Usefulness of the Neutrophil/Lymphocyte ratio Measured Preoperatively as a Predictor of Peritoneal Metastasis in Patients with Advanced Gastric Cancer

Running head：**Neutrophil/lymphocyte ratio in gastric cancer**

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Abstract

Purpose; The prognosis of gastric cancer patients with peritoneal metastasis is poor. Many studies have reported that neutrophil/lymphocyte ratio (NLR) might be useful to predict the degree of progression of gastric cancer. In this study, we attempted to evaluate whether the NLR and other related laboratory parameters might be reliable predictors of the presence of peritoneal metastasis in patients with advanced gastric cancer.

Methods; The data of 359 patients who underwent gastric surgery between June 2008 and December 2011 were reviewed. A retrospective analysis of the preoperative blood data in relation to the presence of peritoneal metastasis was carried out.

Results; Increased serum C-reactive protein (P = 0.022), APTT (P = 0.017) and NLR (P < 0.001), and decreased serum Alb (P = 0.014) were significantly related to the presence of peritoneal metastasis. Multivariate analysis showed that NLR > 2.37 (OR = 2.59, 95%CI = 1.38-4.93, P = 0.003) and clinical T4 stage (OR = 4.36, 95%CI = 2.33-8.24, P < 0.001) were identified as the independent predictors of the presence of peritoneal metastasis.

Conclusion; Our results suggested that the preoperative NLR was a significant independent predictor of the presence of peritoneal metastasis in patients with advanced

gastric cancer.

Introduction

Gastric cancer is the fourth most frequently diagnosed cancer worldwide and the second most frequent cause of cancer death. The estimated total number of newly diagnosed cases of gastric cancer and total number of deaths from gastric cancer in 2008 were 989,600 and 738,000, respectively [1]. Peritoneal metastasis is a common sign of tumor progression in patients with gastric cancer; it is already present in an estimated 5 to 20% of patients undergoing gastrectomy with curative intent [2], and is frequently present in patients with advanced gastric cancer. In regard to the mechanism underlying its development, peritoneal metastasis is considered to result from the rapid growth of single tumor cells detached from the primary lesion that reach the abdominal cavity [2]. Ikeguchi et al reported the existence of close relationship between the area of serosal invasion and the intraperitoneal presence of free cancer cells in patients with gastric cancer [3]. Thus, peritoneal metastasis in gastric cancer patients is closely related to the depth of invasion of the gastric wall by the tumor. Clinically, gastric cancer patients with peritoneal metastasis have a poor prognosis, therefore, accurate diagnosis of peritoneal metastasis is important to select the appropriate therapy.

Recently, a number of reports have suggested the usefulness of measurement of laboratory parameters, such as the neutrophil/lymphocyte ratio (NLR) and serum C-reactive protein (CRP), which can be easily measured in the laboratory, for determining the prognosis of patients with cancer [4-17]. These laboratory parameters are indicators of systemic inflammation, and exacerbation of inflammation is associated with inhibition of apoptosis, promotion of angiogenesis, and DNA damage, thereby increasing the propensity to metastasis [7, 10, 18].

Laboratory data such as the NLR, serum CRP and serum albumin (Alb), all indices of inflammation, have also been reported by many studies to be useful for predicting the prognosis in patients with gastric cancer [4-8, 12, 13, 15, 16]. In particular, the NLR has been reported to not only be of prognostic value in patients with gastric cancer, but to also be a useful predictor of the depth of invasion of the gastric wall in these patients of gastric cancer [19].

We sometimes encounter gastric cancer patients with unexpected peritoneal metastasis at operation. If the laboratory parameters measured preoperatively can be used to predict the presence of peritoneal metastasis, it would be highly beneficial, as it would have major effects on clinical decision making. However, the relationship between the NLR and other related laboratory parameters and the presence of peritoneal metastasis has not yet been sufficiently evaluated.

Because peritoneal metastasis is known to be closely related to the wall invasion depth in gastric cancer patients, we propose that the NLR, which has also been reported to be related to the wall invasion depth of gastric cancer, could be a useful predictor of the presence of peritoneal metastasis; therefore, we examined whether measurement of the NLR and other related laboratory parameters might be of value for predicting the presence of peritoneal metastasis in patients with advanced gastric cancer.

Patients and Methods

Patients

The data of 902 patients who underwent surgery for gastric cancer at the National Cancer Center Hospital East between June 2008 and December 2011 were retrospectively reviewed from our database. In this study, we excluded the patients detected dissemination by preoperative imaging diagnosis in order to investigate the cases diagnosed peritoneal metastasis during an operation. Of these, 543 patients were excluded for the following reasons: administration of neoadjuvant therapy (28 patients), evidence of infection, history of other cancers, or esophagogastric junctional cancer, defined as cancer with its epicenter within 5cm of the gastroesophageal junction and extending into

the esophagus (59 patients). In regard to the wall invasion depth of the tumor, the wall invasion depth did not extend beyond the submucosa (< stage T2) in 404 patients. Sixteen patients had distant metastasis, including liver metastases, lung metastases, and para-aortic lymph node metastases. Therefore, the data of a total of 359 patients with advanced gastric cancer were investigated. The study was approved by the Research Ethics Committee of the National Cancer Center Hospital.

Surgical procedure and disease staging

All patients underwent surgery for gastric cancer. If evidence of peritoneal metastasis, such as peritoneal dissemination and/or positive peritoneal cytology, was detected during the operation, the operative procedure was changed to exploratory laparotomy, palliative gastrojejunostomy. When there were no non-curative factors during the operation, either total or distal gastrectomy with D2 lymphadenectomy was performed. The resected specimens were pathologically classified according to the International Union Against Cancer (UICC) TMN classification (7th edition). The presence of peritoneal metastasis was confirmed by laparotomy or staging laparoscopy. The histopathological diagnosis was evaluated in the resected specimens or preoperative biopsy tissues. Papillary and tubular adenocarcinomas were categorized as differentiated carcinomas, whereas poorly

differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma were classified as undifferentiated carcinomas.

Peripheral blood parameters

Peripheral blood samples were collected from the patients prior to the surgery. Laboratory data, including the white blood cell count (WBC), monocyte count (Mono), serum hemoglobin (Hb), platelet count (Plt), serum albumin (Alb), serum C-reactive protein (CRP), prothrombin time (PT), partial thromboplastin time (APTT), serum carcinoembryonic antigen (CEA), serum carbohydrate antigen (CA) 19-9 were obtained from the medical records. The NLR was calculated as the neutrophil count (Neu) divided by the lymphocyte count (Lym).

Statistical analysis

Data are presented as median and range. The Mann-Whitney *U* test was used to compare the relationship between the presence/absence of peritoneal metastasis and preoperative laboratory data. Receiver operating characteristic (ROC) curves were constructed in order to calculate the sensitivity, specificity, positive predictive value, and negative predictive

value for peritoneal metastasis. Cutoff value of the NLR, with the point on the ROC curves closest to top left corner, was planned to be selected. Pearson's chi-square test was used for univariate comparisons of the laboratory data. Variables found to be significant ($P < 0.05$) on univariate analysis were subjected to multivariate logistic regression model. All statistical analyses were conducted using JMP® 9 (SAS Institute Inc., Cary, NC, USA).

Results

Demographic characteristics

The median age of the 359 patients enrolled in the study at diagnosis was 66 years old. The subject group was composed of 245 (68.2%) men and 114 (31.8%) women. The demographics, clinicopathologic characteristics, and presence/absence of peritoneal metastasis of the study patients are shown in Table.1. In all, 148 (41.2%) patients were classified into the well-differentiated carcinoma category and 211 (58.8%) patients into the poor undifferentiated carcinoma category. The wall invasion depth of the tumor was assessed as clinical T4 in 94 (26.2%) patients and pathological T4 in 165 (46.0%) patients. The number of patients with a positive nodal status was 249 (69.4%). No data about the wall invasion depth of the tumor or nodal status were available for 23 (6.4%) patients,

because of exploratory laparotomy and palliative gastrojejunostomy. According to the TNM classification, the number of patients with stage IB, IIA, IIB, IIIA, IIIB, IIIC, and IV cancer was 35 (9.7%), 51 (14.2%), 53 (14.8%), 42 (11.7%), 56 (15.6%), 64 (17.8%), and 58 (16.2%), respectively. The number of patients with stage III or IV disease was 220 (61.3%). The numbers of patients with and without peritoneal metastasis were 58 (16.2%) and 301 (83.8%).

Relationship between the preoperative laboratory data and the presence/absence of peritoneal metastasis

The relationship between the presence/absence of peritoneal metastasis and the preoperative laboratory data in the 359 patients enrolled in this study is shown in Table.2. An increase of the CRP ($P = 0.022$), APTT ($P = 0.017$) and NLR ($P < 0.0001$), and decrease of Alb ($P = 0.014$) were significantly related to the presence of peritoneal metastasis. The significant difference was not found between dissemination and positive cytology according to the value of CRP, APTT, NLR and Alb.

Predictive significance of various laboratory parameters for the presence of peritoneal metastasis

The ROC curve of NLR is shown in Fig.1. The area under the ROC curve (AUC) was recorded as 0.677 for the NLR. The sensitivity, specificity, positive predictive value and negative predictive value of NLR > 2.37 for predicting the presence of peritoneal metastasis were 63.8, 67.4, 27.4, and 90.6%. We determined the cutoff value of NLR mentioned above, and the cutoff value of NLR was determined as 2.37.

Univariate and multivariate logistic regression analyses were performed to identify significant predictors of the presence of peritoneal metastasis (Table.3). The univariate analysis revealed significant differences in the odds ratio (OR) for NLR > 2.37 (OR = 3.71, 95%CI = 2.06-6.67, P < 0.0001), Alb < 3.5 (OR = 2.54, 95%CI = 1.21-5.36, P = 0.012), APTT > the median (OR = 1.77, 95%CI = 1.00-3.14, P = 0.048), and clinical T4 stage (OR = 5.69, 95%CI = 3.14-10.31, P < 0.001). According to multivariate analysis, NLR > 2.37 (OR = 2.59, 95%CI = 1.38-4.93, P =0.003) and clinical T4 stage (OR = 4.36, 95%CI = 2.33-8.24, P < 0.001) were identified as the independent predictors of the presence of peritoneal metastasis.

Discussion

The first causal link between inflammation and cancer was described by Rudolf Virchow

in 1863, who noted the presence of leukocytes in neoplastic tissues. He suggested that the "lymphoreticular infiltrate" reflected the origin of cancer at sites of chronic inflammation. Our recognition of the inflammatory microenvironment of malignant tissues lends support to Virchow's hypothesis, and recognition of the relationship between inflammation and cancer is starting to have implications for prevention and treatment [18]. Cancer growth and invasion induce local tissue damage, disturb local homeostasis, and cause consecutive systemic acute-phase inflammatory responses. While the role of acute-phase inflammatory responses is immune protection of the host, cancers use the inflammatory responses and continue to progress in a non-self-limiting manner. Therefore, cancers are described as "wounds that do not heal" [20, 21]. In addition, inflammation inhibits apoptosis, promotes angiogenesis, induces DNA damage, and promotes tumor growth and metastasis [7, 10, 18]. Recently, a number of studies have reported that laboratory parameters reflecting inflammation, such as the NLR and serum CRP, may be related to the prognosis of cancer patients; for example, the NLR and CRP have been shown to be associated with the prognosis of gastric cancer, colorectal cancer, metastatic liver cancer, and lung cancer [4, 6, 7, 9, 10-13, 15, 17]. These results suggest the existence of a close relationship between inflammation and cancer progression.

NLR is calculated as the neutrophil count divided by the lymphocyte count, and is an easily measurable and simple index of systemic inflammatory response [11, 22]; it

increases with increase of the neutrophil count and/or decrease of the lymphocyte count. Kusumanto et al reported that the circulating neutrophils contain and secrete the major portion of circulating vascular endothelial growth factor (VEGF) [23]. VEGF is a pro-angiogenetic factor that is known to promote tumor angiogenesis and possibly plays an integral role in tumor growth and progression [10, 24]. Increased angiogenic activity in gastric cancer has been shown to be associated with a poor prognosis [25]. Therefore, an increase of the neutrophil count stimulates and facilitates tumor progression [7]. Some studies have indicated that increased neutrophils in the peripheral blood also suppress the immune reactions of the host, such as the cytolytic activity of the lymphocytes, natural killer cells, and activated T cells [26, 27].

Meanwhile, the immune response of the hosts to tumors depends on the lymphocytes [10, 17]. Okano et al reported that the extent of lymphocytic infiltration at the tumor margin was closely related to the prognosis in patients who underwent hepatic resection for liver metastases from colorectal cancer [28]. The lymphocytes may reflect the defense activity of the host against tumor progression. In this study, decrease of the lymphocyte count was found to be significantly associated with the presence of peritoneal metastasis (Table.4). Thus, decrease of the immune response of the hosts to tumor may be closely related to the mechanism of peritoneal metastasis. Since increase of the neutrophil count and decrease of the lymphocyte count in the peripheral blood have been shown to be

related to tumor progression, and the NLR, calculated based on the neutrophil count and lymphocyte count, may be good index reflecting the degree of tumor progression.

In this study, we examined whether preoperative measurement of the laboratory parameters including the NLR might be of value for predicting the presence of peritoneal metastasis in patients with advanced gastric cancer in order to predict patients with unexpected peritoneal metastasis at laparotomy. And so, patients with other distant metastasis were excluded. The NLR might be related to the other distant metastasis because the NLR might be good index reflecting the degree of tumor progression.

The reported NLR from previous studies investigating the relationship between the prognosis of gastric cancer and the NLR has been reported to vary in the range of 2.0-4.0 [4, 7, 12, 13, 15, 19]. A summary of the cutoff values of the NLR for predicting the prognosis reported from previous studies is shown in Table.5. The differences in the cutoff values among the studies may be attributable to the differences in the cumulative number of patients and disease stage among the studies. ROC curves were constructed in order to evaluate the NLR as a predictor of peritoneal metastasis, and the cutoff value of the NLR was determined to be 2.37 in this study. The percentage of patients with stage III or IV in our study was 61.3%. Thus, our patient characteristics and the cutoff value of the NLR in this study were similar to those in the study reported by Jung et al [7] and Yamanaka et al [13] (NLR > 2.0, NLR >2.5).

Changes in the CRP and Alb reflect the inflammatory and immune responses of the host. Some reports have indicated the existence of a correlation between these laboratory parameters and the prognosis in gastric cancer and colorectal cancer patients [6, 8, 9, 21, 29, 30-32]. Increase of the serum CRP and decrease of the serum Alb and NLR were found to be correlated with the presence of peritoneal metastasis in our study. These findings lend support to the notion that inflammation is closely related to the risk of development of peritoneal metastasis in patients with advanced gastric cancer.

In this study, multivariate logistic regression analysis identified the NLR and clinical T4 stage as the independent predictors of peritoneal metastasis. This study excluded the patients with other non-curative factors (lung, liver and paraaortic LN metastasis are 2, 8 and 6 patients). However, the results were similar even if the patients with other non-curative factors included in this study. Therefore, the NLR and T stage may be specific markers for peritoneal metastasis. Combination of the NLR and clinical T4 stage was highest specificity and odds ratio than other 2 factors (Table.6). But the NLR was higher sensitivity than other 2 factors. Thus, not only T stage but also preoperative measurement of the NLR could provide important information to help predict a preoperative diagnosis of peritoneal metastasis.

Presence of peritoneal metastasis is associated with a poor prognosis in gastric cancer patients; therefore, an accurate diagnosis of peritoneal metastasis is necessary to

determine the appropriate treatment strategy in these patients. Recently, a number of institutions have performed staging laparoscopy in advanced gastric cancer patients with suspected peritoneal metastasis, to obtain an accurate diagnosis. Yamagata et al reported that the time until the start of chemotherapy was significantly shorter in patients subjected to staging laparoscopy than in those subjected to exploratory laparotomy [33]. However, they also reported that peritoneal metastasis could not be detected by staging laparoscopy in 13% of the patients, and argued for refinement of the technique of staging laparoscopy for improving the diagnostic accuracy. Preoperative measurement of the NLR might provide supplemental information about peritoneal metastasis.

This study seems to be the first to report the NLR as an independent predictor of the presence of peritoneal metastasis in gastric cancer patients. Some reports have indicated the correlation between serum markers and peritoneal metastasis in gastric cancer patients [34, 35]. The mechanism of peritoneal metastasis remains unclear. Kinoshita et al. reported the relationship between type IV collagen levels and peritoneal metastasis in gastric cancer patients [34], they explained the relationship according to the mechanism of metastasis. In this study, we explained the relationship between the NLR and peritoneal metastasis according to the inflammation. These results suggested that various factors were associated with peritoneal metastasis.

The limitation of this study was that our results were obtained from the data in the single

institutuion. Our results need to be confirmed by the validation in other institutions.

In conclusion, we found that the NLR was an independent predictor of the presence of peritoneal metastasis. The NLR is a clinically easily measurable index, and its measurement may facilitate the diagnosis of peritoneal metastasis, especially during staging laparoscopy.

Conflict of interest statement: Nakayama Y and other co-authors have no conflict of interest.

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Figure legend

Fig.1: In order to assess the best discriminatory power of the NLR for predicting the presence of peritoneal metastasis, a ROC curve analysis was performed.

Fig.1

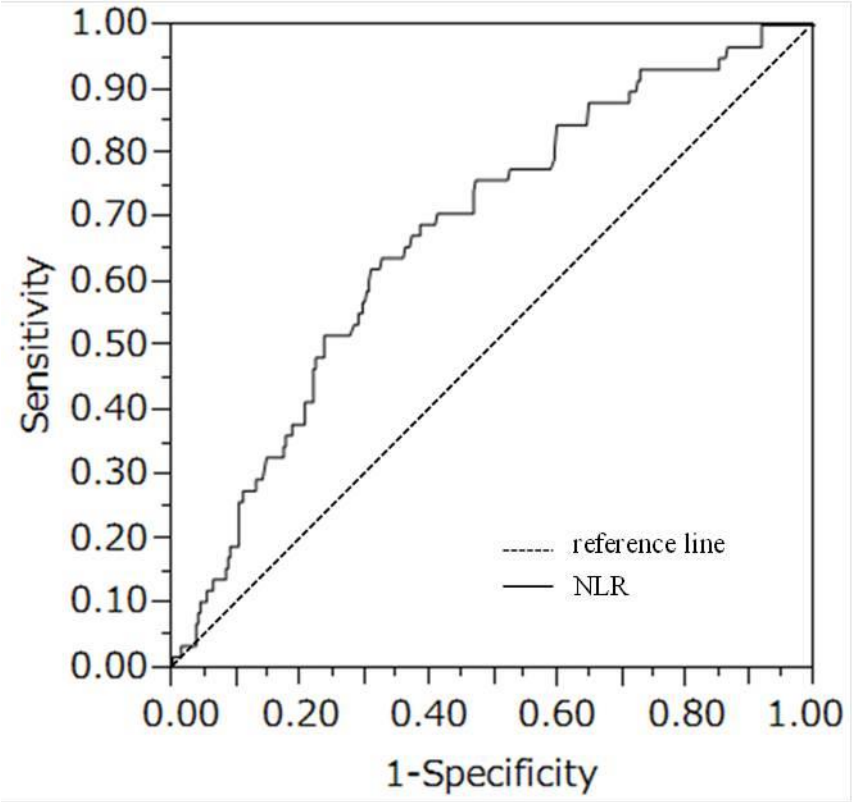

Table 1: Clinicopathologic characteristics of the study patients

Table.1

Number	359
Male : female	245 : 114
Median age (range)	66 (29-86)
Histological features, n (%)	
Papillary	11, (3.0)
Tubular	137, (38.2)
Poorly differentiated	182, (50.7)
Signet ring cell	13, (3.6)
Mucinous	16, (4.5)
Clinical T, n (%)	
T1	53, (14.8)
T2	72, (20.1)
T3	140, (38.9)
T4	94, (26.2)
Pathological T, n (%)	
T2	67, (18.7)
T3	104, (29.0)
T4	165, (46.0)
Tx	23, (6.4)
Pathological N, n (%)	
N0	87, (24.2)
N1	70, (19.5)
N2	64, (17.8)
N3	115, (32.0)
Nx	23, (6.4)
TNM stage, n (%)	
Stage Ⅰ B	35, (9.7)
Stage Ⅱ A	51, (14.2)
Stage Ⅱ B	53, (14.8)
Stage Ⅲ A	42, (11.7)
Stage Ⅲ B	56, (15.6)
Stage Ⅲ C	64, (17.8)
Stage Ⅳ	58, (16.2)
Peritoneal metastasis, n (%)	58, (16.2)

Table 2: Relationship between laboratory parameters and the presence of peritoneal metastasis

Table.2

	Peritoneal metastasis		
Variables	positive	negative	P
WBC (/μl)	5400 (2700-10500)	5700 (2500-10600)	0.339
Mono (/μl)	325 (120-870)	330 (110-870)	0.300
NLR	2.700 (1.179-8.632)	1.989 (0.753-7.848)	<0.001
Hb (g/dl)	12.4 (6.1-15.7)	13.0 (7.2-18)	0.111
Plt ($\times 10^4$/μl)	23.4 (9.4-43.2)	21.9 (7.7-44.8)	0.148
CRP (mg/dl)	0.14 (0.02-6.3)	0.08 (0.01-6.85)	0.022
Alb (g/dl)	3.9 (2.6-4.7)	4.0 (1.9-4.9)	0.014
PT (s)	11.2 (10.3-12.6)	11.0 (9.6-15.6)	0.145
APTT (s)	26.7 (21.4-37.0)	25.3 (0.97-52.6)	0.017
CEA (ng/ml)	2.2 (0.5-102.5)	2.3 (0.2-88.4)	0.703
CA19-9 (U/ml)	11.9 (0.1-3466)	12.2 (0.1-17940)	0.486

Table 3: Univariate and multivariate logistic regression analyses to identify predictors of peritoneal metastasis

Table.3

		Univariate analysis		Multivariate analysis	
Variables	n	OR (95% CI)	P	OR (95% CI)	P
NLR >2.37	134	3.71 (2.06-6.67)	<0.001	2.59 (1.38-4.93)	0.003
Hb <13.0 (g/dl)	181	1.48 (0.84-2.62)	0.172	-	-
Plt >25.0 ($\times 10^4$/μl)	115	1.49 (0.84-2.67)	0.174	-	-
CRP >1.0 (mg/dl)	22	2.06 (0.77-5.50)	0.144	-	-
Alb <3.5 (g/dl)	40	2.54 (1.21-5.36)	0.012	1.23 (0.51-2.80)	0.632
PT >median	172	1.42 (0.80-2.49)	0.227	-	-
APTT >median	174	1.77 (1.00-3.14)	0.048	1.71 (0.93-3.21)	0.087
CEA >5 (ng/ml)	63	0.97 (0.46-2.05)	0.946	-	-
CA19-9 >37 (U/ml)	70	0.96 (0.47-1.96)	0.911	-	-
undifferentiated	211	1.69 (0.93-3.08)	0.085	-	-
cT4 stage	94	5.69 (3.14-10.31)	<0.001	4.36 (2.33-8.24)	<0.001

Table 4: Relationship between the neutrophil and lymphocyte counts and the presence of peritoneal metastasis

Table.4

	Peritoneal metastasis		
Variables	positive	negative	P
Neu (/μl)	3635 (1360-6900)	3440 (1090-8240)	0.419
Lym (/μl)	1365 (570-3950)	1600 (560-4530)	<0.001

Table 5: Previously reported cutoff values of NLR for prediction of the prognosis in gastric cancer patients

Table.5

Reference	n	State (: number)	Comments
Shimada H et al [4]	1028	Stage* I / II / III / IV : 584/132/153/159	NLR>4.0 is significantly poor prognosis (P=0.003).
Jung MR et al [7]	293	Stage** III / IV : 143/150	NLR>2.0 is significantly associated with overall survival (P=0.006).
Aliustaoglu M et al [12]	168	local advanced : 168	NLR<2.56 is significantly good survival (P=0.0001).
Yamanaka T et al [13]	1220	Stage** IV : 1220	NLR>2.5 is significantly poor prognosis ($P=0.019\times10^{-12}$).
Mohri Y et al [15]	357	Stage*** I / II / III : 232/57/68	NLR>2.2 is significantly poor prognosis (P<0.0001).
Aizawa M et al [19]	262	Stage**** I / II / III : 41/116/105	NLR>3.2 is independent predictive factor for T4 (P=0.012).
Present study	359	Stage**** I / II / III / IV : 35/104/162/58	NLR>2.37 is independent predictive value of peritoneal metastasis (P=0.001).

* 13th edition of the Japanese classification of gastric carcinoma
** 6th edition of the American Joint Committee on Cancer Staging Manual
*** 5th edition of the International Union Against Cancer (UICC) classification
**** 7th edition of the International Union Against Cancer (UICC) classification

Table 6: Sensitivity and specificity of 3 factors and univariate logistic regression analysis of the risk factors of peritoneal metastasis

Table.6

Variables	n	sensitivity	specificity	OR (95% CI)	P
NLR >2.37	134	63.8%	67.4%	3.71 (2.06-6.67)	<0.001
cT4 stage	94	58.6%	80.1%	5.69 (3.14-10.31)	<0.001
NLR >2.37 and cT4 stage	55	44.8%	90.1%	7.62 (4.00-14.51)	<0.001