead to severe complications, if untreated [2]. The rarity of this condition and the non-specific nature of its early symptoms often lead to misdiagnosis or delayed diagnosis, contributing to prolonged patient suffering and progression of the disease [3,4].

High-resolution manometry (HRM) has emerged as a cornerstone in the diagnostic process of achalasia, allowing for a detailed assessment of esophageal motility [5,6]. Moreover, in doubtful cases, the use of timed barium swallow, the endoscopic functional lumen probe, and the addition of provocative maneuvers during HRM standard protocol, further refined our ability to correctly diagnose achalasia and establish adequate treatment [7–9].

However, despite these advancements in diagnostic technology, a significant lag between the onset of symptoms and definitive diagnosis persists [4,10,11]. This delay can be attributed to several factors, including initial presentation to non-specialists, the intermittent nature of early symptoms, or wrong attribution of symptoms to more common gastrointestinal disorders [4,12]. Moreover, a relationship between socio-economic status and inequalities in the utilization and distribution of healthcare resources and patient outcomes have been emerged in several conditions with a partic-

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ular significance in gastrointestinal diseases [13]. In our country, the National Health Care System is based on universal coverage and equal access for all citizens, and each region in Italy is responsible for organizing and delivering health services to its population, allowing for some regional variation in healthcare provision while maintaining overall national standards [13]. Nevertheless, several disparities persist and are often rooted in geographic, and economic factors, which can lead to significant variations in the availability and quality of healthcare services [14].

The aim of this study was to assess the diagnostic delay in patients with achalasia, as defined as the time interval from the self-reported onset of symptoms to the definitive diagnosis of the condition. A secondary aim was to identify demographic, clinical, and social factors contributing to the delay in diagnosing achalasia.

2. Patients and methods

This was a retrospective, single-center study involving the review of medical records from a ten-year period (January 2013 - September 2023) at the Gastroenterology Unit of IRCCS Policlinic San Martino Hospital. Patients were included if they were diagnosed with achalasia according to the Chicago Classification version 4.0 and underwent HRM during the study period. Exclusion criteria were previous esophageal surgery, presence of other esophageal motility disorders, or incomplete medical records.

Patient records were systematically reviewed for demographic information [age, gender, body mass index (BMI), and ethnicity], detailed medical history, and clinical presentation. Symptoms such as dysphagia, regurgitation, chest pain, and weight loss were specifically noted. The onset of symptoms was identified based on the patients recollections during their initial clinical evaluations. The severity of achalasia was quantified using the Eckardt score, a validated tool that assesses the severity of key symptoms [4]. This scoring system helped to categorize the patients according to the severity of their clinical presentation.

The diagnostic delay was calculated as the time interval from the self-reported onset of symptoms to the definitive diagnosis of achalasia. This interval was recorded in months and diagnosis was defined “early” when this interval was shorter than 12 months and “late” when was longer than 12 months, in line with the International Rare Diseases Research Consortium (IRDiRC) recommendation. The IRDiRC recommends that patients presenting with suspected rare diseases be diagnosed within one year, provided their condition is documented in medical literature [15].

In this retrospective study, all participant data were anonymized to protect individual privacy and ensure confidentiality.

2.1. High-resolution manometry, endoscopic and radiological evaluations

HRM was performed using a standardized protocol. The manometric findings were classified into one of the three achalasia subtypes as defined by the Chicago 4.0 classification [16,17]. The data from HRM were carefully reviewed and validated by two independent gastroenterologists (EM, AP) to ensure accuracy in classification.

Endoscopic findings were documented, focusing on signs indicative of achalasia including the presence of a dilated esophagus, retained food or saliva, and significant resistance to the passage of the endoscope through the esophagogastric junction [18]. Any available radiological imaging, such as barium swallow tests, was also reviewed and structural abnormalities indicative of achalasia, particularly the characteristic ’bird’s beak’ appearance at the esophagogastric junction, was considered [7]. These complementary tests were used to corroborate the HRM findings and provide a comprehensive assessment of the esophageal condition.

2.2. Material deprivation analysis

Material deprivation refers to the condition of lacking basic necessities and resources essential for an acceptable standard of living. This includes insufficient access to items such as adequate housing, food, clothing, healthcare, education, and other essential goods and services. Material deprivation is often used as an indicator of poverty and social inequality. The material deprivation of patients was calculated basing on a socio-economic deprivation index method which was previously developed in our region of Italy (Liguria). This method involves the construction of Socio-Economic and Health Deprivation Indexes using data from the 2011 Census at the Census Tract level and was based on variables that showed a statistically significant correlation with the standardized mortality ratios of overall mortality. The items considered were educational level and occupation, marital status, family size, and housing characteristics [19,20]. Patients were stratified into these groups: 1 = high deprivation; 2 = medium-high deprivation; 3 = medium deprivation; 4 = medium-low deprivation; 5 = low deprivation. The attribution to each group was allowed thanks to a map that associated residence with material deprivation. Material deprivation was further classified in significant (*i.e.*, high deprivation, medium-high deprivation, and medium deprivation) and non-significant (*i.e.*, medium-low deprivation and low deprivation).

2.3. Statistical analysis

The Kolmogorov-Smirnov test was used to determine if the variables were normally distributed. The median and 95 % confidence interval of the median were used to express the outcomes of continuous variables. Contingency tables were used to show the frequency and proportion of ordinal and nominal variables in the population. When comparing continuous variables between different patient groups, non-parametric Kruskal-Wallis or Mann-Whitney tests were used. Pearson’s χ^2-test and Spearman’s rank correlation index were applied to analyse the relationship between nominal variables and continuous variables. The Bonferroni correction was used to fit tests for all pairwise comparison. Logistic regression was employed to assess the impact of various predictors on dichotomous outcomes, allowing for the estimation of odds ratios and their confidence intervals.

The IBM SPSS Statistics, Release Version 25.0 (SPSS, Inc., 2017, Chicago, IL, USA, www.spss.com) and R (the R project, R version 3.4.3; R Foundation for Statistical Computing, Vienna, Austria and EZR: https://github.com/jinkim3/ezr) were used for the statistical analysis.

3. Results

From an initial sample of 340 patients suspected of achalasia, we excluded 30 patients who presented with recurrence of symptoms after treatment for achalasia in a different medical center, 32 patients with an unsatisfactory HRM evaluation due to impossibility to reach the stomach with the probe. Thus, our study population consisted of 278 patients, with a slightly higher prevalence of males (n = 142, 51.1 %), a median age at diagnosis of 58 years (IQR 43 – 71), and a median BMI of 23 kg/m^2 (IQR 21 – 26). Most patients were non-smokers (n = 208, 74.8 %) and their median alcohol intake was 0 alcoholic unit/day (IQR 0 – 1). The geographical distribution of the place of residence of the study patients across the Liguria region is shown in Fig. 1.

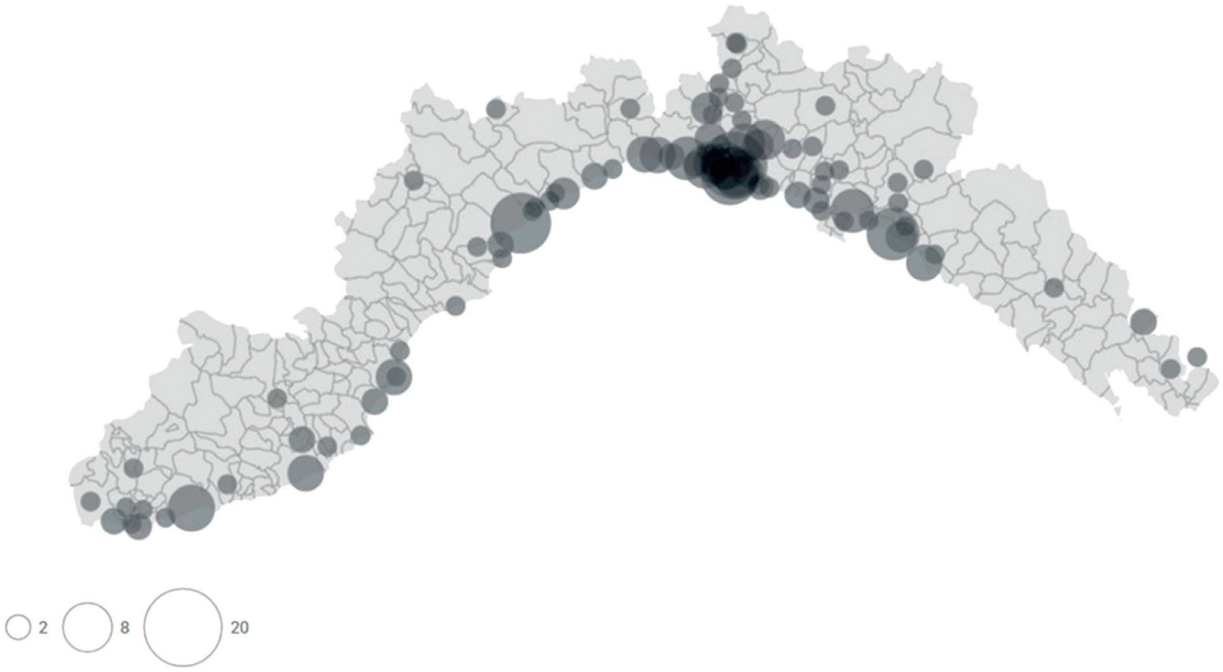

Fig. 1. Distribution of patients with achalasia across the Liguria region.

Table 1
Main symptoms reported by the study patients.

Symptoms	Patients (n = 278)
Dysphagia for solids	267 (96.0)
Dysphagia for liquids	202 (72.7)
Regurgitation	195 (70.1)
Weight loss	130 (46.9)
Chest pain	113 (40.6)
Cough	64 (23.0)
Heartburn	45 (16.2)
Epigastric pain	7 (2.5)

Data are reported as absolute number (frequency).

The most common symptom observed was dysphagia, which was reported in 267 patients (96.0 %), all of them presenting dysphagia for solids while 202 patients (72.7 %) also reported dysphagia for liquids. The other main symptoms were regurgitation (n = 195, 70.1 %), weight loss (n = 130, 46.9 %), and chest pain (n = 113, 40.6 %). Table 1 shows the symptoms reported by the study patients. Overall, the median Eckardt score was 5 (IQR 4 - 7).

The most common diagnosis was type 2 achalasia (n = 167, 60.1 %), followed by type 1 (n = 90, 32.4 %), and type 3 (n = 21, 7.6 %), while the median integrated relaxation pressure (IRP) was 35 (IQR 26 – 45) mmHg. Endoscopic findings suggestive for achalasia (*i.e.*, dilated esophagus, retained food or saliva, and significant resistance to the passage of the endoscope through the esophagogastric junction) and 'bird's beak' appearance at the esophagogastric junction radiological were present in 90 (38.1 %) and 116 patients (77.3 %), respectively.

3.1. Clinical predictors of diagnostic delay

The median diagnostic delay between onset of symptoms and final diagnosis of achalasia was 24 months (IQR 12 – 72), with 65 patients (23.4 %) who received an early diagnosis (*i.e.*, less than 12 months from the onset of symptoms), while 213 patients (76.6 %) received a late diagnosis (*i.e.*, more than 12 months from the onset of symptoms). Fifty-nine patients (21.2 %) had previously been diagnosed with gastroesophageal reflux disease, and were on long-term proton pump inhibitor therapy. The median diagnostic delay did not significantly change across the years (2012: 36, IQR 15 – 66; 2013: 2013: 36, IQR 24 – 90; 2014: 12, IQR 6 – 60; 2015: 36, IQR 8 – 120; 2016: 14, IQR 9 – 24; 2017: 24, IQR 11 – 70; 2018: 30, IQR 6 – 72; 2019: 25, IQR 12 – 120; 2020: 36, IQR 24 – 48; 2021: 12, IQR 6 – 36; 2022: 24, IQR 12 – 60; 2023: 60, IQR 15 – 100).

Table 2 shows the demographic and anthropometric characteristics, and the main symptoms reported by patients subdivided according to the presence of diagnostic delay. Patients with early diagnosis had a higher prevalence of weight loss (63.1% *vs* 42.0 %, p = 0.003) and had lower alcohol consumption (median daily alcohol units: 1 vs 0, p = 0.028) as compared to patients with late diagnosis. The median Eckardt score was significantly higher in patients with early diagnosis (score 6, IQR 5 - 7) as compared to those with late diagnosis group (score 5, IQR 4 - 7, p = 0.045). No significant differences were observed in HRM, endoscopic, and radiological findings between patients with early or late diagnosis (Table 3).

3.2. Diagnostic delay and material deprivation

The majority of patients had low material deprivation (medium-low: n = 113, 46.6 %; low: n = 86, 30.9 %), while 16 (5.8 %), 53 (19.1 %) and 10 patients (3.6 %) had medium, medium-high and high material deprivation, respectively. Thus, a total of 199 patients (71.6 %) resided in geographical areas with non-significant material deprivation, while 79 patients (28.4 %) resided in materially-deprived areas.

The diagnostic delay was longer in patients who lived in materially-deprived areas than those who lived in areas with a non-significant material deprivation (48 months, IQR 18 – 120 vs 24 months, IQR 9 – 60; $p < 0.001$, Fig. 2**A**). The diagnostic delay in the different material deprivation subgroups is shown in Fig. 2**B**. In particular, patients with low material deprivation had significantly shorter median diagnostic delay (24 months, IQR 10- 60) than both patients with medium-high (60 months, IQR 18 – 120; p = 0.001) and high material deprivation (60 months, IQR 36 – 300; p = 0.011), respectively). Moreover, patients with medium-

Table 2
General characteristics of the study patients subdivided according to diagnostic delay.

Characteristics	Early diagnosis (n = 65)	Late diagnosis (n = 213)	p
Gender, male	38 (58.5)	104 (48.8)	0.174
Median age, years	63 (49 – 72)	57 (42 – 70)	0.122
Median Body Mass Index, Kg/m^2	23 (20 – 26)	23 (21 – 26)	0.791
Median alcohol consumption, UI	0 (0 – 1)	1 (0 – 1)	**0.028**
Smoker, status			
Active	10 (15.4)	37 (17.4)	0.593
Former	10 (15.4)	23 (10.8)	
Symptoms			
Dysphagia for solids	64 (98.5)	203 (95.3)	0.253
Dysphagia for liquids	50 (76.9)	152 (71.4)	0.379
Regurgitation	46 (70.8)	149 (70)	0.900
Chest pain	24 (36.9)	89 (41.8)	0.485
Weight loss	41 (63.1)	89 (42.0)	**0.003**
Epigastric pain	1 (1.5)	6 (2.8)	0.565
Heartburn	9 (13.8)	36 (16.9)	0.558
Cough	14 (21.5)	50 (23.5)	0.746
Median Eckardt score	6 (5 – 7)	5 (4 – 7)	**0.045**

Data are shown as absolute value and frequency, and as median and interquartile range.

Table 3
Diagnostic features of the study patients sub divided according to diagnostic delay.

Characteristics	Early diagnosis (n = 65)	Late diagnosis (n = 213)	p
Median IRP, mmHg	40.0 (26.5 - 51.5)	35.0 (26.0 – 42.0)	0.260
Median LES basal pressure, mmHg	39.5 (24.0 – 50.0)	37.0 (25.5 - 54.5)	0.787
Type of achalasia			
1	19 (29.2)	71 (33.3)	0.680
2	42 (64.6)	125 (58.7)	
3	4 (6.2)	17 (8)	
Abnormal barium swallow findings[†]	23 (79.3)	93 (76.9)	0.777
Abnormal endoscopic findings[‡]	19 (37.3)	71 (38.4)	0.884

Data are shown as absolute value and frequency, and as median and interquartile range.
Abbreviations: IRP, integrated relaxation pressure; LES, lower esophageal sphincter;.
[†] dilated esophagus, retained food or saliva, and significant resistance to the passage of the endoscope through the esophagogastric junction.
[‡] 'bird's beak' appearance at the esophagogastric junction.

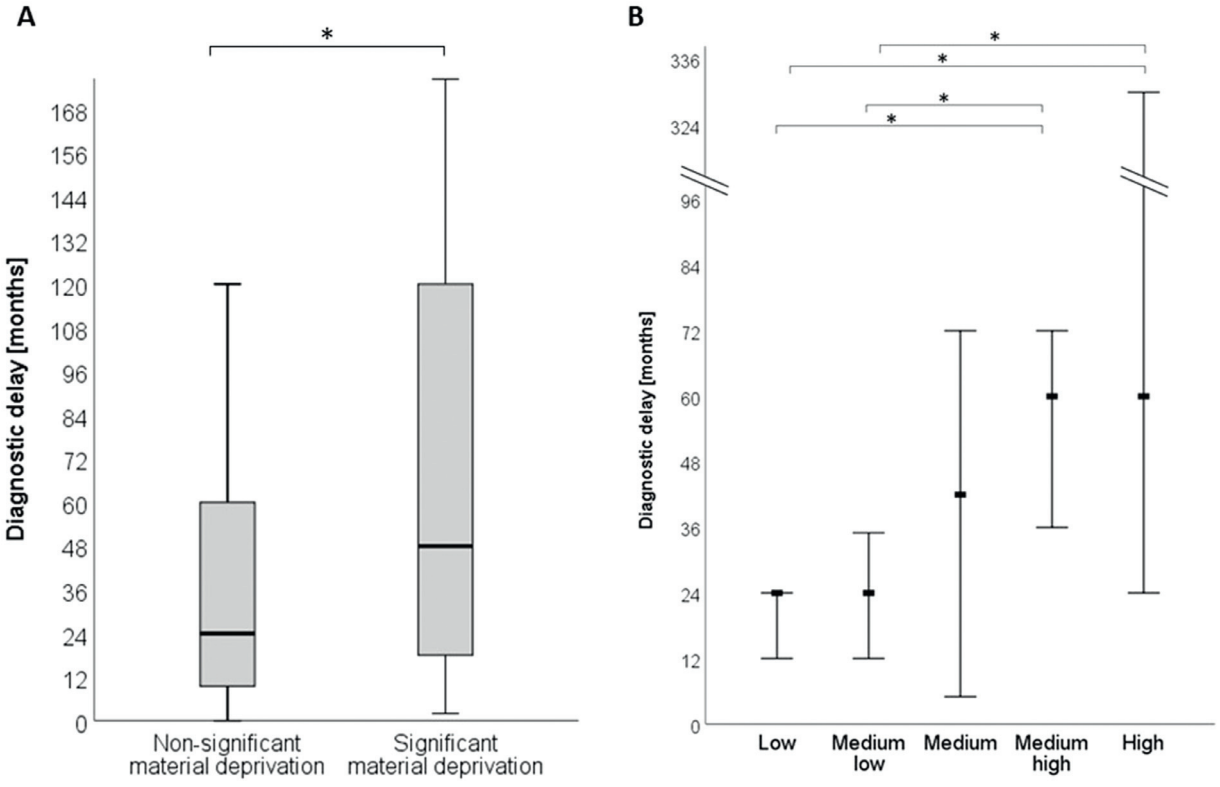

Fig. 2. (A) Boxplots showing the diagnostic delay among patients divided according to the presence of material deprivation and (B) the median value and its 95 % confidence interval of diagnostic delay in the five subgroups of material deprivation.

Table 4
Univariate and multivariate analysis of parameters associated with late diagnosis of achalasia.

Variable	Univariate analysis			Multivariate analysis		
	OR	95 % CI	p	OR	95 % CI	p
Material deprivation (low=ref)	3.05	1.43 – 6.51	**0.004**	1.49	1.12 – 1.97	**0.006**
Weight loss (absent=ref)	0.42	0.24 – 0.75	**0.003**	0.45	0.25 – 0.81	**0.008**
Dysphagia (absent=ref)	0.32	0.04 – 2.53	0.278			
Chest pain (absent=ref)	1.23	0.69 – 2.17	0.485			
Regurgitation (absent=ref)	0.96	0.52 – 1.77	0.900			
Age at diagnosis, years	0.99	0.97 – 1.01	0.161	0.99	0.98 – 1.0	0.277
Alcohol consumption, UA/die	1.19	1.10 – 1.49	**0.028**	1.17	0.95 – 1.45	0.142
Previous diagnosis of gastroesophageal reflux disease (no =ref)	1.91	0.88 – 4.13	0.101	1.74	0.78 – 3.87	0.174
Median integrated relaxation pressure, mmHg	0.98	0.957 – 1.01	0.210			
Alteration at barium radiography (none = *ref*)	0.87	0.32 – 2.34	0.777			
Type of achalasia (type 1 = *ref*)	0.94	0.58 – 1.51	0.782			
Alteration at endoscopy (none = *ref*)	1.05	0.55 – 1.99	0.884			
Body mass index, kg/m2	1.00	0.94 – 1.08	0.869			

Abbreviations: OR, Odds Ratio; ref, reference.

low material deprivation had shorter median diagnostic delay (24 months, IQR 9 – 60) than patients with medium-high ($p = 0.002$) and high material deprivation ($p = 0.020$). Lastly, patients with medium material deprivation showed an intermediate diagnostic delay (42 months, IQR 7 – 72) with no statistically significant difference with other subgroups.

To further analyze the factors associated with early or late diagnosis, a multivariate model was used, and Table 4 shows the results of univariate and multivariate analysis. A late diagnosis was independently significantly associated with absence of weight loss (OR 0.45, 95 %CI 0.25 – 0.81, $p = 0.008$) and higher material deprivation (OR 1.49, 95 %CI 1.12 – 1.97, $p = 0.006$).

4. Discussion

Achalasia is a rare esophageal motility disorder that poses a significant diagnostic challenge due to its non-specific symptomatology and to its complex pathophysiology. This complexity is further compounded by the overlap of achalasia symptoms with those of more common gastrointestinal disorders like gastroesophageal reflux disease, often leading to misdiagnosis or delayed referral to specialized care [21]. The present study aimed to explore the diagnostic delay in patients with achalasia, and the factors influencing the timely diagnosis of this condition.

We observed an overall diagnostic delay of 24 months between the onset of symptoms and final diagnosis, and only one out of four patients received a conclusive diagnosis of achalasia within the first year since the onset of symptoms. In a late 1990s study by Eckardt et al. [4], the median symptom duration before diagnosis spanned between one and two years, which is consistent with our findings, although emphasizes the fact that in the course of approximately 25 years no improvement in early diagnosis of achalasia has been made [4]. This finding might be justified by the evidence that achalasia is a slowly progressive disease, and patients often embrace adaptive behaviors in order to reduce symptom burden, thus leading to delayed diagnosis until more worrisome features, such as weight loss, ensue and brings the patient to medical attention [22].

Indeed, we feel that the critical role of specific symptoms, particularly weight loss, is important in accelerating the diagnostic process, and the presence of more worrisome symptoms should be promptly focused by clinicians to improve a timely intervention [23]. It is worth noting that approximately 20 % of the patients had a prior diagnosis of gastroesophageal reflux disease and were undergoing long-term treatment with proton pump inhibitors. Thus, our result also raises questions about the effectiveness of current diagnostic practice in identifying less severe cases, when symptoms like weight loss might not be as prominent. This gap highlights the need for a more targeted approach in the assessment of achalasia, ensuring that patients with milder symptoms are not overlooked and receive appropriate care [12]. Recognizing that milder symptoms may not always lead to immediate consideration of achalasia, there is a consequential risk that these initial presentations may be dismissed or misattributed to less serious conditions. Such oversight can inadvertently lead to delays in the diagnosis and, potentially, to less optimal outcomes for patients.

A noteworthy element of this investigation is the exploration of the relationship between different burden of material deprivation and the delay in achalasia diagnosis. The Italian Health Care System is based on the principles of universal coverage and equal access for all citizens. The system is funded primarily through taxation, and it emphasizes primary care, preventive measures, and the integration of healthcare services [13]. We found that greater material deprivation was associated with longer delay in diagnosis. These inequalities might be due to people with more material deprivation having different priorities. For them, basic needs like housing often come first before seeking medical help [24]. Additionally, the challenge of geographical mobility for individuals with material deprivation can further hinder their access to timely healthcare services [14,25]. These barriers suggest that despite the principles of the healthcare system, there is an underlying inequity in access to care, particularly for those in more deprived conditions. Furthermore, our methodology for estimating material deprivation included an assessment of educational levels, which may have also played a role in the observed diagnostic delays. Higher levels of education are often associated with better health literacy, enabling individuals to recognize symptoms and seek medical care more promptly [26]. This factor intertwines with the aforementioned challenges of material deprivation, suggesting that a multifaceted approach is needed to address the barriers to timely healthcare access, particularly for those with limited educational and economic resources.

Our findings have several clinical implications. Firstly, they highlight the need for increased awareness of achalasia among general practitioners and non-specialists. Early referral to specialized centers for further testing could reduce diagnostic delays. Secondly, the socio-economic factors influencing diagnostic delays call for policy interventions to ensure equitable access to healthcare services. On the other hand, our study has some limitations, including its retrospective nature, which might lead to recall bias in estimating the onset of symptoms. Additionally, the single-center setting may limit the generalizability of our findings to broader populations. Then, the absence of comprehensive data on the diagnostic pathways undertaken by primary care physicians and specialists, including the specific alternative diagnoses considered prior to confirming achalasia, represents a limitation, as it may in-

terfered the understanding of potential delays and missteps in the diagnostic process.

In conclusion, this study provides critical insights into the challenge of diagnosing achalasia and underscores the need for a more integrated approach that considers both medical and socio-economic factors in patient care. For future research, it would be valuable to explore strategies to reduce diagnostic delays, especially in socio-economically disadvantaged populations. Additionally, further studies are needed investigate the long-term outcomes of patients diagnosed with achalasia, focusing on how early *versus* late diagnosis impacts disease progression and quality of life.

Declarations

Author contributions

AP, FC, EM, EVS, and EGG conceived and drafted the study. AP, FC, AG, MF, GB, EVS, VS and EGG collected, analysed, and interpreted all data. AP, AG, EM, and FC drafted the manuscript. EM, EVS, VS, PZ, GB and EGG commented on drafts of the paper. All authors have approved the final draft of the manuscript.

Data available statement

The data underlying this study are available within the manuscript and supplementary materials. Further information are available upon reasonable request

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Conflicts of interest/Disclosure

AP, FC, AG,VS, PZ, MF, GB, EGG and EM declared no conflict of interest. EVS has served as speaker for Abbvie, Agave, AG-Pharma, Alfasigma, Aurora Pharma, CaDiGroup, Celltrion, Dr Falk, EG Stada Group, Fenix Pharma, Fresenius Kabi, Galapagos, Janssen, JB Pharmaceuticals, Innovamedica/Adacyte, Malesci, Mayoly Biohealth, Omega Pharma, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, Tillots, Unifarco; has served as consultant for Abbvie, Agave, Alfasigma, Biogen, Bristol-Myers Squibb, Celltrion, Diadema Farmaceutici, Dr. Falk, Fenix Pharma, Fresenius Kabi, Janssen, JB Pharmaceuticals, Merck & Co, Reckitt Benckiser, Regeneron, Sanofi, SILA, Sofar, Synformulas GmbH, Takeda, Unifarco; he received research support from Pfizer, Reckitt Benckiser, SILA, Sofar, Unifarco, Zeta Farmaceutici.

The authors have no conflicts of interest to declare. All co-authors have seen and agree with the contents of the manuscript and there is no financial interest to report. We certify that the submission is original work and is not under review at any other publication.

Ethics approval

According to the Italian Medicines Agency det. 20/03/2008 on retrospective observational studies on anonymous data, approval by an ethics committee was not mandatory and the need for informed consent was waived. The study was conducted in accordance with the 1964 Declaration of Helsinki and its later amendments.

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