Chicago classification v4.0 protocol improves specificity and accuracy of diagnosis of oesophagogastric junction outflow obstruction

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Summary

Background: Chicago classification version 4.0 (CCv4.0) introduced stringent diagnostic criteria for oesophagogastric junction outflow obstruction (EGJOO), in order to increase the clinical relevance of the diagnosis, although this has not yet been demonstrated.

Aims: To determine the prevalence of EGJOO using CCv4.0 criteria in patients with CCv3.0-based EGJOO, and to assess if provocative manoeuvres can predict a conclusive CCv4.0 diagnosis of EGJOO.

Methods: Clinical presentation, high resolution manometry (HRM) with rapid drink challenge (RDC), and timed barium oesophagogram (TBE) data were extracted for patients diagnosed with EGJOO as per CCv3.0 between 2018 and 2020. Patients were then re-classified according to CCv4.0 criteria, using clinically relevant symptoms (dysphagia and/or chest pain), and abnormal barium emptying at 5 min on TBE. Receiver operating characteristic (ROC) analyses identified HRM predictors of EGJOO.

Results: Of 2010 HRM studies, 144 (7.2%) fulfilled CCv3.0 criteria for EGJOO (median age 61 years, 56.9% female). Upon applying CCv4.0 criteria, EGJOO prevalence decreased to 1.2%. On ROC analysis, integrated relaxation pressure during RDC (RDC-IRP) was a significant predictor of a conclusive EGJOO diagnosis by CCv4.0 criteria (area under the curve: 96.1%). The optimal RDC-IRP threshold of 16.7 mmHg had 87% sensitivity, 97.1% specificity, 95.7% negative predictive value and 91.3% positive predictive value for a conclusive EGJOO diagnosis; lower thresholds (10 mmHg, 12 mmHg) had better sensitivity but lower specificity.
1 | INTRODUCTION

Oesophagogastric junction outflow obstruction (EGJOO) can manifest as a motor disorder of the oesophagus with incomplete relaxation of the lower oesophageal sphincter (LES) and intact oesophageal body peristalsis on high-resolution manometry (HRM). However, EGJOO can also occur from structural aetiologies, from non-specific mechanisms, and can be an artefact. Clinically, patients with conclusive EGJOO may report dysphagia and/or non-cardiac chest pain (NCCP), while reflux symptoms are less common. Therapeutic strategies include medications and invasive procedures aimed at reducing LES tone.

For EGJOO diagnosis, Chicago Classification version 3.0 (CCv3.0) required elevated LES median integrated relaxation pressure (IRP) with preserved oesophageal body peristalsis and no HRM criteria for achalasia, with prevalence from 5% to 24% among patients undergoing HRM. However, up to 94% of these patients may improve without treatment, raising questions on the significance of the diagnosis.

In the recently published CCv4.0, diagnostic criteria for EGJOO were made more clinically relevant, requiring elevated IRP in both supine and upright positions, intact oesophageal body peristalsis, as well as elevated intrabolus pressure (IBP) in ≥20% of supine swallows. Additionally, manometric EGJOO is considered clinically inconclusive, needing relevant symptoms (i.e., dysphagia and/or chest pain) and supportive non-manometric investigations such as timed barium oesophagogram (TBE) and/or functional luminal imaging probe (FLIP) for a conclusive diagnosis. Oesophageal pressurisation during the rapid drink challenge (RDC) provocative test is considered supportive evidence for EGJOO.

Although diagnostic criteria for EGJOO are now more stringent, impact on disease prevalence and consequently, relevance to clinical practice are currently unknown. The primary aim of this study was to determine EGJOO prevalence using CCv4.0 criteria among patients with EGJOO according to CCv3.0. The secondary aim was to assess whether RDC could predict EGJOO.

2 | MATERIALS AND METHODS

2.1 | Study design and patients

In this multi-centre retrospective cohort study, HRM studies in adults >18 years of age from tertiary referral centres in Pisa, Padova, and Feltre between 2018 and 2020 were retrieved and analysed using both CCv3.0 and CCv4.0. Further data, including clinical presentation, demographics and barium oesophagograms (when available) were collected in patients meeting CCv3.0 criteria for EGJOO. All patients stopped proton pump inhibitors (PPIs), H2-receptor antagonists (H2RA), opioids or prokinetics at least 3 weeks prior to HRM. Exclusion criteria were evidence of luminal stricture, extraluminal compression, or hiatus hernia on endoscopy; history of foregut surgery; neoplasia; eosinophilic oesophagitis; pregnancy and/or breast feeding. Participants were allowed to take alginates as rescue therapy for controlling heartburn. CCv4.0 criteria were applied to the cohort with CCv3.0 EGJOO diagnosis to determine proportions with a clinically relevant conclusive diagnosis of EGJOO.

Prior to the HRM study, all patients underwent a detailed clinical interview, including medical history (with recording of height and weight), current medications, smoking, coffee and alcohol consumption. All patients also completed validated questionnaires evaluating GERD symptoms and dysphagia. Patients were further categorised into those with and without clinically relevant symptoms (dysphagia and/or chest pain). A timed barium oesophagogram (TBE) with assessment of barium retention at 5 min (TBE5) was recommended to all patients for evaluation of oesophageal emptying when EGJOO was identified as per CCv3.0 criteria on HRM, and those who underwent TBE were classified into those with or without a conclusive CCv4.0 diagnosis of EGJOO. The study was conducted in accordance with the Helsinki Declaration (Sixth revision, Seoul 2008). Because all patients were part of each institution’s institutional review board-approved data collection, and only de-identified data were shared across the participating institutions with no links to the original patients, repeat institutional review board approval was not deemed necessary.

2.2 | High-resolution manometry protocol

Oesophageal HRM was performed using a 4.2 mm outer diameter, solid-state catheter assembly with 36 circumferential pressure sensors spaced 1 cm apart (Medtronic Inc) after at least a six-hour fast. The HRM protocol included a 30-second baseline recording, and ten 5-ml water swallows at 20–30s interval in the supine position. Three sets of multiple rapid swallows (MRS) were performed, consisting of five consecutive 2 ml swallows in rapid succession within 10 s. The RDC test consisted of rapidly drinking 200 ml of water through a straw in the sitting position. The HRM studies were analysed using the ManoView™ Analysis Software v3.0 (Medtronic) by experts from each centre.
2.3 | High-resolution manometry analysis

For each tracing, EGJ relaxation with integrated relaxation pressure (IRP), EGJ morphology, distal contractile integral (DCI), distal latency (DL), and intrabolus pressure (IBP) were recorded. The IBP was considered elevated when >20 mmHg. The EGJ-CI was calculated as previously reported.

For each MRS manoeuvre, the time to complete the MRS, oesophageal body inhibition, mean IRP of the three MRS (MRS-IRP), and mean DCI of the three MRS (MRS-DCI) were assessed. Oesophageal body inhibition was considered abnormal if there was a contraction segment with isobaric contour >20 mmHg and >3 cm in length, during the MRS course. Deglutitive inhibition of the LES was considered abnormal if the MRS-IRP was >15 mmHg. The presence of contraction reserve was assessed using the ratio of MRS DCI to SS DCI, and MRS/SS ratio >1 indicated preserved contraction reserve. Therefore, an intact MRS response consisted of complete deglutitive inhibition of the oesophageal body and LES during the repetitive swallows, and the presence of contraction reserve. Pressurisation during MRS (i.e., evidence of pressurisation with isobaric contour >20 mmHg during the repetitive phase of the MRS) was also recorded.

For each RDC test, the time to complete the RDC, post-RDC DCI (RDC-DCI), the IRP of the entire duration of the RDC (RDC-IRP), and the presence of pressurisation (i.e. evidence of pressurisation with isobaric contour >20 mmHg during the repetitive phase of the RDC) were assessed. Finally, the percentage of time with pressure >20 mmHg was calculated as the sum of the duration of the pressurizations divided by the time taken to complete the RDC.

2.4 | Timed barium oesophagogram

TBE was performed in the upright position within 30 days following HRM. Radiological images were obtained in the upright position after ingestion of 200 ml of low-density barium sulphate; frontal spot films of the oesophagus were obtained at baseline and 5 min after ingestion. The height of the barium column was measured vertically from the EGJ using a lead scale placed directly on the patient. Complete emptying was defined as a barium column height of <1 cm at 5 min.

2.5 | Conclusive EGJOO diagnosis according to CCv4.0

A conclusive diagnosis of EGJOO according to CCv4.0 required manometric EGJOO, relevant clinical symptoms, and abnormal TBE5. Only patients with complete HRM, clinical, and TBE5 data were included in the assessment of EGJOO prevalence using CCv4.0 criteria. Since HRM studies were performed using the CCv3.0 protocol, upright single swallows (SS) were not available for assessment.

2.6 | Statistical analysis

Continuous data are described as median and interquartile range (IQR), and categorical data as counts and per cent. Normality was evaluated using Shapiro–Wilks test. Homogeneity of the variances was verified with Fligner–Killeen test. Non-normal continuous variables were evaluated with non-parametric Mann–Whitney U test (one-sided and two-sided), while categorical variables were analysed using Pearson’s χ² test (using Yates’ correction for continuity). Unless otherwise specified, the continuous variables were found to be non-normal and/or to have a non-uniform variance between the two groups, and therefore the non-parametric U-test was used. Correlation between the non-normal continuous variables was tested using the non-parametric Spearman coefficient. Receiver operator characteristic (ROC) curve analyses were used to assess the performance characteristics of predictors of conclusive EGJOO as per CCv4.0, including area under the curve (AUC), sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) with bootstrap 95% confidence intervals (CI) when appropriate. A P-value of <0.05 was considered statistically significant. The statistical analysis was performed using R-studio version 4.1.2.

3 | RESULTS

3.1 | Clinical characteristics

Among 2010 patients undergoing an oesophageal HRM during the study period, 144 (7.2%) were diagnosed as EGJOO using CCv3.0 criteria, and met the inclusion criteria for this study (median age 61 years, 56.9% female). Clinical presentation and demographics of the included patients are described in Table 1. Of these, 54 patients (37.5%) had clinically relevant symptoms of dysphagia and/or chest pain. Demographics, BMI, smoking, coffee and alcohol use were similar between patients with and without clinically relevant symptoms (Table 1). Proportions with heartburn (31.5% vs. 47.8% respectively, p = 0.08) and regurgitation (51.9% vs. 50.0% respectively, p = 0.97) were not statistically different.

3.2 | High-resolution manometry findings

3.2.1 | Single swallows

Patients with EGJOO with clinically relevant symptoms had higher median IRP (p < 0.001), mean DCI (p = 0.017), and mean IBP (p < 0.001) compared to those without clinically relevant symptoms (Table 2). Type 1 EGJ morphology (no hiatus hernia) was significantly more prevalent, in the presence of clinically relevant symptoms (p = 0.013). There were no differences in basal EGJ pressure or mean DL between the two groups (Table 2).
### 3.2.2 Provocative tests

There were significant differences on provocative tests during HRM between EGJOO patients with and without clinically relevant symptoms. With MRS, both mean MRS-IRP ($p < 0.001$) and oesophageal pressurisation ($p < 0.001$) were higher in the presence of clinically relevant symptoms, while the proportion with contraction reserve was lower ($p = 0.014$) (Table 2). Similar findings were noted with RDC, with higher mean RDC-IRP and higher oesophageal pressurisation in the presence of clinically relevant symptoms ($p < 0.001$).

### 3.3 Timed barium oesophagogram findings

Although all 144 patients were asked to undergo TBE, only 95 (66.0%) ultimately underwent TBE. Radiographic evidence of EGJOO was noted in 65.7% (23/35) of patients with clinically relevant symptoms.
compared to none with no clinically relevant symptoms ($p < 0.001$, Table 3). Additionally, the mean barium column height at 5 minutes was significantly higher in the presence of clinically relevant symptoms ($p < 0.001$).

### 3.4 Prevalence of EGJOO according to Chicago classification v4.0

A complete investigation profile (HRM metrics, symptoms, and TBE findings) to determine the prevalence of EGJOO according to CCv4.0 criteria were available for 95/144 patients. Accordingly, the CCv4.0 prevalence of EGJOO was calculated out of a total of 1961 patients, and was 1.2% (23/1961, 95% CI 0.7%–1.6%), significantly lower than the CCv3.0 prevalence of 7.2% (144/2010, 95% CI 6.0%–8.3%). Among patients with clinically relevant symptoms, 23 of 35 patients (65.7%) with a complete investigation profile fulfilled CCv4.0 criteria for EGJOO. In contrast, none of patients with other foregut symptoms had barium retention on TBE5 ($p < 0.001$, Table 3).

### 3.5 Predictors of EGJOO

Median RDC-IRP in patients with a conclusive diagnosis of EGJOO as defined by CCv4.0 (21.4 mmHg, IQR 19.5–25.0 mmHg) were higher compared to those of patients without a conclusive EGJOO diagnosis (6.9 mmHg, IQR 5.3–9.9 mmHg, $p < 0.001$). On ROC analysis, RDC-IRP predicted a conclusive diagnosis of EGJOO as defined by CCv4.0 with an AUC of 96.1% (95% CI 91.5%–100%) (Figure 1). The optimal RDC-IRP cut-off, selected to maximise the sum of specificity and sensitivity, was 16.7 mmHg, with a sensitivity of 87.0% (95% CI 73.9%–100.0%), specificity of 97.1% (95% CI 92.6%–100.0%), NPV of 95.7%, (95% CI 91.3%–100%) and PPV of 91.3% (95% CI 78.6%–100%). Two additional thresholds were evaluated as predictors of conclusive EGJOO. The RDC-IRP threshold of 12 mmHg, corresponding to the upright IRP threshold proposed by CCv4.0, had 87% sensitivity (95% CI 73.9%–100%), 88.2% specificity (95% CI 80.8%–95.6%), 95.3% NPV (95% CI 90.3%–100%), and 71.7% PPV (95% CI 58.8%–87.0%) for a conclusive CCv4.0 diagnosis of EGJOO. The RDC-IRP threshold of 10.0 mmHg, reported to predict abnormal TBE in treated achalasia, had 95.7% sensitivity (95% CI 87.0%–100%), 75.0% specificity (95% CI 64.7%–85.3%), 98.1% NPV (95% CI 94.2%–100%), 56.4% PPV (95% CI 47.7%–67.7%) for a conclusive CCv4.0 diagnosis of EGJOO. When considering patients with a complete clinical, HRM, and TBE profile, 95.7% (22/23) with a conclusive CCv4.0 diagnosis of EGJOO had RDC-IRP above all three thresholds studied (>10.0 mmHg, >12 mmHg and >16.7 mmHg), and 100% (23/23) had oesophageal presurisation for ≥20% of the duration of the RDC. On the other hand, 23.6% (17/72), 11.1% (8/72) and 2.7% (2/72) of those without a conclusive diagnosis of EGJOO had RDC-IRP above the three thresholds, respectively, and 11.8% (8/68) had ≥20% oesophageal presurisation during RDC (Figure 2). There was a strong correlation between RDC-IRP and oesophageal presurisation ($p = 0.61$, $p < 0.001$) with higher RDC-IRP values corresponding to higher HRM metrics, and between RDC-IRP and barium column height at 5 minutes ($p = 0.71$, $p < 0.001$).

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### TABLE 3  Timed upright esophagogram findings

| TBE5 findings | All patients with EGJOO according to CCv3.0 $n = 144$ | Patients with clinically relevant symptoms $n = 54$ | Patients without clinically relevant symptoms $n = 90$ | $p$-value |
|---------------|---------------------------------------------------|-------------------------------------------------|-------------------------------------------------|-----------|
| Patients with TBE performed | 95 (66.0%) | 35 (64.8%) | 60 (66.7%) | 0.96 |
| Radiological signs of obstruction | 23/95 (24.2%) | 23/35 (65.7%) | 0/60 (0%) | <0.001 |
| Median barium column height at 5 min | 0.0 (0.0–0.0) | 1.0 (0.0–2.0) | 0.0 (0.0–0.0) | <0.001 |

Note: Values are reported as median (interquartile range) or counts (per cent). Abbreviations: EGJOO: oesophagogastric junction outflow obstruction; TBE, timed barium esophagogram. *statistical significance at the 0.001 level.
DISCUSSION

The clinical relevance of an EGJOO diagnosis using CCv3.0 has been questioned, with patients likely to undergo unnecessary additional testing and invasive treatments that may not change prognosis, since a large proportion improve with non-specific measures or no therapy. With this background, the recently published CCv4.0 updated diagnostic criteria strived to make EGJOO a more clinically relevant diagnosis, requiring symptoms of dysphagia and/or chest pain, and mandating supportive findings on complementary tests for a conclusive diagnosis. In this retrospective study we estimated the prevalence of conclusive EGJOO among diagnosis made using CCv3.0, which was expected to decline with use of stringent CCv4.0 criteria.

We demonstrate a 6-fold reduction in prevalence of EGJOO based solely on an abnormal median supine IRP, declining from 7.2% using CCv3.0 to 1.2% using CCv4.0 criteria, particularly by selecting out patients with clinically relevant symptoms, and by use of RDC. Our findings further support the use of provocative manoeuvres, especially RDC during HRM, as conclusive EGJOO confirmed by oesophageal barium retention on TBE could be predicted with impressive performance characteristics using RDC metrics, obviating need for adjunctive confirmatory testing when abnormal RDC metrics are found. Additionally, these findings lend further support for the expansion of the HRM test protocol recommended by CCv4.0.

In the years since EGJOO has been clinically recognised, it has become increasingly evident that this manometric pattern is a clinical conundrum. While a small proportion of patients with EGJOO based solely on an abnormal median supine IRP have true motor obstruction that responds to achalasia-like treatments, the majority require no therapy or non-specific medical approaches. Therefore, a singular management approach does not apply to all EGJOO patients. The new CCv4.0 criteria attempts to circumvent the clinical conundrum by requiring not just relevant symptoms, but also confirmation of outflow obstruction using TBE or FLIP.

Several of the steps recommended by CCv4.0 were factored into the current study. The first step involved the identification of patients with clinically relevant symptoms of dysphagia and chest pain, and mandating supportive findings on complementary tests for a conclusive diagnosis. In this retrospective study we estimated the prevalence of conclusive EGJOO among diagnosis made using CCv3.0, which was expected to decline with use of stringent CCv4.0 criteria. We demonstrate a 6-fold reduction in prevalence of EGJOO based solely on an abnormal median supine IRP, declining from 7.2% using CCv3.0 to 1.2% using CCv4.0 criteria, particularly by selecting out patients with clinically relevant symptoms, and by use of RDC. Our findings further support the use of provocative manoeuvres, especially RDC during HRM, as conclusive EGJOO confirmed by oesophageal barium retention on TBE could be predicted with impressive performance characteristics using RDC metrics, obviating need for adjunctive confirmatory testing when abnormal RDC metrics are found. Additionally, these findings lend further support for the expansion of the HRM test protocol recommended by CCv4.0.

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Several of the steps recommended by CCv4.0 were factored into the current study. The first step involved the identification of patients with clinically relevant symptoms of dysphagia and chest pain. When segregated by clinically relevant symptoms, reflux symptoms were reported less often, albeit not statistically significant. Median IRP during single swallows, MRS and RDC, as well as IBP were significantly higher when symptoms were clinically relevant, supporting obstructive pathophysiology. When applying the gold standard of abnormal TBE5, 65.7% with clinically relevant symptoms had radiographic EGJOO, and these patients fulfilled conclusive EGJOO criteria by CCv4.0. In contrast, none of the patients with other upper gastrointestinal symptoms had radiographic obstruction on TBE5. On the other hand, ten patients who reported dysphagia and/or chest pain in the context of an elevated supine median IRP did not have obstruction on TBE5, which is consistent with previous reports where primary EGJOO was associated with normal TBE5.
Although upright swallows were not performed, RDC was effective in identification of patients with radiographic obstruction on TBE. Obstruction during RDC has been associated with abnormal TBE findings, with published evidence supporting its value in confirming latent obstructive processes. Woodland et al. reported that an elevated RDC-IRP correlates with obstructive symptoms (as measured by the Eckardt score) and was the best predictor of EGJ obstruction on TBE. Penagini et al. also demonstrated that RDC-IRP strongly correlates with TBE, with RDC-IRP >10 mmHg providing excellent discrimination between complete from incomplete barium emptying in treated achalasia patients, leading the authors to speculate that RDC-IRP could be discriminative in identifying any obstructive oesophageal syndrome. Our findings support the value of RDC in patients with clinically relevant symptoms, where an RDC-IRP of 10 mmHg had 95.7% sensitivity, 75.0% specificity, 98.1% NPV, and 56.4% PPV in identifying conclusive EGJOO according to CCv4.0. Higher RDC-IRP thresholds had even better performance characteristics, and a threshold of 16.7 mmHg had the best performance characteristics, with sensitivity of 87.0%, specificity of 97.1%, NPV of 95.7%, and PPV of 91.3%. Oesophageal pressurisation during RDC is a surrogate for elevated RDC-IRP, as all patients with 97.1% NPV, and 56.4% PPV in identifying conclusive EGJOO according to CCv4.0. Higher RDC-IRP thresholds had even better performance characteristics, and a threshold of 16.7 mmHg had the best performance characteristics, with sensitivity of 87.0%, specificity of 97.1%, NPV of 95.7%, and PPV of 91.3%. Oesophageal pressurisation during RDC is a surrogate for elevated RDC-IRP, as all patients with elevated RDC-IRP also demonstrated pressurisation of ≥20% during RDC. Our findings thus confirm that RDC is a valuable addition to the HRM protocol, and that higher RDC-IRP values strongly predict RDC. Our findings thus confirm that RDC is a valuable addition to the HRM protocol, and that higher RDC-IRP values strongly predict RDC.

In summary, the more stringent CCv4.0 criteria have significantly reduced the prevalence of EGJOO compared to CCv3.0, allowing identification of clinically relevant radiographically confirmed outflow obstruction. The expansion of the HRM testing protocol to include provocative testing augments the diagnostic yield of conclusive EGJOO, and use of abnormal RDC-IRP may obviate the need for radiographic confirmation of EGJOO. The impact of the new EGJOO criteria on the therapeutic management of the disease remains to be investigated.41

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