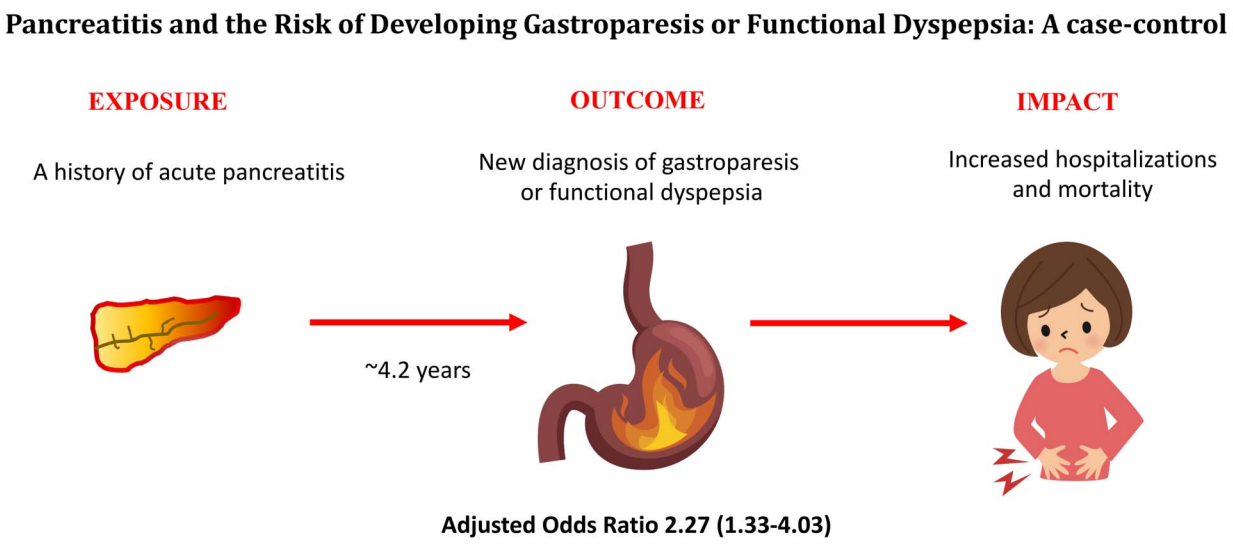
Pancreatitis and the Risk of Developing Gastric Neuromuscular Dysfunction

Trisha S. Pasricha, MD, MPH[1,2], Kyle Staller, MD, MPH[1,2] and Braden Kuo, MD[1,2]

INTRODUCTION: **Most gastroparesis and functional dyspepsia cases (collectively, gastric neuromuscular dysfunction [GND]) remain idiopathic. It is believed that some idiopathic cases of GND may be triggered by an inflammatory insult to the gastrointestinal tract. We theorized that the profound foregut inflammation induced by pancreatitis could result in increased risk of GND.**

METHODS: **This was a case-control study of all patients undergoing gastric emptying scintigraphy between October 2017 and 2020 in an urban medical center with presumed GND. These were age-, sex-, and comparative health-matched to control patients with newly diagnosed microscopic colitis. Adjusted odds ratios (aORs) were calculated using conditional logistic regression.**

RESULTS: **Among the 650 patients with GND, 359 had gastroparesis, and 9.2% had a history of acute pancreatitis (vs 3.1% of controls). Patients with GND demonstrated increased odds of having a history of acute pancreatitis (aOR 2.27, 95% confidence interval [CI] 1.33–4.03, $P = 0.004$) and recurrent pancreatitis (aOR 2.08, 95% CI 1.67–3.48, $P = 0.002$). Median time to GND diagnosis after first acute pancreatitis episode was 1,544 days (477.5, 3,832). Patients with a history of pancreatitis-associated GND had increased mortality vs controls (aOR 3.41, 95% CI 0.96–5.48). In addition, patients with pancreatitis-associated GND had more hospitalizations vs GND alone (13.8 vs 3.7, $P < 0.0001$) during the study period.**



Icon of stomach and woman above are from Openclipart [https://openclipart.org/].

[1]Center for Neurointestinal Health, Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts, USA; [2]Harvard Medical School, Boston, Massachusetts, USA. **Correspondence:** Trisha S. Pasricha, MD, MPH. E-mail: tpasricha@mgh.harvard.edu.
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DISCUSSION: **This is the first study demonstrating an independent association between pancreatitis and the risk of GND, which occurred ~4.2 years after the first episode of acute pancreatitis. Pancreatitis should therefore be regarded as a possible risk factor for developing GND with important consequences for healthcare utilization.**

KEYWORDS: pancreatitis; gastroparesis; functional dyspepsia; gastric neuromuscular dysfunction; inpatient hospitalizations

SUPPLEMENTARY MATERIAL accompanies this paper at http://links.lww.com/CTG/A901 and http://links.lww.com/CTG/A902.

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INTRODUCTION

Despite their prevalence and cost to the healthcare system (1–3), most patients with gastroparesis and functional dyspepsia are "idiopathic" with a cause yet to be identified (4). Historically, gastroparesis has been considered a separate entity from functional dyspepsia, a disorder of chronic upper abdominal symptoms similarly characterized by early satiety and epigastric pain in the absence of the delayed gastric emptying study defining gastroparesis. However, a recent major study confirmed that functional dyspepsia and gastroparesis are indistinguishable clinically and histopathologically with unreliable fluidity of gastric emptying findings, suggesting these 2 diagnoses lie on spectrum of what has been referred to together as gastric neuromuscular dysfunction (GND) (4,5).

Pancreatitis, by contrast, is also a disorder of the foregut with symptom overlap and high healthcare burden similar to GND (6,7); however, its pathophysiology has been far better described. Both pancreatitis and GND can present with abdominal pain, often epigastric, as well as early satiety, nausea, and vomiting, particularly during acute episodes (8,9). Approximately 7% of patients with gastroparesis have a history of pancreatitis (10), and up to 44% of patients with chronic pancreatitis have concomitant gastroparesis (11). A small cross-sectional study demonstrated that patients with both conditions tend to be more symptomatic, are more likely to require total parenteral nutrition, and have worse quality of life compared with those diagnosed with gastroparesis alone (9). Possible theories connecting pancreatitis and gastroparesis include autonomic dysfunction (12), elevated cholecystokinin (13,14), and pancreatic endocrine insufficiency (15). There have been no studies to date, however, to determine whether pancreatitis independently increases the risk of developing GND or increases healthcare utilization and mortality when these diseases overlap.

It is believed that some idiopathic cases of GND may be triggered by an inflammatory insult to the gastrointestinal tract such as a viral illness (16,17) or trauma (18). Indeed, the gastric circular muscle and myenteric plexus of patients with GND have been shown to demonstrate an abnormal inflammatory infiltrate (11,19,20). Given these data, we theorized that the profound foregut inflammation induced by pancreatitis could result in GND.

We therefore designed a case-control study to further examine the temporality and association between GND and pancreatitis as well as better understand the natural history and healthcare utilization of patients with overlapping illness. We hypothesized that patients with a history of acute pancreatitis would have significantly increased risk of developing GND compared with controls associated with increased hospitalizations relative to either disease in isolation.

METHODS

This study was approved by the Massachusetts General Hospital Institutional Review Board. All authors had access to the study data and reviewed and approved the final study report.

Study design and patient population

We designed a case-control study among patients presenting to our tertiary medical care system. The Partners Healthcare Research Patient Data Repository (21) was used to identify cases and controls from the electronic medical record (Figure 1). GND cases were defined by upper gastrointestinal symptoms and a completed 4-hour solid phase gastric emptying scintigraphy between October 2017 and October 2020. In this cohort, gastric emptying scintigraphy was only completed after confirmation of a negative upper endoscopy to rule out mechanical causes of symptoms. Gastric emptying scintigraphy was performed by ingestion of a standardized radiolabeled low-fat, Eggbeaters meal with postprandial nuclear imaging. Greater than 10% 4-hour gastric solid retention was considered consistent with a diagnosis of gastroparesis, and less than 10% 4-hour gastric solid retention was considered consistent with a diagnosis of suspected functional dyspepsia. In patients who had multiple gastric emptying scans in our system, a diagnosis was conferred based on results of their most recent study.

We identified a control group of patients with newly diagnosed microscopic colitis between October 2017 and October 2020 who were matched to GND cases by age, sex, race, date of diagnosis, and comparative health (diagnoses, procedures, diagnosis-related groups, medications, and health history) (22). This control group was chosen as best representing a source population of patients with chronic gastrointestinal complaints evaluated at our tertiary center, but without the predominant upper abdominal symptoms of the GND case set. Patients were subsequently excluded from the control cohort if they had a history of suspected functional dyspepsia or gastroparesis, defined by having undergone gastric emptying scintigraphy. A positive test (less than 90% emptying at 4 hours) was considered consistent with a diagnosis of gastroparesis.

A diagnosis of acute pancreatitis, chronic pancreatitis, microscopic colitis, cystic fibrosis, and alcohol use disorder was based on a clinical diagnosis captured by *International Classification of Diseases* (*ICD*)-code documentation in the patient chart (see Supplementary Table 1, Supplementary Digital Content 1, http://links.lww.com/CTG/A901, for full list of *ICD* codes used). Recurrent pancreatitis was defined as having experienced more than 1 episode of acute pancreatitis. Uncontrolled diabetes was defined as having a hemoglobin A1C of greater than 6.5%. Only episodes of pancreatitis of any kind occurring before study period

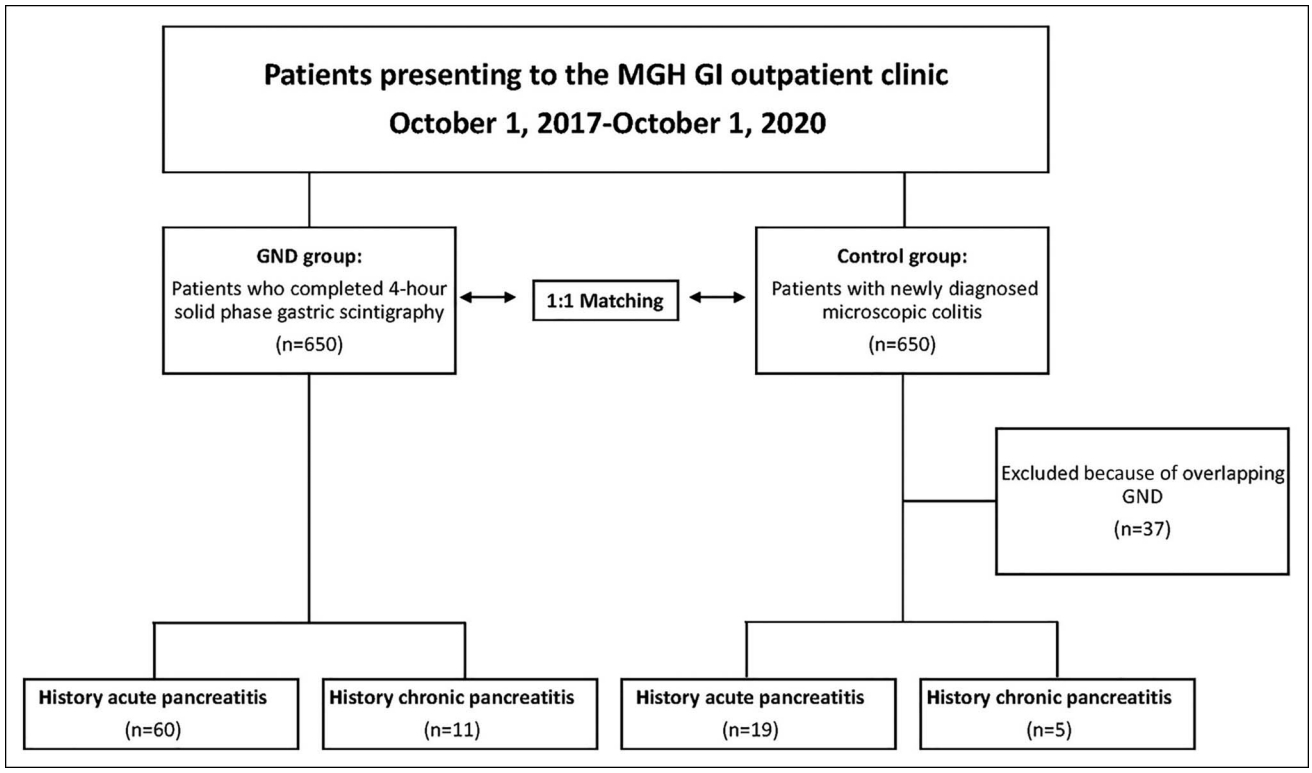

Figure 1. Flowchart of study case-control selection. GI, gastrointestinal; GND, gastric neuromuscular dysfunction; MGH, Massachusetts General Hospital.

of October 2017–October 2020 were considered to be consistent with an exposure, but no subjects were excluded if such episodes occurred during the study period.

To better understand healthcare utilization and mortality of patients with overlapping GND and pancreatitis, we performed a secondary, retrospective analysis of the GND cohort, categorizing patients as having GND alone, a history of acute pancreatitis alone, or GND plus a history of acute pancreatitis.

Assessment of inpatient hospitalizations and mortality

The number of inpatient hospitalizations per patient from October 2017 to October 2020 was assessed by tabulating the total number of unique inpatient encounters per patient during this period. We reported total encounters over this 3-year period to reduce possibility of lead time bias. Mortality within each study group was assessed by tabulating the number of patients with a documented deceased date in our medical records system that fell between October 2017 and October 2020.

Table 1. Patient characteristics between patients with GND and matched controls

Characteristic	GND (N = 650)	Controls (N = 613)	*P* value
Gender, male, n (%)	184 (28.3)	187 (29.9)	NS
Age, mean (SD)	49.32 (19.04)	49.88 (19.22)	NS
Race, White, n (%)	511 (78.5)	497 (79.4)	NS
Uncontrolled diabetes, n (%)	175 (26.9)	116 (18.5)	<0.001
Alcohol use disorder, n (%)	111 (17.1)	85 (13.6)	<0.001
Cystic fibrosis, n (%)	27 (4.2)	9 (1.5)	0.007

GND, gastric neuromuscular dysfunction; NS, nonsignificant.

Statistical analyses

We report descriptive frequencies of patient characteristics among case and control groups with mean values and SDs for continuous variables and total number and percent of total for categorical variables. Descriptive statistics were calculated using *t* tests or χ^2 tests, respectively. We examined the association between pancreatitis and gastroparesis using a logistic regression model to estimate the odds ratio (OR) reported with a 95% confidence interval (CI). Covariates were selected *a priori* based on clinical relevance and included sex, race, and demographic variables as well as disorders known to be associated with both pancreatitis and GND (i.e., uncontrolled diabetes, alcohol use disorder, and cystic fibrosis). Time to diagnosis of GND after first episode of acute pancreatitis was reported as a median number of days with interquartile range.

For number of inpatient hospitalizations, the number of inpatient hospitalizations per patient over the 3-year study period from October 2017 to October 2020 was displayed as mean and SEM. One-way ANOVA testing was performed on all groups with subsequent Tukey's multiple comparison tests performed between individual groups. The most common primary diagnosis for hospitalization was assessed by discerning the most frequent *ICD* code listed as the primary diagnosis for inpatient stays during the study period.

Percent mortality over the 3-year study period was compared using the Fisher exact test, with documented deceased date extracted from the medical record. Logistic regression evaluated the outcome of mortality during the study period between groups with a model

adjusted for age, sex, race, uncontrolled diabetes, alcohol use disorder, and cystic fibrosis. OR with a 95% CI was reported.

Study analyses were performed in R (version 4.0.3) and Prism (version 8). Statistical tests were 2-sided using an alpha level of 0.05.

RESULTS

A total of 650 patients with GND were identified and matched 1:1 to a control set that totaled 613 after excluding those with overlapping GND. Baseline characteristics of cases and controls are summarized in Table 1. Compared with controls, significantly more patients with GND were diagnosed with uncontrolled diabetes (26.9% vs 18.5%), alcohol use disorder (17.1% vs 13.6%), and cystic fibrosis (4.2% vs 1.5%). Among the 650 patients with GND, 359 had a confirmed diagnosis of gastroparesis.

Acute pancreatitis independently increases risk of developing GND

Among patients with GND, 9.2% had a history of acute pancreatitis compared with 3.1% of controls (Table 2). After adjustment, patients with GND demonstrated 2.27 times increased odds of acute pancreatitis compared with controls (95% CI 1.33–4.03, $P = 0.004$). Both patients with GND and controls had similar odds of a history of chronic pancreatitis. When examining any history of pancreatitis (both acute and chronic), those with GND had 2.06 times increased odds compared with controls (95% CI 1.26–3.47, $P = 0.0004$). Subgroup analyses revealed similar trends for both functional dyspepsia and gastroparesis alone as compared to controls (see Supplementary Tables 2A and 2B, Supplementary Digital Content 2, http://links.lww.com/CTG/A902). In addition, after adjustment, patients with GND demonstrated 2.08 times increased odds of a history of recurrent pancreatitis compared with controls (95% CI 1.67–3.48, $P = 0.002$).

Median time to diagnosis of GND after first episode of acute pancreatitis was 1,544 days (477.5, 3,832) or approximately 4.2 years (n = 60).

Patients with pancreatitis-associated GND have increased mortality

There were significant differences in crude mortality between control patients (2.12%), patients with GND alone (5.27%), patients with a history of acute pancreatitis alone (15.79%), and those with GND plus a history of acute pancreatitis (7.94%) ($P = 0.0009$) during the 3-year study period (Figure 2). After controlling for possible confounders, increased odds of mortality were noted among patients with a history of acute pancreatitis alone (adjusted OR [aOR] 4.36, 95% CI 0.96–14.32), GND alone (aOR 2.32, 95% CI 1.23–4.54), and with pancreatitis + GND (aOR 3.41, 95% CI 0.96–5.48) compared with controls (Table 3). Although the latter group trended toward the highest aOR for mortality, the CIs were nonsignificant.

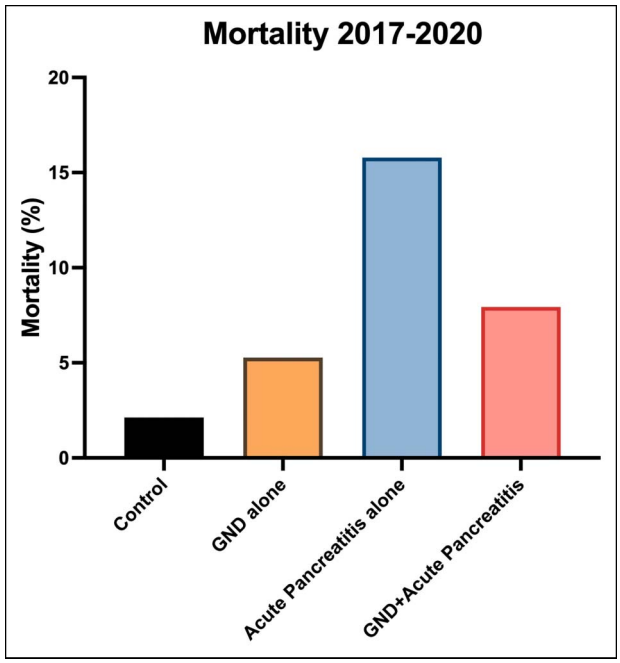

Figure 2. Percent mortality among patients with gastric neuromuscular dysfunction (GND), acute pancreatitis, or both.

Patients with pancreatitis-associated GND have increased inpatient hospitalizations

Inpatient hospitalization frequency differed significantly between groups ($P < 0.0001$) (Figure 3). On average, control patients had 0.8 inpatient hospitalizations (SEM 0.14) during the study period (October 2017–2020), whereas those with GND alone had 3.7 hospitalizations (SEM 0.30) and those with a history of pancreatitis alone had 8.08 hospitalizations (SEM 2.7). The greatest number of hospitalizations was seen among those with both GND and a history of acute pancreatitis. These patients had a mean of 13.79 hospitalizations (SEM 1.9) during the study period. After adjusting for multiple comparisons, those with GND plus a history of pancreatitis had significantly more hospitalizations than both those with a history of pancreatitis alone and those with GND alone ($P = 0.002$ and $P < 0.0001$, respectively).

The most common primary diagnoses for hospitalization among all patients involved end-stage renal disease and cystic

Table 2. Odds ratios of GND with a history of pancreatitis versus matched controls

Exposure	GND (N = 650) n (%)	Controls (N = 613) n (%)	Crude odds ratio	*P* value	95% CI	Adjusted odds ratio[a]	*P* value	95% CI
Acute pancreatitis	60 (9.2)	19 (3.1)	3.18	<0.0001	1.87–5.39	2.27	0.004	1.33–4.03
Chronic pancreatitis	11 (1.7)	5 (0.08)	2.09	0.017	0.72–6.06	1.15	0.81	0.37–3.97
Recurrent pancreatitis	41 (6.3)	12 (2.0)	3.37	0.0003	1.75–6.48	2.08	0.002	1.67–3.48

CI, confidence interval; GND, gastric neuromuscular dysfunction; *ICD*, *International Classification of Diseases*.
[a]Odds ratio adjusted for gender, age, race, uncontrolled diabetes (defined as hemoglobin A1C >6.5%), alcohol use (defined by *ICD* code of medical complication involving alcohol use), and cystic fibrosis (defined by *ICD* code).

Table 3. Odds ratios of all-cause mortality in patients with GND alone, a history of acute pancreatitis alone, or both

Exposure	Alive (N = 1,212) n (%)	Dead (N = 51) n (%)	Crude odds ratio	*P* value	95% CI	Adjusted odds ratio[a]	*P* value	95% CI
Control	600 (50)	13 (25)	—	—	—	—	—	—
Acute pancreatitis alone	16 (1.3)	3 (5.9)	8.65	0.0017	2.2–33.4	4.36	0.027	0.96–14.32
GND	539 (44)	30 (59)	2.2	0.017	1.15–4.32	2.32	0.003	1.23–4.54
Acute pancreatitis + GND	57 (4.7)	5 (9.8)	4.04	0.01	1.39–11.7	3.41	0.04	0.96–5.48

CI, confidence interval; GND, gastric neuromuscular dysfunction; *ICD*, *International Classification of Diseases*.
[a]Odds ratio adjusted for gender, age, race, uncontrolled diabetes (defined as hemoglobin A1C >6.5%), alcohol use (defined by *ICD* code of medical complication involving alcohol use), and cystic fibrosis (defined by *ICD* code).

fibrosis (Table 4). Although patients with GND alone frequently were hospitalized because of "gastroparesis" and patients with pancreatitis alone were hospitalized because of "chronic pancreatitis," a specific abdominal diagnosis was less frequently noted for patients with both GND and a history of acute pancreatitis. For these patients, rather, common primary diagnoses of hospitalization included "unspecified abdominal pain" and "nausea with vomiting, unspecified."

DISCUSSION

This study demonstrates the temporality, strength, and major healthcare outcomes of the association between pancreatitis and development of GND. A history of 1 episode of acute pancreatitis increases the odds of development of GND approximately 2.3 times compared with controls with microscopic colitis, with GND diagnosed approximately 4 years after the first episode of pancreatitis. Patients with pancreatitis-associated GND have increased inpatient hospitalizations than those with GND alone or pancreatitis alone as well as trended toward increased mortality compared with controls. These findings lend credence to the hypothesis that a proportion of GND cases, particularly for those deemed idiopathic, may be related to a history of profound inflammatory insults such as pancreatitis. Our data also suggest that even 1 episode of acute pancreatitis may be a sufficient trigger. It remains to be seen to what extent a history of pancreatitis may further increase risk of GND among those who may otherwise be labeled as "diabetic" in etiology.

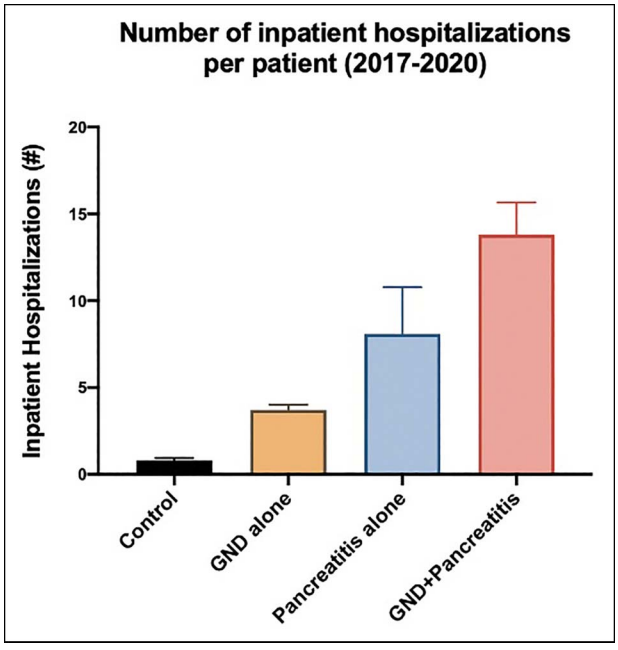

Figure 3. Hospitalization rates among patients with gastric neuromuscular dysfunction (GND) alone, a history of acute pancreatitis alone, or both.

We found that patients with acute pancreatitis-associated GND were hospitalized more than 4 times more frequently than non–pancreatitis-associated GND, no doubt associated with in profound costs to the healthcare system. In recent years, the mean hospital charge per patient for gastroparesis was $34,585 (1). Given previous studies demonstrating increased medication and dependence on total parenteral nutrition, it is possible this subset of patients represents a more severe disease phenotype, given a possible pathophysiology involving an inflammatory state mediated through the vagus nerve. Known complications of pancreatitis include acute respiratory distress syndrome, kidney failure, pancreatic pseudocysts, and splenic vein thromboses, but our study indicates that GND may be considered an additional important complication from an economic and clinical standpoint.

Several studies have demonstrated mixed results regarding elevated mortality rate among patients with gastroparesis compared with the general population (23). We found that patients with GND have a significantly higher mortality rate than controls, with a similar, but nonsignificant trend in pancreatitis-associated GND. Studies designed to evaluate this specifically and assess whether any possible increase mortality is driven by other complications related to their history of pancreatitis or by factors associated with a more severe phenotype of GND should be considered in future.

We made the decision to use patients with microscopic colitis after careful consideration of our study population. An ideal control group would be representative of the population from which our cases were derived, i.e., patients with chronic gastrointestinal symptoms seeking care in a tertiary medical system. We are a center who sees patients by referral from the entire New England area, and so, a general population would not be representative of the advanced patients who come to our center and receive gastric emptying studies. In addition, other more common chronic gastrointestinal diseases such as gastroesophageal reflux disease have considerable overlap with gastroparesis and therefore would skew the results. We therefore chose the microscopic colitis population because these symptoms rarely overlap with those in our cases, but they too are chronic patients who undergo an extensive gastrointestinal workup to arrive at a diagnosis (i.e., invasive colonoscopy with biopsies). Future

Table 4. Most frequent primary diagnoses for hospitalization for patients with GND alone, a history of acute pancreatitis alone, or both

Group (no. of encounters)	GND	Acute pancreatitis	Acute pancreatitis + GND
1	Cystic fibrosis (3,315)	End-stage renal disease (317)	End-stage renal disease (278)
2	Gastroparesis (882)	Unspecified abdominal pain (174)	Cystic fibrosis (141)
3	Gastroesophageal reflux disease without esophagitis (699)	Cystic fibrosis (141)	Unspecified abdominal pain (137)
4	End-stage renal disease (657)	Essential hypertension (112)	Essential hypertension (90)
5	Unspecified abdominal pain (628)	Chronic pancreatitis (89)	Nausea with vomiting, unspecified (79)

GND, gastric neuromuscular dysfunction.

studies should examine similar study questions among a more general population.

Our study has several limitations. One limitation is the use of *ICD* codes for diagnoses of pancreatitis and alcohol use disorder, which may have led to a more sensitive but less specific assessment. However, previous studies have demonstrated relatively good validity of *ICD* coding in the diagnosis of both acute and chronic pancreatitis (with positive predictive values of 0.79 and 0.71, respectively) (24). Although this study did not demonstrate a significant connection between chronic pancreatitis and GND, it is possible that the effect size was smaller, and our study was underpowered for this outcome because other studies have demonstrated an association (25). There remains a possibility of other unmeasured confounders such as illicit drug use or chronic opioid use, which our database did not quantify, but that may interfere with these findings (although notably, in our hospital system, our practice is not to order gastric emptying studies on patients using chronic opioids). In addition, we used referral for gastric emptying study rather than Rome IV criteria to define GND, which may lead to some missed diagnoses (dyspepsia not referred for gastric emptying study or alternative diagnosis discovered), and so these patients can only be considered to have suspected functional dyspepsia. There is additionally the possibility of temporal bias, given gastrointestinal symptoms may have preceded diagnosis by a period, unlike acute pancreatitis where timing of symptom onset and diagnosis are closely intertwined. Furthermore, a possibility of recall bias may exist for remote episodes of acute pancreatitis being subsequently entered into the medical record. Finally, as an observational study, we are unable to make firm conclusions of causality; however, this type of study is novel in its ability to characterize the strength of the association between 2 relatively rare diseases.

Future research should be directed at better elucidating the pathogenesis from acute pancreatitis to GND at a cellular level and further characterizing disease subtypes. Clinicians should consider assessing for history of pancreatitis among patients presenting with upper gastrointestinal symptoms. Like diabetes, vagal injury, or certain neurological conditions, acute and recurrent pancreatitis may be classified as independent risk factors for the development GND, and conversely, GND should be considered as a complication of acute and recurrent pancreatitis.

CONFLICTS OF INTEREST

Guarantor of the article: Trisha S. Pasricha, MD, MPH.

Specific author contributions: T.S.P. and B.K. conceived of the study, conducted main analyses, and wrote the first draft. B.K. and K.S. provided critical feedback, interpreted the data, and revised the manuscript.

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Potential competing interests: B.K. has received research support from AstraZeneca, Takeda, Gelesis, Medtronic, and Genzyme and has served as a consultant to Shire, Takeda, and Ironwood. K.S. has served as a consultant to Arena, Boston Pharmaceuticals, Gelesis, GI Supply, and Shire and received research support from Ironwood Pharmaceuticals and Urovant. T.S.P. has no personal or financial competing interests to declare.

IRB approval: This study was approved by the Massachusetts General Hospital Institutional Review Board.

GND, gastric neuromuscular dysfunction.

Study Highlights

WHAT IS KNOWN

- ✓ A history of pancreatitis has a higher prevalence among patients with gastroparesis and functional dyspepsia or gastric neuromuscular dysfunction (GND); however, the risk is unknown.

WHAT IS NEW HERE

- ✓ A previous episode of acute pancreatitis significantly increased the odds of later developing GND.
- ✓ Patients with pancreatitis-associated GND are more frequently hospitalized than other forms of GND and had increased mortality compared with controls.

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