










Preoperative predictors of postoperative complications after gastrectomy for gastric cancer, a population-based study in Finland

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STRUCTURED ABSTRACT

Introduction: International studies on preoperative risk factors of postoperative complications after gastrectomy for gastric cancer are few, and studies done in a population-based setting or using standardized definitions are lacking. Gastrectomy for gastric cancer is characterized by high complication rates and mortality, and identifying the risk factors for postoperative complications and mortality enables to improve the postoperative outcomes.

Materials and methods: This nationwide population-based cohort study is based on the Finnish National Esophago-Gastric Cancer Cohort, and it included all patients undergoing gastric cancer surgery in Finland during 2005–2016 aged 18 years or older. The Esophagectomy Complications Consensus Group's (ECCG) standardized list of complications was used for describing different types of postoperative outcomes.

Results: This study analyzed a total of 1993 patients. The results suggested that of potential risk factors, higher ASA-class, and advanced tumor stage increased the risk of major postoperative complications after gastrectomy for gastric cancer, whereas age ≥ 70 years and distal tumor location may be protective factors. The results suggested that older age, higher ASA-class, comorbidity, and advanced tumor stage were risk factors for 90-day mortality. Older age seemed to be a risk factor for 90-day mortality, whereas it seemed to protect from major postoperative complications and 90-day reoperations.

Conclusions: Higher ASA-class, and advanced tumor stage were risk factors for major complications after gastrectomy for gastric cancer, while older age and distal tumor location seemed to be protective factors.

1. Introduction

Gastric cancer is the third leading cause of cancer death and led close

to 800,000 annual deaths in the World in 2020 [1,2]. Many patients have advanced stage at the time of diagnosis and even with radical resection (R0), the five-year survival rate is below 30 % [3]. The

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cornerstone of treatment for gastric adenocarcinoma is a curative gastrectomy involving removal of all gross cancer and regional lymph nodes without leaving any macroscopically visible cancer lesions [4]. Gastrectomy is characterized by high complication rates, morbidity and mortality [5]. The incidence of major postoperative complications after gastrectomy varies between studies being 17–19 % in European studies [5,6]. Postoperative complications after gastrectomy associate with worse recovery [7].

The studies on preoperative risk factors of postoperative complications after gastrectomy for gastric cancer are few and the majority focus on a single postoperative complication. A number of preoperative factors are associated with postoperative complications after gastrectomy. Age, obesity, sarcopenia, malnutrition, preoperative systemic inflammation, a low preoperative eGFR, abnormal pulmonary function and hypercoagulation among others have been associated with increased risk of complications [8]. Furthermore, the lack of standardized definitions of complications hampers comparisons between studies.

Identifying risk factors for these outcomes is essential in order to improve both prognosis and life quality of these patients. Population-based studies on risk factors of postoperative complications of gastrectomy are lacking.

This present study aimed to examine whether preoperative factors, such as age, sex, comorbidity, tumor stage, and tumor location are associated with postoperative complications after gastrectomy for gastric adenocarcinoma using the standardized Esophagectomy Complications Consensus Group (ECCG) [9] framework.

2. Methods

2.1. Study design

The population-based nationwide cohort study, Finnish National Esophago-Gastric Cancer Cohort (FINEGO) includes patients with gastric cancer or tumor diagnosis in the Finnish Cancer Registry or the Finnish Patient Registry. This present study is based on patients who underwent elective gastrectomy in Finland during 2005–2016. The inclusion criteria for the patients were diagnosis of gastric adenocarcinoma and age of 18 or over at the time of diagnosis. The data collection is described in previous publications [10,11].

Complication data was collected from individual patient records by upper gastrointestinal surgeons. For classification of the complications, the severity of complications was graded according to the Clavien-Dindo classification of surgical complications [12]. Major complications are defined Clavien-Dindo as grade IIIa or greater. Due to its comprehensive and accurate recording of complications in upper gastrointestinal surgery, the Esophagectomy Complications Consensus Group's (ECCG) standardized list of complications was used for classifying and describing different types of postoperative outcomes [9], as used in several previous studies [5,6].

2.2. Exposures

The exposures in this study were the risk factors age (under 70 or ≥ 70), sex (male/female), ASA-class (1–2, 3, or 4), CCI (Charlson comorbidity score 0, 1, 2, or ≥ 3) [13], pathological cancer stage (0-I, II, III or IV), and tumor location (proximal, body, or distal).

2.3. Outcomes

The primary outcome was major postoperative complications (Clavien-Dindo IIIa or greater). Secondary outcomes were different complication types grouped by the ECCG classification, total complications, 90-day mortality, 90-day reoperations, anastomotic complications, and intra-abdominal collections.

2.4. Statistical analysis

Firstly, patient characteristics, total complications, and the length of postoperative ICU and hospital stay are presented as frequencies and percentages (Table 1). Multivariate logistic regression will be used to provide Odds ratios (OR) with 95 % Confidence Intervals (CI), both

Table 1
Patient characteristics and total occurrence of complications.

	n = 1993 n (%)
Year of surgery	
Median (IQR)	2010 (2007–2013)
BMI ^a	
Median (IQR)	25.1 (22.4–27.9)
Missing	322 (16.2)
Number of lymph nodes removed	
Median (IQR)	15 (7–22)
Missing	434 (21.8)
Age	
Median (IQR)	70 (62–78)
< 70 years	958 (48.1)
≥ 70 years	1035 (51.9)
Sex	
Female	883 (44.3)
Male	1110 (55.7)
ASA class	
1–2	595 (29.9)
3	927 (46.5)
4–5	183 (9.2)
Missing	288 (14.5)
CCI ^b	
0	1009 (50.6)
1	602 (30.2)
2	233 (11.7)
3 or more	149 (7.5)
Pathological (yp/pTNM) stage	
0-I	525 (26.3)
II	596 (29.9)
III	690 (34.6)
IV	146 (7.3)
Missing	36 (1.8)
Tumor location	
Proximal	242 (12.1)
Body	865 (43.4)
Distal	885 (44.4)
Missing	1 (0.1)
Surgical approach	
Open	1898 (95.2)
Laparoscopic	95 (4.8)
Neoadjuvant treatment	
Yes	293 (14.7)
No	1693 (84.9)
Missing or not available	7 (0.4)
Complications	
Total complications	852 (42.6)
Pulmonary complications	304 (15.3)
Cardiac complications	137 (6.9)
Gastrointestinal complications	394 (19.8)
Urologic complications	91 (4.6)
Thromboembolic complications	38 (1.9)
Neurologic complications	46 (2.3)
Infectious complications	343 (17.2)
Wound complications	39 (2.0)
Other complications	45 (2.2)
Pancreatic fistula	14 (0.7)
Anastomotic complication ^c	100 (5.0)
Intra-abdominal collection	159 (8.0)
Major complications	334 (16.8)
90-day mortality	119 (6.0)
90-day reoperations	157 (7.9)

^a BMI meaning Body Mass Index.

^b CCI meaning comorbidity classified with the Charlson Comorbidity Index.

^c * Anastomotic complication includes both anastomotic leak and duodenal stump leak.

crude and adjusted. For survival outcomes, Cox regression will provide Hazard ratios (HR) with 95 % CI, both crude and adjusted. Multiple imputation for exposure and confounding variables with 20 iterations was performed to take account for missing data, assuming that the values were missing at random. The results of the complete case analysis did not differ from the analyses with multiple imputation, resulting in presenting only the analyses with multiple imputation. Risk factors for analysis were age (under 70 or ≥ 70), sex (male/female), ASA-class (1–2, 3, or 4), CCI (Charlson comorbidity score 0, 1, 2, or ≥ 3) [13], pathological cancer stage (0-I, II, III or IV), and tumor location (proximal, body, or distal). In addition to that, discharge year (continuous), neo-adjuvant treatment (yes, or no), Body Mass Index (BMI) (continuous), surgical approach (oper, or laparoscopic), and number of removed lymph nodes (continuous) were taken into account in the analysis as a confounding factors. Lastly, Mann-Whitney *U* test was used to compare distributions of removed lymph nodes in relation to age.

3. Results

3.1. Patients

For this present study, a total of 1993 patients were identified from the registries and were eligible for the analysis. The patient characteristics are described in Table 1. The median age was 70 years, and most patients (51.9 %) were 70 years old or older at the time of surgery. Most patients were male (55.7 %) and had comorbidity of 0–1 (80.8 %) according to the Charlson comorbidity score [13]. The most common pathological stage was III (34.6 %) and the most common tumor location was distal (44.4 %).

3.2. Occurrence of complications

The total occurrence of complications 90 days after gastrectomy for gastric cancer was 42.6 %. The most common complication types according to the ECGG upper-level categories [9] were gastrointestinal (19.8 %), infectious (17.2 %) and pulmonary (15.3 %) complications. The occurrence of major complications was 16.8 % and the 90-day mortality after surgery was 6.0 %. A total of 157 (7.9 %) of patients required a reoperation during 90 days after surgery.

Of potential risk factors, higher ASA-class, Charlson score, and tumor stage were risk factors for major complications in the crude analysis. In the adjusted analysis, the risk factors for major complications were ASA-class 4–5 (OR 2.59; 95 % CI 1.62–4.12), and stage IV (OR 1.61; 95 % CI 1.01–2.56), whereas older age (OR 0.76; 95 % CI 0.58–0.99), and distal tumor location (OR 0.66; 95 % CI 0.45–0.97) were protective factors in adjusted analysis. Major complications are presented in Table 2.

Risk factors for 90-day mortality were older age, higher ASA-class, comorbidity, and advanced tumor stage in both crude and adjusted analysis. In adjusted analysis, distal tumor location was an additional protective factor of 90-day mortality. The only risk factor for reoperation was high comorbidity, but this association attenuated after the adjustment for confounding factors. In adjusted analysis older age seemed to be a protective factor. Risk factors for 90-day mortality and reoperations are presented in Table 3. A post-hoc analysis suggested that older patients had less lymph nodes removed than those up to 70 years old (13 lymph nodes [IQR 6–20] in those 70 or more, compared to 16 [IQR 8–24] in those up to 70 years. $p < 0.001$, Mann-Whitney test).

For any postoperative complication, potential risk factors were higher ASA-class and comorbidity. In adjusted analysis, the risk factors for organ-specific complication 90 days after surgery according to the ECGG classification were diverse. Age ≥ 70 years was associated with cardiac and infectious complications, while higher ASA-class was associated with cardiac, gastrointestinal, and other complications. Higher Charlson score was associated with pulmonary, cardiac, gastrointestinal, neurologic, and wound complications. Higher tumor stage was associated with thromboembolic and other complications, and distal tumor

Table 2

Risk factors for major complications 90 days after surgery. Statistically significant differences are **bolded**.

Variable	Major complications	
	Crude OR	Adjusted OR
	OR (95 % CI)	OR (95 % CI)
Age		
< 70 years	1.00 (reference)	1.00 (reference)
≥ 70 years	0.965 (0.763–1.221)	0.758 (0.575–0.999)
Sex		
Female	1.00 (reference)	1.00 (reference)
Male	0.930 (0.734–1.177)	0.844 (0.661–1.078)
ASA-class		
1-2	1.00 (reference)	1.00 (reference)
3	1.281 (0.966–1.698)	1.349 (0.977–1.865)
4-5	2.588 (1.762–3.802)	2.586 (1.624–4.117)
CCI		
0	1.00 (reference)	1.00 (reference)
1	1.009 (0.762–1.337)	0.931 (0.693–1.252)
2	1.490 (1.041–2.133)	1.277 (0.865–1.884)
3 or more	2.053 (1.375–3.066)	1.572 (0.998–2.475)
Pathological (yp/pTNM) stage		
0-I	1.00 (reference)	1.00 (reference)
II	1.100 (0.799–1.514)	1.147 (0.827–1.590)
III	1.091 (0.800–1.487)	1.103 (0.797–1.527)
IV	1.593 (1.013–2.505)	1.609 (1.011–2.561)
Tumor location		
Proximal	1.00 (reference)	1.00 (reference)
Body	0.945 (0.657–1.361)	0.855 (0.587–1.246)
Distal	0.741 (0.511–1.073)	0.658 (0.449–0.965)

location with pulmonary complications. For anastomotic complications, age > 70 years seemed to be a protective factor in adjusted analysis. None of the analyzed factors were associated with intra-abdominal collections in crude or adjusted analysis. The overall complications, complications grouped by the ECGG upper-level categories, anastomotic complications, and intra-abdominal collections are presented in [Supplementary Tables 1–6](#).

4. Discussion

The present study examined the preoperative risk factors predicting postoperative complications after gastrectomy in gastric cancer in a population-based setting. The results suggest that higher ASA-class, and tumor stage are associated with major postoperative complications, while age 70 years or older and distal tumors may be protective factors.

For major complications, a South Korean study ($n = 881$) suggested that for major postoperative complications (Clavien-Dindo grade IIIa or more) after gastrectomy for gastric cancer risk factors were age of 60 years or more, total gastrectomy and ASA-class III-IV [14]. In addition to that, an Italian study ($n = 265$) suggested that ASA-class $> II$ was an independent risk factor for Clavien-Dindo grade III or more complications after gastrectomy for gastric cancer [15]. This is in line with the present study, where ASA-class 4–5, and pathological stage IV were significant risk factors for major complications after the adjustment with confounding variables. In this present study the type of resection was not assessed, but patients with distal tumor location, enabling distal gastrectomy, had significantly less major postoperative complications compared to patients with proximal tumor location.

For 90-day mortality, in this present study preoperative risk factors were age 70 years or older, higher ASA-class, comorbidity, and advanced pathological stage. Interestingly, a Dutch study [16] ($n = 2315$) suggested that postoperative 30-day mortality in multivariable analysis was not significantly associated with age. They also suggested that ASA-class III-V and total gastrectomy predicted postoperative mortality 30-days after surgery, being in line with the present study. Even though the type of resection was not directly assessed, distal tumor location seemed to be a protective factor of 90-day mortality in adjusted

Table 3Risk factors for mortality and reoperations 90 days after surgery. Statistically significant differences are **bolded**.

Variable	90-day Mortality		90-day Reoperations	
	Crude	Adjusted	Crude	Adjusted
	HR (95 % CI)	HR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Age				
< 70 years	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
≥ 70 years	2.485 (1.664–3.713)	1.785 (1.125–2.832)	0.790 (0.569–1.095)	0.613 (0.420–0.894)
Sex				
Female	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Male	1.141 (0.792–1.644)	0.994 (0.682–1.447)	1.137 (0.817–1.583)	1.098 (0.781–1.544)
ASA-class				
1-2	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
3	1.881 (1.141–3.103)	1.185 (0.667–2.107)	1.019 (0.698–1.488)	1.087 (0.703–1.680)
4-5	4.995 (2.863–8.717)	2.287 (1.146–4.565)	1.624 (0.953–2.770)	1.586 (0.830–3.023)
CCI				
0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
1	1.097 (0.682–1.766)	0.982 (0.600–1.606)	1.093 (0.743–1.607)	1.100 (0.733–1.650)
2	2.531 (1.536–4.171)	1.748 (1.016–3.009)	1.377 (0.835–2.273)	1.269 (0.733–2.196)
3 or more	4.106 (2.492–6.766)	2.370 (1.318–4.260)	1.815 (1.049–3.142)	1.607 (0.858–3.007)
Pathological (yp/pTNM) stage				
0-I	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
II	1.015 (0.581–1.774)	1.087 (0.619–1.908)	1.207 (0.771–1.889)	1.200 (0.759–1.896)
III	1.195 (0.715–1.997)	1.396 (0.820–2.376)	1.142 (0.737–1.772)	1.148 (0.726–1.815)
IV	3.789 (2.158–6.653)	4.587 (2.579–8.159)	1.661 (0.894–3.084)	1.559 (0.828–2.936)
Tumor location				
Proximal	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Body	0.890 (0.525–1.511)	0.877 (0.512–1.502)	1.054 (0.630–1.765)	0.959 (0.566–1.627)
Distal	0.639 (0.369–1.109)	0.561 (0.319–0.989)	0.836 (0.495–1.415)	0.719 (0.419–1.231)

analysis, possibly favoring distal gastrectomy. Taken together, ASA-class IV-V seems to be the most important predictor of postoperative mortality, and in previous studies there has been strong evidence of the association of higher ASA-class and postoperative morbidity [14,15].

For total complications, in this present study preoperative risk factors were higher ASA-class and Charlson score. A Japanese study (n = 214) suggested that patients with 2 or more comorbidities, especially pulmonary and vascular comorbidities, had significantly more often postoperative complications after gastrectomy for gastric cancer compared to patients with less comorbidity (p = 0.001) [17]. Furthermore, a Chinese study (n = 1657) suggested that comorbidities were significantly associated with postoperative complications, whereas also an increase in comorbidity also increased postoperative complications [18]. This is in line with the results of this present study, suggesting that higher Charlson score associated with both major and total postoperative complications.

The aforementioned Dutch study [16] (n = 2315) evaluating the impact of age in postoperative outcomes after gastrectomy for gastric cancer, suggested that patients with age 70 years or older had significantly more total complications after gastrectomy for gastric cancer compared to younger patients, also suggesting that older age was an independent risk factor. A Korean study (n = 719) suggested that age 50 years or older was an independent risk factor predicting postoperative complications after gastrectomy for gastric cancer [19]. In this present study in adjusted analysis with confounding variables, major complications were less common with patients at age 70 years or older (OR 0.758; 95 % CI 0.575–0.999), compared to patients with age under 70 years. However, in the ECGG upper-level categories in this present study patients with age 70 years or older had significantly more cardiac complications and less infectious complications after the adjustment of confounding variables compared to patients with age under 70 years. In the other ECGG upper-level categories or in total complications there was no significant difference, but anastomotic complications were significantly less common with older patients in adjusted analysis. In addition to that, in this present study 90-day reoperations were significantly less common in patients with age 70 years or older. Therefore these results together might indicate that the patients over 70 years selected to surgery were more fit or healthy and thus less prone to

complications in ways not measurable by the variables selected. They also had less lymph nodes removed, suggesting that older patients had less invasive surgery than the younger age group. Another possibility is that the higher number of comorbidities and higher ASA-class resulted in over-adjustment making the patients with higher age appear less prone to major complications in the adjusted analysis. Furthermore, 90-day mortality was higher in older patients, supporting this hypothesis. Taken together, even though previous studies have suggested that age could be an independent risk factor predicting postoperative complications, in this present study older age alone did not predict more total or major complications. However, patients with older age have typically more comorbidities and a higher ASA-class, and in this present study comorbidity of 3 or more was independent risk factor for total postoperative complications, and ASA-class 4–5 for both total and major postoperative complications, possibly indicating that comorbidities are more important for comorbidities than numeric age.

The main strength of this present study was its population-based nationwide design that reduces selection bias, in addition to the large size of the cohort (n = 1993). Another strength was using a standardized classification for complications, the ECGG classification and the Clavien-Dindo classification, enabling future comparisons with other studies. In multivariable adjusted analysis the other significant confounding factors, in this present study the other risk factors, were taken into account in the analysis. However, there are also weaknesses. Since this present study was a retrospective study, it is still possible that some complications may have been missed during the review of patient charts, and also patient record information might have been incomplete. Although, the incidence of total complications and the proportions in different ECGG upper-level categories were in line with previous studies using the ECGG classification in reporting outcomes after gastrectomy for gastric cancer, reducing this concern [5,6,20]. Also, the lack of long-term outcomes in this present study focusing more on the short-term postoperative outcomes, and also lack of frailty or performance indicators could be considered a weakness. A possible weakness could be that at the time of this present study, most patients underwent an open gastrectomy, whereas today many gastric cancer patients have a laparoscopic or robotic assisted gastrectomy, and the results may not be fully generalizable to minimally invasive surgery. However, randomized trials suggest no

difference in postoperative complications comparing laparoscopic and open gastrectomy [21], although a few studies have suggested that the surgical outcomes could differ from one another [22].

To this date, this present study is the first study on this topic done in a population-based setting and using a standardized and comprehensive classification to categorize postoperative complications when assessing their risk factors. Using a standardized classification to categorize the complications when evaluating their risk factors provides a standpoint for comparison in future research. Identifying the most important risk factors for postoperative morbidity and mortality in gastric cancer enables to improve the postoperative outcomes, which results in enhanced prognosis and quality of life in addition to shorter hospital stay with reduced costs.

In conclusion, the present study suggests that higher ASA-class, and tumor stage are risk factors for major postoperative complications after gastrectomy for gastric cancer, while age 70 years or older and distal tumor location seem to be protective factors.

CRediT authorship contribution statement

Emilia Putila: Conceptualization, Methodology, Data Collection, Investigation, Writing – original draft, Writing – review & editing. **Olli Helminen:** Conceptualization, Methodology, Data Collection, Investigation, Writing – review & editing, Supervision. **Joonas H. Kauppila:** Conceptualization, Methodology, Data Collection, Data curation, Formal analysis, Investigation, Resources, Writing – review & editing, Supervision, Project administration, Funding acquisition. All Authors: Methodology, Data Collection, Investigation, Writing - review and editing.

Ethical approval

This study has ethical approval from the Ethical committee in Northern Ostrobothnia (Pohjois-Pohjamaan Sairaanhoidopiiriin Eettinen Toimikunta) (EETMK 115/2016).

Data availability statement

The data can be shared for research purposes upon request by contacting the Chief Investigator, Professor Joonas Kauppila, but may be restricted by and require complimentary permissions from the ethical committee and relevant original data holders.

Declaration of competing interest

Declaration of interest: none. This study or analysis plan have not been pre-registered. Funding of this study is presented below in the “Acknowledgements” section. The funders had no role in the design, analysis, interpretation, or writing of the study, nor in the decision to submit the manuscript for publication.

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Appendix A. Supplementary data

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