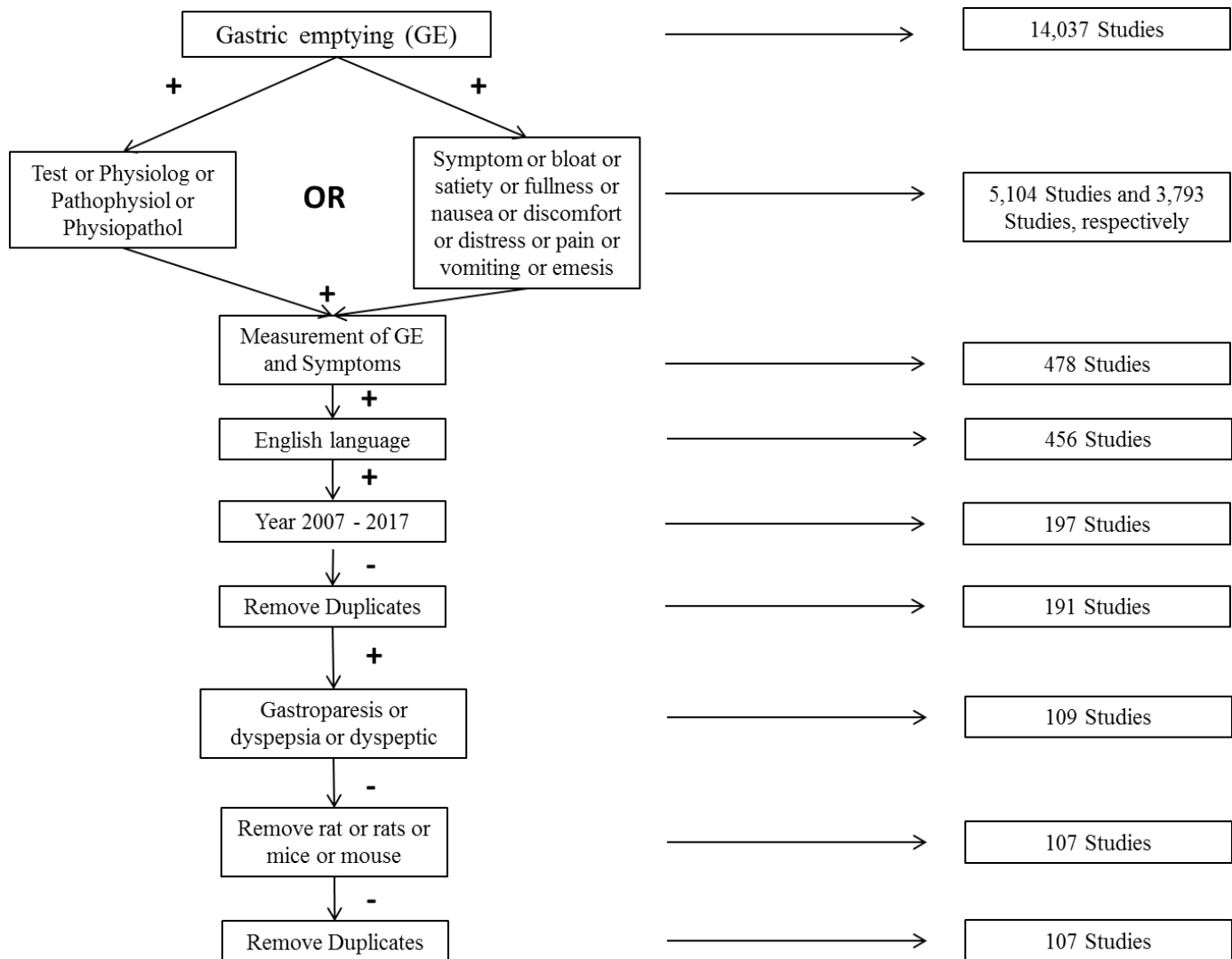


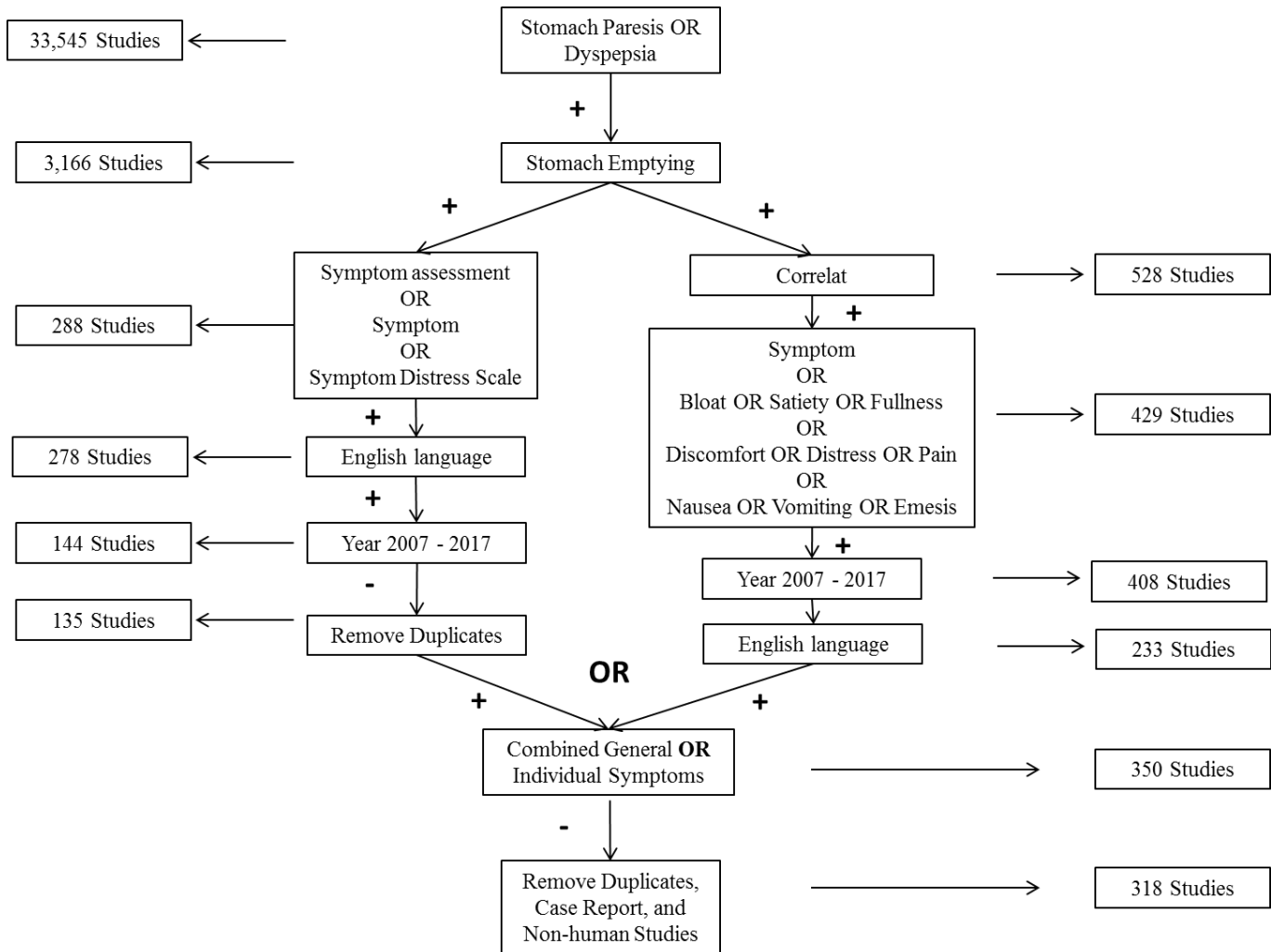
## SUPPLEMENTAL MATERIALS

### Methods – Search Strategy

#### Supplemental Figure 1A – Ovid Medline Search Strategy



# Supplemental Figure 1B – Embase Search Strategy



### **Newcastle Ottawa Scoring for Each Study within the Meta-analysis**

Note: A study can be awarded a maximum of one star for each numbered item within the selection and outcome categories. A maximum of two stars can be given for comparability

#### **Selection**

- 1) Representativeness of the exposed cohort
  - a) Truly representative of the average person who presents with chronic UGI Sx in the community \*
  - b) Somewhat representative of the average person who presents with chronic UGI Sx in the community \*
  - c) Selected group of users, e.g. nurses, volunteers
  - d) No description of the derivation of the cohort
- 2) Selection of the non-exposed cohort
  - a) Drawn from the same community as the exposed cohort \*
  - b) Drawn from a different source
  - c) No description of the derivation of the non-exposed cohort
- 3) Ascertainment of exposure
  - a) Secure record (eg surgical records) \*
  - b) Structured interview \*
  - c) Written self-report
  - d) No description
- 4) Demonstration that outcome of interest was not present at start of study
  - a) Yes \*
  - b) No

#### **Comparability**

- 1) Comparability of cohorts on the basis of the design or analysis
  - a) Study follows optimal GE methodology \*
  - b) Study follows suboptimal GE methodology

#### **Outcome**

- 1) Assessment of outcome
  - a) Independent blind assessment \*
  - b) Record linkage \*
  - c) Self-report
  - d) No description
- 2) Was follow-up long enough for outcomes to occur
  - a) Yes, adequate number with delayed GE \*
  - b) No
- 3) Adequacy of follow up of cohorts
  - a) Complete follow up - all subjects accounted for \*

- b) Subjects lost to follow up unlikely to introduce bias; small number lost, >90% follow up\*
- c) Follow up rate <89% and no description of those lost
- d) No statement

## Supplemental Results

### Nausea

There was a total of 16 studies which evaluated and identified a significant association between gastric emptying and nausea.

#### *Analysis according to covariates*

##### *a. Gastric emptying methodology*

(i) *Optimal methodology*: There was a significant association with similar magnitude of association to that observed when all 16 studies are assessed.

(ii) *Suboptimal methodology*: There was no significant association found. Meta-regression demonstrated significant difference between optimal and suboptimal gastric emptying test methodology.

##### *b. Gastric emptying type*

(i) *Breath test*: The entire complement of breath test gastric emptying studies demonstrated no significant association between nausea and delayed gastric emptying, but when only studies with optimal breath test methodology were considered, there was a significant association.

(ii) *Scintigraphy*: All scintigraphy studies and those with optimal scintigraphy methodology demonstrated a significant association.

##### *c. Patient subgroups:*

(i) *UGI Sx*: There was a significant association in all studies and those with optimal gastric emptying test methodology.

(ii) *Diabetes*: There was no significant association in either all studies or those with optimal gastric emptying test methodology.

(iii) *Gastroparesis*: There was a significant association in all studies and those with optimal gastric emptying test methodology with similar magnitude of association in both groups.

d. *Heterogeneity*: The  $I^2$  throughout all analyses was small except for all breath tests. The heterogeneity improved to 0% in all studies with optimal gastric emptying test methodology.

### **Vomiting**

A total of 13 studies evaluated the association between gastric emptying and vomiting, and demonstrated a significant association.

#### ***Analysis according to covariates***

##### ***a. Gastric emptying test methodology***

(i) *Optimal methodology*: There was a significant association with higher OR compared to the association observed with the entire complement of studies.

(ii) *Suboptimal methodology*: There was no significant association. Meta-regression demonstrated a significant difference between associations noted for the studies using optimal and suboptimal gastric emptying test methods.

##### ***b. Gastric emptying type***

(i) *Breath test*: There was no association found among all breath test studies and studies with optimal breath test methodology. There were only 2 studies that utilized optimal gastric emptying breath test.

(ii) *Scintigraphy*: There was a significant association in all scintigraphy studies and studies with optimal scintigraphy test methodology. Meta-regression demonstrated a significant

difference between breath test and scintigraphy but no significant difference between studies with optimally conducted breath test and scintigraphy studies.

*c. Patient subgroups:*

(i) *UGI Sx*: All studies and studies with optimal gastric emptying test methodology demonstrated a significant association. There was an increase in the magnitude of association in studies with optimal gastric emptying test methodology.

(ii) *Diabetes*: There was no association in either all studies or those with optimal gastric emptying test methodology. However, there were only 4 and 2 studies, respectively.

(iii) *Gastroparesis*: There was a significant association, but there was only one study with optimal gastric emptying in this patient population, precluding evaluation for meta-analysis.

*d. Heterogeneity*: The I<sup>2</sup> was elevated at 63% for all studies, but improved to 14% after evaluation studies with optimal gastric emptying test methodology. A similar improvement in heterogeneity was seen across covariates after evaluating studies with optimal gastric emptying test methodology except for breath tests and patients with UGI Sx, which has only 2 studies in each group.

## **Abdominal Pain**

There was a significant association noted in all 16 studies that evaluated abdominal pain and gastric emptying.

### ***Analysis according to covariates***

*a. Gastric emptying test methodology*

(i) *Optimal methodology*: There was a significant association of similar magnitude seen in all gastric emptying studies.

(ii) *Suboptimal methodology*: There was no association.

*b. Gastric emptying type:*

(i) *Breath test*: There was no association among all studies, but there was a significant association with an increase in the magnitude of association in studies with optimal breath test methodology (OR 5.0, 95% CI 1.1-22.6). There were only 2 studies with optimal breath test methodology.

(ii) *Scintigraphy*: There was no association in all studies with scintigraphy and studies with optimal scintigraphy test methodology.

*c. Patient subgroups*

(i) *UGI Sx*: There was no association found in all studies. However, there was a significant association seen in patients with optimal gastric emptying test methodology.

(ii) *Diabetes*: There was no association seen in all studies or studies with optimal gastric emptying test methodology. There were only 3 and 2 studies in each group, respectively.

(iii) *Gastroparesis*: There was no association in all gastric emptying studies. There were only 3 studies in this group, and 1 study with optimal gastric emptying test methodology.

*d. Heterogeneity*: There was moderate heterogeneity throughout the studies which evaluated abdominal pain. There was little improvement after isolating studies with optimal gastric emptying test methodology, except for patients with UGI Sx.

**Bloating**

Analysis of the entire complement (n=15) studies demonstrated a significant association between bloating and gastric emptying.

***Analysis according to covariates***

*a. Gastric emptying test methodology*

(i) *Optimal methodology*: There was a significant association.

(ii) *Suboptimal methodology*: There was no significant association. Meta-regression did not demonstrate a significant difference between studies with optimal and suboptimal gastric emptying test methodology.

*b. Gastric emptying type*

(i) *Breath test*: There was no association in all studies with breath test, but a significant association with an increase in magnitude (OR 3.7, 95% CI 1.4-9.8) was found in studies with optimal breath test methodology. There were only 3 studies with optimal breath test methodology.

(ii) *Scintigraphy*: Though there was an association seen in all scintigraphy studies, there was no association noted in studies with optimal scintigraphy methodology.

*c. Patient subgroups*

(i) *UGI Sx*: There was an association, which lost significance after analyzing studies with optimal gastric emptying test methodology.

(ii) *Diabetes*: There was no significant association in all studies and studies with optimal gastric emptying test methodology.

(iii) *Gastroparesis*: There was no association in patients with gastroparesis. There was only one study with optimal gastric emptying test methodology.

*d. Heterogeneity*: There was moderate to high heterogeneity throughout the studies with no significant improvement after evaluating all covariates.

**Early Satiety/ Fullness**

There was an overall significant association seen in all studies that evaluated early satiety/fullness.

***Analysis according to covariates***



*a. Gastric emptying test methodology*

(i) *Optimal methodology*: There was a significant association with similar magnitude seen in all studies.

(ii) *Suboptimal methodology*: There was a significant association with similar magnitude seen in all studies.

*b. Gastric emptying type*

(i) *Breath test*: There was a significant association.

(ii) *Scintigraphy*: There continued to be a significant association with a similar magnitude of association seen in breath test and in all studies.

*c. Patient subgroups:*

(i) *UGI Sx*: There was significant association that remained after evaluating optimal gastric emptying test methodology.

(ii) *Diabetes*: Similar to studies that evaluated UGI Sx, there was a significant association between all studies and studies that utilized optimal gastric emptying test methodology.

(iii) *Gastroparesis*: There was no significant association, and there was only 1 study with optimal gastric emptying test methodology, preventing meta-analysis calculation.

*d. Heterogeneity*: There was moderate heterogeneity seen in all studies, with improvement to low heterogeneity in breath test studies and patients with diabetes and gastroparesis. There was no significant improvement when evaluating studies with optimal gastric emptying test methodology.

**Composite symptoms**

Analysis of the entire complement of studies (n=9) demonstrated a significant association between composite symptoms and gastric emptying, OR 2.8, 95% CI 1.5-5.2.

***Analysis according to covariates***

*e. Gastric emptying test methodology*

(i) *Optimal methodology*: There was no significant association.

(ii) *Suboptimal methodology*: There continued to be a significant association to a similar degree as seen after evaluating the association in all studies.

*f. Gastric emptying type*

(i) *Breath test*: There was a significant association. Because there was only one study with optimal breath test methodology, no meta-analysis could be completed.

(ii) *Scintigraphy*: There was a significant association, but didn't continue after evaluating studies with optimal scintigraphy methodology. There were only 2 studies with optimal scintigraphy methodology.

*g. Patient subgroups*

(i) *UGI Sx*: There was a significant association. There was only 1 study with optimal gastric emptying test methodology.

(ii) *Diabetes*: There was no significant association. No further assessment could be completed with studies with optimal gastric emptying test methodology because there was only 1 study within this category.

(iii) *Gastroparesis*: There were no studies that enrolled gastroparesis.

*h. Heterogeneity*: There was moderate heterogeneity among all studies that did not significantly change after analysis of covariates.

**Supplemental Table 1. Breath test studies in patients with or without gastroparesis and relationship with symptoms of nausea (N), vomiting (V), fullness (F), early satiety (ES) and abdominal pain (AP): [OR = odds ratio (95% confidence interval, CI); CS: cross-sectional; DM=diabetes; ESRD on HD: end stage renal disease on hemodialysis; FD= functional dyspepsia; GLY= glycine; OCT: octanoate; P= prospective; PADYQ: Porto Alegre Dyspeptic Symptoms Questionnaire; Pts= Patients]; \* represents an abstract; <sup>T</sup> data from Dr. Jan Tack's group**

Author, Year Reference #	n	Pts	Symptom Assessment	Study Type	GE breath test	Measurement	Symptom/Composite
<sup>1</sup> Tack, 2010 (1)	636	FD	UGI Sx; 4 pt Likert	P	<sup>14</sup> C-OCT 4H solid <sup>13</sup> C-GLY 4H liquid	T <sub>1/2</sub>	Significant association with T <sub>1/2</sub> and N/V, ES/F, epigastric sx (p< 0.0001).
<sup>1</sup> Karamanolis, 2006 (2)	592	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C-OCT 4H solid <sup>13</sup> C-GLY 4H liquid	T <sub>1/2</sub> > 109 min for solids, >74 min for liquids	Pts with combination UGI Sx (AP & F) had a higher prevalence of delayed GE for solids (P=0.03, t test) and a longer GE T <sub>1/2</sub> solids (P=0.02, t test).
<sup>1</sup> Vanheel, 2017 (3)	533	FD	6 UGI Sx; 6 pt Likert	P	<sup>14</sup> C-OCT 4H solid	T <sub>1/2</sub> > 109 min for solids	<b>In the symptomatic group, t<sub>1/2</sub> was associated with N (OR 2.07 [1.31-3.26]) and cumulative symptom score (AP, N, B, F) (p=0.17, P=0.02).</b>
<sup>1</sup> Sarnelli, 2003 (4)	392	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C-OCT 4H solid [n=392] <sup>13</sup> C-GLY 4H liquid [n=330]	T <sub>1/2</sub> >109 min for solids, >74 min for liquids	The severity of UGI Sx [F (P<0.01), B (P<0.01), ES (P<0.05), N (P<0.05), and V (P<0.01), t test] was associated with delayed solid GE. On multivariate analysis V (OR 2.65 [1.62-4.35]) and F (OR 3.08 [1.28 - 9.16]) were independently associated with delayed solid GE.
Perri, 1998 (5)	304	FD	4 UGI Sx; 4 pt Likert	P	<sup>13</sup> C-OCT 4H solid	T <sub>1/2</sub> ≥140 min.	<b>Delayed GE was independently associated with a cumulative score ≥6 for F, N, and V [OR 3.13 (1.06-9.18)]. Delayed GE was associated with F (p, 0.05, t test) as compared to normal GE.</b>
<sup>1</sup> Bisschops, 2008 (6)	218	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C-OCT 4H solid; <sup>13</sup> C-GLY 4H liquid	T <sub>1/2</sub> (minutes)	Based on student t test, F (P<0.005), B (P=0.04), AP (P=0.02) and N (P=0.02) were significantly associated with delayed solid GE. Severity of meal-induced N was significantly associated delayed liquid GE.
<sup>1</sup> Fischler, 2003 (7)	204	FD	8 UGI Sx; 4 point Likert	CS	<sup>14</sup> C- OCT 4H solid	T <sub>1/2</sub> > 80 min	t <sub>1/2</sub> was correlated to a composite of 4 Sx (N, V, ES & weight loss) (P=0.001) and a 2 Sx composite (F & B) (P=0.009).
Samsom, 2003 (8)	186	DM1, DM2	Prior 2 wks: 9 UGI Sx; During GE: 4 UGI Sx; VAS	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> > 120 min; Gastric retention (2h) > 40%	UGI Sx (F, N, V, AP) on 4 point Likert scale, predicted GE (r = 0.46, p < 0.001).
<sup>1</sup> Kindt, 2009 (9)	161	FD	PAGI-SYM	P	<sup>14</sup> C- OCT 4H solid	T <sub>1/2</sub> > 80 min	Pts with delayed GE had higher scores for N/V (r=0.19), F/ES (r=0.2), B and AP (r=0.22, all P<0.05).
Ron, 2011 (10)	111	FD	UGI Sx	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> > 94 min (mild); 200-299 (moderate); ≥ 300 severe; tlag > 52 min; GEC < 2.95	<b>ES was significantly associated with delayed GE based on logistic regression (OR 2.29 [1.01-5.18]).</b>
Bharucha, 2015 (11)	78	DM1	GCSI	P	<sup>13</sup> C-spirulina 4H solid	T <sub>1/2</sub> > 92 min	Composite score of N, F, V & AP score did correlated with GE t <sub>1/2</sub> (rs = 0.25, p=0.049).
Sfarti, 2010 (12)	69	DM1	6 UGI Sx; 4 pt Likert	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> ≥ 135 min and GEC ≥ 3.1	<b>B and AP were more frequently present in diabetic patients with delayed GE as compared to those with normal GE (p&lt;0.05, student t test).</b>
Marie, 2012 (13)	57	Sclero derma	9 GI Sx; 4 pt Likert , global symptom score (GSS)	P	<sup>13</sup> C- OCT 8H solid	T <sub>1/2</sub> >166 min	<b>V, AP, and B are individually associated with delayed GE in inactive CD (p &lt; 0.01, Mann Whitney) as compared to pts without delayed GE. GSS &gt;5 was significantly associated with delayed GE (OR 32.1 [4.99-204]).</b>

Salles Junior, 2013 (14)	50	ESRD on HD	PADYQ	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> > 200 min	Dyspepsia score (AP, N, V, B, ES) was positively correlated with t <sub>1/2</sub> (r=0.366, p=0.009).
<sup>1</sup> Tack, 1998 (15)	40	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C- OCT 4H solid	T <sub>1/2</sub> (min) > 95% CI in HV	Multivariate analysis demonstrated association between severe N and delayed GE (OR 9.52 [2.22-52.8]).
Ziegler, 1996 (16)	34	Insulin treated DM	6 UGI Sx; 4 pt Likert	P	<sup>13</sup> C- OCT 4H solid Scintigraphy 2H solid	T <sub>1/2</sub> breath, lag phase, and GEC T <sub>1/2</sub> scint > 100 min	Gastric Sx (N, V, AP, B, ES, anorexia) score was significantly associated with t <sub>1/2</sub> (rs=0.53, p<0.05), GEC (rs=-0.59, p<0.05) by breath test, and by t <sub>1/2</sub> scintigraphy (rs=0.33, p<0.05).
Lo Cascio, 2016 (17)	33	Duchenne MD	Short Form Leeds Dyspepsia Questionnaire	P	<sup>13</sup> C OCT 8H solid	T <sub>1/2</sub> >117.2 min Tlag>80.3 min	Significant association between UGI Sx (indigestion, heartburn, regurgitation, N) and Tlag (p = 0.047). No such association seen with GCSI.
Sales, 2015 * (18)	27	14 CD 13 UC	PADYQ	P	<sup>13</sup> C- OCT solid	T <sub>1/2</sub> (minutes)	IBD patients with UGI Sx (AP, ES, N, V, B) (T <sub>1/2</sub> =265.9 ± 21.7 min) had significantly longer GE (p<0.05) as compared to IBD controls (T <sub>1/2</sub> = 220.2 ± 16.1 min).
Nobrega, 2012 (19)	26	CD	PADYQ	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> > 200 min; t lag > 150 min	CD with dyspepsia (≥ 6 sx assessment of AP, ES, N, V, B) had significantly prolonged t <sub>1/2</sub> (p=0.04, t test), not T <sub>lag</sub> . Only V associated with delayed GE (P<0.05, t test) based on t <sub>1/2</sub>
Gourcerol, 2007 (20)	15	Chronic N/V	UGI Sx; 5 pt Likert	P	<sup>13</sup> C OCT 4H solid	Gastric retention >10%	No significant associations
<sup>1</sup> Kindt, 2008 (21)	78	FD	9 UGI Sx; 4 pt Likert	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> > 94 min; tlag > 52 min	
Mori, 2017 (22)	126	FD	UGI Sx	P	<sup>13</sup> C-acetate 1.5H liquid	Tmax - M > 60 min; F > 75 min	
<sup>1</sup> Kindt, 2011 (23)	253	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C- OCT 4H solid; <sup>13</sup> C-GLY 4H liquid	T <sub>1/2</sub> > 109 min for solids, >74 min for liquids	
<sup>1</sup> Clauwaert, 2012 (24)	259	FD	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C- OCT 4H solid	T <sub>1/2</sub> > 80 min	
Talley, 2001 (25)	798	FD (551) and DM1 (247)	8 UGI Sx; VAS	P	<sup>13</sup> C- OCT 4H solid	T <sub>1/2</sub> and lag (min), and β; T <sub>1/2</sub> >123–192 min moderate delay; T <sub>1/2</sub> >192 min severe delay	

**Supplemental Table 2. Details of the gastric scintigraphy studies in patients with or without gastroparesis and relationship with symptoms of nausea (N), vomiting (V), fullness (F), early satiety (ES) and abdominal pain (AP): [OR = odds ratio (95% confidence interval, CI); AIG: Autoimmune Gastritis; CS: cross-sectional; GCSI: gastroparesis cardinal symptom index; P= prospective study; PAGI-SYM: Patient Assessment of Gastrointestinal Disorders Symptom Severity Index; R= retrospective study; Sx=symptoms; FD= functional dyspepsia); \* represents an abstract; <sup>c</sup> data from Dr. Michael Camilleri's group; <sup>o</sup> data from Gastroparesis Registry from National Institute of Diabetes and Digestive and Kidney Diseases; <sup>H</sup> data from Dr. Michael Horowitz's group – both FD and DM; <sup>o</sup> data from Dr. Eva Olausson; <sup>P</sup> data from Dr. Henry Parkman's group; <sup>S</sup> data from Dr. Stanghellini group; <sup>T</sup> data from Dr. Jan Tack group**

Author, Year Reference #	n	Pts	Symptom Assessment	Study Type	GE Method	Measurement	Symptom/Composite
<sup>P</sup> Pathikonda, 2012 (26)	1499	UGI Sx	PAGI-SYM	P	Solid 4H	Delayed: 1h >90%, 2h >60%, 3h >30%, 4h >10% Severity 4h: mild 10-20%, moderate 20-35%, severe 35-50%, very severe >50%; Rapid: 1h <30%, 2h <10%	N, V, AP were more prevalent in delayed GE as compared to normal or rapid GE (all p < 0.001, t test with bonferroni correction).
<sup>c</sup> Park, 2017 (27)	1287	UGI Sx	UGI Sx	R	Solid 4H	GE delay: 4h <84% Rapid: 1h>39%	Pts with delayed GE has significantly more frequent N and V (all p<0.05, multiple variable logistic regression model). Delayed GE associated with increased N: OR 1.50 [1.13, 2.00], and weight loss >10% OR 1.69 [1.22, 2.35], and reduced B OR 0.69 [0.53, 0.91] Accelerated GE associated with reduced abdominal discomfort/pain OR 0.73 [0.53, 0.91]
Talley, 2006 (28)	864	FD	5 UGI Sx; 4 point Likert	R	Solid 4H	Retention at 4h > 6.3%	Univariate analysis demonstrated significant association between delayed GE and ES, F, B, N, AP. (all p<0.03) Multivariate analysis demonstrated an association between F and delayed GE (OR 1.98, [1.02-3.86]).
<sup>P</sup> Sachdeva, 2011(29)	449	UGI Sx	PAGI-SYM	CS	Solid 4H Liquid 6H	Solid: Delayed: Retention at 2h >60% & 4h >10% -Rapid: Retention at 1h <35% Liquid: Delayed: retention at 1h >50%	N (r = 0.136, p <0.05), V (r = 0.173, p <0.05), ES (r = 0.133, p <0.05), F (r = 0.173, p<0.05), and total GCSI subscore (N/V, F, B) (r = 0.141, p<0.05) was associated with GE at 4h.
<sup>P</sup> Khayyam, 2010 #123 (30)	388	UGI Sx	PAGI-SYM	P	Solid 4H	Delayed GE: Retention at 2h >60% & 4h >10% Rapid GE: Retention at 1h <35%	F, B, and AP were significant higher in patients with delayed GE as compared to controls. (all p<0.05 t test)
<sup>S</sup> Stanghellini, 1996 (31)	343	FD	4 UGI Sx; 4 point Likert	P	Solid 3H	Emptying rate < 0.42%/h (M) and < 0.35%/h (F) Lag phase > 54 min (M) and > 37 min (F)	Lower GE rates in patients with UGI Sx (≥3 sx score measuring AP, F, N, V) as compared to controls (p=0.0001). Logistic regression analysis demonstrated an independent correlation of severe V (OR 4.04 [1.3-12.54]) and severe F (OR 2.34 [1.45-3.75]) to delayed GE.
<sup>S</sup> Stanghellini, 2003(32)	327	UGI Sx	7 UGI Sx; 5 point Likert	P	Solid 3H	Emptying rate < 0.42%/h (M) and < 0.35%/h (F) Lag phase > 54 min (M) and > 37 min (F)	Multivariate analysis demonstrated F was independently associated with delayed GE (OR 4.1[1.7-10.2]). Mann Whitney demonstrated an association between F, B, and N in delayed GE as compared to healthy controls (all p<0.05).
Musaib-Ali, 2012* (33)	324	UGI Sx	GCSI	P	Solid 3H Liquid 0.5H	Liquid: delayed t1/2 > 22 min Solid: delayed GE (4h) <90%	Loss of appetite (p=0.03, t test) and V (p<0.01, t test) was associated with delayed GE.

Halawi, 2017 (34)	285	26 obese 259 healthy	UGI Sx in response to dyspeptogenic meal	P	Solid 4H	GE T <sub>1/2</sub> ; GE 2h, 4h; GE lag time	GE T <sub>1/2</sub> was significant associated with N (r=0.145, p=0.026), AP (r=0.149, p=0.012), and higher aggregate Sx score (F, N, B, AP) (r=0.132, p 0.026).
DiBaise, 2016 (35)	266	UGI Sx	GCSI	P	Solid 4H	Retention at 2h >60% and 4h ≥16%	<b>N/V, F/ES, and total GCSI total score (N, retching, V, F, ES, F, anorexia, B, stomach enlargement) was significantly associated with abnormal GE at 4 hours (all p&lt;0.03, t test). Logistic regression demonstrated a significant correlation between increased GCSI score and delayed GE (OR= 1.551 [1.153-2.087]).</b>
<sup>P</sup> Cassilly, 2008 (36)	226	UGI Sx	GCSI	P	Solid 4H	Retention at 2h < 50% & 4h <10%	N and V were significantly associated with gastroparesis at 4 hours as compared to healthy controls (p<0.05, based on student t test).
Boltin, 2014 (37)	193	UGI Sx	UGI Sx	R	Solid 2H	T <sub>1/2</sub> > 100 min	<b>V was associated with delayed GE (OR 2.54 [1.2-5.35])</b>
<sup>P</sup> Parkman, 2017* (38)	177	UGI Sx	PAGI-SYM	P	Solid 4H	Delayed: Retention >60% (2h) and/or >10% (4h)	Increased solid gastric retention 4h was associated with vomiting (p=0.03). Increased solid gastric retention 1h was associated with increased severity of F (p=0.04) and B (p=0.04).
Stanghellini, 2002 (39)	146	IBS	4 UGI Sx; 4 point Likert	P	Solid 3H	Emptying rate < 0.42%/h (M) and < 0.35%/h (F) Lag phase > 54 min (M) and > 37 min (F)	<b>Logistic regression demonstrated that F (OR =4.7, [1.8-12.5]) and N (OR=3.3, CI 1.2-9.3) were independently associated with delayed GE. IBS patients with UGI Sx (F, B, V, V) had delayed GE rates as compared to controls (p&lt;0.01).</b>
<sup>O</sup> Olausson, 2013 (40)	115	Insulin treated DM	PAGI-SYM	P	Solid 3H	Retention at 2h (%) M > 51%; F >55-66% based on age	Spearman correlation demonstrated a positive correlation between N/V (r=0.3, p<0.001) and F/ES (r=0.34, p<0.0001) with GE. No median subscale score differences were noted between normal GE and gastroparesis.
<sup>H</sup> Jones, 2001 (41)	101	DM1 and DM2	9 UGI Sx; 4 point Likert	P	Solid and liquid 2H	Solid: Retention at 100min > 61% ; Liquid: T <sub>1/2</sub> > 31 min	UGI Sx (anorexia, N, ES, B,F, V, AP) was associated with increased GE (p<0.005). Severity of UGI Sx correlated with solid GE (r = 0.22, p<0.05). B/F was related to solid GE (r=0.29, p<0.005).
<sup>H</sup> Horowitz, 1991 (42)	87	DM1 and DM2	9 UGI Sx; 4 point Likert	P	Solid and liquid 2H	Solid: Lag phase (min) and retention at 100min (5%) Liquid: Retention at 10min (%) and T <sub>1/2</sub> (minutes)	UGI Sx (anorexia, N, ES, AP, V, B) correlated with amount of solid meal remaining in the stomach at 100 min (r=0.36, p<0.01).
<sup>P</sup> Gonlachavit, 2006 (43)	83	FD & GERD	8 UGI Sx; 4 point Likert	P	Solid 4H	Retention at 2h >50%	Pts with V demonstrated greater total gastric retention at 2 and 3 h (p<0.05, t test). Delayed GE had more N and ES as compared to normal GE controls. (all p<0.05, t test) In a multivariable regression analysis demonstrated N was associated with GE. (OR 5.19 [1.43-18.89])
<sup>O</sup> Olausson, 2014 (44)	83	DM1 and DM2	PAGI-SYM	P	Solid 3H	Delayed: Retention at 2h(%) M >51%; F (<50 yo) >66% & (>50 yo) >55%	UGI Sx (N/V, F/ES, B, AP, heartburn/regurgitation) were more severe in diabetic gastroparesis as compared to diabetics with normal GE (p=0.0001). UGI Sx severity had the best discriminative validity to identify diabetic gastroparesis (Area under the ROC curve =0.85).
Hellstrom, 2013* (45)	72	DM (58 type 1,	GCSI	P	Solid 4H	Retention > 10%	Significant association between gastric retention and GCSI ((N, retching, V, F, ES, F, anorexia, B, stomach

		14 type 2)					enlargement), $r=0.43$ , $p<0.01$ .
Kalkan, 2016 (46)	62	AIG	GCSI	P	Solid 2H	$T_{1/2} > 110$ min	Mean GCSI (total score- N, retching, V, F, ES, F, anorexia, B, stomach enlargement) was significantly higher in patients with delayed GE compared to patients with normal GE ( $1.89 \pm 1.16$ vs $0.4 \pm 0.3$ , $p<0.001$ ).
Tseng, 2014 (47)	60	30 FD, 30 DM1 + UGI Sx	GCSI	P	Solid 4H	Lag phase, $T_{1/2}$ , Retention at 1h $>65\%$ , 2h $>28\%$ , and 3 h $>8\%$	N ( $r_s = 0.339$ , $p < 0.01$ ) and V ( $r_s = 0.271$ , $p < 0.05$ ) was significantly associated with $t_{1/2}$ (3h). B was significantly associated with retention at 3 h ( $r_s = 0.292$ , $p < 0.05$ ).
Grad, 2012 (48)	55	DM	GCSI	P	Solid 2H	Retention at 1h $> 90\%$ and 2h $>60\%$	<b>Based on the student t test, F and ES were present more frequently in delayed GE (<math>p&lt;0.05</math>). Nausea (<math>r = -0.65</math>, <math>p&lt;0.05</math>) and ES (<math>r=-0.58</math>, <math>p&lt;0.05</math>) significantly correlated with severity of GE.</b>
<sup>P</sup> Cuomo, 2001 (49)	52	FD	8 UGI Sx; 4 point Likert	P	Solid 3H	$T_{1/2} > 90$ min Emptying rate $< 0.5\%/min$ Lag phase $> 10$ min	<b>ES severity showed significantly increased severity of Sx with delayed GE based on lag phase and GE rate (<math>p&lt;0.01</math>) Multivariate analysis demonstrated B was directly associated with delayed GE based on <math>T_{1/2}</math> (OR 2.2, [1.02-4.84]).</b>
<sup>H</sup> Horowitz, 1986 (50)	45	IDDM1	9 UGI Sx; 4 point Likert	P	Solid and liquid 2H	Solid: Lag phase (min) and retention at 100min (5%) Liquid: Retention at 10min (%) and $t_{1/2}$ (minutes)	The lag period ( $r=0.37$ , $P<0.02$ ) and percentage retention of solid at 100 min ( $r=0.37$ , $P=0.02$ ) correlated with UGI Sx (anorexia, N, ES, AP, B, V, AP). If patients score $> 4/18$ on UGI Sx assessment, they were more likely to have abnormal GE. ( $p<0.05$ )
Faraj, 2007 (51)	31	DM1, DM2 + UGI Sx	16 GI Sx	P	Solid 1.2H	$T_{1/2} > 70$ min	F was associated with delayed gastric emptying ( $P = 0.02$ ).
Kawamura, 2012 (52)	24	Chronic Hep C	UGI Sx	P	Solid 2H	Distal $T_{1/2} > 105$ min	Distal $T_{1/2}$ was significantly associated with ES ( $r=0.48$ , $p=0.02$ )
Nowak, 1995 (53)	21	DM1	3 symptoms by structured interview	P	Solid 3H	$T_{1/2} > 272.9$ min (mean + 2 SD healthy controls)	<b>Diabetics with UGI Sx (N, V, ES) had statistically significant delay in GE (<math>p&lt;0.05</math>).</b>
van Wijk, 1992 (54)	16	IBS-C	4 UGI Sx; 4 pt Likert	P	Solid 1H	Lag phase (min) GE rate (%/min)	No significant associations
<sup>H</sup> Jones, 1996 (55)	16	DM2	9 UGI Sx; 4 point Likert	P	Liquid 3H	$T_{1/2}$ (min) & lag phase (min)	
<sup>H</sup> Horowitz, 1989 (56)	20	DM2	9 UGI Sx; 4 point Likert	P	Solid and liquid 2H	Solid: Lag phase (min) and retention at 100min (5%) Liquid: Retention at 10min (%) and $T_{1/2}$ (min)	
<sup>H</sup> Trahair, 2016 (57)	21	Mild – mod Parkinsonism	8 UGI Sx; 4 pt Likert	P	Liquid 3H	$T_{1/2} > 157$ min	
Punkkinen, 2008 (58)	27	DM1	9 UGI Sx	P	solid and liquid 1.5H	$T_{1/2} < 137$ min	
Talley, 1989	32	UGI Sx	4 UGI Sx	P	Solid 2.3H	$T_{1/2}$ , lag parameter and rate of	

(59)						emptying	
<b>Wegener, 1989 (60)</b>	<b>43</b>	<b>UGI Sx</b>	<b>5 UGI Sx; 4 point Likert</b>	<b>P</b>	<b>Liquid 1H</b>	<b>Retention at 1h &gt; 82%</b>	
Waldron, 1991 (61)	50	UGI Sx	7 UGI Sx; VAS	P	Solid: until $t_{1/2}$ visualized	$T_{1/2}$ > 106 min & Lag phase (min)	
Yu, 2012(62)	59	27 migraine, 32 FD	UGI Sx	P	Solid 2H	$T_{1/2}$ > 100 min	
Lawal, 2007 (63)	61	Autonomic dysfunction	GI Sx	R	Solid 3H	$T_{1/2}$ > 120.6 min (M) and > 159.6 min (F)	
Christensen, 2008 (64)	67	CVS	UGI Sx	R	Solid 4H	Gastric retention > 10%	
Anaparthi, 2009 (65)	69	UGI Sx	GCSI	R	Solid 4H	Gastric retention > 10%	
Gustafsson, 2011 (66)	84	DM1 & DM2	15 GI Sx	P	Solid 1.2H	$T_{1/2}$ > 70 min	
<b>Guo, 2012 (67)</b>	<b>93</b>	<b>FD</b>	<b>8 UGI Sx; 4 point Likert</b>	<b>CS</b>	<b>Solid 2H</b>	<b><math>T_{1/2}</math> &gt; 116.62 min</b>	
<b>Bharucha, 2009 (68)</b>	<b>129</b>	<b>DM1 &amp; DM2</b>	<b>UGI Sx</b>	<b>R</b>	<b>Solid 4H</b>	<b>Delayed emptying 2h &lt; 40%; 4h &lt; 84%</b> <b>Rapid: Emptying 1h &gt; 39% 2h &gt; 76%</b>	
Anudeep, 2016 (69)	140	DM2	GCSI	CS	Solid 3H	Delayed: Retention at 2h > 35%; 3h > 10%; Rapid: Retention at 1h < 30%	
<sup>c</sup> Bredenoord, 2003 (70)	173	UGI Sx	UGI Sx	R	Solid 4H	Delayed: Emptying at 4h < 84% Rapid: Emptying at 1h > 39%	
Lee, 2015* (71)	214	UGI Sx	6 UGI Sx	--	Solid 4H	Delayed: > 10% retention (4h) Rapid: < 16% (2h)	
<sup>c</sup> Pasricha, 2015 (72)	262	UGI Sx	GCSI	R	Solid 4H	Gastric retention > 20%	
<b>Hyett, 2009* (73)</b>	<b>282</b>	<b>DM</b>	<b>UGI Sx</b>	<b>R</b>	<b>Solid 2H</b>	<b>&lt; 50% emptying at 50 min</b>	
<sup>c</sup> Pasricha, 2011 (74)	425	N & V: 319 DGE; 106 NGE	GCSI	P	Solid 4H	Delayed: Retention at 2h > 60% & 4h > 10% Rapid: Retention at 1h < 30%	

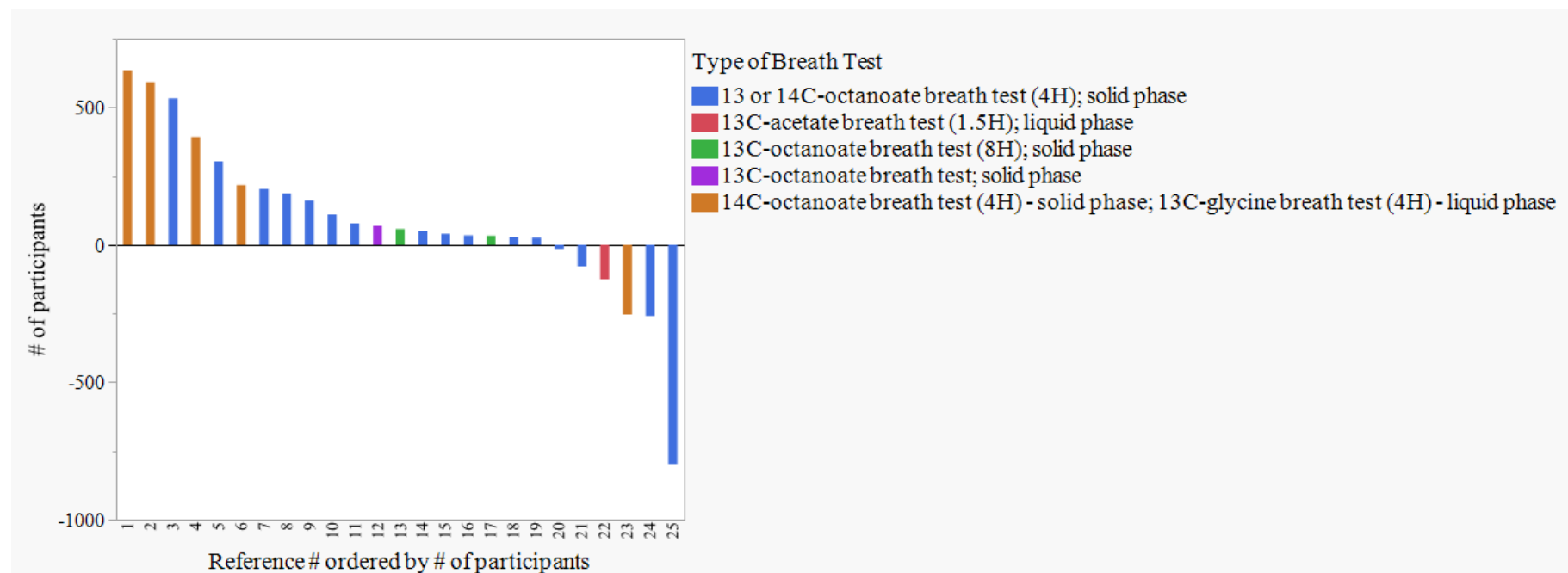


**Supplemental Table 3. Gastric emptying studies in patients with gastroparesis and relationship with symptoms of nausea (N), vomiting (V), fullness (F), early satiety (ES) and abdominal pain (AP):** [DG= diabetic gastroparesis; GLY: glycine; IG= idiopathic gastroparesis; OCT: octanoate; P= prospective study; R= retrospective study; Sx=symptoms]; \* represents abstract; <sup>G</sup> data from Gastroparesis Registry from National Institute of Diabetes and Digestive and Kidney Diseases; <sup>P</sup> data from Dr. Henry Parkman's group

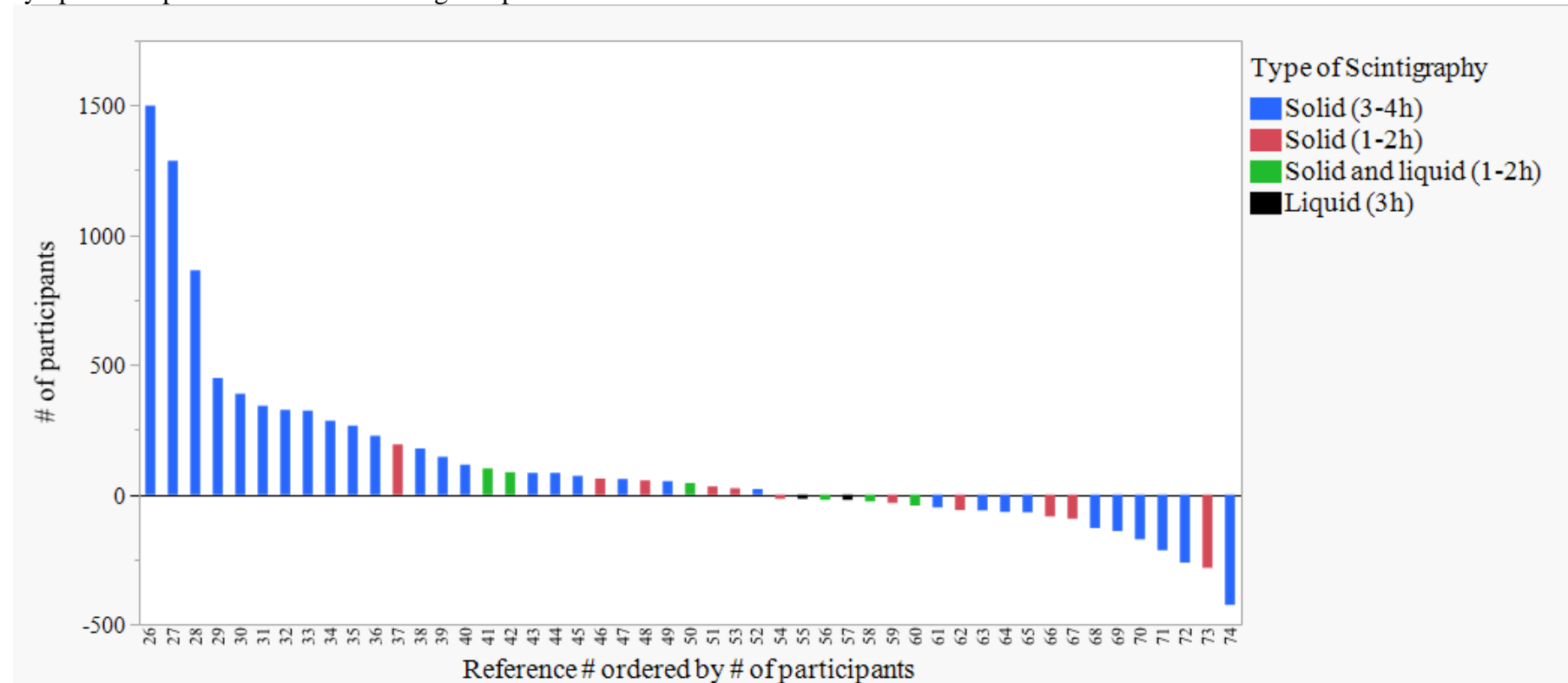
Author, Year, (Reference #)	n	Pts	Symptom Assessment	Study type	GE Method	Measurement	Symptom/Composite
Ardila-Hani, 2013 (75)	325	230 IG, 70 DG, 25 Post Surgical	GCSI	P	Scintigraphy 4H solid	T <sub>1/2</sub> (min) & lag phase (min) Delayed: Gastric Retention at 1h >90%, 2h >60%, or 4h >10% Rapid: Gastric Retention at 0.5 h <70% or 1h <30%	V was present more frequently in patient is idiopathic delayed GE as compared to normal GE (p=0.01). N was associated with post-surgical delayed GE as compared to normal GE (p=0.004). Severity of N and V positively correlated with retention at 2 h (p = 0.03 and p = 0.01, respectively).
<sup>G</sup> Parkman, 2011 (76)	243	IG	PAGI-SYM	P	Scintigraphy 4H solid	Retention at 4h (%) Mild ≤20%, moderate 20-35%, and severe >35%	Patients with severe gastroparesis had more N, V, AP and higher total GCSI score(N, retching, V, F, ES, F, anorexia, B, stomach enlargement) as compared to mild to moderate gastroparesis. (all p<0.05) Multivariable logistic regression demonstrated more severe N in patients with severe gastroparesis as compared to mild to moderate gastroparesis. (OR 1.25, p=0.02; 95% CI not given)
<sup>G</sup> Parkman, 2017 (77)	198	134 IG 64 DG	PAGI-SYM	P	Scintigraphy 4H solid and liquid	Solid: Retention at 2h >60% and 4h >10%: GE solid @4h: mild ≤20%; moderate 20-35%; severe >35% Liquid: Retention at 1h >50%	Increasing severity of ES and F was associated with increasing gastric retention of a solid meal at 4 hours (all p=0.01).
<sup>G</sup> Koch, 2014*(78)	104	IG	UGI sx – VAS	P	Scintigraphy 4H solid	4h retention Mild 10-20% Moderate 20-25% Severe > 35%	F at 15 and 30 min after the start of a meal was associated with degree of gastroparesis (p=0.05)
Borges, 2013 (79)	41		UGI Sx	R	Scintigraphy 2H solid or liquid	Solid (T <sub>1/2</sub> min): mild = 121-132; moderate= 133-144; severe = 145-156; very severe > 156 Liquid (T <sub>1/2</sub> min): mild = 91-99; moderate = 100-108; severe = 109-117; very severe > 117	No significant associations
Modiri, 2012*(80)	56		PAGI-SYM	P	Scintigraphy 4H solid		
<sup>P</sup> Jaffe, 2011 (81)	59	20 DG, 39 IG	Nausea Profile / PAGI-SYM	P	Scintigraphy 4H solid	Retention at 2h >60% & 4h >10%	
<sup>P</sup> Cherian, 2010 (82)	68	50 IG, 18 DG	PAGI-SYM	P	Scintigraphy 4H solid	Retention at 2h >60% & 4h >10%	

McCallum, 2007(83)	106		UGI Sx	P	Scintigraphy 4H solid	Retention > 6%	
<sup>G</sup> Parkman, 2016 (84)	159	107 IG, 52 DG	PAGI-SYM	P	Scintigraphy 4H solid and liquid	Solid delayed: Retention 2h >60% and 4h >10%; Liquid delayed: Retention at 1h >50%	
<sup>P</sup> Hassam, 2014* (85)	229	154 IG 53 DG	PAGI-SYM	P	Scintigraphy 4H solid		
Kowalczyk, 2011* (86)	255		PAGI-SYM	P	Scintigraphy 4H solid		
<sup>G</sup> Hasler, 2011 (87)	335	219 IG, 116 DG	GCSI	P	Scintigraphy 4H solid	Retention at 2h >60% & 4h >10%	
<sup>G</sup> Hasler, 2013 (88)	393	256 IG, 137 DG	PAGI-SYM	P	Scintigraphy 2&4H solid	Retention at 2h >60% & 4h >10%	
<sup>P</sup> Karamanolis, 2007 (89)	58	IG	8 UGI Sx; 4 pt Likert	P	<sup>14</sup> C-OCT BT 4H solid <sup>13</sup> C-GLY BT 4H liquid	T <sub>1/2</sub> > 109 min for solids, >74 min for liquids	
Butt, 2014*(90)	15	Parkinso nism	GCSI	P	WMC		
Barshop, 2015 (91)	39	26 IG 13 DG	GCSI	R	WMC	AUC duodenal and antral motility. WMC defines gastric emptying based on changes in pH profile. The 5 h time point was used to mark delayed gastric emptying.	

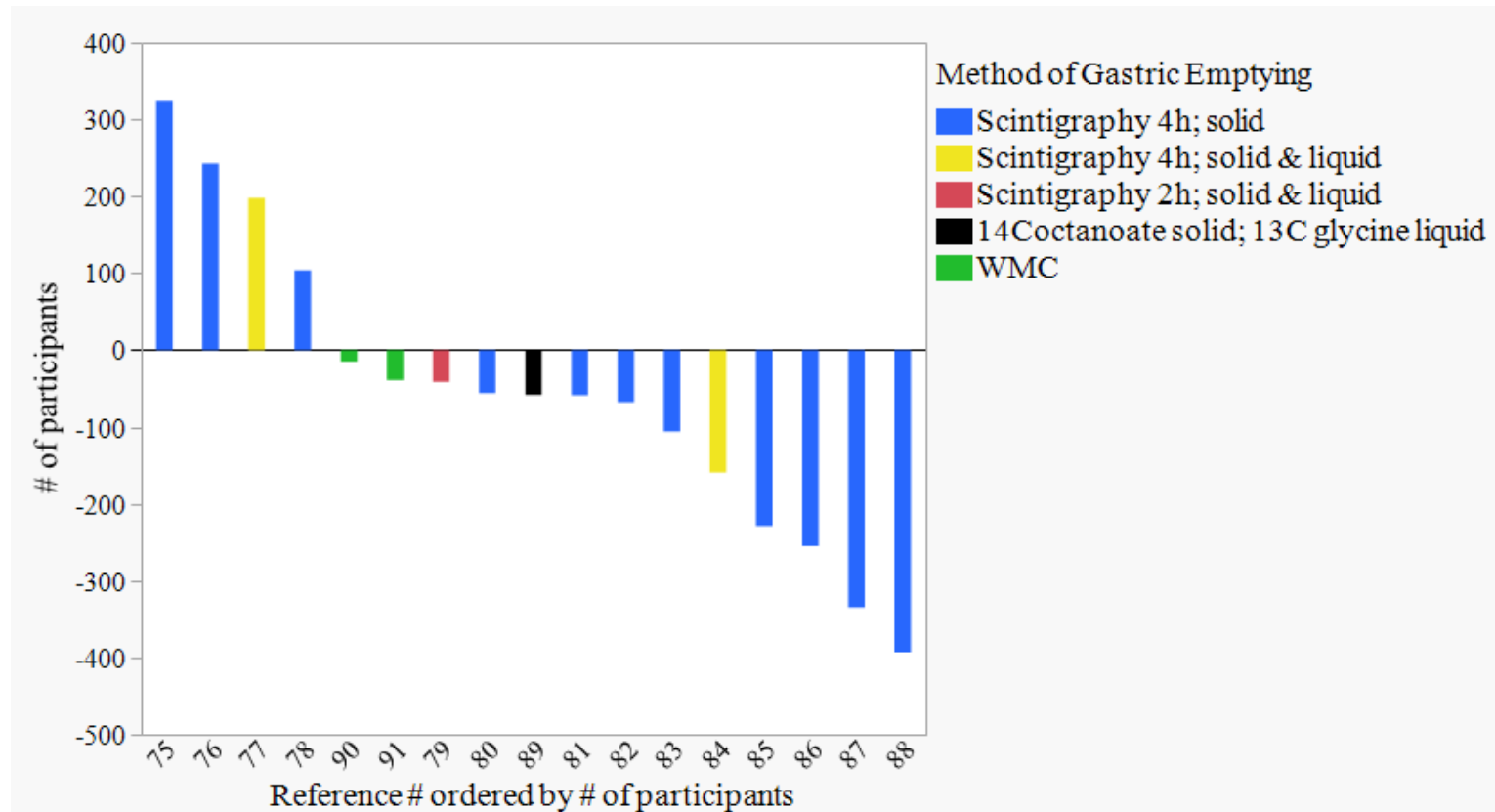
Supplemental Figure 2. Waterfall plot demonstrating association between gastric emptying breath test and upper gastrointestinal symptoms in patients with or without gastroparesis



Supplemental Figure 3. Waterfall plot demonstrating association between gastric emptying by scintigraphy and upper gastrointestinal symptoms in patients with or without gastroparesis



Supplemental Figure 4. Waterfall plot demonstrating association between gastric emptying and upper gastrointestinal symptoms in patients with gastroparesis.



## Supplemental References

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