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Endoscopic Prediction of Achalasia: Putting the CART Before the CARS

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ABSTRACT

Background and Aims: Endoscopy can detect features indicative of esophageal dysmotility, but standardized approaches for diagnosing achalasia based on these findings remain limited. Recently, the CARS score was developed to address this gap. This study aimed to evaluate the diagnostic utility of endoscopy in identifying achalasia, using the STARD framework and current reference standards.

Methods: Adult patients with esophageal symptoms were prospectively enrolled from 2018 to 2023 and evaluated using endoscopy, esophageal manometry, FLIP panometry, and barium esophagram. The CARS score was assigned to endoscopic videos by two raters blinded to other clinical details. The diagnostic accuracy of the CARS score for predicting achalasia, based on Chicago Classification v4.0, was assessed through two interpretation methods: binary cutoffs for the total score and a classification tree model.

Results: 316 patients were included: 115 patients with achalasia (36%), 113 with normal motility (36%), and 88 with other manometric findings (28%). A CARS score ≥ 4 demonstrated 72% sensitivity and 99% specificity for achalasia, while a score ≥ 3 had 83% sensitivity and 96% specificity. The optimal classification tree had three levels (resistance score at the top, followed by anatomy and content scores, with hernia presence at the bottom) and had a sensitivity of 90% and a specificity 92% for achalasia.

Conclusion: Endoscopy can accurately identify achalasia with high specificity using the CARS score. While motility testing to confirm an achalasia diagnosis remains essential prior to therapy, a high CARS score may help in the early identification of achalasia, especially in settings where motility testing is not readily available.

Summary

- The novel endoscopic scoring system, the CARS score, demonstrated exceptionally high diagnostic specificity in differentiating patients with achalasia.
- A classification tree model incorporating the CARS score and hernia presence provides a step-wise framework for interpreting the endoscopic probability of achalasia.
- Endoscopy can accurately diagnose achalasia and may serve as a viable alternative when formal motility testing is unavailable.

1 | Introduction

High-resolution esophageal manometry (HRM) is the typically used test to evaluate and diagnose esophageal motility disorders when an overt mechanical obstruction is not identified on upper endoscopy. Achalasia, a primary esophageal motility disorder, is characterized by impaired lower esophageal sphincter (LES) relaxation and absence of peristalsis, with diagnostic criteria on high-resolution manometry (HRM) defined according to the Chicago Classification version 4.0 (CCv4.0) [1, 2]. Despite its importance, achalasia diagnosis is often delayed due to limited HRM availability outside tertiary medical centers, required expertise for interpretation, and underestimation of esophageal motility testing's clinical relevance [3, 4]. Studies indicate that only 70% of patients presenting with non-obstructive dysphagia undergo timely esophageal manometry during their diagnostic evaluation [3]. Delayed manometric evaluation contributes to prolonged symptom burden and diagnostic uncertainty for patients. Consequently, inaccurate and delayed diagnosis of achalasia remains a significant clinical challenge, with many patients enduring multiple specialist visits and repeated testing before receiving a correct diagnosis. These limitations in HRM accessibility and frequent diagnostic delays underscore the need for complementary methods to facilitate early screening and diagnosis of achalasia.

Endoscopy, typically the initial evaluation for patients with dysphagia, is crucial for ruling out mechanical obstruction and malignancy. Emerging evidence supports endoscopy's role in detecting and diagnosing primary esophageal motility disorders [5]. Several endoscopic findings, including a dilated or tortuous esophagus, retained contents, and functional stenosis at the esophagogastric junction (EGJ), are frequently observed in achalasia patients [5–7]. However, data supporting a standardized algorithm incorporating these endoscopic findings for achalasia diagnosis are limited. Recently, a scoring system based on esophageal Contents, Anatomy, Resistance to traverse the EGJ, and Stasis (CARS score) was developed. In a real-world clinical setting, a CARS score of ≥ 4 demonstrated 68% sensitivity and 99% specificity for diagnosing achalasia [8].

In light of the newly proposed CARS score, we sought to further validate this approach and evaluate the accuracy of endoscopy using the CARS for diagnosing esophageal motility disorders. Additionally, we hypothesized that including additional endoscopic features into a classification tree model could enhance diagnostic performance for predicting achalasia. Therefore, this study aimed to assess the diagnostic accuracy of endoscopy for achalasia, as defined by HRM and CCv4.0, following the Standards for Reporting of Diagnostic Accuracy Studies (STARD) approach; Table S1 [9].

2 | Materials and Methods

2.1 | Subjects

Adult patients (aged 18–89) presenting to the Esophageal Center of Northwestern for evaluation of esophageal symptoms between August 2018 and June 2023 had data prospectively maintained in an esophageal motility registry. Patients who completed HRM and had a stored video of endoscopy without prior foregut surgery were identified for inclusion in this study (Figure 1). Patients with prior foregut surgery, esophageal mechanical obstruction (esophageal stricture, eosinophilic esophagitis, severe reflux esophagitis [Los Angeles-classification C or D], large hiatal hernia [>3 cm] or paraesophageal hernia), or technically limited endoscopic videos were excluded. Patients with esophagogastric junction outflow obstruction (EGJOO) who had not undergone either timed barium esophagram (TBE) or functional luminal imaging probe (FLIP) were excluded due to the uncertainty of their HRM findings.

Initially, an "enriched batch cohort" consisting of 300 videos from 292 patients was selected, divided into three batches of 100 videos each. The first two batches included patients with either normal motility, ineffective esophageal motility (IEM), or achalasia, randomly selected from the esophageal motility database. The third batch comprised 70% of patients with achalasia, normal motility, or IEM, and 30% with "abnormal" HRM (EGJOO, distal esophageal spasm, hypercontractile esophagus, or absent contractility). Additionally, a "consecutive patient cohort" was formed from consecutive patients in the motility database that met inclusion criteria (i.e., had stored endoscopic videos and underwent HRM for evaluation of primary esophageal motility disorders) between November 2022 and March 2024.

Clinical evaluations (e.g., TBE or FLIP) and management decisions were made at the discretion of the primary treating gastroenterologist. No endoscopic or surgical treatments occurred between the FLIP, HRM, or TBE studies. No adverse events were reported during the performance of HRM or FLIP. The study protocol was approved by the Northwestern University Institutional Review Board as minimal risk, with a waiver of informed consent for the analysis of deidentified, coded patient data.

2.2 | Videoscopic Scoring

Recorded endoscopic videos were reviewed by two independent gastroenterologists (M.L. and P.P.) using the CARS scoring system. This system evaluates four esophageal components: contents, anatomy, resistance to traversing the EGJ, and stasis. Each component was scored from 0 to 2, except for stasis, which received 1 point for chronic stasis changes or Candida esophagitis (Table S2) [8]. The raters were blinded to clinical data, including

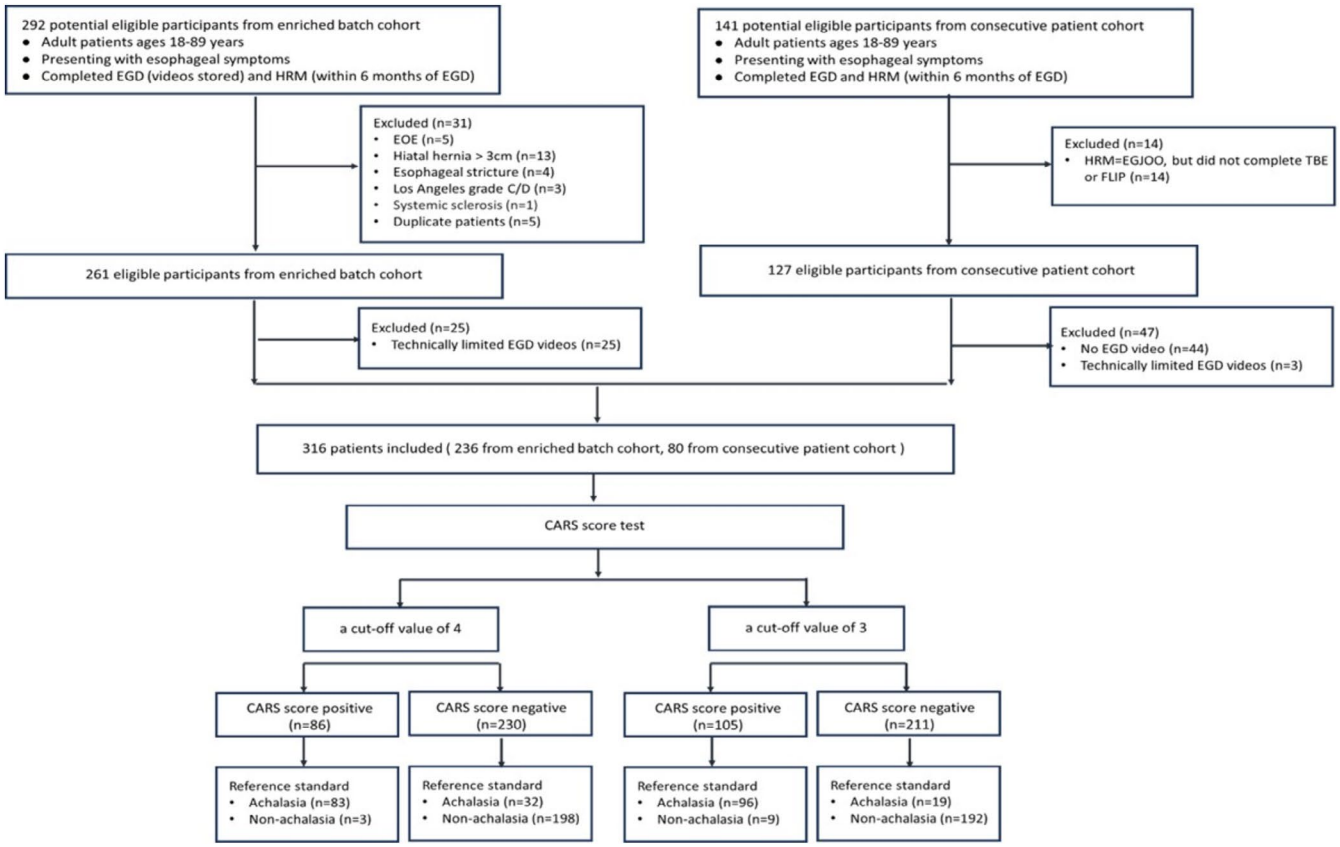

FIGURE 1 | Standards for Reporting of Diagnostic Accuracy (STARD) flow chart of the 316 patients enrolled in the study. The endoscopic CARS scoring system served as the index test, with HRM and FLIP/TBE used as reference standards. EGD, esophagogastroduodenoscopy; EGJOO, esophagogastric junction outflow obstruction; EOE, eosinophilic esophagitis; HRM, high-resolution manometry; TBE, timed barium esophagram.

HRM, FLIP, and TBE results. Final scores were determined by consensus between the two raters. In cases of disagreement, a third expert (EG) made the final determination.

2.3 | HRM Protocol and Analysis

After a minimum 6-h fast, HRM studies were completed using a 4.2-mm outer diameter solid-state assembly with 36 circumferential pressure sensors at 1-cm intervals (Medtronic Inc., Shoreview, MN). The HRM assembly was inserted transnasally and positioned to record pressure data from the hypopharynx to the stomach, including approximately 3 intragastric pressure sensors. After a 2-min baseline recording, the HRM protocol was performed with ten 5-mL liquid swallows in a supine position and with five 5-mL liquid swallows in an upright, seated position [10]. Manometry studies were interpreted according to the CCv4.0 and independent of the endoscopic results [2].

2.4 | Additional Baseline Clinical Evaluation

Adjunct testing with TBE or FLIP was reviewed when available. TBE was performed with the patient ingesting 200 mL of low-density barium sulfate in the upright position, with images captured at 1 and 5 min. If liquid barium was cleared by 5 min, a 12.5-mm barium tablet was administered. A TBE was considered abnormal if the barium column height exceeded 5 cm at 5 min or if the column height was greater than 5 cm at 1 min, accompanied by impaction of the 12.5-mm barium tablet (i.e., inability of the tablet to pass from the esophagus) [11]. FLIP Panometry results indicative of obstruction included a distensibility index $< 2.0\,mm^2/mmHg$ at the 60 mL fill volume and a maximum diameter < 12 mm at the 60 mL or 70 mL fill volume [12–14].

In cases where HRM results were inconclusive (e.g., EGJOO or absent contractility with an integrated relaxation pressure [IRP] at the upper limit of normal), FLIP or TBE was used to establish the diagnosis according to CCv4.0 recommendations. EGJOO with abnormal TBE or FLIP was classified as conclusive EGJOO, while those with normal TBE or FLIP were considered negative for EGJOO. Negative EGJOO studies were further categorized as normal motility or IEM based on the HRM contractile pattern. For patients with distal esophageal spasm, hypercontractile esophagus, or absent contractility on HRM, a comprehensive clinical assessment, including clinically relevant symptoms, TBE with a barium tablet, or FLIP, were carefully reviewed when available to obtain a clinically relevant diagnosis and differentiate conditions within the achalasia spectrum.

2.5 | Statistical Analysis

The primary outcome was binary: identification of achalasia (subtypes I, II, or III) was classified as "positive" while the

absence of such disorders was classified as "negative" The endoscopic CARS scoring system served as the index test, with HRM and FLIP/TBE used as reference standards. A positive CARS score was defined as ≥4 [8]. A post hoc sensitivity analysis was conducted using a positive CARS score of ≥3 after assessing the results of the ROC curve and the optimal cutoff point. Additionally, a classification tree incorporating CARS score components and other endoscopic features (e.g., hiatal hernia) was applied to identify positive cases. Positive reference results were defined according to CCv4.0, with FLIP and/or TBE performed in cases where HRM diagnosis was inconclusive.

Prior to developing the classification tree model, the accuracy of the total CARS score was evaluated using receiver operating characteristic (ROC) curves, the calculation of the area under the ROC curve (AUROC), and the construction of interval likelihood ratio (LR) tables. The intervals were selected based on visual inspection of variable distributions.

The classification tree model was developed sequentially, fitting multiple trees using all possible combinations of CARS score components and other endoscopic findings (small hiatal hernia presence). The best-performing classification tree model was selected, which incorporated the contents score, anatomy score, resistance score, and presence of hiatal hernia (Supporting Information, Figure S1). The robustness of the model was assessed through bootstrap resampling ($n=1000$) and performance was evaluated using out-of-bag samples. For each bootstrap iteration, the classification tree was reconstructed with the same hyperparameters, and the resulting accuracy estimates, variable selection patterns, and performance metrics were analyzed (Supporting Information).

Results were expressed as *n* (%), mean (standard deviation; SD), or median (interquartile range; IQR), depending on the variable type and data distribution. Groups were compared using the Chi-squared test for categorical variables and ANOVA/*t*-tests or Kruskal–Wallis/Mann–Whitney *U* tests for continuous variables, based on data distribution. Performance of the index test was assessed using sensitivity, specificity, accuracy, and AUROC. Cohen's Kappa statistic (quadratically weighted Cohen's Kappa for ordinal scales) was used to evaluate agreement between raters for individual score components and the total score. The 95% confidence intervals for AUROC were calculated using the DeLong method. Statistical significance was set at a two-tailed P value of <0.05. Post hoc comparisons, as appropriate, were adjusted using the Bonferroni correction to account for multiple comparisons. The classification tree model was generated using R version 4.4.0, while the remaining analyses were conducted with IBM SPSS Statistics (version 29.0.1.0, Armonk, NY: IBM Corp).

3 | Results

3.1 | Subjects

A total of 236 patients from the enriched batch cohort (mean age 49, 55% female) and 80 patients from the consecutive patient cohort (mean age 56, 55% female) were included in the primary analysis (Table 1, Figures 1, S2). The majority of patients (87%) were evaluated for dysphagia, and 228 patients (72%) underwent esophagogastroduodenoscopy (EGD) and HRM on the same day. The remaining patients had a median interval of 1.3 months (IQR 0.2–2.2) between HRM and EGD. The most common HRM diagnoses were achalasia (115 patients, 36%) and normal motility (113 patients, 36%). Eleven patients (3%) were diagnosed with EGJOO, all of whom completed TBE or FLIP. Of these, eight were confirmed to have conclusive EGJOO, one was reclassified as having normal motility, and two were reclassified as IEM based on HRM contraction patterns. Additionally, four out of 15 patients with absent contractility on HRM were diagnosed with type I achalasia, while two of three patients with DES were reclassified as type III achalasia based on TBE and FLIP Panometry findings per CCv4.0 (Table S3).

The two cohorts were comparable in terms of demographics and clinical characteristics (Table 1). However, patients in the consecutive patient cohort more frequently presented with small hiatal hernias. Per study design, the consecutive patient cohort also had a higher prevalence of other HRM-classified motility disorders, such as EGJOO and hypercontractile esophagus.

3.2 | CARS Score by Esophageal Motility Category

Interrater reliability was assessed using scores from two raters across 316 endoscopy videos (Table S4). The overall interrater reliability for the total CARS score was excellent ($\kappa=0.89$), with individual CARS components demonstrating good to excellent agreement ($\kappa=0.73$–0.85). Additionally, the reliability for detecting achalasia using a CARS score cutoff of 4 was excellent ($\kappa=0.82$), with a 92% agreement between raters.

Patients with achalasia had significantly higher mean CARS scores compared to those with normal motility, IEM, and hypercontractile esophagus ($p<0.05$) (Figure 2). Among the achalasia subtypes, type III had the lowest CARS scores. Patients with conclusive EGJOO also had higher CARS scores compared to those with normal motility ($p<0.05$). Sub-score analysis revealed that type I achalasia had higher anatomy scores compared to type III ($p<0.05$), while type III had lower stasis scores compared to both type I and type II ($p<0.05$). Among 224 patients with FLIP findings, the maximum EGJ diameter in patients with a resistance score of 2 or 1 was significantly lower than in patients with a resistance score of 0. Additionally, the maximum EGJ diameter was also lower in patients with a resistance score of 2 compared to those with a resistance score of 1. All $p<0.05$ (Figure 3).

3.3 | Evaluation of CARS Score

An increased likelihood of having achalasia was observed with CARS scores of 3 (LR 3.79) and ≥4 (LR 48.36). Conversely, a CARS score of 2 or less indicated a decreased probability of achalasia (LR < 1), with an LR of 0.06 for a CARS score of 0 (Table 2). The AUROC for the CARS score was 0.943 (95% CI: 0.915–0.971). Using the suggested cutoff value of 4 yielded a sensitivity of 72%, a specificity of 99%, a positive predictive value (PPV) of 97%, and a negative predictive value (NPV) of 86% [8]. Of the 86 patients with a CARS score of 4 or higher,

TABLE 1 | Cohort characteristics.

	Total cohort ($n = 316$)	Enriched batch cohort ($n = 236$)	Consecutive patient cohort ($n = 80$)
Age, mean (SD), year	51 (18)	49 (18)	56 (17)
Sex, female, *n* (%)	173 (55)	129 (55)	44 (55)
Indication, *n* (%)*			
Dysphagia[a]	274 (87)	200 (85)	74 (93)
Reflux symptoms	28 (9)	26 (11)	2 (3)
Chest pain	4 (1)	0	4 (5)
Other	10 (3)	10 (4)	0
Endoscopy findings, *n* (%)			
Los Angeles grade A/B	17 (5)/10 (3)	16 (7)/6 (3)	1 (1)/4 (5)
Hiatal hernia*	84 (27)	55 (23)	29 (36)
HRM-CCv4.0, *n* (%)			
Type I achalasia	42 (13)	30 (13)	12 (15)
Type II achalasia	55 (17)	45 (19)	10 (13)
Type III achalasia	18 (6)	12 (5)	6 (8)
Conclusive EGJOO	8 (3)	0	8 (10)
Hypercontractile	9 (3)	2 (1)	7 (9)
Distal esophageal spasm	1 (1)	1 (1)	0
Absent contractility	11 (4)	7 (3)	4 (5)
IEM	60 (19)	47 (20)	13 (16)
Normal motility	112 (35)	92 (39)	20 (25)

Abbreviations: CCv4, Chicago Classification version 4.0; EGJOO, esophagogastric junction outflow obstruction; HRM, high-resolution manometry; IEM, ineffective esophageal motility.
*$p < 0.05$ on comparison between 2 cohorts.
[a]Dysphagia +/− reflux symptoms or chest pain.

85 (99%) had either a diagnosis of achalasia (83 patients) or conclusive EGJOO (2 patients). The remaining patient with a CARS score ≥4 was diagnosed with IEM but also had a known hiatal hernia identified during EGD, with FLIP showing absent contractile response. Using a cutoff value of 3 provided a sensitivity of 84%, a specificity of 96%, a PPV of 91%, and an NPV of 91%. Of the 105 patients with a CARS score of 3 or higher, 99 (94%) had either a diagnosis of achalasia (96 patients) or conclusive EGJOO (3 patients).

3.4 | Accuracy of Classification Tree Model

The best performing 3-level classification tree constructed using components of the CARS score and endoscopic findings had the resistance score at the top, the contents score and anatomy score at the second level, and hiatal hernia presence at the bottom (Figure 4). Earlier splits are generally considered more important for classification, as they capture the most significant patterns in the data, influencing subsequent splits. Thus, the resistance score can be considered the most important variable for identifying achalasia, followed by the anatomy score, contents score, and hiatal hernia presence. The overall AUROC of the classification tree, when applied to the test data, was 0.867 (95% CI 0.785–0.949), with a sensitivity of 82.8% and a specificity of 88.2%. When applied to the entire dataset using the STARD approach, the classification tree achieved a sensitivity of 89.6%, a specificity of 92.0%, a PPV of 87%, and an NPV of 94% (Figure 4). Of the 119 patients identified by the CART model as achalasia, 107 (90%) had either a diagnosis of achalasia (103 patients) or conclusive EGJOO (4 patients). The mean accuracy across bootstrap iterations was 89.3% (95% CI: 83.9%–94.7%). The mean sensitivity and specificity were 92.1% (95% CI: 85.9%–98.3%) and 84.4% (95% CI: 71.2%–97.6%), respectively.

4 | Discussion

The main findings from this study demonstrate that motility assessment via endoscopy using the CARS score offers an effective method for identifying achalasia. A composite CARS score of 4 or higher exhibited high specificity, accurately identifying 99% of patients with achalasia or conclusive EGJOO. The classification tree based on individual CARS score components provides a structured framework for interpreting the score and could

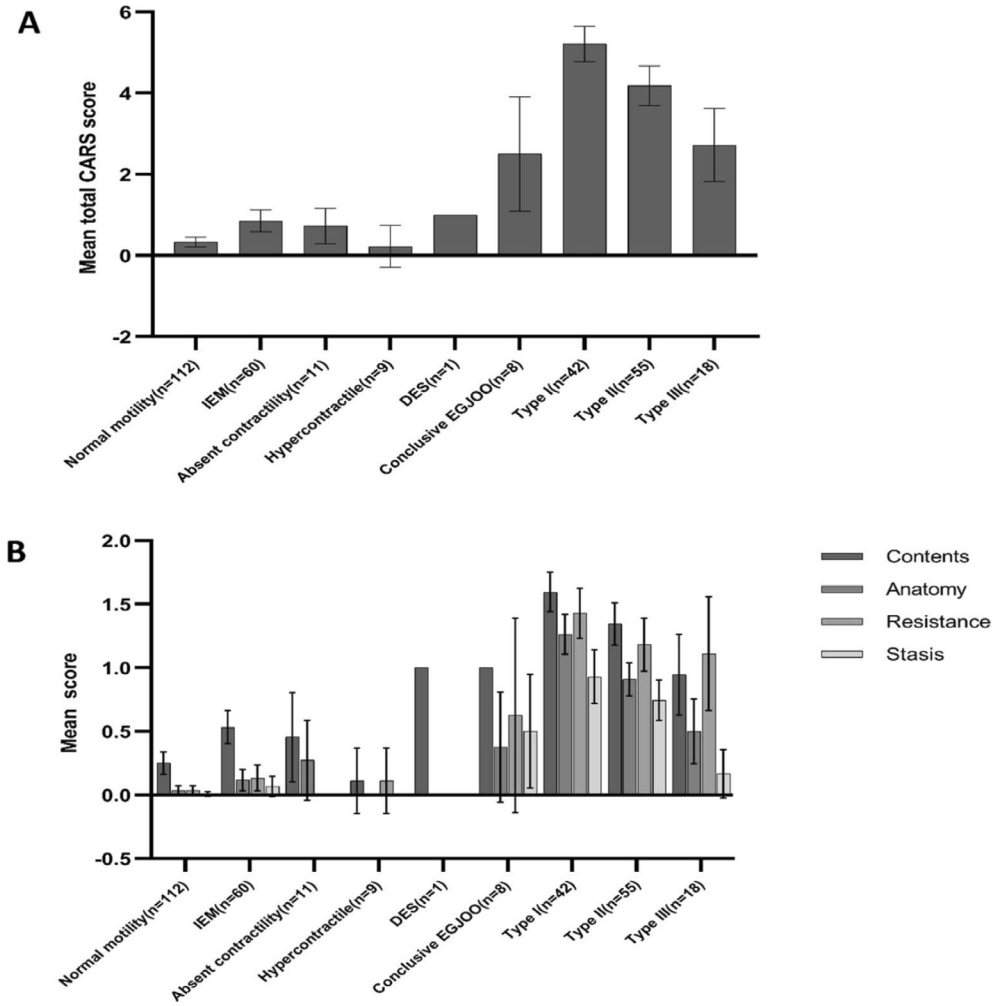

FIGURE 2 | CARS score by Chicago Classification v4.0 motility group. DES, distal esophageal spasm; EGJOO, esophagogastric junction outflow obstruction; IEM, ineffective esophageal motility. The bars represent the mean and error bars 95% confidence intervals. Pairwise comparisons were performed using the Kruskal–Wallis test. (A) Total CARS score by CCv4.0 diagnosis. (B) CARS score components by CCv4.0 diagnosis.

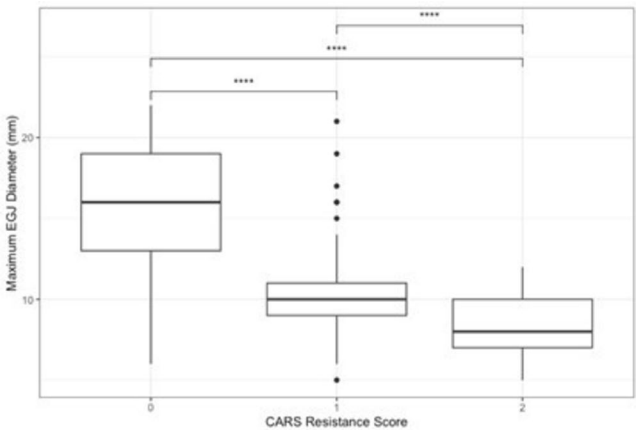

FIGURE 3 | Distribution of maximum EGJ diameter by CARS resistance score. Boxplots show the distribution of maximum EGJ diameter for each CARS resistance score. The central line represents the median, boxes the interquartile range, and whiskers extend to 1.5 times the interquartile range. Pairwise comparisons are performed using the Mann–Whitney *U* test. Significance levels: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$, **** $p < 0.0001$. EGJ, esophagogastric junction.

TABLE 2 | Interval likelihood ratios for CARS score.

CARS score	Positive within interval	Negative within interval	Interval LR
≥4	83	3	48.36
3	13	6	3.79
2	6	15	0.70
1	9	56	0.28
0	4	121	0.06

Note: Patients were classified as positive if they had achalasia, as determined by high-resolution esophageal manometry (HRM) and, when indicated, TBE or functional lumen imaging probe (FLIP). Likelihood ratios (LRs) indicate the probability of achalasia: LR > 1.0 suggests increased probability, LR < 1.0 suggests decreased probability, and LR = 1.0 indicates no change in probability. To calculate post-test odds, multiply pre-test odds by the appropriate LR.

further improve the utilization of the CARS score to diagnose achalasia over a binary score threshold. This study is the first to apply a standardized STARD approach to evaluate endoscopy

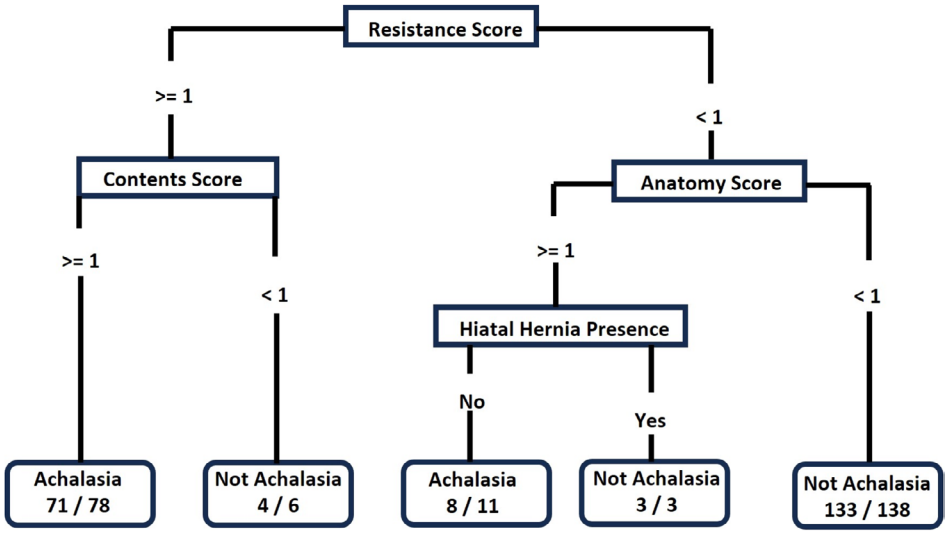

FIGURE 4 | CART model. This tree was constructed using a training set of 236 patients (75% of the total dataset). Start at the top and follow the path through subsequent nodes until you reach the bottom. Each "leaf" at the bottom of the tree represents a classification. Inside each leaf, the proportion of correctly classified patients within that class is shown.

for achalasia diagnosis and validate the accuracy of the CARS score. These results support its potential use as a reliable, efficient diagnostic tool to identify achalasia.

Although HRM is often regarded as the primary diagnostic tool for esophageal motility disorders in patients with non-obstructive dysphagia, it involves the placement of a transnasal catheter. This can cause discomfort and often necessitates an additional healthcare visit, leading to diagnostic delays [15]. One study found that the time to first diagnosis of achalasia can take nearly 2 years [3]. Although this duration has decreased in recent years due to the wider availability and use of HRM, many centers do not have the required equipment or expertise for motility testing. As such, there is an unmet need for alternative methods to facilitate earlier diagnosis of motility disorders, particularly those that emphasize patient-centered approaches to improve tolerance, acceptance, and convenience. Hence, this CARS approach may facilitate earlier identification of achalasia where formal esophageal motility testing is unavailable.

Endoscopy is a key component in the assessment of dysphagia, as it is essential to exclude mechanical obstructions before investigating primary motility disorders. Some endoscopic features have been linked to achalasia, potentially indicating this rare condition. However, most described endoscopic findings are binary in nature, and their diagnostic accuracy for achalasia has been inconsistent, with poor sensitivity [5–7]. The CARS score is the first scoring system that incorporates typical endoscopic findings, offering a probability spectrum for achalasia. This approach is demonstrated by the interval likelihood ratio table, which can be used to estimate the post-endoscopy probability of achalasia (Table 2). In our larger cohort, we revalidated the CARS score's diagnostic performance, demonstrating similarly high specificity (99%) and interrater reliability at a threshold score of 4 or higher. The single patient misclassified as achalasia with a score of ≥ 4 had a history of autoimmune disease and possible CREST syndrome associated with esophageal hypomotility and a hiatal hernia, which can elevate IRP and mimic achalasia [16]. Overall, our study suggests that using a CARS score of ≥ 4 provides a high degree of specificity for diagnosing achalasia. Moreover, applying a cutoff of ≥ 3 improves sensitivity (84%) with only a small reduction in specificity (96%), also supporting its clinical utility.

The application of the classification tree served two purposes. First, it provided insight into the hierarchical significance of the components comprising the CARS score. Among these, the resistance score was the most important for classification, followed by the anatomy score and contents score. The prominence of the resistance score was not surprising, as impaired LES relaxation and EGJ outflow resistance are the hallmarks of achalasia (as also represented by the integrated relaxation pressure at the initial branch point in the Chicago Classification for HRM) [2]. The resistance score was shown to correlate directly with EGJ diameter (Figure 3). Interestingly, the stasis score was excluded from the model, suggesting that stasis-type mucosal changes or Candida presence were less important predictors of achalasia. Second, the classification tree incorporated an additional endoscopic metric, hiatal hernia presence, which improved sensitivity from 72% (CARS ≥ 4) to 83%. Given that the classification tree offers better sensitivity and CARS ≥ 4 provides superior specificity, a combined approach may be beneficial when identifying achalasia endoscopically. For instance, the classification tree could assist in ruling out achalasia, while a CARS score of ≥ 4 would strongly support the diagnosis.

Compared to the high specificity, the relatively lower sensitivity of the total CARS score may be attributed to the generally lower scores observed in Type III achalasia compared to Types I and II (Figure 2). Type III achalasia is unique due to its spastic esophageal activity. In our cohort, all 18 patients with Type III achalasia had an anatomy score of 1 or less, and only 10 (56%) had a CARS score of 3 or higher. Of those 10, two had an anatomy score of 0. For patients with abnormal CARS scores but an anatomical subscore of 0, HRM could be considered to further characterize potential spasm.

This study also has several limitations. First, although advanced methods such as HRM, FLIP, and CCv4.0 were used as reference standards to assess diagnostic performance, we acknowledge that there is no perfect 'gold standard' for diagnosing esophageal motility disorders. Additionally, achalasia was overrepresented in our study population, which may limit the generalizability of our findings to other clinical settings. However, this overrepresentation also serves as a strength, as achalasia is the most critical and actionable outcome of esophageal motility evaluations. An achalasia-enriched cohort also allows for a more rigorous assessment of the CARS score's ability to differentiate this important motility disorder. Another limitation is that the CARS score was graded using stored endoscopy videos rather than real-time assessments. This approach may miss dynamic changes or evaluations requiring tactile feedback, particularly those related to LES resistance. Despite this, our study showed that resistance scores correlated appropriately with maximum EGJ diameter, and using video enabled detailed, multi-rater evaluations, which contributed to the assessment of interrater variability—Figure 3.

In conclusion, this study demonstrated that the standardized use of the CARS score during endoscopy can identify achalasia with high specificity. A composite score at a specified threshold offers optimal predictive performance for identifying achalasia, while the classification tree enhances interpretability and improves sensitivity by incorporating individual characteristics and values to assess the likelihood of achalasia. These findings enhance endoscopic diagnostic capabilities and could be crucial for the early identification of achalasia, especially when formal motility testing is not readily available to stress the need for seeking a motility referral. Nevertheless, the decision for achalasia therapy should not be made with only endoscopic evidence. The confirmation of impaired EGJ opening and peristaltic abnormalities by HRM is still crucial for the diagnosis and treatment of achalasia. Future research should focus on validating the CARS approach with external data and improving diagnostic performance by integrating FLIP metrics, which can be measured concurrently during endoscopy. Ultimately, this study showcases the potential of using endoscopy alone to accurately diagnose achalasia, marking a significant advancement in the evaluation of motility disorders.

Author Contributions

M.L. contributed to data analysis, drafting of the manuscript, and approval of the final version. O.Z.F. contributed to data analysis, interpretation, drafting of the manuscript, and approval of the final version. P.P., E.G., K.K., E.K., and M.E. contributed to data analysis and approval of the final version. A.E., V.J.A.K., and R.N.K. edited the manuscript critically and approved the final version. J.E.P. contributed to obtaining funding, data interpretation, editing the manuscript critically, and approval of the final version. D.A.C. contributed to study concept and design, drafting of the manuscript, obtaining funding, data analysis, data interpretation, and approval of the final version.

Conflicts of Interest

R.N.K.: Boston Scientific (Consulting), Medtronic (Consulting, Research Support). V.J.A.K.: Exact (Consulting, Advisory Board), Castle Biosciences (Consulting), Medtronic (Speaking, Consulting), Pentax (Consulting), Sebela/Braintree (Consulting, Advisory Board). J.E.P.: Sandhill Scientific/Diversatek (Consulting, Grant), Takeda (Speaking), AstraZeneca (Speaking), Medtronic (Speaking, Consulting, Patent, License), Torax/Ethicon (Speaking, Consulting), EndoGastric Solutions (Advisory Board), Phathom (Speaking, Consulting). D.A.C.: Medtronic (Speaking, Consulting, License); Diversatek (Consulting); Braintree (Consulting); Medpace (Consulting); Phathom Pharmaceuticals (Speaking; Consulting); Regeneron/Sanofi (Speaking). Other authors declare no conflicts to interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request and completion of necessary privacy and ethical approvals.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.