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ORIGINAL ARTICLE

The prognostic significance of the comprehensive complication index in patients with gastric cancer

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Abstract

Purpose Postoperative complications worsen the prognosis of gastric cancer patients. The Clavien–Dindo classification is used to evaluate postoperative complications. The prognostic significance of the comprehensive complication index (CCI), a new tool for evaluating postoperative complications, remains unclear.

Methods This study included 452 gastric adenocarcinoma patients who underwent curative surgery.

Results The CCI values were significantly higher in older patients ($\geq$70 years; $P<0.0001$), male patients ($P<0.0001$), those with lymphatic invasion ($P=0.039$), and those with vascular invasion ($P=0.037$). The five-year overall survival (OS) and disease-specific survival (DSS) rates were significantly higher in patients without postoperative complications and those with Clavien–Dindo grade 1 complications in comparison to those with Clavien–Dindo grade 2–4 complications (80.4% vs. 66.2%, $P=0.0011$; 89.7% vs. 82.3%; $P=0.045$, respectively). Among patients with Clavien–Dindo grade 2–4 complications, the 5-year OS and DSS rates in the CCI^{High} group ($\geq$32.15) were significantly lower than those in the CCI^{Low} group (<32.15; 47.5% vs. 74.9%, $P=0.0086$; 63.1% vs. 90.0%, $P=0.0003$). A multivariate analysis identified the CCI as an independent prognostic indicator in patients with Clavien–Dindo grade 2–4 complications.

Conclusions The CCI was closely associated with the prognosis of patients with Clavien–Dindo grade 2–4 complications and may be a prognostic indicator.

Keywords Clavien–Dindo classification · Comprehensive complication index · Gastric cancer · Prognosis

Introduction

Gastric cancer (GC) is one of the most common malignancies. The mainstay curative treatment for GC is gastrectomy with regional lymph node dissection. In Japan, gastrectomy with D2 lymph node dissection has been the standard treatment for advanced GC [1] and has led to lower morbidity and mortality rates. However, D2 lymph node dissection and esophago-jejunostomy after total gastrectomy are technically demanding, and some patients suffer from postoperative complications [2], which can worsen the short-term outcomes (such as increased hospital stay or the need for longer fasting). Furthermore, some complications, such as anastomotic leakage and pancreatic fistula, may become serious or even life threatening.

In 2004, the Clavien–Dindo classification was reported as a tool for evaluating the severity of postoperative complications [3]. The Clavien–Dindo classification is useful for predicting short-term outcomes and has become a standard tool for evaluating postoperative complications in many fields of surgery [3, 4]. The Clavien–Dindo classification system grades complications according to the most severe complication or events that are judged to be relevant. This system does not account for complications of lesser magnitude or the total number of complications [3]; however, patients who suffer severe complications that involve organ failure usually experience multiple collateral complications. To address this issue, in 2013, Slankamenac et al. presented a new scoring tool, the so-called comprehensive complication index (CCI) [5]. The CCI is calculated as the sum of all complications weighted by severity. The formula for the CCI yields a range of scores to rank the severity of a combination

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of complications from 0 (no complications) to 100 (death) in a single patient. A recent study demonstrated that the CCI was more strongly correlated with the postoperative hospital stay than the Clavien–Dindo classification in patients who underwent radical GC surgery [6], indicating the possibility that the CCI may be more useful for predicting short-term outcomes than the Clavien–Dindo classification system.

Postoperative complications also negatively affect the long-term outcome for a wide range of cancers [7–10], including GC [11, 12]. In most studies showing a correlation between postoperative complication and prognosis, the Clavien–Dindo classification was used to evaluate postoperative complications. A recent report showed that the CCI predicts cancer-specific survival after resection of colorectal metastases independently of the RAS mutation status [13]. This indicates the possibility that CCI is also more useful than the Clavien–Dindo classification system for predicting both the short-term and long-term outcomes. However, the prognostic significance of the CCI in GC patients remains unclear. Thus, the aim of the current study was to investigate the prognostic significance of the CCI in GC patients.

Materials and methods

Patients

This study was based on a retrospective analysis of 452 gastric adenocarcinoma patients who underwent curative gastrectomy (R0 resection) at our institution between January 2005 and December 2013. The clinicopathological findings were determined according to the Japanese Classification of Gastric Carcinoma [14]. All patients underwent either distal partial, proximal partial, or total gastrectomy with regional lymph node dissection. Five patients received neoadjuvant chemotherapy, 65 received adjuvant chemotherapy, and 10 received perioperative chemotherapy. None of the patients underwent radiation therapy. Patients were periodically checked for early recurrence by diagnostic imaging (chest X-ray, upper gastrointestinal fibroscopy, ultrasonography, and computed tomography). Causes of death and patterns of recurrence were determined by reviewing medical records, including laboratory data, ultrasonography, computed tomography, scintigraphy, peritoneal puncture, and laparotomy, or by asking family members. In some cases, postmortem examinations were performed to determine the cause of death. Complications that occurred within 30 postoperative days were considered to be relevant to the surgical procedure, regardless of whether it involved re-admission or a re-visit. Complications that occurred at more than 30 days after surgery were collected when they occurred during the same hospitalization period. The Clavien–Dindo classification system was used to evaluate the severity of all complications. The CCI was calculated as the sum of all complications weighted by severity using the CCI calculator available at (https://www.assessurgery.com/aboutcci-calculator/) [5].

From the patient's records we collected postoperative blood test data measured one month after the operation, including the total peripheral blood lymphocyte and neutrophil counts (/mm^3). The neutrophil–lymphocyte ratio (NLR) was determined by dividing the peripheral neutrophil count by the peripheral lymphocyte count.

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional Research Committee and with the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards. The Institutional Review Board of our institution approved the study. The requirement for informed consent was waived.

Statistical analysis

Differences in the clinicopathological characteristics of the two groups were evaluated using the Mann–Whitney *U* test. Fisher's exact test was used to compare the frequency of recurrence according to the CCI. The Youden index was calculated using a receiver operating characteristic (ROC) analysis to determine the optimal cutoff value for the CCI in the survival analysis. Survival curves were calculated according to the Kaplan–Meier method. For the analysis of disease-specific survival (DSS), patients who died from causes other than GC were considered lost to follow-up at the time of death. Differences between survival curves were identified by a log-rank test. A multivariate analysis of factors associated with overall survival (OS) and DSS was performed together with a Cox's proportional hazards analysis and a stepwise procedure. P values of < 0.05 were considered to indicate statistical significance. The GraphPad Prism (GraphPad Software, Inc., La Jolla, CA, USA) and Stat View (Abacus Concepts, Inc., Berkeley, CA, USA) software programs were used to perform the statistical analyses.

Results

Among the 452 gastric adenocarcinoma patients included in the study, 172 patients (38%) developed postoperative complications. Among the 172 patients, 104 patients (60.5%) developed a single complication and 68 patients (39.5%) developed multiple complications. The severity of the complications, according to the Clavien–Dindo classification system was graded as follows: grade 1, $n = 36$; grade 2, $n = 72$; grade 3, $n = 61$; and grade 4, $n = 3$.

The distribution of patients, according to the CCI is shown in Fig. 1. Each grade of complication is assigned a

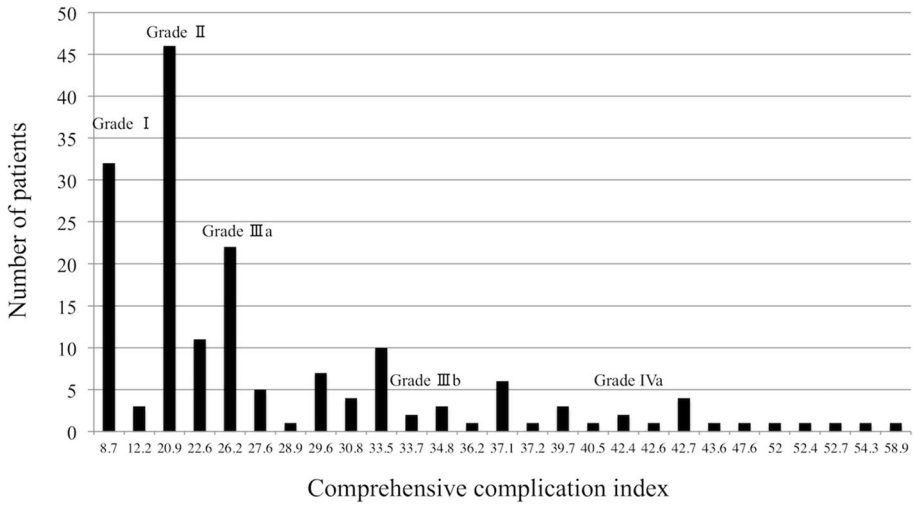

Fig. 1 The distribution of the comprehensive complication index values in the gastric cancer patients in the current study

prefixed score (grade 1 = 8.7, grade 2 = 20.9, grade 3a = 26.2, grade 3b = 33.7, grade 4a = 42.4, grade 4b = 46.2), and consistent with the Clavien–Dindo classifications, spikes were observed at 8.7, 20.9, and 26.2. However, there were no spikes at 33.7 or 42, indicating that the prevalence of multiple complications was high in patients with Clavien–Dindo grade 3b and 4. The mean CCI was 9.4 (range 0–58.9). Table 1 shows the correlation between the CCI and the clinicopathological variables in GC patients. The CCI values in elderly patients (≥ 70 years), male patients, those with lymphatic invasion, and those with vascular invasion were significantly higher than those in non-elderly patients (< 70 years; $P < 0.0001$), female patients ($P < 0.0001$), those without lymphatic invasion ($P = 0.039$), and those without vascular invasion ($P = 0.037$), respectively.

The 5-year OS rates in patients without postoperative complication and those with Clavien–Dindo grade 1 complications (80.4%) were significantly higher than those in patients with Clavien–Dindo grade 2–4 complications (66.2%; $P = 0.0011$, Fig. 2a). Furthermore, the 5-year DSS rates in patients without postoperative complications and those with Clavien–Dindo grade 1 complications (89.7%) were significantly higher than those in patients with Clavien–Dindo grade 2–4 complications (82.3%; $P = 0.045$, Fig. 2b). The ROC analysis indicated that the AUCs of CCI for 5-year OS and 5-year DSS were 0.586 ($P = 0.0066$, Fig. 3a) and 0.563 ($P = 0.15$, Fig. 3b), respectively, in all patients in the current study and 0.579 ($P = 0.14$, Fig. 3c) and 0.664 ($P = 0.023$, Fig. 3d) in patients with Clavien–Dindo grade 2–4 complications, indicating that the CCI could most successfully predict 5-year DSS in patients with Clavien–Dindo grade 2–4 complications.

The ROC analysis for 5-year DSS indicated that the optimal cut-off value of the CCI was 32.15 in patients with Clavien–Dindo grade 2–4 complications. Based on this optimal cut-off value, we divided patients with Clavien–Dindo grade 2–4 complications into a high CCI group (CCI^{High}; ≥ 32.15; $n = 41$) and a low CCI group (CCI^{Low}; < 32.15%; $n = 95$). Within this subgroup of patients, the 5-year OS rate in the CCI^{High} group (47.5%) was significantly lower than that in the CCI^{Low} group (74.9%; $P = 0.0086$, Fig. 4a). Furthermore, in this same subgroup, the 5-year DSS rate in the CCI^{High} group (63.1%) was significantly lower than that in the CCI^{Low} group (90.0%; $P = 0.0003$, Fig. 4b). We performed further analyses of patients with Clavien–Dindo grade 2 complications and those with Clavien–Dindo grade 3–4 complications. The 5-year OS rates of patients with Clavien–Dindo grade 2 complications were 73.2% and 20.0% in the CCI^{Low} and CCI^{High} groups, respectively ($P = 0.011$, Fig. 5a). The 5-year DSS rates of patients with Clavien–Dindo grade 2 complications were 90.6% and 50.0% in the CCI^{Low} and CCI^{High} groups, respectively ($P = 0.015$, Fig. 5b). Furthermore, the 5-year OS rates of patients with Clavien–Dindo grade 3–4 complications were 81.0% and 53.4% in the CCI^{Low} and CCI^{High} groups, respectively ($P = 0.11$, Fig. 6a). A significant difference was observed in the 5-year DSS rates of the CCI^{High} group (66.3%) and CCI^{Low} group (92.4%) in patients with Clavien–Dindo grade 3–4 complications ($P = 0.049$, Fig. 6b). Furthermore, among patients with Clavien–Dindo grade 3–4 complications, 11 and 2 patients experienced recurrence after operations in the CCI^{High} and CCI^{Low} groups, respectively, and the difference was statistically significant ($P = 0.028$). A multivariate analysis was performed using covariates, including age, sex, tumor size, histology, CCI, depth of invasion, lymph node metastasis, lymph node metastasis, lymphatic invasion, vascular invasion, surgical approach, and adjuvant chemotherapy. The results indicated that CCI was an independent prognostic indicator for both OS (Table 2) and DSS (Table 3) in patients with Clavien–Dindo grade 2–4 complications.

Finally, we determined the possible mechanisms responsible for the poor prognosis observed in the GC patients

Table 1 Correlation of patient characteristics with the comprehensive complication index

Variables	CCI	*P* value
Age (years)		< 0.0001
< 70 (*n* = 221)	6.9 ± 12.0	
≥ 70 (*n* = 231)	11.7 ± 14.8	
Gender		< 0.0001
Male (*n* = 330)	10.7 ± 14.4	
Female (*n* = 122)	5.7 ± 10.9	
Tumor size (cm)		0.365
< 4 (*n* = 278)	8.9 ± 13.5	
≥ 4 (*n* = 174)	10.1 ± 14.1	
Histology[a]		0.287
Differentiated (*n* = 246)	9.9 ± 13.9	
Undifferentiated (*n* = 206)	8.7 ± 13.5	
Depth of invasion		0.487
T1 (*n* = 284)	9.0 ± 13.5	
T2/3/4 (*n* = 168)	9.9 ± 14.0	
Lymph node metastasis		0.418
Absent (*n* = 344)	9.1 ± 13.5	
Present (*n* = 108)	10.2 ± 14.4	
Lymphatic invasion		0.039
Absent (*n* = 186)	7.9 ± 13.3	
Present (*n* = 266)	10.3 ± 14.0	
Vascular invasion		0.037
Absent (*n* = 233)	8.0 ± 12.9	
Present (*n* = 219)	10.7 ± 14.4	
Stage of disease		0.478
I (*n* = 310)	9.1 ± 13.7	
II/III/IV (*n* = 142)	9.8 ± 13.7	

[a]Differentiated, papillary, or tubular adenocarcinoma; undifferentiated, poorly differentiated, mucinous adenocarcinoma, and signet-ring cell carcinoma

All results are expressed as the mean ± SD

T1 tumor invasion of the lamina propria or submucosa, *T2* tumor invasion of the muscularis propria, *T3* tumor invasion of the subserosa, *T4* tumor penetration of the serosa or tumor invasion of adjacent organs

with postoperative complications. Since it is likely that the presence of postoperative complications was associated with prolonged inflammation, we determined the correlation between the presence of postoperative complications and the postoperative NLR, which was one of the most frequently used inflammation-based markers. The postoperative NLR in patients with Clavien–Dindo grade 2–4 complications (2.28 ± 1.34) was significantly higher than that in those without postoperative complications and those with Clavien–Dindo grade 1 complications (1.88 ± 1.08; $P = 0.0096$). Furthermore, among the subgroup of patients with Clavien–Dindo grade 2–4 complications, the postoperative NLR in the CCI^{High} group was significantly higher than that in the CCI^{Low} group (3.03 ± 1.37 vs. 2.03 ± 0.94, respectively; $P = 0.037$). Delayed initiation of adjuvant chemotherapy after a radical operation for GC might also be associated with a poor prognosis in GC patients with postoperative complications. In fact, among patients with stage II/III GC, the post-surgical interval before the initiation of S-1 adjuvant chemotherapy in patients with Clavien–Dindo grade 2–4 complications (52.9 ± 35.6 days) was significantly longer than that in patients without postoperative complications and those with Clavien–Dindo grade 1 complications (31.8 ± 14.2 days; $P = 0.0097$). Furthermore, in stage II/III GC patients with Clavien–Dindo grade 2–4 complications, the interval between surgery and the initiation of S-1 adjuvant chemotherapy in the CCI^{High} group was significantly longer than that in the CCI^{Low} group (81.1 ± 46.7 vs. 38.7 ± 10.1, respectively; $P = 0.034$).

Discussion

In the current study, we demonstrated that the 5-year OS and DSS rates in patients without postoperative complications and those with Clavien–Dindo grade 1 complications were significantly higher in comparison to those with Clavien–Dindo grade 2–4 complications, indicating that postoperative complications worsened the prognosis of GC. There are some possible explanations for the close correlation between postoperative complications and a poor prognosis in GC patients. In the current study, the postoperative

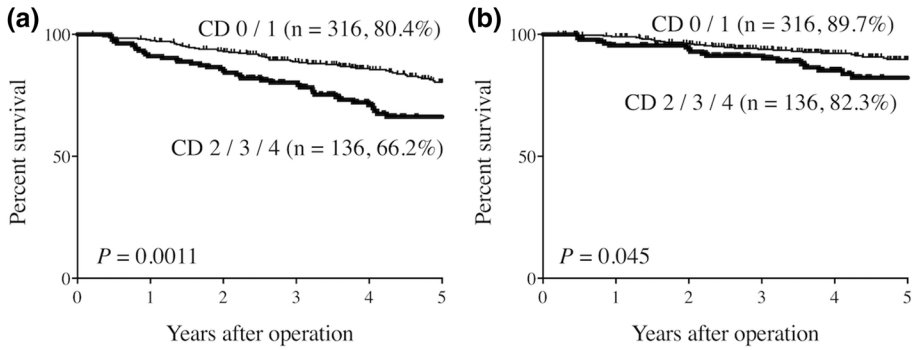

Fig. 2 Overall survival curves (**a**) and disease-specific survival curves (**b**) in gastric cancer patients, according to the Clavien–Dindo classification

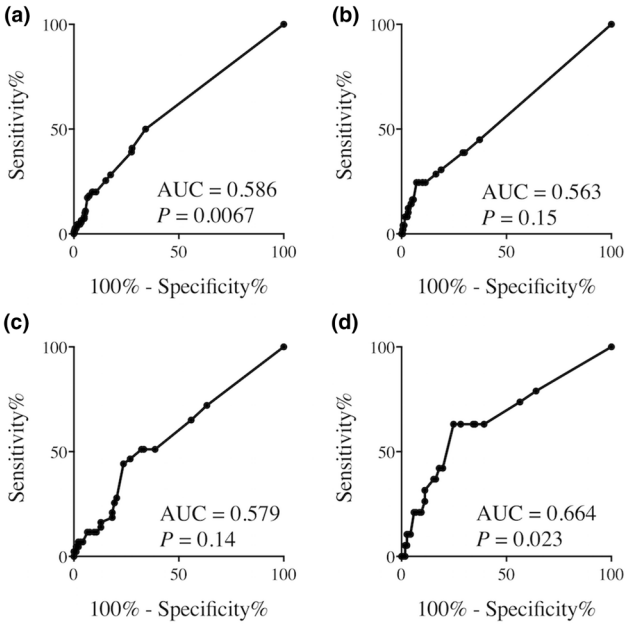

Fig. 3 ROC curves of the comprehensive complication index for overall survival and disease-specific survival in all patients (**a**, **b**) and those with Clavien–Dindo grade 2–4 complications (**c**, **d**), respectively

NLR measured at one month after surgery in patients with Clavien–Dindo grade 2–4 complications was significantly higher in comparison to those without postoperative complication and those with Clavien–Dindo grade 1 complications. A high NLR reflects a decreased lymphocyte count, which is associated with impaired immunity. In fact, previous studies demonstrated that prolonged inflammation induces impaired immunity [15, 16]. Recurrence usually arises from micrometastases, which cannot be detected by ordinary diagnostic imaging, including ultrasonography, computed tomography, and positron emission tomography. The success of immune checkpoint inhibitors, such as antibodies to programmed cell death protein 1 and cytotoxic T lymphocyte antigen-4, in the treatment of various tumor types clearly indicates that effective immunity can be induced in cancer patients [17–19]. Dunn et al. suggested that the adaptive immune system could identify and eliminate nascent tumor cells [20]. Therefore, the impaired immunity induced by postoperative complications may allow micrometastatic cancer cells to grow, resulting in recurrence.

A high NLR also reflects an increased neutrophil count. We recently reported that an increased postoperative neutrophil–lymphocyte ratio (NLR) is closely associated with a poor prognosis in GC patients [21]. Ock et al. recently demonstrated that the NLR is mainly associated with osteopontin and interleukin-6 (IL-6) in GC patients. Osteopontin and IL-6 are well-known chemotactic factors for neutrophils [22, 23]. High levels of osteopontin and IL-6 are associated with a poor prognosis in patients with

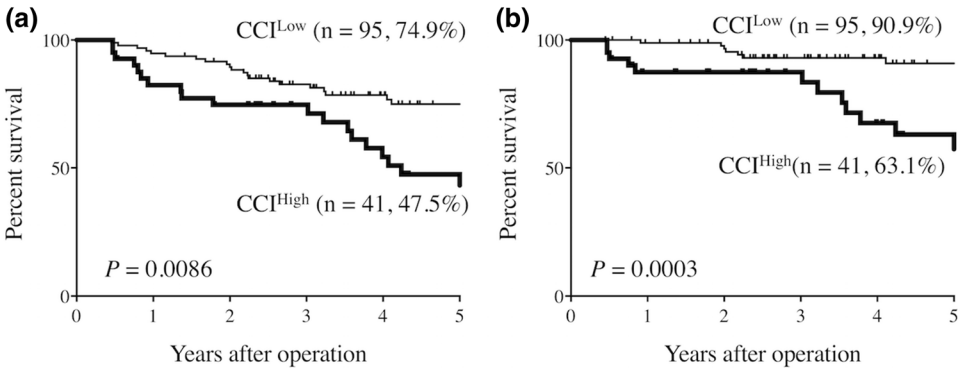

Fig. 4 Overall survival curves (**a**) and disease-specific survival curves (**b**) according to the comprehensive complication index in gastric cancer patients with Clavien–Dindo grade 2–4 complications

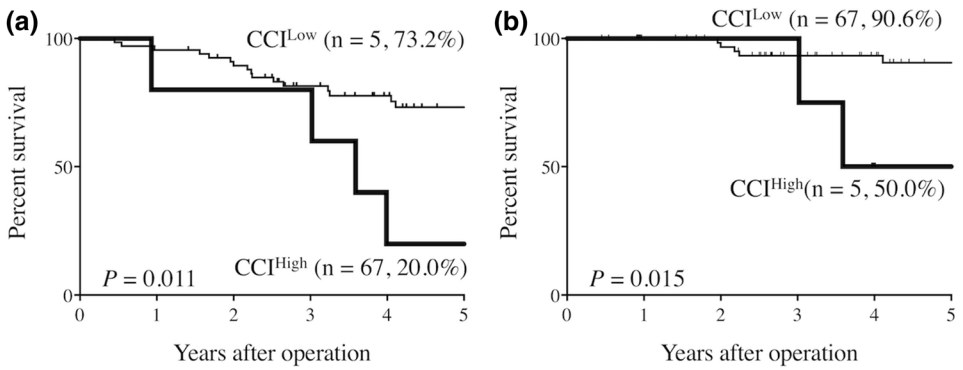

Fig. 5 Overall survival curves (**a**) and disease-specific survival curves (**b**) according to the comprehensive complication index in gastric cancer patients with Clavien–Dindo grade 2 complications

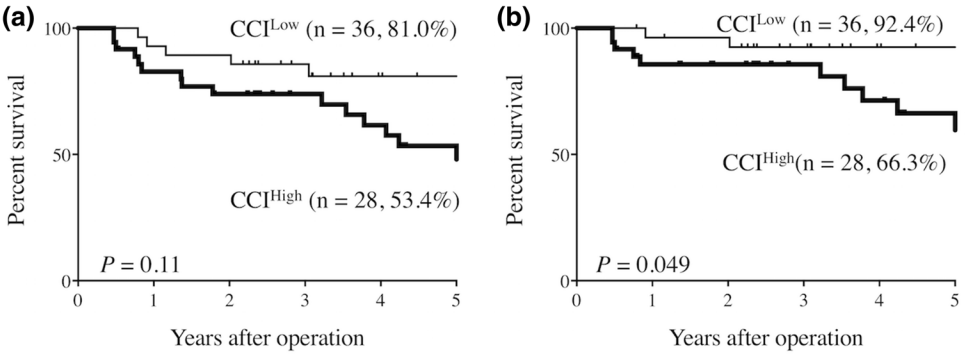

Fig. 6 Overall survival curves (**a**) and disease-specific survival curves (**b**) according to the comprehensive complication index in gastric cancer patients with Clavien–Dindo grade 3–4 complications

Table 2 The multivariate analysis using a Cox proportional hazards model and a stepwise procedure to identify independent prognostic factors for overall survival in gastric cancer patients with CDC2/3/4

	P value	Hazard ratio	95% CI
Age[a]	0.01	1.055	1.013–1.1
Tumor size[a]	0.016	1.163	1.029–1.316
Lymph node metastasis (N0–N3)	0.001	1.607	1.209–2.137
CCI (CCI^{High} versus CCI^{Low})	0.014	2.147	1.171–3.937

[a]Continuous variables

N0 no regional lymph node metastases, *N1* metastasis in 1–2 regional lymph nodes, *N2* metastasis in 3–6 regional lymph nodes, *N3* metastasis in 7 or more regional lymph nodes

CI confidence interval

Table 3 The multivariate analysis using a Cox proportional hazards model and a stepwise procedure to identify independent prognostic factors for disease-specific survival in gastric cancer patients with CDC2/3/4

	P value	Hazard ratio	95% CI
Depth of invasion (T1–4)	0.002	2.450	1.387–4.326
Lymph node metastasis (N0–N3)	0.009	1.760	1.15–2.693
CCI (CCI^{High} versus CCI^{Low})	0.007	3.762	1.443–9.807

Depth of invasion is described in Table 1

Lymph node metastasis is described in Table 2

CI confidence interval

most types of tumors, including GC [24–26]. Osteopontin can modulate extracellular remodeling to promote the epithelial–mesenchymal transition and angiogenesis [27, 28]. IL-6 can activate the signal transducer and activator of transcription signaling pathway, which induces cancer progression [23, 26]. Furthermore, IL-6 can induce the N2 neutrophil phenotype, which promotes tumor growth and metastasis. Overall, these effects of neutrophils may promote the growth of residual micrometastatic cancer cells, resulting in post-operative recurrence.

The delayed initiation of adjuvant chemotherapy after a radical operation for GC might be associated with the poor prognosis of GC patients with postoperative complications. The principle of adjuvant chemotherapy is that the circulation of anticancer drugs throughout the entire body via the bloodstream can control micrometastasis and prevent recurrence. The effectiveness of postoperative adjuvant chemotherapy in preventing recurrence has been shown in patients with GC who underwent curative surgery. Nakajima et al. revealed a significant survival benefit of postoperative adjuvant chemotherapy with uracil–tegafur in patients with serosa-negative, node-positive GC [29]. The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) also showed a survival benefit from adjuvant chemotherapy after D2 gastrectomy in comparison to surgery alone for patients with stage II/III gastric cancer [30]. The Japanese Gastric Cancer Treatment Guideline recommends adjuvant chemotherapy with S-1 for 1 year for patients with stage II/III GC patients who undergo gastrectomy with D2 lymph node dissection, based on the results of ACTS-GC [1]. Furthermore, adjuvant capecitabine and oxaliplatin treatment significantly improved 3-year disease-free survival in stage II and III GC patients who had undergone gastrectomy with D2 lymph node dissection [31]. These results strongly indicate that adjuvant chemotherapy is an indispensable component of treatment aimed at preventing recurrence in patients with resectable advanced GC. A meta-analysis demonstrated that a 4-week delay in the initiation of adjuvant chemotherapy was associated with a significant decrease in both OS and disease-free survival in colorectal cancer patients [32]. In addition, the initiation of adjuvant chemotherapy at more than 61 days after surgery was associated with adverse outcomes among patients with stage II breast cancer [33]. Thus, it would be theoretically better to start adjuvant chemotherapy promptly after curative surgery to prevent recurrence. Most clinical trials mandate that adjuvant chemotherapy begins within 6–8 weeks after surgery.

The Japanese Gastric Cancer Treatment Guideline also recommends starting adjuvant chemotherapy with S-1 within 6 weeks post-surgery for patients with stage II–III GC

[1]. Based on this recommendation, Yamamoto et al. examined stage II/III GC patients who underwent S-1 adjuvant chemotherapy and showed that the prognosis of advanced GC was significantly related to the initiation of S-1 adjuvant treatment within 6 weeks after surgery [34]. In this regard, we previously reported that the interval between surgery and the initiation of adjuvant chemotherapy differed significantly between patients with and without postoperative complications. We also showed that among patients with stage II–III GC, the prognosis of patients who started adjuvant chemotherapy within 6 weeks after surgery tended to be better than that of those who started adjuvant chemotherapy at more than 6 weeks after surgery [35]. The present study demonstrated that among stage II/III GC patients, the interval between surgery and the initiation of S-1 adjuvant chemotherapy in patients with Clavien–Dindo grade 2–4 complications was significantly longer than that in patients without postoperative complications and those with Clavien–Dindo grade 1 complications.

In this study, multiple complications were more prevalent in patients with Clavien–Dindo grade 2–4 complications than in other patients. Thus, we hypothesized that other complications, which are not accounted for in the Clavien–Dindo classification system, might affect the prognosis of GC patients, especially in patients with Clavien–Dindo grade 2–4 complications because prolonged inflammation, impaired immunity, and the delayed initiation of adjuvant chemotherapy with S-1 were likely to be observed more frequently in patients with multiple complications than in those with a single complication. We found that the 5-year DSS rate in the CCI^{High} group was significantly worse than that in the CCI^{Low} group in both patients with Clavien–Dindo grade 2 complications and patients with Clavien–Dindo grade 3–4 complications. Furthermore, the multivariate analysis indicated that CCI was an independent prognostic indicator in patients with Clavien–Dindo grade 2–4 complications. Thus, combining the Clavien–Dindo classification and the CCI might be superior to the single use of either system in predicting the prognosis of GC. The short-term outcome (duration of hospital stay) was reported to be closely correlated with the CCI in GC patients [6]. To the best of our knowledge, however, this study is the first to demonstrate the prognostic significance of the CCI in GC patients. Our results also support the possibility that prolonged inflammation, impaired immunity, and the delayed initiation of S-1 adjuvant chemotherapy were responsible for the poor prognosis of GC patients with Clavien–Dindo grade 2–4 complications and high CCI values.

The present study was associated with several limitations. First, our study was retrospective in nature and was thus subject to bias. Second, a previous study, which demonstrated a correlation between CCI and cancer-specific survival after resection of colorectal metastases, used 26.2 as a cut-off value for the CCI [13], which is smaller than our cut-off value. The optimal cut-off value for the CCI remains unclear and might be heterogeneous in different types of cancer. Third, study population was relatively small. Thus, these results must be confirmed in a large-scale trial.

In conclusion, the CCI was closely associated with the prognosis of patients with Clavien–Dindo grade 2–4 postoperative complications and could be used as a prognostic indicator. Furthermore, to improve the prognosis of GC patients, every effort should be made to avoid the development of postoperative complications.

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Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest in association with the present study.

Ethical approval All procedures performed in studies involving human participants were carried out in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki Declaration and its later amendments or with comparable ethical standards.

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