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Predictive Postoperative Inflammatory Response Indicators of Infectious Complications Following Gastrectomy for Gastric Cancer

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Background: Perioperative factors are useful for predicting postoperative infectious complications (PIC) in gastric cancer. Specifically, postoperative inflammatory response indicators (PIRI), [C-reactive protein (CRP) level, body temperature (BT), and white blood cell (WBC) count], are widely used in clinical practice. We investigated predictive factors for PIC, including PIRI, to establish a simple and practical indicator of postoperative complications after gastrectomy.

Methods: We retrospectively collected clinical data from 200 patients with fStage I-III gastric cancer. Univariate/multivariate analysis was performed to evaluate the relationship of predictive factors [host factors, clinicopathological factors, and PIRI (BT, WBC count, and CRP level on postoperative day (POD) 1 and 3)]. Cut-off values of the predictive factors were analyzed using receiver operating characteristic (ROC) curve modulated by the presence/absence of PIC Grade II, III (Clavien-Dindo classification).

Results: Age [Odds ratio (OR): 5.67], smoking history (OR: 3.51), and CRP level (OR: 5.65), WBC count (OR: 8.96), and BT (OR: 3.37) on POD3 were selected as independent factors from multivariate analysis. Cut-off values were 77 years, 14.8 mg/dL, 116.0×10^2/μL, and 37.4°C, respectively.

Conclusions: Predictive factors relative to PIC in gastric cancer were CRP level ≥ 14.8 mg/dL, WBC count ≥ 116.0×10^2/μL, and BT ≥ 37.4°C all on POD3. Age ≥ 77 years, and history of smoking were relative to PIC, suggesting a simple and practical indicator applicable in clinical practice.

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Key words: C-reactive protein, gastric cancer, inflammatory response indicators, postoperative complications

Introduction

In Japan, surgical resection for gastric cancer is typically managed using a clinical pathway, and is thus performed safely. The morbidity of postoperative complications is 23.0-27.8% with even lower proportions (9.7-11.3%) limited to severe complications, which require invasive intervention[1,2]. However, postoperative complications are associated with progressively increasing healthcare costs[3] and poor survival outcomes of gastric cancer[2], which cannot be overlooked.

Host factors and clinicopathological factors are known to correlate with postoperative complications. Moreover, postoperative inflammatory response indicators (PIRI), including serum C-reactive protein (CRP) level, body temperature (BT), and white blood cell (WBC) count, are useful factors in clinical practice. Specifically, serum CRP level on postoperative day (POD) 3 to 4 is reported to be an inflammatory marker with superior sensitivity and specificity for predicting postoperative infectious complications (PIC)[4–6]. Additionally, Guner et al.[7] investigated the safe discharge criteria after gastrectomy including serum CRP level, BT and neutrophil count on POD 3.

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However, no investigations of predictive factors for PIC that included BT and WBC count have been performed in previous studies. Therefore, we investigated the predictive factors for PIC including host factors, clinicopathological factors, and PIRI to establish a simple and practical indicator of postoperative complications after gastrectomy.

Material and Methods

Patients and Predictive Factors

During the period from April 2013 through August 2019, 215 patients with fStage I-III gastric cancer underwent gastric resection at our institution. In total, 7 patients with exacerbation of other diseases during the admission period, 7 others who had insufficient clinical data, and 1 patient who underwent simultaneous surgery for colon cancer were excluded. Clinical data from 200 patients was included in the analysis. For the second cohort to confirm reproducibility, clinical data from 108 fStage I-III gastric cancer patients with gastric resection during September 2019 through December 2022 was collected. Predictive factors included in the analysis relative to PIC were host factors [age, sex, body mass index (BMI), smoking history, comorbidities (diabetes mellites, cerebrovascular disease, cardiovascular disease, pulmonary disease, and hepatic dysfunction), American Society of Anesthesiologists Physical Status (ASA-PS) classification, preoperative serum albumin level, serum CRP level, modified Glasgow Prognostic Score (GPS), prognostic nutritional index (PNI), neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR)], clinicopathological factors [operative time, blood loss, approach (open/laparoscopic), extent of gastric resection (distal, proximal, total gastrectomy), extent of lymph node dissection (D0/D1/D1+/D2), reconstruction modality after gastrectomy (Billroth I, Roux-en-Y, double tract), Stage], and PIRI (BT/WBC count/serum CRP level on POD1 and POD3). The diagnostic criteria of comorbidities are as follows; Smoking history: current or previous cigarette smokers who had smoked at least 100 cigarettes and/or smoked more than 6 months. Diabetes mellites: fasting plasma glucose ≥126 mg/dL or a 2-hour plasma glucose ≥200 mg/dL following a glucose load, a clearly documented history of diabetes, and/or current treatment for hypoglycemia (including insulin)[8]. Cerebrovascular disease: All disorders in which an area of the brain is temporarily or permanently affected by ischemia or bleeding and one or more of the cerebral blood vessels are involved in the pathological process, such as stroke, cerebral hemorrhage, subarachnoid hemorrhage, carotid stenosis, vertebral stenosis, intracranial stenosis, aneurysms, and vascular malformations. Cardiovascular disease: group of disorders of the heart and blood vessels including arrythmia, coronary heart disease, congenital heart disease, heart failure, valvular disease, aortic disease, peripheral arterial disease, deep vein thrombosis and pulmonary embolism. Pulmonary disease: group of disorders of the lung, mainly airway diseases (asthma, chronic obstructive pulmonary disease, bronchiolitis, and bronchiectasis), lung tissue diseases (lung cancer, pneumonia, pulmonary fibrosis, and sarcoidosis), and lung circulation diseases (pulmonary hypertension). Hepatic dysfunction: Child-Pugh score[9] of grade B (7-9 points) or grade C (10-15 points) calculated by serum albumin, serum bilirubin, prothrombin time, hepatic encephalopathy, and ascites. Clinicopathological data were described with reference to the TNM classification (8th edition)[10].

The study protocol was approved by the institutional review board of Tokyo Women's Medical University (Approval No. 2021-0206). All methods were carried out based on the Japanese gastric cancer treatment guidelines[11]. The requirement for informed consent was waived by the Tokyo Women's Medical University Ethics Committee. Instead, opt-out consent was approved by the committee and made available on our websites, where permission was requested to use the personal information of participants in this study.

Perioperative Management

Most cases were managed using a clinical pathway after gastric resection. For antibiotic prophylaxis, an intravenous dose of 1 g cefazolin was administered at the time of skin incision and repeated every 3 h intraoperatively. Epidural anesthesia was administered for analgesia and perioperative pain management in all patients. Celecoxib was administered orally from POD1, and additional intravenous analgesics were provided if needed. On POD1, patients began ambulation and water intake was initiated. On POD2, epidural/urinary catheters were removed, and liquid diet was initiated for patients who underwent distal/total gastrectomy. On POD4-5, liquid diet was initiated for patients who had proximal gastrectomy. Liquid diet was gradually advanced to solid diet in all patients. BT was measured three times a day (morning, afternoon, and evening) and the maximum value on each day was used for the analysis on POD1, 3, and 7. Blood samples were collected on POD1, 3, and 7 while drains were removed on POD4-5 if the drain effluent was clear. Hospital discharge was decided upon

when the patients' food intake exceeded 50% of the provided diet without fever, wound pain, vomiting, or other postoperative complications.

Definition of Postoperative Infectious Complications

PICs were defined as the following events, which occurred during the postoperative hospital stay. Pneumonia: clinical signs of pneumonia with radiographic evidence and positive sputum culture. Surgical site infection: purulent effluent from the wound and positive wound culture. Anastomotic leak: positive findings on fluoroscopy and CT scans. Pancreatic fistula: drain effluent on or after POD3 with an amylase level greater than 3 times the serum amylase level or requiring percutaneous drainage/reoperation[12]. Biliary fistula: drain effluent on or after POD3 with a bilirubin level greater than 3 times the serum bilirubin level or requiring percutaneous drainage/reoperation. Abdominal abscess: complication that could occur due to anastomotic leak, pancreatic fistula, or cholecystitis; requiring percutaneous drainage or reoperation with positive abscess culture. Cholecystitis: confirmed using clinical signs, laboratory findings, and CT scans followed by antibiotic treatment, percutaneous gallbladder drainage or reoperation. Each PIC was evaluated according to the Clavien-Dindo (CD) Classification[13,14]. Pneumonia is a common PIC and is especially life-threatening in elderly patients. This was mostly Grade II in the CD classification, and so we further classified the PIC group into no PIC or PIC of CD Grade I (n =167) and PIC of CD Grade II, III (n=33) groups.

Statistical Analysis

Continuous data are presented as median or mean ± SD. The Mann-Whitney *U* test was used for nonparametrical analysis of continuous variables. The χ^2 test was used to compare categorical variables when appropriate. Pearson's correlation coefficient was used to assess correlations between continuous variables. Cut-off and area under the curve (AUC) values for each predictive factor were computed using the receiver operating characteristic (ROC) curve, which was adjusted for the presence/absence of PIC grade II, III based on the CD classification. Univariate and multivariate logistic regression analysis were used to identify predictive factors relative to PIC. In univariate analysis, variables with a p value less than 0.05 were selected as candidates for multivariate analysis. A p value less than 0.05 was considered to indicate statistical significance. All statistical data were generated using JMP® Pro version 15 software (SAS Institute, Cary, NC).

Results

Patient Characteristics

Table 1 shows the perioperative characteristics (host factors, clinicopathological factors, and PIRI) of all patients (n=200) as well as patients with no PIC or PIC of CD Grade I (n=167) and PIC of CD Grade II, III (n=33). Grade II, III patients were significantly older (median age 78 years vs 72 years, p = 0.007). They also had significantly higher rates of smoking history (60.6% vs 40.7%, p = 0.036). Preoperative serum CRP level was significantly higher in Grade II, III patients (0.16 mg/dL vs 0.09 mg/dL, p = 0.033). They also had significantly longer operative time (248 min vs 214 min, p = 0.040) and significantly more blood loss (289 mL vs 100 mL, p = 0.018). Regarding the approach, open laparotomy was significantly more frequent (open 78.8%, laparoscopic 21.2% vs open 58.1%, laparoscopic 41.9%, p = 0.026) in Grade II, III patients. Roux-en-Y reconstruction was performed significantly more frequently (Billroth I/Roux-en-Y/double tract: 27.3% / 69.7% / 3.0% vs 53.3% / 44.9% / 1.8 %, p = 0.024) in Grade II, III patients. Stage was significantly more advanced (I/II/III: 21.2% / 21.2% / 57.6% vs 46.1% / 14.4% / 39.5%, p = 0.030) in Grade II, III patients. There was no significant difference in sex, BMI, comorbidities, ASA-PS, serum albumin level, modified GPS, PNI, NLR, PLR, extent of gastric resection, and extent of lymph node dissection between no PIC or PIC of CD Grade I or PIC of CD Grade II, III.

Postoperative Inflammatory Indicators

We classified the patients as having no PIC or PIC of CD Grade I or PIC of CD Grade II, III. Median values of PIRI (BT, WBC count, and serum CRP level) on POD1, 3, and 7 were collected and compared between the groups (**Fig. 1**). BT peaked but did not differ between the groups on POD1. Fever declined in no PIC or PIC of Grade I patients, but was prolonged and significantly increased in Grade II, III patients on POD3 and POD7 ($p < 0.001$, p = 0.004; **Fig. 1A**). WBC count also peaked on POD1 in both groups but inflammation was prolonged and significantly increased in Grade II, III patients on POD1, 3, and 7 (p = 0.020, $p < 0.001$, $p < 0.001$; **Fig. 1B**). CRP level peaked on POD3 in both groups but was significantly elevated in Grade II, III patients on POD 1, 3, and 7 (p = 0.003, $p < 0.001$, $p < 0.001$; **Fig. 1C**).

Postoperative Infectious Complications

Figure 2 shows the cumulative number of PICs occurred according to the CD classification. PIC of Grade I occurred in 19 patients which were all surgical site infections. PICs of Grade II, III occurred in 41 (cumulative

Table 1 Patient characteristics

	All (n=200)	No PIC or PIC of CD Grade I (n=167)	PIC of CD Grade ≥ II (n=33)	*p* value
Age, median (range)	73.5 (36-90)	72 (36-90)	78 (52-89)	0.007
Sex, n (%)				0.072
Male	144 (72.0)	116 (69.5)	28 (84.8)	
Female	56 (28.0)	51 (30.5)	5 (15.2)	
Body mass index, kg/m^2, median (range)	22.7 (15.1-36.9)	22.5 (15.1-36.9)	23.2 (15.9-29.1)	0.259
Smoking history, n (%)	88 (44.0)	68 (40.7)	20 (60.6)	0.036
Diabetes mellites, n (%)	38 (19.0)	31 (18.6)	7 (21.2)	0.723
Cerebrovascular disease, n (%)	27 (13.5)	21 (12.6)	6 (18.2)	0.389
Cardiovascular disesase, n (%)	110 (55.0)	91 (54.5)	19 (57.6)	0.745
Pulmonary disesase, n (%)	27 (13.5)	21 (12.6)	6 (18.2)	0.389
Hepatic dysfunction, n (%)	5 (2.5)	4 (2.4)	1 (3.0)	0.831
ASA-PS, 1/2/3, n (%)	63 (31.5)/83 (41.5)/54 (27.0)	55 (32.9)/68 (40.7)/44 (26.4)	8 (24.2)/15 (45.5)/10 (30.3)	0.616
Serum albumin level, g/dL, median (range)	4.1 (1.9-5.0)	4.1 (2.2-5.0)	4.0 (1.9-4.7)	0.396
Serum CRP level, mg/dL, median (range)	0.10 (0.02-4.12)	0.09 (0.02-4.12)	0.16 (0.02-0.82)	0.033
Modified GPS score, 0/1/2, n (%)	147 (73.5)/35 (17.5)/18 (9.0)	128 (76.6)/25 (15.0)/14 (8.4)	19 (57.6)/10 (30.3)/4 (12.1)	0.064
PNI, median (range)	48.0 (26-71.6)	48.1 (26.8-62.0)	47.1 (26.0-71.6)	0.426
NLR, median (range)	2.38 (0.45-26.50)	2.38 (0.45-26.5)	2.31 (0.70-6.34)	0.967
PLR, median (range)	155.5 (40.5-844.7)	156.8 (50.1-844.7)	143.6 (40.5-437.8)	0.205
Operative time, min, median (range)	218 (93-491)	214 (93-436)	248 (110-491)	0.040
Blood loss, mL, median (range)	107 (1-2,025)	100 (1-2,025)	289 (10-1,236)	0.018
Approach, n (%)				0.026
Open	123 (61.5)	97 (58.1)	26 (78.8)	
Laparoscopic	77 (38.5)	70 (41.9)	7 (21.2)	
Extent of gastric resection, n (%)				0.085
Distal gastrectomy	136 (68.0)	119 (71.3)	17 (51.5)	
Proximal gastrectomy	4 (2.0)	3 (1.8)	1 (3.0)	
Total gastrectomy	60 (30.0)	45 (26.9)	15 (45.5)	
Extent of lymph node dissection (D0/D1/D1+/D2), n (%)	4 (2.0)/55 (27.5)/46 (23.0)/95 (47.5)	4 (2.4)/50 (29.9)/40 (24.0)/73 (43.7)	0 (0.0)/5 (15.1)/6 (18.2)/22 (66.7)	0.092
Reconstruction modality after gastrectomy, n (%)				0.024
Billroth I	98 (49.0)	89 (53.3)	9 (27.3)	
Roux-en-Y	98 (49.0)	75 (44.9)	23 (69.7)	
Double tract	4 (2.0)	3 (1.8)	1 (3.0)	
Stage, I/II/III, n (%)	84 (42.0)/31 (15.5)/85 (42.5)	77 (46.1)/24 (14.4)/66 (39.5)	7 (21.2)/7 (21.2)/19 (57.6)	0.030
Body temperature, ℃, median (range)				
POD1	37.6 (36.2-39.6)	37.6 (36.2-39.5)	37.6 (36.8-39.6)	0.454
POD3	37.0 (35.5-39.3)	36.9 (35.5-38.4)	37.4 (36.0-39.3)	<0.001
White blood cell count, ×10^2 /μL (range)				
POD1	98.5 (40.0-210.0)	96.0 (40.0-210.0)	107.0 (61.0-206.0)	0.020
POD3	84.5 (21.0-233.0)	80.0 (21.0-227.0)	101.0 (46.0-233.0)	<0.001
Serum CRP level, mg/dL (range)				
POD1	6.93 (1.09-20.16)	6.56 (1.09-20.16)	8.45 (2.70-13.45)	0.003
POD3	9.89 (1.04-30.75)	9.19 (1.04-26.28)	15.35 (5.40-30.75)	<0.001

CD: Clavien-Dindo classification, ASA-PS: American Society of Anesthesiologists-physical status, GPS: Glasgow Prognostic Score PNI: Prognostic Nutritional Index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, POD: Postoperative day

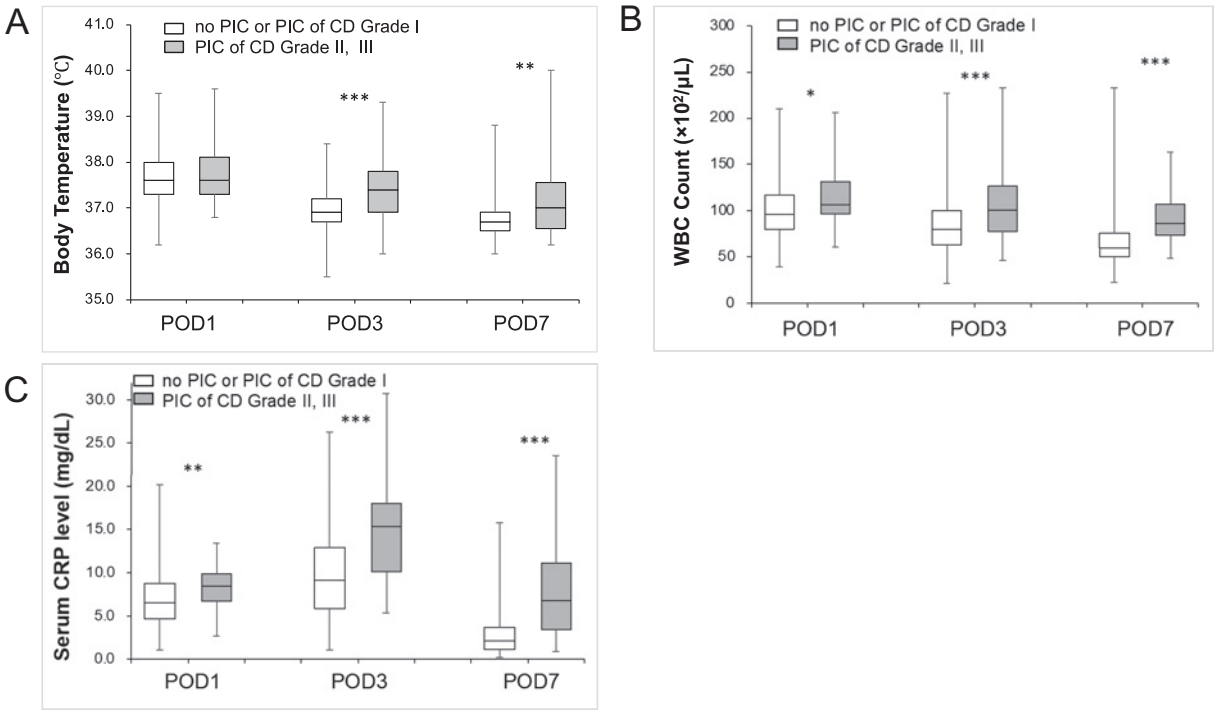

Fig. 1 Vital signs and Laboratory data after gastrectomy including (**A**) body temperature, (**B**) white blood cell (WBC) count, and (**C**) C-reactive protein (CRP) level on postoperative day (POD) 1, 3, and 7 (*p<0.05 **p<0.01 ***p<0.001; Mann-Whitney U test: no postoperative infectious complication (PIC) or PIC of Clavien-Dindo (CD) Grade I vs. PIC of CD Grade II, III)

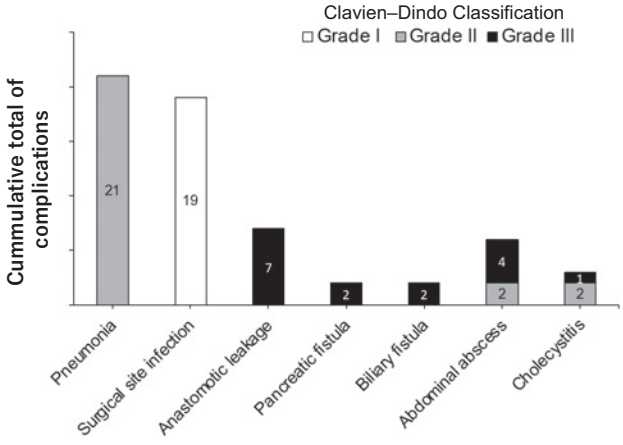

Fig. 2 Cumulative total of postoperative infectious complications based on the Clavien-Dindo (CD) classification

number), 33 out of 200 patients (actual number; 16.5%). In detail (cumulative number), pneumonia in 21 patients (10.5%), anastomotic leak in 7 patients (3.5%), pancreatic fistula in 2 patients (1.0%), biliary fistula in 2 patients (1.0%), abdominal abscess in 6 patients (3.0%), and cholecystitis in 3 patients (1.5%). Duplicates/triplicates of PICs Grade II, III are as follows. Anastomotic leak and abdominal abscess (2 patients), Abdominal abscess and cholecystitis (2 patients), pneumonia, abdominal abscess, and cholecystitis (1 patient), pneumonia and abdominal abscess (2 patients).

Table 2 shows the postoperative day of symptoms onset of PIC and diagnosis of PIC. The symptoms onset of PIC was significantly earlier than the diagnosis of PIC regarding pneumonia (POD3 vs POD4; $p < 0.001$), anastomotic leak (POD3 vs POD5; $p = 0.004$), and abdominal abscess (POD3 vs POD5.5; $p = 0.003$). Cholecystitis showed a trend, and pancreatic fistula/ biliary fistula showed no difference between the onset of symptoms and diagnosis of PIC, which we think the number of cases was insufficient to reach statistical significance.

Cut-off Value and Predictive Factors for PIC

Table 3 shows the cut-off and AUC values computed from the ROC curve, which were adjusted for the presence/absence of PIC Grade II, III based on the CD classification. Variables with AUC ≥ 0.7 were BT on POD3 (cut-off value: 37.4°C, AUC: 0.713, sensitivity: 57.6%, specificity: 84.4%; **Fig. 3A**), WBC on POD3 (cut-off value: 116.0×10^2/μL, AUC: 0.706, sensitivity: 48.5%, specificity: 88.0%; **Fig. 3B**) and serum CRP level on POD3 (cut-off value: 14.8 mg/dL, AUC: 0.755, sensitivity: 63.6%, specificity: 84.4%; **Fig. 3C**). AUC on POD3 was higher than on POD1 in terms of BT, WBC, and CRP level. Predictive factors related to PIC were analyzed using univariate and

Table 2 Onset of symptoms and diagnosis of PIC

	n	Symptoms onset of PIC (POD)	Diagnosis of PIC (POD)	p value
Pneumonia	21	3 (2-3)	4 (2-6)	<0.001
Anastomotic leak	7	3 (3-5)	5 (4-7)	0.004
Pancreatic fistula	2	2 (1-3)	5 (3-7)	0.414
Biliary fistula	2	3 (3)	5 (4-5)	0.194
Abdominal abscess	6	3 (3)	5.5 (5-9)	0.003
Cholecystitis	3	3 (3)	6 (5-9)	0.064

Values are described as median (range)
POD: Postoperative day, PIC: Postoperative infectious complications

multivariate analysis and are also shown in **Table 3**. Univariate analysis selected age [Odds ratio (OR): 5.96], smoking history (OR: 6.98), operative time (OR: 6.79), extent of lymph node dissection (OR: 7.80) as well as BT on POD3 (OR: 9.70), WBC count on POD3 (OR: 13.86), and CRP level on POD3 (OR: 5.72). Multivariate analysis was performed with these variables and the following were selected as independent predictive factors: age (OR: 5.67), smoking history (OR: 3.51), and POD3 values for CRP level (OR: 5.65), WBC (OR: 8.96), and BT (OR: 3.37). To confirm the reproducibility of the independent predictive factors of the first results, we examined a second cohort with an additional group of patients. As shown in **Table 4**, univariate analysis selected age, smoking history, BT on POD3, WBC count on POD3, and CRP level on POD3. Multivariate analysis showed that age (OR: 13.35), POD3 values for BT (OR: 17.01), WBC (OR: 8.83), and CRP level (OR: 22.85) were selected as independent predictive factors, which the results were similar to the first cohort.

Association between PIC and PIRI in the Elderly and Non-Elderly Patients

Table 5 shows the incidence rate of each PIC in elderly (age ≥ 77 years) and non-elderly (age < 77 years) patients who had CRP level ≥ 14.8 mg/dL, WBC count ≥ 116.0×10^2/μL, and BT ≥ 37.4°C on POD3. Among the elderly patients, frequency of pneumonia was significantly higher in patients with BT ≥ 37.4°C (40.9% vs 9.6%, p = 0.002), WBC count ≥ 116.0×10^2/μL (43.8% vs 12.1%, p = 0.004), and CRP level ≥ 14.8 mg/dL (38.1% vs 11.3%, p = 0.008) compared to those patients with no PIRI on POD3. There were also significantly higher rates of anastomotic leak in those with CRP level ≥ 14.8 mg/dL (19.1% vs 0.0%, p = 0.001) and significantly higher pancreatic fistula rates with WBC count ≥ 116.0×10^2/μL (12.5% vs 0.0%, p = 0.006). Regarding the non-elderly patients, the frequency of pneumonia was also significantly higher in patients with BT ≥ 37.4°C (17.4% vs 2.9%, p = 0.006), WBC count ≥ 116.0×10^2/μL (25.0% vs 1.9%, p < 0.001), and CRP level ≥ 14.8 mg/dL (17.2% vs 2.1%, p = 0.002). Moreover, the frequency of abdominal abscess was significantly higher in those with BT ≥ 37.4°C (13.0% vs 0.0%, p < 0.001), and CRP level ≥ 14.8 mg/dL (10.3% vs 0.0%, p = 0.001). There were also significantly higher rates of cholecystitis in those with BT ≥ 37.4°C (8.7% vs 0.0%, p = 0.003), and CRP level ≥ 14.8 mg/dL (6.9% vs 0.0%, p = 0.009).

Figure 4 shows serum CRP level on POD3 in elderly and non-elderly patients with PIC of CD Grade II, III. Median CRP level was significantly lower in the elderly patients compared to non-elderly patients [14.5 (range 6.1-19.1) mg/dL vs 17.9 (range 5.4-30.8) mg/dL; p = 0.045].

Discussion

This study highlights three important findings. First, the main predictive factor for postoperative complications after gastrectomy was serum CRP level ≥ 14.8 mg/dL on POD3. Second, other PIRI relative to postoperative complications were WBC count ≥ 116.0×10^2/μL, and BT ≥ 37.4°C on POD3. Third, age ≥ 77 years and smoking history were also predictive factors for postoperative complications.

Serum CRP level on POD3-4 is a useful inflammatory marker for predicting PIC. This was stated in previous studies in which AUC computed from the ROC curve was above 0.73. The cut-off value of CRP ranged from 16.6-22.0 mg/dL, indicating a satisfactory sensitivity (56-70%) and specificity (76-91%)[4,5,15,16]. In our study, the cut-off value for serum CRP level on POD3 was 14.8 mg/dL, which was slightly lower compared to previous studies. We surmise that the lower cut-off value can be attributed to the following. 1. Median age in our study was higher than in previous studies (73.5 years vs 60-68 years). 2. The proportion of advanced cancer cases was higher

Table 3 Univariate and multivariate analysis of the first cohort

Variables	AUC	Cut-off value	n	Univariate		Multivariate	
				Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age, years	0.650	< 77	126	1.00	0.016	1.00	0.001
		≥ 77	74	5.96 (1.39-25.65)		5.67 (1.95-16.49)	
Sex	NA	Male	144	2.05 (0.35-11.97)	0.428		
		Female	56	1.00			
Body mass index, kg/m^2	0.562	< 24.3	140	1.00	0.076		
		≥ 24.3	60	4.76 (0.85-26.65)			
Smoking history	NA	Yes	88	6.98 (1.33-36.60)	0.022	3.51 (1.26-9.75)	0.016
		No	112	1.00		1.00	
Diabetes mellites	NA	Yes	38	4.79 (0.35-66.24)	0.243		
		No	162	1.00			
Cerebrovascular disease	NA	Yes	27	0.83 (0.08-8.35)	0.872		
		No	173	1.00			
Cardiovascular disesase	NA	Yes	110	3.32 (0.48-22.71)	0.222		
		No	90	1.00			
Pulmonary disesase	NA	Yes	27	0.77 (0.09-6.76)	0.813		
		No	173	1.00			
Hepatic dysfunction	NA	Yes	5	2.98 (0.04-235.15)	0.625		
		No	195	1.00			
ASA-PS	NA	Class 1-2	146	1.00	0.112		
		Class 3-5	54	12.30 (0.56-271.48)			
Albumin, g/dL	0.547	< 3.2	22	1.00	0.931		
		≥ 3.2	178	1.11 (0.11-11.47)			
modified GPS	NA	score 0	147	1.00	0.510		
		score 1, 2	53	2.33 (0.19-28.92)			
PNI	0.544	< 43.1	56	1.50 (0.15-14.58)	0.727		
		≥ 43.1	144	1.00			
NLR	0.502	< 2.3	90	1.00	0.079		
		≥ 2.3	110	4.63 (0.84-25.71)			
PLR	0.570	< 160.4	109	1.00	0.950		
		≥ 160.4	91	1.05 (0.21-5.35)			
Body temperature (POD1), ℃	0.541	< 38.4	175	1.00	0.169		
		≥ 38.4	25	3.94 (0.56-27.87)			
Body temperature (POD3), ℃	0.713	< 37.4	155	1.00	0.005	1.00	0.020
		≥ 37.4	45	9.70 (2.01-46.83)		3.37 (1.21-9.39)	
WBC (POD1), × 10^2/μL	0.628	< 95.0	83	1.00	0.061		
		≥ 95.0	117	8.22 (0.91-74.22)			
WBC (POD3), × 10^2/μL	0.706	< 116.0	164	1.00	0.004	1.00	< 0.001
		≥ 116.0	36	13.86 (2.33-82.43)		8.96 (2.94-27.28)	
CRP (POD1), mg/dL	0.664	< 6.2	80	1.00	0.397		
		≥ 6.2	120	2.53 (0.30-21.64)			
CRP (POD3), mg/dL	0.755	< 14.8	150	1.00	0.042	1.00	0.001
		≥ 14.8	50	5.72 (1.07-30.60)		5.65 (2.00-15.92)	
Operative time, min	0.613	< 220	102	1.00	0.044	1.00	0.072
		≥ 220	98	6.79 (1.05-43.86)		2.67 (0.92-7.76)	
Blood loss, mL	0.631	< 289	145	1.00	0.109		
		≥ 289	55	3.98 (0.73-21.60)			
Approach	NA	Open	123	7.97 (0.22-295.22)	0.260		
		Laparoscopic	77	1.00			
Extent of gastric resection	NA	Distal gastrectomy	136	1.00	0.516		
		Total/Proximal gastrectomy	64	1.82 (0.30-11.15)			
Extent of lymph node dissection	NA	D0/D1	59	1.00	0.047	1.00	0.106
		D1+/D2	141	7.80 (1.02-59.43)		3.16 (0.78-12.73)	
Reconstruction modality after gastrectomy	NA	Billroth I	98	1.00	0.466		
		Roux-en-Y/Double tract	102	2.55 (0.20-31.85)			
Stage	NA	I	84	1.00	0.207		
		II, III	116	7.67 (0.32-181.85)			

ASA-PS: American Society of Anesthesiologists-physical status, GPS: Glasgow Prognostic Score, PNI: Prognostic Nutritional Index, NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio, POD: Postoperative day, NA: Not applicable

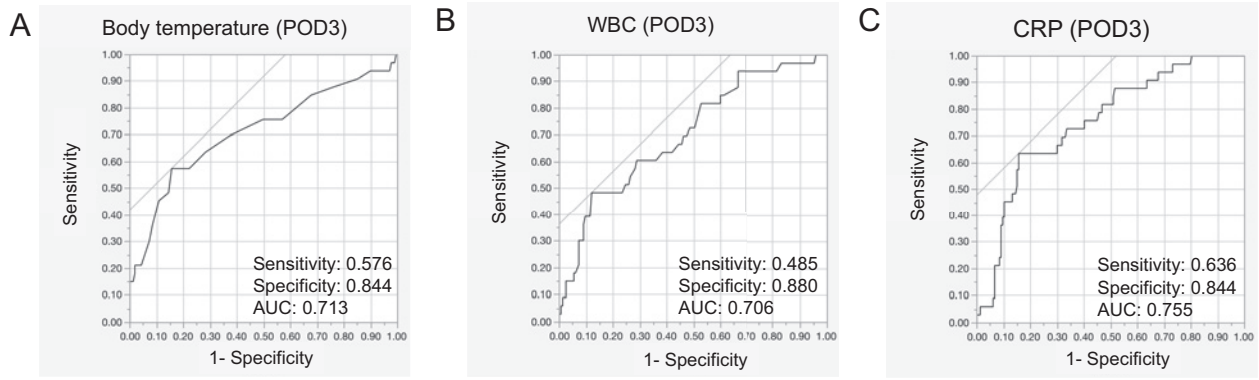

Fig. 3 Receiver operating characteristic curves for (**A**) body temperature on POD3 (cut-off value: 37.4°C, area under the curve (AUC): 0.713, sensitivity: 57.6%, specificity: 84.4%), (**B**) WBC on POD3 (cut-off value: 116.0×10²/μL, AUC: 0.706, sensitivity: 48.5%, specificity: 88.0%), and (**C**) CRP on POD3 (cut-off value: 14.8 mg/dL, AUC: 0.755, sensitivity: 63.6%, specificity: 84.4%)

Table 4 Univariate and multivariate analysis of the second cohort

Variables	AUC	Cut-off value	n	Univariate		Multivariate	
				Odds ratio (95% CI)	*p* value	Odds ratio (95% CI)	*p* value
Age, years	0.543	< 76	57	1.00	0.027	1.00	0.028
		≥ 76	51	21.71 (1.41-334.10)		13.35 (1.32-135.53)	
Sex	NA	Male	73	5.21 (0.19-17.23)	0.215		
		Female	35	1.00			
Smoking history	NA	Yes	63	13.10 (0.94-81.90)	0.045	4.13 (0.65-26.37)	0.134
		No	45	1.00		1.00	
Body temperature (POD1), ℃	0.490	< 38.6	100	1.00	0.107		
		≥ 38.6	8	7.97 (0.39-16.41)			
Body temperature (POD3), ℃	0.871	< 37.1	80	1.00	0.013	1.00	0.007
		≥ 37.1	28	42.32 (0.36-148.91)		17.01 (2.15-134.28)	
WBC (POD1), × 10²/μL	0.572	< 98.0	62	1.00	0.975		
		≥ 98.0	46	1.05 (0.04-27.66)			
WBC (POD3), × 10²/μL	0.725	< 75.0	40	1.00	0.023	1.00	0.048
		≥ 75.0	68	58.65 (1.76-195.53)		8.83 (0.79-99.11)	
CRP (POD1), mg/dL	0.770	< 7.1	61	1.00	0.305		
		≥ 7.1	47	8.48 (0.14-50.43)			
CRP (POD3), mg/dL	0.891	< 18.1	86	1.00	0.016	1.00	0.003
		≥ 18.1	22	29.45 (1.89-45.95)		22.85 (2.95-176.75)	
Stage	NA	I	54	1.00	0.147		
		II, III	54	13.85 (0.40-48.39)			

POD: Postoperative day, NA: Not applicable

compared to previous studies (Stage III: 42.5% vs 15-20%). On this basis, we considered that the slightly lower cut-off value in our study was because of the low threshold for onset of PIC. Further, the larger number of elderly patients may also account for the slightly higher complication rate compared with previous studies limited to East Asian countries (16.5% vs 7.5-11.1%).

According to Kim et al.[4], WBC count ≥ 96.6×10²/μL on POD4 was designated an independent predictive factor of PIC but with a predictive ability lower than serum CRP level. Nonetheless, BT and WBC count were not analyzed in previous studies. In our study, BT and WBC count on POD3 were selected as predictive factors of PIC other than CRP level, which the reproducibility of these findings was confirmed in a second cohort. Additionally, the symptom onset of PIC was earlier than the diagnosis of PIC, indicating that PIRI was considered as predictors of PIC. Generally, tumor cells release several cytokines and chemokines and activate inflammatory cells via the innate immune system during carcinogenesis[17]. Our study

Table 5 Detailed postoperative complictations and postoperative inflammatory response indicators in elderly vs non-elderly patients

PIRI of POD3	BT ≥ 37.4℃	BT < 37.4℃	*p* value	WBC ≥ 116.0 × 10^2/μL	WBC < 116.0 × 10^2/μL	*p* value	CRP ≥ 14.8 mg/dL	CRP < 14.8 mg/dL	*p* value
≥ 77 years (n=74)	n=22	n=52		n=16	n=58		n=21	n=53	
Pneumonia, n (%)	9 (40.9)	5 (9.6)	0.002	7 (43.8)	7 (12.1)	0.004	8 (38.1)	6 (11.3)	0.008
Anastomotic leak, n (%)	2 (9.1)	2 (3.9)	0.362	1 (6.3)	3 (5.2)	0.866	4 (19.1)	0 (0.0)	0.001
Pancreatic fistula, n (%)	1 (4.6)	1 (1.9)	0.525	2 (12.5)	0 (0.0)	0.006	1 (4.8)	1 (1.9)	0.492
Biliary fistula, n (%)	1 (4.6)	0 (0.0)	0.122	0 (0.0)	1 (1.7)	0.597	0 (0.0)	1 (1.9)	0.526
Abdominal abscess, n (%)	1 (4.6)	2 (3.9)	0.889	2 (12.5)	1 (1.7)	0.053	2 (9.5)	1 (1.9)	0.133
Cholecystitis, n (%)	0 (0.0)	1 (1.9)	0.513	1 (6.3)	0 (0.0)	0.055	0 (0.0)	1 (1.9)	0.526
< 77 years (n=126)	n=23	n=103		n=20	n=106		n=29	n=97	
Pneumonia, n (%)	4 (17.4)	3 (2.9)	0.006	5 (25.0)	2 (1.9)	< 0.001	5 (17.2)	2 (2.1)	0.002
Anastomotic leak, n (%)	1 (4.4)	2 (1.9)	0.494	1 (5.0)	2 (1.9)	0.402	2 (6.9)	1 (1.0)	0.069
Pancreatic fistula, n (%)	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA	0 (0.0)	0 (0.0)	NA
Biliary fistula, n (%)	0 (0.0)	1 (1.0)	0.635	0 (0.0)	1 (0.9)	0.663	0 (0.0)	1 (1.0)	0.583
Abdominal abscess, n (%)	3 (13.0)	0 (0.0)	< 0.001	1 (5.0)	2 (1.9)	0.402	3 (10.3)	0 (0.0)	0.001
Cholecystitis, n (%)	2 (8.7)	0 (0.0)	0.003	1 (5.0)	1 (0.9)	0.183	2 (6.9)	0 (0.0)	0.009

PIRI: Postoperative inflammatory response indicators, POD: Post operative day, BT: Body temperature, WBC: White blood cell, CRP: C-reactive protein, NA: Not applicable

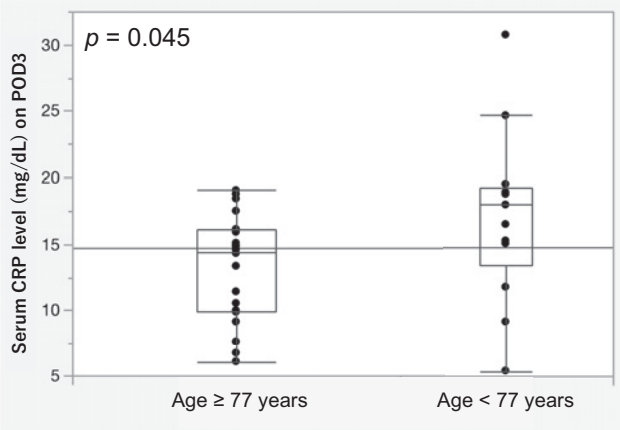

Fig. 4 Serum CRP level on POD3 in elderly patients (age ≥ 77 years) and non-elderly (age < 77 years) with PIC of CD Grade II, III. Median CRP level was significantly lower in the elderly patients compared to non-elderly patients (14.5 mg/dL vs 17.9 mg/dL; $p = 0.045$).

included patients with more advanced cancer, serving as a proinflammatory state, for which we speculated that BT and WBC count were selected as predictive factors of PIC. In contrast PNI, an inflammatory prognostic indicator, and NLR/PLR, an index of systemic inflammation, anti-tumor immunity, and nutritional status were not selected as predictive factors for PIC. Nevertheless, the predictive ability of BT and WBC count on POD3 were lower than that of CRP level. These factors may support the proposed diagnostic criteria for postoperative complications during the early postoperative course along with CRP level.

Since history of smoking is a risk factor for postoperative pneumonia in elderly patients with gastric cancer[18], we speculated that our results showing smoking history as a predictive factor for PIC were affected by the presence of postoperative pneumonia. Elderly adults have been reported as having risk factors for postoperative complications[5,15,19]. In patients above 75 years of age, circulating IL-6 and TNF-α on POD1 were significantly lower than in younger patients after distal gastrectomy[20]. In our study, median age was significantly higher in patients with PIC of CD Grade II, III than those with no PIC or PIC of Grade I. CRP is produced in the liver via inflammatory cytokines (IL-6, TNF-α) signaling generated from monocyte/macrophage activation from stimulation by a diffuse inflammatory reaction/response and tissue damage[21]. Thus, we speculated that the slightly lower cut-off value of CRP level on POD3 compared with previous studies was due to suppressed production of circulating IL-6 and TNF-α in the elderly, resulting in lower hepatic CRP production. Indeed, elderly patients showed significantly lower serum CRP levels compared to non-elderly patients on POD3 with PIC of CD Grade II, III in this study (**Fig. 4**).

As shown in **Table 5**, 38.1-43.8% of elderly patients developed pneumonia when one of the PIRI exceeded the threshold (CRP level ≥ 14.8 mg/dL, WBC count ≥ 116.0× 10^2/μL, or BT ≥ 37.4°C) on POD3. Therefore, chest X-rays and sputum culture-based antibiotic treatment are requi-

site in this context. Additionally, detailed exploration with CT scans and fluoroscopy should be considered for those with WBC count ≥ $116.0\times10^2/\mu L$ or CRP level ≥ 14.8 mg/dL on POD3, since these PIRI are associated with pancreatic fistula and anastomotic leak. For non-elderly patients, the frequency of pneumonia was 17.2-25.0%, which is lower than that in elderly patients; it is still associated with each of the PIRI on POD3. Furthermore, detailed exploration with CT scans should be considered with BT ≥ 37.4°C or CRP level ≥ 14.8 mg/dL, since these PIRI are associated with abdominal abscess and cholecystitis.

The limitations of this study are several. First is its retrospective design in a single center and the absence of long-term follow-up, which was limited to short-term outcomes that developed during the postoperative hospital stay. Based on this study, a prospective study will be needed to further elucidate the reproducibility and scientific premise of these results obtained retrospectively. Second, we did not measure other infectious indicators such as procalcitonin, lactic acid, and presepsin, which has higher sensitivity and specificity compared to CRP. Third, postoperative antipyretic analgesic treatment may mask fever aggravation. However, no studies have included postoperative BT measurements after gastric resection for gastric cancer. Thus, we think that our study constitutes useful clinical research, quantifying postoperative BT along with other conventional predictive factors.

Conclusion

Predictive factors relative to PIC in gastric cancer were CRP level ≥ 14.8 mg/dL, WBC ≥ $116.0\times10^2/\mu L$, and BT ≥ 37.4°C on POD3. Further, age ≥ 77 years, and history of smoking were predictive factors of PIC, which suggests this as a simple and practical indicator in clinical practice.

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Conflict of Interest: None declared.

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