Nutritional deficiencies and predictors of mortality in diabetic and nondiabetic gastroparesis

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Abstract

Background Gastroparesis is a debilitating condition that may impact morbidity and mortality, but there is a lack of long-term studies examining this relation. The aim of this study was to determine the predictors of mortality in gastroparesis and to determine the nutritional deficiencies.

Methods Between September 30, 2009 and January 31, 2020, we identified 320 patients (mean age 47.5±5.3 years, 70% female, 71.3% Whites, 39.7% diabetic and 60.3% nondiabetic) with gastroparesis. ⁹⁹mTc sulfur-labeled food was used to diagnose gastroparesis. Cox proportional-hazard regression was used to compute the association of mortality predictors.

Results Of the 320 patients, 46 (14.4%) died during the study period. Among diabetics, advanced age (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.03-1.10; P<0.001), chronic kidney disease (CKD) (HR 4.69, 95%CI 1.62-13.59; P=0.004), and malnutrition (HR 10.95, 95%CI 3.23-37.17; P<0.001) were associated with higher mortality, whereas in nondiabetics older age (HR 1.05, 95%CI 1.01-1.09; P=0.04), CKD (HR 10.2, 95%CI 2.48-41.99; P=0.001), chronic obstructive pulmonary disease (COPD) (HR 7.5, 95%CI 2.11-26.82; P=0.002), coronary artery disease (CAD) (HR 9.7, 95%CI 1.8-52.21; P=0.008), and malnutrition (HR 3.83, 95%CI 1.14-29.07; P=0.03) were associated with increased mortality. Overall, 48.8% had vitamin D, 18.2% had vitamin B₁₂, and 50.8% had iron deficiencies. Only 19.4% of the whole cohort was evaluated by a nutritionist.

Conclusions Advanced age, CAD, CKD, COPD and malnutrition were associated with higher mortality in gastroparesis. Despite the high prevalence of nutritional deficiencies, consultation of a specialist nutritionist was uncommon.

Keywords Gastroparesis, diabetes mellitus, nutritional deficiencies, gastric emptying study

Introduction

Gastroparesis is a complex, debilitating syndrome with symptoms that include nausea, vomiting, and postprandial abdominal pain or fullness [1]. The Olmstead community study showed estimates of almost 2%, higher than the national prevalence. Gastroparesis is underdiagnosed, as the gastric emptying test is not commonly performed, and the patients identified are the tip of the iceberg [2]. It afflicts 5.2% of type 1 diabetics, 1% of type 2 diabetics, and 0.2% of individuals without diabetes mellitus (DM) [3]. It is more common in women than men. The prevalence of diabetic gastroparesis is expected to rise with the increasing prevalence of DM.

The poor oral intake in severe cases of gastroparesis can lead to malnutrition [4]. Micronutrient deficiencies are commonly observed in this population and may contribute to the disease burden [5]. Because of their poor nutrition, these patients require frequent hospitalizations secondary to gastroparesis, which impose a major burden on the health care system [6,7].

Long-term studies examining the impact of gastroparesis on morbidity and mortality are lacking. To date, the few epidemiological studies have shown heterogeneous results in terms of mortality [8-10]. The data regarding populations at risk of high mortality are deficient. Therefore, it is prudent to examine
the risk factors and predictors of adverse outcomes in patients with gastroparesis. The literature shows that gastroparesis patients consume food deficient in essential nutrients [5,11]. The effect of poor nutrition on the clinical outcomes is not well documented. Therefore, we aimed to study the predictors of mortality in diabetic and non-diabetic gastroparesis, and to estimate the prevalence of clinical undernutrition and micronutrient deficiencies among these patients.

**Patients and methods**

**Study population**

This retrospective cohort study was conducted at a tertiary care hospital in Albany, located in upstate New York, which has a large catchment area. After the chart review, we identified all patients diagnosed with gastroparesis between Sept 30, 2009 and January 31, 2020. The follow up was 100% in our patients because they were followed by the same gastroparesis clinic. The study was approved by the institutional review board of Albany Medical Center, with patient consent waived.

The hospital record was reviewed, and the patients labeled with gastroparesis and had a delayed gastric emptying study were identified. We included patients older than 18 years diagnosed with gastroparesis on the solid and/or liquid gastric emptying study (outpatient and inpatient). Patients were excluded if they were older than 90 years. The cases with incomplete gastric emptying scintigraphy (n=15), evidence of mechanical gastric outlet obstruction (n=6), peptic ulcer disease (n=17), and those with clinically diagnosed gastroparesis with a normal gastric emptying study (n=518) were excluded. The date of the first gastric emptying study was considered as the baseline date.

**Baseline data and covariates**

Gastroparesis was defined as delayed gastric emptying of solids and liquids on a scintigraphic gastric emptying study. $^{99m}$Tc sulfur colloid-labeled liquid and solid foods were used as test meals. Gastric retention of ≥10% of solids at 4 h and ≥5% of liquids at 1 h were identified as delayed gastric emptying. The definition of delayed gastric emptying of liquids at 60 min was based on the institutional nuclear radiology consensus. In a few cases when tests were performed for both solids and liquids, the date of the first test was recorded. The cases with isolated delayed gastric emptying with liquids were also considered as gastroparesis. Severe gastroparesis was defined as gastric retention of >35% of the test meal after 4 h for solids and 1 h for liquids [12]. Per institutional policy, opiates were stopped at least 24-48 h before the study.

Vitamin D deficiency was defined as 25-OH-vitamin D3 levels less than 30 ng/mL. Vitamin B12 deficiency was defined as levels below 300 ng/mL. Patients diagnosed with vitamin deficiencies and received supplements (inaccessible labs) were also included. Iron deficiency was diagnosed if ferritin levels were less than 30 ng/mL.

In patients with indeterminate range ferritin (30-100 ng/mL), iron deficiency anemia was differentiated from anemia of chronic disease with low serum iron, low serum transferrin saturation and normal or high total iron binding capacity [13].

DM was defined based on one of the following criteria before the diagnosis of gastroparesis: a) International Classification of Diseases ICD-9 and ICD-10 codes and treated with insulin or oral hypoglycemics for at least 30 days; b) glucose levels ≥200 mg/dL on 2 separate occasions; c) glucose ≥200 mg/dL at least once and treated with oral hypoglycemics or insulin for at least 30 days) glucose levels above 126 mg/dL on least 2 separate occasions and treated for at least 30 days [14]. Chronic kidney disease (CKD) was defined as GFR <60 mL/min/1.73m$^2$ measured on 2 separate occasions [15]. Malnutrition was defined as a lack of intake of essential nutrients, leading to altered body composition, poor clinical outcomes and decreased physical function. Although individuals with overnutrition can also suffer from malnutrition, our study only labeled patients with undernutrition as malnourished. In accordance with the guidelines of the American Society for Parenteral and Enteral Nutrition, these patients were identified objectively by 2 of the following criteria: reduced weight, muscle wasting, loss of subcutaneous fat, fluid accumulation and decreased hand grip [16,17]. Patients with body mass index (BMI) ≥30 kg/m$^2$ were classified as obese. Biochemical values, including hemoglobin, liver function test, glycated hemoglobin A1c, serum creatinine, albumin, calcium, vitamin B12 and D levels, were extracted from the routine laboratory data, taking the mean of the 2 most recent values before the baseline. Type 1 and 2 DM were not differentiated. Injectable medications such as glucagon-like peptide-1 agonists were recorded as non-insulin injectables.

Baseline demographic data, including age, sex, race, and comorbidities such as obesity, hypertension, gastroesophageal reflux disease (GERD), coronary artery disease (CAD), chronic obstructive pulmonary disease (COPD), history of cancer, and autoimmune disorder, were extracted after careful chart review. Medication use, including proton-pump inhibitor, H$_2$-receptor blocker, opiates, antidepressants, prokinetics, oral hypoglycemics, insulin, vitamin supplements and benzodiazepines, were recorded from the medication history at the time of diagnosis or from the most recent prescription record before the gastric emptying study.

During the study period 320 patients were included in the study. The study subjects were segregated into diabetics and non-diabetics.

**Outcomes**

Our primary outcome was all-cause mortality in diabetics and non-diabetics. Patients were censored when mortality occurred or when the last day of follow up was achieved, whichever came earlier. We also aimed to determine the predictors of mortality among diabetics and nondiabetics. The secondary outcome was the prevalence of clinical malnutrition, vitamin D, vitamin B12, and iron deficiencies.

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*Annals of Gastroenterology* 34
Statistical analysis

The baseline characteristics were presented as percentages for the categorical variables and means ± SD for continuous variables, and were compared between diabetic and nondiabetic gastroparesis patients. A multivariate logistic regression model was used to assess the association of diabetes and other covariates with mortality during the study period. These models were adjusted for age, sex, race, obesity, BMI, hypertension, diabetes, GERD, CKD, CAD, obesity, COPD, autoimmune disease, cancer, neuromuscular disease, use of proton-pump inhibitor, use of H2-receptor blocker, use of opioids, use of antidepressants, use of prokinetic, use of oral or injectable non-insulin drugs, use of insulin, and vitamin D and B12 deficiencies. We also evaluated the same predictors among the diabetic and nondiabetic subgroups. To keep the multivariate model brief, we performed backward stepwise regression and only variables with an association of P<0.05 were included in the model. We also compared levels of calcium, vitamin D, vitamin B12, albumin and folate between diabetics and nondiabetics, using a t-test or Mann-Whitney U test if the distribution was skewed. All analysis was conducted using statistical software PASW v. 18 (SPSS Inc., Chicago, IL). A P-value <0.05 was considered significant.

Results

Demographics

During the study period 1148 patients had a gastric emptying study with suspicion of gastroparesis. Of these patients, 272 were either younger than 18 years or older than 90. Among the reviewed charts 38 patients were excluded because of an incomplete study, endoscopic diagnosis of mechanical obstruction, gastric cancer, or peptic ulcer disease. A negative gastric emptying study was observed in 518 patients. Thus, a total of 320 patients were included in the analysis (Fig. 1), of whom 127 (39.7%) had DM and 193 (60.3%) did not.

The patients’ mean age was 47.5±5.3 and 70% were female. The major secondary diagnoses were obesity (42.8%), hypertension (39.7%), GERD (63.8%), CKD (18.8%), CAD (15.3%), COPD (13.4%), autoimmune disease (10.3%), neuromuscular disease (5.9%), cancers (10%), clinical malnutrition (20%), and history of gastric bypass (8.1%). Of 204 patients with GERD, 17.1% had esophagitis on endoscopy. This was observed in 20% of the GERD patients with DM and 15.4% of the nondiabetics (P=0.4).

At the time of the diagnosis, a proton-pump inhibitor (80.3%) was the most commonly prescribed medication in both groups, followed by antidepressants (60.6%), opiates (41.6%), H2-receptor blockers (23.7%), and prokinetics (17.5%). The prokinetic used prior to diagnosis was metoclopramide in 49 patients (15% in DM and 10% in nondiabetics), erythromycin in 3 patients, and combined metoclopramide and erythromycin in 7 patients.

The DM population was older (51.0±15.0 vs. 45.3±16.9 years, P=0.002) while the non-DM population had a more female (76.2% vs. 60.6%, P=0.003) and Caucasian (76.7% vs. 63%, P=0.008) population. Obesity (54.3% vs. 35.2%, P=0.001), hypertension (63.0% vs. 24.4%, P<0.001), CKD (35.4% vs. 7.8%, P<0.001) and CAD (29.1% vs. 6.2%, P<0.001) were more common in the diabetic population, whereas GERD (68.9% vs. 55.9%, P=0.02) was more common in nondiabetics. The DM gastroparesis patients had lower hemoglobin levels and higher white blood cell counts, serum creatinine and alkaline phosphate levels (Table 1). The median duration of DM at the time of the diagnosis of gastroparesis was 10 years (interquartile range 4-18). DM-related complications were seen in 66 patients (52%): these included 15% retinopathy, 18.9% nephropathy, and 36.2% neuropathy.

A total of 42 (13.1%) patients had a history of bariatric or esophageal surgery (26 bariatric surgery and 18 esophageal surgery). Post-surgical gastroparesis was more common in nondiabetics 8 (6.3%) vs. 35 (18.1%), P=0.002. The causes

![Figure 1 Flowchart showing gastroparesis patient population](image-url)
of nondiabetic gastroparesis included a history of bariatric surgery (9.8%), esophageal surgery (8.3%), neuromuscular disease (5.8%), infections (4.6%), potential drug use (opiates 38.3%, antidepressants 59.6%), and idiopathic (35.5%). A few patients had more than one of these causes.

The mean duration of follow up was 3.71±2.32 years (3.44±2.31 years in DM and 3.9±2.31 years in nondiabetics).

### Mortality and clinical outcomes

Of the 320 patients, 46 died during the study period, of whom 27 had DM and 19 did not have DM. When compared to nondiabetic gastroparesis, patients with diabetic gastroparesis had a higher cumulative incidence of death within the study period (Fig. 2). This is explained by the fact that the diabetic patients...
died earlier during the study period. However, multivariate analysis showed that there was no significant difference in mortality between the 2 groups (P=0.82). Heart disease was the most common cause of death in DM (33%), followed by kidney disease and cancer (18.5% each), whereas heart disease (26.3%) and infections (26.3%) were the most common causes of death in nondiabetics (Supplementary Table 1).

Patients with older age (hazard ratio [HR] 1.06, 95% confidence interval [CI] 1.02-1.11; P=0.009), CKD (HR 12.94, 95%CI 3.48-48.16; P<0.001), CAD (HR 3.42, 95%CI 1.03-11.3; P=0.04), COPD (HR 3.32, 95%CI 1.02-10.81; P=0.046), and malnutrition (HR 5.63, 95%CI 1.58-20.03; P=0.008) had higher mortality. Deficiencies in vitamins B12 (HR 0.60, 95%CI 0.09-3.86; P=0.38) and D (HR 1.62, 95%CI 0.14-18.92; P=0.7), and iron deficiency anemia (HR 1.22, 95%CI 0.34-4.39; P=0.76) were not associated with higher mortality. Other comorbidities, including obesity, hypertension, GERD, autoimmune disorders, cancer, and history of gastroesophageal surgery, were not associated with higher mortality (Table 2).

A subgroup analysis was performed to determine the predictors of mortality in diabetics and nondiabetics (Table 3). Among diabetics, older age, CKD and malnutrition were associated with higher mortality, whereas nondiabetics with older age, CKD, CAD, COPD, and malnutrition had higher mortality (Fig. 3A, B).

Severe gastroparesis

A total of 115 (35.9%) patients had severe gastroparesis. DM was associated with a higher incidence of severe gastroparesis (47.2% vs. 27.9%, odds ratio 2.17, 95%CI 1.23-3.83; P=0.007).

A gastrojejunostomy tube was required in 11.5% of the gastroparesis population (6.3% in DM and 15.0% in non-DM, P=0.01).

Clinical recovery

Clinical recovery was identified from the provider’s documentation. At 12 weeks from baseline, 88 patients (27.4%) had no clinical recovery. Of these, 28 (22.1%) diabetics and 60 (31.1%) nondiabetics had no recovery. These patients had higher mortality (HR 2.96, 95%CI 1.6-5.47; P=0.001).

Malnutrition and micronutrient deficiency

Clinical malnutrition was observed in 22.8% patients with DM and 17.8% nondiabetics. Their BMI decreased

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**Table 2 Predictors of outcome (multivariate model)**

| Variable                  | Hazard ratio (95% confidence interval) | P-value |
|---------------------------|----------------------------------------|---------|
| Age                       | 1.06 (1.02-1.11)                       | 0.009   |
| Female                    | 1.26 (0.42-3.79)                       | 0.69    |
| Race                      | 0.55 (1.13-2.25)                       | 0.41    |
| Vitamin D deficiency      | 1.62 (0.14-18.92)                      | 0.7     |
| Vitamin B12 deficiency    | 0.60 (0.09-3.86)                       | 0.38    |
| Iron deficiency anemia    | 1.22 (0.34-4.39)                       | 0.76    |
| Obesity                   | 2.21 (0.17-3.8)                        | 0.46    |
| BMI                       | 0.19 (0.78-1.05)                       | 0.93    |
| Hypertension              | 0.22 (0.06-0.79)                       | 0.02    |
| Diabetes mellitus         | 1.31 (0.12-14.43)                      | 0.82    |
| Malnutrition              | 5.63 (1.58-20.03)                      | 0.008   |
| GERD                      | 1.4 (0.38-5.18)                        | 0.61    |
| Chronic kidney disease    | 12.94 (3.48-48.16)                     | <0.001  |
| Coronary artery disease   | 3.42 (1.03-11.3)                       | 0.04    |
| COPD                      | 3.32 (1.02-10.81)                      | 0.046   |
| Autoimmune                | 0.65 (0.12-3.42)                       | 0.61    |
| Cancer                    | 1.43 (0.32-6.32)                       | 0.64    |
| Neuromuscular             | 0.72 (0.06-0.04)                       | 0.79    |
| Proton-pump inhibitor     | 1.68 (0.3-9.33)                        | 0.55    |
| H₂-receptor blocker       | 0.62 (0.17-2.23)                       | 0.46    |
| Opiate                    | 2.1 (0.63-6.98)                        | 0.23    |
| Antidepressants           | 0.79 (0.29-2.14)                       | 0.65    |
| Prokinetic                | 0.49 (0.07-3.26)                       | 0.46    |
| Oral and injectable non-insulin | 0.89 (0.14-5.67)                 | 0.9     |
| Insulin                   | 0.86 (0.09-8.43)                       | 0.9     |

BMI, body mass index; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; H₂, histamine receptor 2
Gastroparesis outcomes and predictors

by 0.55±3.9 kg/m² in 6 months from baseline, there was no correlation of this BMI change with the presence or absence of DM (r=0.2, P=0.59). The diabetics had a greater drop in serum albumin after 6 months from diagnosis compared to nondiabetics (0.13±0.5 vs. -0.03±0.5 mg/dL, r=0.15, P=0.03). The vitamin and mineral deficiencies were similar in both diabetics and nondiabetic gastroparesis. Vitamin D deficiency was seen in 49.7% of the population. The mean vitamin D level was 22.6±10.7 ng/mL. Vitamin B12 deficiency was observed in 17.5% (mean 456.6±214.7 pg/mL), whereas iron deficiency was observed in 50.3% of the population. The mean albumin level was 3.6±0.7 g/dL. The nutritional service evaluated 19.4% of the population (Table 1). Patients who had undergone nutritional evaluation had higher mortality (diabetics HR 2.37, 95%CI 0.88-6.36; P=0.08 vs. nondiabetics HR 4.68, 95%CI 1.44-15.18; P=0.01).

Discussion

To date, this is the largest study to examine the outcomes of patients with nondiabetic and diabetic gastroparesis confirmed by a gastric emptying study. Our study found that the mortality rate in gastroparesis patients over 3.7-year period was 14.4%. We observed that malnutrition and common comorbid conditions, such as CAD, CKD, and COPD, played an important role in defining the prognosis of these patients. DM itself was not associated with increased risk of mortality in these patients. Advanced age, a history of CKD, CAD, COPD and malnutrition were associated with greater mortality in both diabetics and nondiabetics. We also found that both the groups had a high incidence of micronutrient deficiencies, including iron, and vitamins B12 and D. Despite the high nutritional deficiencies, only 19.4% patient had a documented nutritional evaluation. Our study is novel, as it determined the

### Table 3 The predictors of mortality in diabetic and nondiabetic gastroparesis

| Variables      | Diabetic gastroparesis HR (95%CI) | P-value | Nondiabetic gastroparesis HR (95%CI) | P-value |
|----------------|----------------------------------|---------|-------------------------------------|---------|
| Age            | 1.06 (1.03-1.10)                 | <0.001  | 1.05 (1.01-1.09)                    | .04     |
| Sex            | 0.55 (0.2-1.46)                  | 0.23    | 2.35 (0.67-8.3)                     | .18     |
| Race           | 0.75 (0.35-1.59)                 | 0.45    | 0.77 (0.11-5.35)                    | .79     |
| Iron deficiency| 1.31 (0.45-3.78)                 | 0.62    | 2.49 (0.63-9.85)                    | 0.19    |
| Obesity        | 2.45 (0.78-7.74)                 | 0.13    | 0.30 (0.06-1.62)                    | .16     |
| Hypertension   | 0.63 (0.21-1.92)                 | 0.42    | 0.37 (0.09-1.53)                    | 0.17    |
| CKD            | 4.69 (1.62-13.59)                | 0.004   | 10.21 (2.48-41.99)                  | .001    |
| CAD            | 2.44 (0.98-6.05)                 | 0.05    | 9.71 (1.8-52.21)                    | .008    |
| COPD           | 0.42 (0.08-2.21)                 | 0.31    | 7.51 (2.11-26.82)                   | .002    |
| Cancer         | 1.33 (0.37-4.77)                 | 0.66    | 2.90 (0.67-12.44)                   | .15     |
| Neurimuscular  | 1.47 (0.14-15.59)                |         |                                    | .75     |
| Malnutrition   | 10.95 (3.23-37.17)               |         | 3.83 (1.14-29.07)                   | .03     |

**HR**, hazard ratio; **CI**, confidence interval; **CAD**, coronary artery disease; **CKD**, chronic kidney disease; **COPD**, chronic obstructive pulmonary disease

**Figure 3** (A) Forest plot of predictors of mortality in diabetics with gastroparesis. (B) Forest plot showing the predictors of mortality in nondiabetic gastroparesis

**HTN**, hypertension; **CAD**, coronary artery disease; **CKD**, chronic kidney disease; **COPD**, chronic obstructive pulmonary disease; **HR**, hazard ratio; **CI**, confidence interval
Advanced age, malnutrition, chronic kidney disease, chronic obstructive pulmonary disease, and coronary artery disease were associated with higher mortality in gastroparesis. Patients with diabetes mellitus had more severe gastroparesis compared to nondiabetics. Gastroparesis patients with diabetes mellitus died earlier during the disease course.

### Summary Box

**What is already known:**
- Gastroparesis is associated with high morbidity and mortality
- Nutrition evaluation is underutilized in the gastroparesis population
- Micronutrient deficiencies are commonly seen in gastroparesis patients

**What the new findings are:**
- Advanced age, malnutrition, chronic kidney disease, chronic obstructive pulmonary disease, and coronary artery disease were associated with higher mortality in gastroparesis
- Patients with diabetes mellitus had more severe gastroparesis compared to nondiabetics
- Gastroparesis patients with diabetes mellitus died earlier during the disease course
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### Supplementary Table 1 Causes of death in diabetics and nondiabetics with gastroparesis (percentage of total deaths in the groups)

| Causes of death              | Diabetes mellitus (%) | Nondiabetic (%) |
|------------------------------|-----------------------|-----------------|
| Heart disease                | 33.3                  | 26.3            |
| Chronic kidney disease       | 18.5                  | 5.3             |
| Cancer                       | 18.5                  | 0               |
| Infections                   | 14.8                  | 26.3            |
| Cerebrovascular disease      | 3.7                   | 10.5            |
| Chronic lung disease         | 0                     | 15.8            |
| Chronic liver disease        | 3.7                   | 0               |
| Malnutrition                 | 7.4                   | 0               |
| Alcohol abuse                | 0                     | 5.3             |
| Accidents                    | 0                     | 5.3             |