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ORIGINAL ARTICLE

Hypergastrinemia and mortality in gastric adenocarcinoma: a population-based cohort study, the HUNT study

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ABSTRACT

Purpose: Hypergastrinemia increases the risk of developing proximal gastric adenocarcinoma. However, it is unclear if hypergastrinemia affects the survival in patients with gastric adenocarcinoma. This study aimed to examine the hypothesis that hypergastrinemia is associated with increased risk of mortality in patients with gastric adenocarcinoma.

Materials and methods: This prospective population-based cohort study based on the Trøndelag Health Study (HUNT) included 78,962 adult individuals (≥20 years). During the baseline assessment period (1995–2008) of these participants, serum samples were collected and frozen. All participants with a newly diagnosed gastric adenocarcinoma in the cohort in 1995–2015 were identified and their gastrin levels were measured in the pre-diagnostic serum samples. Gastrin levels were analysed in relation to all-cause mortality until year 2020 using multivariable Cox regression providing hazard ratios (HRs) with 95% confidence intervals (CIs), adjusted for sex, age, body mass index (BMI), tobacco smoking, tumour stage, completeness of surgical resection, and peri-operative chemotherapy.

Results: Among 172 patients with gastric adenocarcinoma, 81 (47%) had hypergastrinemia (serum gastrin >60 pmol/L) and 91 (53%) had normal gastrin level. The tumour location was proximal in 83 patients (43%) and distal in 78 (41%). Hypergastrinemia was not associated with any increased risk of all-cause mortality in all patients (adjusted HR 0.8, 95% CI 0.5–1.1), or in sub-groups of patients with proximal tumour location (HR 0.9, 95% CI 0.4–2.2) or distal tumour location (HR 0.9, 95% CI 0.5–1.7).

Conclusion: This population-based cohort study indicates that hypergastrinemia may not increase the risk of mortality in patients with gastric adenocarcinoma.

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Adenocarcinoma; cohort; gastrin; mortality; population-based; stomach

Introduction

Gastric cancer is the 5th most common cancer worldwide [1]. In Western populations, most gastric cancers are diagnosed at advanced stages and the mortality is high, ranking third in cancer related mortality only after lung and liver cancer. The Laurén's diffuse histological type of adenocarcinoma responds less to chemotherapy regimens and has shorter survival compared to the intestinal type [2,3]. Other factors associated with gastric cancer related survival include age, tumour sub-location, tumour stage, and radicality of the surgical resection [4,5]. Pangastritis associated with *Helicobacter pylori* (*Hp*) is a main risk factor of gastric cancer [6], and the incidence of gastric cancer has decreased paralleling the reduced prevalence of *Hp* infection. However, in recent years, the incidence of gastric adenocarcinoma in the proximal stomach has increased in younger cohorts (<50 years of age) in the United States and the United Kingdom [7–9]. Suggested causes of this increase include the increased use of long-term proton pump inhibitor (PPI) treatment and increased prevalence of autoimmune chronic atrophic gastritis [10–13]. This increased gastric cancer risk could be mediated by hypergastrinemia [14]. Gastrin is a hormone which stimulates gastric acid secretion and oxyntic mucosal growth in the proximal stomach (corpus), but not in the distal stomach (antrum) [15]. Loss of negative feedback on gastrin release by reduced gastric acid secretion, regardless of cause, leads to hypergastrinemia [16,17]. Hypergastrinemia can increase the risk of neoplasia of the gastric corpus in animal models [14,18–24] and of proximal gastric adenocarcinoma in humans [25]. Hypergastrinemia has also been associated with decreased survival in patients with gastric

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adenocarcinoma [26], but the available evidence is limited and not conclusive.

The aim of this study was to assess the hypothesis that hypergastrinemia is associated with increased mortality in patients with gastric adenocarcinoma.

Methods

Design

This was a prospective population-based cohort study based on the Trøndelag Health Study (HUNT) during the study period 1995–2020. In HUNT, adult residents (≥20 years) in Nord-Trøndelag County, Norway, were invited to participate in repeated health surveys. In the present study, the second (HUNT2) and third (HUNT3) surveys were used as baseline. HUNT2 was performed between 15 August 1995 and 18 June 1997 and included 65,237 individuals (response rate 69.5%), and HUNT3 was performed between 3 October 2006 and 25 June 2008 and included 50,807 individuals (54.1%) [27]. The surveys included questionnaires on various health related factors, standardized clinical examinations, and blood samples collected and stored at −80 °C.

Using the unique 11-digit personal identification number assigned to every Norwegian, HUNT data were linked to the Cancer Registry of Norway, the Norwegian Patient Registry and to patient records at the treating hospitals of the population (Nord-Trøndelag Hospital Trust and St. Olav's Hospital, Trondheim University Hospital). The Cancer Registry has since 1951 collected data on all cancers in Norwegian citizens. The Patient Registry has since 2008 collected data on all diagnoses and procedures from specialized health care in Norway.

Participants in HUNT2 or HUNT3 with a newly diagnosed gastric adenocarcinoma during follow-up until 31 December 2015 were identified from the registries based on the third version of the International Classification of Diseases for Oncology (ICD-O-3: C16). Participants with any previous or prevalent gastric cancer were excluded. Clinical data were retrieved from medical records at the treating hospitals, and included tumour sub-location, tumour stage, completeness of surgical resection, peri-operative chemotherapy, and date of death until 1 October 2020. The individual medical records were reviewed by two upper gastrointestinal surgeons (E. A. B. and J. E. G.) and one gastroenterologist (E. N. J.). The tumour sub-location was categorized into three groups: proximal (corpus, fundus or Siewert's cardia type III [28]), distal (antrum), and indefinite or unknown. Siewert's cardia type I and type II [28] and gastric stump cancers were excluded. The histological type (adenocarcinoma) and a uniform histological classification according to Laurén (diffuse, intestinal, mixed or indeterminate) [29] was determined by a pathologist (P. M.). Other histological types of gastric tumours than adenocarcinomas were excluded. The reviewers were blinded to the serum gastrin values.

Exposure

Serum gastrin levels for patients that later developed gastric adenocarcinoma were analysed on stored pre-diagnostic serum samples collected during the HUNT surveys. In patients who participated in both HUNT2 and HUNT3, the gastrin level in the most recent serum sample was used.

The gastrin analyses were performed using a radioimmunoassay kit (Euria Gastrin MD302, Euro Diagnostica, Malmö, Sweden) that measures not only G-17, but also cross-reacts with G-34, sulphated G-17 and CCK-8, according to the manufacturer's instructions. This kit is reported to have superior diagnostic accuracy among the available kit's and with hypergastrinemia defined as values >60 pmol/L [30]. The gastrin analyses were run as two parallel analyses from each sample and the mean value was used.

The exposed patients had hypergastrinemia (serum gastrin >60 pmol/L) and these were compared with non-exposed patients with normal gastrin level (serum gastrin ≤60 pmol/L).

Outcome

The outcome was all-cause mortality among patients with gastric adenocarcinoma. All-cause mortality was further analysed in sub-groups of patients stratified by tumour sub-location (proximal and distal) and by Laurén's histological type (diffuse and intestinal).

Confounders

Sex, age, body mass index (BMI), tobacco smoking, tumour stage, completeness of surgical resection, and peri-operative chemotherapy were included as confounding factors possibly affecting the mortality of the patients.

Age was assessed at date of diagnosis. BMI (in kg/m^2) was assessed based on objective measures of weight and height performed by trained personnel during the HUNT studies. Tobacco smoking status was assessed based on self-reported questionnaires. Tumour stage was assessed using the 7th edition of the Union for International Cancer Control (UICC) manual for staging of cancer [31], based on radiology and histology, if available. Completeness of surgical resection was assessed using the residual tumour (R) classification as defined by the UICC, where R0 corresponds to complete microscopic resection, R1 to microscopic residual tumour, and R2 to macroscopic residual tumour [31]. Peri-operative chemotherapy was introduced as national standard in 2007 for patients with resectable gastric cancer and age below 75 years.

Statistical analyses

The all-cause mortality rates from date of gastric adenocarcinoma diagnosis until date of death or end of the study period for patients with hypergastrinemia and those with normal gastrin level were compared using Chi-square tests, Kaplan–Meier curves and Cox regression analysis. The Kaplan–Meier curves were compared using the log-rank test. The multivariable Cox regression provided unadjusted and adjusted hazard ratios (HRs) with 95% confidence intervals (CIs). The first multivariable model was adjusted for sex

(woman or man) and age (continuous). Because tumour stage, resection and chemotherapy could be mediators of the association between hypergastrinemia and mortality, a second multivariable model excluded these variables, while the third multivariable model was adjusted for all confounders: sex (woman or man), age (continuous), BMI (continuous), tobacco smoking (never, previous or current), tumour stage (I, II, III or IV), completeness of surgical resection (R0/R1, R2 or no resection), and peri-operative chemotherapy (yes or no). The proportionality assumption was assessed by the log–log plot of survival and was fulfilled for all models. The data management and statistical analyses were conducted using Stata/MP version 17.0 (StataCorp LLC, College Station, TX).

Results

Patients

Among the 191 patients who developed gastric adenocarcinoma during follow-up, gastrin could be measured in pre-diagnostic samples in 172 (90%) who were thus included in the present study. Characteristics of these 172 patients are presented in Table 1. Nearly half of the patients had hypergastrinemia ($n = 81$, 47%). The proportion of deaths was lower in the hypergastrinemia group ($n = 74$, 81%) than in the group with normal gastrin level ($n = 85$, 93%). The mean age was higher among the patients with hypergastrinemia (79 years) than the patients with normal gastrin level (75 years). There was no difference in mean BMI or current tobacco smokers between the comparison groups, but more patients with hypergastrinemia were never smokers ($n = 29$, 36%) than patients with normal gastrin level ($n = 24$, 26%). The tumour stage was somewhat more favourable among the patients with hypergastrinemia. The proportion of R0/R1 resection was comparable between the patients with hypergastrinemia and normal gastrin level, but a higher proportion of patients with hypergastrinemia was not resected ($n = 40$, 49%), compared to patients with normal gastrin level ($n = 36$, 40%). Few patients received peri-operative chemotherapy, and fewer patients with hypergastrinemia ($n = 2$, 3%), compared to patients with normal gastrin level ($n = 10$, 11%).

Table 1. Characteristics of the gastric adenocarcinoma patients ($n = 172$) with hypergastrinemia and normal gastrin level.

	Hypergastrinemia Number (%)	Normal gastrin levels Number (%)
Patients	81 (47)	91 (53)
Deaths	74 (81)	85 (93)
Time from baseline to diagnosis, years		
Mean, SD	6.4 (4.3)	6.5 (4.3)
Median, IQR	5.5 (2.7–8.9)	5.5 (3.0–8.3)
Time from diagnosis to death		
Person-years	192	179
Tumour location		
Proximal[a]	40 (49)	32 (35)
Distal[b]	31 (38)	42 (46)
Indefinite	9 (11)	17 (19)
Unknown	1 (1)	0 (0)
Histological tumour type		
Diffuse	20 (25)	40 (44)
Intestinal	43 (53)	30 (33)
Mixed	8 (10)	5 (5)
Indeterminate	6 (7)	13 (14)
Unknown	4 (5)	3 (3)
Sex		
Women	37 (46)	42 (46)
Men	44 (54)	49 (54)
Age at diagnosis, years		
Mean, SD	79 (10)	75 (11)
Median, IQR	81 (76–86)	77 (69–84)
Body mass index, kg/m^2		
Mean, SD	27 (4)	27 (4)
Median, IQR	27 (25–30)	26 (24–30)
Missing	0 (0)	1 (1)
Tobacco smoking		
Never	29 (36)	24 (26)
Previous	32 (40)	46 (51)
Current	18 (22)	19 (21)
Missing	2 (2)	2 (2)
Tumour stage		
I	9 (11)	9 (10)
II	5 (6)	7 (8)
III	12 (15)	16 (18)
IV	34 (42)	42 (46)
Missing	21 (26)	17 (19)
Completeness of surgical resection		
R0/R1	26 (32)	31 (34)
R2	15 (19)	24 (26)
No resection	40 (49)	36 (40)
Peri-operative chemotherapy		
Yes	2 (2)	10 (11)
No	79 (98)	81 (89)

IQR: interquartile range; SD: standard deviation.
[a]Proximal: corpus, fundus, cardia type III.
[b]Distal: antrum.

Crude all-cause mortality rates

The crude mortality rate for gastric adenocarcinoma patients with hypergastrinemia was not statistically different than for patients with normal gastrin level (Table 2). The Kaplan–Meier survival curves for gastric adenocarcinoma patients with hypergastrinemia and normal gastrin levels are shown in Figure 1.

The mortality rate for patients with proximal adenocarcinomas was also not statistically different than for patients with distal adenocarcinomas, irrespective of gastrin level (Table 2). The Kaplan–Meier survival curve comparing gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level by tumour location are presented in Figure 2.

For patients with the diffuse histological tumour type, the mortality rate seemed to be lower for patients with hypergastrinemia than for patients with normal gastrin level, and for patients with the intestinal type histology, the mortality rate seemed to be higher for patients with hypergastrinemia than patients with normal gastrin level, but this was also not statistically significant (Table 2). The Kaplan–Meier survival curve for gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level by histological type are presented in Figure 3 and showed no significant difference.

Risk of all-cause mortality

Compared to normal gastrin levels, hypergastrinemia was not associated with any increased risk of all-cause mortality

Table 2. All-cause mortality among gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level.

	Hypergastrinemia ($n = 81$)		Normal gastrin level ($n = 91$)			
	Deaths (n)	Mortality rate/year	Deaths (n)	Mortality rate/year	Rate ratio	p-value[c]
Overall	74	0.39	85	0.47	0.81	*.920*
By tumour location						
Proximal[a]	35	0.32	28	0.37	0.87	*.356*
Distal[b]	29	0.38	40	0.44	0.87	*.383*
By histological tumour type						
Diffuse	18	0.32	38	0.56	0.57	*.061*
Intestinal	39	0.36	26	0.31	1.18	*.093*

[a]Proximal: corpus, fundus, cardia type III.
[b]Distal: antrum.
[c]Chi-square test.

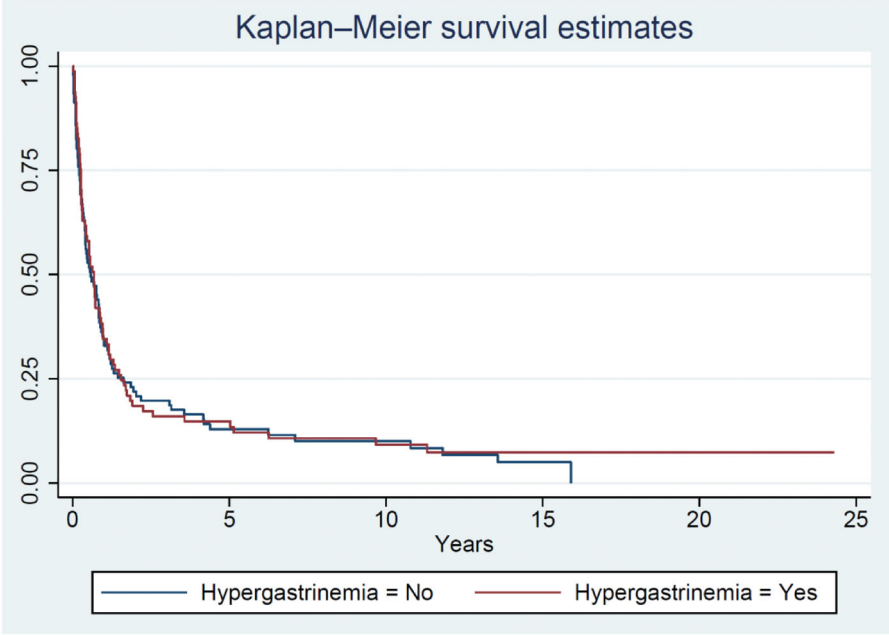

Figure 1. Kaplan–Meier curve for gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level (log-rank test $p = .7248$).

in gastric adenocarcinoma after adjustment for all confounders (HR 0.77, 95% CI 0.52–1.14) (Table 3). Similarly, the subgroup analyses revealed no statistically significant increased risk among patients with proximal tumour location (HR 0.93, 95% CI 0.40–2.15), distal tumour location (HR 0.89, 95% CI 0.46–1.74), diffuse histological type (HR 1.53, 95% CI 0.52–4.53), or intestinal histological type (HR 0.67, 95% CI 0.33–1.36). None of the HRs were statistically significant in the unadjusted model or in the adjusted model with removal of the possible mediators (tumour stage, surgical resection and chemotherapy).

Discussion

This population-based cohort study showed no association between hypergastrinemia and all-cause mortality in patients with gastric adenocarcinoma, independent of tumour sublocation or Laurén's histological type.

Strengths of the present study include the population-based design, which avoids selection-bias compared to hospital-based studies. The study population is stable with neglectable migration and all relevant investigations and treatments are performed at the included hospitals, which argues for a complete follow-up and registration of patients. The prospective design with pre-diagnostic sampling of blood years before cancer diagnosis, argues for validity. The well-validated Norwegian health registries and thorough and systematic review of medical records and histological assessment by experts in the field reduce information bias. The systematic registration of confounders reduce residual confounding. Yet, a weakness is that confounding cannot be excluded despite adjustment for several relevant confounders. Hypergastrinemia is associated with use of PPIs and users tend to have more comorbidities which could impact mortality, but we did not have data on PPIs in the present study. Another weakness is the small sample size, introducing a risk of type II errors. The serum gastrin level used as cut-off in the present study (>60 pmol/L) was based on the recommendation of the manufacturer. However, even more moderate elevation of gastrin (>20 pmol/L) is associated with pathology, e.g. *Hp*-infection and early gastrinoma, and with PPI treatment [32]. The small sample size of the present study did not allow for an assessment of the optimal cut-off for serum gastrin level exposure. In this study, gastrin was measured at baseline and not at the time of diagnosis. Thus, the analyses address the question of whether

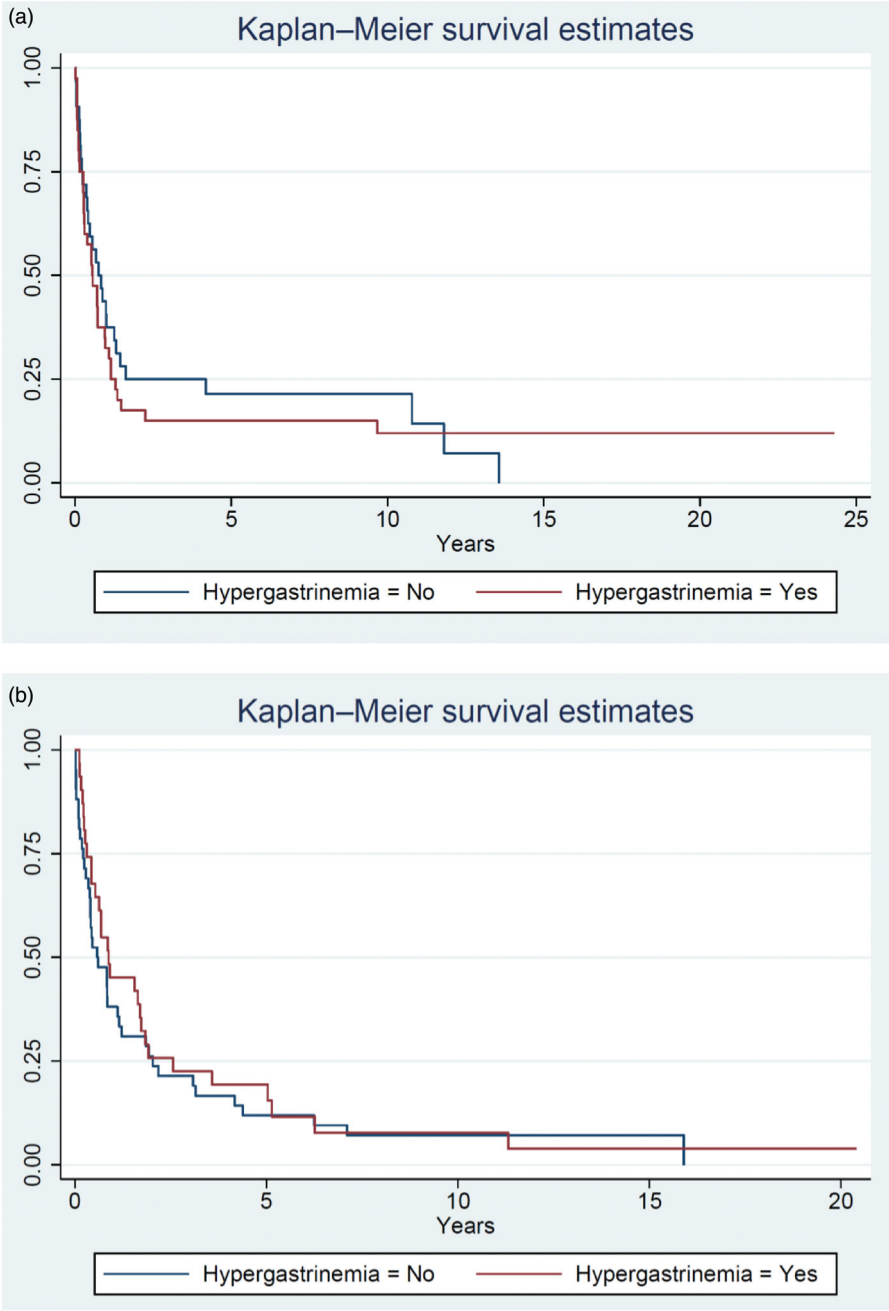

Figure 2. Kaplan–Meier curve for gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level, stratified by tumour location. Panel (a) proximal (corpus, fundus, cardia Siewert type III) tumour location (log-rank test $p = .6149$) and panel (b) distal (antrum) tumour location (log-rank test $p = .4975$).

hypergastrinemia promotes the development of a more aggressive tumour, but does not address whether hypergastrinemia promotes more aggressive tumour behaviour in patients who have already developed a gastric adenocarcinoma.

Gastrin is a hormone and the main stimulator of gastric acid secretion and oxyntic mucosal growth [15]. In response to elevation of intragastric pH and protein-containing meals, gastrin is released by the antral G-cells in the distal stomach [16,33]. The gastrin secreted from the antral G-cells is mainly gastrin-17 (G-17), a major fraction among all total circulating gastrins. Subsequently, gastrin stimulates enterochromaffin-like (ECL) cells of the oxyntic mucosa in the proximal stomach to secrete histamine by binding to the gastrin receptor and stimulating the key enzyme in histamine synthesis, histidine decarboxylase [17]. Histamine in turn stimulates the parietal cells to secrete acid by binding to the histamine-2 receptor [17]. Gastritis causing atrophy of the oxyntic mucosa and loss of ECL- and parietal cells thus leads to reduction in acid secretion, and the resulting loss of negative feedback on the antral G-cells and gastrin release leads to hypergastrinemia. Gastrin promotes carcinogenesis in the oxyntic mucosa by binding to gastrin receptors on the neuroendocrine ECL-cells [34] and cancers in patients with hypergastrinemia due to autoimmune chronic atrophic gastritis often have neuroendocrine differentiation [35]. Hypergastrinemia was associated with adenocarcinomas in the proximal stomach of both Laurén's diffuse or intestinal type histology in

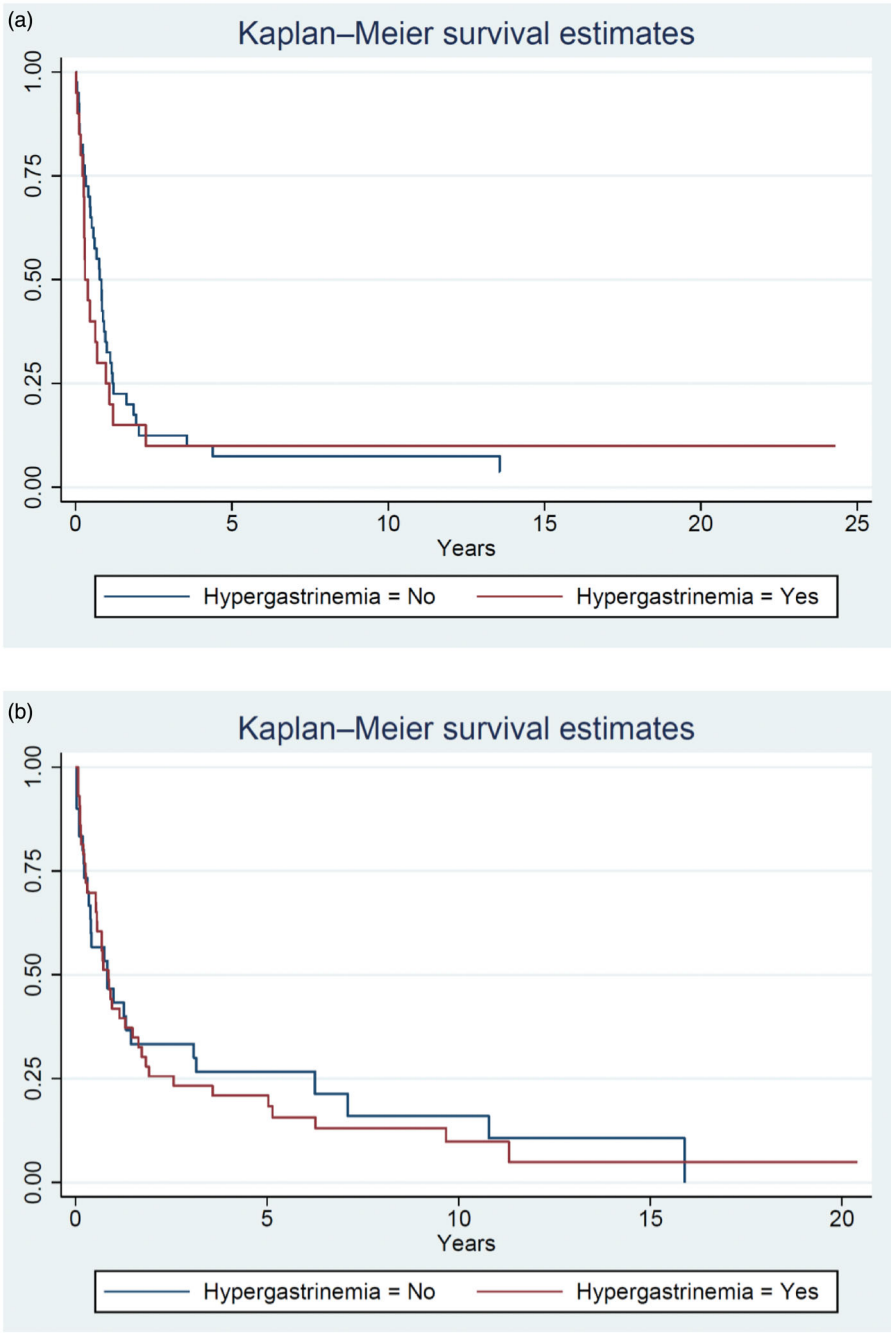

Figure 3. Kaplan–Meier curve for gastric adenocarcinoma patients with hypergastrinemia and normal gastrin level, stratified by histological type. Panel (a) diffuse histological tumour type (log-rank test $p = .5444$) and panel (b) intestinal histological tumour type (log-rank test $p = .7679$).

Table 3. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality among gastric adenocarcinoma patients with hypergastrinemia compared to patients with normal gastrin level (reference).

	Unadjusted		Adjusted[a]		Adjusted[b]		Adjusted[c]	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall	0.95	0.69–1.29	0.85	0.62–1.16	0.83	0.60–1.15	0.77	0.52–1.14
By tumour location								
Proximal[d]	1.14	0.69–1.87	0.90	0.54–1.51	0.97	0.55–1.72	0.93	0.40–2.15
Distal[e]	0.85	0.52–1.37	0.82	0.51–1.33	0.70	0.42–1.17	0.89	0.46–1.74
By histological tumour type								
Diffuse	1.19	0.68–2.09	1.11	0.63–1.97	1.20	0.62–2.33	1.53	0.52–4.53
Intestinal	1.08	0.66–1.77	1.04	0.63–1.73	1.06	0.63–1.77	0.67	0.33–1.36

[a]Adjusted for sex and age.
[b]Adjusted for sex, age, body mass index, and tobacco smoking.
[c]Adjusted for sex, age, body mass index, tobacco smoking, tumour stage, completeness of surgical resection, and peri-operative chemotherapy.
[d]Proximal: corpus, fundus, cardia Siewert type III.
[e]Distal: antrum.

our previous study of the HUNT cohort, while no such association was found with distal gastric adenocarcinomas [25]. As hormone concentrations affect both risk and prognosis of for instance breast cancer (increased survival with amenorrhea) [36], it was relevant to examine a potential prognostic role of hypergastrinemia in gastric cancers. The assay used in this study measures not only G-17, but also cross-reacts with G-34, sulphated G-17 and CCK-8, that all have affinity for the gastrin receptor. We have not been able to assess the source of gastrin and distinguish antral from non-antral. The present study could not find that hypergastrinemia affects the prognosis of those developing gastric adenocarcinoma associated with hypergastrinemia. In gastric neuroendocrine tumours, the prognosis is better in patients with hypergastrinemia than in those with normal gastrin level [37]. This could be a possible explanation also in gastric adenocarcinomas, as more important mutations, not related to the continuous over-stimulation of proliferation by hypergastrinemia, are needed to affect the prognosis.

The hypothesis of this study that hypergastrinemia is associated with increased mortality in patients with gastric adenocarcinoma could be mediated through different tumour stage at presentation in patients with hypergastrinemia compared to patient with normal gastrin level and subsequently different rates of surgical resection and chemotherapy. However, removing these possible mediators from the analyses did not affect the conclusion of no association between hypergastrinemia and mortality. Peri-operative chemotherapy could also have compensated for the possible effect of hypergastrinemia on stage and mortality, but very few patients received chemotherapy in this study and this did not influence the conclusion. A previous Norwegian study also found that peri-operative chemotherapy did not translate into any long-term survival benefit compared to surgery alone in patients with resectable gastric cancer [3].

In another previous Norwegian study of 80 gastric adenocarcinoma patients, hypergastrinemia was associated with shorter survival in patients with advanced stages (stages II–IV) [26]. However, that study was hospital-based and gastrin was analysed in samples retrieved after the cancer diagnosis, which might have caused bias. Moreover, only patients considered for surgery were included in the previous Norwegian study and not patients with advanced stage or patients too fragile for surgery. The main factors influencing overall survival in population-based as well as surgical cohorts is patient age and tumour stage. Laurén's histological type was also found to influence survival in a population-based study from Central Norway, where patients with intestinal type cancers had longer survival than patients with diffuse type histology [5]. This could be due to diffuse cancers being diagnosed in a more advanced disease and operated with a lower proportion of R0/R1 resections [5], and the influence of Laurén's type histology on survival after R0 resection in other populations has been inconsistent [38,39]. Still, diffuse type histology predicts lower response to various forms of oncological treatment [2,3,40,41]. The Cancer Genome Atlas has recently suggested four molecular subtypes of gastric cancer i.e. tumours positive for Epstein-Barr virus, tumours with microsatellite instability, tumours which are genomically stable and tumours with chromosomal instability [42]. These suggested four molecular subtypes of gastric cancer also seem to translate into a clinically relevant influence on survival [43], but it is not known if hypergastrinemia is associated with one particular molecular subtype. In the present study, hypergastrinemia was not associated with increased mortality for neither the diffuse nor the intestinal histological tumour type. In the crude analyses, mortality suggested to be lower in patients with hypergastrinemia and diffuse histological tumour type and higher in patients with hypergastrinemia and intestinal histological tumour type. However, the number of patients was low in these stratified analyses and the estimates were not statistically significant. Any possible difference needs to be clarified in a larger study.

In conclusion, this prospective population-based cohort study, although with limited statistical power, indicates that hypergastrinemia may not be associated with any increased risk of mortality in patients with gastric adenocarcinoma, regardless of tumour sub-location or histological sub-type.

Acknowledgements

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Data from the Cancer Registry of Norway and Norwegian Patient Registry have been used in this publication. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the registries is intended nor should be inferred.

Institutional review board statement

The study was approved by the Reginal Committee for Medical and Health Research Ethics, South-East (reference number 2016/112).

Informed consent statement

At participation, the HUNT participants gave a broad written consent to future research, including linkage to registries and medical records.

Disclosure statement

The authors declare no conflict of interest.

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Data availability statement

The research data used in this study were provided by the Trøndelag Health Study (The HUNT Study), the Cancer Registry of Norway and the Norwegian Patient Registry. The data are available through application to the providers.

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