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Delayed gastric emptying as an independent predictor of mortality in gastroparesis

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Summary

Background: Whether gastroparesis is associated with a shortened life expectancy remains uncertain as no systematic study has evaluated the impact of gastroparesis on mortality, based on gastric emptying (GE) tests.

Aim: This study aimed to assess whether delayed GE was predictive of mortality.

Methods: GE was measured using a ¹³C-octanoic acid breath test in 1563 consecutive patients. Delayed GE at baseline defined the gastroparesis group. Patients were followed up for a mean of 8.9 years, yielding 13 466 patients per year. Mortality was assessed using the French CepiDc database with data from local civil registries. The cause of death was determined from medical records. Mortality rates were assessed using the Kaplan-Meier method and hazard ratio (HR) was calculated using the Cox regression model.

Results: Age and symptoms severity were not different among patients with normal GE (n = 1179) and with delayed GE (n = 384) while diabetes mellitus was more frequent in the gastroparesis group. Kaplan-Meier analysis showed increased mortality in the gastroparesis group compared to patients with normal GE. Cox regression model identified delayed GE as independently associated with increased mortality (HR = 1.63[1.09–2.42]; P = 0.02). Other independent factors associated with increased mortality included age, male sex, and diabetes. No difference was observed between groups for the cause of death, with cancer and cardiovascular disease being the leading causes.

Conclusion: This study has shown that gastroparesis, diagnosed on GE tests, was associated with increased mortality, independently of age, sex, BMI or diabetes status (NCT04918329).

1 | INTRODUCTION

Gastroparesis is defined as delayed gastric emptying (GE) associated with symptoms, including nausea, vomiting, postprandial fullness, early satiation and epigastric pain.¹ Gastroparesis may lead, in the

most severe cases, to altered quality of life and nutritional impairment and ultimately to death. The epidemiology as well as the natural history of gastroparesis remains poorly investigated. A recent study evaluated the economic burden of gastroparesis between US\$4000 and US\$9000 per patient per year.² Two studies based on symptom

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patterns, medical records or diagnostic code estimated gastroparesis prevalence at 0.24% in the United States and 0.14% in the United Kingdom.^{3,4} Whether gastroparesis is associated with a shortened life expectancy remains unknown. In a first study, the 9-year follow-up of 86 patients with diabetic gastroparesis did not evidence an association between mortality rates and GE when adjusted for co-morbidities.⁵ In a UK database study based on diagnostic coding, mortality rates were shown to be higher in diabetic compared to idiopathic gastroparesis patients, but the impact of GE on mortality with regards to the general population was not assessed.⁴ To date, only one study, conducted in Olmsted County, Minnesota, USA, has investigated the mortality rates of gastroparesis in a population-based cohort.³ This study showed that gastroparesis was associated with higher mortality rates compared to the expected mortality for the reference population. Of note, the presence of gastroparesis in the later study was defined either as the presence of a proven delay in GE using medical records or by food retention during endoscopy^{6,7} or symptom patterns evocative of gastroparesis. However, the last two criteria, although easy to record and monitor at the general population level, have been shown to be far from specific for gastroparesis diagnosis.^{8,9} As a result, the statement "Gastroparesis is associated with decreased life expectancy" obtained 72% of disagreement among expert and was not endorsed by the recent United European Gastroenterology and European Society for Neurogastroenterology and Motility consensus group.¹⁰

Since gastroparesis diagnosis requires GE measurement, there is currently no systematic study that has addressed the impact of gastroparesis on mortality, based on motility testing. In addition, there is to date no study that has assessed overall survival in gastroparetic patients using direct comparison with a control group (i.e. with normal GE). Therefore, the aim of this study was to assess whether delayed GE was predictive of all-cause and/or disease-specific mortality.

2 | PATIENTS AND METHODS

This retrospective study included all consecutive patients referred to Rouen University Hospital for a GE test between January 2000 and December 2019. Data from the year 2020 were not collected nor analysed due to Covid-19 issues. The study was carried out in accordance with the Helsinki declaration, and has received ethical approval (Comité d'Ethique pour la Recherche sur Données Existantes: no E2021-11). The use of informatic data was declared to the Commission Nationale de l'Informatique et des Libertés (CNIL) (no 817.917), in compliance with French legislation. Database and final analysis were made available for each co-author who all reviewed and validated the current manuscript (NCT04918329).

2.1 | Patients

All patients undergoing a GE test in our centre were considered for this study. These patients were identified using both an automatic

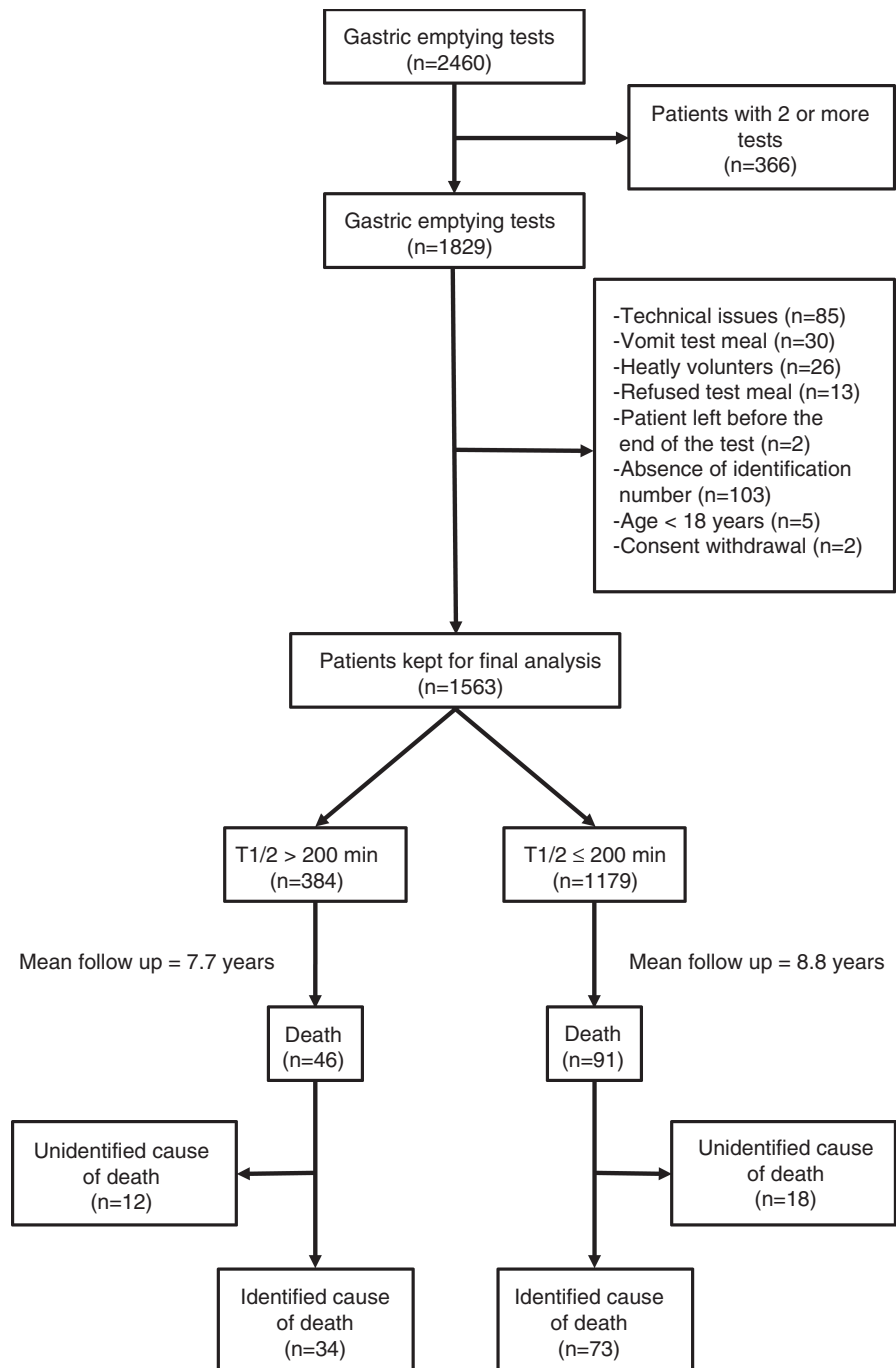
search for appointments in the hospital's appointment database and a semi-automatic search for GE tests in medical/inpatient records with GE measurement (98.3% match). In patients with multiple tests, the first GE test was considered for each patient ($n = 366$). This resulted in the identification of 1830 patients, 266 of whom were not considered for final analysis as illustrated in the flowchart in [Figure 1](#). A GE test was performed because of symptoms evocative of gastroparesis (nausea, vomiting, gastric fullness, early satiety). Obstructive causes were ruled out in all patients by at least one normal upper gastrointestinal endoscopy. In 184 patients, a second GE test was performed (at least 3 months after the first test) during the follow-up. Medical information was collected by reviewing inpatients' medical records and included age, sex, body mass index (BMI), presence of diabetes mellitus, opioid intake. The accuracy of collected information was ensured in a random sample of 92 patients by undertaking a parallel analysis using our centre's Health Data Warehouse that monitors medical conditions by mixing inpatients' and outpatients' records, diagnostic coding and treatment intake.

Systematic questionnaires, including symptom scores and quality of life questionnaires were prospectively monitored in patients tested from 2013 to 2019 ($n = 375$, [Figure 1](#)). Questionnaires were given at the time of GE measurement. Symptomatic Likert scales were used to quantify gastroparesis symptoms, including nausea, vomiting, gastric fullness, early satiety, abdominal pain, and regurgitation. Each symptom was rated from 0 (absent) to 4 (extremely severe). Quality of life was evaluated by Gastrointestinal Quality of Life Index (GIQLI). The GIQLI score is a mixed symptomatic and quality of life score that varies from 0 (worst quality of life possible) to 144 (best quality of life). The GQLI score was validated in French and is specific for digestive diseases.¹¹ Some results from these questionnaires (from 2013 to 2016) have been published elsewhere.¹²

2.2 | GE test

Patients were investigated off prokinetic, anticholinergic and opioid agents. GE measurement was performed in all patients after 12-hour overnight fasting, by 13C-octanoic acid breath test as previously published.¹²⁻¹⁴ All patients ingested a 250 kcal test meal between 8:00 AM and 9:00 AM (19% protein, 43% carbohydrate, and 38% fat) consisting of white bread (50 g), butter (17 g), and an egg doped with 91 mg 13C-octanoic acid (Euriso-Top, Saint Aubin, France). Breath samples were collected before the meal and every 15 minutes after the meal for at least 4 hours. The presence of $^{13}\text{CO}_2$ in samples was detected by isotope-selective non-dispersive infrared spectrometry (IRIS; Wagner/Analysen Technik, Bremen, Germany). The half-time rate ($T_{1/2}$) of solid GE was calculated by linear regression analysis using IRIS software GE2. DEM. $T_{1/2}$ was considered as delayed when >200 minutes. This threshold was selected as we previously showed that GE correlated with symptoms only if $T_{1/2}$ was >200 minutes.¹² Additional analyses were also carried out using a 166-minute threshold as reported elsewhere¹⁵ ([Figure S1](#)).

FIGURE 1 Flowchart of the study population



2.3 | Determination of date and cause of death

The date and place of death were systematically determined for all patients using the CepiDc (Centre d'épidémiologie sur les causes médicales de décès, <https://www.cepidec.inserm.fr/>) database. The CepiDc database is derived from the French institute of statistics and economic studies (INSEE, <https://www.insee.fr>) which computes open access data from local civil registries, including the date and place of births, marriages and deaths. The cause of death was determined by reviewing the medical records of the primary, secondary, or tertiary care centre to which the patient was referred. The cause of death was classified as cancer, cardiovascular (including

coronary artery disease and ischemic stroke), pneumopathy (including inhalation pneumopathy), worsening of the underlying condition (including diabetes and systemic sclerosis), and denutrition. Other unspecific causes included, among others, suicide, car accident, sepsis, neurodegenerative disease, etc.

2.4 | Statistics

Patients were categorised in one of two groups: a gastroparetic group, defined as having a delay in gastric $T_{1/2}$, or a control group, defined as having a normal GE time. Univariate group comparison

was carried out using T-test or chi-squared test for quantitative or qualitative data, respectively. Overall survival between the two groups was calculated using the Kaplan-Meier method according to the product-limit life table method followed by a log Rank test for each group. Death occurrence hazard ratio (HR) was calculated using the Cox proportional hazards regression model. Sub-group analyses were done according to diabetic and sex status. Data are expressed as mean with 95% confidence intervals [95%CI] unless otherwise specified.

3 | RESULTS

3.1 | Study population

Among the 1563 patients retained for final analysis, 384 had a delay in GE of >200 minutes and were therefore assigned to the gastroparetic group. The 1179 patients with normal GE ($T_{1/2} \leq 200$ minutes) were assigned to the control group. Patients were mostly women (66.0%) with a mean age of 48.9 years at the time of GE measurement. As illustrated in Table 1, male sex and diabetes mellitus were more prevalent in the gastroparesis group. By contrast, age, opioid intake or symptom severity were not different between the gastroparetic group and the control group (Table 1). Mean follow-up was 103 months per patient (92 months for the gastroparetic group and 106 months for the control group), totalling 13 466 patients per year.

	T1/2 ≤ 200	T1/2 > 200	Total	P
Demographic characteristics (n)	1179	384		
Sex (women %)	67.4	61.7	66.0	0.04
Age (mean years old [SD])	48.8 [15.6]	49.1 [15.5]	48.9 [15.6]	0.85
Diabetes (%)	4.9	13.5	7.0	<0.0001
Type 1 diabetes (%)	3.0	8.9	4.5	<0.0001
Type 2 diabetes (%)	1.9	4.6	2.5	<0.01
Insulin treatment (%)	4.1	9.9	5.5	<0.0001
BMI (kg/m ² ; mean [SD])	24.7 [5.9]	25.8 [5.9]	25.0 [5.9]	<0.01
Mean follow-up (years[SD])	9.0 [5.5]	7.8 [5.2]	8.7 [5.4]	<0.001
Clinical characteristics (n)	260	113	373	
Abdominal pain (mean [SD])	1.8 [1.2]	1.9 [1.3]	1.8 [1.2]	0.75
Gastric fullness (mean [SD])	1.7 [1.2]	1.4 [1.3]	1.6 [1.3]	0.07
Vomiting (mean [SD])	1.8 [1.2]	2.0 [1.3]	1.8 [1.3]	0.26
Early satiety (mean [SD])	2.2 [1.2]	1.9 [1.1]	2.1 [1.2]	0.08
Regurgitation (mean [SD])	2.2 [1.3]	2.3 [1.2]	2.2 [1.3]	0.36
Nausea (mean [SD])	2.3 [1.3]	2.1 [1.4]	2.2 [1.3]	0.26
Heartburn (mean [SD])	2.2 [1.2]	2.4 [1.3]	2.3 [1.2]	0.15
GIQLI (mean [SD])	78.7 [23.6]	78.8 [24.0]	78.7 [23.7]	0.90
Opioids (%)	4.0	4.4	4.1	0.70

Abbreviations: BMI, body mass index; GIQLI, gastrointestinal quality of life index; SD, standard deviation; T1/2, gastric emptying half time.

3.2 | Overall survival

At the end of follow-up in December 2019, 137 patients had died, 46 in the gastroparesis group and 91 in the control group. Death occurred in a mean delay of 85 months [95% CI: 8-186 months] after GE measurement. Figure 2 shows the Kaplan-Meier survival probability from the time of GE measurement. The gastroparetic group had a higher incidence of death (15.5 per 1000 person-year) compared to the control group (8.7 per 1000 person-year) with a HR of death occurrence of 1.87 95% CI (1.25-2.81). The 5 and 10 year estimated mortality was 6.1% (95% CI, 3.4%-8.7%) and 15.5% (95% CI, 10.6%-20.3%) in gastroparetic group while it was estimated at 3.1% (95% CI, 2.1%-4.2%) and 8.0% (95% CI, 6.0%-9.9%) in the control group, respectively. In the 284 patients with two GE tests, no difference was noted according to the normalisation or the delay observed in the second test (Table 2).

3.3 | Sub-group analysis

Sub-group analyses carried out in diabetic vs non-diabetic patients or according to sex status showed similar results. Kaplan-Meier analysis found an increased mortality in women (HR = 1.78 [1.03-3.08]; $P = 0.02$) and men (HR = 2.31 [1.09-3.67]; $P = 0.007$) from the gastroparetic group as compared with the control group (Figure 3A,B). Decreased survival probability was also observed non diabetic

TABLE 1 Baseline demographic (n = 1563) and clinical (n = 373) characteristics of the study population

FIGURE 2 Kaplan–Meier survival probability over time in the gastroparetic group ($T_{1/2} > 200$ min) and the control group ($T_{1/2} < 200$ min) from gastric emptying measurement

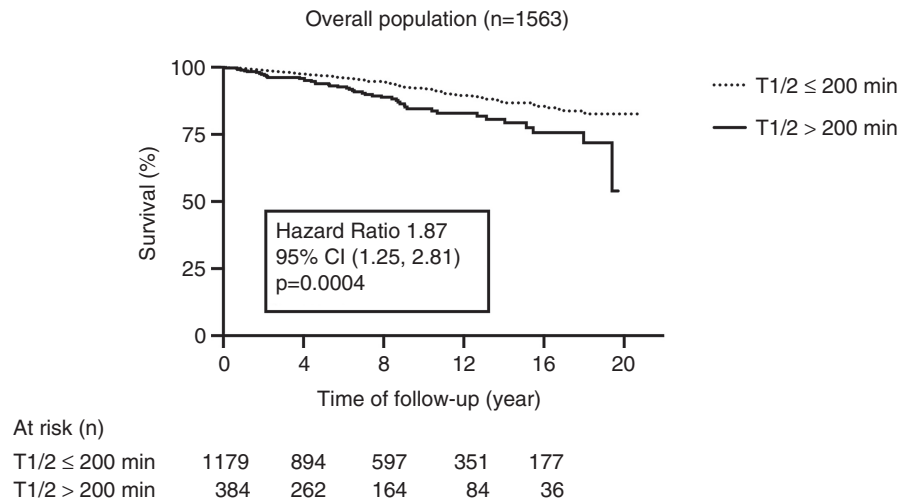


TABLE 2 Mortality rate according to the second gastric emptying test performed during the follow-up

	n	5 years	10 years
Delayed-normalised	46	2.2%	2.2%
Delayed-delayed	35	4.5%	9.1%
Normal-normal	85	1.3%	1.6%
Normal-delayed	13	6.7%	6.7%
P value		0.60	0.40

patients with delayed GE as compared with the non-diabetic control group (HR = 1.88 [1.22-2.9]; [Figure 3C](#)). In diabetic patients, a trend towards increased mortality was observed in gastroparetic patients (HR = 3.09 [0.93-10.17]) compared with the diabetic control group, although this did not reach statistical significance ($P = 0.06$; [Figure 3D](#)). Survival probability was not different between gastroparetic patients taking or not opioids (HR = 0.59 [0.10-3.56]; $P = 0.57$) and between patients treated by opioids with delayed or normal GE (HR = 0.37 [0.09-1.54]; $P = 0.17$).

3.4 | Multivariate analysis

The Cox proportional hazards regression model identified older age, male sex and presence of diabetes mellitus as associated with decreased survival, but not BMI ([Table 3](#)). In this model, delayed GE, based on $T_{1/2} > 200$ minutes, was independently associated with increased mortality (HR = 1.63 [1.09-2.42]; $P = 0.02$). Similar analyses were carried out by modifying the GE delay threshold at 166 minutes and identified similar results (HR = 1.44 [1.03-2.02]; $P = 0.04$; [Figure S1](#)).

3.5 | Cause of death

The cause of death was identified in 107 (79.5%) patients. The leading cause of death was cancer in the gastroparetic group (38.2%),

compared to 23.3% in the control group ($P = 0.17$; [Figure 4](#)). Cardiovascular disease, including coronary heart disease and vascular stroke lead to death in 24.7% and 17.6% of the gastroparetic and control groups, respectively ($P = 0.42$).

4 | DISCUSSION

Traditionally, brain–gut interaction and motility disorders have never been shown to be associated with decreased overall survival and therefore have been considered as benign. Our study provides evidence, based on motility tests, that impaired gastrointestinal motility is associated with increased mortality. Indeed, we have shown that patients with accurately diagnosed gastroparesis had a decreased life expectancy independently of classic co-morbidities including age, sex or diabetes status. In most cases, gastroparesis management involves dietary therapy and pharmacologic treatments.¹⁰ In the most severe patients, aggressive management strategies, including pyloric botulinum toxin injection, pyloromyotomy or gastric electrical stimulation, have been suggested.^{10,16-18} Whether these therapeutic strategies are associated with a normalisation of mortality rate in gastroparetic patients remains to be investigated.

Several studies have attempted to depict the outcome of gastroparetic patients, either based on a cohort of patients with proven gastroparesis, or by studying a population-based registry. For example, two uncontrolled cohort studies, including respectively 83 and 146 patients with GE test-proven gastroparesis, observed that 25% and 7% of patients died after 10 and 6 years of follow-up.^{5,19} On the other hand, two other population-based studies estimated gastroparesis-related mortality. Both of these studies had the advantage of including a much larger number of subjects, but gastroparesis status was not systematically diagnosed using GE test and the control population, when present, was not matched on medical history or disease severity. In the first study performed in Olmsted County,³ Minnesota, USA, patients were followed up for a median of 5 years and gastroparesis-associated mortality was compared to estimated expected mortality rates adjusted for age and

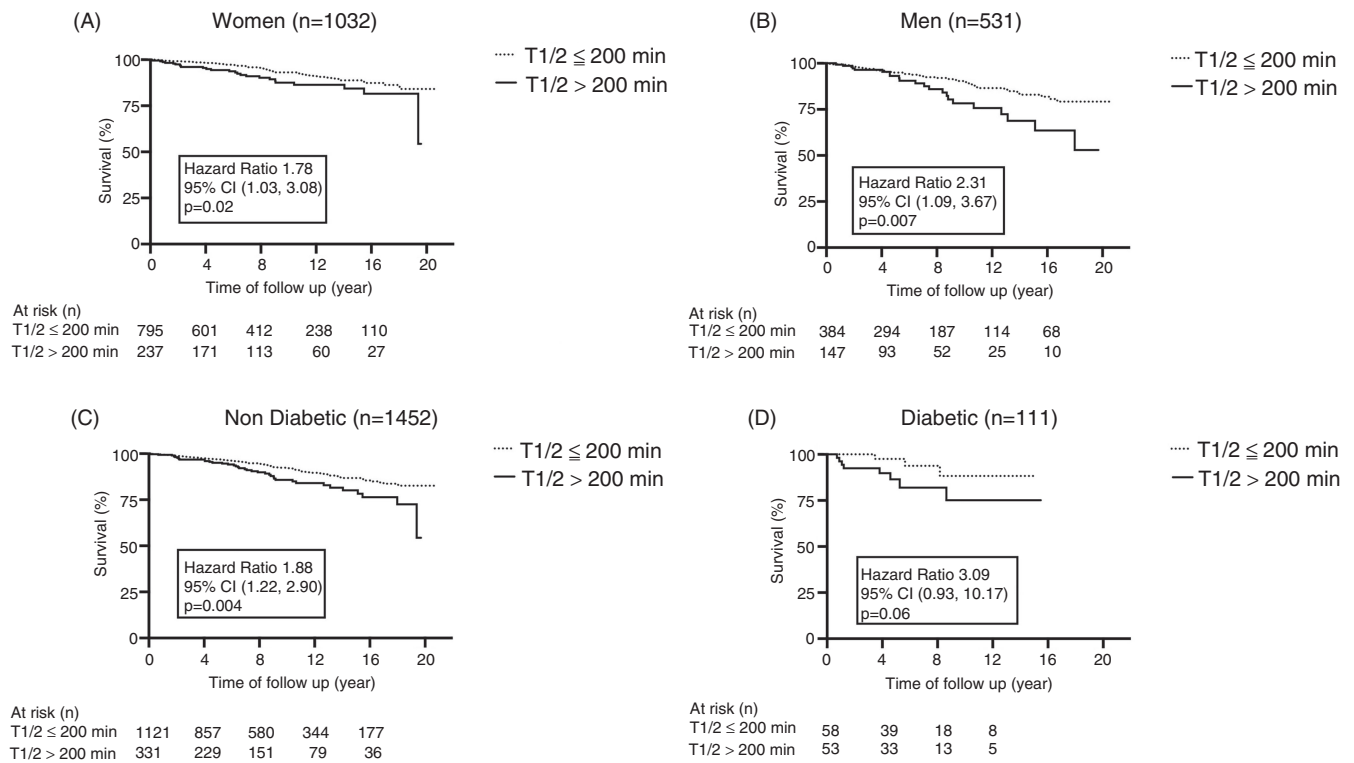


FIGURE 3 Kaplan-Meier survival probability over time according to sex (A, B) or diabetes (C, D) status in the gastroparetic group (T1/2 > 200 min) and the control group (T1/2 < 200 min) from gastric emptying measurement

TABLE 3 Association with mortality according to the cox proportional hazards regression model (n = 1332)

Variable	HR	95% CI	P
Age	1.06	1.05-1.08	<0.0001
Men	1.84	1.26-2.69	0.002
T1/2 > 200	1.63	1.09-2.42	0.02
Diabetes	1.96	1.04-3.71	0.002
BMI	0.97	0.93-1.01	0.14

Abbreviations: BMI, body mass index; CI, confidence interval; HR, hazard ratio; T1/2, gastric emptying half time.

sex, but not for symptom and/or disease severity nor diabetic status. Gastroparesis was found to be associated with a decreased life expectancy compared to the general population, with an estimated mortality rate of 33% at 5 years. The study was unfortunately not powered to assess whether underlying conditions, including diabetes, were predictable of worse outcome or not. Unfortunately, gastroparesis was defined in the study either based on medical records (n = 83) or suspected from food retention and symptom patterns evocative of gastroparesis (n = 127). The latter definition may be arguable since neither symptom pattern nor food retention at endoscopy has been proven to correlate with GE measurement, which may have led to an overestimation of gastroparesis diagnosis. A second population-based study included 873 gastroparetic patients identified using diagnostic codes from the Clinical Practice Research Datalink database in the U.K. and followed up for 4.7 years.⁴

Although gastroparesis-associated mortality was not compared to general population nor controlled for age, sex and disease severity-matched patient cohorts, this study identified diabetic gastroparesis as associated with increased mortality at 5 years (19.2%) as compared with idiopathic gastroparesis (8.7%). As expected, mortality in the diabetic group was mostly driven by the involvement of diabetes mellitus, including cardiovascular diseases. In this study, gastroparesis diagnosis was based on diagnostic codes, which again may not have an optimal specificity. For example, "gastric dysmotility" ("J16y800" code), may encompass delayed GE, impaired gastric relaxation, and gastric resection surgery-induced dysmotility. With regards to the literature, our study appears therefore as the most powered using a large cohort of 1564 patients, with the longest follow-up (mean follow-up = 8.6 years). In addition, gastroparesis in our cohort was systematically diagnosed using GE test. Last, we used a control population adjusted either on age, sex, disease severity or diabetic status. Using our patients' cohort, we were able to show that delayed GE was associated with increased mortality independently of the classic co-morbidities listed above. Indeed, patients' symptom severity and quality of life measured prospectively from 2013 to 2019 in 373 patients were not different among patients with or without delayed GE (except for bloating). In these patients investigated prospectively, we previously reported that the rate of classic co-morbidities, including constipation, gastro-oesophageal reflux symptoms, irritable bowel syndrome, sleep disorders, anxiety, depression, post-infectious origin, as well as surgical diagnostics were similar in patient with delayed and normal GE.¹² In addition, change

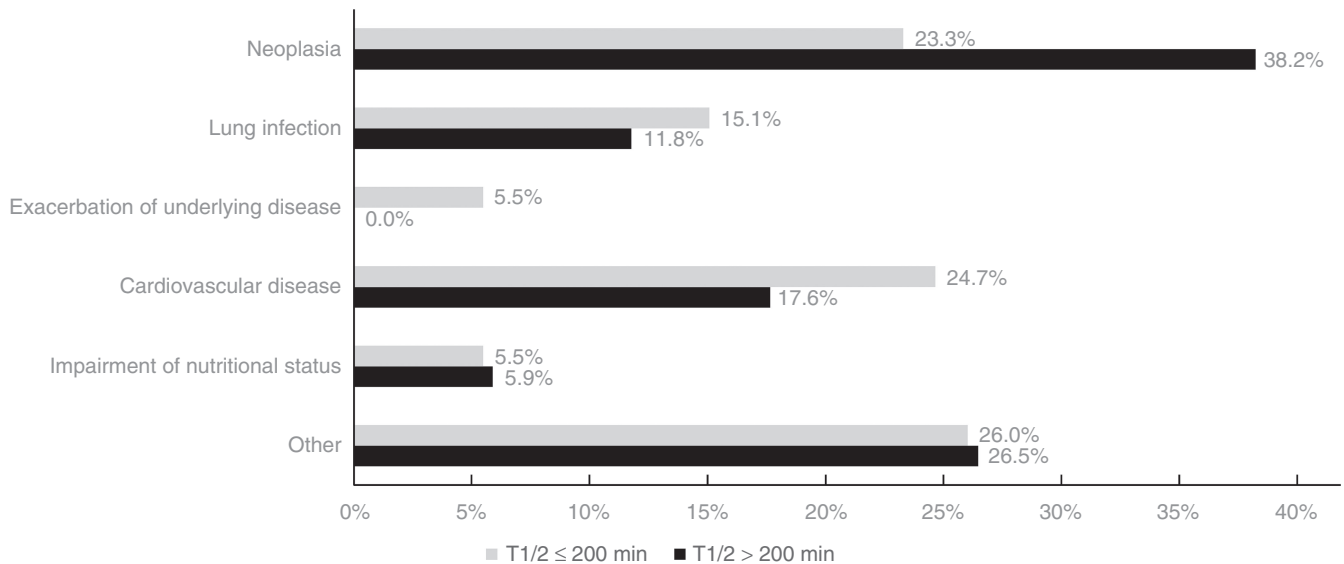


FIGURE 4 Causes of death in the gastroparetic group ($T_{1/2} > 200$ min) and the control group ($T_{1/2} < 200$ min)

in the threshold (200 vs 166 min) defining delayed or normal GE resulted in similar findings. Therefore, symptoms, or gastroparesis severity may have had very limited impact on the difference in mortality observed among the two groups since the symptomatic profiles as well as associated diagnostics were similar among the two groups. Moreover, gastroparetic and control groups were similar in terms of age, while the prevalence of male sex, although statistically significant, was only 5% superior in the gastroparetic group. As expected, and comparably to previous studies^{3,4} a higher frequency of diabetes as well as increased BMI were observed in the gastroparetic group, both parameters being related when considering type 2 diabetes. Last, opioid intake was not different among the two groups and was similar to previous report in patient with disorders of brain-gut interaction in France.²⁰ Noteworthy, the opioid intake in our cohort was lower compared to US gastroparesis cohorts with nearly 40% of patient taking opioids in a regular base.²¹ However, overall opioid use is considered to be at least four times lower in Europe than in United States or Canada.^{22,23} In addition, while opioid consumption increased dramatically in US over the past two decades, it remained stable and even decreased for step II in France during the same period.²³ We have previously reported that opioid consumption in a large cohort of nearly 3000 patients with gastrointestinal motility disorders was higher compared to the general population, but remained below 5% of patients.²⁰ Therefore, the low rate of 4% of opioid consumption in our cohort is in fact not unexpected and reflects some extent the lower burden of opioid crisis in France as compared to what may be observed in other countries, especially the US. Therefore, our study may have been not powered enough to evidence opioids influence on mortality considering the low rate of opioid consumption in our cohort. Therefore, it is unlikely that baseline characteristics have contributed to the difference observed between gastroparetic patients and control group. This suggests therefore that part of the mortality rate observed in the gastroparetic population may be directly driven by impaired GE. Interestingly,

delay or normalisation of a second GE test did not impact significantly survival in our study. Of note, this part of the study involved only 184 patients and is clearly unpowered to state firmly whether the acceleration of GE in gastroparetic patients is associated with normalisation of mortality rate.

Interestingly, no difference was observed in the cause of death in our study between the gastroparetic group and the control group. In both groups, deaths were mostly related to cardiovascular disease or cancer. Regarding causes directly related to gastroparesis, including denutrition or inhalation, similar rates were found in both groups. Increased mortality in the gastroparetic group may have been accentuated by a worsening of the underlying disease or the nutritional status. This may have included impairment of blood glucose control in diabetic patients, which was not recorded as the direct cause of death but may have contributed to the development of diabetes complication. Importantly, no fatal adverse events related to gastroparesis treatment (domperidone and/or erythromycin induced cardiac arrhythmia, gastric stimulator infection, or pyloromyotomy-related perforation, etc.) were identified among the medical records of deceased patients.

The main limit of the present study is the retrospective nature of data acquisition. This may ultimately lead to selection, recruitment, collection and recall bias. However, parts of the data, including symptoms, were monitored prospectively. In addition, this cohort included consecutive patients undergoing GE in our centre. Missing data were prevented by cross-checking the list of GE tests and medical conditions, including history and treatments, using at least two different databases. Furthermore, selection or recruitment biases that are usually encountered in tertiary centres are very unlikely in our study, since, to our knowledge, our centre is the only one to perform GE studies in the Normandy region of France. Moreover, loss of follow-up was improbable in our study since both local and ultimately national civil registry were used to assess whether patients were alive or not. However, the cause

of death was not identified in nearly 20% of our study population, mostly due to the loss of medical records (GP retirement), the absence of medical cause in patients' medical records or to the loss of follow-up. Last, recall bias in our study may be considered as marginal since all data regarding the primary endpoint (GE and deaths) are, by definition, objective measures. Another main limit is that our study was not carried out in the general population, by contrast with previous studies. However, systematic GE tests are difficult to run at the general population level. In addition, a cohort representative of the general population is expected to display increased life expectancy due mostly to younger age, the absence of symptoms evocative of gastroparesis, or the absence of diabetes. Therefore, our study can be viewed as complementary to previous general population studies suggesting that gastroparesis is associated with increased mortality. A last limit of our study was the low prevalence of diabetic patients in the gastroparetic group. This low prevalence may reflect both our local recruitment and the lower prevalence of diabetes (mostly type 2) 20 years ago in France when recruitment started, as compared with the US or the UK population. Nonetheless, this study was powered enough to demonstrate that diabetes was associated with delayed GE as expected, and ultimately to evidence that gastroparesis was associated with shorter life expectancy among diabetic patients.

In conclusion, this study has shown for the first time that gastroparesis, diagnosed on motility tests, was associated with increased mortality, independently of confounding factors including symptom severity, age, sex or diabetes status. Therefore, gastroparesis should be considered as a morbid and lethal condition. Further studies are warranted to assess whether acceleration of GE using pharmacologic or endoscopic approaches is associated with a normalisation of mortality rate in gastroparetic patients.

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AUTHORSHIP

Guarantor of the article: Guillaume Gourcerol.

Author contributions: GG initiated the study, obtained the funding, obtained ethical agreements, analysed data and drafted the manuscript. MPT was responsible for the methodology, helped to build the data base, run statistical analysis, analysed data, helped to finalise the manuscript, and helped to obtain ethical agreements. CM helped to analyse and to interpret data, helped to finalise the manuscript, and helped to obtain ethical agreements. CD, FW, GP, helped to analyse and to interpret data and helped to finalise the manuscript. JG helped to build the database. AML helped to build the database, helped to analyse and to interpret data, helped to

finalise the manuscript, and helped to obtain ethical agreements. Database and final analysis were made available for each co-author who all reviewed and validated the current manuscript.

DATA AVAILABILITY STATEMENT

access to data is restricted due to privacy regulation but can be made available upon reasonable request

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SUPPORTING INFORMATION

Additional supporting information will be found online in the Supporting Information section.

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