

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. ^{99m}Tc 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

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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

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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 nondiabetic gastroparesis, and to estimate the prevalence of clinical malnutrition 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 $\geq 10\%$ of solids at 4 h and $\geq 5\%$ 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/1.73m² 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/m² 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, H₂-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 nondiabetics.

Outcomes

Our primary outcome was all-cause mortality in diabetics and nondiabetics. 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.

Statistical analysis

The baseline characteristics were presented as percentages for the categorical variables and means \pm 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

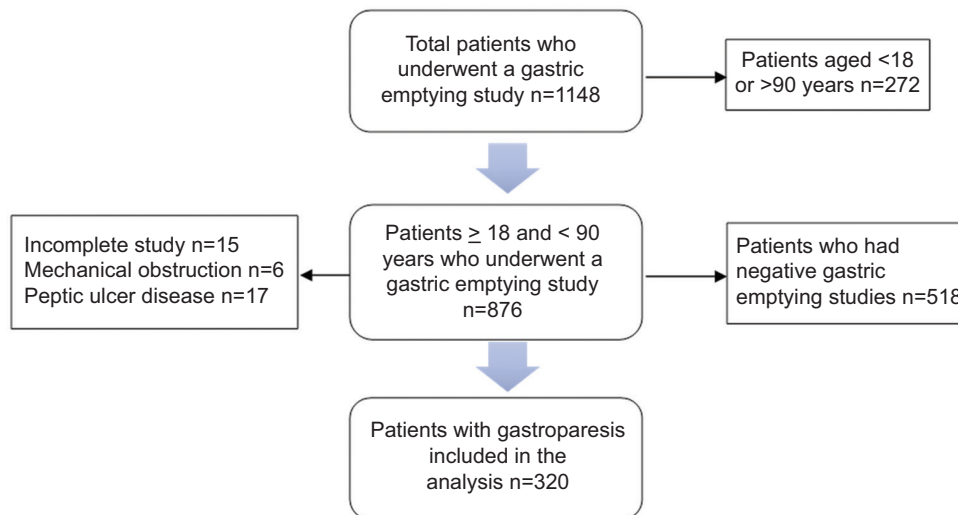


Figure 1 Flowchart showing gastroparesis patient population

Table 1 Patients' characteristic and comparison of diabetic gastroparesis with nondiabetic gastroparesis

Variables	Total cases	Diabetic gastroparesis N=127	Nondiabetic gastroparesis N=193	Two-group comparison (P-value)
Demographics				
Age (mean ± SD)	47.5±5.3	51.0±15.0	45.3±16.9	0.002
Females	224 (70%)	77 (60.6%)	147 (76.2%)	0.003
Whites	228 (71.3%)	80 (63.0%)	148 (76.7%)	0.008
Comorbid conditions				
BMI, kg/m ² (mean±SD)	29.2±8.8	31.6±8.7	27.7±8.3	<0.001
Obesity	137 (42.8%)	69 (54.3%)	68 (35.2%)	0.001
Hypertension	127 (39.7%)	80 (63.0%)	47 (24.4%)	<0.001
GERD	204 (63.8%)	71 (55.9%)	133 (68.9%)	0.02
CKD	60 (18.8%)	45 (35.4%)	15 (7.8%)	<0.001
CAD	49 (15.3%)	37 (29.1%)	12 (6.2%)	<0.001
COPD	43 (13.4%)	14 (11.0%)	29 (15.0%)	0.30
Gastric bypass	26 (8.1%)	7 (5.5%)	19 (9.8%)	0.21
Esophageal surgery	18 (5.6%)	2 (1.2%)	16 (8.3%)	0.004
Autoimmune	33 (10.3%)	13 (10.2%)	20 (10.4%)	0.97
Cancer	32 (10%)	15 (11.8%)	17 (8.8%)	0.15
Neuromuscular disease	19 (5.9%)	8 (6.3%)	11 (5.7%)	0.81
Nutritional deficiencies				
Clinical malnutrition	64 (20%)	29 (22.8%)	35 (18.1%)	0.39
Vitamin D deficiency	159 (49.7%)	68 (53.5%)	91 (47.3%)	0.26
Vitamin B12 deficiency	56 (17.5%)	16 (12.6%)	40 (20.7%)	0.06
Iron deficiency	161 (50.3%)	70 (55.1%)	91 (47.2%)	0.17
Nutrition evaluation	62 (19.4%)	29 (22.8%)	33 (17.1%)	0.18
Biochemistry data				
Hemoglobin, g/dL (mean±SD)	12.0±2.0	11.7±2.1	12.2±1.9	0.03
WBC, K/ μ L (mean±SD)	7.8±2.8	8.4±3.1	7.4±2.6	0.002
Platelets, K/ μ L (mean±SD)	269.4±92.2	265.5±90.9	272.0±93.2	0.54
Creatinine, mg/dL (mean±SD)	1.2±1.6	1.6±2.3	0.85±0.61	<0.001
Total bilirubin, mg/dL (mean±SD)	0.7±0.8	0.8±1.1	0.6±0.3	0.06
AST, IU/L (mean±SD)	26.0±28.6	28.4±36.1	24.2±22.0	0.21
ALT, IU/L (mean±SD)	25.1±23.6	26.6±23.6	24.2±22.0	0.37
ALP, IU/L (mean±SD)	85.7±69.4	98.6±101.2	76.7±29.8	0.006
HbA1c in percentage	7.3±2.4	8.3±2.3	5.6±1.5	<0.001
Calcium, mg/dL (mean±SD)	9.0±0.6	9.0±0.7	9.0±0.5	0.91
Vitamin D levels, ng/mL (mean±SD)	22.6±10.7	21.6±9.8	23.4±11.3	0.32
Vitamin B12 levels, pg/mL (mean±SD)	456.6±214.7	446.8±186.1	462.7±231.6	0.67
Albumin levels, g/dL (mean±SD)	3.6±0.7	3.5±0.7	3.6±0.6	0.07
Folate, ng/mL (mean±SD)	13.6±6.4	12.4±5.2	14.2±7.0	0.20
Medications				
PPI	257 (80.3%)	100 (78.7%)	157 (81.3%)	0.66
H ₂ -receptor blocker	76 (23.7%)	27 (21.3%)	49 (25.4%)	0.40
Opiates	133 (41.6%)	59 (46.5%)	74 (38.3%)	0.15
Antidepressants	194 (60.6%)	79 (62.2%)	115 (59.6%)	0.64
Prokinetics	56 (17.5%)	25 (19.7%)	31 (16.1%)	0.40

Reference ranges: calcium 8.6-10.3 mg/dL; vitamin D 30-100 ng/mL; vitamin B12 300-900 pg/mL; albumin 4-5.2 gm/dL; folate 4-20 ng/mL

SD, standard deviation; GERD, gastroesophageal reflux disease; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; BMI, body mass index; WBC, white blood cell count; AST, aspartate transaminase; ALT, alanine transaminase; ALP, alkaline phosphatase; HbA1c, glycated hemoglobin; PPI, proton-pump inhibitor; H2, histamine receptor 2

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; $P=0.007$).

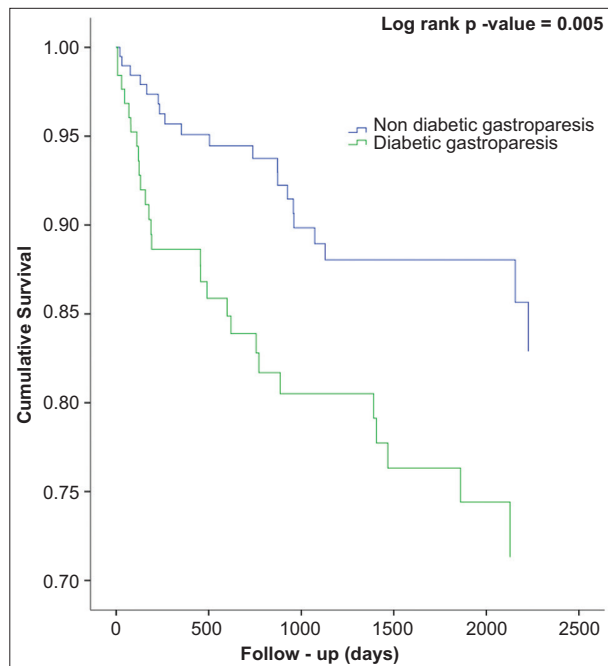


Figure 2 Cumulative incidence of survival by diagnosis (diabetic vs. nondiabetic gastroparesis)

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 (0.06-8.04)	0.79
Proton-pump inhibitor	1.68 (0.3-9.33)	0.55
H ₂ -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

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%) patients 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

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	10.2(2.48-41.99)	.001
CAD	2.44 (0.98-6.05)	0.05	9.7 (1.8-52.21)	.008
COPD	0.42 (0.08-2.21)	0.31	7.5 (2.11-26.82)	.002
Cancer	1.33 (0.37-4.77)	0.66	2.9 (0.67-12.44)	.15
Neuromuscular			1.47 (0.14-15.59)	.75
Malnutrition	10.95 (3.23-37.17)	<0.001	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

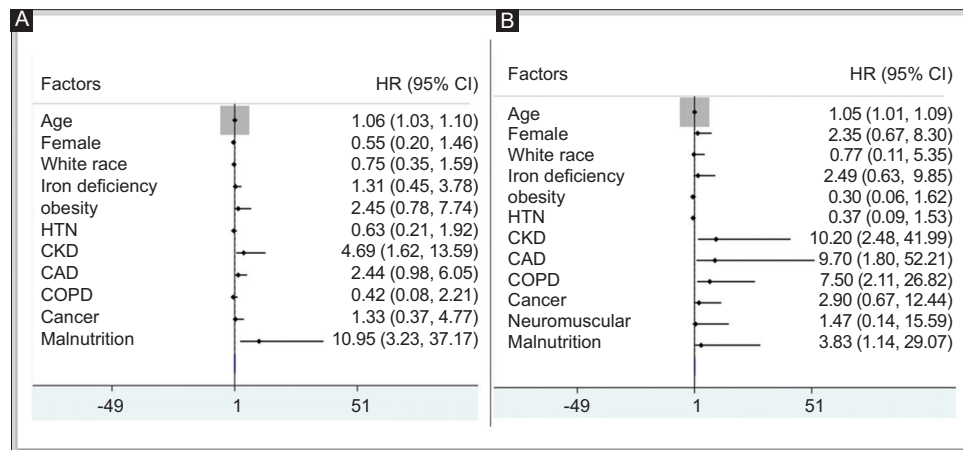


Figure 3 (A) Forest plot of predictors of mortality in diabetics with gastroparesis. (B) Forest plot showing the predictors of mortality in nondiabetic gastroparesis

HTN, hypertension; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease

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

predictors of a poor outcome in gastroparesis patient, which have not previously been discussed in detail in the literature.

A strength of this study is the use of a gastric emptying study to define gastroparesis, rather than using gastrointestinal symptoms that are vague and subjective. Prior population-based studies are limited because the diagnosis of gastroparesis was based on the symptoms rather than on the purely objective evidence of a nuclear gastric emptying study, as in our study [3,18,19]. Rapid gastric emptying and functional dyspepsia can also present with symptoms similar to gastroparesis; thus, reported delayed gastric transit is important for the diagnosis of gastroparesis [1,20]. Another strength of our study is the inclusion of both nondiabetic and diabetic gastroparesis. Previously reported studies were limited to patients with diabetic gastroparesis [3,21]. One popular study based on the Rochester Epidemiology Project (REP) [8] showed that gastroparesis patients had higher than expected mortality (33% in 5 years). In our cohort, the average age of death for gastroparesis patients was 61.4±14.9 years, much lower than the overall life expectancy in the USA [22]. The REP study also demonstrated that age, male sex, and non-idiopathic gastroparesis (including DM) were associated with poor survival. We observed that the survival of nondiabetic gastroparesis was better than the survival of diabetic gastroparesis. This could be explained by the higher comorbidity burden of diabetic patients.

A 1998 study of 146 patients diagnosed with gastroparesis based on a mix of gastric emptying study and symptoms showed greater morbidity among these patients. Over 6 years follow up 7% patients died [9]. A smaller study of 86 Australian adults showed that DM itself was not associated with increased mortality, but rather the duration of DM: the mortality rate was 33.7% over 25 years [10,23]. However, this study could have suffered from beta error due to its small sample size, and may have missed the impact of diabetic gastroparesis on mortality. Our study further strengthens the previously expected notion that diabetic gastroparesis patients tend to have a higher mortality.

Studies based on the National Health and Nutrition Examination Survey have shown that the prevalence of vitamin D deficiency in the general population is 5.4-7.5%, while approximately 3.2% of the population have low vitamin B12 and iron deficiency anemia is 2-3% (although females and toddlers may have a higher prevalence) [24-26]. Our study showed that patients with gastroparesis have a significantly higher number of vitamin D (49.7%), vitamin B12 (17.5%), and iron (50.3%) deficiencies compared to the general population. The mean hemoglobin level was lower in diabetic gastroparesis ($P=0.03$), whereas vitamin D and B12 levels were not statistically different in the 2 groups. The prevalence of proton-pump inhibitor use was higher in this cohort, which could have contributed to the iron and vitamin deficiency [27]. A study by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Gastroparesis Registry [5] showed a greater prevalence of micronutrient deficiency in gastroparesis, including iron, calcium, potassium, and vitamins C, D, E and K. Only 32% of patients in NIDDK gastroparesis registry (January 2007 to March 2010) received nutritional counseling [5]. Our study showed an even lower utilization of nutritional consultation (19.4%), which could explain the

higher prevalence of nutritional deficiencies. Interestingly, the patients seen by nutritional service had higher mortality. It is possible that nutritional counselling was considered in patients who were sicker and had more comorbid conditions.

Other strengths of our study include the diversity of the patient population, the large sample size, granularity in obtaining patient characteristics, and complete follow up for the duration of the study period. The gastroparesis diagnosis was based on the Tougas protocol, unlike previous studies that used the older criteria of 50% or less emptying of stomach at 60 min, which is a less specific protocol [28]. To better understand the outcomes, we avoided overmatching subjects diagnosed with gastroparesis but had a normal gastric emptying study.

Our study also had several limitations, including the retrospective study design and single-center setting. We tried to avoid the errors by using 2 reviewers independently collecting information from the medical records. ICD 9 and ICD 10 codes were used to identify the patients. It is possible that a few patients might have been misclassified, though careful chart auditing was performed to limit the misdiagnosis. Nondiabetic gastroparesis was not further classified into idiopathic and other causes. The DM cases were not categorized into type 1 and 2, and as a result the outcomes were not studied in further subgroups.

In summary, gastroparesis with or without DM has a poor prognosis. The traditional risk factors of increased mortality in the general population, including older age, CAD, CKD, COPD and malnutrition, remained the major predictors of mortality. Clinical malnutrition, vitamin D, B12 and iron deficiencies were commonly observed in both diabetic and nondiabetic gastroparesis. Nutritional counseling was underutilized. More epidemiological studies in the community are indicated to better understand the course of the disease.

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

References

1. Camilleri M, Parkman HP, Shafi MA, Abell TL, Gerson L; American College of Gastroenterology. Clinical guideline: management of gastroparesis. *Am J Gastroenterol* 2013;**108**:18-37.
2. Rey E, Choung RS, Schleck CD, Zinsmeister AR, Talley NJ, Locke GR 3rd. Prevalence of hidden gastroparesis in the community: the gastroparesis “iceberg”. *J Neurogastroenterol Motil* 2012;**18**:34-42.
3. Choung RS, Locke GR 3rd, Schleck CD, Zinsmeister AR, Melton LJ 3rd, Talley NJ. Risk of gastroparesis in subjects with type 1 and 2 diabetes in the general population. *Am J Gastroenterol* 2012;**107**:82-88.
4. Abell TL, Bernstein RK, Cutts T, et al. Treatment of gastroparesis: a multidisciplinary clinical review. *Neurogastroenterol Motil* 2006;**18**:263-283.
5. Parkman HP, Yates KP, Hasler WL, et al; NIDDK Gastroparesis Clinical Research Consortium. Dietary intake and nutritional deficiencies in patients with diabetic or idiopathic gastroparesis. *Gastroenterology* 2011;**141**:486-498, 498.e1-e7.
6. Wadhwa V, Mehta D, Jobanputra Y, Lopez R, Thota PN, Sanaka MR. Healthcare utilization and costs associated with gastroparesis. *World J Gastroenterol* 2017;**23**:4428-4436.
7. Wang YR, Fisher RS, Parkman HP. Gastroparesis-related hospitalizations in the United States: trends, characteristics, and outcomes, 1995-2004. *Am J Gastroenterol* 2008;**103**:313-322.
8. Jung HK, Choung RS, Locke GR 3rd, et al. The incidence, prevalence, and outcomes of patients with gastroparesis in Olmsted County, Minnesota, from 1996 to 2006. *Gastroenterology* 2009;**136**:1225-1233.
9. Soykan I, Sivri B, Sarosiek I, Kiernan B, McCallum RW. Demography, clinical characteristics, psychological and abuse profiles, treatment, and long-term follow-up of patients with gastroparesis. *Dig Dis Sci* 1998;**43**:2398-2404.
10. Kong MF, Horowitz M, Jones KL, Wishart JM, Harding PE. Natural history of diabetic gastroparesis. *Diabetes Care* 1999;**22**:503-507.
11. Ogorek CP, Davidson L, Fisher RS, Krevs B. Idiopathic gastroparesis is associated with a multiplicity of severe dietary deficiencies. *Am J Gastroenterol* 1991;**86**:423-428.
12. Camilleri M. Clinical practice. Diabetic gastroparesis. *N Engl J Med* 2007;**356**:820-829.
13. Johnson-Wimbley TD, Graham DY. Diagnosis and management of iron deficiency anemia in the 21st century. *Therap Adv Gastroenterol* 2011;**4**:177-184.
14. Sacks DB, Arnold M, Bakris GL, et al; Evidence-Based Laboratory Medicine Committee of the American Association for Clinical Chemistry. Guidelines and recommendations for laboratory analysis in the diagnosis and management of diabetes mellitus. *Diabetes Care* 2011;**34**:e61-e99.
15. Levey AS, Stevens LA, Schmid CH, et al; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009;**150**:604-612.
16. Cederholm T, Bosaeus I, Barazzoni R, et al. Diagnostic criteria for malnutrition - An ESPEN Consensus Statement. *Clin Nutr* 2015;**34**:335-340.
17. White JV, Guenter P, Jensen G, Malone A, Schofield M; A.S.P.E.N. Board of Directors. Consensus statement: Academy of Nutrition and Dietetics and American Society for Parenteral and Enteral Nutrition: characteristics recommended for the identification and documentation of adult malnutrition (undernutrition). *JPEN J Parenter Enteral Nutr* 2012;**36**:275-283.
18. Talley NJ, Howell S, Jones MP, Horowitz M. Predictors of turnover of lower gastrointestinal symptoms in diabetes mellitus. *Am J Gastroenterol* 2002;**97**:3087-3094.
19. Bytzer P, Talley NJ, Leemon M, Young LJ, Jones MP, Horowitz M. Prevalence of gastrointestinal symptoms associated with diabetes mellitus: a population-based survey of 15,000 adults. *Arch Intern Med* 2001;**161**:1989-1996.
20. Bredenoord AJ, Chial HJ, Camilleri M, Mullan BP, Murray JA. Gastric accommodation and emptying in evaluation of patients with upper gastrointestinal symptoms. *Clin Gastroenterol Hepatol* 2003;**1**:264-272.
21. Maleki D, Locke GR 3rd, Camilleri M, et al. Gastrointestinal tract symptoms among persons with diabetes mellitus in the community. *Arch Intern Med* 2000;**160**:2808-2816.
22. Murphy S, Xu J, Kochanek K, Arias E. Mortality in the United States, 2017. *CDC NCHS Data Brief* 2018;**(328)**:1-8.
23. Chang J, Rayner CK, Jones KL, Horowitz M. Prognosis of diabetic gastroparesis—a 25-year evaluation. *Diabet Med* 2013;**30**:e185-e188.
24. Schleicher RL, Sternberg MR, Lacher DA, et al. The vitamin D status of the US population from 1988 to 2010 using standardized serum concentrations of 25-hydroxyvitamin D shows recent modest increases. *Am J Clin Nutr* 2016;**104**:454-461.
25. Evatt ML, Terry PD, Ziegler TR, Oakley GP. Association between vitamin B12-containing supplement consumption and prevalence of biochemically defined B12 deficiency in adults in NHANES III (third national health and nutrition examination survey). *Public Health Nutr* 2010;**13**:25-31.
26. Centers for Disease Control and Prevention (CDC). Iron deficiency—United States, 1999-2000. *MMWR Morb Mortal Wkly Rep* 2002;**51**:897-899.
27. Heidelbaugh JJ. Proton pump inhibitors and risk of vitamin and mineral deficiency: evidence and clinical implications. *Ther Adv Drug Saf* 2013;**4**:125-133.
28. Tougas G, Eaker EY, Abell TL, et al. Assessment of gastric emptying using a low fat meal: establishment of international control values. *Am J Gastroenterol* 2000;**95**:1456-1462.

Supplementary material

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