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ORIGINAL ARTICLE

Preoperative total cholesterol-lymphocyte score as a novel immunonutritional predictor of survival in gastric cancer

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Abstract

Purpose Immunonutritional status is a known prognostic correlate in the context of gastric cancer (GC). In the present study, we investigated the prognostic relevance of a lipid profile-based immunonutritional score in patients with GC.

Methods Data pertaining to 224 patients with stage II and III GC who underwent curative gastrectomy were retrospectively analyzed. The total cholesterol-lymphocyte score (TL score) was defined as follows: patients with both low total cholesterol (TC) and total lymphocyte count were allocated a score of 2; patients with only one or none of these biochemical abnormalities were allocated a score of 1 or 0, respectively.

Results Among the serum lipid indices, low TC was the strongest predictor of cancer-specific survival (CSS; $p = 0.001$). On multivariate analysis, both low prognostic nutritional index (PNI) ($p < 0.001$) and high TL score ($p = 0.003$) were independent prognostic factors. PNI was significantly associated with peritoneal recurrence ($p = 0.047$), while TL score was significantly associated with locoregional and distant metastasis ($p = 0.004$ and $p = 0.003$, respectively).

Conclusions TL score may facilitate risk stratification of patients based on CSS. TL score plus PNI may help predict the recurrence pattern in patients with stage II and III GC.

Keywords Gastric cancer · Immunonutritional score · Lipid profile · Cholesterol · Lymphocyte count

Introduction

Gastric cancer (GC) is one of the main causes of disease-related deaths globally despite considerable advances in diagnostic and therapeutic modalities. Globally, GC is the fifth most common cancer and the third leading cause of cancer-related mortality [1]. The pathological staging of the resected tumor (TNM criteria) is widely used to predict outcomes of GC patients in clinical practice. However, there is considerable variability in the prognosis of patients with the same disease stage, which suggests the existence of additional factors that affect prognosis. Therefore, identification of additional biomarkers that may help predict the outcomes of individual GC patients is a key imperative.

GC causes debilitating malnutrition and impaired immune response due to decreased oral intake, digestive tract obstruction, persistent bleeding, and inflammation associated with the primary tumor. Impaired immunonutritional status has an adverse effect on treatment outcomes in cancer patients; it is associated with increased surgical morbidity and poor tolerance to chemotherapy [2–5]. Therefore, objective indices for evaluation of preoperative immunonutritional status can help predict postoperative prognosis of patients with GC.

Several useful immunological and nutritional prognostic biomarkers for cancer patients have been identified including prognostic nutritional index (PNI) [6, 7]. Serum lipid profile [including triglyceride, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and the LDL-C to HDL-C ratio (LHR)] was shown

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to be associated with prognosis of cancer patients [8–11]. However, the relationship of various serum lipid indices with survival outcomes of patients with advanced GC (AGC) is not well characterized. CONUT score is a scoring system calculated from serum albumin level, total cholesterol, and lymphocyte count; it has been shown to be associated with prognosis in the context of several cancers [12–14]. However, the predictive ability of CONUT score was shown to vary according to cancer progression [14], which suggests that appropriate immunonutritional indices should be considered for each stage of the primary tumor.

In the present study, we sought to construct a new, convenient, and optimal immunonutritional scoring system based on serum lipid indices and evaluated its utility as a prognostic marker in patients with stage II and III GC.

Material and Methods

Patients

Data pertaining to 224 patients with pathological stage II and III GC who underwent curative gastrectomy at the Kyoto Prefectural University of Medicine between 2008 and 2015 were retrospectively analyzed. Clinical data were reviewed from the medical record database of our institution. Preoperative diagnosis of gastric adenocarcinoma was confirmed by endoscopic biopsy. Gastrectomy and lymph node dissection were performed according to the Japanese Gastric Cancer Treatment Guidelines. [15]. Tumor staging was determined based on the 8th edition of the International Union Against Cancer tumor, node, metastasis (TNM) classification system [16]. Classification of the macroscopic and histological type, and lymphatic or venous invasion was based on the Japanese Classification of Gastric Carcinoma 3rd edition [17]. Postoperatively, patients were followed up every 3–6 months for the first 2 years, and follow-up was continued for at least 5 years. Follow-up evaluation consisted of physical examination, blood investigations, computed tomography (CT), and gastroscopy. The presence of recurrence was confirmed by imaging, which typically included CT. Recurrence was confirmed histologically if possible, via surgical biopsy, needle biopsy, or appropriate fluid cytology.

Immunonutritional markers

Preoperative peripheral blood samples were routinely collected from patients within 30 days before the potentially curative surgery. The laboratory data included serum albumin level, total lymphocyte count, and lipid profile [serum total cholesterol, HDL-C, LDL-C, non-HDL non-LDL (remnant cholesterol), and triglyceride levels]. The PNI was calculated as [albumin (g/L) + 0.005 × total lymphocyte count (count/mm^3)] [18]. The CONUT score was calculated from the serum albumin levels, lymphocyte count, and total cholesterol level (Table S1) [19]. The minimum p value approach (log-rank test) was used to determine the optimal cut-off value of immunonutritional factors that best predicted cancer-specific survival (CSS) [20].

Furthermore, we developed a new immunonutritional score using the strongest prognostic factor among lipid indices and lymphocyte count with cut-off values derived from a minimum p value approach. The details of this score are described in the "Results" section.

Statistical analysis

Between-group differences with respect to categorical variables were compared using the chi-squared test. The primary endpoint in this study was CSS to exclude the effect of deaths from other causes such as cardiovascular event. Survival curves for CSS and the estimated cumulative incidence rate for each recurrence pattern (peritoneal dissemination, locoregional metastasis, and distant metastasis) were derived using the Kaplan–Meier method and compared by log-rank test. Cox proportional hazards regression models were used to calculate the hazard ratios (HRs) and the respective 95% confidence intervals (CIs) for each variable. Multivariate survival analysis was performed using Cox's proportional hazard regression model. p values < 0.05 were considered indicative of statistical significance. The JMP 10.0 statistical software for Macintosh (SAS Institute, Cary, NC, USA) was used for all analyses.

Results

Predictive values of nutritional or immunological factors for CSS

The optimal cut-off values of serum albumin level and lymphocyte count that best predicted CSS were 4.1 g/dL and 2130 count/mm^3, respectively. Patients with low albumin ($p < 0.001$, HR 2.48, 95% CI 1.51–4.09) or low lymphocyte count ($p = 0.04$, HR 1.69, 95% CI 0.99–3.00) showed significantly worse CSS as compared to their counterparts (Fig. 1).

Figure 2 illustrates the association between serum lipid indices and CSS. The optimal cut-off values of serum total cholesterol, LDL-C, HDL-C, remnant cholesterol, triglyceride levels, and LHR were 196 mg/dL, 127 mg/dL, 46 mg/dL, 23.8 mg/dL, 118 mg/dL, and 1.497 respectively. Serum total cholesterol, LDL-C, HDL-C, and remnant cholesterol levels showed a significant association with CSS ($p = 0.001$, 0.009, 0,025, and 0.010, respectively; Fig. 2a–d). Serum triglycerides and LHR were not associated with CSS ($p = 0.055$ and 0.440, respectively; Fig. 2e, f). Among these serum lipid indices, low

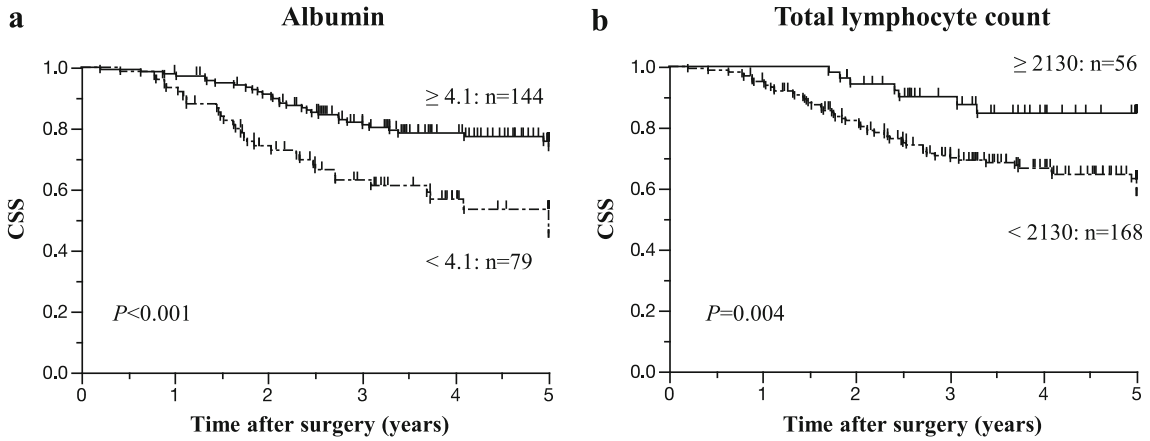

Fig. 1 Survival curves of gastric cancer patients stratified by serum albumin level and lymphocyte count. Kaplan–Meier survival curves for cancer-specific survival according to serum albumin level (**a**) and lymphocyte count (**b**)

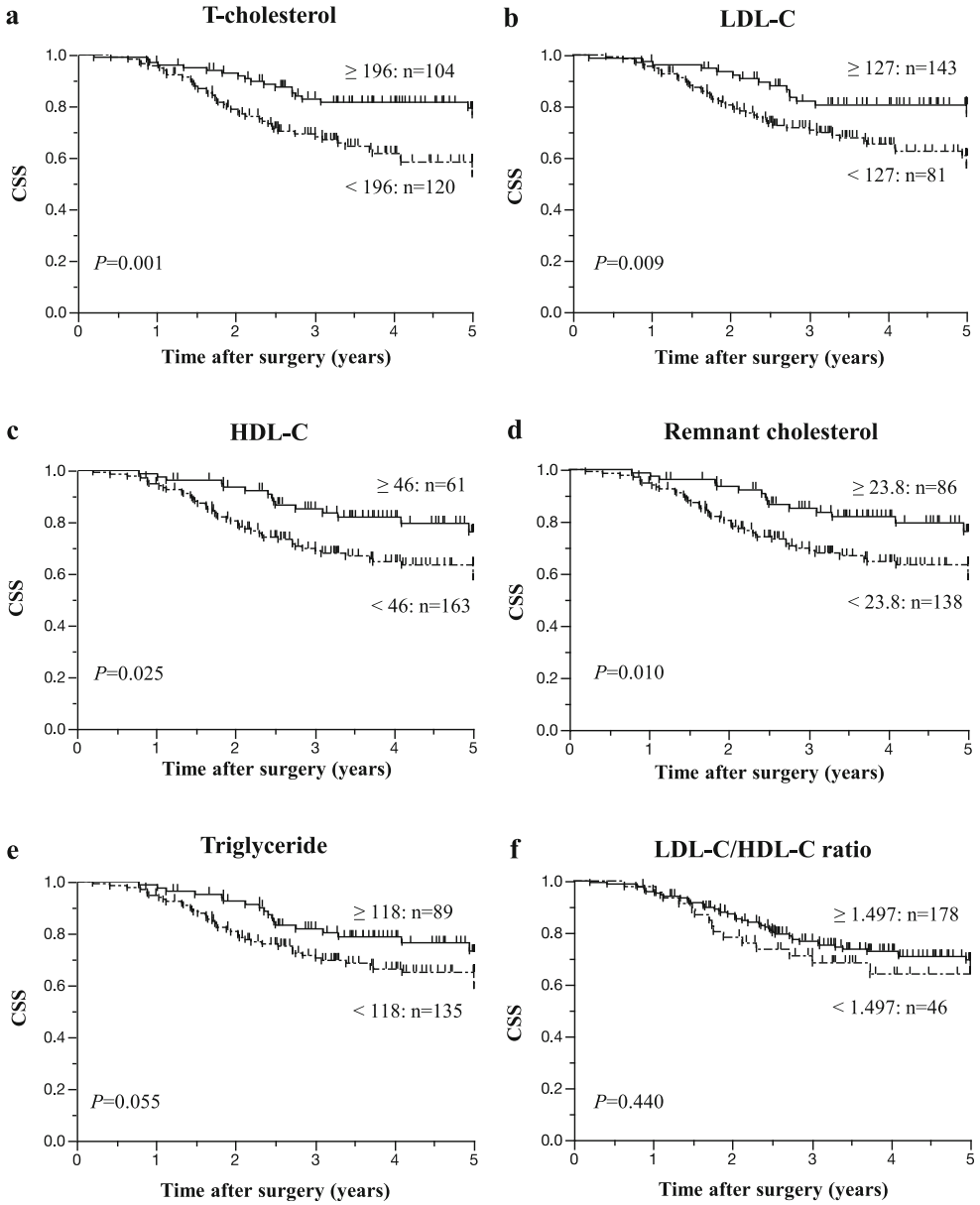

Fig. 2 Evaluation of the prognostic relevance of various serum lipid indices. Kaplan–Meier survival curves for cancer-specific survival according to serum total cholesterol level (**a**), LDL cholesterol level (**b**), HDL cholesterol level (**c**), remnant cholesterol level (**d**), triglyceride level (**e**), and HDL cholesterol to LDL cholesterol ratio (**f**)

total cholesterol level was the strongest predictor of CSS (p = 0.001, HR 2.34, 95% CI 1.38–4.10; Fig. 2a).

Total cholesterol-lymphocyte score

We constructed the total cholesterol-lymphocyte score (TL score) as follows: patients with both low total cholesterol (< 196 mg/dL) and lymphocyte count (< 2130 count/mm^3) were allocated a score of 2; patients with only one or none of these biochemical abnormalities were allocated a score of 1 or 0, respectively. Twenty-nine patients (13%) had a score of 0, 102 (45%) had a score of 1, and 93 patients (42%) had a score of 2.

TL score was associated with cancer progression

Table 1 shows the association between TL score status and clinicopathogical factors. On univariate analysis, high TL score (TL score 2) was significantly associated with older age (≥ 65 years, p = 0.041), larger tumor size (≥ 60 mm, p = 0.007), deeper tumor invasion (T4, p = 0.039), and pathological stage III (p = 0.026). On multivariate analysis, a larger tumor size was an independent risk factor for high TL score (p = 0.042, OR 1.79, 95% CI 1.02–3.17).

Association between immunonutritional markers and adjuvant chemotherapy

In patients with low PNI, the frequency of patients without chemotherapy was significantly higher and that of those with TS1 adjuvant chemotherapy was significantly lower than in patients with high PNI (p < 0.001; 47% vs. 25%; 35% vs. 64%; Table S2). Conversely, TL score was not significantly associated with the presence of adjuvant chemotherapy (p = 0.551; Table S2).

Immunonutritional markers predicted poor CSS in stage II and III GC

We investigated the association between prognosis and immunonutritional markers (Fig. 3). As previously reported, low PNI (< 49) was significantly associated with poor CSS (p < 0.001, HR 2.60, 95% CI 1.58–4.32; Fig. 3a), while high CONUT score (≥ 3) was not associated with poor CSS in this cohort (p = 0.098, HR 1.51, 95% CI 0.91–2.48; Fig. 3b). Moreover, the prognosis in GC patients was stratified according to TL score (score 0: 5y–CSS 91.7%; score 1: 72.7%; score 2: 48.3%, p < 0.001; Fig. 3c), and patients with high TL score showed significantly worse CSS compared to patients with low TL score (p < 0.001, HR 2.72, 95% CI 1.65–4.59; Fig. 3d).

Immunonutritional markers were independent prognostic factors

Table 2 shows the results of univariate and multivariate analyses to identify independent prognostic factors for CSS in patients with stage II and III GC. On univariate analysis, larger tumor size (p < 0.001), deeper tumor invasion (p < 0.001), presence of lymph node metastasis (p < 0.001), and low PNI plus high TL score (p < 0.001) were significantly associated with prognosis. On multivariate analysis, both PNI (p < 0.001, HR 2.36, 95% CI 1.43–3.95) and TL score (p = 0.003, HR 2.13, 95% CI 1.27–3.65) were independent predictors of CSS.

Correlation between estimated cumulative recurrence rates for each recurrence pattern and immunonutritional markers

We also investigated the association between the immunonutritional markers and the estimated cumulative recurrence rates for each recurrence pattern (Fig. 4). Patients with low PNI showed significantly higher recurrence rate via peritoneal dissemination (p = 0.047; Fig. 4a) compared to patients with high PNI, while no significant association in this respect was observed for locoregional and distant metastasis (p = 0.059 and p = 0.411, respectively; Fig. 4b, c). On the other hand, recurrence rates via locoregional and distant metastases in patients with high TL score were significantly higher compared to patients with low TL score (p = 0.004 and p = 0.003, respectively, Fig. 4e, f); however, no significant difference in this respect was observed for recurrence rate via peritoneal dissemination (p = 0.105; Fig. 4d).

Discussion

In the present study, low total cholesterol level was the strongest prognostic factor among the serum lipid indices for patients with stage II and III GC. To the best of our knowledge, this is the first study that evaluated the prognostic significance of the various preoperative serum lipid indices in patients with stage II and III GC. Moreover, we constructed a new immunonutritional score (TL score), which consists of total cholesterol level and total lymphocyte count. TL score facilitated risk stratification of patients and helped predict the specific pattern of recurrence in patients with stage II and III GC, which is different from PNI.

Generally, a decreased serum total cholesterol level reflects caloric depletion [21]. Moreover, a lower cholesterol level may affect intracellular signaling involved in cancer progression and impair the anti-tumor immune response [22, 23]. In previous studies, decreased levels of total cholesterol [8, 24, 25], HDL-C [8, 9, 23, 25, 26], LDL-C [10, 24], triglyceride [11, 26], and elevated levels of LHR [27] were shown to be

Table 1 Association between TL score and clinicopathological factors

Variables		$n = 224$	Univariate					Multivariate		
			TL score: 0, 1 $n = 131$		TL score: 2 $n = 93$		p value[d]	OR	95% CI	p value[e]
Age, years	≥ 65	139	74	(56%)	65	(70%)	0.041	1.75	0.99–3.15	0.052
	< 65	85	57	(44%)	28	(30%)				
Sex	Female	66	38	(29%)	28	(30%)	0.858			
	Male	158	93	(71%)	65	(70%)				
BMI, kg/m^2	< 22	120	66	(50%)	54	(58%)	0.255			
	≥ 22	104	65	(50%)	39	(42%)				
Neoadjuvant chemotherapy	Presence	10	5	(4%)	5	(5%)	0.577			
	Absence	214	126	(96%)	88	(95%)				
Cholesterol-lowering medication	Presence	45	26	(20%)	19	(20%)	0.914			
	Absence	179	105	(80%)	74	(80%)				
Location	U	68	46	(35%)	22	(24%)	0.066			
	ML	156	85	(65%)	71	(76%)				
Tumor size, mm	≥ 60	111	55	(42%)	56	(60%)	0.007	1.79	1.02–3.17	0.042
	< 60	113	76	(58%)	37	(40%)				
Histopathological type[a]	por/sig/muc	129	71	(54%)	58	(62%)	0.222			
	tub/pap	95	60	(45%)	35	(38%)				
T stage[b]	T4	72	35	(27%)	37	(40%)	0.039	1.59	0.87–2.90	0.127
	T1-3	152	96	(73%)	56	(60%)				
N stage [b]	N2-1	162	92	(70%)	70	(75%)	0.404			
	N0	62	39	(30%)	23	(25%)				
pStage [b]	III	108	55	(42%)	53	(57%)	0.026	–	–	–
	II	116	76	(58%)	40	(43%)				
Lymphatic invasion [a]	Presence	167	93	(71%)	74	(80%)	0.143			
	Absence	57	38	(29%)	19	(20%)				
Venous invasion [a]	Presence	137	79	(60%)	58	(62%)	0.755			
	Absence	87	52	(40%)	35	(38%)				
Intra-abdominal complication [c]	Presence	19	9	(7%)	10	(11%)	0.304			
	Absence	205	122	(93%)	83	(89%)				
Adjuvant chemotherapy TS1 ($n = 120$)	Presence	151	91	(70%)	60	(65%)	0.436			
	Absence	73	40	(30%)	33	(35%)				

[a] According to the Japanese Classification of Gastric Carcinoma 3rd edition

[b] According to the 7th edition of UICC/TNM staging system

[c] Grade II or above according to the Clavien-Dindo classification

[d] p values are from chi-squared test

[e] p values are from p values are from multivariable logistic regression

BMI body mass index, *U* upper third of stomach, *ML* middle or lower third of stomach, *tub* tubular adenocarcinoma, *pap* papillary adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma, *pStage* pathological stage, *OR* odds ratio, *CI* confidence interval

associated with poor prognosis in patients with various cancers. We also demonstrated that decreased levels of triglyceride, total cholesterol, LDL-C, HDL-C, and remnant cholesterol were associated with poor CSS in patients with GC. On the contrary, some previous studies demonstrated that high levels of LDL-C and triglycerides were associated with worse prognosis in patients with small-cell lung cancer and breast cancer [28, 29]. One of possible reasons for this discrepancy is the overexpression of a receptor for LDL in certain types of cancer cells. The receptor for LDL has a pro-tumorigenic effect that is mediated via enhancement of cell growth or migration [30–32]. For patients with GC, severe malnutrition and tumor cachexia due to decreased oral intake and loss of body weight would be prevalent in advanced stage, resulting in a decrease of various serum lipid indices. This may be one of the reasons why all serum lipid index decreases were poor survival indicators in GC.

Lymphocytes play a key role in cell-mediated immunity, and total lymphocyte count is a marker of immunological status [33]. In previous studies, lower peripheral lymphocyte count was associated with worse prognosis in various cancer patients due to the impaired anti-tumor immune response [34, 35]. Therefore, we sought to develop an immunonutritional score that combines total lymphocyte count and total cholesterol as a new prognostic marker.

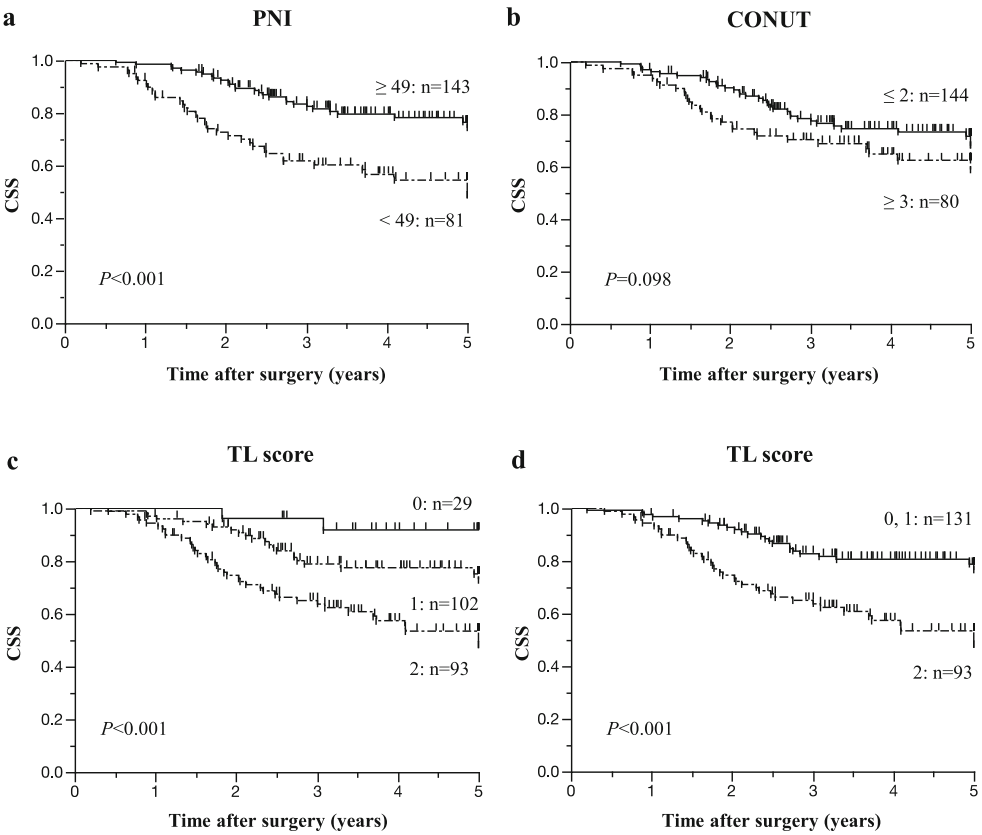

Fig. 3 Cancer-specific survival based on immunonutritional markers. Kaplan–Meier survival curves for cancer-specific survival according to PNI (**a**), CONUT score (**b**), and total cholesterol-lymphocyte score (**c**). PNI, prognostic nutritional index

CONUT score, one of the immunonutritional scores, has been shown to predict prognosis in various cancers, including GC [12–14]. However, CONUT score showed no significant association with CSS in stage II and III GC patients in our cohort. In a study by Kuroda et al., CONUT score was not associated with overall survival (OS) of patients with stage III GC; however, CONUT score predicted prognosis of patients with stage I and II GC [14]. Moreover, Ryo et al. reported that CONUT score was significantly associated with OS of patients with stage II or III GC, while it was not associated with disease-free survival [13]. Immunonutritional status probably changes in patients with advanced cancer [7, 13, 14]. Therefore, stratification index based on cut-off values similar to early GC may not be suitable for advanced stage disease because of changes in the immunonutritional status of patients with AGC. This may explain the lack of observed association between CONUT score and prognosis in patients with stage II and III GC in the present study.

Inflammatory scores, such as the Glasgow prognostic score (GPS), neutrophil-to-lymphocyte ratio (NLR), and platelet-to-lymphocyte ratio (PLR), have been reported to be prognostic biomarkers for cancer patients. In this cohort, GPS, NLR, and PLR were associated with CSS (data not shown). Although these inflammatory scores were strongly associated with immunonutritional status, multivariate analysis revealed that high TL score was more strongly associated with poor CSS than high GPS (data not shown). The other immunonutritional score, PNI, has also been shown to be associated with prognosis of patients with GC [7, 36, 37]. In the present study, PNI and TL score showed almost similar predictive ability for CSS in stage II and III GC (Table 2). However, TL score predicted the specific pattern of recurrence, which is different from the predictive ability of PNI (Fig. 4). The underlying mechanism of this differential predictive ability of immunonutritional scores for recurrence pattern is not clear. In the present study, low PNI (< 49) was not significantly associated with tumor progression (data not shown). However, patients with low PNI had a significantly low frequency of adjuvant chemotherapy, mainly TS1 (Table S2). This might be the one of the reasons for the association between recurrence rate of peritoneal recurrence and PNI. In a previous study, PNI was found to be associated with peritoneal recurrence rather than hematogenous and lymph node recurrence [36], which is consistent with our results. Our findings suggest that a combination of TL score and PNI may facilitate better prediction of recurrence in patients with GC.

There were certain limitations of our study. First, this was a single-center retrospective study. Therefore, the cut-off values used for each factor may not be applicable to other institutions. Second, several clinicopathological

Table 2 Univariate and multivariate analyses of prognostic factors

Variables		$n = 224$	Univariate		Multivariate			Multivariate		
			5 years CSS (%)	p value [d]	HR	95% CI	p value [e]	HR	95% CI	p value [e]
Age, years	≥ 65	139	61.8	0.559						
	< 65	85	69.0							
Sex	Female	66	54.3	0.222						
	Male	158	69.4							
BMI, kg/m^2	< 22	120	59.2	0.089						
	≥ 22	104	71.3							
Neoadjuvant chemotherapy	Presence	10	66.6	0.529						
	Absence	214	65.0							
Cholesterol-lowering medication	Presence	45	59.6	0.204						
	Absence	179	66.3							
Location	U	68	64.2	0.669						
	ML	156	65.4							
Tumor size, mm	≥ 60	111	54.1	< 0.001	1.79	1.03–3.20	0.036	1.73	0.99–3.11	0.052
	< 60	113	75.9							
Histopathological type [a]	por/sig/muc	129	60.0	0.094						
	tub/pap	95	71.0							
T stage [b]	T4	72	42.7	< 0.001	2.78	1.66–4.69	< 0.001	2.74	1.47–4.16	< 0.001
	T1-3	152	75.4							
N stage [b]	N2-1	162	56.9	< 0.001	3.27	1.57–7.95	< 0.001	3.59	1.74–8.71	< 0.001
	N0	62	84.4							
Lymphatic invasion [a]	Presence	167	61.3	0.069						
	Absence	57	74.4							
Venous invasion [a]	Presence	137	61.5	0.220						
	Absence	87	69.9							
Intra-abdominal complication [c]	Presence	19	68.0	0.646						
	Absence	205	64.8							
Adjuvant chemotherapy	Presence	151	66.8	0.569						
	Absence	73	60.7							
PNI	< 49	81	48.9	< 0.001	2.36	1.43–3.95	< 0.001			
	≥ 49	143	74.5							
TL score	2	93	76.7	< 0.001				2.13	1.27–3.65	0.003
	0, 1	131	48.3							

[a] According to the Japanese Classification of Gastric Carcinoma 3rd edition

[b] According to the 7th edition of UICC/TNM staging system

[c] Grade II or above according to the Clavien-Dindo classification

[d] p values are from log-rank test

[e] p values are from Cox's proportional hazard model

BMI body mass index, *U* upper third of stomach, *ML* middle or lower third of stomach, *tub* tubular adenocarcinoma, *pap* papillary adenocarcinoma, *por* poorly differentiated adenocarcinoma, *sig* signet-ring cell carcinoma, *muc* mucinous adenocarcinoma, *CSS* cancer-specific survival, *HR* hazard ratio, *CI* confidence interval

factors including comorbidities and medications that may influence the immunonutritional status were not controlled for in the analysis. Especially, statin use can affect cholesterol level. Moreover, statin use for more than 6 months was shown to be associated with increased survival of patients with stage II and III GC [38]. However, in the present study, the presence of cholesterol-lowering medication was not associated with TL score and CSS (Tables 1 and 2). Besides, in a previous study, LDL-C was a significant prognostic factor for prostate cancer even after adjusting for statin use [10]. This result could support our data to some degree. Third, we could not evaluate the effect of preoperative improvement in immunonutritional score on prognosis and type of recurrence because there were few patients who required a preoperative nutritional intervention owing to severe malnutrition in this cohort. However, recent studies have reported that perioperative nutrition improved postoperative nutritional status and immune function or reduced systemic perioperative inflammatory response, postoperative complications, and body weight loss. Therefore, we believe that immunonutritional status such as TL score may provide valuable information regarding gastric cancer patients who should receive nutritional intervention [39–42].

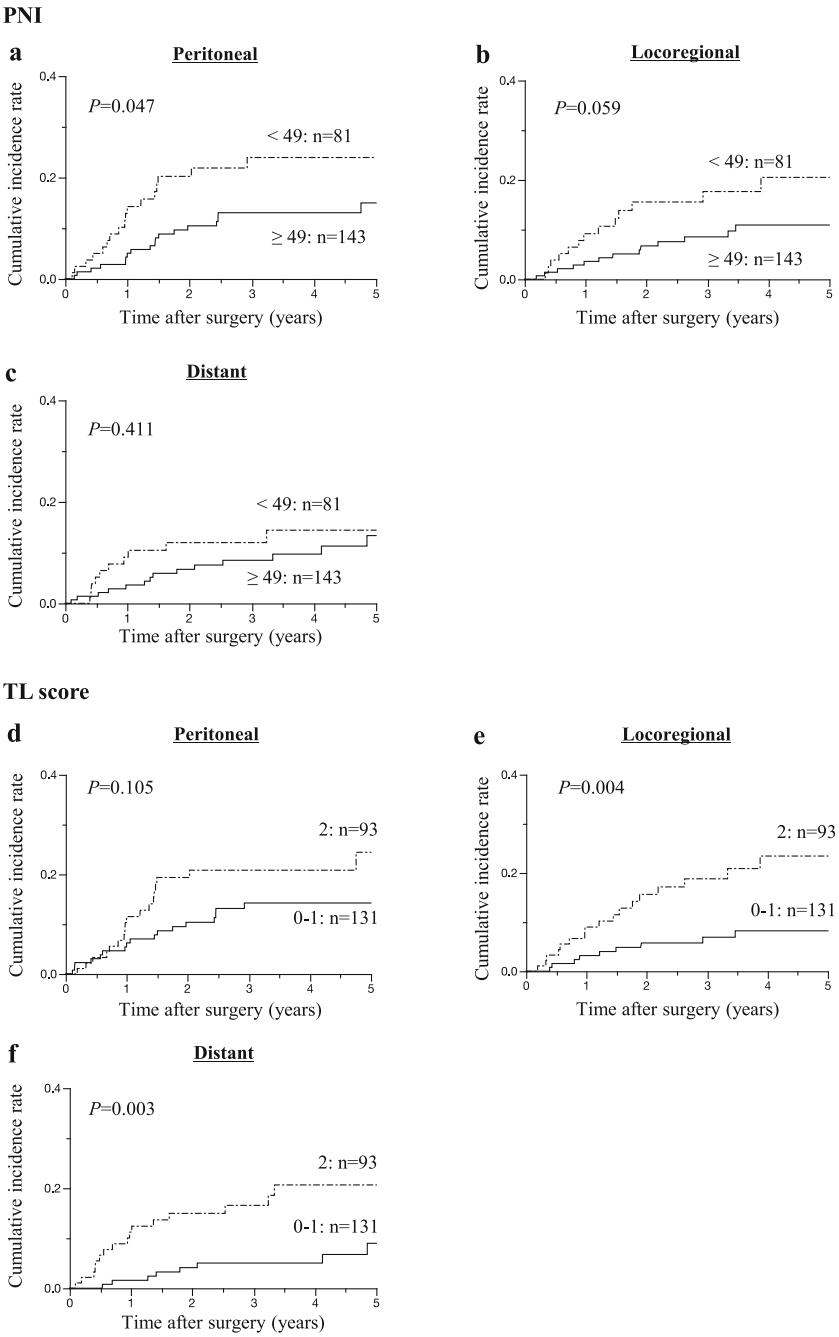

Fig. 4 Analysis of recurrence patterns according to immunonutritional markers. Estimated rates of peritoneal dissemination (**a**), locoregional (**b**), and distant (**c**) metastasis according to PNI (**d**–**e**). Estimated rates of peritoneal dissemination (**d**), locoregional (**e**), and distant (**f**) metastasis according to total cholesterol-lymphocyte score

Due to these limitations, further prospective validation studies with large numbers of patients are required to confirm our results and to evaluate the optimal cut-off values of immunonutritional markers.

Conclusion

In conclusion, among the serum lipid indices, total cholesterol level was the strongest prognostic factor for patients with stage II and III GC. Our findings suggest that TL score may facilitate risk stratification of patients by predicting CSS; in addition, TL score in combination with PNI may help predict the specific recurrence pattern in patients with stage II and III GC. Serum total cholesterol and lymphocyte count are routinely measured as part of preoperative evaluation. The new immunonutritional score may provide prognostically relevant information and facilitate personalized therapy.

Authors' contributions This study was designed by D.M., K.S., T.K., and E.O.; D.M. and K.S. performed statistical analyses. The clinical information and materials were collected and kept by K.S., T.K., T.K., H.K., A.S., H.F., K.O., T.A., M.K., R.M., Y.M., H.I., Y.K., and M.N.; D.M. and K.S. drafted the manuscript. T.K. edited and revised the manuscript. E.O. approved the final version of manuscript.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflicts of interest.

Ethical approval 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 comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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