Risk factors for infectious complications after gastrectomy in older patients

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Received January 20, 2024; Accepted April 29, 2024

DOI: 10.3892/etm.2024.12608

Abstract. The present study aimed to identify preoperative and perioperative risk factors for postoperative infectious complications in older patients with gastric cancer. The present retrospective study included 504 patients with gastric cancer aged >65 years who underwent radical gastrectomy. After determining the cutoff values for various perioperative factors in the receiver operating characteristic curve analysis, preoperative and perioperative risk factors for the development of infectious complications after gastrectomy were examined using logistic regression analysis. Of the 504 patients who underwent gastrectomy, 95 (18.8%) developed infectious complications of grade II-V based on the Clavien-Dindo classification. In an analysis restricted to preoperative factors, male sex, low prognostic nutritional index, high visceral fat area and total gastrectomy were independent risk factors for infectious complications after gastrectomy. Among all perioperative factors, a low prognostic nutritional index and long operative duration were identified as independent risk factors for infectious complications after gastrectomy. The patients were divided into five groups according to the number of positive preoperative risk factors for infectious complications, and the incidence of infectious complications differed among the five groups (0 factors, 6.7%; 1 factor, 10.4%; 2 factors, 18.9%; 3 factors, 27.8%; and 4 factors, 47.6%; P<0.001). Older patients with gastric cancer who have a number of preoperative risk factors require careful consideration of the indication for gastrectomy and a shorter operative time to reduce infectious complications.

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Key words: gastrectomy, gastric cancer, infectious complication, older person, risk factors

Introduction

Aging societies are progressing rapidly worldwide, and the proportion of older people with cancer is increasing (1). In Japan, which has one of the most aged populations in the world, older patients aged >65 years account for >70% of gastrectomies performed on patients with gastric cancer (2). Postoperative complications have been reported to increase after gastrectomy in older patients because they often have more comorbidities and poorer physical and organ functions than younger patients (3).

Among the complications after gastrectomy for gastric cancer, infectious complications (ICs) are more likely to be severe and prolong the hospital stay of patients (4). The Japanese national database analysis reported that surgical site infections, such as an anastomotic leak, pancreatic fistula, and intraabdominal abscess, and remote infections, such as pneumonia and urinary tract infections, are closely associated with postoperative mortality in patients with gastric cancer, and that ICs, in general, require attention (5). When treating cancer in older persons, it is necessary to construct a treatment strategy considering short-term risks such as postoperative complications and the benefit of prolonged survival after surgery (6). Endoscopic treatment with expanded indications and surgery with reduced dissection have been recently reported for high-risk patients (7,8). Identifying high-risk patients for gastrectomy can be important in determining which patients should undergo reduced treatment. However, the risk of postoperative complications in older patients with gastric cancer has not been well documented, especially regarding risk factors for ICs.

This study aimed to examine the risk factors for postoperative ICs in patients with gastric cancer aged ≥65 years who underwent radical gastrectomy to determine whether only preoperative or all perioperative factors can be used to identify high-risk patients for ICs.

Materials and methods

Patients. This retrospective analysis involved 514 consecutive individuals aged over 65 years, pathologically confirmed with stage I-III primary gastric cancer, and who underwent curative gastrectomy at Yamaguchi University Medical Hospital in Yamaguchi, Japan, between January 2007 and December 2021. Ten participants were excluded from the retrospective analysis due to either the absence of preoperative computed tomography (CT; n=6) or the presence of simultaneous double cancer (n=4), resulting in a total of 504 included patients. Written informed consent was obtained from all participants, who agreed to provide blood and tissue samples for clinical examination and to be contacted during follow-up. The Institutional Review Board of Yamaguchi University Hospital approved this study (2022-032).

Perioperative parameters. All perioperative parameters were assessed and calculated following the methodology outlined in the authors' previous study (9). In summary, demographic information (age and gender), comorbidity data [modified frailty index (mFI) (10) and Charlson comorbidity index (CCI)], and performance status (PS) data were extracted from medical records. Body mass index (BMI) was the ratio of body weight (kg) to the square of height (m2). Preoperative laboratory assessments, including blood cell counts and serum albumin levels, were routinely conducted within a 2-week timeframe preceding surgery. The calculation of laboratory-related parameters was performed as follows: prognostic nutritional index (PNI)=serum albumin value (g/L)+0.005 x total lymphocyte count in peripheral blood (per mm3); neutrophil-to-lymphocyte ratio (NLR)=neutrophil count/lymphocyte count; and platelet-to-lymphocyte ratio (PLR)=platelet count/lymphocyte count.

Multidetector CT (MDCT) scans were conducted on all patients within 4 weeks prior to surgery. Body composition parameters, such as visceral fat area (VFA) and skeletal muscle area (SMA), were determined using MDCT and fat rate software (AZE Virtual Place, Aze Ltd. Tokyo, Japan), as outlined in a prior study (11). In brief, VFA was measured as the fat area at the umbilical level on preoperative MDCT. The SMA of the abdominal, psoas, and paraspinal muscle areas was measured using axial slices at the third lumbar vertebra level. The skeletal muscle index (SMI) was computed as SMA divided by height squared. Preoperative lymph node metastasis (N factor) was evaluated through preoperative CT, with metastatic nodes diagnosed as having a short-axis diameter >10 mm or round nodes with a short diameter of 5-9 mm. Histological types were categorized as differentiated and undifferentiated. The depth of tumor invasion (T factor), N factor, and stage were classified according to the Third English edition of the Japanese Classification of Gastric Carcinoma (12). Of the 504 patients, preoperative CRP values were not measured in 79 patients, so the category of preoperative CRP values has missing data for 79 cases.

Definitions of infectious and noninfectious complications. ICs were defined as postoperative complications in which infection by pathogens was suspected from culture, imaging, or blood test findings. The main IC definitions are as follows: anastomotic leakage (escape of a water-soluble contrast agent, administered endoluminally, as seen on radiography), abdominal abscess formation (collection of pus within the intraabdominal space, confirmed by radiographic evidence or drainage), pancreatic fistula (drainage of a measurable volume of fluid occurring on or after the third postoperative day, with an amylase content exceeding three times the serum amylase activity. This condition requires medical intervention, such as antibiotics or drainage.) (13), pneumonia (lung infection identified through radiographic evidence and sputum culture), urinary tract infections (infection of the urinary tract diagnosed by urinary culture), and incisional surgical site infection (infection of the superficial and deep incisional surgical site diagnosed through culture).

Noninfectious complications (non-ICs) were defined as postoperative complications in which the patient was suspected of not being infected with a pathogen. The severity of ICs or non-ICs was classified, according to the Clavien-Dindo (CD) classification (14), as grade 0-V, and patients with grade II or higher were defined as having ICs or non-ICs.

Surgical procedure. All patients underwent distal gastrectomy (DG), total gastrectomy (TG), or proximal gastrectomy (PG) with D1, D1+, or D2 lymphadenectomy, according to the Japanese guidelines. In principle, lymph node dissection adhered to the guidelines as a general practice; however, there were instances where the surgeon chose to undertake a more limited dissection based on the overall health condition of the patient. Consequently, this study aimed to assess whether the lymph node dissection performed was in line with established standards. Lymph node dissection carried out in accordance with the recommended guidelines was categorized as standard, while dissection falling below the prescribed range was termed reduced lymph node dissection. DG reconstruction involved the utilization of Billroth I, Billroth II, or Roux-en Y techniques, TG reconstruction employed Roux-en Y, and PG reconstruction utilized double tract reconstruction.

Statistical analysis. The optimal cutoff values for continuous variable parameters, such as age, PS, mFI, CCI, PNI, NLR, PLR, BMI, VFA, and SMI, were determined using receiver operating characteristic (ROC) curves. Categorical variables are presented as numbers (percentages), and continuous variables are presented as means ± standard error. Categorical variables were analyzed using the chi-squared or Fisher's exact tests, and continuous variables were analyzed using the unpaired Student's t-test or Mann-Whitney test. Multivariate analysis of the risk of developing infectious and noninfectious complications were performed using logistic regression, and the hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated. Statistical significance was set at P<0.05. The confidence intervals for 10-fold cross-validated area under the ROC curve (AUC) estimates were calculated by dividing the 503 observations randomly into 10 folds, stratifying by the event. We defined a function to fit a model on the training data and to generate predicted values for the observations in the validation fold, for a single iteration of the cross-validation procedure. Then we applied this function across all folds to generate predicted values for each validation fold (15). The 10-fold cross-validation algorithm was computed using the R statistical programming language (version 4.2.0). All statistical analyses except the 10-fold cross-validation were performed using SPSS version 25.0 (SPSS Corp., Armonk, NY, USA).

Table I. Details of postoperative complications in older patients.

Type of complication	All grades, n	Grade			
		II, n	III, n	IV, n	V, n
Infectious complications (total events)	108	60	40	8	0
Anastomotic leakage	29	12	16	1	0
Abdominal abscess	23	13	8	2	0
Pancreatic fistula	12	5	6	1	0
Pneumonia	26	17	7	2	0
Urinary tract infections	3	3	0	0	0
Incisional surgical site infection	3	2	1	0	0
Perforation of the digestive tube	2	0	1	1	0
Enteritis	2	2	0	0	0
Retrograde infection of abdominal drain	2	1	0	1	0
Vascular catheter infection	2	2	0	0	0
Splenic infarction	2	2	0	0	0
Infectious pleural effusion	1	0	1	0	0
Cholangitis	1	1	0	0	0
Non-infectious complications (total events)	104	87	15	1	1
Delirium	53	53	0	0	0
Delayed gastric emptying	12	12	0	0	0
Hemorrhage	10	4	4	1	1
Anastomotic hemorrhage	7	4	3	0	0
Intra-abdominal hemorrhage	2	0	1	1	0
Cerebral hemorrhage	1	0	0	0	1
Anastomotic stenosis	10	5	5	0	0
Ileus	7	4	3	0	0
Ascites	3	2	1	0	0
Arrhythmia	3	3	0	0	0
Pleural effusion	3	1	2	0	0
Neurogenic bladder	2	2	0	0	0
Dermatitis	1	1	0	0	0

Results

Postoperative complications. Of the total patients, 165 (32.7%) developed postoperative complications, of which 95 (18.8%) and 96 (19.0%) developed ICs and non-ICs, respectively. Twenty-six patients (5.2%) developed ICs and non-ICs. Serious grade ≥III complications of the CD classification were observed in 48 (50.5%) IC and 18 (18.8%) non-IC cases.

A total of 108 ICs occurred in the 95 patients. The most common ICs were anastomotic leakage (n=29), pneumonia (n=26), intraabdominal abscesses (n=23), and pancreatic fistulas (n=12). Intraabdominal ICs (anastomotic leakage, intraabdominal abscess, and pancreatic fistula) accounted for 59.2% of all ICs. In contrast, 104 non-ICs were observed in 96 patients. The most common non-ICs were delirium (n=53), delayed gastric emptying (n=12), hemorrhage (n=10), and anastomotic stenosis (n=10). Details of postoperative complications are shown in Table I.

Patient characteristics. The clinicopathological factors for all patients and a comparison of clinicopathological factors between patients with IC and those without IC are shown in Table II. The mean patient age was 74.8 (65-94) years, and 71.4% of the patients were male. Furthermore, 32.9% of patients had mFI scores ≥2, and 58.7% had comorbidities with CCI scores ≥1. The pathological stages were I, II, and III in 66.4, 15.8, and 17.6% of patients, respectively. The operative modes were DG, TG, and PG in 71.0, 24.8, and 4.2% of patients, respectively, with laparoscopy in 73.8% and laparotomy in 26.2%. Standard and reduced lymph node dissections were performed in 94.0 and 6.0% of the patients for guideline-based lymph node dissection.

Patients in the IC group were more likely to be male and had preoperative lymph node metastasis, TG, pathological T3/T4, pathological lymph node metastasis, pathological stage III, higher VFA, longer operation times, and excessive intraoperative blood loss than those in the non-IC group.

Diagnostic accuracy and cutoffs of perioperative parameters. ROC curve analysis was performed to determine the cutoff values and areas under the ROC curves (AUCs) of the perioperative factors for ICs and non-ICs. The AUCs and optimal cutoff values of each perioperative parameter for ICs

Table II. Comparison of clinicopathological factors between patients with and without ICs.

Characteristic	All patients (n=504)	IC group (n=95)	Without-IC group (n=409)	P-value
Age, years	74.8±6.3	75.3±5.7	74.7±6.4	0.337
Sex, n (%)				0.005[a]
Male	360 (71.4)	79 (83.2)	281 (68.7)	
Female	144 (28.6)	16 (16.8)	128 (31.3)	
PS, n (%)				0.241
0	431 (85.5)	78 (82.1)	353 (86.3)	
1	59 (11.7)	12 (12.6)	47 (11.5)	
≥2	14 (2.8)	5 (5.3)	9 (2.2)	
Modified frailty index, n (%)				0.674
0	117 (23.2)	21 (22.1)	96 (23.5)	
1	221 (43.8)	38 (40.0)	183 (44.7)	
2	111 (22.0)	23 (24.2)	88 (21.5)	
≥3	55 (10.9)	13 (13.7)	42 (10.3)	
Charlson comorbidity index, n (%)				0.072
0	208 (41.3)	37 (38.9)	171 (41.8)	
1	133 (26.4)	21 (22.1)	112 (27.4)	
2	76 (15.1)	12 (12.6)	64 (15.6)	
≥3	87 (17.3)	25 (26.3)	62 (15.2)	
Use of steroids, n (%)				0.523
Negative	488 (96.8)	91 (95.8)	397 (97.1)	
Positive	16 (3.2)	4 (4.2)	12 (2.9)	
Preoperative CRP, mg/dl	0.34±0.90	0.41±0.93	0.32±0.90	0.480
PNI	48.1±6.2	47.0±7.1	48.4±5.9	0.055
NLR	2.7±1.9	2.8±1.9	2.7±1.9	0.477
PLR	153.8±84.8	157.5±79.4	152.9±86.0	0.634
BMI, kg/m^2	22.4±3.3	23.2±3.4	22.2±3.2	0.007[a]
VFA, cm^2	130.2±65.5	151.6±73.1	125.2±62.7	<0.001[a]
SMI, cm^2/m^2	43.3±8.1	44.0±8.3	43.1±8.1	0.311
Preoperative T factor, n (%)				0.054
T1	309 (61.3)	50 (52.6)	259 (63.3)	
T≥2	195 (38.7)	45 (47.4)	150 (36.7)	
Preoperative N factor, n (%)				0.039[a]
N0	395 (78.4)	67 (70.5)	328 (80.2)	
N≥1	109 (21.6)	28 (29.5)	81 (19.8)	
Type of resection, n (%)				0.009[a]
Distal gastrectomy	358 (71.0)	54 (56.8)	304 (74.3)	
Proximal gastrectomy	21 (4.2)	7 (7.4)	14 (3.4)	
Total gastrectomy	125 (24.8)	34 (35.8)	91 (22.2)	
Approach, n (%)				0.065
Open	132 (26.2)	32 (33.7)	100 (24.4)	
Laparoscopy	372 (73.8)	63 (66.3)	309 (75.6)	
Extent of node dissection, n (%)				0.055
D1/D1+	319 (63.3)	52 (54.7)	267 (65.3)	
D2	185 (36.7)	43 (45.3)	142 (34.7)	
Node dissection according to guidelines, n (%)				0.426
Standard	474 (94.0)	91 (95.8)	383 (93.6)	
Reduced	30 (6.0)	4 (4.2)	26 (6.4)	

Table II. Continued.

Characteristic	All patients (n=504)	IC group (n=95)	Without-IC group (n=409)	P-value
Operative duration, min	328.7±89.9	366.2±98.4	320.0±471.1	<0.001[a]
Operative blood loss, ml	250.9±337.8	392.7±471.1	217.9±289.4	0.001[a]
Pathological stage, n (%)				0.003[a]
I	335 (66.5)	55 (57.9)	280 (68.5)	
II	80 (15.9)	12 (12.6)	68 (16.6)	
III	89 (17.7)	28 (29.5)	61 (14.9)	
Hospital stay, days	21.2±17.6	41.4±30.3	16.4±6.9	<0.001[a]

[a]P<0.05. Data are presented as the mean ± SD or number (%). IC, infectious complication; PS, performance status; CRP, C-reactive protein; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; BMI, body mass index; VFA, visceral fat area; SMI, skeletal muscle index ratio.

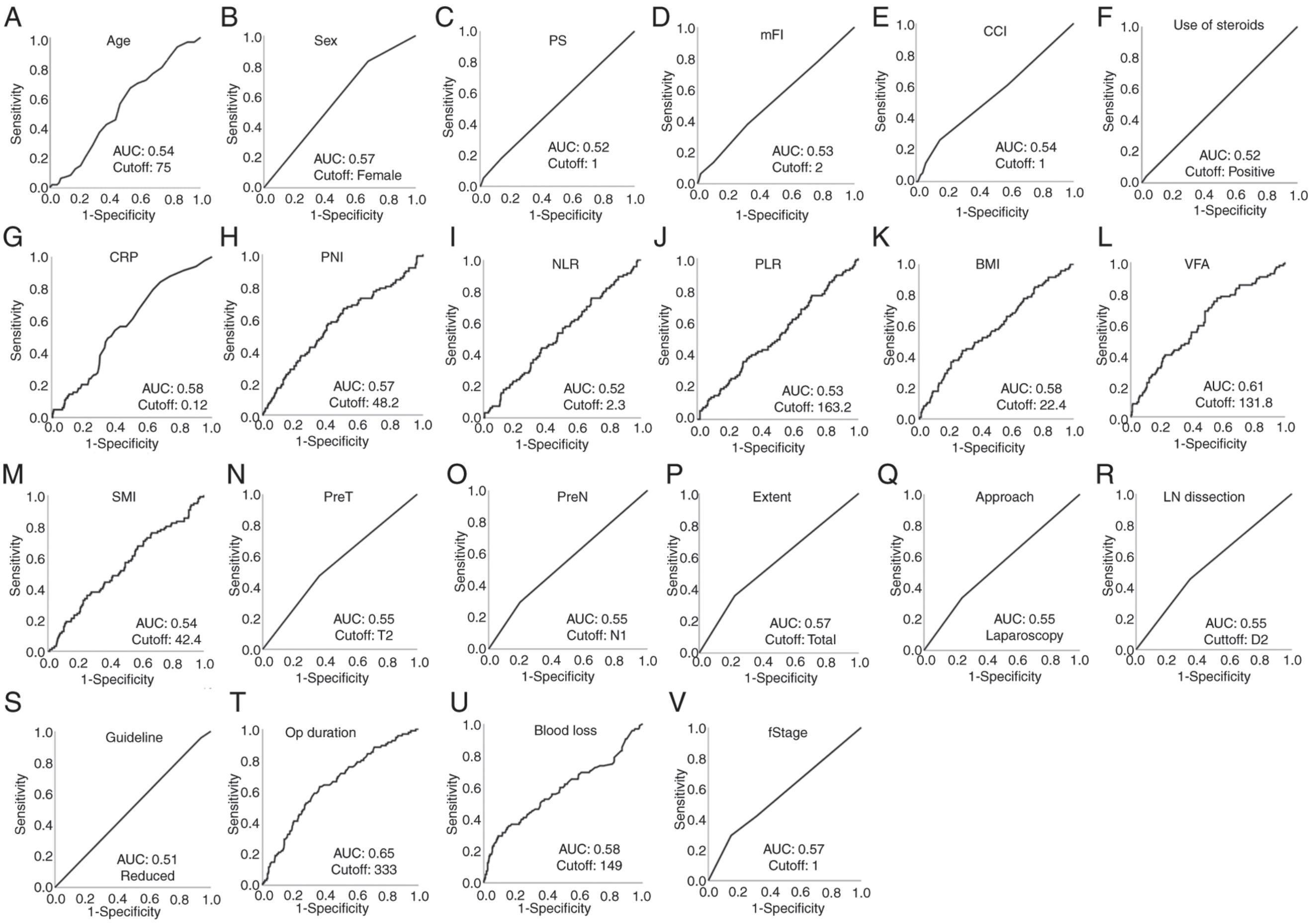

Figure 1. Receiver operating characteristic curves of infectious complications for perioperative factors were used to determine the cutoff values and AUCs. (A) Age, (B) sex, (C) PS, (D) mFI, (E) CCI, (F) use of steroids, (G) preoperative CRP levels, (H) PNI, (I) NLR, (J) PLR, (K) BMI, (L) VFA, (M) SMI, (N) PreT, (O) PreN, (P) extent of resection, (Q) surgical approach, (R) extent of LN dissection, (S) node dissection according to guidelines, (T) Op duration, (U) blood loss and (V) fStage. AUC, area under the receiver operating characteristic curve; BMI, body mass index; CCI, Charlson comorbidity index; CRP, C-reactive protein; fStage, final stage; LN dissection, lymph node dissection; mFI, modified frailty index; NLR, neutrophil-to-lymphocyte ratio; Op duration, operative duration; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; PreN, preoperative N factor; PreT, preoperative T factor; PS, performance status; SMI, skeletal muscle index; VFA, visceral fat area.

are shown in Fig. 1. The AUCs and optimal cutoff values of each perioperative parameter for non-ICs are shown in Fig. S1.

Perioperative risk factors for ICs. Table III summarizes the results of the univariate analysis for ICs after categorizing all variables with cutoff values using the ROC curve. Univariate

Table III. Univariate analysis of risk factors for infectious complications in older patients.

Variables	Infectious complication		P-value
	Yes, n (%) (n=95)	No, n (%) (n=409)	
Preoperative factor			
Age, years			0.101
<74	42 (44.2)	219 (53.5)	
>74	53 (55.8)	190 (46.5)	
Sex			0.005[a]
Male	79 (83.2)	281 (68.7)	
Female	16 (16.8)	128 (31.3)	
PS			0.294
1	78 (82.1)	353 (86.3)	
≥2	17 (17.9)	56 (13.7)	
Modified frailty index			0.077
<2	71 (74.7)	267 (65.3)	
≥2	24 (25.3)	142 (34.7)	
Charlson comorbidity index			0.610
0	37 (38.9)	171 (41.8)	
≥1	58 (61.1)	238 (58.2)	
Use of steroids			0.523
No	91 (95.8)	397 (97.1)	
Yes	4 (4.2)	12 (2.9)	
CRP, mg/dl			0.052
≤0.12	36 (43.4)	189 (55.3)	
>0.12	47 (56.6)	153 (44.7)	
PNI			0.012[a]
≤48.24	54 (56.8)	174 (42.5)	
>48.24	41 (43.2)	235 (57.5)	
NLR			0.339
≤2.3	45 (47.4)	216 (52.8)	
>2.3	50 (52.6)	193 (47.2)	
PLR			0.842
≤136.23	48 (50.5)	202 (49.4)	
>136.23	47 (49.5)	207 (50.6)	
BMI, kg/m^2			0.175
≤22.38	44 (46.3)	221 (54.0)	
>22.38	51 (53.7)	188 (46.0)	
VFA, cm^2			0.017[a]
≤131.75	41 (43.2)	232 (56.7)	
>131.75	54 (56.8)	177 (43.3)	
SMI, cm^2/m^2			0.608
≤42.41	46 (48.4)	210 (51.3)	
>42.41	49 (51.6)	199 (48.7)	
Preoperative T factor			0.054
T1	50 (52.6)	259 (63.3)	
>T2	45 (47.4)	150 (36.7)	
Preoperative N factor			0.039[a]
N0	67 (70.5)	328 (80.2)	
≥N1	28 (29.5)	81 (19.8)	
Operation, pathological, and postoperative factors			
Extent of resection			0.006[a]
Distal/proximal gastrectomy	61 (64.2)	318 (77.8)	
Total gastrectomy	34 (35.8)	91 (22.2)	

Table III. Continued.

Variables	Infectious complication		P-value
	Yes, n (%) (n=95)	No, n (%) (n=409)	
Approach			0.065
Open	32 (33.7)	100 (24.4)	
Laparoscopy	63 (66.3)	309 (75.6)	
Lymph node dissection			0.055
D1/D1+	52 (54.7)	267 (65.3)	
D2	43 (45.3)	142 (34.7)	
Node dissection according to guidelines			0.426
Standard	91 (95.8)	383 (93.6)	
Reduced	4 (4.2)	26 (6.4)	
Operative duration, min			<0.001[a]
≤333	35 (36.8)	257 (62.8)	
>333	60 (63.2)	152 (37.2)	
Amount of blood loss, ml			0.047[a]
≤149	42 (44.2)	227 (55.5)	
>149	53 (55.8)	182 (44.5)	
Pathological stage			0.001[a]
I/II	67 (70.5)	348 (85.1)	
III	28 (29.5)	61 (14.9)	

[a]P<0.05. PS, performance status; CRP, C-reactive protein; PNI, prognostic nutritional index; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; BMI, body mass index; VFA, visceral fat area; SMI, skeletal muscle index.

analysis revealed that among the perioperative factors, sex, PNI, VFA, preoperative N factor, the extent of resection, operative duration, amount of blood loss, and pathological stage were significantly associated with ICs. Table IV summarizes the results of the multivariate analysis of independent preoperative factors and a combination of all perioperative factors for ICs. Multivariate analyses of only preoperative parameters with P<0.05 in the univariate analyses revealed that sex, PNI, VFA, and TG were independent risk factors for ICs (HR: 1.897, 95% CI: 1.044-3.448, P=0.036; HR: 1.865, 95% CI: 1.153-3.019, P=0.011; HR: 1.673, 95% CI: 1.040-2.697, P=0.034; and HR: 1.815, 95% CI: 1.098-3.000, P=0.020, respectively). Multivariate analyses of all perioperative parameters with P<0.05 in univariate analyses revealed that PNI and operative duration were independent risk factors for ICs (HR: 1.961, 95% CI: 1.201-3.200, P=0.007; and HR: 2.555, 95% CI: 1.504-4.341, P=0.001, respectively).

Preoperative risk factors for ICs after laparoscopic and open gastrectomy. Table SI summarizes the results of the univariate analysis for ICs in a subgroup restricted to laparoscopic and open gastrectomy. In univariate analysis, age, sex, PNI and VFA in laparoscopic gastrectomy and preoperative T factor, extent of resection and extent of lymph node dissection in open gastrectomy were extracted as factors significantly associated with ICs. Table SII summarizes the results of the multivariate analysis of independent preoperative factors for ICs. In multivariate analyses, age, PNI and VFA in laparoscopic gastrectomy were independent risk factors for ICs (HR: 1.841, 95% CI: 1.021-3.3191, P=0.043; HR: 2.122, 95% CI: 1.180-3.815, P=0.012; and HR: 1.984, 95% CI: 1.040-2.697, P=0.034, respectively), but no statistically significant independent risk factors were identified in open gastrectomy.

Perioperative risk factors for non-ICs. Univariate and multivariate analyses were performed to compare the risk factors for non-ICs and ICs. The results of univariate analyses for non-ICs are summarized in Table SIII. Univariate analyses revealed that, among the perioperative factors, age, mFI, surgical approach, and node dissection according to the guidelines were significantly associated with non-ICs. Supplementary Table SIV summarizes the results of the multivariate analysis for non-ICs performed first with only preoperative factors and then with all perioperative factors. Multivariate analyses of only preoperative parameters with P<0.05 in the univariate analyses revealed that age and mFI were independent risk factors for non-ICs (HR: 1.744, 95% CI: 1.093-2.781, P=0.020; and HR: 1.616, 95% CI: 1.011-2.584, P=0.045, respectively). Multivariate analyses of all perioperative parameters with P<0.05 in the univariate analyses revealed that failure to perform lymph node dissection according to guidelines was an independent risk factor for non-ICs (HR: 3.019, 95% CI: 1.356-6.722, P=0.007).

IC incidence rate according to the number of positive preoperative IC risk factors. The incidence rate of ICs was stratified using the number of positive preoperative risk factors for ICs detected by multivariate analysis (sex, positive for males;

Table IV. Multivariate analysis of risk factors for infectious complications in older patients.

	Preoperative factors and planned surgical procedures		All perioperative factors	
Variables	HR (95% CI)	P-value	HR (95% CI)	P-value
Sex		0.036[a]		0.070
Male	1.897 (1.044-3.448)		1.775 (0.953-3.304)	
Female	1		1	
PNI		0.011[a]		0.009[a]
≤48.24	1.865 (1.153-3.019)		1.929 (1.179-3.155)	
>48.24	1		1	
VFA, cm^2		0.034[a]		0.174
≤131.75	1		1	
>131.75	1.673 (1.040-2.697)		1.408 (0.860-2.305)	
Preoperative N factor		0.256		0.942
N0	1		1	
≥N1	1.320 (0.817-2.132)		1.024 (0.536-1.958)	
Extent of resection		0.020[a]		0.498
Distal/proximal gastrectomy	1		1	
Total gastrectomy	1.815 (1.098-3.000)		1.215 (0.692-2.131)	
Operative duration, min				0.001[a]
≤333	n/a		1	
>333	n/a		2.440 (1.430-4.118)	
Amount of blood loss, ml				0.798
≤149	n/a		1	
>149	n/a		1.069 (0.643-1.777)	
Pathological stage				0.107
I/II	n/a		1	
III	n/a		1.736 (0.888-3.396)	

[a]P<0.05. HR, hazard ratio; n/a, not applicable; PNI, prognostic nutritional index; VFA, visceral fat area.

PNI, positive for scores <48.24; VFA, positive for values >131.75 cm^2; and extent of gastrectomy, positive for TG). The patients were divided into five categories according to the number of risk factors as follows: i) risk factor 0 (no positive risk factors; n=45), ii) risk factor 1 (one positive risk factor; n=124), iii) risk factor 2 (two positive risk factors; n=206), iv) risk factor 3 (three positive risk factors; n=108), and v) risk factor 4 (four positive risk factors; n=21). The IC rates for patients with 0, 1, 2, 3 and 4 risk factors were 6.7, 10.4, 18.9, 27.8, and 47.6%, respectively, showing a significant correlation with the number of risk factors (P<0.001; Fig. 2). The AUC for the number of preoperative risk factors of entire cohort was 0.653 (95% CI: 0.592-0.713, P=0.000), while the AUC for the number of preoperative risk factors by 10-fold cross-validation was 0.551 (95% CI: 0.485-0.617, P=0.0638).

Discussion

This study focused on identifying risk factors for ICs after gastrectomy for gastric cancer in older patients, especially those that can be assessed preoperatively. The results showed that preoperative factors such as male sex, low PNI, high VFA, and TG were independent risk factors for postgastrectomy ICs in older persons. Additionally, the higher the number of positive preoperative risk factors, the higher the incidence of ICs.

Decision-making regarding cancer treatment in older persons should consider short-term risks, such as postoperative complications, and the benefits of surgery, such as prolonged prognosis. In Japan, approximately 70% of radical gastrectomies for gastric cancer are undergone by patients with stage I gastric cancer (16). Hence, minimally invasive treatment options such as ESD with expanded indications or palliative local stomach resection may be options if patients with a high risk for complications after gastrectomy are identified preoperatively (7,8). ICs are likelier to be more severe and lead to postoperative mortality than non-ICs (17). Furthermore, ICs are associated with worse long-term prognoses after surgery, and preoperative assessment of the risk of ICs after gastrectomy is valuable for decision-making in older persons undergoing treatment (18).

The National Clinical Database (NCD) in surgery has been established in Japan, and a prediction system for postoperative complications based on preoperative factors in distal

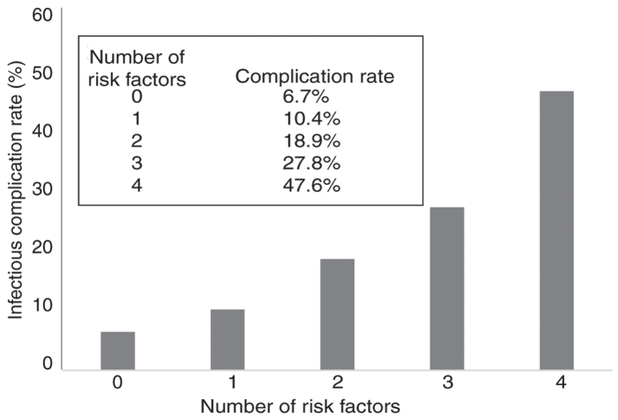

Figure 2. Incidence of ICs according to the number of positive preoperative risk factors. The IC rates for 0, 1, 2, 3 and 4 risk factors were 6.7, 10.4, 18.9, 27.8 and 47.6%, respectively. IC, infectious complication.

gastrectomy and total gastrectomy has been reported and shown to be useful (5,19). The risk factors for intraabdominal ICs in patients with gastric cancer using the NCD were male sex, high BMI, use of steroids, peripheral vascular disease, and TG (20). Although this previous study included all age groups, similar risk factors were possibly identified in the present study as patients aged ≥65 years accounted for 72% of the total study population. In contrast, the NCD complication prediction model is based on registered clinical data and does not include all factors that are known to be useful in predicting ICs. VFA and PNI, which were independent risk factors for ICs in our study, have been reported as risk factors for ICs but are not included in the NCD analysis, so it is possible that different risk factors are extracted in our study and the NCD prediction model.

Very few reports have examined in detail the risk of ICs after gastrectomy in older individuals. Liu *et al* (21) analyzed the risk factors for ICs after gastrectomy in patients aged >70 years. They reported that preoperative weight loss ≥5%, CCI scores ≥3, and preoperative C-reactive protein levels were risk factors. Their study may have differed from the present study's data in that two-thirds of the patients had stage >2 advanced cancer, they did not analyze detailed body composition data such as VFA, and the cutoff values were set independently.

In the present study, among the preoperative factors for gastric cancer in older patients, male sex, low PNI, high VFA, and TG were independent risk factors for ICs after gastrectomy. The male sex is a well-known risk factor for pneumonia after gastrectomy. It has also been reported as a risk factor for all complications and ICs after gastrectomy (20,22). PNI has been reported as a predictive indicator of postoperative complications after gastric cancer surgery and has also been reported as a risk factor for ICs after various abdominal surgical procedures. It has also been shown that PNI is low in older patients with postoperative complications after gastric cancer surgery (23,24). VFAs have been reported to be associated with postoperative complications of gastric cancer and are a better predictor of postoperative complications than BMI (25). High VFA values have been reported to increase the incidence of surgical site infections after gastrectomy (26). TG is reported to be a risk factor for all postoperative complications and ICs (20,22), and TG in older persons is reported to be a risk for pneumonia (27).

However, it is unclear from this study alone whether the risk factors identified are themselves the underlying causes of ICs, and whether preoperative interventions for the risk factors are effective in reducing ICs. PNI is associated with a patient's nutritional status, and preoperative nutritional management for gastric cancer patients has been shown to decrease postoperative complications (28). Preoperative exercise programs for obese patients have also shown promise in reducing postoperative complications (29). However, whether these preoperative interventions lead to a reduction in ICS in elderly patients needs to be prospectively evaluated. A risk factor analysis of all perioperative factors, including intraoperative factors, was also performed. Low PNI and prolonged operative time were independent risk factors for ICs. Procter *et al* (30) reported in the American College of Surgeons National Surgical Quality Improvement Program database that prolonged operative time generally increases the incidence of ICs after general surgery. Wang *et al* (31) also reported that prolonged operative time was a risk factor for complications after gastrectomy performed by the same surgeon. Therefore, when performing gastrectomy in older patients, it is important to consider the surgical technique and device selection while shortening the operative time.

To explore the risk factors for ICs, cutoff values were set for all continuous variables to facilitate their use in daily clinical practice. No appropriate method has been established for determining cutoff values for each indicator, and different cutoff values are often used in different reports. Hence, this study determined cutoff values using an ROC curve analysis, which is considered advantageous in terms of objectivity (32). Among the factors extracted from the analysis of preoperative factors, PNI and VFA were continuous variables. No significant measurement differences were observed among the centers, and they may be used as standard cutoff values. However, the operative time is expected to vary among surgeons and institutions, and the cutoff may differ among institutions and surgeons.

This study had several limitations. First, the main limitations of this study was the use of a small amount of sample data from a single institution. The identified risk factors must be validated using prospective data from a larger population. Furthermore, predicting the incidence of ICs by the number of identified risk factors was not validated by cross-validation. The results shown in Fig. 2 simply show the number of risk factors and the incidence of ICs in the cohort studied here, and should be validated in a different sample population in the future. There is room for developing more accurate criteria by assessing more cases with multiple institutions to establish more precise criteria, and we aim to conduct a prospective study to verify the validity of this study's findings. Second, the analysis used factors from the preoperative examination, which is usually performed before gastrectomy, but did not include items from a detailed functional assessment of older patients, such as a comprehensive geriatric assessment (CGA). A CGA is reportedly useful in predicting postoperative complications and may also be useful in predicting ICs after gastrectomy (33). Third, the definition of older persons in this study was ≥65 years of age, according to the internationally accepted WHO definition. However, reports on short-term results after gastrectomy for older persons have included various age definitions, such as ≥65, 70, 75, and 80 years of age. This may lead to discrepancies in results depending on the age definition (6,21,34,35). We performed univariate and multivariate analyses of risk factors also in the subgroups aged 75 years and older in the present study (Tables SV and SVI). Independent multivariate risk factors for ICs aged 75 years and older were men and high BMI, which differed from risk factors for those aged 65 years and older. To identify more accurate risk factors for ICS, it may be necessary to subdivide the analysis by age groups, such as 65-74, 75-84, and 84-94, rather than categorizing the age definition of the elderly as >65 or >75 years old.

In conclusion, male sex, low PNI, high VFA, and TG are risk factors for ICs after gastrectomy in older patients with gastric cancer. For patients with multiple risk factors, the indications for gastrectomy should be carefully considered, and close postoperative management should be performed.

Acknowledgements

The authors would like to thank Dr Shoichi Hazama (Department of Surgery, Shunan Memorial Hospital, Shunan, Yamaguchi 744-0033, Japan), Dr Shigefumi Yoshino (Department of Surgery, National Hospital Organization Kanmon Medical Center, Shimonoseki, Yamaguchi 752-8510, Japan) and Professor Tatsuya Ioka (Oncology Center, Yamaguchi University Hospital, Ube, Yamaguchi 755-8505, Japan) for suggesting the topic studied in this paper. The authors would also like to thank Dr Gen Kanesada (Department of Gastroenterological, Breast and Endocrine Surgery, Yamaguchi University Graduate School of Medicine, Ube, Yamaguchi 755-8505, Japan) for sharing his dataset.

Funding

No funding was received.

Availability of data and materials

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

Authors' contributions

MI and STa conceived the presented idea. MI wrote the manuscript. TY, CN, MN and YW contributed to data collection. YS, YT, HT and YN performed analytical calculations. STo and HN helped interpret the results. HN revised the manuscript critically for important intellectual content and gave final approval of the version to be published. All authors provided critical feedback, and helped shape the research, analysis and manuscript. MI and CN confirm the authenticity of all the raw data. All authors 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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