Annals of Surgical Oncology, **9**(3):287–291
Published by Lippincott Williams & Wilkins

Poor Prognosis Associated With Thrombocytosis in Patients With Gastric Cancer

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Background: Thrombocytosis is commonly associated with malignant disease and has recently been suggested to be a poor prognostic indicator in patients with lung cancer and gynecological cancers. The prevalence of thrombocytosis in patients with gastric cancer was reviewed, and its association with poor prognosis was investigated.

Methods: Platelet count (PLT) and hemoglobin concentrations (Hb) were reviewed in 369 consecutive patients with histologically verified gastric cancer from 1994 to 2000. Differences between categories were analyzed with analysis of variance, and survival was compared by using the log-rank test on the Kaplan-Meier life table. Multivariate Cox regression analysis was used to evaluate whether thrombocytosis is an independent prognostic marker.

Results: Thrombocytosis was found in 42 patients, and anemia was found in 200 patients. PLT was negatively correlated with Hb. Mean PLT was significantly increased in patients with noncurative operations. There was a positive correlation between the depth of tumor invasion and PLT. One- and 3-year survival expectancies in patients with or without thrombocytosis were 52.4% and 23.4% and 85.7% and 72.9%, respectively. PLT was identified as an independent prognostic factor after lymph node metastasis and depth of tumor invasion.

Conclusions: Thrombocytosis is an independent prognostic indicator of survival in patients with gastric cancer.

Key Words: Gastric cancer—Platelet count—Prognostic factors—Thrombocytosis—Anemia.

The association of thrombocytosis with malignancies has been known for more than 100 years.[1] Recently, thrombocytosis was reported in patients with lung cancer, colon[2] and renal cell carcinomas,[3] and gynecological malignancies such as cervical cancer,[4,5] ovarian cancer,[6] and vulvar cancer.[7] However, the effect of thrombocytosis on prognosis is controversial in the literature and needs to be further clarified.

Received June 29, 2001; accepted December 5, 2001.

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Presented at the 4th International Gastric Cancer Congress, New York, New York, April 29–May 2, 2001.

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Anemia is also common in a variety of hematological malignancies, as well as in solid malignant tumors.[8,9] Particularly in gastrointestinal cancers, such as gastric and colorectal carcinoma, bleeding directly from tumors induces anemia. Changes in iron metabolism, suppression of erythroid progenitor cells, and impaired erythropoietin responses might be responsible for anemia.

In this study, we investigated the incidence of thrombocytosis and anemia in patients with gastric cancer and attempted to evaluate the relationship between thrombocytosis and anemia. The purpose of this study was to establish the prognostic significance of anemia and thrombocytosis in patients with gastric cancer.

PATIENTS AND METHODS

Patients

The records of 369 consecutive patients (258 men and 111 women) with gastric cancer treated surgically at the

Department of Surgery, Sakai Municipal Hospital, between January 1, 1994, and December 31, 2000, were reviewed. Patients with liver cirrhosis or severe inflammatory conditions were excluded from this study. The mean age of the patients was 63.5 ± 11.2 years (range, 27 to 87 years). In all patients, the diagnosis of gastric cancer had been verified by histology. The data gathered included platelet count (PLT; $\times 10^4/\mu$L), hemoglobin concentrations (Hb; g/mL), tumor size (cm), location, histological type, lymphatic invasion, vascular invasion, lymph node metastasis, depth of tumor invasion (T), operative curability, and survival time. Operative curability was defined as follows: operative curability A, no residual disease, with high probability of cure (T1 or T2, and treated by sufficient lymph node dissection); operative curability B, no residual disease but not fulfilling criteria for operative curability A; and operative curability C, definite residual disease. The normal range for PLT is 14 to 34, and thrombocytosis was defined as a PLT at or >40, in agreement with other reports.[2–5] Anemia was defined as Hb <13 in men and <12 in women. PLT and Hb were taken at or close to the time of diagnosis. Staging of gastric cancer and the clinicopathological factors used in this study were based on the fifth edition of the American Joint Committee on Cancer *AJCC Cancer Staging Manual*.[10]

Clinical Management

After histological diagnosis was established, surgical intervention for all 369 patients was performed. Of 369 patients, total gastrectomy was performed on 95 patients, and partial gastrectomy was performed on 236 patients. Palliative bypass surgery and explorative laparotomy were performed on 24 and 14 patients, respectively. In 295 patients who underwent potentially curative gastric resection, 53 patients received oral 5-fluorouracil (5-FU), and 6 patients received administration of cisplatin or mitomycin C plus 5-fluorouracil as an adjuvant therapy.

Statistical Analysis

Statistical analysis was performed with a Power Macintosh™ G3 (Apple, Inc., Cuptertino, CA) and StatView™ 5.0 (SAS Institute, Berkeley, CA) software. All data are expressed as mean ± SD. The relationship between PLT and Hb was examined by linear regression. Analysis of variance followed by the Fisher procedure was used to evaluate PLT, T, and curative potential of gastric resection. Cumulative survival rates according to PLT were obtained by the Kaplan-Meier method, and the log-rank test was used for the analysis of difference. A multivariate Cox proportional hazard model with backward variable elimination was performed for evaluation of independent prognostic factors. A P value <.05 was considered significant.

TABLE 1. *Incidence of thrombocytosis and anemia in patients with gastric cancer*

Variable	n	%
Platelet count ($\times 10^4/\mu$L)		
<34	302	81.8
34 ≤PLT <40	25	6.8
≥40	42	11.4
Hb (g/dL)		
men: Hb ≤10; women: Hb ≤9	60	16.3
men: 10 <Hb ≤13, women: 9 <Hb ≤12	140	37.9
men: 13 <Hb, women: Hb >12	169	45.8

Hb, hemoglobin; PLT, platelet count.

RESULTS

The mean pretreatment PLT for all patients was 27.3 ± 10.7 (range, 5.1 to 81.0). The number of patients with PLT <34 was 302 (81.8%), and the number of patients with thrombocytosis was 42 (11.4%) (Table 1). The mean pretreatment Hg for all patients was 12.2 ± 2.5 (range, 4.1 to 17.2). The number of patients with anemia was 200 (54.2%). There was a significant negative linear relationship between PLT and Hb ($r = -.476$, $P < .0001$) (Fig. 1).

Characteristics of the clinicopathological factors in patients with normal PLT and with thrombocytosis are listed in Table 2. There were no significant differences found between sex, age, location, microscopic classification, or venous invasion. However, tumor size, lymph

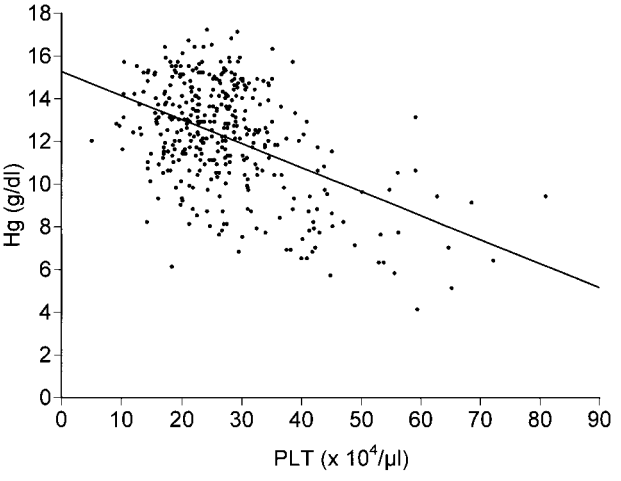

FIG. 1. Scatterplot showing the relationship between pretreatment platelet count (PLT) and hemoglobin (Hg). The solid line represents the linear fit to the data (Spearman's regression test; $r = -.476$, $P < .0001$).

TABLE 2. *Comparison of clinicopathological factors in patients with normal platelet count and with thrombocytosis*

Variable	PLT <34 (n = 302)	PLT ≥40 (n = 42)	*P* value
Sex (male/female)	216/86	25/17	NS
Age (y)	63.6 ± 11.6	64.6 ± 10.1	NS
Tumor size (cm)	7.8 ± 4.0	4.1 ± 2.8	<.0001
Location			
Upper	44	6	
Middle	132	17	NS
Lower	119	18	
Unknown	7	1	
Microscopic classification			
Differentiated	164	16	
Undifferentiated	138	25	NS
Unknown	0	1	
Lymph node metastasis			
Positive	175	6	
Negative	106	25	<.0001
Unknown	21	11	
Lymphatic invasion			
ly0,1	126	24	
ly2,3	142	4	<.0001
Unknown	34	14	
Venous invasion			
v0,1	59	6	
v2,3	209	22	NS
Unknown	34	14	
Serosal invasion			
Positive (T3, T4)	62	20	
Negative (T1, T2)	233	16	<.0001
Unknown	7	6	

NS, not significant; PLT, platelet count; ly0, 1, no or minimal lymphatic invasion; ly 2, 3, moderate or marked lymphatic invasion; v0, 1, no or minimal venous invasion; v2, 3, moderate or marked venous invasion.

node metastasis, lymphatic invasion, and serosal invasion were significantly associated with thrombocytosis.

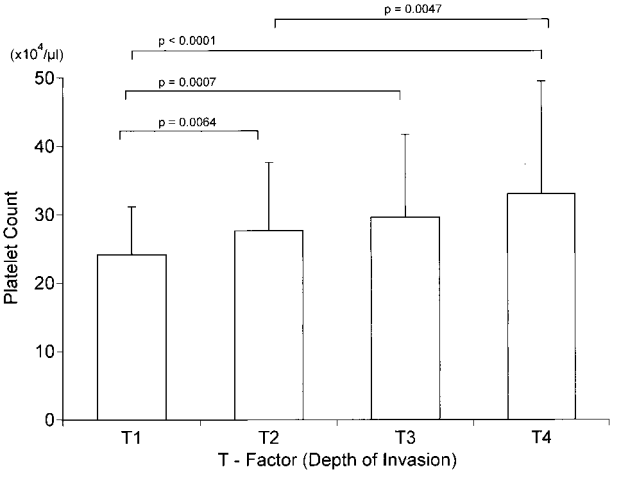

FIG. 2. Mean platelet count according to the depth of tumor invasion (T factor). Values are expressed as mean ± SD.

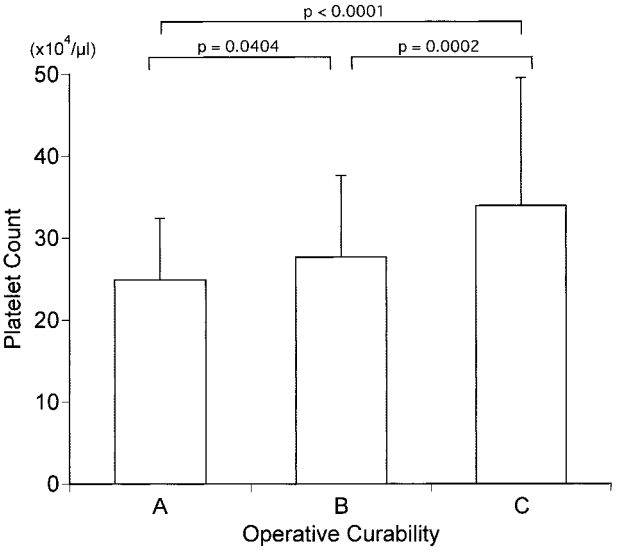

FIG. 3. Mean platelet count according to the curability of operation. Operative curability A, no residual disease with high probability of cure (T1 or T2, and treated by sufficient lymph node dissection); operative curability B, no residual disease but not fulfilling criteria for operative curability A; operative curability C, definite residual disease. Values are expressed as mean ± SD.

PLT differed significantly among the subgroups defined by the depth of invasion (T factor) and curative potential, with the proportion of patients with thrombocytosis greatest in the more advanced stages. There was a positive correlation between the extent of the T factor and PLT: T1, 24.2 ± 7.0 (n = 133); T2, 27.6 ± 10.0 (n = 135); T3, 29.6 ± 12.1 (n = 63); and T4, 33.0 ± 16.4 (n = 38) (Fig. 2; $P < .0001$). Mean PLT was significantly increased in patients who underwent noncurative

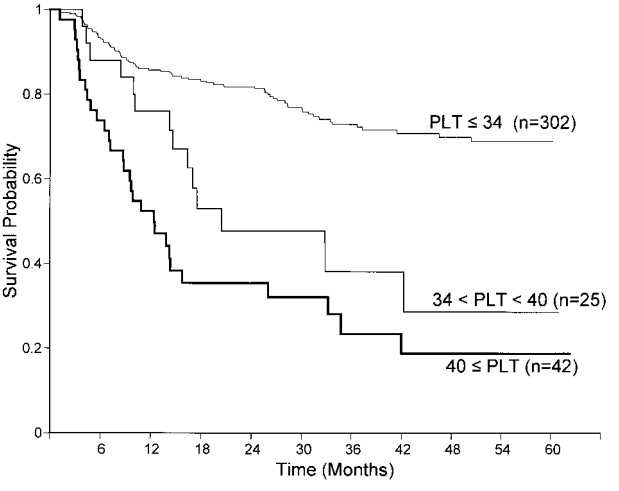

FIG. 4. Kaplan-Meier survival curves stratified by platelet count (PLT) in patients with gastric cancer.

operations (resection C): in curative potential of resection, A, 24.9 ± 7.5 (n = 218); B, 27.7 ± 10.0 (n = 78); and C, 34.0 ± 15.6 (n = 73) (Fig. 3; $P < .0001$).

One- and 3-year survival expectancies in patients with normal PLT were 85.7% and 72.9%, respectively. However, 1- and 3-year survival expectancies in patients with thrombocytosis were 52.4% and 23.4%, respectively (Fig. 4). The difference in survival between patients with thrombocytosis and normal PLT was significant ($P < .0001$). As for Hb, patients with severe anemia (men, Hb ≤10; women, Hb ≤9) had 1- and 3-year survival expectancies of 50.4% and 27.4%, respectively. In patients with normal Hb, survival expectancies for 1 and 3 years were 90.6% and 80.8%, respectively.

Before multivariate analysis, univariate analysis was performed for the prognostic factors listed in Table 2: sex, age, tumor size (≤4 or ≥4 cm), tumor location, microscopic classification, lymph node metastasis, lymphatic invasion, venous invasion, and depth of invasion (T1, T2 or T3, and T4). From the findings, sex, age, tumor location, microscopic classification, and venous invasion were excluded. In a multivariate analysis, tumor size, lymph node metastasis, lymphatic invasion, depth of invasion, PLT, Hb, operative curability, and tumor, node, metastasis staging were evaluated. Of the eight factors, lymph node metastasis, depth of invasion, and PLT were identified as independent prognostic indicators of survival. Patients with thrombocytosis had a relative risk of death of 2.48 ($P = .015$) (Table 3).

DISCUSSION

In this study, we found thrombocytosis (PLT ≥40) and anemia (Hb <13 in men and <12 in women) in 11.4% and 54.2%, respectively, of patients with gastric cancer. Thrombocytosis was more common among patients with more advanced-stage disease. Anemia and thrombocytosis were associated with a poor prognosis. Although anemia was of no independent prognostic value, thrombocytosis was an independent prognostic factor in patients with gastric cancer after lymph node metastasis and depth of invasion. Jatzko et al.[9] reported that preoperative anemia was an independent prognostic factor in patients with gastric cancer. In this study, anemia was associated with poor survival; however, it was not an independent prognostic factor when thrombocytosis was considered.

TABLE 3. *Multivariate analysis of prognostic factors by stepwise method (Cox proportional hazard model)*

Prognostic factor		RH	95% CI	*P* value
Lymph node metastasis	N0	1.00	–	
	N1	1.58	0.64–7.02	.22
	N2	4.11	1.09–22.49	.0004
	N3	10.24	1.58–60.65	<.0001
Depth of invasion	T1	1.00	–	
	T2	3.04	1.22–9.72	.012
	T3	3.46	1.08–13.69	.018
	T4	11.95	2.63–63.30	.0001
Platelet count ($\times 10^4/\mu L$)	<34	1.00	–	
	34–40	1.2	0.45–2.95	.62
	≥40	2.48	1.13–5.22	.015

RH, relative hazard; CI, confidence interval.

Thrombocytosis is observed frequently in patients with malignancies, and prognostic significance has been found in patients with gynecological cancers,[4,5] renal cell carcinoma,[3] and lung cancer.[11,12] Thrombocytosis in patients with gastric cancer was first reported by Levin and Conley,[13] but the prognostic significance of thrombocytosis was not analyzed. Therefore, this is the first evaluation of the prevalence and prognostic effect of thrombocytosis in patients with gastric cancer. The prevalence of thrombocytosis in patients with gynecological cancers[5,6,14] was 14% to 38%, was 32% to 46% with primary lung cancer,[2,12] and was 33% with colon cancer.[2] Compared with these studies, the incidence of thrombocytosis in all 369 patients with gastric cancer (11.4%) is low, because our study included many early-stage patients. Thrombocytosis was found in 3.6% (7 of 191) of stage IA and IB patients; however, 19.7% (35 of 178) of stage II to IV patients had thrombocytosis.

Although the specific mechanisms by which thrombocytosis develops in malignancies remain speculative, several hypotheses have been proposed on this subject. One possibility is the host response to malignancy, including bone marrow–stimulating cytokines such as interleukin-6 (IL-6), IL-1, and macrophage colony-stimulating factor.[15] IL-6 is a potent stimulator of megakaryocytopoiesis. The levels of IL-6 and IL-1 are significantly increased in patients with gastric cancer.[16,17] Macrophage colony-stimulating factor has also been shown to be increased in patients with gastrointestinal cancer.[18] These observations strongly suggest a role of the cytokines induced by the host response to tumors in tumor-associated thrombocytosis.

Thrombocytosis may adversely affect survival by facilitating cell invasion and metastasis. A number of studies have suggested that platelets play an integral role in the metastatic process. There is evidence that platelets protect tumor cells by shielding them from the host's immune system.[19,20] Platelets also facilitate tumor cell adhesion to the vascular endothelium by forming tumor thrombi and through interactions between tumor and platelet ligands. P selectin on activated platelets has an important role in tumor growth and metastasis,[21] and

platelets support cancer cell adhesion under dynamic flow conditions via P selectin, $\alpha_{IIb\beta3}$, and von Willebrand factor.[22] After adhesion, platelets may promote tumor cell growth through secreting several tumor growth factors or angiogenic factors, such as thrombospondin, vascular endothelial growth factor (VEGF), and platelet-derived endothelial growth factor. Thrombospondin is increased in patients with metastatic disease. It was proposed that this protein, in the presence of a normal clotting system, promotes adhesion of tumor cells to the vascular endothelium and potentiates experimental tumor cell metastasis.[23] VEGF, a potent angiogenic factor, is secreted by tumor cells and is also released by platelets on activation, and serum VEGF concentrations are highly correlated with PLT,[24] suggesting the important role of platelets in plasma VEGF production. It has been further demonstrated that the pretreatment plasma VEGF level was a prognostic indicator of survival in patients with gastric cancer.[25] In addition to VEGF, platelet-derived endothelial growth factor, recently defined as thymidine phosphorylase, also has prognostic significance in gastric cancer patients.[25]

Whether thrombocytosis is simply an end result of growth factors secreted by tumor cells and the host response, or whether thrombocytosis is an event that directly increases the risk of disease spread and worsened prognosis, will require additional research.

In conclusion, the incidence of thrombocytosis in patients with gastric cancer was 11.4%. Although the incidence is low compared to other malignancies, patients with thrombocytosis have a poor prognosis, and thrombocytosis was found to be an independent prognostic factor.

Acknowledgments: This study was supported in part by a Grant-in-Aid from the Japan Ministry of Health and Welfare (9-3).

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