Prognostic value of thrombocytosis and the neutrophil/lymphocyte ratio in patients with gastric cancer: A retrospective study.

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Abstract

Numerous studies conducted within the last decade regarding the clinical use of prognostic systems based on systemic inflammation in patients with different types of cancer have suggested that these systems can be used in predicting the postoperative survival in cancer patients and for classifying patients before operation. In this study, prognostic value of thrombocytosis and neutrophil/lymphocyte ratio in gastric cancer patients after surgical resection was assessed retrospectively cancer patients after surgical resection was assessed retrospectively.

The patient's files and electronic data of 121 patients who underwent resection due to gastric cancer were retrospectively examined. The effects of the COP, NLR and COPNLR classifications on survival were investigated as well. In addition; tumour localisation, tumour histological type, the extent of tumour differentiation, vascular and lymphatic invasion, CEA level, haemoglobin level, tumour depth, lymph node status, lymph node metastasis, n-ratio, CA19.9 level, perineural invasion, lymph node metastasis and tumour size were assessed with respect to COP-NLR classification.

No statistically significant differences were observed when the effects of tumour localisation histological type, the extent of differentiation, vascular and lymphatic invasion, CEA level, haemoglobin level, tumour depth and lymph node status on survival were assessed with respect to COP-NLR classification ($p>0.005$). Assessment of lymph node metastasis, n-ratio, CA19.9 level and mortality according to the COP-NLR classification revealed a statistically significant difference ($p<0.005$). A statistically significant difference was observed when effect of perineural invasion, lymph node metastasis, tumour size, n-ratio and CA 19.9 on survival were assessed ($p<0.005$). A statistically significant difference was also observed when the effect of thrombocyte count on survival was assessed ($p<0.005$). A statistically significant difference was observed when the effect of thrombocyte count on survival was assessed ($p<0.005$). A statistically significant difference was identified between the median survival times of the cases with respect to COP-NLR classes ($p<0.001$).

Tumour type, tumour size, perineural invasion, lymph node metastasis, n-ratio, Ca 19-9 level, thrombocytosis and the neutrophil/lymphocyte ratio have an effect on survival. COP-NLR classification can be used to estimate survival.

Keywords: Gastric cancer, Reactive thrombocytosis, Adenocarcinoma.

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Introduction

Worldwide, gastric cancer is the fifth most frequent type of cancer, as well as the third most common cause of cancer-related deaths [1]. In the last decade, numerous studies have been performed regarding the clinical use of prognostic systems based on systemic inflammation in patients with different types of cancer [2]. Such studies have assessed the Glasgow Prognostic Score, neutrophil/lymphocyte ratio and reactive thrombocytosis. These studies have demonstrated that these systems may be used in predicting the post-operative survival in cancer patients and for classifying the patients before operation [3].

In the present study, the prognostic value of thrombocytosis (COP) and the neutrophil/lymphocyte ratio (NLR) in gastric cancer patients after surgical resection was assessed retrospectively.

Materials and Methods

The patient files and electronic data of 121 patients who underwent resection due to gastric cancer were retrospectively examined. The patients who did not undergo resection and whose survival rates could not be reached were excluded from the study. Routine laboratory assays were conducted before the patients were operated. Preoperative inflammation was not observed in any of the patients. None of the patients were administered preoperative chemotherapy. Adjuvant therapy protocol for all the patients was determined by the multidiscipline oncology council.

Definition of COP-NLR

The cut-off value of the preoperative thrombocyte count was taken as 300,000/µl. The cut-off value of the preoperative neutrophil/lymphocyte ratio was taken as ≥ 3. When calculating

the thrombocyte count-neutrophil/lymphocyte ratio (COP-NLR), a score of 2 was assigned if both the thrombocyte count and the neutrophil/lymphocyte ratio were above the cut-off value, while a score of 1 was assigned if one of these was above the cut-off value, and a score of 0 if both were below the cut-off value.

A CH-1015 super thermostatic bath (Shanghai Yueping Scientific Instrument Co. Ltd., China) was used for maintaining temperature of 37°C, ML110 Powerlab amplifier, ML740 four-channel recorder and MLT02021D ton transducer used for analysis of physiological data (AD Instruments Shanghai Trading Co. Ltd, were used for collecting data of tissue tension, and Power Lab/4sp analysis system Labchart7 was Pudong New Area, Shanghai, China).

Pathological findings

The cases were classified as adenocarcinoma, neuroendocrine tumour, gastrointestinal stromal tumor (GIST) and lymphoma according to the pathological findings. The adenocarcinomas were graded as well differentiated, moderately differentiated and poorly differentiated among themselves. The cases were also classified with respect to the presence of lymphatic invasion, vascular invasion and perineural invasion. The staging of the cases was made according to the AJCC tumor staging system 7th edition.

Calculation of the metastatic lymph nodes to examined lymph nodes (N-ratio)

The N-ratio was calculated as 0 when the N-ratio was 0%; as 1 when the N-ratio was between 11% and 25%; and as 3 when the N-ratio was above 25%.

Statistical analysis

The statistical data analysis was performed using the IBM SPSS Statistics Version 22 package programme. Categorical variables were summarized as n and %, and continuous variables as mean and standards deviation. The independent sample t test was used for comparing the ages of the male and female patients, while the Pearson Chi-Square, Fisher's Exact test and Chi-Square trend statistical analyses were used and for comparing categorical variables between groups. The survival times according to COP-NLR classes were evaluated by LogRank analysis, and the factors considered to be related to survival were evaluated with the Cox Regression analysis. P-values <0.05 were considered to be statistically significant.

Results

Of the patients, 74 (61.15%) were male, while 47 (38.85%) were female. The age average was 62 (34-87). There was no statistically significant difference between the ages of the male and female cases included in the study (p>0.05) (Table 1).

No statistically significant differences were observed when the age (≤ 75/ >75), gender, tumour location (proximal, medium, distal, diffuse), tumour type (adenocarcinoma, GIST, neuroendocrine tumour), tutor size (<5 cm, ≥ 5 cm), lymphatic invasion (present, absent), vascular invasion (present, absent), perineural invasion (present, absent), tumour differentiation (well, moderate, poor), carcino embriyonic antigen (CEA) (≤ 4 ng/ml, >4 ng/ml), T stage (T1, T2, T3, T4a, T4b), N stage (N0, N1, N2, N3a, N3b) of the cases were examined with respect to COP-NLR classification (p>0.05). A statistically significant difference was observed when the lymph node metastasis (present, absent), n-ratio (n- ratio -0, n-ratio-1, n-ratio-2, n-ratio-3), cancer antigen 19-9 (CA19-9) (≤ 14 U/ml, >14 U/ml), stage (1A, 1B, 2A, 2B, 3A, 3B, 3C, 4), mortality (live, exitus) of the cases were examined with respect to COP-NLR classification (p<0.05). The characteristics of the cases according to COP-NLR classification is shown in Table 2.

Among the study cases; age, gender, tumour localisation, lymphatic invasion, vascular invasion, tumour differentiation, haemoglobin level, CEA level did not have a statistically significant effect on survival (p>0.05). On the other hand; tumour type, tumour size, perineural invasion, lymph node metastasis, N-ratio, CA19-9, thrombocytosis, neutrophil/lymphocyte ratio had a statistically significant effect on survival (p>0.05). The factors affecting survival are shown in Table 3.

Based on the calculation of the COP-NLR score, 49 patients had a score of 0 (40%,50),44 patients had a score of 1 (36%,36), and 28 patients had a score of 3 (23%,14). A statistically significant difference was found between the median survival times of the cases with respect to COP-NLR classes (LogRank X2:17.476, p<0.001) (Table 4)

Discussion

The incidence of gastric cancer increases with age, and is more frequent in the sixth and seventh decades. Studies have demonstrated that age is a prognostic factor in gastric cancer [4]. In gastric cancer; the region where the tumour is located, T stage, N stage, N ratio and TNM stage have a marked effect on survival [5].

The role of the immune system in cancer propagation has been previously investigated, and the prognostic value of the leukocyte count, thrombocyte count and MPV in different types of cancer is well-evidenced. Furthermore, it is considered that the neutrophil/lymphocyte ratio is a simple indicator of the systemic inflammatory response in cancer patients. It was also demonstrated that the neutrophil/lymphocyte ratio is a factor indicative of survival in pancreatic cancers [6].

The previous studies have shown that thrombocytes play an important role in the metastatic process by protecting tumour cells against the immune system [6]. Thrombocytosis may affect survival by affecting the invasion, adhesion and proliferation of tumours. Thrombocytes ensure adhesion to cancer cells through glycoprotein-1b-IX, IIb/IIIa r adenosine diphosphate [7]. In gastric cancer, the tumour cells and the stromal cells produce various angiogenic factors such as VEGF, interleukin-8 and TP/PD-ECGF. TP/PD-ECGF, which was first isolated from

Table 1. *Mean age distribution of cases according to gender Independent sample t test.*

Gender	Age		p
	Mean ± SD.	Min-Max	
Men	62,24 ± 10,92	34-85	0,771
Women	61,62 ± 12,36	37-87	
Total	62 ± 11,45	34-87	

Table 2. *Relationships between clinical background characteristics and the COP-NLR Pearson Chi-Square,Fisher's Exact test,Chi-Square trend analysis.*

Variable		COP-NLR-0 (n=49) (%40,5)	COP-NLR-1 (n=44) (%36,4)	COP-NLR-2 (n=28) (%3,1)	p
Age (yr)	≤ 75	46 (41,1)	40 (35,7)	26 (23,2)	0,906
	>75	3 (33,3)	4 (44,4)	2 (22,2)	
Gender	Male	36 (48,6)	24 (32,4)	14 (18,9)	0,067
	Female	13 (27,7)	20 (42,6)	14 (29,8)	
Tumor site	Upper	11 (45,8)	6 (25)	7 (29,2)	0,435
	Lower	22 (44)	19 (38)	9 (18)	
	Middle	12 (30)	18 (45)	10 (25)	
	Diffuse	4 (57,1)	1 (14,3)	2 (28,6)	
Pathology	Adenocarcinoma	46 (40,7)	39 (34,5)	28 (24,8)	0,508
	GIST	1 (25,0)	3 (75)	0 (0)	
	Neuroendocrine	2 (50)	2 (50)	0 (0)	
Tumor size	<5 cm	25 (44,6)	20 (35,7)	11 (19,6)	0,605
	≥ 5 cm	24 (36,9)	24 (36,9)	17 (26,2)	
Lymphatic Invasion	Absence	9 (60)	4 (26,7)	2 (13,3)	0,491
	Presence	16 (43,2)	11 (29,7)	10 (27)	
Venous Invasion	Absence	9 (60)	4 (26,7)	2 (13,3)	0,491
	Presence	16 (43,2)	11 (29,7)	10 (27)	
Tumor Differentiation	Poor	17 (45,9)	7 (18,9)	13 (35,1)	0,903
	Intermediate	10 (27,8)	20 (55,6)	6 (16,7)	
	Well	2 (33,3)	3 (50)	1 (16,7)	
Perineural Invasion	Absence	6 (50)	4 (33,3)	2 (16,7)	0,914
	Presence	19 (47,5)	11 (27,5)	10 (25)	
Lymph node Metastasis	Absence	29 (36,3)	27 (33,8)	24 (30)	0,034
	Presence	17 (51,5)	12 (36,4)	4 (12,1)	
N-ratio	N-ratio 0	17 (51,5)	12 (36,4)	4 (12,1)	0,020
	N-ratio 1	10 (45,5)	7 (31,8)	5 (22,7)	
	N-ratio 2	7 (38,9)	5 (27,8)	6 (33,3)	
	N-ratio 3	12 (30)	15 (37,5)	13 (32,5)	
CEA	≤ 4,0 (ng/ml)	32 (42,1)	29 (38,2)	15 (19,7)	0,252
	>4,0 (ng/ml)	12 (34,3)	11 (31,4)	12 (34,3)	
CA19-9	≤ 14 (U/ml)	32 (49,2)	21 (32,3)	12 (18,5)	0,016
	>14 (U/ml)	10 (22,7)	19 (43,2)	15 (34,1)	
Depth of tumor	T1	8 (66,7)	2 (16,7)	2 (16,7)	0,223
	T2	3 (30)	3 (30)	4 (40)	
	T3	8 (47,1)	7 (41,2)	2 (11,8)	
	T4a	27 (38)	24 (33,8)	20 (28,2)	
	T4b	0 (0)	3 (100)	0 (0)	
Level of lymph node	N0	17 (51,5)	12 (36,4)	4 (12,1)	0,091
	N1	8 (38,1)	9 (42,9)	4 (19)	
	N2	6 (40)	3 (20)	6 (40)	
	N3a	7 (31,8)	5 (22,7)	10 (45,5)	
	N3b	8 (36,4)	10 (45,5)	4 (18,2)	
Stage	IA	8 (66,7)	2 (16,7)	2 (16,7)	0,034
	IB	2 (50)	2 (50)	0 (0)	
	IIA	3 (27,3)	5 (45,5)	3 (27,3)	
	IIB	8 (61,5)	4 (30,8)	1 (7,7)	
	IIIA	6 (37,5)	6 (37,5)	4 (25)	
	IIIB	6 (35,3)	6 (35,3)	5 (29,4)	
	IIIC	13 (33,3)	13 (33,3)	13 (33,3)	
	IV	0 (0)	1 (100)	0 (0)	
Mortality	Alive	12 (46,2)	14 (53,8)	0 (0)	0,034
	Exitus	37 (38,9)	30 (31,6)	28 (29,5)	

thrombocytes, is an angiogenic factor with both mitogenic and angiogenic potential, and is also an enzyme of the pyrimidine nuclease metabolism. TP/PD-ECGF production increases in various types of tumours such oesophagus, gastric, colon, rectum, pancreas and lung carcinomas. TP/PD-ECGF plays an important role in angiogenesis, tumour growth, invasion and metastasis. Thus, thrombocytosis may be observed in various malignant neoplasms [8]. Another hypothesis concerning the observation of thrombocytosis in malignant neoplasms is the increase of interleukin-6 and interleukin-1 secretion from the bone marrow as an immune response to malignancy. Interleukin-6 is a potent stimulator of megakaryopoiesis, which also increases the thrombocyte count. Interleukin-6 and interleukin-1 rise noticeably in gastric cancer as well [9].

***Table 3**. Cox Regresyon analysis of selected clinical characteristics in relation to overall survival.*

Variables		B	SE	Wald	df	Sig.	Exp (B)	95,0% CI
Age (≤ 75, >75)		0,217	0,427	0,257	1	0,612	1,242	0,538-2,866
Gender (Male, Female)		0,140	0,214	0,430	1	0,512	1,150	0,757-1,748
Tumor site	Upper	--	--	3,925	3	0,270	--	--
	Lower	-0,475	0,276	2,955	1	0,086	0,622	0,362-1,069
	Middle	-0,135	0,282	0,228	1	0,633	0,874	0,503-1,519
	Diffuse	-0,543	0,502	1,169	1	0,280	0,581	0,217-1,554
Pathology (Others, Adenocarcinoma)		2,493	1,006	6,142	1	*0,013*	12,101	1,685-86,925
Tumor size (<5 cm; ≥ 5 cm)		0,824	0,213	14,902	1	*0,001*	2,279	1,5-3,463
Lymph Invasion (absence, presence)		0,749	0,421	3,171	1	0,075	2,115	0,927-4,822
Vascular Invasion (absence, presence)		0,581	0,400	2,106	1	0,147	1,787	0,816-3,916
Perinoral Invasion (absence, presence)		1,388	0,532	6,817	1	*0,009*	4,008	1,414-11,362
Tumor Differentiation	Well	--	--	2,290	2	0,318	--	--
	Intermediate	0,810	0,535	2,289	1	0,130	2,247	0,787-6,414
	Poor	0,724	0,536	1,822	1	0,177	2,063	0,721-5,903
Lymph Node Metastasis (absence, presence)		-1,023	0,245	17,407	1	*0,000*	0,359	0,222-0,581
Hemoglobin		-0,091	0,218	,177	1	0,674	0,913	0,596-1,398
N Ratio (0/1,2,3)		1,023	0,245	17,407	1	*0,000*	2,782	1,72-4,499
CEA (≤ 4,0; >4,0)		0,415	0,227	3,340	1	0,068	1,514	0,97-2,362
CA19-9 (≤ 14,>14)		0,512	0,221	5,382	1	*0,020*	1,669	1,083-2,572
COP (0,1)		0,498	0,208	5,746	1	*0,017*	1,646	1,095-2,473
NLR (0,1)		0,476	0,208	5,227	1	*0,022*	1,609	1,07-2,419
COP-NLR (0/1,2)		0,366	0,211	3,001	1	0,083	1,442	0,953-2,182

***Table 4**. Median survival of cases according to COP-NLR classification.*

Variables	Median			
	Estimate	Std. Error	95% CI	
COP-NLR-0	38,0	10,72	17,867	58,133
COP-NLR-1	28,0	16,50	0,00	60,634
COP-NLR-2	10,0	2,646	4,814	15,186
Overall	26,0	2,793	20,526	31,474

While thrombocytosis in gastric cancer patients was first reported by Levin and Conley, its prognostic value was initially not examined [10]. In the study by Hu et al. it was stated that thrombocytosis is an indicator of tumour size, TNM staging, extent of invasion, prognosis and tumour recurrence. The same study also demonstrated that the D-dimer and fibrinogen concentrations are indicators as well [7]. Levin and Conley showed in their study that thrombocytosis does not have a prognostic importance in gastric cancer [10]. In the present study, it is demonstrated that thrombocytosis is associated with reduced survival (Figure 1).

In the study by Bruckner et al. a neutrophil value below 6000/mm³and a lymphocyte value above 1500/mm³ were determined to be good prognostic factors with respect to survival [11]. Various studies have shown that increased neutrophil/lymphocyte ratio in various types of cancer is associated with poor prognosis. Increased neutrophil counts and decreased lymphocyte counts may decrease lymphokine activated killer cells, and thereby increase the likelihood of metastasis [12]. High NLR indicates increased neutrophil counts and/or decreased lymphocyte counts. Teramukai et al. described that increased neutrophil counts indicate poor prognosis in non-small cell lung cancer [13]. In their study, Shimada et al. described that although the number of neutrophils is not an indicator of poor prognosis by itself, NLR is [12]. In the present study, high NLR was an indicator of poor prognosis.

The neutrophil/lymphocyte ratio and the thrombocyte count is related not only to tumour progression, but also to the systemic inflammatory response triggered depending on the relationship/interaction between patient and tumour [4]. In their study, Ishizuka et al. demonstrated that the combination of neutrophil/lymphocyte ratio and thrombocyte count is an indicator of postoperative survival in colorectal cancer patients [14]. In another study by Ishizuka et al. it was reported that the neutrophil/lymphocyte ratio and thrombocyte count combination has prognostic value in gastric cancer [3]. In the present study, it was also demonstrated that the combination of neutrophil/lymphocyte ratio and thrombocyte count has prognostic value in gastric cancer.

Smith et al. described that the thrombocyte/lymphocyte ratio has prognostic value in patients who underwent resection due to pancreatic adenocarcinoma [15]. In another study, Smith et al. showed that increased CA19-9 level and thrombocyte/lymphocyte ratio in pancreas cancer is a factor indicative of poor prognosis [16]. In the present study, CA19-9 level was also found to be a factor of poor prognosis.

Conclusion

In conclusion; tumour type, tumour size, perineural invasion, lymph node metastasis, N-ratio, CA19-9 level, thrombocytosis and the thrombocyte/lymphocyte ratio were all observed to have an effect on survival. COP-NLR classification can be effectively used in predicting survival.

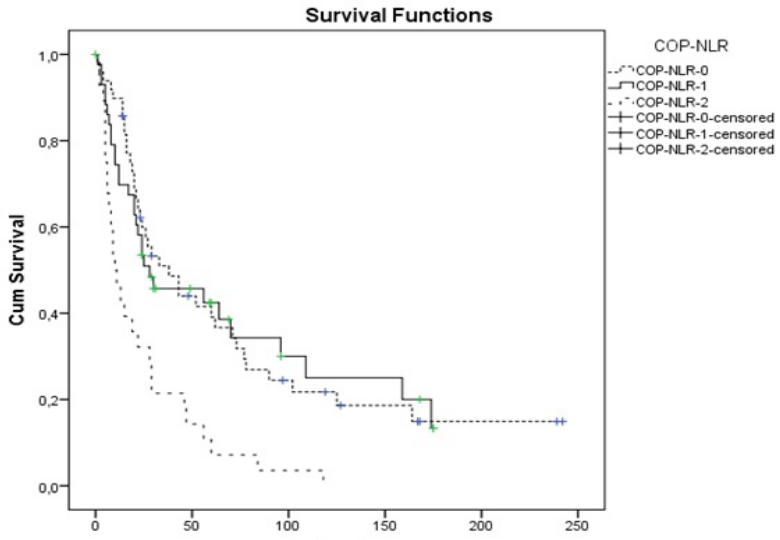

Figure 1. *Relationships among the three COP-NLR groups and overall survival in gastric cancer patients undergoing surgery.*

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