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ORIGINAL ARTICLE

Score of the preoperative absolute number of lymphocytes, monocytes, and neutrophils as a prognostic indicator for patients with gastric cancer

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Abstract

Purpose The association between the preoperative absolute neutrophil count (NC), lymphocyte count (LC), and monocyte count (MC) in the peripheral blood and the prognosis of gastric cancer (GC) patients has not been investigated widely.

Methods We enrolled 445 patients who underwent surgery for GC between January, 2005 and April, 2013 to analyze the correlations among NC, LC, and MC and their prognoses.

Results Based on cut-off values calculated by ROC analysis, patients were sub grouped as having: NC ≥ 4477 (NC^{High}), NC < 4477 (NC^{Low}); and as LC ≥ 1447 (LC^{High}), LC < 1447 (LC^{Low}); and as MC ≥ 658.5 (MC^{High}), MC < 658.5 (MC^{Low}). Each group was assigned as follows; NC^{High} group = 1, NC^{Low} group = 0, LC^{High} group = 0, LC^{Low} group = 1, MC^{High} group = 1, MC^{Low} group = 0, and the sum of each score was defined as the lymphocyte–monocyte–neutrophil score (LMN score). The overall 5-year survival rates were 89%, 74%, 57.8%, and 53.3% for LMN scores of 0, 1, 2, and 3, respectively ($P = 0.0004$). Multivariate analysis indicated that the LMN score was an independent prognostic indicator.

Conclusions The combination of preoperative NC, LC, and MC appears to be a useful indicator of GC prognosis.

Keywords Gastric cancer · Lymphocyte · Monocyte · Neutrophil · Prognosis

Introduction

Gastric cancer (GC) is one of the most common malignancies worldwide. While greater availability of diagnostic techniques and more effective intraoperative and postoperative care have improved prognosis, GC still ranks second among all cancer-related deaths worldwide [1]. As such, establishing the postoperative prognostic factors in GC patients is of clinical importance. To this end, serum tumor markers (TMs), such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9), are easy to measure, and useful for making a diagnosis, predicting survival rates, and monitoring disease recurrence following surgery [2, 3].

The outcome for cancer patients is largely determined by tumor-related factors such as the depth of invasion and lymph node metastasis, and also by patient-related factors such as inflammation, malnutrition, and immune status. Establishing non-invasive prognostic predictors from hematological and serologic markers for various cancers has garnered widespread interest. Some serum markers that reflect inflammation, immunity, and nutrition can be obtained from routine blood tests and are reportedly related to GC prognosis [4, 5]. We reported previously that several inflammation- and nutrition-based indicators that use those serum markers, such as the neutrophil–lymphocyte ratio (NLR), C-reactive protein (CRP)–albumin (Alb) ratio and prognostic nutritional indicator, platelet–lymphocyte ratio (PLR), and the platelet × CPR multiplier value, can help predict the prognosis of GC patients [6–10].

The cells in peripheral blood that reflect the inflammation, malnutrition, and immune status of patients include lymphocytes, monocytes, and neutrophils. Lymphocytes are involved in cell-mediated immunity and play an important role in the host anticancer defense mechanisms.

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A decreased lymphocyte count (LC) and functional impairment of lymphocytes have been reported in various types of cancers [3]. Preoperative lymphopenia is associated with poor prognosis in several cancers, which indicates that preoperative lymphopenia may reflect impaired host anticancer defense mechanisms [11–13].

Neutrophils play an important role in the systemic inflammatory response, which is involved in cancer development and progression. Neutrophils function as the first-line of defense against infection and are responsible for the containment and elimination of pathogens. They are prevalent at sites of tissue trauma and are the hallmark of acute inflammation [14]. At the site of inflammation, neutrophils kill invading pathogens by phagocytosis, extracellular reactive oxygen species release, and by producing neutrophil extracellular traps [15]. Activated neutrophils produce cytokines, which attract other immune cells, and are responsible for modulating the inflammatory response. Studies have linked increased levels of circulating neutrophils with significantly worse outcomes in non-small cell lung cancer [16], cervical cancer [17], prostate cancer [18], gastric cancers [19–21], bladder cancer [22], and colorectal cancer [23].

Monocytes and macrophages also play an important role in tumor-generated inflammatory response, which contributes to the development and progression of different types of solid tumors. Tumor-associated macrophages constitute a significant component of the inflammatory infiltrate of several malignancies. They are derived from circulating monocytes and are recruited to the tumor site by soluble tumor-derived chemotactic factors [24]. Tumor-associated macrophages release potent angiogenic and lymphangiogenic growth factors, cytokines, and proteases to enhance angiogenesis and lymphangenesis, remodel the extracellular matrix, and blunt the antitumor response, which all promote the invasion and metastasis of cancer cells [25]. Epidemiological evidence has revealed that a high density or elevation of circulating tumor-associated macrophages are significantly associated with poor prognosis in a wide spectrum of human cancers [26–28].

Based on the functions of the lymphocytes, monocytes, and neutrophils, we speculate that preoperative evaluation of these three types of cells in the peripheral blood will help us to predict the prognosis of GC patients. Because these data can be obtained from a routine full blood count, it is more convenient than previously defined score systems and easily applicable in the routine clinical setting. Therefore, the aim of this study was to establish the prognostic value of the combination of the preoperative absolute lymphocyte count (LC), monocyte count (MC), and neutrophil count (NC) in GC patients.

Materials and methods

Patients

This study was a retrospective analysis of 445 patients with gastric adenocarcinoma who underwent gastrectomy at our institution between January, 2005 and April, 2013. The clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma [29]. No patient had received preoperative chemotherapy or radiation therapy. Patients were checked periodically for early recurrence by diagnostic imaging (chest X-ray, upper gastrointestinal fiberscopy, ultrasonography, and computed tomography). Causes of death and patterns of recurrence were established by reviewing medical records, including laboratory data, ultrasonography, computed tomography, scintigrams, peritoneal punctures, and laparotomies, or by direct inquiry of family members. Clinicopathologic data such as age, sex, tumor localization, tumor size, depth of invasion, lymph node metastasis, distant metastasis, lymphatic invasion, and venous invasion were obtained from the database. We also collected data on the NC, LC, MC, and platelet count (PC) from preoperative (within 1 month before surgery) blood test results documented in the patients' records. The NLR and PLR were calculated by dividing the peripheral NC and PC by the peripheral LC, respectively. The LMR were calculated by dividing the peripheral LC by the peripheral MC. Institutional review board approval was obtained and the informed consent requirement was waived for this study.

Statistical analysis

Differences between the two groups were evaluated using the Mann–Whitney *U* test. Correlations among the NC, LC, MC, and carcinoembryonic antigen (CEA) value were analyzed using the Spearman rank correlation coefficient. The Youden index was calculated using receiver operating characteristic (ROC) analysis to calculate the optimal cutoff value for the NC, LC, and MC for survival analysis. Survival curves were calculated according to the Kaplan–Meier method. For disease-specific survival (DSS), patients who died of causes other than GC were considered lost to follow-up at the time of death. Differences between survival curves were examined with the log rank test. Univariate and multivariate analysis of factors considered prognostic of overall survival (OS) were performed using Cox's proportional hazards model. The covariates with $P < 0.05$ in a univariate analysis were included in a multivariate analysis. $P < 0.05$ was considered significant. GraphPad Prism (GraphPad Software,

Inc., La Jolla, CA, USA) and Stat View (Abacus Concepts, Inc., Berkeley, CA, USA) software were used for statistical analyses.

Results

The NC, LC, and MC in the peripheral blood were 3758 ± 1486, 1663 ± 560.8, and 452 ± 161.6, respectively. There were significant correlations between the LC and MC ($r = 0.28$, $P < 0.0001$, Fig. 1a), the LC and NC ($r = 0.12$, $P < 0.013$, Fig. 1b), and the MC and NC ($r = 0.42$, $P < 0.0001$, Fig. 1c), respectively. As CEA is the most frequently used TM, we investigated its correlation with the NC, LC, and MC. There were no significant correlations between CEA and the NC (Fig. 2a) or between CEA and the LC (Fig. 2b). However, we found a significant but weak correlation between CEA and the MC ($r = 0.15$, $P = 0.0015$; Fig. 2c).

Table 1 shows the relationships among the clinicopathologic characteristics, NC, LC, and MC. The NCs of patients with large tumors (≥ 3.5 cm) were significantly higher than those of patients with small tumors (< 3.5 cm; $P = 0.029$). They were also significantly higher in patients with advanced gastric cancer, those with lymph node metastasis, and those with venous invasion than in patients with early gastric cancer patients ($P = 0.0002$), those without lymph node metastasis ($P = 0.032$), and those without venous invasion ($P = 0.038$), respectively. The LCs of elderly patients were significantly lower than those of younger patients ($P = 0.0001$). They were also significantly lower in patients with advanced gastric cancer, those with lymphatic invasion, and those with venous invasion than in those with early gastric cancer ($P = 0.04$), those without lymphatic invasion ($P = 0.029$), and those without venous invasion ($P = 0.049$), respectively. The MCs of male patients were significantly higher than those of female patients ($P < 0.0001$). They were also significantly higher in patients with large tumors, those with differentiated tumors, those with advanced cancer, and those with lymphatic and venous invasion than in those with small tumors ($P = 0.04$), those with undifferentiated tumors ($P = 0.017$), those with early cancer ($P = 0.0005$), and those without lymphatic ($P = 0.049$) or venous invasion ($P = 0.0009$).

ROC analysis of the status of OS indicated that 4477/μl, 1447/μl, and 658.5/μl had the highest Youden indices (sensitivity + specificity–1) and were considered to be optimal cutoff values for NC ($P = 0.37$, area under

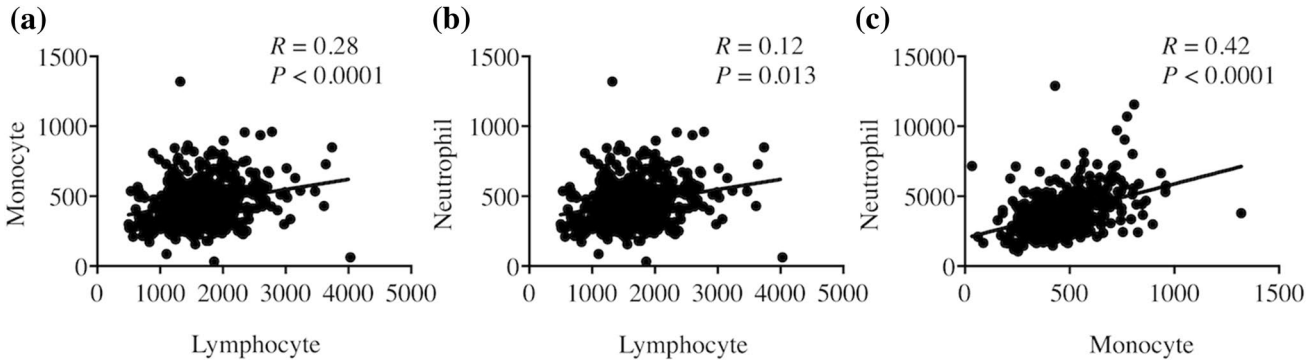

Fig. 1 Correlation between the lymphocyte count (LC) and monocyte count (MC) (**a**), the LC and neutrophil count (NC) (**b**), and the MC and NC (**c**)

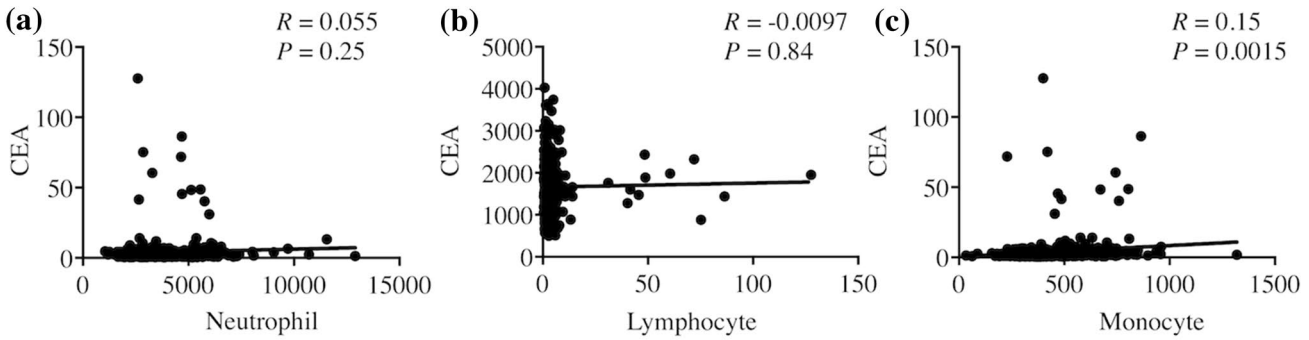

Fig. 2 Correlation between the serum concentrations of CEA and either the NC (**a**), LC (**b**), or MC (**c**)

Table 1 Comparison of patient characteristics in relation to the neutrophil count, lymphocyte count, and monocyte count

Variables	Neutrophils	*P* value	Lymphocytes	*P* value	Monocytes	*P* value
Age (years)		0.93		< 0.0001		0.45
< 70 (*n* = 217)	3808 ± 1560		1781 ± 567.4		445.3 ± 163.5	
≥ 70 (*n* = 228)	3710 ± 1414		1550 ± 531.8		458.3 ± 160	
Gender		0.75		0.34		< 0.0001
Male (*n* = 328)	3735 ± 1411		1671 ± 552.7		472.5 ± 154.5	
Female (*n* = 117)	3822 ± 1683		1641 ± 584.7		394.4 ± 167.8	
Tumor size (cm)		0.029		0.096		0.04
< 3.5 (*n* = 236)	3637 ± 1485		1698 ± 532.5		441.7 ± 159	
≥ 3.5 (*n* = 209)	3895 ± 1479		1624 ± 589.9		463.5 ± 164.2	
Histology[a]		0.7		0.81		0.036
Differentiated (*n* = 244)	3702 ± 1341		1657 ± 537.6		466.4 ± 160.5	
Undifferentiated (*n* = 201)	3827 ± 1646		1669 ± 589.1		434.5 ± 161.7	
Depth of invasion[b]		0.0002		0.04		0.0005
T1 (*n* = 284)	3563 ± 1379		1701 ± 559.5		430 ± 142.1	
T2/3/4 (*n* = 161)	4102 ± 1606		1596 ± 558.5		490.7 ± 185.5	
Lymph node metastasis		0.032		0.91		0.06
Absent (*n* = 342)	3687 ± 1487		1670 ± 583.4		443.5 ± 153.4	
Present (*n* = 103)	3993 ± 1464		1638 ± 480		480 ± 184.5	
Lymphatic invasion		0.08		0.029		0.017
Absent (*n* = 186)	3638 ± 1498		1743 ± 604.5		427.8 ± 140.5	
Present (*n* = 259)	3845 ± 1474		1605 ± 520.8		469.4 ± 173.4	
Venous invasion		0.038		0.049		0.0009
Absent (*n* = 232)	3637 ± 1453		1722 ± 573.3		427.9 ± 151.2	
Present (*n* = 213)	3890 ± 1514		1598 ± 540.8		478.2 ± 168.7	

[a]Histology: differentiated, papillary or tubular adenocarcinoma; undifferentiated, poorly differentiated or mucinous adenocarcinoma, or signet ring cell carcinoma

[b]Depth of invasion: 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

the curve (AUC): 0.5294, 95% confidence interval (CI): 0.4621–0.5968), LC ($P = 0.1$, AUC: 0.5537, 95% CI: 0.4906–0.6167), and MC ($P = 0.33$, AUC: 0.532, 95% CI: 0.4648–0.5992), respectively. Based on these results, patients were sub grouped as: NC ≥ 4477 (NC^{High}, $n = 112$), NC < 4477 (NC^{Low}, $n = 333$); LC ≥ 1447 (LC^{High}, $n = 275$), LC < 1447 (LC^{Low}, $n = 170$); and MC ≥ 658.5 (MC^{High}, $n = 47$), MC < 658.5 (MC^{Low}, $n = 398$). The 5-year OS rates differed significantly between the NC^{High} group (67.5%) and the NC^{Low} group (81.6%, $P = 0.023$; Fig. 3a). The 5-year OS rates also differed significantly between the LC^{High} group (82.7%) and the LC^{Low} group

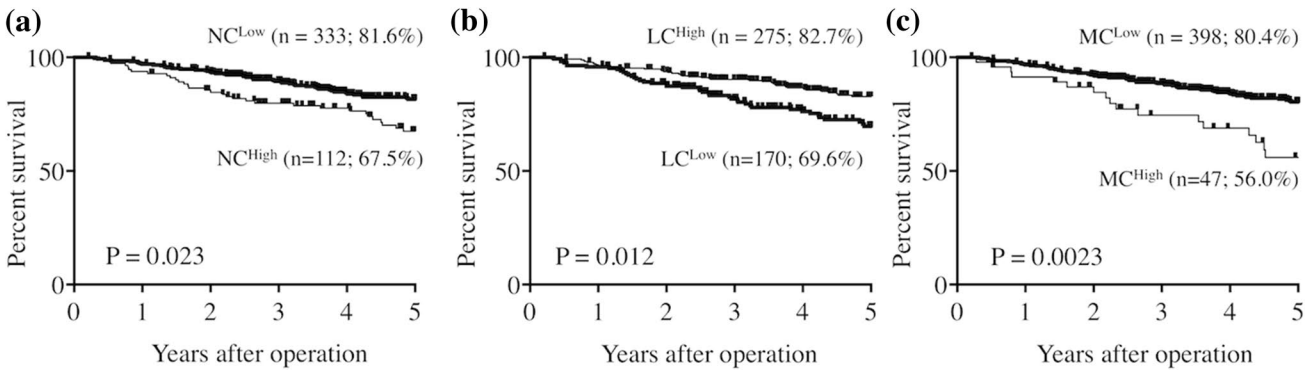

Fig. 3 Overall survival curves based on the NC (**a**), LC (**b**), and MC (**c**)

(69.6%, $P=0.012$; Fig. 3b). The 5-year OS rates also differed significantly between the MC^{High} group (56.0%) and the MC^{Low} group (80.4%, $P=0.0023$; Fig. 3c).

Each group was assigned a score as follows: NC^{High} group = 1, NC^{Low} group = 0, LC^{High} group = 0, LC^{Low} group = 1, MC^{High} group = 1, MC^{Low} group = 0. The sum of each score was defined as the lymphocyte–monocyte–neutrophil score (LMN score). ROC analysis of the LMN score to the status of OS was performed and the AUC values were compared to assess the discriminatory ability of the LMN score, NC, LC, and MC. The AUC of the LMN score was 0.6092 ($P=0.0008$, 95% CI 0.5463 to 0.6721), which was higher than the AUC of the NC, LC, or MC. This indicated that the LMN score was more useful than the other indicators alone in predicting the prognosis of GC patients. Furthermore, the AUCs of the NLR, LMR, and PLR were 0.5862 ($P=0.0084$, 95% CI 0.5223–0.6502), 0.5908 ($P=0.0055$, 95% CI 0.5249–0.6566), and 0.5359 ($P=0.27$, 95% CI 0.4695–0.6023), respectively; lower than the AUC of the LMN score, indicating that the LMN score was also more useful than the NLR, LMR, and PLR in predicting the prognosis of GC patients.

Next, we investigated the prognostic significance of the LMN score in patients with GC. The 5-year OS rates were 89%, 74%, 57.8%, and 53.3% for LMN score 0, LMN score 1, LMN score 2, and LMN score 3, respectively, and these differences were significant ($P=0.0004$, Fig. 4a). The 5-year DSS rates were 93.1%, 88.9%, 79.6%, and 61% for LMN score 0, LMN score 1, LMN score 2, and LMN score 3, respectively, and these differences were also significant ($P=0.0059$, Fig. 4b). Figure 5 showed the prognostic significance of the LMN score in patients with early vs. those with advanced GC. The 5-year OS rates of patients with early GC were 95.2%, 79.5%, 69.2%, and 75.0% for LMN score 0, LMN score 1, LMN score 2, and LMN score 3, respectively, and these differences were significant ($P=0.0021$, Fig. 5a). The 5-year OS rates of patients with advanced GC were 75.1%, 65.3%, 48.4%, and 40.0% for LMN score 0, LMN score 1, LMN score 2, and LMN score 3, respectively, and these differences were significant ($P=0.041$, Fig. 5b).

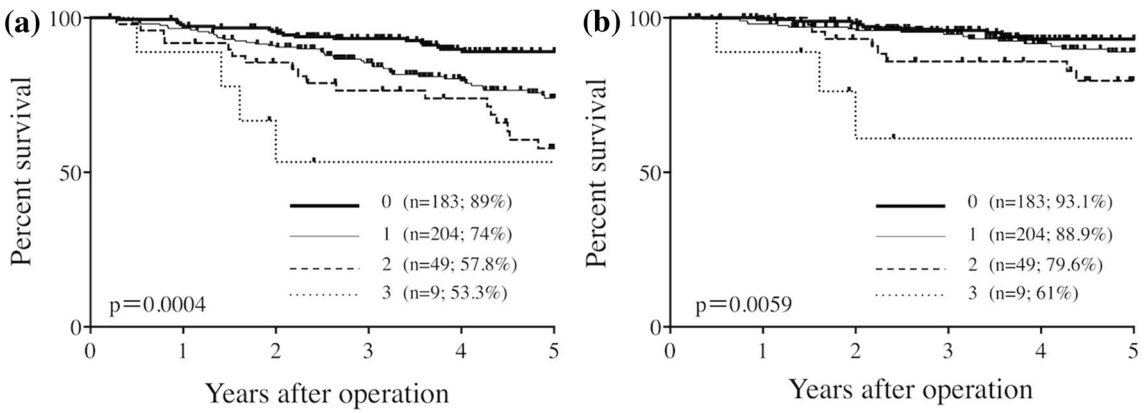

Fig. 4 Survival curves based on the lymphocyte–monocyte–neutrophil score (LMN score). **a** Overall survival. **b** Disease-specific survival

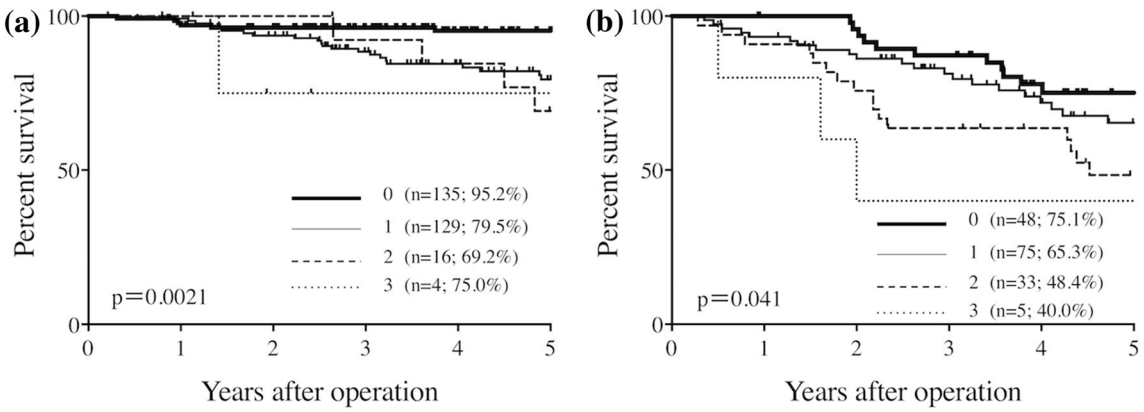

Fig. 5 Overall survival curves based on the lymphocyte–monocyte–neutrophil score (LMN score). **a** Early gastric cancer. **b** Advanced gastric cancer

Univariate analysis indicated that age, tumor size, depth of invasion, lymph node metastasis, lymphatic invasion, venous invasion, and LMN score were significantly associated with OS (Table 2). Then, we included covariates with $P < 0.05$ in the univariate analysis in a multivariate analysis. Multivariate analysis revealed that the LMN score was an independent prognostic indicator, along with age and lymphatic invasion (Table 2).

Discussion

The findings of the current study showed that the NC, LC, and MC were significantly associated with the prognosis of GC patients. Several studies have found that a low preoperative LC is related to poor prognosis in various cancers, including pancreatic cancer [11], esophageal cancer [12], renal cancer [13], as well as sarcoma and lymphoma [30]. Lymphocytes include $CD4^+$ and $CD8^+$ T cells, NK cells, NKT cells, gamma-delta T cells, and B cells, which are reported to be closely associated with tumor immunity. Therefore, it is likely that decreased numbers of those cells are associated with impaired tumor immunity with subsequent tumor progression. In fact, several studies have shown that numbers of tumor infiltrating lymphocytes such as $CD4^+$ and $CD8^+$ T cells were associated with poor prognosis in some cancers [31–33]. A close correlation between decreased numbers of immune cells, such as NK cells, B cells, and gamma-delta T cell, and poor prognosis has also been demonstrated in both peripheral blood and cancer tissue for some cancer types [34–36]. Therefore, peripheral LC might be a good indicator of cell-mediated immune status, including both acquired and adaptive immunity, and humoral immune status against GC.

Preoperative lymphopenia is frequently observed in advanced cancers, but details of the mechanisms of lymphopenia in GC patients remain unclear. In this regard, we previously reported that upregulated Fas expression in $CD8^+$ T cells is largely involved in increased apoptosis of circulating $CD8^+$ T cells in patients with gastric cancer [37]. This mechanism might affect lymphopenia in GC patients. Further investigations of these lymphopenic mechanisms in GC patients are required.

In the current study, increased numbers of neutrophils and monocytes were significantly related to the poor prognosis of GC patients. Neutrophils are important components of the inflammatory response, playing dual roles in tumor development and metastasis. In response to cytokine stimulation, neutrophils have the potential to diverge towards antitumor (N1) or protumor (N2) phenotypes [38]. In the acute inflammation state, neutrophils are activated to exert an antitumor effect. Conversely, they are activated by chronic inflammation to promote tumor growth and metastasis. Inflammatory cytokines such as G-CSF, IL-6, and TGF-β1 can induce the N2 phenotype of neutrophils in bone marrow and the tumor microenvironment [39]. Moreover, priming with IFN-γ and TNF-α can convert the phenotype from N2 to N1 [40]. Thereby, neutrophils may exert either an antitumor or a protumor function, which mainly depends on the regulation of inflammatory cytokines. We reported previously that the serum concentration of IL-6 was increased in GC patients [41]. Therefore, it is likely that most of the high levels of

Table 2 Multivariate analysis of gastric cancer patients using the Cox proportional hazard model and a stepwise procedure

	Univariate analysis			Multivariate analysis		
	P value	HR	95% CI	*P* value	HR	95% CI
Age[a]	< 0.0001	1.069	1.046–1.092	< 0.0001	1.058	1.035–1.081
Gender (male vs. female)	0.056	1.613	0.988–2.632			
Size[a]	< 0.0001	1.205	1.127–1.288	0.053	1.088	0.999–1.185
Histology (differentiated vs. undifferentiated)	0.76	1.063	0.717–1.574			
Depth of invasion (T1–T4)	< 0.0001	1.754	1.463–2.102	0.92	1.013	0.773–1.328
Lymph node metastasis (N0–N3)[b]	< 0.0001	1.804	1.519–2.142	0.061	1.269	0.989–1.628
Lymphatic invasion (Ly0–Ly3)[c]	< 0.0001	2.006	1.639–2.455	0.029	1.384	1.035–1.851
Venous invasion[d]	< 0.0001	1.734	1.449–2.076	0.23	1.162	0.910–1.485
Neutrophil/lymphocyte/monocyte	< 0.0001	1.663	1.312–2.108	0.043	1.310	1.009–1.700

See Table 1 for the detail of histology and depth of invasion

HR, hazard ratio; CI, confidence interval

[a]Continuous variable

[b]Lymph node metastasis: N0, no regional lymph node metastasis; 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

[c]Lymphatic invasion: Ly0–Ly3, grade of lymphatic invasion

[d]Venous invasion: V0–V3, grade of venous invasion

neutrophils observed in GC patients are of the N2 phenotype and that the neutrophils exert a protumor function. This could explain the close correlation between the increased NC and the poor prognosis of GC patients observed in the current study.

Monocytes are also important components of the inflammatory response. A recent study demonstrated that PD-1 expression by tumor-associated macrophages inhibits phagocytosis and tumor immunity [42]. We previously demonstrated that peripheral monocytes upregulated PD-L1 expression in GC patients [43]. These results indicated that monocytes were closely associated with inflammatory status and immunosuppression in cancer patients. In fact, an increased number of monocytes was associated with poor prognosis in this study.

Predicting the postoperative prognosis of GC patients is important for planning the optimal treatment strategy. Many studies have indicated that depth of invasion and lymph node metastasis are the most important prognostic factors in GC [44, 45]. Moreover, serum TMs are easy to measure and useful for diagnosing, predicting survival rates, and monitoring recurrence following surgery [2, 3]. CEA is the most frequently used TM in GC. Shimada et al. reported that the positivity of the serum CEA level was 24.0% in GC patients [46]. Although the positivity of CEA was relatively low, accumulating reports indicate that CEA is a prognostic factor in GC patients [46–48]. Our results indicate that the NC, LC, and MC are also useful to predict the prognosis of GC patients. As the correlation between these markers and the serum concentration of CEA was weak, these markers can be used as prognostic indicators regardless of the CEA. The correlations among these markers were also weak in this study; therefore, we hypothesized that their combination would be more useful than either indicator alone for predicting the prognosis of GC patients. Indeed, the AUC of the LMN score was much higher than the AUCs obtained for either measurement alone, suggesting its greater utility in predicting the prognosis of GC patients. Furthermore, our results suggested that the LMN score is an independent prognostic indicator. Its use allows for an assessment of a patient's inflammatory and immune status, which is considered to be a patient-related prognostic factor.

Gastrectomy with regional lymph node dissection is the mainstay of gastric cancer treatment to achieve cure; however, recurrence can develop even after complete tumor removal (R0 resection). Early detection of recurrence reportedly improves survival after curative gastrectomy for GC [49, 50]. Recurrence can develop because of micrometastases that cannot be detected by standard diagnostics, including ultrasonography, computed tomography, and positron emission tomography. Therefore, it is extremely important to identify and follow-up gastric cancer patients with a high possibility of recurrence after curative gastrectomy to improve their prognosis. Since the LMN score was useful for predicting the DSS of GC patients, it can be used to identify patients with a high possibility of recurrence, who might need intensive follow-up for the early detection of recurrence.

This study had a few limitations. First, it was a retrospective analysis, which could generate some bias. Second, lymphocytes include regulatory cells such as regulatory T cells, which may have negative effects on cancer prognoses [51], although the scope is unclear in the current study. Third, the number of patients included in this study was small. A large-scale, prospective study is needed to verify our results.

In conclusion, the LMN score appears to be a useful indicator of GC prognosis. Because the peripheral blood cell count is a quick, easy, and non-invasive assay, the LMN score could be an inexpensive and practical biomarker for the prognosis of GC patients in the routine clinical setting.

Compliance with ethical standards

Conflict of interest We have no conflicts of interest to declare.

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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