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Prevalence of delayed gastric emptying in patients with gastroparesis-like symptoms

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Summary

Background: The European consensus defined gastroparesis as a condition characterised by delayed gastric emptying (GE) in the absence of mechanical obstruction, with a symptom pattern of predominant nausea and/or vomiting and overlapping postprandial distress syndrome (PDS). The distinction between patients with gastroparesis and those with functional dyspepsia (FD), another gastrointestinal condition characterised by predominant PDS or epigastric pain syndrome symptoms, is ongoing.

Aim: To investigate the extent that symptom patterns may differentiate gastroparesis from FD.

Methods: This retrospective study included 637 patients from Leuven University Hospital in 2006–2021 who had upper gastrointestinal symptoms, underwent a GE test, and completed the Dyspepsia Symptom Severity (DSS) questionnaire. Patients were identified as with gastroparesis-like symptoms (GPLS; *i.e.*, moderate to severe nausea with moderate to severe PDS) or FD symptoms (not fitting GPLS). We excluded patients aged <18 years, and those with diabetes, organic gastrointestinal disease or a history of abdominal surgeries. Demographic and clinical variables were compared.

Results: Among 545 patients, 238 reported GPLS and 307 reported FD symptoms. Those with GPLS had a significantly higher prevalence of delayed GE (half emptying time (T1/2) ≥109 min) and lower body mass index than those with FD (33.2% vs 17.6%, $p < 0.01$; 19.9 vs 21.2, $p < 0.01$, respectively). Among GPLS patients, those with delayed GE had higher DSS than those without (13.0 vs 12.0, $p < 0.01$).

Conclusions: In tertiary care patients who reported gastroparesis or FD symptoms, the presence of delayed GE was associated with GPLS. In patients with GPLS, delayed GE was associated with higher symptom severity.

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1 | INTRODUCTION

Gastroparesis (GP) and functional dyspepsia (FD) are two common sensorimotor disorders in the gastroduodenal region.[1,2] GP is a clinical syndrome characterised by delayed gastric emptying (GE) in the absence of a mechanical obstruction.[3-5] Several symptoms have been reported in GP patients, including nausea and vomiting, post-prandial fullness, early satiety and bloating.[6] On the contrary, FD is defined by symptoms of postprandial fullness, early satiation, epigastric pain and/or epigastric burning and is diagnosed based on the ROME IV diagnostic criteria.[7] Symptom recognition is crucial for the diagnosis and treatment of gastrointestinal functional and motility disorders. Currently, symptom-based management of GP and FD forms the mainstay of therapy.[8] A recent study by the Gastroparesis Clinical Research Consortium showed that patients with GP and FD at tertiary hospitals are not distinguishable based on clinical symptoms and pathologic features and concluded that GP and FD are both on a spectrum of gastric sensorimotor dysfunction.[9] The distinction between patients with GP from those with FD is a matter of ongoing debate over the last decade because of the large symptom overlap and the variable correlation between symptoms and delayed GE.[10-12] The recent United European Gastroenterology (UEG) and European Society for Neurogastroenterology and Motility (ESNM) consensus identified nausea and vomiting as cardinal symptoms of GP, in the presence of overlapping postprandial distress syndrome (PDS).[13] In addition, the European consensus on FD identifies early satiation, postprandial fullness, and epigastric pain or burning as predominant symptoms in FD.[14] These two recent consensuses seem to provide directions for both the diagnostic process and treatment options in both conditions. However, it remains to be established to what extent the symptom patterns may differentiate GP versus FD.

Therefore, in the current study, the database of the University Hospitals Leuven was used to estimate the prevalence of delayed GE, using the GE breath test in patients with a symptom pattern suggestive of GP, compared to those with a FD symptom pattern.

2 | MATERIALS AND METHODS

2.1 | Study population

This was a retrospective study that included 637 patients with upper gastrointestinal symptoms who underwent a ^{13}C-octanoic acid GE breath test and completed the Dyspepsia Symptom Severity (DSS) questionnaire at least once in the last 15 years (2006–2021). DSS questionnaires were obtained from consecutive patients with upper gastrointestinal symptoms seen at the Leuven Neurogastroenterology and Motility clinic. Gastric emptying tests were routinely scheduled for both research purposes and clinical indications unless the patient had a previous test at another hospital. The interval of DSS–GE evaluation was less than 2 months. All patients had chronic dyspeptic symptoms for at least 6 months and normal upper endoscopy. The DSS consists of eight dyspeptic symptoms (epigastric pain, postprandial fullness, upper abdominal bloating, early satiation, nausea, vomiting, epigastric burning, belching) evaluated during the last 2 weeks on a 4-point Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and is widely used in clinical research as it is reproducible and sensitive to change.[15,16] DSS score is defined as the sum of all eight items. Since diabetic and surgical GP with potentially different pathophysiology, the aim of the current work focused on discriminating idiopathic GP from FD. Exclusion criteria were age below 18 years (18 included), the presence of organic gastrointestinal disease, diabetic mellitus, a history of abdominal surgery or eating disorders based on the medical records. Accessible data of sensitivity to gastric distention, gastric accommodation by barostat and Rome II Diagnostic Criteria for Irritable Bowel Syndrome (IBS) in included patients were also analysed to provide additional insights on potential mechanisms of symptom patterns and concomitant lower gastrointestinal symptoms in the spectrum.

2.2 | Case definition of subjects with gastroparesis-like symptoms

Using the DSS questionnaire, we defined individuals with symptoms of nausea (Likert scale moderate to severe) and/or vomiting combined with postprandial fullness (Likert scale moderate to severe) or early satiety (Likert scale moderate to severe) as gastroparesis-like symptoms (GPLS). Individuals with severe nausea, accompanying severe postprandial fullness or early satiety were subcategorised into having severe GPLS; the remaining GPLS patients were categorised into the moderate GPLS group. Those with chronic dyspeptic symptoms but not fulfilling the GPLS criteria were categorised as having FD symptoms. Patients with FD symptoms were rated as severe (scores 3 in more than or equal to 2 symptoms) and the remaining patients were categorised into the mild/moderate FD symptoms group.

2.3 | Gastric emptying test

The GE rate for solid food (pancake) was measured by the ^{13}C-octanoic acid breath test for 4 h.[17-19] The pancake contains 11.2 g fat, 31.7 g carbohydrate and 8.4 g protein with 250 kcal. All drugs potentially affecting gastrointestinal motility, such as narcotic pain relievers, anticholinergic medication and prokinetic agents, were discontinued at least 2 days prior to the gastric emptying studies. The $T_{1/2}$ was calculated according to either modified power exponential formula based on the scintigraphic retention curve from Siegel et al. (t1/2 s = (−1/k)×ln(1–2(−1/ß))) or a purely mathematical formula from the characteristic shape of a *CO2 excretion curve described by Maes et al. (t1/2 ex $=\int_0^{0.5} f(t)dt$).[20,21] Delayed emptying was defined as $T_{1/2}$ above the 95% confidence interval (CI) in healthy volunteers (≥109 min for solids).

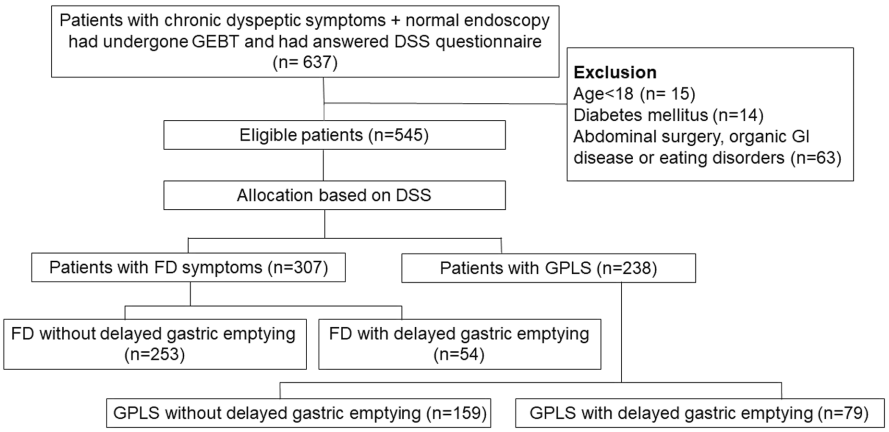

FIGURE 1 The flowchart of patient inclusion and exclusion. FD, functional dyspepsia; GPLS, gastroparesis-like symptoms; DSS, Dyspepsia Symptom Severity.

TABLE 1 Characteristics of patients in functional dyspepsia and gastroparesis-like symptom group (*N*, %/median [interquartile range])

	FD symptoms (*n* = 307)	GPLS (*n* = 238)	*p* value
Gender			
Female	194 (63.2%)	188(79.9%)	<0.01
Age (years)	41 (31–56)	38.0 (27.8–49)	<0.01
BMI	21.2[a] (18.2–24.8)	19.9[b] (15.7–23.1)	<0.01
DSS	8.0 (6–11)	13.0 (11–15)	<0.01
$T_{1/2}$ (min)	76.0 (61.0–97.0)	86.5 (65.8–119.3)	<0.01
Delayed gastric emptying	54 (17.6%)	79 (33.2%)	<0.01

Note: Results expressed as median (interquartile range) for a continuous variable or count (%) for a categorical variable.

Abbreviations: BMI, body mass index; DSS, Dyspepsia Symptom Severity; FD, functional dyspepsia; GPLS, gastroparesis-like symptoms; $T_{1/2}$, half gastric emptying time.

[a]50 FD symptoms patients missing BMI data.

[b]55 GPLS patients missing BMI data.

2.4 | Gastric barostat study

The gastric barostat study was the same as described in previous studies.[22-24] Following an overnight fast, a double-lumen polyvinyl tube (Salem sump tube 14 Ch.; Sherwood Medical, Petit Rechain, Belgium) with a folded adherent plastic bag (1200-ml capacity; maximal diameter, 17 cm) was introduced through the mouth. The polyvinyl tube was then connected to a programmable barostat device (Synectics Visceral Stimulator). The bag was unfolded by inflating a fixed volume of 300 ml air and was deflated completely. The subjects were then positioned with the knees bent (80°) and the trunk upright comfortably. Then, minimal distending pressure (MDP) was determined by increasing intrabag pressure by 1 mm Hg until a volume of 30 ml was reached for 2 min. This pressure level was equal to the intra-abdominal pressure. Subsequently, isobaric distentions were performed in stepwise increments of 2 mm Hg starting from MDP, each lasting for 2 min. The corresponding intragastric volume was also recorded. Gastric compliance was calculated as the slope of the best-fit straight line of gastric volume vs gastric pressure. Subjects were instructed to score their perception of upper abdominal sensations at the end of every distending step on a scale graded 0–6. The endpoint of each sequence of distentions was established at an intrabag volume of 1000 ml or when the subjects reported discomfort or pain (score of 5 or 6). Gastric sensitivity to distention was defined as perception or discomfort pressure above MDP. After a 30-min adaptation period with the bag completely deflated, the pressure level was set at MDP +2 mm Hg for 90 min to measure gastric accommodation. After 30 min, a liquid meal (200 ml, 300 kcal, 13% proteins, 48% carbohydrates and 39% lipids; Nutridrink) was administered. The gastric tone measurement was continued for 60 min after the meal. Gastric accommodation was expressed as the difference between average pre- and post-prandial intra-balloon volumes.

2.5 | Statistical analysis

Quantitative data are presented as the median and interquartile range (IQR_{25-75}) for variables not normally distributed. The prevalence of delayed GE was calculated as a percentage with a 95% CI of patients with GPLS. Symptom severity scores were also compared in the GE subgroups (delayed vs. normal). Categorical variables were analysed using the chi-squared test and continuous variables were compared with the Mann–Whitney *U* test. Barostat values were

expressed as mean ± SEM and compared using the unpaired t test. For the analysis of multi-group comparisons, the Kruskal–Wallis test was performed, followed by the Dunn–Bonferroni test. Post hoc comparisons, adjusted for multiple comparisons by Bonferroni's correction, were also performed if chi-square results showed significant effects. Throughout, the statistical significance level used was 0.05. All statistics have been performed with SPSS 22 (SPSS) for Windows.

3 | RESULTS

3.1 | Prevalence of delayed gastric emptying in gastroparesis-like symptoms and functional dyspepsia symptoms

The flowchart of patient inclusion is depicted in Figure 1. Amongst 545 eligible patients (70.1% female; median age 40 [30–52] years), a total of 133 had delayed GE (24.4%). Based on the data collected via the DSS questionnaire, 238 patients reported GPLS and 307 patients reported FD symptoms. Patients with GPLS were younger than FD symptoms (41 [31–56] vs 38.0 [27.8–49] years, $p < 0.01$) and were more likely to be female (79.0% vs 63.5%, $p < 0.01$). The prevalence of delayed GE in patients with GPLS was significantly higher than in the FD symptoms group (33.2% [27.2–39.7] vs 17.6% [13.5–22.3], $p < 0.01$). The median $T_{1/2}$ was significantly longer in GPLS, compared to in FD symptoms (86.5 [65.8–119.3] vs 76.0 [61.0–97.0] min, $p < 0.01$). In addition, patients with GPLS had a significantly lower body mass index (BMI, 19.9 [15.7–23.1] vs 21.2 [18.2–24.8], $p < 0.01$; Table 1).

When subgrouping GPLS patients into moderate ($n = 189$) and severe ($n = 49$), the baseline characteristics of patients in 3 groups are shown in Table 2. The DSS score was statistically significantly higher in severe GPLS, compared to moderate GPLS (16.0 [13.0–20.0] vs 12.0 [11.0–14.0], $p < 0.01$, respectively). The median $T_{1/2}$ of FD symptoms, moderate GPLS and severe GPLS were 76.0 (61.0–97.0), 84.0 (64–117) and 100 (71–128) minutes with significant differences between the three groups. According to the Dunn-Bonferroni post hoc test, the median $T_{1/2}$ was significantly longer in patients with severe GPLS and moderate GPLS compared to FD symptoms ($p < 0.01$, $p = 0.04$, respectively). However, there were no significant differences between moderate and severe GPLS ($p = 0.25$). In patients with severe GPLS, the prevalence of delayed emptying was 42.9% (28.8–57.8). The prevalence of delayed GE was not statistically significantly different between moderate (30.7%) and severe GPLS after post hoc tests ($p = 0.32$) (Figure 2). Similarly, when subgrouping FD symptoms patients into mild/moderate ($n = 234$) and severe ($n = 73$), the DSS in severe FD was significantly higher than mild/moderate FD (13 [10–15] vs 8 [6–10], $p < 0.01$). The prevalence of delayed GE was not significantly different in the mild/moderate and severe FD symptoms groups (17.8% [9.8–28.5] vs 17.5% [12.8–23.0], $p = 0.96$). The BMI of moderate GPLS was significantly lower compared to FD symptoms (20.0 [15.2–23.3] vs 21.2 [18.2–24.8], $p = 0.03$). The pairwise comparison of moderate GPLS vs severe GPLS and FD symptoms vs severe GPLS in BMI showed no significant difference ($p = 1.0$, 0.6, respectively). In contrast, the BMI was significantly different between the mild/moderate and the severe FD symptoms group (21.1 [17.8–24.2] vs 22.4 [19.8–26.2], respectively, $p = 0.04$).

The prevalence of delayed GE stratified by age and sex is given in Table 3. The prevalence of delayed GE was similar in males and females with GPLS and FD symptoms (34.0% [21.2–48.8] vs 32.6% [26.1–39.8], $p = 0.80$; 14.3% [8.4–22.2] vs 19.5% [14.2–25.8], $p = 0.25$, in GPLS and FD symptoms, respectively). When looking at specific age groups, there were also significant differences in the prevalence of delayed GE between FD symptoms and GPLS in the 18–39 and 65 and above age groups (both $p < 0.01$). However, there was only a tendency towards difference in the 40–64 age group ($p = 0.06$).

3.2 | Gastric barostat study

There were 218 patients (108 with GPLS and 110 with FD symptoms) who underwent gastric barostat studies for research purposes as part of pathophysiological studies at the unit. The values of

TABLE 2 Characteristics of patients in functional dyspepsia, moderate gastroparesis-like symptoms and severe gastroparesis-like symptoms group (*N*, %/median [interquartile range])

	FD symptoms ($n = 307$)	Moderate GPLS ($n = 189$)	Severe GPLS ($n = 49$)	*p* value
Gender				
Female	194 (63.2%)	151 (79.9%)	37 (75.5%)	<0.01
Age (years)	41 (31–56)	39 (27–50)	37 (30–45)	0.01
BMI	21.2[a] (18.2–24.8)	20.0[b] (15.2–23.3)	18.8[c] (16.5–22.4)	<0.01
DSS	8.0 (6–11)	12.0 (11–14)	16.0 (13–20)	<0.01

Note: Results expressed as median (interquartile range) for a continuous variable or count (%) for a categorical variable.

Abbreviations: BMI, body mass index; DSS, Dyspepsia Symptom Severity; FD, functional dyspepsia; GPLS, gastroparesis-like symptoms; $T_{1/2}$: half gastric emptying time.

[a]50 FD symptom patients missing BMI data.

[b]46 moderate GPLS patients missing BMI data.

[c]9 severe GPLS patients missing BMI data.

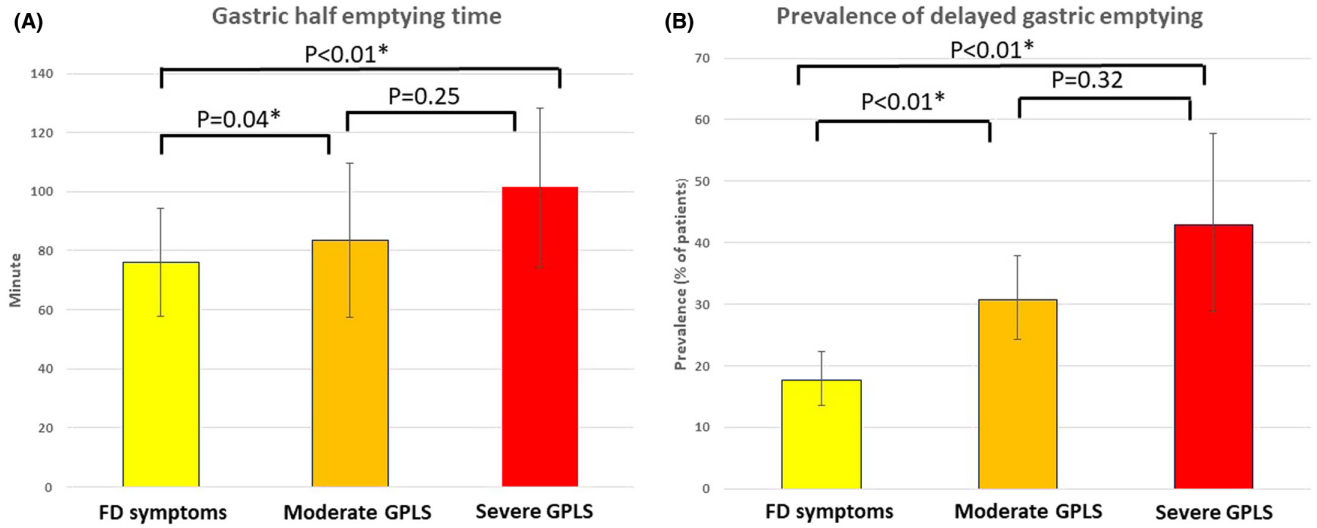

FIGURE 2 Gastric half emptying time (A) and prevalence of delayed gastric emptying (B) in FD symptoms, moderate GPLS and severe GPLS. FD, functional dyspepsia, GPLS, gastroparesis-like symptoms.

TABLE 3 Age-specific prevalence of delayed gastric emptying in two patient groups (% and 95% CI)

	FD symtoms (n = 307)	GPLS (n = 238)	p value
Overall prevalence	17.6% (13.5–22.3)	33.2% (27.2–39.6)	<0.01
Prevalence by sex			
Female	19.5% (14.2–25.8)	33.0% (26.3–40.2)	<0.01
Male	14.3% (8.4–22.2)	34.0% (21.2–48.8)	<0.01
Prevalence by age group			
18–39	18.7% (12.6–26.2) 26/139	34.1% (26.0–43.0)	<0.01
40–64	18.7% (12.5–26.3)	29.2% (20.3–39.3)	0.06
65 and above	8.8% (1.9–23.7)	53.9% (25.1–80.8)	<0.01

Abbreviations: FD, functional dyspepsia; GPLS, gastroparesis-like symptoms.

barostat studies were shown in Table 4. The MDP of GPLS and FD symptom groups were not different (6.6 ±2.6 vs 6.6 ±2.5, p = 0.92). Patients with GPLS had significantly lower thresholds for discomfort during isobaric distensions (8.0 ±3.4 vs 9.9 ±5.0 mmHg above MDP, p = 0.01), but not for first perception (3.4 ±2.6 vs 4.0 ±3.0 mm Hg above MDP, p = 0.28). No significant differences between GPLS and FD symptoms were found in gastric compliance (61.0 ±23.0 vs 64.9 ±36.4 ml/mm Hg, p = 0.051) and accommodation (147.3 ±144.7 vs 121.0 ±136.2 ml, p = 0.37). GPLS and FD symptom groups had similar prevalences of hypersensitivity to gastric distention and impaired gastric accommodation (58.3% [48.5–67.8] vs 69.1% [60.0–77.6], p = 0.10, 32.4% [23.7–41.2] vs 33.6% [24.9–43.3], p = 0.85, respectively).

3.3 | Gastroparesis-like symptoms and irritable bowel syndrome

The ROME II IBS Diagnostic questionnaire was used in 105 patients with GPLS and 159 patients with FD symptoms. There were 56 IBS patients in GPLS, including 41.1% IBS with constipation, 30.4% IBS with diarrhoea, 5.4% IBS mixed type and 23.2% unspecified IBS. In contrast, 68 patients fulfilled IBS criteria in the FD symptoms group, including 38.2% IBS with constipation, 17.6% IBS with diarrhoea, 10.3% IBS mixed type and 33.8% unspecified IBS. The prevalence of overlap with IBS in the two groups was not significantly different (53.3% [43.3–63.1], 42.8% [35.0–50.9], respectively, p = 0.09). Including all four IBS subtypes, the distribution did not differ significantly between both groups (p = 0.23).

3.4 | Comparison of symptom severity between patients with and without delayed gastric emptying in the gastroparesis-like symptoms and functional dyspepsia groups

Symptoms based on patient recall using the DSS were significantly higher in the GPLS group, compared to FD symptoms (8.0 [6–11] vs 13 [11–15], p <0.01). A confirmed diagnosis of GP requires

	FD symptoms ($n = 110$)	GPLS ($n = 108$)	p value
Minimal distending pressure (MDP, mm Hg)	6.6 ± 2.5	6.6 ± 2.6	0.92
Pressure at perception (mm Hg)	4.0 ± 3.0	3.4 ± 2.6	0.28
Pressures at discomfort (mm Hg)	9.9 ± 5.0	8.0 ± 3.4	0.01
Hypersensitivity to gastric distention (<6.6 mm Hg above MDP) (% and 95% CI)	69.1% (60.0–77.6)	58.3% (48.5–67.8)	0.10
Compliance (ml/mm Hg)	64.9 ± 36.4	61.0 ± 23.0	0.051
Volume of gastric accommodation (expressed as Δ volume in postprandial h 1) (ml)	121.0 ± 136.2	147.3 ± 144.7	0.37
Impaired fundus accommodation (mean volume increase < 64 ml) (% and 95% CI)	33.6% (24.9–43.3)	32.4% (23.7–41.2)	0.85

TABLE 4 Overview values of the FD symptoms and GPLS group during gastric barostat studies for gastric sensitivity and gastric accommodation

Abbreviations: FD, functional dyspepsia; GPLS, gastroparesis-like symptoms.

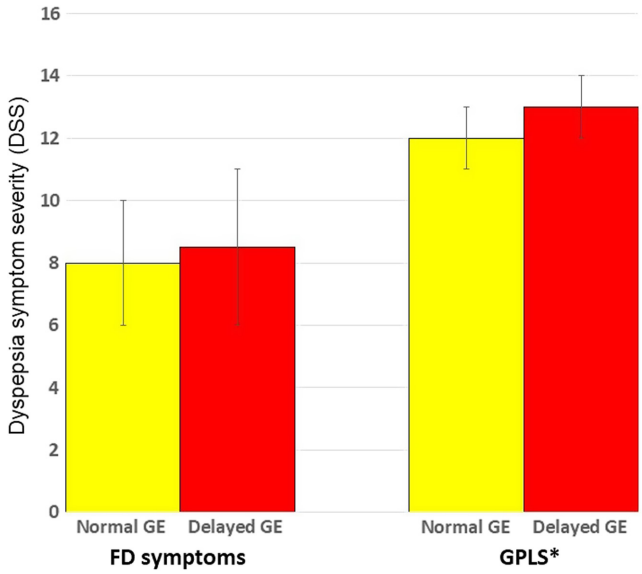

FIGURE 3 Relationship between symptom severity and delayed gastric emptying in FD symptoms and GPLS. *$p < 0.05$ normal GE vs delayed GE. FD, functional dyspepsia; GPLS, gastroparesis-like symptoms; GE, gastric emptying.

measurement of delayed GE after the recognition of the clinical symptoms. Patients with GPLS and FD symptoms were divided into a normal GE group and a delayed GE group according to the previously defined cut off for $T_{1/2}$ of 109 min. Patients with GPLS and confirmed delayed GE had significantly higher DSS than patients with GPLS without delayed GE (13 [12–16] vs 12 [11–15], $p < 0.01$). In contrast, in the FD symptoms group, there was no difference in DSS between patients with delayed and with normal GE (8.0 [6.0–11.0] vs 8.5 [6.0–11.3], $p = 0.96$; Figure 3). For individual symptoms, severe symptoms of postprandial fullness and upper abdominal bloating were significantly more frequent in the delayed GE group, compared to the normal GE group, amongst patients with GPLS. Table 5 summarises the grading of dyspeptic symptoms in the different groups.

4 | DISCUSSION

In order to establish the epidemiology of GP, the prevalence of subjects with the appropriate symptom pattern needs to be known, as well as the proportion of those in whom delayed GE can be confirmed. A recent study from the Rome IV Global Epidemiology survey showed symptoms suggestive of GP affected 0.9% of the adult population worldwide.[25] In the current study, we used a database of subjects who underwent a GE study and filled out symptom questionnaires, allowing us to evaluate the prevalence of delayed emptying in those with GPLS according to the European consensus, in comparison to patients who underwent GE testing and who did not fulfil these symptom criteria. In order to investigate the correlation between symptom severity and GE rate, we used DSS to define GPLS in the present study, instead of the ROME IV Diagnostic Questionnaires applied in the previous epidemiological study.

The overall prevalence of delayed GE in the entire cohort (24.4%) is comparable to findings of a study involving 1333 GE scintigraphy scans which showed 21% of delayed GE and another study including 1287 patients with upper gastrointestinal symptoms which found 27.1% of patients had delayed GE in the US.[26,27] In addition, one study focusing on diabetes also reported 19.4% of diabetic patients with upper gastrointestinal symptoms had delayed gastric emptying.[28] In those with "GPLS", a combination of symptoms of nausea and vomiting with those of PDS, based on the European consensus on GP, a significantly higher prevalence of delayed GE was found, compared to those not fulfilling these criteria. The findings confirm that the symptom pattern as supported by the European consensus identifies a group of subjects with an increased likelihood of having delayed emptying and thus being diagnosed with GP. Furthermore, the symptom-based approach not only increased the proportion of delayed GE in the identified GPLS group but also reduced the proportion of delayed GE in the patients with FD symptoms (not fulfilling GPLS criteria) to 18%. When investigating potentially important abnormalities other than GE, we found similar prevalences

TABLE 5 Frequency of severity for each of eight DSS symptoms in gastroparesis-like symptoms and functional dyspepsia symptoms groups with and without delayed gastric emptying (%).

Questionnaires	Level	FDS without delayed GE ($n = 253$)	FDS with delayed GE ($n = 54$)	p	GPLS without delayed GE ($n = 159$)	GPLS with delayed GE ($n = 79$)	p
Epigastric pain	Absent	81 (32.0)	23 (46.6)	0.34	50 (31.4)	17 (21.5)	0.10
	Mild	46 (18.2)	11 (20.4)		19 (11.9)	8 (10.1)	
	Moderate	67 (26.5)	12 (22.2)		61 (38.4)	29 (36.7)	
	Severe	59 (23.3)	8 (14.8)		29 (18.2)	25 (31.6)	
Postprandial fullness	Absent	44 (17.4)	4 (7.4)	0.14	10 (6.3)	3 (3.8)	0.02
	Mild	55 (21.7)	10 (18.5)		10 (6.3)	2 (2.5)	
	Moderate	102 (40.3)	23 (42.6)		98 (61.6)	38 (48.1)	
	Severe	52 (20.6)	17 (31.5)		41 (25.8)	36 (45.6)	
Upper abdominal bloating	Absent	49 (19.4)	9 (16.7)	0.03	18 (11.3)	6 (7.6)	0.02
	Mild	31 (12.3)	15 (27.8)		11 (6.9)	5 (6.3)	
	Moderate	120 (47.4)	19 (35.2)		99 (62.3)	38 (48.1)	
	Severe	53 (20.9)	11 (20.4)		31 (19.5)	30 (38.0)	
Early satiation	Absent	109 (43.1)	23 (42.6)	0.58	30 (18.9)	16 (20.3)	0.99
	Mild	53 (20.9)	8 (14.8)		19 (11.9)	9 (11.4)	
	Moderate	70 (27.7)	16 (29.6)		60 (37.7)	29 (36.7)	
	Severe	21 (8.3)	7 (13.0)		50 (31.4)	25 (31.6)	
Nausea	Absent	140 (55.3)	32 (59.3)	0.03	0 (0.0)	0 (0.0)	0.67
	Mild	90 (35.6)	15 (27.8)		0 (0.0)	0 (0.0)	
	Moderate	11 (4.3)	7 (13.0)		111 (69.8)	53 (67.1)	
	Severe	12 (4.7)	0 (0.0)		48 (30.2)	26 (32.9)	
Vomiting	Absent	204 (80.6)	41 (75.9)	0.13	90 (56.6)	30 (38.0)	0.054
	Mild	18 (7.1)	9 (16.7)		14 (8.8)	10 (12.7)	
	Moderate	21 (8.3)	3 (5.6)		26 (16.4)	18 (22.8)	
	Severe	10 (4.0)	1 (1.9)		28 (17.6)	21 (26.6)	
Belching	Absent	94 (37.2)	27 (50.0)	0.32	55 (34.6)	24 (30.4)	0.30
	Mild	60 (23.7)	11 (20.4)		19 (11.9)	16 (20.3)	
	Moderate	76 (30.0)	10 (18.5)		69 (43.4)	29 (36.7)	
	Severe	22 (8.7)	6 (11.1)		16 (10.1)	10 (12.7)	
Epigastric burning	Absent	119 (47.0)	19 (35.2)	0.18	69 (43.4)	28 (35.4)	0.66
	Mild	61 (24.1)	13 (24.1)		30 (18.9)	17 (21.5)	
	Moderate	46 (18.2)	11 (20.4)		45 (28.3)	24 (30.4)	
	Severe	27 (10.7)	11 (20.4)		15 (9.4)	10 (12.7)	

Note: p-value of association between delayed gastric emptying and different variables.

Abbreviations: DSS: dyspepsia symptom severity; FDS, functional dyspepsia symptoms; GPLS, gastroparesis-like symptoms.

of hypersensitivity to gastric distention and impaired gastric accommodation in the two groups, which probably implicates no strict separation of pathophysiological mechanisms involving gastric sensitivity and accommodation between GP and FD.[29] It is also worth mentioning that the cross-sectional snapshot of DDS questionnaire collection from patients based on a 2-week recall may temporarily disconnect from the GE test as patients' symptoms may have overtime variations. Herein, close to two-thirds of the patients presenting with GPLS symptoms, were still found to have normal GE. As proposed in previous reports, these patients might be diagnosed as having chronic nausea and vomiting disorders with normal GE, and the therapeutic approach can focus on the control of nausea and vomiting.[13,30] Although an older cohort study showed an association of delayed GE with the female sex, the prevalence of delayed GE did not differ between males and females in our current series.[31]

This study also documented whether and to what extent this symptom pattern distinguishes GP and FD in specific age groups. As reported, FD is most common in younger adults and its prevalence decreases with increasing age.[32] On the contrary, the prevalence of GP has been reported to rise with age based on the data of

general practitioners in the UK healthcare system.[33] We found that the prevalence of delayed GE was significantly different between FD symptoms and the GPLS group in the aged 18–39 and 65+ cohorts. These observations further illustrate the effectiveness of a symptom-based approach in separating GP from other diagnoses.

We also found that patients with delayed GE had higher total symptom scores than patients with normal GE in the GPLS group, but not in the FD symptoms group. These observations support a significant relationship between delayed gastric emptying and specific symptoms as reported in previous cohorts and meta-analyses.[5,8,11,40] Our findings are consistent with the 2013 and 2022 American College of Gastroenterology (ACG) clinical guidelines for GP which strongly recommend measurement of gastric emptying by scintigraphy or stable isotope breath test as the tests for identifying delayed GE in patients with symptoms suggestive of GP. Our findings also support the current ACG clinical guidelines, British Society of Gastroenterology guidelines, and UEG/ESMN consensus on FD that GE measurement is not useful for the diagnosis and management of patients when considering FD.[3,34,35,36,37] This finding may further implicate different roles of GE rate as a marker of the pathophysiology of GPLS and FD symptoms. Whilst GE delay may be an epiphenomenon in FD, its presence seems more crucial to the symptom presentation and severity in GPLS patients. In line with previous research, a higher frequency of severe symptoms of postprandial fullness was reported in patients with GPLS and delayed GE, compared to patients with cardinal symptoms of GP and a normal GE.[38,39] Nevertheless, the symptom severity of nausea and early satiation showed no difference between the two subgroups. This probably reflects the selection criteria, with all patients in the GPLS group displaying nausea as well as early satiation because of the inclusion criteria of "GPLS" in this study. It is also noticed that the diagnosis of GP was defined as delayed GE scintigraphy of >60% at 2 h or >10% at 4 h in the paper by Pasrich et al. which showed that clinical and pathologic features were indistinguishable between FD and GP.[9] In the present study, $T_{1/2}$ for a 4 h GE breath test was used to determine delayed GE. The recent report, comparing per cent retention at 1, 2 and 4 h and $T_{1/2}$, demonstrated that $T½$ was not sensitive but relatively specific for detecting GP.[40] Furthermore, the ACG consensus on GP this year pointed out potential confounders, such as the use of an Egg Beaters meal and a cutoff of value to define delayed GE, between GP and FD, and addressed the need for further studies on optimal meal composition and cutoff of the GE tests.[3] Determining a consistent symptom pattern and a valid cutoff value of delayed GE in the diagnosis, to allow distinguishing GP from other conditions is essential to advance the field.

Although it is not substantiated in the literature that GP may cause weight loss, we found that patients with GPLS had a lower BMI than patients with FD symptoms. This evidence suggests that the symptoms of GP may lead to weight loss, which has not been evident from previous cohort studies in the literature.[38,41] Consistent with our findings that there was no significant difference between moderate and severe GPLS in both prevalence of delayed GE and $T_{1/2}$, we did not observe that increased symptom severity is associated with progressive weight loss in patients with GPLS. This study also documented that patients with GPLS or FD symptoms commonly have overlapping IBS symptoms. The result is in accordance with previous studies.[25,42]

The present study has potential clinical implications but also has a number of limitations. First, inherent to a retrospective study, the analysis is limited to the available data cohort and sets and cannot avoid some missing data. Second, because diabetic patients are assumed to have gastropathy, enteropathy, or other diabetic complication, this is a group with potentially different pathophysiology. Therefore, we excluded patients with diabetes and hence were not able to estimate the prevalence of delayed GE in diabetic patients with GPLS. Finally, the study was conducted in a tertiary care centre which limits the generalizability of results. Future epidemiological research needs to be done in the primary care population.

In summary, in tertiary care patients reporting GP or FD symptoms, the prevalence of delayed GE is associated with GPLS as defined by the European consensus, and delayed GE is associated with a progressive increase in symptom severity in patients with GPLS. These findings support the distinction between GP and FD as proposed by the European consensus and the relevance of delayed gastric emptying for patients presenting with GPLS.

AUTHOR CONTRIBUTIONS

I-Hsuan Huang: Data curation (lead); formal analysis (lead); investigation (lead); methodology (equal); project administration (equal); writing – original draft (lead). **Jolien Schol:** Conceptualization (equal); investigation (equal); methodology (equal); project administration (equal); writing – review and editing (equal). **Florencia Carbone:** Conceptualization (equal); data curation (equal); investigation (supporting); methodology (equal); resources (supporting); supervision (supporting); writing – review and editing (equal). **Yaozhu J. Chen:** Conceptualization (supporting); funding acquisition (equal); project administration (equal); supervision (equal); writing – review and editing (lead). **Karen Van den Houte:** Investigation (supporting); writing – review and editing (equal). **Lukas Mmichaja Balsiger:** Investigation (supporting); writing – review and editing (equal). **Bert W L C M Broeders:** Investigation (supporting); writing – review and editing (equal). **Tim Vanuytsel:** Conceptualization (equal); methodology (supporting); supervision (equal); writing – review and editing (equal). **Jan Tack:** Conceptualization (lead); formal analysis (equal); funding acquisition (lead); investigation (lead); methodology (lead); project administration (equal); resources (lead); supervision (lead); writing – review and editing (lead).

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CONFLICT OF INTEREST

None of the other authors has any conflict of interest.

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