The impact of risk factors on gastroparesis at an urban medical center

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Abstract	**Background** Gastroparesis is a complex and poorly understood disease. The literature is lacking with respect to the epidemiology of patient comorbidities and their effect on gastric emptying. We aimed to describe the most common comorbid conditions among patients with gastroparesis in an urban population and quantify the effect of these comorbidities on the severity of delayed gastric emptying (DGE). **Methods** We examined the medical records of all patients diagnosed with gastroparesis at a quaternary care center between 2014 and 2015. The severity of DGE was analyzed after patients were stratified for possible causative etiologies. Likelihood ratio tests were used to assess the significance of demographic and scintigraphic variation in this population. **Results** Of the 221 patients, 56.1% were Caucasian and 31.7% were African American. Among these patients, 29.4% had evidence of medication-associated gastroparesis, 29.0% had diabetes-associated gastroparesis, and 31.7% had idiopathic disease. African American patients with gastroparesis were more likely to have diabetic gastroparesis than patients of other races (P=0.01). There was a statistically significant relationship between the number of major risk factors and the severity of a patient's DGE (P=0.004). **Conclusions** Among a diverse urban population, patients with DGE often carry multiple comorbid conditions that serve as risk factors for the development of gastroparesis, including prescriptions for narcotic medications. Greater numbers of these comorbid conditions are associated with more severe disease. Demographics are significantly associated with the etiology and severity of gastroparesis; in particular, African American patients are more likely to have diabetic gastroparesis than patients of other races. **Keywords** Delayed gastric emptying, diabetes mellitus, narcotic medications *Ann Gastroenterol 2020; 33 (3): 250-256*

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Introduction

Gastroparesis is a syndrome of objective delayed gastric emptying (DGE) in the setting of symptoms such as nausea, vomiting, early satiety, bloating, and upper abdominal pain, and in the absence of a mechanical obstruction [1,2]. The gold standard for diagnosis is gastric emptying scintigraphy (GES) [2,3]. The epidemiology of gastroparesis in the community is not well described. Two previous studies have described the epidemiology of the disease, but these were limited to relatively uniform suburban and rural locations [4,5].

While a multitude of etiologies of gastroparesis have been suggested, most studies group patients into 2 categories: diabetic and idiopathic. Diabetic gastroparesis has been extensively studied [6-11], but the most common form of gastroparesis is thought to be idiopathic, with a possible correlation to a prior viral infection [2,12,13]. Other cases of gastroparesis can be attributed to various medications, post-

surgical changes, neurologic diseases, autoimmune syndromes, and connective tissue disease [14-21].

The relationship between patient demographics, the objective severity of DGE, and the specific etiology of the disease is not well understood. Our goal was to describe the most common comorbidities among an urban patient population diagnosed with gastroparesis and to determine whether certain comorbidities correlate with disease severity.

Patients and methods

This is a retrospective chart review including all patients who underwent GES at Thomas Jefferson University Hospital in Philadelphia, PA, between 2014 and 2015. This study was evaluated and approved by the Institutional Review Board at our institution (Control #18D.081). The electronic medical record was reviewed to collect information regarding patient demographics, medical history, medications prescribed at the time of diagnosis and GES data. Data were collected and managed using REDCap electronic data capture tools hosted at Thomas Jefferson University [22].

Patients were included in the study if their GES showed >50% retention of gastric contents 2 h following ingestion of a solid meal consisting of an egg and bread sandwich labeled with 0.5 mCi of Technetium 99m-sulfur colloid. This is the standard for diagnosing DGE at our institution; it is based on industry standards for the Philips Medical Systems' JetStream software as well as institution-specific analyses. Patients were excluded

from the presented analyses if they had a mechanical gastric outlet obstruction precluding the diagnosis of gastroparesis.

The presence of comorbid conditions serving as risk factors for the development of gastroparesis was evaluated for each patient in the study population. Major risk factors were defined as comorbid conditions that have been well established in the literature to be strongly associated with gastroparesis. Minor risk factors were defined as those postulated to be related to gastroparesis in *in vivo* studies or smaller case reports, but not consistently proven to be associated. Patients were assigned to categories as outlined in Fig. 1; patients with one or more major risk factors were assigned to the appropriate mutually inclusive groups 1-3, while patients with minor risk factors only or idiopathic disease were assigned to exclusive groups 4 or 5.

Statistical analysis

To analyze the significance of demographic and scintigraphic variation, likelihood ratio tests were performed on a linear model fit to predict the percentage of gastric contents retained at 2 h, or a generalized linear model with a logit linking function to predict the presence of a particular etiologic category. P-values were calculated using chi-square test, which assessed the significance of individual variables within linear models when controlling for other potential sources of variation. All analyses were performed using R 3.4.
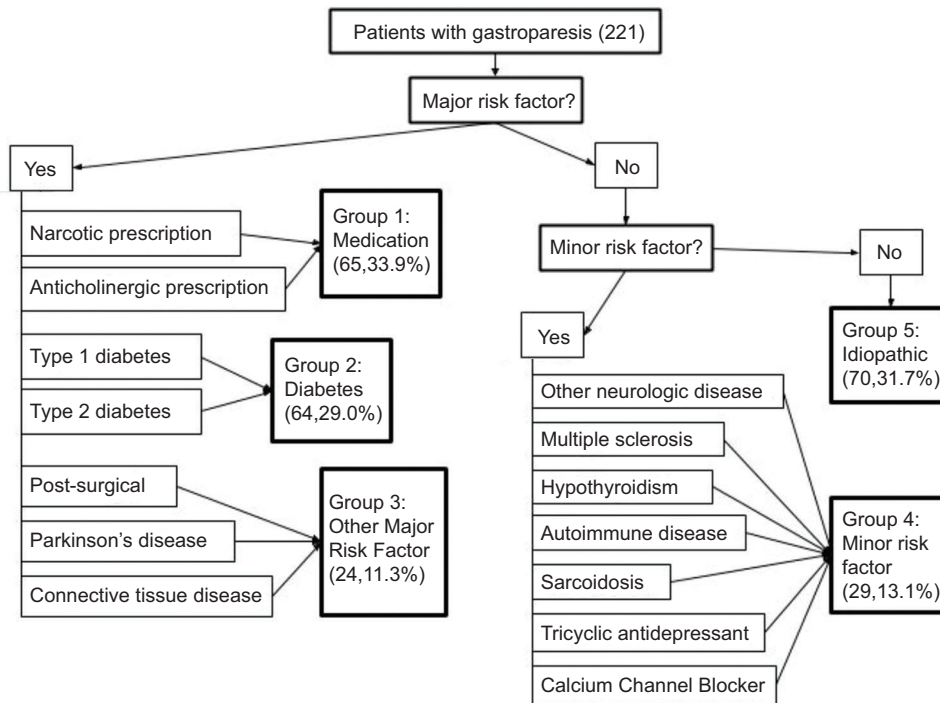

Figure 1 Grouping of patients

Results

There were 703 patients who completed solid-phase GES at Thomas Jefferson University Hospital during 2014 and 2015. Of these patients, 262 had accelerated gastric emptying and 210 had normal gastric emptying. Ten patients were excluded because they had a physical gastric outlet obstruction, precluding a diagnosis of gastroparesis.

In total, 221 patients were included in the study. Of these patients, 77.4% were female; 56.1% were Caucasian and 31.7% were African American; 29.8% of patients had a diagnosis of diabetes mellitus; and 33.9% of patients had an active prescription for narcotics or anticholinergic medications (Table 1). The mean body mass index (BMI) of patients included in the study was 27.6 kg/m².

Patients were grouped based on their comorbidities and risk factors for the purposes of our descriptive analysis. There were 65 (29.4%) patients who met the criteria for medication-associated gastroparesis; 64 (29.0%) had diabetic gastroparesis, 24 (11.3%) had gastroparesis associated with another major risk factor, 29 (13.1%) had minor risk factors but no major risk factors, and 70 (31.7%) were classified as true idiopathic gastroparesis. There was significant demographic variation among the etiologic categories.

In a model comparing patients with and without diabetes-associated gastroparesis, patient race (P=0.01), age (P=0.02), sex (P=0.008), and BMI (P<0.001) were independent, statistically significant predictors of having diabetes-associated gastroparesis. While only 31.7% of the study population was African American, 64.1% of patients with diabetes-associated gastroparesis in this population were African American. Men, patients with an elevated BMI, and patients diagnosed at an older age had a statistically significantly greater probability of having diabetes-associated gastroparesis than females, patients with a lower BMI, and younger patients (Tables 2,3).

In a model comparing patients with and without medication-associated gastroparesis, age (P=0.04) and BMI (P=0.02) were independent, statistically significant predictors of having medication-associated gastroparesis after controlling for patient sex and race. Patients with a higher BMI or diagnosed at an older age had a higher likelihood of having medication-associated gastroparesis than patients with a lower BMI and those younger at diagnosis.

Among patients with idiopathic disease, there was also a statistically significant variation in age (P<0.001) and BMI (P=0.009) compared to patients in the study population without idiopathic disease after controlling for sex and race. Patients with a lower BMI or those diagnosed at a younger age were more likely to have idiopathic disease than patients with a higher BMI or those older at diagnosis.

Two of the major risk factors significantly contributed to more severe delays in gastric emptying after controlling for race and sex: medications (P=0.02) and diabetes (P=0.03) (Table 4). In addition, after controlling for age, sex, BMI, and race, there was a statistically significant relationship between the number of major risk factors and the severity of a patient's DGE (P=0.004) (Table 5). There was no statistically significant

relationship between the number of minor risk factors and the severity of DGE (P=0.33).

Table 1 Overall patient characteristics

Category	N (%)
Sex	
Female	171 (77.4)
Male	50 (22.6)
Race	
Caucasian	124 (56.1)
African American	70 (31.7)
Other	23 (10.4)
Major risk factors	
Narcotic prescription	55 (24.9)
Anticholinergic prescription	20 (9.0)
Type 1 diabetes mellitus	9 (4.1)
Type 2 diabetes mellitus	55 (24.9)
Post-surgical	9 (4.1)
Parkinson's	2 (0.9)
Connective tissue disease	17 (7.8)
Minor risk factors	
Hypothyroidism	37 (16.7)
Multiple sclerosis	7 (3.2)
Other neurologic disease	3 (1.4)
Autoimmune disease	22 (10.0)
Sarcoidosis	4 (1.8)
Calcium channel blocker prescription	33 (14.9)
Tricyclic antidepressant prescription	15 (6.8)
True idiopathic	70 (31.7)

Discussion

This study examined the most common comorbid conditions among an urban patient population diagnosed with gastroparesis. Female patients represented 77.4% of the study population, and 42.9% of patients were from minority groups. The majority of patients carried at least one risk factor for gastroparesis, while 32% of patients had true idiopathic disease. A higher burden of major risk factors was significantly associated with a more severe delay in gastric emptying.

To our knowledge, this is the first study to examine the comorbidities, or risk factors for DGE among an urban population of gastroparesis patients, and the first to attempt to establish the impact of multiple comorbid conditions on the objective severity of DGE. Our patient demographics are similar to those in previous publications with regard to the average age of patients at the time of diagnosis and the

Table 2 Race and risk factors

Patient Group	Total	Race (%)			P-value*
		Caucasian	African American	Other	
Overall	221	56.1	31.7	12.2	NA
Medication-associated	65	56.9	32.3	10.8	NS
Diabetes mellitus	64	*34.4*	*64.1*	1.5	0.01
Other major risk factor	24	*75.0*	*20.8*	4.2	0.04
Minor risk factor only	29	62.1	27.6	10.3	NS
True idiopathic	70	58.6	24.3	17.1	NS

*P-values represent a controlled comparison between patients within a specific gastroparesis group and patients not in that group

NA, not applicable; NS, nonsignificant

Table 3 Demographics and risk factors

Patient Group	Total	Average age (years)	P-value	Average BMI	P-value*
Overall	221	47.9	NA	27.6	NA
Medication-associated	65	51.1	0.02	*29.4*	0.04
Diabetes mellitus	64	53.9	0.02	31.5	<0.001
Other major risk factor	24	52.3	NS	27.2	NS
Minor risk factor only	29	51.4	NS	25.5	NS
True idiopathic	70	39.6	<0.001	25.0	0.009

*P-values represent a controlled comparison between patients within a specific gastroparesis group and patients not in that group

NA, not applicable; NS, nonsignificant; BMI, body mass index

Table 4 Risk factors and severity of delayed gastric emptying

Risk factors	Mean percent retained at 2 h (%)
Medication-associated	74.5 (n=65, SD=14.2), P=0.02
Diabetes mellitus	73.5 (n=64, SD=14.8), P=0.03
Other major risk factor	73.0 (n=24, SD=14.5)
Minor risk factor only	68.7 (n=29, SD=13.4)
True idiopathic	67.1 (n=70, SD=11)
Overall	70.3 (n=221, SD=13.3)

SD, standard deviation

Table 5 Number of risk factors and severity of delayed gastric emptying (P=0.004)

Number of major risk factors	Mean percentage retained at 2 h (%)
0	67.6 (n=99, SD=11.7)
1	70.9 (n=82, SD=13.3)
2	76.3 (n=36, SD=15.1)
3	90.6 (n=3, SD= 22.6)
4	85 (n=1)

SD, standard deviation

predominance of female patients [12,23-25]. Importantly, our study is among the first to include a significant representation of minority populations in its analysis.

Previous studies have attempted to correlate patient symptoms with the degree of DGE, but few have examined the relationship between etiology of gastroparesis and the severity of DGE [25-28]. We have shown that patients with diabetic or medication-associated gastroparesis and those with multiple major risk factors in combination had significantly more severe DGE compared to those with idiopathic gastroparesis.

A wide range of medications have been implicated in delaying gastric emptying. Based on the available evidence, we considered narcotic analgesics and anticholinergic medications to be significantly related to DGE [29-31]. In our study, 25% of patients had an active prescription for narcotics at the time of diagnosis – higher than the national opioid prescribing rate [32].

Calcium channel blockers and tricyclic antidepressants are thought to impact gastric motility, but data are lacking on a clear relationship with DGE [33-36]. For this reason, we considered both of these medications to be minor risk factors for the disease.

A majority of our patients had a prescription for at least one medication that has been implicated in delaying gastric emptying, a finding that has not previously been well described. According to the 2008 Consensus Recommendations for Gastric Emptying Scintigraphy, most centers recommend that patients stop gastric motility-delaying agents 48-72 h prior to undergoing GES [3]. Perhaps it could be beneficial to perform GES while patients are still taking all medications; this would provide the most accurate representation of the patient's DGE as it occurs on a daily basis.

Gastroparesis is a well-known complication of diabetes [7,37]. In this study, African American patients were more likely to have diabetic-associated gastroparesis than gastroparesis patients of any other race. This supports the findings of prior studies with a smaller proportion of minority patients [38,39]. While rates of diabetes mellitus in the community are also greater among African Americans (12.1 vs. 7.6% for Caucasians) [40], our findings indicate a disproportionate impact on minority populations.

Medical conditions that have been clearly linked with gastroparesis include post-surgical nerve injury, Parkinson's disease, autoimmune diseases and connective tissue diseases, such as systemic sclerosis and Sjögren's syndrome [14,16-18,20,41-48]. Interestingly, our population included a significant percentage of patients with hypothyroidism (16.7%), significantly higher than the national prevalence of 4.6% [48]. While the hypothyroidism state is associated with delayed esophageal and gastric motility, we did not consider a diagnosis of hypothyroidism to be a major risk factor for gastroparesis, as evidence suggests that once patients are stabilized on appropriate medication, the impact on motility is typically resolved [49-52].

Idiopathic gastroparesis is diagnosed when no other cause is identified, though it is often unclear in previous studies which potential causes were considered before patients were labeled with the diagnosis [13,52,53]. As is standard in the literature [54-56], we included patients with a post-viral syndrome as patients with idiopathic disease, assuming that they did not have a major risk factor.

In our study, we relied on the available literature to describe exposures and comorbid conditions as risk factors for gastroparesis. Our individual patient data were limited to the availability of details in the medical record. We were unable to gather information regarding indicators of the severity and control of patients' underlying chronic diseases, or the doses of their prescribed medications, both of which can impact gastric emptying. In addition, the gold standard for evaluation of DGE is 4-h nuclear emptying scintigraphy. However, at our institution patients classically undergo a 2-h scan unless there is doubt regarding the results. Finally, it is difficult to determine which medications were held prior to scintigraphic testing and for how long. These patient instructions are physician-dependent and there is no clear documentation in our record system regarding the instructions provided to the patient or followed by the patient.

In conclusion, the results of this retrospective study indicate that patients diagnosed with gastroparesis often have multiple comorbid conditions, and the number of risk factors that they carry significantly impacts the severity of their disease. If we continue to limit patients into broad categories of diabetic and idiopathic gastroparesis, we may be missing opportunities to better address the true underlying etiology of the disease and to treat patients optimally. In addition, we have demonstrated a racial disparity in the etiology of gastroparesis, with African American patients being more likely to have diabetic disease than patients of other races.

Further research should be done to better elucidate the impact of certain medications, comorbid conditions and socioeconomic status on gastric emptying. Additionally, physicians should consider patients' individual risk factors when ordering, protocoling, and interpreting GES studies in order to best evaluate the extent of the disease and to provide optimal medical management.

Summary Box

What is already known:

- Little is known about the causes of gastroparesis beyond severe diabetes
- Many patients are characterized as having idiopathic gastroparesis

What the new findings are:

- A large proportion of gastroparesis patients receive narcotic prescriptions
- African American patients seem to be at higher risk for diabetic gastroparesis than patients of other races
- Patients with more conditions known to be associated with gastroparesis had more severe objective delays in gastric emptying

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