J Neurogastroenterol Motil, Vol. 29 No. 1 January, 2023
pISSN: 2093-0879 eISSN: 2093-0887
https://doi.org/10.5056/jnm21250
Journal of Neurogastroenterology and Motility

Original Article

Clinical Characteristics of Patients With Ineffective Esophageal Motility by Chicago Classification Version 4.0 Compared to Chicago Classification Version 3.0

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Background/Aims
Chicago classification version 4.0 (CCv4.0) of esophageal motility disorders developed a more stringent diagnostic criteria for ineffective esophageal motility (IEM) than version 3.0. We studied the implications of the new diagnostic criteria on the prevalence of IEM, and clinically characterized and compared the population of patients who no longer meet diagnostic criteria for IEM to those who retain the diagnosis.

Methods
We included all consecutively performed high-resolution esophageal impedance manometries from 2014 to 2021. Three cohorts of patients with IEM were created: Patients with IEM by Chicago classification version 3.0 (CCv3.0; CC3 group), by CCv4.0 only (CC4 group), and by CCv3.0 who are now considered normal (Normal group). Demographics, manometric and reflux parameters, and clinical outcomes were compared.

Results
A total of 594 manometries were analyzed. Of those, 66 (11.1%) met criteria for IEM by CCv3.0 (CC3), 41 (62.0%) retained an IEM diagnosis using CCv4.0 criteria (CC4), while 25 (38.0%) patients no longer met criteria for IEM (Normal). The CC4 group had higher esophageal acid exposure, especially supine (% time - 18.9% vs 2.2%; $P = 0.005$), less adequate peristaltic reserve (22.0% vs 88.0%; $P = 0.003$), and higher Demeester score (49.0 vs 21.2; $P = 0.017$) compared to the Normal group. There was no difference in bolus clearance between the groups.

Conclusions
IEM under CCv4.0 has a stronger association with pathologic reflux, especially supine reflux, and inadequate peristaltic reserve, but impairment in bolus clearance is unchanged when compared with IEM diagnosed based on CCv3.0. Further studies are required to determine the implications of these findings on management strategies.
(J Neurogastroenterol Motil 2023;29:38-48)

Key Words
Esophageal motility disorders; Gastroesophageal reflux; Gastrointestinal motility; Manometry; Peristalsis

Received: December 24, 2021 Revised: September 16, 2022 Accepted: September 16, 2022

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Introduction

Ineffective esophageal motility (IEM) is a disorder of esophageal peristalsis in which the vigor and/or amplitude of contractions are decreased.[1] IEM is a relatively common finding on high-resolution esophageal impedance manometry (HRIM), thought to be found in as many as 31.0% of patients.[2] It is a diagnosis whose definition has changed over time. According to the Chicago classification version 3.0 (CCv3.0), IEM is diagnosed when at least 50% of swallows are ineffective, defined as a distal contractile integral (DCI) < 450 mmHg·sec·cm^3 without evidence of esophagogastric junction obstruction.[4] CCv3.0 also acknowledged a separate disorder termed fragmented peristalsis (FP), defined as at least 50% of swallows with a peristaltic break (PB) of at least 5 cm.[3] Together IEM and FP made up the category of minor motility disorders, indicating that their clinical significance is not absolute, but dependent on the clinical context.

Studies both prior and subsequent to the publication of the CCv3.0 raised questions about the clinical significance of the IEM diagnosis. There is overlap of GERD and IEM. One study suggested that approximately 60% of patients with IEM also have evidence of pathologic esophageal acid exposure on pH testing.[5] The patients with pathologic esophageal acid exposure were much more likely to respond to acid suppression compared to patients with IEM but normal esophageal acid exposure (74% vs 10%; $P < 0.001$). On the other hand, it has been noted that as many as 15% of healthy controls meet CCv3.0 criteria for IEM.[6] Furthermore, 1 study found that patients who met the criteria for IEM had decreased bolus clearance but no worse symptoms of dysphagia compared to patients with normal manometry results.[7] Other studies found that higher proportions of failed swallows better predicted deficits of bolus clearance, more severe symptoms of dysphagia, and increased gastroesophageal reflux burden than IEM alone.[8,9] In the most influential study, Rogers et al[10] showed that ≥ 50% failed swallows, and > 70% ineffective or fragmented swallows, were more predictive of pathologic esophageal acid exposure time (AET) and mean nocturnal baseline impedance compared to the CCv3.0 criteria for IEM.

These findings led to a change in criteria for IEM diagnosis in CCv4.0. According to the CCv4.0 criteria, > 70% of swallows must be ineffective, or at least 50% of swallows failed (DCI < 100 mmHg·sec·cm), in order to diagnose IEM. IEM under the CCv4.0 criteria is no longer considered a minor motility disorder, as that category has been eliminated. The real-world implications of these changes, in terms of describing the patients diagnosed with IEM under the CCv3.0 criteria who no longer meet criteria for IEM, have not yet been studied. In this study we demographically and clinically characterize patients who met criteria for IEM by CCv3.0 but are now considered to have normal motility, and compare them to patients who maintain the diagnosis of IEM under CCv4.0.

Materials and Methods

Sample Selection

All adult patients above age 18 who underwent HRIM in our healthcare system from December 2014 to February 2021 were included in the study. Patients were identified from the electronic medical record using current procedural terminology codes "91010," "91299," or "91037," and by searching for "manometry (esophageal)" on the Provation software using the procedure data export feature. Duplicate records were deleted. Four authors (M.K., S.A.A, S.D., and S.T.) performed focused manual chart review of all manometries identified, to extract the diagnosis given for each manometry by the reading physician. In order to ensure all potential cases of IEM were captured, we applied the following criteria to create a cohort of "potential IEM" patients, where patients would qualify if they met any of the criteria:

- The interpreting physician gave a diagnosis of IEM.
- There were at least 50% ineffective swallows (DCI < 450 mmHg·sec·cm) in the absence of a diagnosis of achalasia or absent contractility.
- There were at least 70% of a combination of ineffective swallows and swallows with a PB of > 5 cm, even in the absence of meeting the above 2 criteria (ie, 4 ineffective swallows and 4 swallows with PB).

All HRIMs that did not meet the above criteria were not reviewed further; the diagnosis given by the interpreting physician was documented. After creating the cohort of "potential IEM" patients in this manner, a panel of 2 authors with expertise in interpreting HRIM (Michael Kurin and Katarina Greer) reviewed each HRIM to determine whether they agreed with the diagnosis of IEM. Patients who had been initially diagnosed with by the interpreting physician of the HRIM but were determined by the panel to have a different diagnosis were excluded, as were patients who had an uninterpretable study due to inadequate acceptable swallows, and patients otherwise determined by the 2-author panel to be misdiagnosed with IEM. A determination was made by consensus of

these 2 authors. "Potential IEM" patients who did not meet this exclusion criteria formed the "confirmed IEM" cohort. This cohort was further subdivided into patients who met CCv3.0 criteria for IEM (CC3) vs those who only met criteria by CCv4.0 alone. The CC3 group was further subdivided into patients who met both CCv3.0 and CCv4.0 criteria for IEM (CC4 group), and patients who met only CCv3.0 criteria but have normal motility per CCv4.0 (Normal group).

Cohort Analysis

Further extensive chart review was performed to characterize all "confirmed IEM" patients. The medical record was reviewed for demographics, comorbidities, history of esophageal disease (GERD, eosinophilic esophagitis, and Barrett's esophagus), medical and surgical management before and after the HRIM, and indications for the HRIM. Additionally, findings on upper endoscopy, barium esophagogram or upper gastrointestinal contrast study, pH or pH/impedance testing, and gastric emptying studies were reviewed when available. HRIM parameters including bolus clearance were also reviewed, as were records pertaining to improvement in symptoms after HRIM. Charlson comorbidity index (CCI) was calculated for each patient based on presence of the relevant comorbid diseases as determined by the manual chart review.[11] Indications for HRIM were included if the symptom was identified in the documentation by the referring gastroenterologist as a symptom that warrants HRIM for further evaluation, or if they were listed by the motility nurse in the HRIM report as the indication. It is possible for each patient to have multiple indications for the HRIM. History of GERD and borderline GERD were determined by review of the findings on endoscopy and pH testing, using the Lyon consensus criteria.[12] Listing of GERD in the past medical history was not counted as GERD in this study unless the diagnosis could be verified in this manner. Presence of Barrett's esophagus required both endoscopic appearance of salmon-colored mucosa and histologic findings of goblet cells and intestinal metaplasia. Presence of hiatal hernia was determined by hiatal hernia noted on upper endoscopy, upper gastrointestinal contrast study, barium esophagogram, or HRIM. All HRIMs were completed with the Medtronic HRIM system (Medtronic Inc, Minneapolis, MN, USA), and studies were analyzed using either the Manoview or Sandhill Zvu (Sandhill Scientific Inc, Highland Ranch, CO, USA) software. All HRIMs at our institution are performed in the semi-recumbent position with 10 liquid swallows and when tolerated an additional 10 viscous swallows. Protocols for use of additional provocative maneuvers changed over the study period. When multiple rapid swallows (MRS) was performed, it was done only once. HRIM parameters collected included median integrated relaxation pressure (IRP), mean DCI, PB > 5 cm, mean distal latency (DL), number of ineffective and failed swallows, fragmented swallows, premature swallows, bolus clearance as measured by impedance, and results of MRS technique if performed. Bolus clearance was automatically determined by the software, and percent bolus clearance is the percentage of total swallows with complete bolus clearance. Peristaltic reserve was deemed adequate if the ratio of the DCI after MRS to the mean DCI was greater than 1:1.[1]

pH testing was either wireless ambulatory pH monitoring using the Bravo, or pH/impedance testing using Bravo (Medtronic, Covidien, CA, USA) and pH/impedance (Medtronic). Parameters collected from pH monitoring included AET, upright AET, supine AET, total reflux events, acid reflux events, supine reflux events, Demeester score, longest reflux event, number of reflux events > 5 minutes, symptom association probability, and symptom index. In order to pool reflux parameters from wireless pH testing and catheter-based pH/impedance testing for comparison between the cohorts, all numbers of reflux events from ambulatory pH testing were divided by 2 to provide a mean number of events per 24 hours. In order to avoid confounding by proton pump inhibitor (PPI) use, results of pH testing that was performed with the patient on a PPI were excluded from the final analysis of pH parameters.

The study protocol was approved in its entirety by our institution's institutional review board (IRB No. 20191652).

Statistical Methods

Continuous variables are reported as mean ± standard deviation, or median with interquartile range (IQR). Categorical data were compared using Fisher's exact test. Continuous data were compared using the Mann Whitney *U* test for a 2-tailed alpha. Statistical significance was presumed for $P < 0.05$. When calculating sample size, we estimated an IEM diagnosis yield of 11.0% in the CC3 group and yield of 7.0% in the CC4 group. Assuming 90% power and 0.05 significance level, a sample of 553 patients was needed to detect a significant difference between the 2 study arms.

Results

Using the aforementioned current procedural terminology codes, 345 HRIMs performed at our institution during the study period were identified. Using the Provation software, an additional 249 unique HRIMs were identified, for a total of 594 HRIMs. Initial review based on the initial inclusion criteria revealed that a

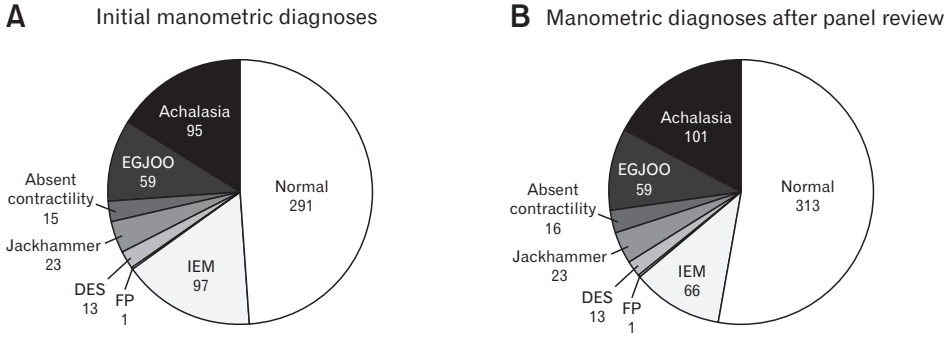

Figure 1. Breakdown of manometric diagnoses. EGJOO, esophagogastric junction outflow obstruction; DES, distal esophageal spasm; FP, fragmented peristalsis; IEM, ineffective esophageal motility.

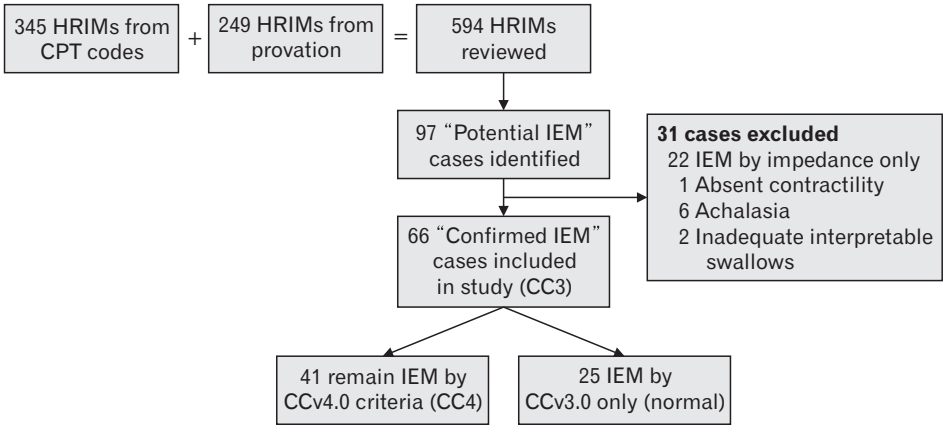

Figure 2. Selection of study cohorts. HRIM, high-resolution impedance manometry; CPT, Current Procedural Terminology; IEM, ineffective esophageal motility; CCv4.0, Chicago classification version 4.0; CCv3.0, Chicago classification version 3.0.

diagnosis of IEM in 97 (16.3%) of the 594 HRIMs, and a diagnosis of FP was made in 1 (0.0%) HRIM (Fig. 1A). After further review by the 2 physician expert interpreters of HRIM, 31 of these 97 were excluded, leaving 66 (11.1%) confirmed cases of IEM (Fig. 1B). The excluded cases were excluded either because they did not meet Chicago 3 or Chicago 4 criteria for IEM despite being originally diagnosed as IEM by the interpreting physician, the study was deemed uninterpretable due to the frequent presence of double swallows, or because they were found to have an alternative diagnosis of esophageal peristalsis such as achalasia or absent contractility (Fig. 2).

Of the 66 confirmed cases of IEM, all met CCv3.0 criteria for IEM (CC3 group), and none met CCv4.0 criteria alone. Of the 66 patients in the CC3 group, 41 (62.0%; 6.9% of entire study population) met criteria for IEM under CCv4.0 as well (CC4 group). The other 25 (38.0%) only met CCv3.0 criteria but not CCv4.0 (Normal group) (Fig. 3). There were no significant differences detected between the 3 groups in terms of age, gender, body mass index, race, substance use history, surgical history, or medication exposures (Table 1). More patients in the Normal group had pulmonary disease, but the CCI was greater in the CC4 group.

There were no significant differences between the 3 groups in

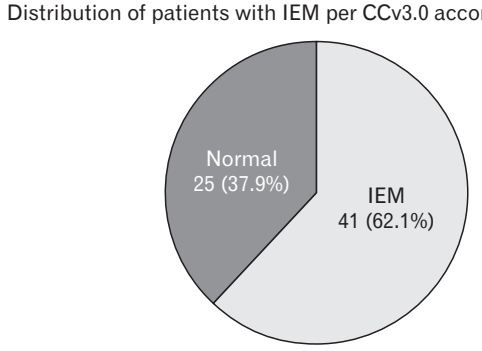

Figure 3. Distribution of patients with ineffective esophageal motility (IEM) per Chicago classification version 3.0 (CCv3.0), according to Chicago classification version 4.0 (CCv4.0) criteria.

prevalence of other esophageal disorders such as GERD, eosinophilic esophagitis, or the presence of endoscopically visualized reflux esophagitis (Table 1). Indications for the HRIM procedure were also similar in the 3 cohorts, with the most common indications in both groups being heartburn, dysphagia, dyspepsia, and reflux/regurgitation (Table 2). Five patients (20.0%) in the Normal group and 6 patients (15.0%) of the CC4 group had the HRIM for preoperative evaluation prior to planned anti-reflux surgery.

Table 1. Pre-test Characteristics

Characteristics	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
Demographics				
Gender male	24 (36)	8 (32)	16 (39)	NS
African American	14 (21)	5 (20)	9 (22)	NS
Caucasian	37 (56)	13 (52)	24 (59)	NS
Unknown/other race	15 (23)	7 (28)	8 (20)	NS
Current tobacco use	5 (8)	3 (12)	2 (5)	NS
Former tobacco use	14 (21)	7 (28)	7 (17)	NS
Current cannabis use	6 (9)	4 (16)	2 (5)	NS
Current heavy alcohol use	2 (3)	2 (8)	0 (0)	NS
Former heavy alcohol use	3 (5)	3 (12)	0 (0)	NS
Social alcohol use	33 (50)	12 (48)	21 (51)	NS
Age (yr)	55.6 ± 16.6	53.6 ± 17.3	56.9 ± 16.2	NS
BMI (kg/m^2)	29.6 ± 6.6	30.7 ± 6.4	29.0 ± 6.6	NS
Esophageal disease				
Proven GERD	14 (21)	5 (20)	9 (22)	NS
Borderline GERD	6 (9)	2 (8)	4 (10)	NS
Hiatal hernia	37 (56)	17 (68)	20 (49)	NS
Small	16 (24)	7 (28)	9 (22)	NS
Medium	8 (12)	3 (12)	5 (12)	NS
Large	7 (11)	5 (20)	2 (5)	NS
Unknown	6 (9)	2 (8)	4 (10)	NS
History of BE	2 (3)	1 (4)	1 (2)	NS
Reflux Esophagitis	9 (14)	3 (12)	6 (15)	NS
Grade A	2 (3)	1 (4)	1 (2)	NS
Grade B	3 (5)	2 (8)	1 (2)	NS
Grade C	1 (1)	0 (0)	1 (2)	NS
Grade D	1 (1)	0 (0)	1 (2)	NS
Unknown	2 (3)	0 (0)	2 (5)	NS
EoE	1 (1)	1 (4)	0 (0)	NS
Treatment exposures				
History of fundoplication	6 (9)	0 (0)	6 (15)	0.08
History of hiatal hernia repair	6 (9)	2 (8)	4 (10)	NS
History of bariatric surgery	8 (12)	2 (8)	6 (15)	NS
Sleeve	5 (8)	2 (8)	3 (7)	NS
RYGB	3 (5)	0 (0)	3 (7)	NS
PPI use	54 (82)	22 (88)	32 (78)	NS
H2B use	9 (14)	5 (20)	4 (10)	NS
Prokinetic use	2 (3)	1 (4)	1 (2)	NS
Comorbid conditions				
DM2	12 (18)	4 (16)	8 (20)	NS
Cardiac disease	11 (17)	5 (20)	6 (15)	NS
Lupus	2 (3)	0 (0)	2 (5)	NS
MCTD	2 (3)	1 (4)	1 (2)	NS
Scleroderma	1 (1)	0 (0)	1 (2)	NS
RA	1 (1)	0 (0)	1 (2)	NS
Sjogren's syndrome	4 (6)	0 (0)	4 (10)	NS
Asthma or COPD	12 (18)	8 (32)	4 (10)	0.04
CCI	2.2 ± 2.3	1.9 ± 1.9	2.4 ± 2.5	< 0.001

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
BMI, body mass index; GERD, gastroesophageal reflux disease; BE, Barrett's esophagus; RYGB, Roux-en-Y Gastric Bypass; PPI, proton pump inhibitor; H2B, histamine-2 receptor blocker; DM2, diabetes mellitus type 2; MCTD, mixed connective tissue disease; RA, rheumatoid arthritis; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index; CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as n (%) or mean ± SD.

Table 2. Indications for Manometry

Indications	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
Chest pain	11 (17)	4 (16)	7 (17)	NS
Heartburn	21 (32)	8 (32)	13 (32)	NS
Dysphagia	34 (52)	12 (48)	22 (54)	NS
Reflux/regurgitation	30 (45)	15 (60)	15 (37)	0.08
Dyspepsia/epigastric pain	11 (17)	5 (20)	6 (15)	NS
Cough	3 (5)	1 (4)	2 (5)	NS
Foreign body/globus	9 (14)	3 (12)	6 (15)	NS
Nausea or vomiting	4 (6)	1 (4)	3 (7)	NS
Belching	1 (1)	1 (4)	0 (0)	NS
Hiccups	2 (3)	1 (4)	1 (2)	NS
Pre-operative	11 (17)	5 (20)	6 (15)	NS

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as n (%).

Table 3. Results of pH Testing

pH Test parameter	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
Wireless pH testing	17 (26)	8 (32)	9 (22)	NS
pH/impedance	5 (8)	3 (12)	2 (5)	NS
AET (%)	8.1 (4.3-12.9)	5.2 (3.0-9.2)	12.8 (6.5-13.3)	0.026
Supine AET (%	3.8 (2.2-21.6)	2.2 (0.9-2.8)	18.9 (7.8-24.8)	0.0045
Total reflux events	37.3 (30.9-62.9)	38.5 (35.5-58)	34 (26.0-72.5)	NS
Acid reflux events	36.8 (21.3-55.8)	40.5 (23.6-60.3)	32 (24-35.5)	NS
Supine reflux events	7.0 (2.0-22.0)	2.8 (1.9-7.4)	22 (6.6-25.1)	0.040
Upright reflux events	35.0 (23.0-48.0)	34.5 (20.4-50.6)	36 (25-42.5)	NS
Reflux events > 5 min	5.0 (3.0-8.5)	5.5 (2-9)	4.8 (4-8.3)	NS
Longest reflux event (min)	21.0 (8.8-38.5)	14 (8.2-35.2)	21 (19.4-52.6)	NS
Demeester score	27.0 (19.5-49.1)	21.2 (13.0-25.9)	49 (28.6-54.8)	0.017
SAP (%)	97.5 (79.5-100)	97 (41-100)	98 (85-100)	NS
SI	50.0 (21.5-77.5)	50.8 (25.7-65.8)	36.0 (16.7-80.0)	NS

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
AET, acid exposure time; SAP, symptom association probability; SI, symptom index.
CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as n (%) or median (interquartile range).

Of the 66 CC3 patients, 28 (42.0%) underwent either ambulatory wireless pH testing, or catheter-based pH/impedance testing. These 28 patients were comprised of 14 (56.0%) of the patients in the Normal group, and 14 (34.0%) in the CC4 group. Three from each of these groups were performed on PPI and thus results of 11 tests in each group were analyzed. Patients in the CC4 group had significantly higher AET (median 12.8%, IQR 6.5-13.3 vs 5.2%, IQR 3.0-9.2; $P = 0.026$), supine AET (median 18.9%, IQR 7.8-24.8 vs 2.2%, IQR 0.9-2.8; $P = 0.005$), more supine reflux events (median 22, IQR 6.6-25.1 vs median 2.8, IQR 1.9-7.4), and a higher Demeester score (49, IQR 28.6-54.8 vs 21.2, 13.0-25.9; $P = 0.017$) compared to the Normal group (Table 3).

In terms of manometric findings, all 3 groups had similar measurements of IRP, lower esophageal sphincter pressure, upper esophageal sphincter pressure, and DL (Table 4). All groups had minimal fragmented, premature, or hypercontractile swallows. Bolus clearance measured by impedance for both liquid and viscous swallows were similar among the 3 groups. As expected, the CC4 group had a lower median DCI compared to the Normal group (495, IQR 408-666 vs 253.5, IQR 177-319).

Table 4. Manometric Findings

Finding	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
Median IRP	7.0 (5.0-11.0)	7.0 (5.0-10.0)	7.5 (5.0-11.0)	NS
Baseline LESP	14.5 (8.0-23.8)	14.0 (8.0-24.0)	16.0 (8.0-23.0)	NS
Baseline UESP	65.0 (43.0-101.8)	81.0 (58.0-121.0)	60.5 (43.0-97.0)	NS
Mean DCI	332.0 (232.0-518.0)	495.0 (408.0-666.0)	253.5 (177.0-319.0)	< 0.001
Distal latency	8.1 ± 2.2	8.2 ± 1.4	8.0 ± 2.7	NS
Ineffective swallows (%)	80.0 (60.0-90.0)	57.0 (50.0-60.0)	90.0 (80.0-100.0)	NA
Failed swallows (%)	30.0 (10.0-40.0)	20.0 (10.0-30.0)	36.0 (18.0-60.0)	NA
Premature swallows (%)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	0.0 (0.0-0.0)	NS
Fragmented swallows (%)	0.0 (0.0-0.0)	0.0 (0.0-10.0)	0.0 (0.0-0.0)	NS
Impedance bolus clearance liquid (%)	44.0 (25.3-63.7)	43.0 (30.0-70.0)	50.0 (20.0-62.0)	NS
Impedance bolus clearance viscous (%)	40.0 (30.0-60.0)	50.0 (40.0-65.0)	40.0 (20.0-57.0)	NS

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
IRP, integrated relaxation pressure; LESP, lower esophageal sphincter pressure; UESP, upper esophageal sphincter pressure; DCI, distal contractile integral; NS, not significant; NA, not applicable.
CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as median (interquartile range) or mean ± SD.

Table 5. Peristaltic Reserve

Intervention	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
MRS done	26 (39)	8 (32)	18 (44)	NS
Peristaltic reserve[b]	11 (17)	7 (88)	4 (22)	0.003
Subsequent antireflux surgery	13 (20)	7 (28)	6 (15)	NS
Complete wrap	9 (14)	5 (20)	4 (10)	NS
Partial wrap	4 (6)	2 (8)	2 (5)	NS
Sphincter augmentation surgery	1 (1)	1 (4)	0 (0)	NS

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
[b]Indicates n (%) of patients who had multiple rapid swallow (MRS) done.
NS, not significant.
CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as n (%).

Among the 18 patients from the CC4 group who had the MRS technique performed during their HRIM, 4 (22.0%) had adequate peristaltic reserve; whereas 7 of the 8 (88.0%) patients in the Normal group who had the MRS performed had adequate peristaltic reserve (Table 5). The 4 patients from the CC4 group who had adequate peristaltic reserve did not undergo antireflux surgery, and we were unable to determine whether their symptoms improved or resolved over time. Among the 14 patients from that cohort with inadequate peristaltic reserve, only 1 underwent antireflux surgery, and they received a partial wrap (Toupet fundoplication). For the majority of these patients we were also unable to determine whether their symptoms improved. The 1 patient from the Normal group who did not have adequate peristaltic reserve underwent Toupet fundoplication, and did experience symptom improvement after surgery. Among the 7 who had adequate peristaltic reserve, 4 did not undergo antireflux surgery, and 3 did (1 had a Toupet fundoplication, 1 had a Nissen fundoplication, and 1 had a magnetic sphincter augmentation). None of these 3 patients were found to have symptom improvement after their surgeries.

Management of patients after their HRIM was similar in all groups (Table 6). Nearly half of the patients in each cohort were recommended anti-reflux lifestyle modifications. A similar number in each cohort remained on PPI therapy or increased intensity of PPI therapy. Each had a small number who started a histamine H2 receptor antagonist, a tricyclic antidepressant, or a prokinetic agent. In terms of surgical management, a similar portion of each cohort underwent hernia repair alone, while 13 patients (20.0%) from the CC3 group (7 [28.0%] from the Normal group, and 6 [15.0%]

Table 6. Management and Outcomes

Outcome	CC3 group (n = 66)	Normal group (n = 25)	CC4 group (n = 41)	*P*-value[a]
Start/add/continue PPI	32 (48)	13 (52)	19 (46)	NS
Start/add/continue H2B	7 (11)	2 (8)	5 (12)	NS
Lifestyle modifications	27 (41)	10 (40)	17 (41)	NS
Increase PPI to BID	8 (12)	4 (16)	4 (10)	NS
Added prokinetic	2 (3)	1 (4)	1 (2)	NS
Added TCA	3 (5)	1 (4)	2 (5)	NS
No change or unknown	22 (33)	4 (16)	18 (44)	0.030
Hernia repair alone	3 (5)	1 (4)	2 (5)	NS
Antireflux surgery + hernia repair	13 (20)	7 (28)	6 (15)	NS
Nissen fundoplication	9 (14)	5 (20)	4 (10)	NS
Toupet fundoplication	4 (6)	2 (8)	2 (5)	NS
Sphincter augmentation surgery	1 (1)	1 (4)	0 (0)	NS
Documented symptom improvement	24 (36)	13 (52)	11 (27)	0.064
Documented lack of improvement	18 (27)	3 (12)	15 (37)	0.045
Unknown outcome	24 (36)	9 (36)	15 (37)	NS

[a]All reported *P*-values pertain to a comparison of Normal group to CC4 group.
PPI, proton pump inhibitor; H2B, histamine-2 receptor blocker; BID, bis in die (twice daily); TCA, tricyclic antidepressant; NS, not significant.
CC3 group, patients with ineffective esophageal motility (IEM) by Chicago classification version 3.0; CC4 group, patients with IEM by Chicago classification version 4.0; Normal group, patients who had IEM by Chicago classification 3.0 who no longer meet criteria under Chicago classification version 4.0.
Data are presented as n (%).

from the CC4 group) underwent anti-reflux surgery with hernia repair. One in the Normal group underwent magnetic sphincter augmentation while none did in the CC4 group.

In terms of outcomes after the HRIM, 24 patients (36.0%) from the CC3 group (13 [52.0%]) of the patients in the Normal group and 11 [27%] in the CC4 group experienced symptom improvement, as determined by review of subsequent clinician notes in the medical record (Table 6).

Discussion

One of the most clinically relevant changes in the CCv4.0 for the interpretation of HRIM is the increased stringency in the diagnostic criteria for IEM. Rather than a minor motility disorder requiring only 50% ineffective swallows, it is now a disorder of esophageal peristalsis that requires > 70% ineffective swallows or at least 50% failed swallows. CCv4.0 does not distinguish between major and minor motility disorders.[13] Our study is the first to investigate the real-world implications of this change on the prevalence and clinical characteristics of the population of patients diagnosed with IEM.

The main finding of our study is that among a group of 66 patients with a confirmed diagnosis of IEM according to the CCv3.0 criteria, 41 (62.0%) of them would retain this diagnosis under the CCv4.0 criteria. The remaining 25 (38.0%) would not meet criteria for any motility disorder according to the CCv4.0 criteria. Although theoretically possible to meet IEM CCv4.0 criteria but not CCv3.0, none of the patients in our study had this result. Therefore, the number of patients diagnosed with IEM as CCv4.0 is adopted across more centers can be expected to decrease substantially.

In our study, the overall prevalence of confirmed IEM changed from 11.1% under the CCv3.0 to 6.9% per the CCv4.0 criteria. To our knowledge, the prevalence of IEM per the CCv4.0 criteria has not yet been reported. However, the prevalence of IEM per CCv3.0 in our study is lower than reported in previous literature. Sikavi et al[14] reported a prevalence of IEM of 30.0%, though this was in a population previously diagnosed with laryngopharyngeal reflux. Boland et al[2] also reported a prevalence of 31.0%, a number that had increased with the advent of HRIM. However, this study was conducted in 2012-2013 prior to development of the CCv3.0 criteria, which were more stringent. A subsequent study by Monroy et al[15] demonstrated a prevalence of IEM per CCv3.0 criteria as 25.0% in symptomatic individuals, and 15.0% in healthy volunteers. The reasons for the substantially lower prevalence of IEM by CCv3.0 criteria in our study compared to previous literature (11.0% vs 25.0%) are unclear, but may in part be related to a referral bias of a higher proportion of patients at our center coming as referrals for invasive procedures as treatment of motility disorders. Disorders

with a higher prevalence in our study that make up this difference include achalasia (17.0% in our study vs 9.0% in Monrroy et al[15]), and esophagogastric junction outflow obstruction (10.0% in our study vs 2.5% in Monrroy et al[15]).

Our study's comparison of the CC3, Normal, and CC4 groups largely supports the notion that the increased stringency of the CCv4.0 criteria will provide a diagnosis of IEM that is more clinically significant than the CCv3.0 criteria. Patients in the CC4 group were significantly less likely to see their symptoms improve after their HRIM compared to the Normal group, suggesting that IEM in the latter group may have been a transient issue, or one more easily managed supportively. Moreover, we demonstrated that the CC4 group had significantly higher total AET, and that this difference was most pronounced with supine reflux. These findings support recent literature suggesting a higher pathologic acid burden co-occurs with IEM using criteria similar to the CCv4.0, but not the CCv3.0 criteria, a finding that was influential in making the IEM criteria more stringent in CCv4.0.[10] IEM is purported to lead to increased pathologic AET due to delayed clearance of refluxate,[12] mostly by secondary peristalsis.[16] This effect has been shown to be most pronounced in supine reflux.[17,18] Our study demonstrates that patients who meet CCv4.0 IEM criteria are substantially more likely to experience this pathologic acid exposure while supine. IEM is also thought to occur more frequently in patients with more severe GERD phenotypes.[19,20] Our study suggests this connection is likely strongest under the more stringent CCv4.0 criteria for IEM. It is interesting to note that despite these differences the number of patients able to be definitively diagnosed with GERD according to the Lyon consensus was not different between the 2 groups.

Only 22.0% of patients in the CC4 group had adequate peristaltic reserve as determined by MRS, compared to 88.0% of the Normal group. The lack of peristaltic reserve indicates a higher likelihood of dysphagia after antireflux surgery,[21] and is therefore often an important determining factor when deciding about surgical management of GERD. Our findings suggest that inadequate peristaltic reserve will be found in most cases of IEM under the CCv4.0 criteria, which may allow for clearer recommendations in the future pertaining to antireflux surgery in patients with IEM.

The clinically significant differences between the cohorts did not extend to parameters that would be related to transit symptoms. As expected based on the change in diagnostic criteria from CCv3.0 to CCv4.0, the CC4 group had a significantly lower median mean DCI. However, there were no other differences between the 2 groups in other manometric parameters. Additionally, there was no significant difference between the 2 groups in median liquid or viscous bolus clearance based on impedance measurements. Bolus clearance by impedance measurement is currently not a component of the CCv4.0 criteria, nor was it in the CCv3.0 criteria, so these impedance findings have no bearing on the manometric diagnosis. However, a prior study found an association between IEM and decreased bolus clearance compared to normal controls.[7] Another recent study demonstrated that both $\geq$ 30% failed swallows and $\geq$ 70% ineffective swallows were highly predictive of altered bolus transit.[22] As these parameters are similar to the CCv4.0 criteria for IEM, our finding of no difference in bolus clearance between the Normal and CC4 groups is in contrast to this study. Our findings may suggest that in terms of transit deficits and associated symptoms such as dysphagia, there may be no clinically significant difference between patients with IEM under CCv3.0 compared to CCv4.0. Further research is required, ideally with prospective studies, to resolve this question.

There were also no important differences between the 3 groups in terms of indications for the HRIM, demographics, or comorbid diseases. Although the CCI was higher in the CC4 group and this reached statistical significance compared to the Normal group, the small difference is unlikely to be clinically significant. The importance of the greater incidence of pulmonary disease in the Normal group is also difficult to interpret.

Whether there are effective ways to manage IEM independent of GERD remains unknown, and typically no specific therapeutic intervention is recommended.[1] The mainstay of IEM management is optimization of GERD management.[23] Other agents such as prokinetics have not been found to be effective at improving esophageal contractility and are not currently recommended.[1] Our comparison did not find any significant differences in management strategies between the groups.

We acknowledge our study has limitations. It is a single center study from a tertiary care academic center with a relatively low prevalence of IEM, and may not be generalizable to all centers or populations. Similarly, there is a possibility of selection bias if a particular disease phenotype is more likely to be referred for HRIM at our center. However, collection of 8 years of HRIMs allowed for a robust sample size, and based on power calculations, our sample of 594 manometries is sufficient to detect the 4.2% difference in the prevalence of IEM by CCv3.0 (11.1%) and CCv4.0 (6.9%). However, sample sizes were smaller when comparing pH, manometric, impedance parameters, and clinical outcomes between the Normal and CC4 groups, and these results should be interpreted cautiously, especially since only a minority of patients from each group underwent reflux testing. Due to sample size constraints,

we also pooled together data from 2 different types of reflux testing, wireless pH testing and catheter-based pH/impedance testing. While we do recognize these are different tests and the results may differ, the breakdown of portion of patients who underwent each type of reflux test was similar between the groups and it is thus unlikely to impact our outcomes. Additionally, as this is a retrospective study data is dependent on the electronic medical records. Manual chart review was performed and individual studies were reviewed for diagnostic accuracy. However, complete data, especially about outcomes and management strategies, was not always available for all patients. The retrospective nature of the study also did not allow for use of validated questionnaires to assess symptom severity at the time of the HRIM or during follow-up.

In conclusion, our study demonstrated that more than one third of patients previously diagnosed with IEM under the CCv3.0 criteria will no longer meet diagnostic criteria under the CCv4.0. Those diagnosed with IEM under the new, more stringent, criteria, have a disease process less likely to improve over time, associated with more pathologic esophageal acid exposure, especially when supine, and with frequent inadequate peristaltic reserve. However, they are not more likely to have impaired bolus transit. While these changes to the diagnostic criteria for IEM have increased the likelihood that patients with IEM will have pathologic GERD, future adjustments to the Chicago classification may allow IEM to be more predictive of pathologic GERD. Further studies are required to determine whether new management strategies can be developed that will be beneficial to this population.

Financial support: None.

Conflicts of interest: None.

Author contributions: Michael Kurin designed the study; Michael Kurin, Syed A Adil, Sofi Damjanovska, and Samuel Tanner collected the data, Michael Kurin and Katarina Greer reviewed all IEM diagnoses and analyzed the data; Michael Kurin wrote the manuscript; and Katarina Greer, Syed A Adil, Samuel Tanner, and Sofi Damjanovska critically edited the manuscript. All co-authors approved the final version of the manuscript for submission.

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