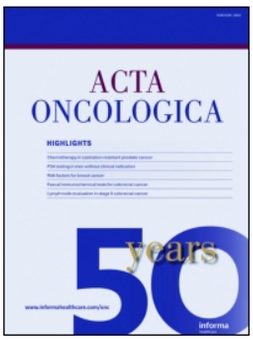

Acta Oncologica

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ionc20

Prognosis after surgery for gastric adenocarcinoma in the Swedish Gastric Cancer Surgery Study (SWEGASS)

Johannes Asplund , Eivind Gottlieb-Vedi , Wilhelm Leijonmarck , Fredrik Mattsson & Jesper Lagergren

To cite this article: Johannes Asplund , Eivind Gottlieb-Vedi , Wilhelm Leijonmarck , Fredrik Mattsson & Jesper Lagergren (2021): Prognosis after surgery for gastric adenocarcinoma in the Swedish Gastric Cancer Surgery Study (SWEGASS), Acta Oncologica, DOI: 10.1080/0284186X.2021.1874619

To link to this article: https://doi.org/10.1080/0284186X.2021.1874619

Published online: 27 Jan 2021.

ACTA ONCOLOGICA
https://doi.org/10.1080/0284186X.2021.1874619

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Prognosis after surgery for gastric adenocarcinoma in the Swedish Gastric Cancer Surgery Study (SWEGASS)

Johannes Asplund[a], Eivind Gottlieb-Vedi[a], Wilhelm Leijonmarck[a], Fredrik Mattsson[a] and Jesper Lagergren[a,b]

[a]Department of Molecular Medicine and Surgery, Upper Gastrointestinal Surgery, Karolinska University Hospital, Karolinska Institutet, Stockholm, Sweden; [b]School of Cancer and Pharmaceutical Sciences, King's College London, London, UK

ABSTRACT

Background: Most studies examining prognostic factors after gastrectomy come from selected patients and non-Western populations. This nationwide population-based cohort study aims to identify prognostic factors after surgery for gastric adenocarcinoma in an unselected Western cohort.

Methods: This study included 98% of patients who underwent gastrectomy for gastric adenocarcinoma in Sweden in 2006–2015, with follow-up through 2019. Data were collected from medical records and national registries. Exposures were sex, age, education, comorbidity, tumor sub-localization, tumor stage, calendar period, and pre-operative chemotherapy. Outcomes were 3-year all-cause and disease-specific mortality. Cox regression produced hazard ratios (HRs) with 95% confidence intervals (95% CIs), adjusted for the other study exposures.

Results: Among all 2154 patients, 3-year all-cause mortality was 53.3%. Factors influencing 3-year all-cause mortality after multivariable adjustment were tumor stage (stage IV vs. stage 0–I: HR 8.72, 95% CI 6.77–11.24), comorbidity (Charlson comorbidity score $\geq$2 vs. 0: HR 1.63, 95% CI 1.39–1.90), age (>75 vs. <65 years: HR 1.48, 95% CI 1.24–1.78), and calendar period (2006–2010 vs. 2011–2015: HR 0.83, 95% CI 0.73–0.95). No independent prognostic influence was found for sex (women vs. men: HR 1.01, 95% CI 0.85–1.09), pre-operative chemotherapy (yes vs. no: HR 0.92, 95% CI 0.78–1.08), tumor sub-localization (non-cardia vs. cardia: HR 1.01, 95% CI 0.83–1.22), or education ($\geq$13 vs. $\leq$9 years: HR 0.89, 95% CI 0.74–1.07). The results were similar for 3-year disease-specific mortality.

Conclusion: Survival after gastrectomy for gastric adenocarcinoma needs further improvement. Tumor stage, comorbidity, age, and calendar period were independently prognostic, while sex, pre-operative chemotherapy, tumor sub-localization, and education were not.

ARTICLE HISTORY
Received 6 December 2020
Accepted 7 January 2021

KEYWORDS
Gastric cancer; stomach cancer; survival; gastrectomy; postoperative survival

Introduction

Gastric cancer (>95% adenocarcinoma) is the third most common cause of cancer-related death worldwide with approximately 800,000 deaths yearly [1]. Gastric adenocarcinoma can be anatomically subdivided into cardia and non-cardia because of differences in etiology, treatment, and incidence patterns [2,3]. There are also four genomic and molecular subtypes of gastric adenocarcinoma, i.e., Epstein–Barr virus-positive tumors, micro satellite instable tumors, genomically stable tumors and tumors with chromosomal instability, which may respond differently to adjuvant therapies [4]. The incidence of gastric cardia adenocarcinoma has increased over the past decades and the main risk factors are gastroesophageal reflux disease and obesity, whereas the incidence of gastric non-cardia adenocarcinoma has steadily decreased with *Helicobacter pylori* as the main risk factor [5–9]. Patients are often asymptomatic until the gastric tumor has become advanced, which contributes to the poor overall 5-year survival (10–30% in European countries) [9]. Surgery with total or sub-total gastrectomy is the main curative treatment for most patients with gastric adenocarcinoma, and pre-operative or peri-operative chemotherapy may be beneficial in patients with resectable but locally advanced disease [2]. The survival has slightly improved over the last decades, but the population-based 5-year postoperative survival is still not higher than 40% [10,11]. Knowledge about factors that influence survival after gastrectomy for gastric adenocarcinoma is important for allowing improvement of treatment strategies. Most studies examining factors influencing the prognosis after gastrectomy come from non-Western populations, and selection bias is a threat to the validity of the results of most existing research because few studies have been population-based in design.

The main aim of this study was to identify independent prognostic factors in an unselected cohort of patients who had undergone gastrectomy for gastric adenocarcinoma in a Western country. Another aim was to present this new and

CONTACT Jesper Lagergren jesper.lagergren@ki.se Department of Molecular Medicine and Surgery, Karolinska Institutet, Campus Solna, Retzius Street 13a, Floor 4, Stockholm 171 77, Sweden

comprehensive cohort in order to promote collaborative research.

Methods

Design

This was the first study from the Swedish Gastric Cancer Surgery Study (SWEGASS), a nationwide and population-based cohort of patients who underwent gastrectomy for gastric adenocarcinoma in Sweden between 1 January 2006 and 31 December 2015. The follow-up for all-cause mortality lasted until 31 December 2019, and until 31 December 2018 for disease-specific mortality, thus allowing at least 3 years of follow-up for all patients. The cohort included patients with gastric cardia cancer of Siewert type III, but not those with Siewert type I or II tumors. Other histological types of gastric malignancies than adenocarcinoma were not included because of differences in treatment and prognosis. Eight potential prognostic factors were analyzed as exposures and confounders: sex, age, education, comorbidity, tumor sub-localization, pathological tumor stage, calendar period, and pre-operative chemotherapy. The primary outcome was 3-year all-cause mortality and the secondary outcome was 3-year disease-specific mortality. Data were retrieved from medical records and national Swedish health data registries as described below. The identification of each patient and the exact linkages of individuals' data between the data sources were enabled by the unique personal identity number of each Swedish resident, a successful system that has been in use since 1947. We used the STROBE guidelines for cohort studies when writing our report [12]. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (diary number 2017/141-31/2).

Data collection

Figure 1 gives an overview of the data sources and study variables used in the study. Potentially eligible patients were first identified from the *Swedish Patient Registry* and the *Swedish Cancer Registry* as a result of having a diagnosis of gastric adenocarcinoma in either of these registries (C16 in the 10th version of the International Classification of Diagnoses and 1510, 1511, 1518, or 1519 according to the 7th version, and the histology code 096) combined with a surgical code for resectional surgery in the *Swedish Patient Registry* (JCC, JDC, or JDD). The *Swedish Cause of Death Registry* provided data on all-cause and disease-specific mortality. The *Longitudinal Integration Database for Health Insurance and Labour Market* (LISA) had information about education. These four national registries are described in short:

The *Swedish Patient Registry* became nationwide in 1987 and holds information about all in-hospital healthcare, including all diagnoses and surgical procedures. A primary diagnosis is registered at discharge in more than 99% of patients, and the positive predictive value is 99.6% for resectional surgery of upper gastrointestinal cancer [13,14]. Except for data on registration of diagnosis of gastric adenocarcinoma and gastrectomy, this registry also provided information about comorbidities included in the Charlson Comorbidity Index, an index developed to assess comorbidity in research examining mortality after surgery [15].

The *Swedish Cancer Registry* was founded in 1958 and registration by clinicians and pathologists is compulsory for all newly diagnosed cases of cancer in Sweden. The registry holds information about the type, site, histology, and date of the cancer diagnosis. The overall completeness of the recording of gastric cancer is 98% [16], and is probably even higher for patients who undergo gastrectomy.

The *Swedish Cause of Death Registry* started in 1952 and includes information about date of death and causes of death for Swedish residents, as well as for those who die abroad. The recording of date of death is 100% complete, and 96% of all registered deaths have at least one specific cause of death recorded [17].

The LISA holds data from 1990 onwards and contains information on years of formal education [18].

The other main data source was medical records, and we asked for medical records for 4570 patients from all 60 hospitals in Sweden that conducted gastrectomies during the study period. These records mainly consisted of surgical charts, pathology reports, discharge summaries, and reports from multidisciplinary meetings. The final cohort was defined after review of these medical records, and most clinical variables came from this review. Data from the medical records were manually reviewed by four study investigators. Excluded were patients who were revealed to have been operated outside of the surgery period (2006–2015) or who received a final diagnosis other than gastric adenocarcinoma. The variables to be included in the cohort were defined in a detailed study protocol and were entered into a database using Microsoft Access 2010, which counteracted entering incorrect data. Overall, 98% of the collected medical records had sufficient information for allowing patient inclusion. Three versions of the American Joint Committee on Cancer (AJCC) tumor staging system were used during the study period (6th edition in 2006–2009, 7th edition in 2010–2016, and 8th edition from 2017 onwards), but the staging from the pathology reports was converted to the 8th version for all patients. The review of the medical records was validated by comparing the entered data of two of the investigators for two key variables, i.e., number of lymph node metastases and T-stage, in 80 randomly selected records. The results were identical between the reviewers for 99% (158/160) of evaluated variables.

Statistical analysis

Data on patient characteristics, tumor characteristics, treatment, complications, and mortality were presented as numbers and frequencies. Kaplan–Meier's curves depicted the overall survival as well as the survival stratified by tumor stage (0–I, II, III, or IV) and tumor sub-localization (gastric cardia or non-cardia). Cox regression analysis was used to produce unadjusted and adjusted hazard ratios (HRs) with 95%

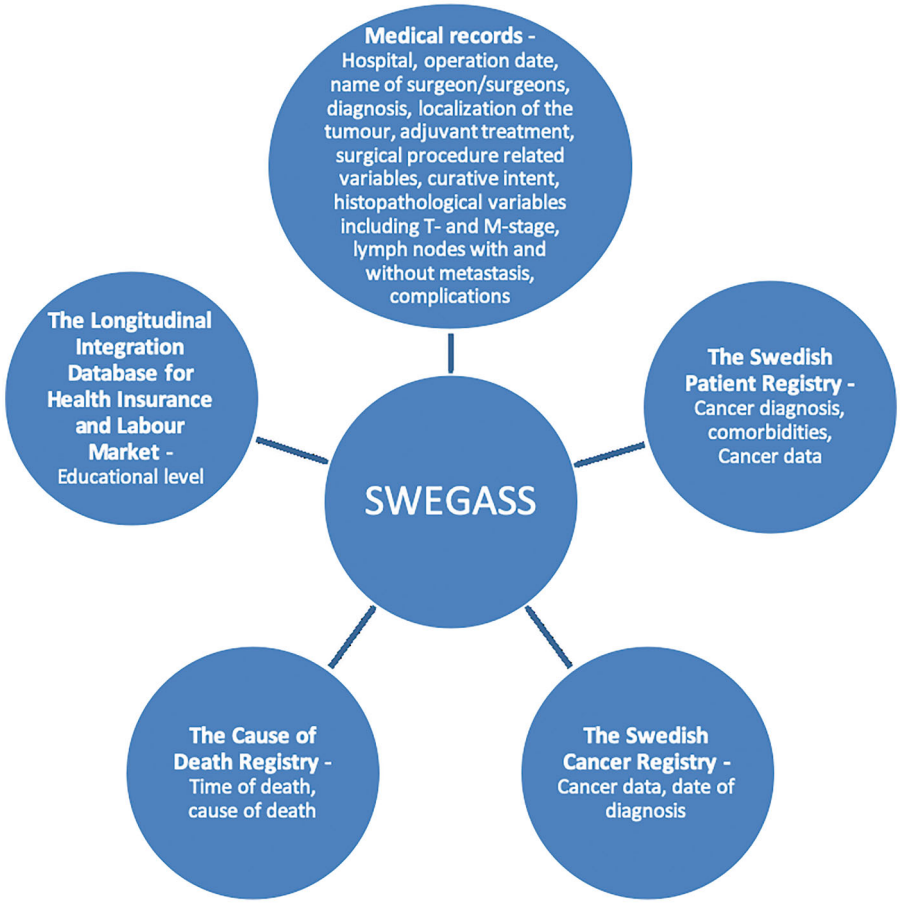

Figure 1. Data sources and variables for creating a national cohort of patients who had undergone gastrectomy for gastric adenocarcinoma in Sweden (SWEGASS).

confidence intervals (CIs) for the eight study exposures in relation to the outcomes. The eight exposures (with categorizations) were also included in the multivariable model, except for the exposure under analysis, in order to reduce confounding and identify independent prognostic factors: sex (male or female), age (<65, 65–70, or >75 years), education (≤9, 10–12, or ≥13 years of formal education), comorbidity (0, 1, or ≥2 in the Charlson Comorbidity Index, not counting the gastric adenocarcinoma diagnosis), tumor sub-localization (gastric cardia or non-cardia), pathological tumor stage (0–I, II, III, or IV), calendar period (2006–2010 or 2011–2015), and pre-operative chemotherapy (yes or no). Missing data were handled by complete case analysis, i.e., by including only patients with complete data on exposures and outcomes. Multiple imputation was intended to be used for variables with >10% missing, but the variable with the highest missing rate (tumor stage) was only 7.1%. An experienced biostatistician conducted the data management and statistical analyses according to a detailed and pre-defined study protocol. The analyses were conducted using the SAS/STAT Statistical Package, Version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patients

A flowchart shows the inclusion and exclusion of patients into and out of the SWEGASS cohort (Figure 2). Among 4570 potentially eligible patients originally identified, 2154 patients had undergone gastrectomy for gastric adenocarcinoma during the study period, and these constituted the final cohort. Table 1 presents patient and tumor characteristics of the study participants as well as information on treatment and outcomes. The cohort included more men (57.9%) than women, and the age group 65–75 years was slightly overrepresented (36.2%) compared to younger and older patients. A minority of patients (16.9%) had 13 years or more of formal education, and a majority (57.3%) had at least one comorbidity included in the Charlson Comorbidity Index. The dominating tumor sub-localization was gastric non-cardia (88.5%), and the intestinal subtype according to Laurén's classification was almost equally common as the diffuse type. A majority of patients received no pre-operative chemotherapy (71.3%), and sub-total gastrectomy was slightly more common (52.6%) than total gastrectomy. The resection margins were free from cancer involvement (R0) in most patients (81.6%), and pathological tumor stage III was more common (33.5%) than other stages. Overall, 39.4% of the patients had at least one pre-defined complication, and of these 51.9% had a complication of Clavien–Dindo grade I–II.

Absolute mortality rates

The all-cause mortality rates were 2.9% within 30 days, 7.1% within 90 days, 53.3% within 3 years, and 65.1% within

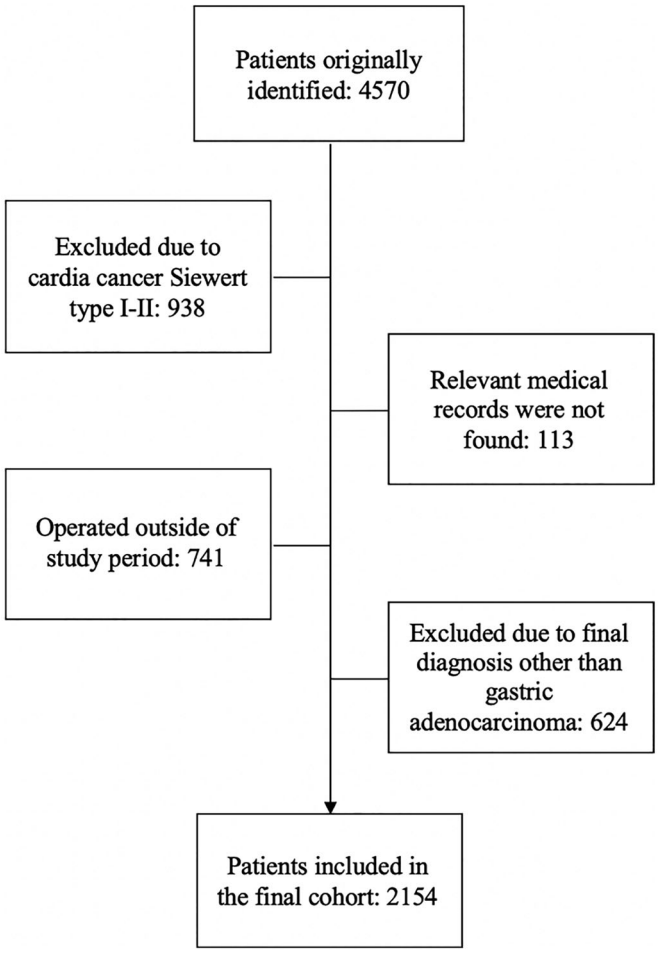

Figure 2. Flowchart illustrating inclusion and exclusion leading to a cohort of patients who underwent gastrectomy for gastric adenocarcinoma in 2006–2015 in Sweden (SWEGASS).

5 years of surgery (Table 1 and Figure 3(A)). The disease-specific 3-year and 5-year mortality rates were 47.6% and 56.3%, respectively. The survival curves were similar for tumor sub-localization (Figure 3(B)), but appeared to be distinctly different depending on the tumor stage (Figure 3(C)).

Risk of 3-year all-cause mortality

The risk estimates for the eight study exposures in relation to all-cause mortality within 3 years of surgery are presented in Table 2. The adjusted HRs were increased in patients of older age (HR 1.48, 95% CI 1.24–1.78 for age >75 vs. <65 years), with comorbidity (HR 1.63, 95% CI 1.39–1.90 for Charlson comorbidity score ≥2 vs. 0), and with more advanced pathological tumor stage (HR 8.72, 95% CI 6.77–11.24 for stage IV vs. stage 0–I), and was decreased in the more recent calendar period (adjusted HR 0.83, 95% CI 0.73–0.95 for surgery in 2006–2010 vs. 2011–2015). The adjusted HRs were not influenced by sex (HR 1.01, 95% CI 0.85–1.09 for women vs. men), pre-operative chemotherapy (HR 0.92, 95% CI 0.78–1.08 for yes vs. no), tumor sub-localization (HR 1.01, 95% CI 0.83–1.22 for non-cardia vs. cardia), or education (HR 0.89, 95% CI 0.74–1.07 for ≥13 vs. ≤9 years of education).

Table 1. Patient and tumor characteristics and treatments and outcome in 2154 patients who had undergone gastrectomy for gastric adenocarcinoma and were included in a national Swedish cohort (SWEGASS).

Variable	Number (%)[a]
Sex	
Male	1247 (58)
Female	907 (42)
Age at surgery (years)	
<65	622 (29)
65–75	779 (36)
>75	753 (35)
Formal education (years)	
≤9	889 (41)
10–12	850 (40)
≥13	365 (17)
Charlson Comorbidity Index score[b]	
0	919 (43)
1	711 (33)
≥2	524 (24)
Tumor sub-localization	
Gastric cardia	235 (11)
Non-cardia	1907 (89)
Histologic subtype according to Laurén	
Intestinal subtype	711 (33)
Diffuse subtype	733 (34)
Mixed subtype	79 (4)
Indeterminate subtype	10 (1)
Pathological tumor stage	
0–I	478 (22)
II	596 (28)
III	721 (34)
IV	206 (10)
Calendar period (years)	
2006–2010	1175 (55)
2011–2015	979 (46)
Pre-operative chemotherapy	
No	1535 (71)
Yes	601 (28)
Type of surgical resection	
Total gastrectomy	947 (44)
Sub-total gastrectomy	1133 (53)
Resection margin	
R0	1758 (82)
R1	262 (12)
Unclear	134 (6)
In-hospital complication	
No	1305 (61)
Yes	849 (39)
Severity grading	
Clavien–Dindo I–II	441 (52)
Clavien–Dindo III	243 (29)
Clavien–Dindo IV	97 (11)
Clavien–Dindo V	68 (8)
Mortality	
30-day all-cause mortality	63 (3)
90-day all-cause mortality	153 (7)
3-year all-cause mortality	1149 (53)
5-year all-cause mortality[c]	1188 (65)
3-year disease-specific mortality	1025 (48)
5-year disease specific mortality[c]	1028 (56)

[a]When percentages in one variable do not add up to 100% it is due to missing data.
[b]Excluding the gastric adenocarcinoma.
[c]Analysis limited to 1896 patients with at least 5 years of follow-up.

Risk of 3-year disease-specific mortality

As presented in Table 2, the associations between the exposure variables and risk of 3-year disease-specific mortality were similar to those for all-cause 3-year mortality. Two exceptions were that age was a possibly weaker risk factor (adjusted HR 1.34, 95% CI 1.11–1.62 for age >75 vs. <65 years) and that tumor stage was a seemingly stronger

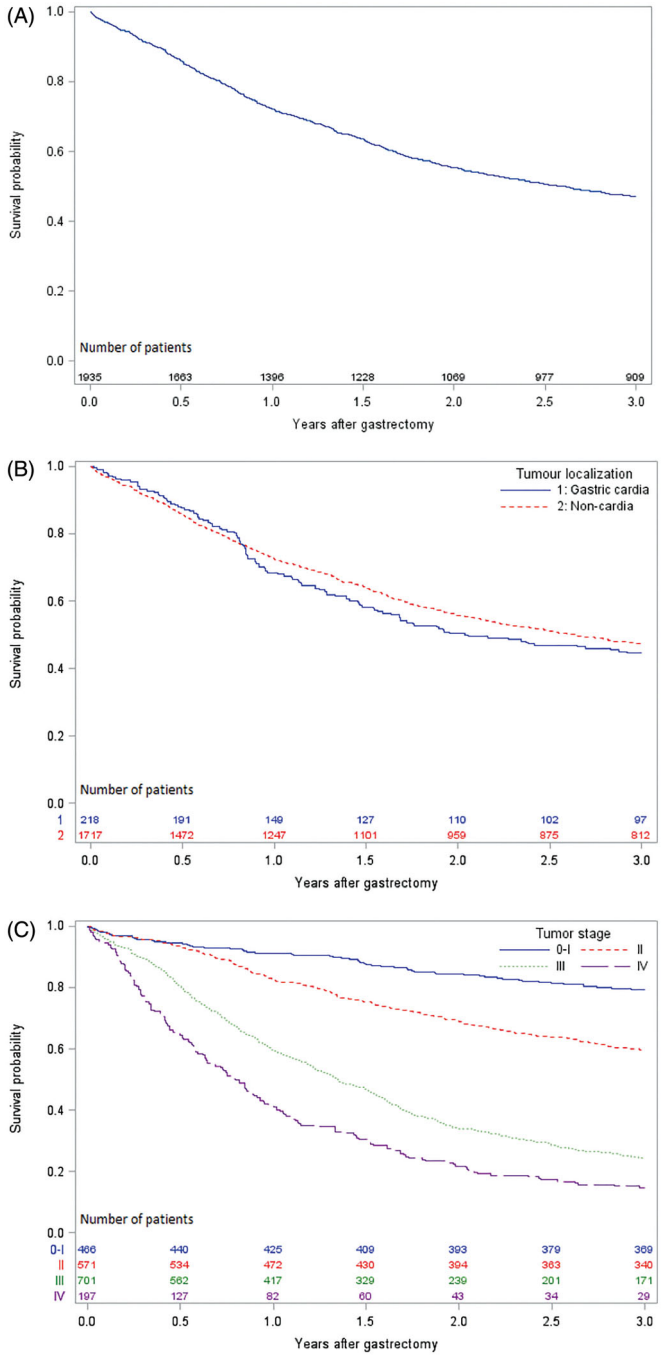

Figure 3. Kaplan–Meier's curves illustrating the 3-year survival after gastrectomy for gastric adenocarcinoma in Sweden for all patients (A), stratified by tumor sub-localization (B), and stratified by tumor stage (C).

risk factor (adjusted HR 13.43, 95% CI 9.93–18.17 for stage IV vs. stage 0–I) for disease-specific mortality.

Discussion

This study presents data from an unselected nationwide Swedish cohort of patients who had undergone gastrectomy for gastric adenocarcinoma. Independent risk factors for all-cause and disease-specific mortality within 3 years of surgery were advanced tumor stage, comorbidity and older age, while surgery during a later calendar period was followed by a decreased risk. Sex, pre-operative chemotherapy, tumor sub-localization, and education level did not influence the 3-year mortality after adjustment for the other exposures.

Among strengths of the study is the population-based cohort design with almost complete (98%) inclusion of patients who underwent gastrectomy for gastric adenocarcinoma in the entire Sweden during a 10-year period, and the complete follow-up of all patients for at least 3 years after surgery. This design increased the generalizability of the study results. The data collection was comprehensive and combined information from medical records with well-established national registries. The avoidance of self-reported data counteracted information and selection bias. Although the results were adjusted for several confounders, a weakness is the lack of data for some other variables that might confound the results, e.g., post-operative chemotherapy, body mass index, tobacco smoking, and alcohol overconsumption. However, these factors were indirectly adjusted for by adjusting for education (socioeconomic status), which is associated with all these factors, and the Charlson Comorbidity Index, which includes diseases associated with these exposures.

The postoperative complication rates and short- and long-term mortality rates in the present cohort were in agreement with those reported in studies from other Western countries [19,20]. The survival after gastrectomy for gastric adenocarcinoma is however generally higher in Eastern than Western populations [9]. This difference is mainly explained by differences in tumor stage distribution, although a meta-analysis of randomized clinical trials found a remaining survival advantage in Eastern countries after adjustment for some prognostic factors [21].

The findings that tumor stage, comorbidity, age, and calendar period are prognostic factors after surgery for gastric adenocarcinoma is supported by previous evidence [11,22,23]. The suggested differences in strengths of associations with disease-specific and all-cause mortality for tumor stage and age were also expected. Possible explanations for the improved survival during the more recent calendar period may include stricter selection of patients for surgery and centralization to fewer hospitals or surgeons. These findings stress the need to carefully consider tumor stage, comorbidity, and age in the pre-operative assessment of patients with gastric adenocarcinoma. The results also lend validity to the SWEGASS cohort.

The negative findings regarding sex, pre-operative chemotherapy, tumor sub-localization, and education warrant more discussion. The lack of survival influence of sex is in conflict with the results of two registry-based studies that found better prognosis in women [24,25]. But is supported by the similar mortality between the sexes in two other studies [11,26]. Taken together, it seems unlikely that sex is a strong and independent prognostic factor, and sex should not be considered in any clinical decision-making.

The crude analysis suggested a survival benefit from pre-operative chemotherapy, but no improvement remained after adjustment for other prognostic factors. Two randomized clinical trials that have been important for the treatment regimens in Europe demonstrated a survival benefit with

Table 2. Hazard ratios (HRs) with 95% confidence intervals (CIs) of 3-year mortality in patients who had undergone gastrectomy for gastric adenocarcinoma and were included in a National Swedish Cohort (SWEGASS).

Variable	3-year all-cause mortality		3-year disease-specific mortality	
	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]	Unadjusted HR (95% CI)	Adjusted HR (95% CI)[a]
Sex				
Male	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Female	0.96 (0.85–1.09)	1.01 (0.89–1.14)	1.01 (0.89–1.15)	1.04 (0.91–1.19)
Age at surgery (years)				
<65	1 (reference)	1 (reference)	1 (reference)	1 (reference)
65–75	1.26 (1.08–1.48)	1.23 (1.05–1.45)	1.22 (1.03–1.43)	1.21 (1.02–1.43)
>75	1.58 (1.35–1.85)	1.48 (1.24–1.78)	1.38 (1.17–1.62)	1.34 (1.11–1.62)
Formal education (years)				
≤9 year	1 (reference)	1 (reference)	1 (reference)	1 (reference)
10–12 years	0.91 (0.79–1.03)	0.96 (0.84–1.10)	0.93 (0.80–1.1)	0.95 (0.83–1.10)
≥13 years	0.77 (0.64–0.92)	0.89 (0.74–1.07)	0.81 (0.67–0.98)	0.90 (0.74–1.09)
Charlson Comorbidity Index score[b]				
0	1 (reference)	1 (reference)	1 (reference)	1 (reference)
1	1.25 (1.08–1.45)	1.15 (0.99–1.33)	1.22 (1.05–1.42)	1.12 (0.96–1.31)
≥2	1.92 (1.66–2.24)	1.63 (1.39–1.90)	1.81 (1.54–2.12)	1.56 (1.32–1.84)
Tumor sub-localization				
Gastric cardia	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Non-cardia	1.09 (0.90–1.32)	1.01 (0.83–1.22)	1.06 (0.87–1.30)	0.96 (0.78–1.18)
Pathological tumor stage				
0–I	1 (reference)	1 (reference)	1 (reference)	1 (reference)
II	2.20 (1.73–2.79)	2.04 (1.61–2.59)	3.12 (2.34–4.18)	2.95 (2.20–3.95)
III	5.94 (4.78–7.39)	5.84 (4.69–7.26)	9.14 (6.97–11.98)	9.05 (6.90–11.87)
IV	9.04 (7.03–11.63)	8.72 (6.77–11.24)	13.98 (10.35–18.88)	13.43 (9.93–18.17)
Calendar period				
2006–2010	1 (reference)	1 (reference)	1 (reference)	1 (reference)
2011–2015	0.86 (0.76–0.98)	0.83 (0.73–0.95)	0.86 (0.76–0.98)	0.83 (0.72–0.95)
Pre-operative chemotherapy				
No	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Yes	0.72 (0.62–0.82)	0.92 (0.78–1.08)	0.79 (0.68–0.92)	0.98 (0.83–1.15)

[a]Adjusted for: sex (male or female), age (<65, 65–70, or >75), calendar period (2006–2010 or 2011–2015), Charlson comorbidity score (0, 1, or ≥2), tumor sub-localization (gastric cardia or non-cardia), pre-operative chemotherapy (no or yes), tumor stage (0–I, II, III, or IV), and education (≤9 years, 10–12 years, or ≥13 years).
[b]Excluding the gastric adenocarcinoma.

pre-operative chemotherapy. In the MAGIC trial, the 5-year overall survival was 36% in patients who received chemotherapy in addition to surgery and 23% for those who received surgery alone [19], and in the FNCLCC/FFCD trial, the corresponding 5-year survival rates were 38% and 24%, respectively [27]. The difference in results between the present study and these trials could be due to unmeasured confounding in the present study, and the results of this study should not lead to any changes in the use of pre-operative chemotherapy in patients who undergo surgery for gastric adenocarcinoma. Nevertheless, the population-based design of this study meant that all patients were included, and not only those who are selected before being included in randomized clinical trials. A recent randomized controlled study showed perioperative treatment with FLOT (fluorouracil, leucovorin, oxaliplatin, and docetaxel) improved survival compared to the EFC (epirubicin, fluorouracil, and cisplatin) that was used in the MAGIC study, and FLOT has become standard regimen for perioperative treatment of gastric cancer [28].

The lack of survival difference between patients with cardia and non-cardia gastric adenocarcinoma in the current study does not deviate much from previous research. Although some studies have found worse survival after surgery for gastric cardia adenocarcinoma compared to gastric non-cardia adenocarcinoma, the survival rates were similar when analyzed by tumor stage [29–31].

Longer education was associated with lower mortality in the unadjusted model of this study, but this association did not remain after adjustment for prognostic factors [32,33]. To our knowledge, no other study has investigated the association between education and survival after surgery for gastric adenocarcinoma. However, a Swedish cohort study found a reduced overall risk of mortality in gastric adenocarcinoma in patients with higher education level [34], while no such association was found in a Japanese cohort study [35]. A study examining patients who had undergone surgery for esophageal cancer found no decreased risk of mortality with higher education after adjustment for confounders [36]. Older patients generally have shorter education than younger patients [35], and patients with shorter education might be less health conscious, present with more advanced tumor stage and have lower adherence to treatment recommendations [37]. Thus, the adjustment for age, tumor stage and pre-operative chemotherapy may have eliminated associations between higher education and survival after surgery for gastric adenocarcinoma. Taken together, education level should not influence clinical decision-making.

This study provides some valuable information in a group of patients that has not been extensively investigated before. The population-based design in an entire Western country, with detailed information from an unselected cohort of patients operated for gastric adenocarcinoma and without losses to follow-up adds essential knowledge about the

major prognostic factors. This knowledge can be used for evidence-based clinical decision-making and for the development of prognostic prediction models. Additionally, the SWEGASS cohort offers possibilities for further studies on various prognostic factors and for collaborations with other researchers and clinicians in the field.

In conclusion, this population-based cohort study from a Western country showed that the survival after surgery for gastric adenocarcinoma needs to be further improved. The main independent prognostic factors were tumor stage, comorbidity, age, and calendar period, and these should be considered in the pre-operative assessment of patients. In contrast, sex, pre-operative chemotherapy, tumor sub-localization, and education level were not independent prognostic factors and should therefore not influence clinical decision-making. There is a need for more research on prognostic factors in Western populations in order to identify strategies for improving the survival in gastric adenocarcinoma, and SWEGASS may provide opportunities for such studies.

Disclosure statement

The authors report no conflicts of interest.

Funding

This study was supported by the Swedish Research Council (Vetenskapsrådet) and Swedish Cancer Society (Cancerfonden).

References

[1] Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2018;68(6):394–424.
[2] Van Cutsem E, Sagaert X, Topal B, et al. Gastric cancer. Lancet. 2016;388(10060):2654–2664.
[3] Colquhoun A, Arnold M, Ferlay J, et al. Global patterns of cardia and non-cardia gastric cancer incidence in 2012. Gut. 2015;64(12):1881–1888.
[4] Cancer Genome Atlas Research Network. Comprehensive molecular characterization of gastric adenocarcinoma. Nature. 2014;513(7517):202–209.
[5] Arnold M, Karim-Kos HE, Coebergh JW, et al. Recent trends in incidence of five common cancers in 26 European countries since 1988: analysis of the European Cancer Observatory. Eur J Cancer. 2015;51(9):1164–1187.
[6] Ang TL, Fock KM. Clinical epidemiology of gastric cancer. Singapore Med J. 2014;55(12):621–628.
[7] Etemadi A, Safiri S, Sepanlou S, et al. The global, regional, and national burden of stomach cancer in 195 countries, 1990–2017: a systematic analysis for the Global Burden of Disease study 2017. Lancet Gastroenterol Hepatol. 2020;5(1):42–54.
[8] Smyth EC, Nilsson M, Grabsch HI, et al. Gastric cancer. Lancet (London, England). 2020;396(10251):635–648.
[9] Sitarz R, Skierucha M, Mielko J, et al. Gastric cancer: epidemiology, prevention, classification, and treatment. Cancer Manag Res. 2018;10:239–248.
[10] Samverkan R. Nationell kvalitetsregisterrapport matstrups- och magsäckscancer. Regionalt Cancercentrum Norr, Umeå; 2019.
[11] Asplund J, Kauppila JH, Mattsson F, et al. Survival trends in gastric adenocarcinoma: a population-based study in Sweden. Ann Surg Oncol. 2018;25(9):2693–2702.
[12] von Elm E, Altman DG, Egger M, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: guidelines for reporting observational studies. Int J Surg. 2014;12(12):1495–1499.
[13] Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
[14] Lagergren K, Derogar M. Validation of oesophageal cancer surgery data in the Swedish Patient Registry. Acta Oncol. 2012;51(1):65–68.
[15] Armitage JN, van der Meulen JH, Royal College of Surgeons Comorbidity Consensus Group. Identifying co-morbidity in surgical patients using administrative data with the Royal College of Surgeons Charlson Score. Br J Surg. 2010;97(5):772–781.
[16] Ekstrom AM, Signorello LB, Hansson LE, et al. Evaluating gastric cancer misclassification: a potential explanation for the rise in cardia cancer incidence. J Natl Cancer Inst. 1999;91(9):786–790.
[17] Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765–773.
[18] Ludvigsson JF, Svedberg P, Olén O, et al. The longitudinal integrated database for health insurance and labour market studies (LISA) and its use in medical research. Eur J Epidemiol. 2019;34(4):423–437.
[19] Cunningham D, Allum WH, Stenning SP, et al. Perioperative chemotherapy versus surgery alone for resectable gastroesophageal cancer. N Engl J Med. 2006;355(1):11–20.
[20] Lello E, Furnes B, Edna TH. Short and long-term survival from gastric cancer. A population-based study from a county hospital during 25 years. Acta Oncol. 2007;46(3):308–315.
[21] Markar SR, Karthikesalingam A, Jackson D, et al. Long-term survival after gastrectomy for cancer in randomized, controlled oncological trials: comparison between West and East. Ann Surg Oncol. 2013;20(7):2328–2338.
[22] Saito H, Osaki T, Murakami D, et al. Effect of age on prognosis in patients with gastric cancer. ANZ J Surg. 2006;76(6):458–461.
[23] Siewert JR, Böttcher K, Stein HJ, et al. Relevant prognostic factors in gastric cancer: ten-year results of the German Gastric Cancer Study. Ann Surg. 1998;228(4):449–461.
[24] Maguire A, Porta M, Sanz-Anquela JM, et al. Sex as a prognostic factor in gastric cancer. Eur J Cancer. 1996;32(8):1303–1309.
[25] Li H, Wei Z, Wang C, et al. Gender differences in gastric cancer survival: 99,922 cases based on the SEER database. J Gastrointest Surg. 2020;24(8):1747–1757.
[26] Alshehri A, Alanezi H, Kim BS. Prognosis factors of advanced gastric cancer according to sex and age. World J Clin Cases. 2020;8(9):1608–1619.
[27] Ychou M, Boige V, Pignon JP, et al. Perioperative chemotherapy compared with surgery alone for resectable gastroesophageal adenocarcinoma: an FNCLCC and FFCD multicenter phase III trial. J Clin Oncol. 2011;29(13):1715–1721.
[28] Al-Batran SE, Homann N, Pauligk C, et al. Perioperative chemotherapy with fluorouracil plus leucovorin, oxaliplatin, and docetaxel versus fluorouracil or capecitabine plus cisplatin and epirubicin for locally advanced, resectable gastric or gastro-oesophageal junction adenocarcinoma (FLOT4): a randomised, phase 2/3 trial. Lancet (London, England). 2019;393(10184):1948–1957.
[29] Zhao J, Zhao J, Du F, et al. Cardia and non-cardia gastric cancer have similar stage-for-stage prognoses after r0 resection: a large-scale, multicenter study in China. J Gastrointest Surg. 2016;20(4):700–707.
[30] An JY, Baik YH, Choi MG, et al. The prognosis of gastric cardia cancer after R0 resection. Am J Surg. 2010;199(6):725–729.
[31] Amini N, Spolverato G, Kim Y, et al. Clinicopathological features and prognosis of gastric cardia adenocarcinoma: a multi-institutional US study. J Surg Oncol. 2015;111(3):285–292.

[32] Rota M, Alicandro G, Pelucchi C, et al. Education and gastric cancer risk-An individual participant data meta-analysis in the StoP project consortium. Int J Cancer. 2020;146(3):671–681.
[33] Lagergren J, Andersson G, Talbäck M, et al. Marital status, education, and income in relation to the risk of esophageal and gastric cancer by histological type and site. Cancer. 2016;122(2):207–212.
[34] Ljung R, Drefahl S, Andersson G, et al. Socio-demographic and geographical factors in esophageal and gastric cancer mortality in Sweden. PLoS One. 2013;8(4):e62067.
[35] Kuwahara A, Takachi R, Tsubono Y, et al. Socioeconomic status and gastric cancer survival in Japan. Gastric Cancer. 2010;13(4):222–230.
[36] Brusselaers N, Ljung R, Mattsson F, et al. Education level and survival after oesophageal cancer surgery: a prospective population-based cohort study. BMJ Open. 2013;3(12):e003754.
[37] Liu Y, Zhang J, Huang R, et al. Influence of occupation and education level on breast cancer stage at diagnosis, and treatment options in China: a nationwide, multicenter 10-year epidemiological study. Medicine (Baltimore). 2017;96(15):e6641.