Impact of infectious complications after gastrectomy on non-gastric cancer-related deaths

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Abstract. Infectious complications (ICs) have been reported as major causes of postoperative mortality in patients with cancer. However, to the best of our knowledge, the impact of ICs after gastrectomy on non-gastric cancer-related deaths (NGCDs) remains unexplored. The present study aimed to identify the impact of ICs after gastrectomy on NGCDs. A retrospective analysis of 712 patients with gastric cancer who underwent curative gastrectomy was conducted. The participants were categorized into IC and non-IC groups based on the incidence of postoperative IC. Clinicopathological factors and non-gastric cancer-related survival (NGCS) rates were compared between groups. Further NGCD and associated risk factor analyses were performed in a background factor-adjusted cohort using multivariate analysis. Among the 712 patients, 112 developed ICs (Clavien-Dindo classification grade ≥II). In the entire cohort, the IC group had a significantly worse 5-year cumulative incidence of NGCD (17.8 vs. 10.6%; Gray's P=0.021) compared with the non-IC group. Although a number of clinicopathological factors differed between the groups, including patient background, operative factors and tumor factors, the risk factors for NGCD identified in the multivariate analysis were older age, low prognostic nutritional index, low skeletal muscle index and Charlson comorbidity index ≥1, excluding IC incidents. The IC group exhibited more background factors contributing to NGCDs, suggesting a potential increase in NGCD regardless of IC incidence.

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Introduction

Gastric cancer is the fifth most prevalent malignancy worldwide, with a high mortality rate, making it the third most common cause of cancer-related deaths (1). Despite surgery being a curative treatment for gastric cancer, postoperative infectious complications (ICs), including intra-abdominal complications such as anastomotic leakage, pancreatic fistulas, and intra-abdominal abscesses, as well as distant infections such as pneumonia, affect 9-26% of patients following gastrectomies (2,3). Postoperative ICs are crucial for determining short-term prognoses and have been reported as a major cause of postoperative mortality based on a nationwide Japanese database analysis (4).

Furthermore, postoperative ICs have been reported to negatively impact long-term prognoses in various carcinomas, including colorectal, esophageal, and liver cancers (5-7). Regarding the impact of ICs on long-term prognoses after gastrectomy, Tokunaga *et al* (8) reported that the 5-year overall survival (OS) and relapse-free survival (RFS) rates were better in the non-IC group than in the IC group among patients with pathological stage II and III malignancies. Kubota *et al* (9) reported that the cumulative incidence of disease-specific mortality was significantly worse in patients with ICs. Their clinical data suggest that the primary mechanism underlying poor long-term prognoses in patients with ICs is an increase in cancer recurrence with IC onset. Molecular and biological evidence supports a link between ICs and cancer recurrence. Xia *et al* (10) highlighted the role of neutrophil extracellular traps, which are deoxyribonucleic acid meshes released by neutrophils in response to infections, in promoting gastric cancer cell proliferation, invasion, migration, and epithelial-mesenchymal transition via transforming growth factor-β signaling.

However, the relationship between ICs and OS in patients with gastric cancer remains unclear. Despite reports by Hayashi *et al* (11) and others (12) indicating poor survival in patients with ICs, even in stage I gastric cancer after curative resections, the underlying causes remain unclear. The challenge lies in elucidating the poor OS in patients with stage I gastric cancer, which is characterized by a low recurrence rate solely

based on the recurrence of gastric cancer. This suggests that poor OS in patients with stage I cancer and ICs may indicate higher rates of non-gastric cancer-related deaths (NGCDs). Stage I cases account for 70% of all cases of curative resection of gastric cancer in Japan (13), and it is an important issue to clarify the risk of NGCD, which is the main cause of death after gastrectomy with stage I gastric cancer. However, the impact of ICs after gastrectomy on NGCDs remains unknown, as no existing reports address this aspect.

This study aimed to retrospectively examine the impact of ICs on NGCDs following gastrectomy.

Materials and methods

Patients. This single-center retrospective study utilized a database of 805 consecutive patients with gastric cancer who underwent radical gastrectomy at Yamaguchi University Hospital between 2006 and 2020. Patients with stage IV gastric cancer (n=78), gastroesophageal junction cancer (n=9), or remnant gastric cancer (n=6) were excluded. No mortality or recurrence occurred within 30 days postoperatively. All participants provided written informed consent. The study was conducted in accordance with the Declaration of Helsinki's ethical principles for medical research involving human participants and was approved by the Institutional Ethics Review Board of Yamaguchi University (H28-182).

Definition of ICs. ICs were defined as postoperative systemic inflammation resulting from infectious causes, encompassing i) anastomotic leakage, diagnosed via radiographic evidence of water-soluble contrast medium extravasation from the lumen; ii) abdominal abscess formation, identified by pus accumulation in the abdominal cavity observed on computed tomography (CT); iii) pancreatic fistula, diagnosed by drainage amylase levels exceeding three times the serum level, irrespective of drainage volumes; iv) pneumonia, diagnosed based on CT images and sputum cultures; v) urinary tract infections, diagnosed through urine cultures; and vi) central venous catheter infections, diagnosed using positive blood cultures. The severity of ICs was graded from 0 to V based on the Clavien-Dindo (CD) classification. Patients with grade II or higher ICs during hospitalization and within 30 days postoperatively constituted the IC group, whereas those with grade I or lower ICs formed the non-IC group. A detailed breakdown of NGCD is provided in Table I.

Clinical data. Preoperative patient characteristics, including age, sex, comorbidities [Charlson comorbidity index (CCI)], American Society of Anesthesiologists physical status (ASA-PS), and modified frailty index (mFI) were obtained from medical records. Body mass index (BMI) was calculated as the weight (kg) divided by the height-squared (m^2). Laboratory-related parameters were assessed within 2 weeks preoperatively, and the prognostic nutritional index (PNI) was calculated as follows: PNI=serum albumin level (g/l) + 0.005 x peripheral blood total lymphocyte count (per mm^3).

Sarcopenia was evaluated using the skeletal muscle index (SMI). All patients underwent preoperative CT within 4 weeks. As outlined in previous studies, SMI was measured from CT images using fat rate software (AZE Virtual Place, Aze Ltd., Tokyo, Japan). SMI, calculated as the total area of the abdominal, psoas major, and paraspinal muscles, was calculated using an axial slice at the height of the third lumbar vertebra. Muscle area was normalized to height in square meters (m^2) and reported as lumbar SMI (cm^2/m^2) (14). The method of calculating SMI from skeletal muscle cross-sectional area at the L3 level using CT does not require dedicated software like DXA or BIA, as studies involving cancer follow-up routinely perform CT examinations and can calculate SMI retrospectively. This measurement method is widely used today to examine prognostic factors for gastric and non-gastric cancers (15-17) because of its accuracy, reproducibility, and objectivity. Sarcopenia was defined as an SMI <44.84 cm^2/m^2 for males and <35.81 cm^2/m^2 for females when assessing NGCDs, derived using the time-dependent receiver operating characteristic (ROC) curve for NGCD in this study.

Surgical procedure. The choice between total gastrectomy (TG) and partial gastrectomy, encompassing distal gastrectomy (DG) and proximal gastrectomy (PG), was guided by tumor localization. D2 dissection was typically performed for advanced cancers, whereas D1+ dissection is employed for early-stage cancers. If preoperative CT scans showed invasion of other organs or BurkyN2 lymph node metastasis, surgery was performed after neoadjuvant chemotherapy.

For DG, reconstruction involved options such as Billroth I, Billroth II, or Roux-en-Y, whereas PG reconstruction used a double-tract approach. Multiple organs, including the spleen, gallbladder, pancreas, and transverse colon, were simultaneously resected. The histological type was categorized as either differentiated or undifferentiated, with staging according to the Third English Edition of the Japanese Classification of Gastric Carcinoma.

Follow-up. Routine follow-up was conducted following the Fourth Edition of the Guidelines (18) for the Treatment of Gastric Cancer. Patients diagnosed with pathological stage II or III gastric cancer received postoperative adjuvant therapy with S-1 alone or in combination with taxane or platinum for 1 year. Follow-up data were collected from the database and updated on January 1, 2023. The median follow-up duration was 60 months (range: 1.0-60.0). OS was defined as the time from surgery to death from any cause or the final follow-up within 5 years. Cancer-specific survival (CSS) was defined as the duration from surgery to death caused by gastric cancer, with deaths from other diseases considered censored. Non-gastric cancer-related survival (NGCS) was defined as the duration from surgery to death caused by a condition unrelated to gastric cancer, with deaths due to gastric cancer treated as censored.

Statistical analysis. An ROC curve analysis using the time-dependent ROC curve for NGCDs in the presence of censored data with a competing risk (i.e., gastric cancer-related deaths) was used to determine cutoff values based on the point closest to the (0, 1) criterion for age, BMI, ASA-PS score, CCI, mFI, PNI, operation time, and blood loss over a 5-year period. Group differences were evaluated using the chi-squared test or the Fisher's exact test for categorical variables. Survival curves were estimated using the Kaplan-Meier method and cumulative

Table I. Details of postoperative complications in older patients.

Type of complication	All grades, n	Grade			
		Grade II, n	Grade III, n	Grade IV, n	Grade V, n
Infectious complications	112	65	44	3	0
Anastomotic leakage	35	16	18	1	0
Pneumonia	24	17	5	2	0
Abdominal abscess	23	13	10	0	0
Pancreatic fistula	18	10	8	0	0
Urinary tract infections	3	3	0	0	0
Retrograde infection of abdominal drain	3	1	2	0	0
Enteritis	2	2	0	0	0
Perforation of the digestive tube	1	0	1	0	0
Vascular catheter infection	1	1	0	0	0
Splenic infarction	1	1	0	0	0
Pancreatitis	1	1	0	0	0

incidence function, and they were analyzed using the log-rank and Gray's tests. The cause-specific Cox (CSC) proportional hazards regression model for competing risks was used to estimate hazard ratios (HRs) and determine the relationship between NGCDs and various characteristics. Variables were included in the multivariate CSC model when a P-value of <0.05 was observed in the univariate CSC model. Statistical analyses were performed using JMP Pro 16 (SAS Institute Inc., Cary, NC, USA) and R (R Core Team, https://www.R-project.org/, Vienna, Austria). The time-dependent ROC curve analysis, estimation of the cumulative incidence function and Gray's test, and CSC proportional hazards regression model were conducted using the timeROC::SeSpPPVNPV/timeROC, cmprsk::cuminc, and riskRegression::CSC functions, respectively. A P-value of <0.05 was considered statistically significant.

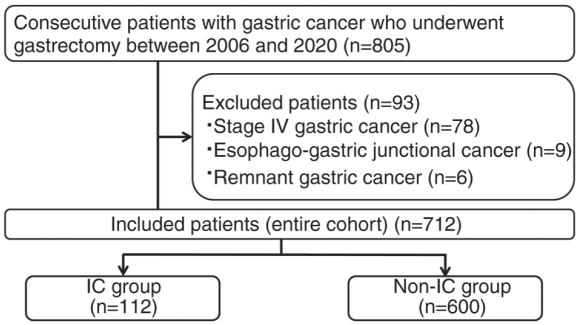

Figure 1. Consolidated Standards of Reporting Trials diagram illustrating the inclusion of patients with gastric cancer in the present study. A total of 712 patients were included. IC, infectious complication.

Results

Patient characteristics. This study included 712 patients, as shown in Fig. 1. Among them, 112 (15.7%) patients exhibited systemic ICs of CD grade ≥II, forming the IC group. The remaining 600 (84.3%) patients without ICs constituted the non-IC group. The mean patient age was 67.7 years (range: 27-94), and 70.7% of the patients were male. Seventy-eight percent of the patients had an ASA-PS of 2 or more. In the CCI and mFI, 49.0 and 63.5% of the patients had a comorbidity with a score of 1 or more, respectively. The median PNI was 49.63. The median SMI was 47.11 cm^2/m^2 for males and 37.77 cm^2/m^2 for females. The pathological stages were I, II, and III in 68.7, 16.2, and 15.2% of the patients, respectively. The gastrectomy patterns were DG, TG, and PG in 74.2, 24.3, and 1.5% of the patients, respectively, with laparoscopy in 72.6% and laparotomy in 27.4% of the patients. Further details of the clinicopathological findings are presented in Table II.

Compared to the non-IC group, the IC group demonstrated characteristics such as older age (P=0.005), lower PNI (P=0.010), a higher proportion of males (P<0.001), more frequent laparotomies (P<0.001), TGs (P<0.001), D2 lymphadenectomies (P<0.001), resections of another organ (P=0.012), longer surgery durations (P<0.001), greater blood loss (P<0.001), more advanced cancers (P<0.001), and more frequent postoperative adjuvant therapy (P<0.001), as shown in Table III.

Long-term outcomes. In the entire cohort, the IC group had significantly worse 5-year OS than the non-IC group, as shown in Fig. S1A (70.5% vs. 81.0%, P=0.005), but there was no statistically significant difference in CSS, as shown in Fig. S1B (87.2% vs. 91.2%, P=0.153). In the subgroup analysis of stage I gastric cancer, the IC group also had significantly worse 5-year OS than the non-IC group, as shown in Fig. S1C (81.4% vs. 90.4%, P=0.017), but there was no statistically significant difference in CSS, as shown in Fig. S1D (100% vs. 98.6%, P=0.448).

Regarding deaths from other causes, in the entire cohort, the IC group demonstrated a significantly worse 5-year cumulative incidence of NGCD (17.8% vs. 10.6%, Gray's P=0.021) compared to the non-IC group (Fig. 2A). In the subgroup analysis of stage I gastric cancer, The IC group demonstrated

Table II. Clinicopathological findings of patients in the entire cohort.

Characteristics	Value
Mean age ± SD, years (min-max)	67.74±12.02 (27-94)
Sex, n (%)	
Male	503 (70.65)
Female	209 (29.35)
Mean BMI ± SD, kg/m^2 (min-max)	22.48±3.26 (14.24-36.82)
ASA-PS, n (%)	
1	157 (22.05)
2	457 (64.19)
3	98 (13.76)
Charlson comorbidity index, n (%)	
0	363 (50.98)
1	171 (24.02)
2	86 (12.08)
>3	92 (12.92)
Modified frailty index, n (%)	
0	260 (36.52)
1	268 (37.64)
2	127 (17.84)
>3	57 (8.00)
Mean SMI ± SD, cm^2/m^2 (min-max)	
Male	47.11±7.82 (24.56-77.59)
Female	37.77±5.27 (27.49-54.92)
Mean PNI ± SD (min-max)	49.63±6.16 (27.33-76.21)
Surgical approach, n (%)	
Open	195 (27.39)
Laparoscopy	517 (72.61)
Gastrectomy, n (%)	
Distal gastrectomy	528 (74.16)
Total gastrectomy	173 (24.30)
Proximal gastrectomy	11 (1.54)
Lymphadenectomy, n (%)	
<D2	450 (63.20)
≥D2	262 (36.80)
Resection of other organs, n (%)	
No	592 (83.15)
Yes	120 (16.85)
Perioperative blood transfusion, n (%)	
No	637 (89.47)
Yes	75 (10.53)
Mean operation time ± SD, min (min-max)	329.88±86.15 (140-841)
Mean blood loss ± SD, ml (min-max)	269.57±351.20 (0-2310)
Infectious complication, n (%)	
No	600 (15.73)
Ye	112 (84.27)
Histological type, n (%)	
Differentiated	418 (58.71)
Undifferentiated	294 (41.29)
Pathological stage, n (%)	
I	489 (68.68)
II	115 (16.15)
III	108 (15.17)
Neoadjuvant chemotherapy, n (%)	
No	703 (98.74)
Yes	9 (1.26)
Adjuvant chemotherapy, n (%)	
No	555 (77.95)
Yes	157 (22.05)

ASA-PS, American Society of Anesthesiologists physical status; max, maximum; min, minimum; PNI, prognostic nutritional index; SMI, skeletal muscle mass index.

a significantly worse 5-year cumulative incidence of NGCD (18.6% vs. 8.3%, Gray's P=0.0065) compared to the non-IC group (Fig. 2B).

Overall, within 5 years, there were 59 deaths from gastric cancer and 76 deaths from non-gastric cancer-related causes. Details of the NGCDs were known for 59 patients: pneumonia in 19 patients, cardiovascular disease in 11 patients, other carcinomas in 14 patients, cerebrovascular disease in 5 patients, senility in 3 patients, suicide in 2 patients, gastrointestinal hemorrhage in 1 patient, renal failure in 1 patient, liver disease in 1 patient, sepsis in 1 patient, and trauma in 1 patient. Pneumonia, which was the most common NGCD, accounted for 25% (19/76) of NGCDs. The risk factors for death from pneumonia were age and sarcopenia (Table SI) in univariate and multivariate analyses.

Univariate and multivariate analysis of risk factors for NGCD. Univariate analysis revealed that older age (P<0.001), high BMI (P=0.015), ASA-PS scores ≥2 (P<0.001), CCIs ≥1 (P<0.001), mFIs ≥1 (P<0.001), lower PNIs (P<0.001), sarcopenia (P<0.001), differentiated type (P=0.049), perioperative blood transfusions (P<0.001), neoadjuvant chemotherapy (P=0.038), and IC (P=0.014) were significantly associated with NGCS. Multivariate analysis incorporating predictive biomarkers with significant values from the univariate analysis confirmed that older age [HR: 3.609, 95% confidence interval (CI): 2.358-5.526, P<0.001], lower PNIs (HR: 2.250, 95% CI: 1.506-3.360, P<0.001), CCIs ≥1 (HR: 2.030, 95% CI:

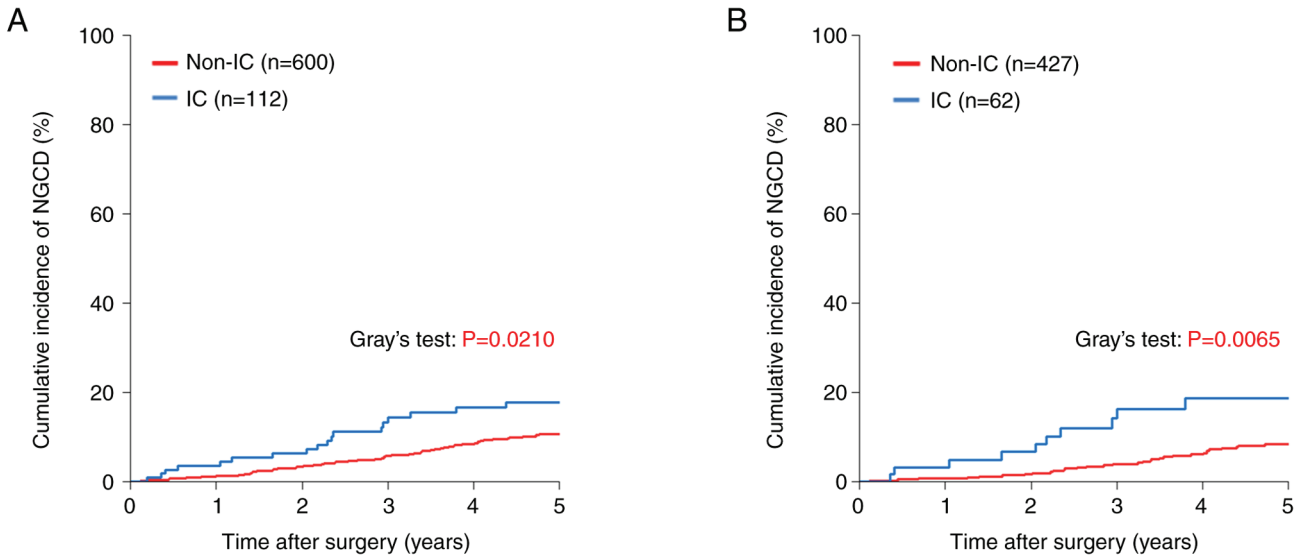

Figure 2. Five-year cumulative incidence of NGCD in the infectious complication and non-IC groups. (A) In the entire cohort, the IC group exhibited a significantly worse 5-year cumulative incidence of NGCD (17.8 vs. 10.6%; Gray's P=0.021) compared with the non-IC group. (B) In the subgroup analysis of stage I gastric cancer, the IC group exhibited a significantly worse 5-year cumulative incidence of NGCD (18.6 vs. 8.3%; Gray's P=0.0065) than the non-IC group. IC, infectious complication; NGCD, non-gastric cancer-related death.

1.295-3.181, P=0.002), and sarcopenia (HR: 1.778, 95% CI: 1.196-2.641, P=0.004) were independent risk factors for NGCS, while IC was not (HR: 1.359, 95% CI: 0.829-2.228, P=0.224) (Table IV).

Discussion

This study examined the correlation between ICs and NGCD after surgery in patients with resectable gastric cancer. The IC group demonstrated a significantly worse 5-year cumulative incidence of NGCD (17.8% vs. 10.6%, Gray's P=0.021) compared to the non-IC group (Fig. 2A). However, owing to substantial variations in background factors between the groups, determining whether ICs directly affected NGCS was unfeasible. IC was identified as a risk factor for NGCD in univariate analysis but not in multivariate analysis. These results suggest that the incidence of IC itself did not directly contribute to an increased NGCD risk. Instead, the higher NGCD rates in the IC group compared with those in the non-IC group could be attributed to background factors that elevated the NGCD risk in the IC group. To the best of our knowledge, this is the first study to examine the relationship between ICs and NGCD.

In recent years, the global rise in the aging population has led to an increasing proportion of older patients undergoing gastric cancer surgery, drawing attention to NGCD after curative resection (19,20). In Japan, >40% of patients undergoing gastrectomies for gastric cancer are aged ≥75 years (21). Hashimoto *et al* (22) reported that 70% of deaths within 5 years post-gastrectomy among those aged ≥75 years were attributed to other causes. The cohort in this study comprised 32.0% of patients aged ≥75 years, with 56.3% of deaths within 5 years attributed to other causes, whereas 43.7% were attributed to the current disease (data not shown). Nunobe *et al* (23) reported an increasing proportion of deaths from other causes post-gastrectomy with an increasing number of patients ages. With surgeries in older patients becoming more prevalent, attention to NGCD warrants an increase. Previous reports have associated ICs after radical gastric cancer resection with factors such as poor OS and RFS (8,24).

The mechanism underlying poor long-term prognosis in patients with ICs has primarily centered on gastric cancer-related deaths. However, the impact of ICs on NGCDs remains poorly understood. By focusing on NGCS, this study compared survival outcomes between the IC and non-IC groups. Although the results showed no significant differences in CSS, both OS and NGCS were worse in the IC group than in the non-IC group (Figs. 2A, and S1A and B). Additionally, when the survival analysis was limited to patients with stage I gastric cancer, no difference in CSS was observed. Nevertheless, OS and NGCS were significantly worse in the IC group (Figs. 2B, and S1C and D). These findings suggest that the poorer OS in patients with stage I gastric cancer in the IC group may be attributed to an increase in NGCD rather than to cancer recurrence. Our multivariate analysis of risk factors for OS in the stage I subgroup showed that older age, male, low PNI, high CCI, sarcopenia, and laparotomy were independent risk factors (Table SII).

This study initially examined the backgrounds of patients with and without ICs to understand the impact of IC development on the increase in NGCDs. The results revealed that patients with ICs were older, predominantly male, and exhibited significantly different preoperative factors, such as lower PNIs, compared with those without ICs (Table III). Hashimoto *et al* (22) reported low PNIs and multiple comorbidities, Kuwada *et al* (25) reported comorbidities and sarcopenia, and Iida *et al* (26) reported that male sex, low SMIs, and high CCIs were risk factors for NGCD after gastrectomy. Numerous patients with ICs in this study exhibited these risk factors for NGCDs, such as older age and low PNIs, suggesting that their patient backgrounds may have influenced the increased rate of NGCDs.

To investigate whether the onset of ICs increased NGCD incidence or whether patients with a high NGCD risk developed ICs,

Table III. Comparison of clinicopathological characteristics between the IC and non-IC groups in the entire cohort (n=712).

Characteristics	IC group (n=112)	Non-IC group (n=600)	P-value
Age, years			0.005
<74	58 (51.79)	395 (65.83)	
≥74	54 (48.21)	205 (34.17)	
Sex			<0.001
Male	98 (87.50)	405 (67.50)	
Female	14 (12.50)	195 (32.50)	
BMI, kg/m^2			0.064
<21.08	30 (26.79)	215 (35.83)	
≥21.08	82 (73.21)	385 (64.17)	
ASA-PS score			0.359
<2	21 (18.75)	136 (22.67)	
≥2	91 (81.25)	464 (77.33)	
CCI			0.294
<1	52 (46.43)	311 (51.83)	
≥1	60 (53.57)	289 (48.17)	
mFI			0.207
<1	35 (31.25)	225 (37.50)	
≥1	77 (68.75)	375 (62.50)	
Sarcopenia			0.827
No	66 (58.93)	356 (60.03)	
Yes	46 (41.07)	237 (39.97)	
PNI			0.010
<47.02	44 (39.29)	163 (27.17)	
≥47.02	68 (60.71)	437 (72.83)	
Surgical approach			<0.001
Open	45 (40.18)	150 (25.00)	
Laparoscopic	67 (59.82)	450 (75.00)	
Gastrectomy			<0.001
Partial	68 (60.71)	471 (78.50)	
Total	44 (39.29)	129 (21.50)	
Lymphadenectomy			<0.001
<D2	54 (48.21)	396 (66.00)	
≥D2	58 (51.79)	204 (34.00)	
Resection of other organs			0.012
No	84 (75.00)	508 (84.67)	
Yes	28 (25.00)	92 (15.33)	
Perioperative blood transfusion			0.081
No	95 (84.82)	542 (90.33)	
Yes	17 (15.18)	58 (9.67)	
Operation time, min			<0.001
<356	51 (45.54)	434 (72.33)	
≥356	61 (54.46)	166 (27.67)	
Blood loss, ml			<0.001
<131	36 (32.14)	304 (50.67)	
≥131	76 (67.86)	296 (49.33)	
Histological type			0.375
Differentiated	70 (62.50)	348 (58.00)	
Undifferentiated	42 (37.50)	252 (42.00)	

Table III. Continued.

Characteristics	IC group (n=112)	Non-IC group (n=600)	P-value
Pathological stage			<0.001
I	62 (55.36)	427 (71.17)	
II/III	50 (44.64)	173 (28.83)	
Neoadjuvant chemotherapy			0.639
No	110 (98.21)	593 (98.83)	
Yes	2 (1.79)	7 (1.17)	
Adjuvant chemotherapy			<0.001
No	72 (64.29)	483 (80.50)	
Yes	40 (35.71)	117 (19.50)	

ASA-PS, American Society of Anesthesiologists physical status; CCI, Charlson comorbidity index; IC, infectious complication; mFI, modified frailty index; PNI, prognostic nutritional index.

Table IV. Univariate and multivariate analysis of risk factors for non-gastric cancer-related deaths in the entire cohort.

		Univariate analysis				Multivariate analysis			
			95% CI				95% CI		
Factor	Cutoff	HR	Lower	Upper	P-value	HR	Lower	Upper	P-value
Age, years	74	9.701	5.426	17.345	<0.001	3.609	2.358	5.526	<0.001
Sex	Male	1.613	0.929	2.800	0.089				
BMI, kg/m^2	21.08	0.571	0.364	0.896	0.015	0.808	0.542	1.204	0.294
ASA-PS score	2	4.513	2.818	7.227	<0.001	1.645	0.691	3.913	0.261
CCI	1	3.819	2.250	6.482	<0.001	2.030	1.295	3.181	0.002
mFI	1	3.066	1.688	5.572	<0.001	1.184	0.687	2.038	0.543
Sarcopenia	(+)	3.251	2.023	5.223	<0.001	1.778	1.196	2.641	0.004
PNI	47.02	7.084	4.339	11.567	<0.001	2.250	1.506	3.360	<0.001
Surgical approach	Open	2.582	1.646	4.051	<0.001	1.534	0.936	2.514	0.089
Gastrectomy	TG	1.563	0.968	2.522	0.068				
Lymphadenectomy	≥D2	0.887	0.550	1.432	0.625				
Resection of other organs	(+)	0.921	0.497	1.705	0.792				
Perioperative blood transfusion	(+)	3.025	1.763	5.193	<0.001	1.357	0.818	2.249	0.237
Operation time, min	356	1.401	0.884	2.219	0.151				
Blood loss, ml	131	1.389	0.877	2.200	0.162				
Histological type	Undifferentiated	0.595	0.365	0.971	0.038	0.835	0.549	1.269	0.399
Pathological stage	II/III	2.176	1.383	3.423	<0.001	0.742	0.441	1.247	0.260
Neoadjuvant chemotherapy	(+)	4.122	1.005	16.904	0.049	2.720	0.619	11.952	0.185
Adjuvant chemotherapy	(+)	0.732	0.395	1.357	0.322				
IC	(+)	1.943	1.145	3.299	0.014	1.359	0.829	2.228	0.224

ASA-PS, American Society of Anesthesiologists physical status; CCI, Charlson comorbidity index; HR, hazard ratio; IC, infectious complication; mFI, modified frailty index; PNI, prognostic nutritional index; TG, total gastrectomy.

we conducted a CSC proportional hazards regression model for a competing risk in the entire cohort. The risk factors for NGCD identified by multivariate analysis were older age, low PNIs, low SMIs, and CCIs ≥1, excluding incidental ICs (Table IV). This suggests that ICs did not independently affect NGCS and that the higher rate of NGCDs observed among patients who developed ICs might be attributed to the existing high risk of NGCD.

Although a few reports have assessed the impact of ICs on survival using PSM, Pang *et al* (12) showed that OS was poorer in patients with complications after radical gastrectomy than in those without complications in a model using PSM adjusted for background factors.

The study by Pang *et al* (12) involved a cohort in which >70% of patients had advanced cancer and <40% were aged >65 years. Their findings indicated higher mortality rates from gastric cancer and lower mortality rates from other causes, implying a potential association between IC development and increased cancer recurrence, thereby affecting OS, as previously reported. Conversely, cohorts with a significant proportion of older patients and those with stage I cancer, such as the cohort in this study, typically experienced more deaths from other diseases.

This study had some limitations. First, this was a single-center retrospective study, and validation in a multicenter study with a larger sample size is warranted. Second, residual unmeasured confounding factors may be present despite efforts to minimize bias through multivariate analysis. Additionally, the follow-up duration for some patients was <5 years, potentially influencing the observed higher survival rates.

In conclusion, although postoperative ICs did not directly increase NGCDs, they indirectly contributed to such outcomes through factors associated with NGCDs.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

CN and MI conceived the study. CN and MI confirm the authenticity of all the raw data. CN wrote the manuscript. MI, MN and YW contributed to data collection. YS, YT, ST, HT and HN aided in the interpretation of the results. YN performed the analytic calculations. HN supervised this project. All authors provided critical feedback, and helped shape the research, analysis and manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Yamaguchi University Hospital (approval no. 2022-032; Ube, Japan). Written informed consent was obtained from the patients.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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