World Journal of Gastroenterology

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DOI: 10.3748/wjg.v22.i9.2818

World J Gastroenterol 2016 March 7; 22(9): 2818-2827
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

ORIGINAL ARTICLE

Retrospective Study

Prognostic value of perioperative leukocyte count in resectable gastric cancer

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Supported by The National Natural Science Foundation of China, No. 81301896; the Natural Science Foundation of the Colleges and Universities in Jiangsu Province, China, No. 13KJB320011; the Program for Development of Innovative Research Teams, Jiangsu Province Clinical Science and Technology Projects (Clinical Research Center, BL 2012008); the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD); and Provincial Initiative Program for Excellency Disciplines, Jiangsu Province, China.

Institutional review board statement: The study was reviewed and approved by the Science and Research Office of The First Affiliated Hospital of Nanjing Medical University.

Informed consent statement: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

Conflict-of-interest statement: There are no conflicts of interest to report.

Data sharing statement: No additional data are available.

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Received: May 31, 2015
Peer-review started: June 5, 2015
First decision: September 9, 2015
Revised: November 19, 2015
Accepted: December 8, 2015
Article in press: December 8, 2015
Published online: March 7, 2016

Abstract

AIM: To investigate the prognostic significance of perioperative leukopenia in patients with resected

gastric cancer.

METHODS: A total of 614 eligible gastric cancer patients who underwent curative D2 gastrectomy and adjuvant chemotherapy were enrolled in this study. The relationship between pre- and postoperative hematologic parameters and overall survival was assessed statistically, adjusted for known prognostic factors.

RESULTS: The mean white blood cell count (WBC) significantly decreased after surgery, and 107/614 (17.4%) patients developed p-leukopenia, which was defined as a preoperative WBC $\geqslant 4.0 \times 10^9$/L and postoperative WBC $< 4.0 \times 10^9$/L, with an absolute decrease $\geqslant 0.5 \times 10^9$/L. The neutrophil count decreased significantly more than the lymphocyte count. P-leukopenia significantly correlated with poor tumor differentiation and preoperative WBC. A higher preoperative WBC and p-leukopenia were independent negative prognostic factors for survival [hazard ratio (HR) = 1.602, 95% confidence interval (CI): 1.185-2.165; $P = 0.002$, and HR = 1.478, 95%CI: 1.149-1.902; $P = 0.002$, respectively] after adjusting for histology, Borrmann type, pTNM stage, vascular or neural invasion, gastrectomy method, resection margins, chemotherapy regimens, and preoperative WBC count. The patients with both higher preoperative WBC and p-leukopenia had a worse prognosis compared to those with lower baseline WBC and no p-leukopenia (27.5 mo *vs* 57.3 mo, $P < 0.001$).

CONCLUSION: Preoperative leukocytosis alone or in combination with postoperative leukopenia could be independent prognostic factors for survival in patients with resectable gastric cancer.

Key words: Gastric cancer; Leukocytosis; Leukopenia; Postoperative; Prognosis

Core tip: It has been noted that a subset of gastric cancer patients who underwent gastrectomy with normal baseline white blood cell counts experience mild to moderate leukopenia after surgery. This retrospective analysis investigated preoperative and postoperative leukocyte counts in gastric cancer patients to assess their relationship with clinicopathologic characteristics and their potential prognostic value. The results show, for the first time, that preoperative leukocytosis and postoperative leukopenia significantly correlated with overall survival in resectable gastric cancer treated with adjuvant chemotherapy. This suggests the prognostic importance of perioperative total leukocyte count for operable gastric cancer.

Chen XF, Qian J, Pei D, Zhou C, Røe OD, Zhu F, He SH, Qian YY, Zhou Y, Xu J, Xu J, Li X, Ping GQ, Liu YQ, Wang P, Guo RH, Shu YQ. Prognostic value of perioperative leukocyte count in resectable gastric cancer. *World J Gastroenterol* 2016; 22(9): 2818-2827 Available from: URL: http://www.wjgnet.com/1007-9327/full/v22/i9/2818.htm DOI: http://dx.doi.org/10.3748/wjg.v22.i9.2818

INTRODUCTION

Gastric cancer is the fourth most common malignancy and the second leading cause of cancer deaths worldwide[1]. The incidence of gastric cancer is especially high in East Asia, and nearly half of the world's total cases each year occur in China[2]. Gastrectomy still remains the mainstay of curative treatment for patients with localized disease. Despite advances in multidisciplinary care and comprehensive treatment modalities, the overall five-year survival after curative gastrectomy is only about 30%[3-5]. Thus, the identification of surrogate predictors for prognosis would be of paramount importance for resectable gastric cancer before adjuvant therapy.

Elevated leukocyte count preoperatively predicts poor outcomes or recurrence in lung[6], anal[7], and cervical[8] cancers, while leukopenia in cancer patients is usually seen during the course of chemotherapy, and arises in association with thrombocytopenia and anemia as a consequence of bone marrow suppression[9]. We noted that a subset of gastric cancer patients who underwent gastrectomy with a normal baseline white blood cell count (WBC) experienced mild to moderate leukopenia after surgery, but before any adjuvant treatment. Most of these patients had no infection or disease of the hematopoietic system to explain this phenomenon, and few published studies described a similar observation. We therefore carried out a retrospective analysis to investigate preoperative and postoperative leukocyte counts, and to assess their relationship with clinicopathologic characteristics and their potential prognostic value.

MATERIALS AND METHODS

Patients

A retrospective search of the medical records of The First Affiliated Hospital of Nanjing Medical University was conducted spanning the period from January 1, 2008 to August 31, 2012. Cases were included when they fulfilled the following criteria: (1) management with primary curative gastrectomy, and at least two cycles of adjuvant chemotherapy commencing at most 2 mo after surgery (the detailed indications for chemotherapy is shown in Method S1); (2) histopathologically confirmed gastric cancer; (3) routine blood tests available for review from both pre- and postoperative periods (with the postoperative counts taken between 3 wk and 2 mo after surgery, but before chemotherapy was administered); and (4)

available survival data. The exclusion criteria included: (1) patients with recorded myeloproliferative disease; (2) patients with bony or bone marrow metastasis diagnosed before chemotherapy administration; (3) patients with a previous history of gastric surgery; (4) patients in whom neoadjuvant chemotherapy was indicated; (5) patients with additional pathology or postoperative complications that would significantly impact the WBC, such as infection or autoimmune diseases; and (6) patients who had undergone splenectomy. These exclusion criteria were used to eliminate potential alternative reasons for leukopenia or leukocytosis. The study was approved by the Ethics Committee of The First Affiliated Hospital of Nanjing Medical University and has been performed in accordance with the ethical standards of the Declaration of Helsinki.

Laboratory test results and other clinical data

Routine blood tests were performed by electrical impedance with a Beckman coulter LH750 instrument (Beckman Coulter, Inc., Brea, CA, United States). Preoperative blood counts, including total WBC, WBC differential counts (including neutrophil and lymphocyte count); hemoglobin (HGB) and platelets were usually measured in the week before surgery. Postoperative blood counts were measured before chemotherapy, usually 21-60 d after surgery. For patients in whom chemotherapy was not indicated, postoperative blood tests were also performed during this time frame. Detailed clinicopathologic information was obtained from the medical records system. All cases were restaged according to the 7th edition of the American Joint Committee on Cancer and International Union Against Cancer classification for gastric cancer[10]. Survival data were acquired from patients' records, death certificates, or patients' families by telephone follow-up. The last follow-up date was August 31, 2014. Survival time was calculated from the date of surgery to the date of death or to the last follow-up.

Definitions of normal blood values and postoperative leukopenia (p-leukopenia)

Normal ranges of clinical blood tests were based on the latest standards published by the Ministry of Health of China (WBC: 4.0-10.0 × 10^9/L; platelet count: 100-300 × 10^9/L; HGB: 120-160 g/L in male patients and 110-150 g/L in female patients).

For total leukocyte count, the preoperative WBC was divided into two categories (< 5.6 or ≥ 5.6) based on the median value of preoperative WBC. P-leukopenia required a preoperative WBC ≥ 4.0 × 10^9/L and postoperative WBC < 4.0 × 10^9/L, and an absolute decrease postoperatively of ≥ 0.5 × 10^9/L in patients of both sexes. This concept of an absolute decrease value was used to better define patients who experienced "real" leukopenia and to avoid clinically insignificant changes distorting the results. However, we also analyzed the data using the current leukopenia standard definition (postoperative WBC < 4.0 × 10^9/L).

Statistical analysis

All statistical data were analyzed using the SPSS 18.0 software (SPSS Inc., Chicago, IL, United States). Changes in blood counts were analyzed with the paired *t* test. The correlations between WBC and clinicopathologic parameters were evaluated with Pearson's χ^2 or Fisher's exact tests. Survival was visualized by the Kaplan-Meier method, and the log-rank test was used to compute differences between the curves. Potential factors correlated with prognosis were analyzed using Cox regression to estimate the hazard ratios (HR) and their 95% confidence intervals (CI). Multivariate survival analysis was performed using a forward stepwise method, with a significance level of 0.05 for entering, and 0.10 for removing the variables. Statistical significance was set at a $P < 0.05$.

RESULTS

Patient characteristics

A total of 614 patients who had undergone D2 curative gastrectomy (48.0% distal gastrectomy, 38.9% total gastrectomy, and 13.1% promixal gastrectomy) for gastric cancer were eligible for inclusion in the study. The clinicopathologic features of all the patients are listed in Table 1. The cohort comprised 430 male and 184 female patients, with a median age of 58 years. The most common pathologic features included tumors of undifferentiated type (85.5%), Borrmann Ⅰ/Ⅱ/Ⅲ type (96.6%), T4 (58.6%), TNM stage Ⅲ (57.7%), with affected lymph nodes (75.6%), and R0 (71.0%). The cutoff of intraoperative blood loss (IBL) was determined from a previous study[11]. Approximately 92.7% of cases had an IBL < 200 mL, and 12.5% received intraoperative blood transfusions. The majority of subjects received double (48.0%) or triple (41.2%) chemotherapy regimens. No patients were given radiotherapy. All the chemotherapy regimens used are described in Table S1.

Blood counts before and after operation

Patients were grouped by normal maximum and minimum counts, and showed a significantly lower incidence of leukopenia before surgery than after surgery, at 8.8% and 22.8% respectively ($P < 0.001$, Table 2). The postoperative WBCs were significantly lower than the preoperative counts. The mean WBC was 6.08 × 10^9/L preoperatively and 5.25 × 10^9/L postoperatively ($P < 0.001$, Table 2). Interestingly, the mean WBC of patients with preoperative leukopenia increased from 3.45 × 10^9/L to 3.90 × 10^9/L after surgery ($P = 0.02$). According to our definition, a total of 107 (17.4%) patients developed p-leukopenia, among whom 11 (10%) had a decrease to < 1.0 × 10^9/L and 19 to < 3.0 × 10^9/L. According to the

Table 1 Patient characteristics

Variables	*n*	%	Variables	*n*	%
All patients	614		pTNM stage		
Age (yr)			I	76	12.4
Median (range)	58 (18-85)		II	149	24.3
Sex			III	354	57.7
Male	430	70.0	IV	35	5.7
Female	184	30.0	Vascular or neural invasion		
Tumor site			Negative	337	54.9
Cardia	148	24.1	Positive	277	45.1
Fundus	10	1.6	Operation method		
Body	241	39.3	Promixal gastrectomy	80	13.1
Antrum	193	31.4	Distal gastrectomy	295	48.0
Borrmann type			Total gastrectomy	239	38.9
I / II / III	578	94.1	Resection margins		
IV	36	5.9	R0	436	71.0
Histology			R1	178	29.0
Differentiated	89	14.5	Chemotherapy regimens		
Undifferentiated	525	85.5	Triplet	253	41.2
Tumor status			Doublet	295	48.0
pT1	51	8.3	Singlet	45	7.3
pT2	80	13.0	None	21	3.4
pT3	123	20.0	Intraoperative blood loss (mL)		
pT4	360	58.6	Median (range)	120 (50-1500)	
Node status			≤ 200	569	92.7
pN0	150	24.4	> 200	49	7.3
pN1	122	19.9	Intraoperative blood transfusion		
pN2	158	25.7	No	537	87.5
pN3	184	30.0	Yes	77	12.5

Table 2 Blood cell counts pre- and postoperatively

Factors	mean ± SD	Range	*P* value	*n* (%)		
				Low[1]	Normal[1]	High[1]
WBC ($\times 10^9$/L)						
Before operation	6.08 ± 2.11	1.5-17.3	< 0.001	54 (8.8)	530 (86.3)	30 (4.9)
After operation	5.25 ± 1.97	2.1-17.8		140 (22.8)	455 (74.1)	19 (3.1)
HGB (g/L)						
Before operation	124.2 ± 22.92	55-176	< 0.001	159 (25.9)	441 (71.8)	14 (2.3)
After operation	117.1 ± 13.68	79-161		300 (48.9)	313 (51.0)	1 (0.2)
PLT ($\times 10^9$/L)						
Before operation	214.9 ± 77.15	55-706	0.838	22 (3.6)	527 (85.8)	65 (10.6)
After operation	214.2 ± 84.76	42-793		22 (3.6)	520 (84.7)	72 (11.7)

[1]Low represents the values that were lower than the lower limit of the normal range; Normal represents the values that were within the normal range; High represents the values that were higher than the upper limit of the normal range. HGB: Hemoglobin; PLT: Platelet count; WBC: White blood cell count.

Common Terminology Criteria for Adverse Events version 3.0, 85 and 22 cases had grade 1 and grade 2 leukopenia, respectively. No leukopenia of grade 3 or more was recorded. Furthermore, there was a significant association between preoperative WBC and p-leukopenia (P = 0.008, Table 3).

Although both the neutrophil and lymphocyte counts declined after surgery, neutrophil loss was the major contributor to the drop in WBC, thus leading to a significant decrease of neutrophil to lymphocyte ratio (NLR) (Figure 1). Accordingly, neutrophil count and NLR dropped more in the p-leukopenia population than in the non-p-leukopenia group (Figure 1, Table S2). The mean value of HGB in patients both with and without p-leukopenia decreased after surgery (Figure S1B, Table 2), while there was no significant correlation between the variation of WBC and HGB (Figure S2). Likewise, the platelet counts before and after surgery showed no significant difference (P = 0.838, Figure S1C, Table 2).

According to the conventional definition, without the additional requirement for an absolute decrease in the WBC, which we used to define post-leukopenia, 140/614 (22.8%) patients had leukopenia postoperatively. Similar results were found with regard to the change of HGB, platelet count(s) (Table S3), neutrophils, and lymphocytes (Figure 1, Table S2) in patients with and without post-leukopenia.

WBC and clinicopathologic features

The preoperative WBC was significantly associated with patient sex (P = 0.011), tumor stage (P = 0.015),

Table 3 Relationships between white blood cell count and patients' clinicopathologic features *n* (%)

Factors	Preoperative WBC count ($\times 10^9$/L)		*P* value	P-leukopenia		*P* value
	< 5.6	⩾ 5.6		Positive	Negative	
All patients	295 (48.0)	319 (52.0)		107 (17.4)	507 (82.6)	
Age (yr)						
< 58	143 (51.1)	137 (48.9)	0.194	51 (18.2)	229 (81.8)	0.670
⩾ 58	152 (45.5)	182 (54.5)		56 (16.8)	278 (83.2)	
Sex						
Male	192 (44.7)	238 (55.3)	0.011	70 (16.3)	360 (83.7)	0.248
Female	103 (56.0)	81 (44.0)		37 (20.1)	147 (79.9)	
Tumor site						
Cardia	74 (50.0)	74 (50.0)	0.823	29 (19.6)	119 (80.4)	0.664
Fundus	6 (60.0)	4 (40.0)		1 (10.0)	9 (90.0)	
Body	112 (46.5)	129 (53.5)		39 (16.2)	202 (83.8)	
Antrum	94 (48.7)	99 (51.3)		36 (18.7)	157 (81.3)	
Multi-site	9 (40.9)	13 (59.1)		2 (9.1)	20 (90.9)	
Histology						
Differentiated	35 (39.3)	54 (60.7)	0.085	8 (9.0)	81 (91.0)	0.023
Undifferentiated	260 (49.5)	265 (50.5)		99 (18.9)	426 (81.1)	
Borrmann type						
Ⅰ / Ⅱ / Ⅲ	278 (48.1)	300 (51.9)	0.919	101 (17.5)	477 (82.5)	0.901
Ⅳ	17 (47.2)	19 (52.8)		6 (16.7)	30 (83.3)	
Tumor status						
pT1 + pT2	78 (59.5)	53 (40.5)	0.003	18 (13.7)	113 (86.3)	0.198
pT3 + pT4	217 (44.9)	266 (55.1)		91 (18.8)	392 (81.2)	
Node status						
pN0	84 (56.0)	64 (44.0)	0.011	25 (16.7)	125 (83.3)	0.901
pN1 + pN2 + pN3	209 (45.0)	255 (55.0)		82 (17.7)	382 (82.3)	
pTNM stage						
Ⅰ + Ⅱ	123 (54.7)	102 (45.3)	0.015	38 (16.9)	187 (83.1)	0.743
Ⅲ + Ⅳ	172 (44.2)	21 (55.8)		71 (18.3)	318 (81.7)	
Vascular or neural invasion						
Negative	168 (49.9)	169 (50.1)	0.331	60 (17.8)	277 (82.2)	0.831
Positive	127 (45.8)	150 (54.2)		47 (17.0)	230 (83.0)	
Gastrectomy method						
Promixal	41 (51.3)	39 (48.7)	0.742	15 (18.7)	65 (81.3)	0.598
Distal	143 (48.5)	152 (51.5)		55 (18.6)	240 (81.4)	
Total	111 (46.4)	128 (53.6)		37 (15.5)	202 (84.5)	
Resection margins						
R0	215 (49.3)	221 (50.7)	0.329	77 (17.7)	359 (82.3)	0.907
R1	80 (44.9)	98 (55.1)		30 (16.9)	148 (83.1)	
Intraoperative blood loss (mL)						
⩽ 200	273 (48.0)	296 (52.0)	0.906	101 (15.1)	468 (84.9)	0.545
> 200	22 (48.9)	23 (51.1)		6 (21.1)	39 (78.9)	
Intraoperative blood transfusion						
No	251 (46.7)	286 (53.3)	0.099	98 (18.2)	439 (81.8)	0.198
Yes	44 (57.1)	33 (42.9)		9 (11.7)	68 (88.3)	
Preoperative WBC count ($\times 10^9$/L)						
< 5.6	-	-	-	64 (21.7)	231 (78.3)	0.008
⩾ 5.6	-	-		43 (13.5)	276 (86.5)	

P-leukopenia, defined as a preoperative WBC ⩾ 4.0×10^9/L and postoperative WBC < 4.0×10^9/L, and an absolute decrease postoperatively of ⩾ 0.5×10^9/L. WBC: White blood cell count.

node status (P = 0.011) and TNM stage (P = 0.003). Male patients with advanced TNM stage were more likely to have a higher preoperative WBC (Table 3). P-leukopenia was significantly associated with poor tumor differentiation (P = 0.023, Table 3) and low preoperative WBC count (P = 0.008).

Correlation between WBC and overall survival

Of the 614 patients studied, 259 (42.2%) died during follow-up. The median follow-up time was 45.1 mo, and the median overall survival (mOS) was 47.8 mo. Log-rank survival analysis showed that patients with higher WBC before surgery were associated with a worse clinical outcome (mOS: 46.9 mo *vs* 55.6 mo, P = 0.001, Figure 2A). Moreover, patients who experienced p-leukopenia had significantly worse outcome than those who did not (36.5 mo *vs* 62.1 mo, P = 0.009, Figure 2B). We also analyzed the outcome of patients with postoperative WBC < 4.0×10^9/L; these patients also had a significantly shorter mOS (35.9 mo *vs* 62.1 mo, P = 0.005, Figure 2C).

Univariate analysis revealed that differentiation, Borrmann type, tumor status, lymph node involvement, TNM stage, vascular or neural invasion, operation

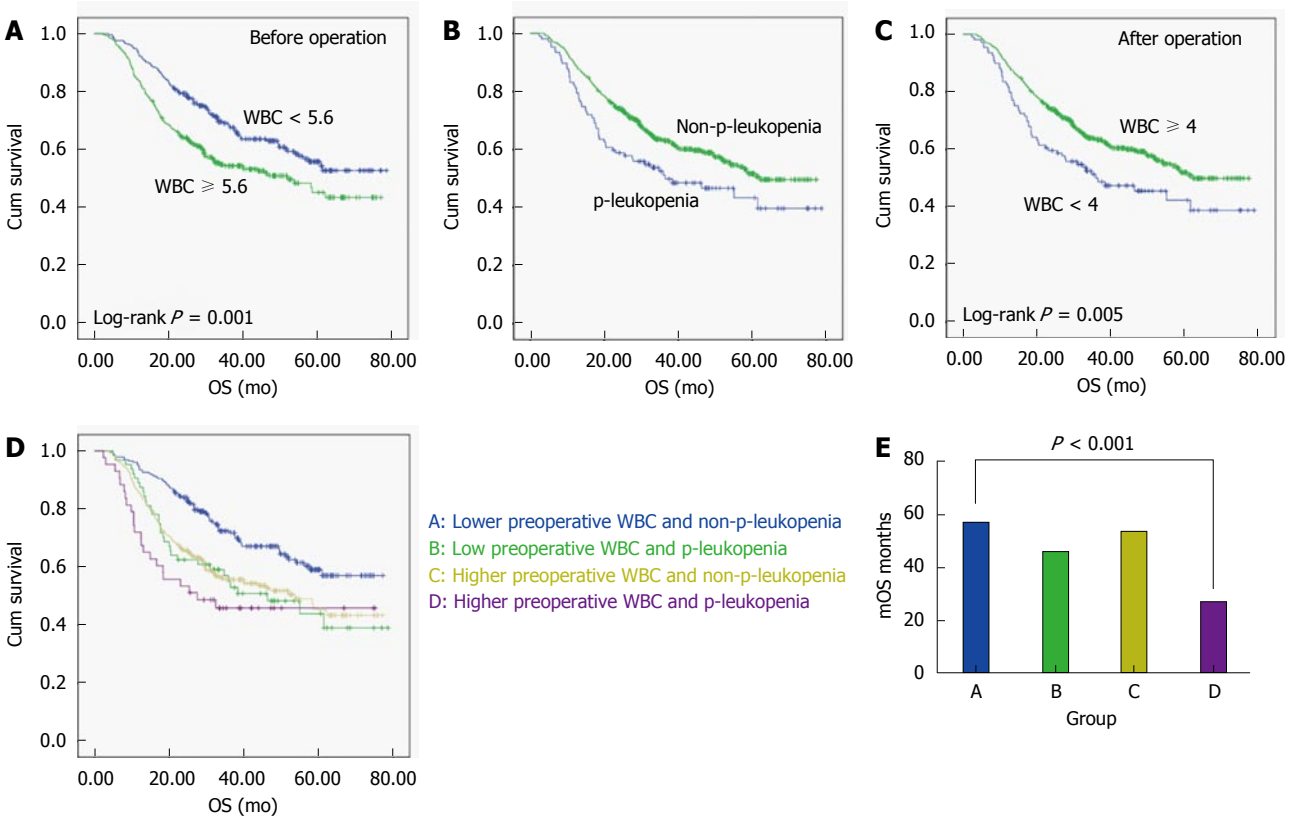

Figure 1 Kaplan-Meier curves depicting overall survival. A: Patients with higher preoperative white blood cell count (WBC) had shorter overall survival (OS) when divided by the median; B: Patients affected by p-leukopenia had worse OS; C: Patients whose WBC < 4.0 × 10^9/L after surgery had lower OS than those whose WBC ⩾ 4.0 × 10^9/L; D: Combined analysis of OS by pre- and postoperative WBC. Patients with low preoperative WBC but without p-leukopenia showed the optimal OS, significantly longer than that in patients who had both high preoperative WBC and p-leukopenia.

method, resection margins, chemotherapy regimens, preoperative WBC count, and p-leukopenia correlated with survival. Interestingly, both a high preoperative WBC and p-leukopenia remained significantly correlated with worse survival after adjusting for prognostic factors such as Borrmann Ⅳ type, TNM stage, vascular or neural invasion, margins R1, chemotherapy regimens (both $P = 0.001$, Table 4).

Finally, as a higher preoperative WBC and p-leukopenia both correlated with lower mOS, we combined these two factors. Patients were divided into four groups according to median preoperative WBC (⩾ 5.6 × 10^9/L or < 5.6 × 10^9/L) and the presence or absence of p-leukopenia. Patients with the combination of higher preoperative WBC and p-leukopenia had the worst mOS (27.5 mo), while patients with lower preoperative WBC and no p-leukopenia had significantly increased mOS (57.3 mo, $P < 0.001$, Figure 2D).

DISCUSSION

There is mounting evidence that an elevated WBC count correlates with cancer mortality[12,13] and worse prognosis in patients with non-small cell lung[6], anal[7], and cervical[8] cancers. Here we identified a novel prognostic role for a simple WBC count before and after curatively intended gastric cancer surgery.

Few studies have assessed the postoperative change of leukocyte count and its potential role in prognosis of cancer patients in general. Dallal *et al*[14] reported that the incidence of leukopenia (WBC ⩽ 4.0 × 10^9 /L) increased significantly from 2.0% before surgery to 14.6% postoperatively ($P < 0.0005$) in 590 patients with Roux-en-Y gastric bypass surgery during a mean follow-up of 398 d (range 30-1484 d). They also demonstrated that the mean WBC count decreased from a preoperative value of 7.5 × 10^9/L to 6.0 × 10^9/L after surgery ($P < 0.0005$), though the duration of monitoring for leukopenia was much longer in this report than in our study. In our study, to exclude other potential factors that could influence the WBC counts, we used a strict temporal cutoff for the diagnosis of p-leukopenia of 21-60 d after surgery, but before chemotherapy administration. Moreover, cases with known factors as infection or other diseases that may affect bone marrow were excluded. The clinical observation that initiated this study was that some patients unexpectedly had leukopenia after gastric cancer surgery. The purpose of this study was thus to determine if this observation was important. The results clearly showed a fall in WBC count after gastrectomy, where the rate of leukopenia significantly increased from 8.8% to 22.8% postoperatively. To eliminate the bias produced by detection error and the normal fluctuations of WBC in different physical

Table 4 Univariate and multivariate Cox regression analysis for gastric cancer-related survival

Factors	Univariate			Multivariate		
	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (yr)						
⩾ 58 *vs* < 58	1.036	0.811-1.324	0.776	-	-	-
Sex						
Female *vs* male	1.033	0.794-1.345	0.809	-	-	-
Histology						
Differentiated *vs* undifferentiated	1.661	1.115-2.475	< 0.001	1.261	0.839-1.896	0.265
Borrmann type						
Ⅳ *vs* Ⅰ / Ⅱ / Ⅲ	2.634	1.726-4.018	< 0.001	1.886	1.207-2.948	0.005
Tumor status						
pT3 + pT4 *vs* pT1 + pT2	3.186	2.123-4.782	< 0.001	1.230	0.667-2.268	0.507
Lymph node metastasis						
Yes *vs* no	3.098	2.128-4.512	< 0.001	1.485	0.871-2.533	0.147
pTNM stage						
Ⅱ *vs* Ⅰ	2.713	1.318-5.583	0.007	1.813	0.756-4.350	0.183
Ⅲ *vs* Ⅰ	6.449	3.301-12.597	< 0.001	2.723	1.941-7.882	0.015
Ⅳ *vs* Ⅰ	10.624	4.909-22.995	< 0.001	4.849	1.610-14.610	0.005
Vascular or neural invasion						
Yes *vs* no	1.780	1.393-2.274	< 0.001	1.324	1.023-1.713	0.033
Operation method						
Total gastrectomy *vs* Subtotal gastrectomy	1.425	1.113-1.824	0.005	1.198	0.931-1.542	0.159
Resection margins						
R1 *vs* R0	2.081	1.624-2.667	< 0.001	1.904	1.298-2.792	0.001
Chemotherapy regimens						
Triplet or doublet *vs* singlet or none	2.522	1.379-4.614	0.003	2.369	1.289-4.356	0.005
Intraoperative blood loss (mL)						
> 200 *vs* ⩽ 200	1.146	0.718-1.828	0.568	-	-	-
Intraoperative blood transfusion						
Yes *vs* No	1.237	0.835-1.831	0.289	-	-	-
Preoperative WBC count (× 10^9/L)						
⩾ 5.6 *vs* < 5.6	1.542	1.204-1.975	0.001	1.553	1.205-2.001	0.001
P-leukopenia						
Positive *vs* negtive	1.479	1.100-1.988	0.010	1.660	1.226-2.247	0.001

P-leukopenia, defined as a preoperative WBC ⩾ 4.0 × 10^9/L and postoperative WBC < 4.0 × 10^9/L, and an absolute decrease postoperatively of ⩾ 0.5 × 10^9/L. CI: Confidence interval; HR: Hazard ratio; WBC: White blood cell count.

situations, we defined p-leukopenia as an absolute decrease of WBC ⩾ 0.5 × 10^9/L. Intriguingly, we found that 17.8% of the cases developed p-leukopenia, which was not related to any decrease in HGB or platelets, nor to IBL or blood transfusion.

Leukocytosis (defined as WBC > 10 × 10^9/L) has been reported to predict poor survival in several malignancies, including lung[6,14], cervical[8], and anal[7] cancers, but not in gastric cancer[15]. In our study, 94% patients were stage Ⅰ-Ⅲ, and only 4.9% had leukocytosis. We used the median WBC value as cutoff and showed that an elevated baseline WBC was related to poor OS, consistent with clinicopathologic findings, while a higher WBC correlated with advanced TNM stage, a well-known index for worse outcome. In contrast, after surgery, patients with a lower WBC had worse outcome, irrespective of whether our definition of p-leukopenia or the simple criterion of WBC < 4.0 × 10^9/L was employed. Furthermore, when combined, these two factors showed a significant synergetic prognostic effect indicating that joint analysis of pre- and postoperative WBC could be helpful for prognostication of patients who undergo a curative resection for gastric cancer.

The mechanism underlying a generalized decrease in WBC after gastrectomy is still unclear. Emerging evidence has shown that copper deficiency due to impaired copper absorption is one cause of leukopenia or anemia, but is unlikely to be the major cause for the postoperative short-term leukopenia as it seems to require years to develop after gastric surgery[16,17]. It is recognized that surgical interventions, especially major surgery, can cause immunosuppression[18]. Immunosuppression is a complex process characterized by a decrease in T lymphocyte number, and a shift in the balance between the immunesuppressive regulatory T lymphocytes and the immune-promoting helper T and cytotoxic T cells[19]. A decrease in T cells may be detected from the immediate postoperative period[20,21] to 30 d following surgery[22]. A recent study reported that the postoperative peripheral blood lymphocyte count correlates with outcome in patients with gallbladder carcinoma treated by radical resection, indicating an important prognostic role of postoperative immune function[20]. However, in our study, the decrease in neutrophils was more pronounced, and led to a decreased NLR. Furthermore, compared with the non-p-leukopenia population, patients with p-leukopenia

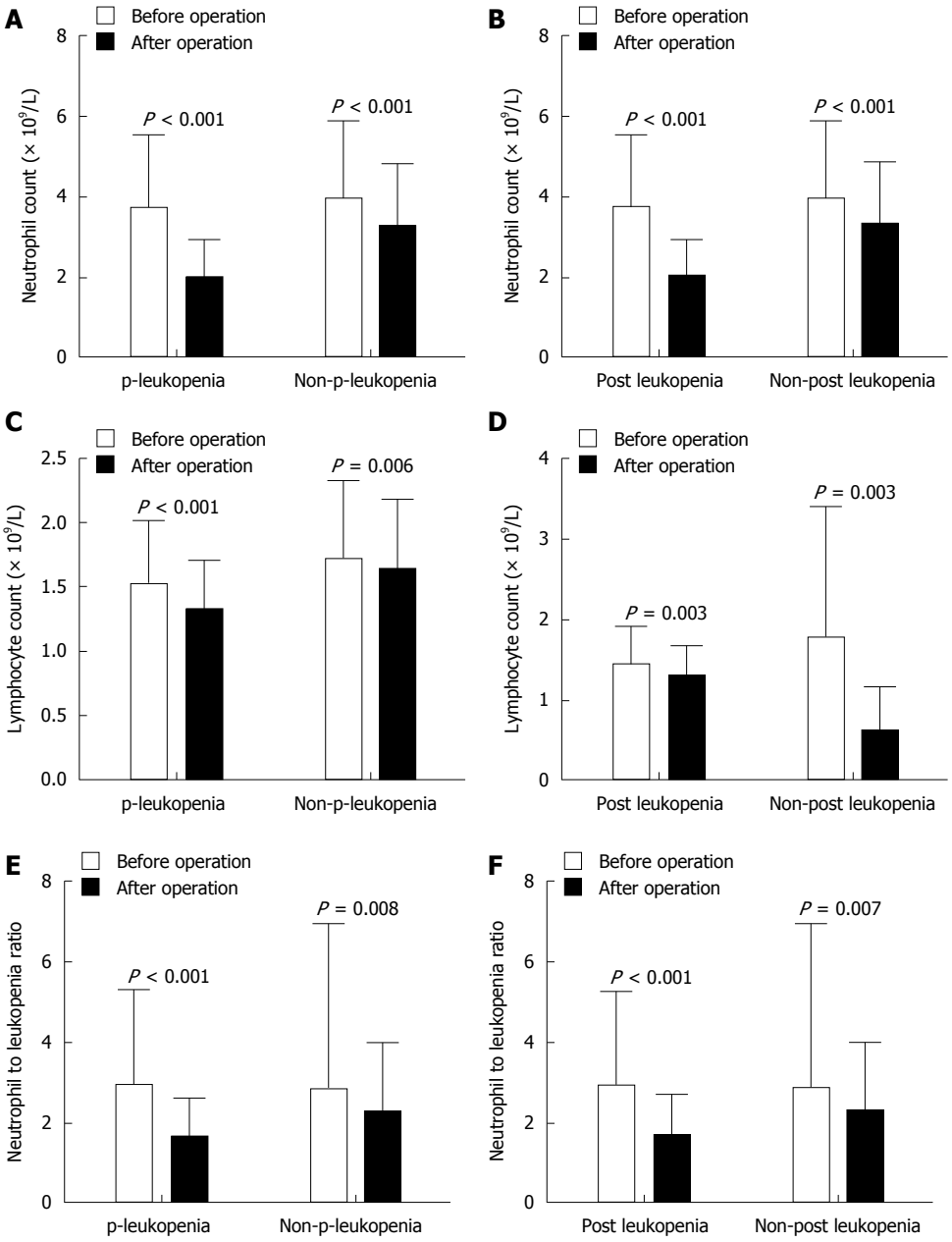

Figure 2 Neutrophil count (A, B), lymphocyte count (C, D), and neutrophil to lymphocyte ratio (E, F) in patients with and without p-leukopenia or postoperative leukopenia before and after surgery. P-leukopenia refers to preoperative WBC ⩾ 4.0 × 10^9/L and postoperative WBC < 4.0 × 10^9/L, with an absolute decrease ⩾ 0.5 × 10^9/L WBC. Postoperative leukopenia (Post leukopenia) here was defined as WBC < 4.0 × 10^9/L. Data was presented as mean ± SD. *P* values were determined by Student's *t* test compared with the corresponding values before operation. WBC: White blood cell.

had an even greater reduction in their neutrophil count and NLR. Thus, it is reasonable to postulate that the neutrophils also could be involved in the postoperative immune disturbance in some patients, though the intrinsic mechanism underlying this and how it contributes to the prognosis remains unknown. IBL or blood transfusion may greatly affect postoperative WBC, which was corrected for in the correlation and survival analyses. In a recent study, IBL > 200 mL was found to be a risk factor for resected gastric cancer, but this was not confirmed in our study. This could be due to the low number of patients with such blood loss (45 cases, 7.32%), and timely treatment with intraoperative and postoperative blood transfusion was conducted on the patients with massive blood loss. In addition, the time of 21 d after surgery could allow the hematopoietic system to compensate for the fall in blood components.

Drawbacks of our study are that it is based on retrospective data and that there are several scenarios we did not examine, such as those not receiving chemotherapy and cases with D1 surgery. Moreover, we did not have banked blood samples to study other indices of immunologic function, and thus we could not examine the basic reasons for the development of p-leukopenia in this cohort. Prospective biologic and immunologic analyses of blood components are

planned to elucidate the basic mechanisms of this phenomenon. Such studies may also pave the way to new knowledge of the interactions between the immune system and cancer, currently a very hot area of research given encouraging results targeting PD1, PDL1 and CTL4[22].

To the best of our knowledge, this is the first study to describe the phenomenon of p-leukopenia, as well as demonstrating that a higher preoperative WBC and p-leukopenia significantly correlate with OS in resectable gastric cancer treated with adjuvant chemotherapy. This unique finding, if validated in a large-scale prospective study, could help decision making for the treatment of resectable gastric cancer patients.

COMMENTS

Background

Elevated leukocyte count preoperatively predicts poor outcomes or recurrence in several cancers, while leukopenia in cancer patients is usually seen during the course of chemotherapy, and arises in association with thrombocytopenia and anemia as a consequence of bone marrow suppression. However it is noted that a subset of gastric cancer patients who underwent gastrectomy with a normal baseline white blood cell count experienced mild to moderate leukopenia after surgery, but before any adjuvant treatment. Most of these patients had no infection or disease of the hematopoietic system to explain this phenomenon, and few published studies described a similar observation.

Research frontiers

The authors therefore carried out a retrospective analysis to investigate the preoperative and postoperative leukocyte counts, and to assess their relationship with clinicopathologic characteristics and their potential prognostic value.

Innovations and breakthroughs

The retrospective study demonstrated for the first time that preoperative leukocytosis and postoperative leukopenia significantly correlated with overall survival in resectable gastric cancer treated with adjuvant chemotherapy.

Applications

The unique finding suggests the prognostic importance of perioperative total leukocyte count for operable gastric cancer. If it is validated by a large-scale prospective study, it could help decision making for further adjuvant treatment after gastrectomy for gastric cancer patients with an easily available laboratory blood examination.

Terminology

Leukopenia is a decrease in the number of white blood cells (leukocytes) found in the blood, which places individuals at increased risk of infection. Leukopenia can be identified with a complete blood count. Leukocytosis is a white blood cell count (the leukocyte count) above the normal range in the blood. It is frequently a sign of an inflammatory response, most commonly the result of infection, but may also occur following certain parasitic infections or bone tumors.

Peer-review

This is a very interesting manuscript evaluating the prognostic value of perioperative leukocyte count in resectable gastric cancer. It is well written and improves the current knowledge about gastric cancer. However future perspectives should be better analyzed and more accurately described.

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P- Reviewer: Gurkan A **S- Editor**: Yu J **L- Editor**: Filipodia
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ISSN 1007-9327