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Department of Obstetrics and Gynecology, Peking University People's Hospital,

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ABC Xiaowei Li

Chong Tan

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Correlation Between Platelet and Hemoglobin Levels and Pathological Characteristics and Prognosis of Early-Stage Squamous Cervical Carcinoma

Beijing P.R. China

Collection B al Analysis C rpretation D reparation E ure Search F Collection G	DE AC DF EF ACD CE	Wanxuan Zhang Jingyi Zhou Zhiqi Wang Shijun Wang Jianliu Wang Lihui Wei					
Corresponding Author: Source of support:		Jianliu Wang, e-mail: wangjianliu@pkuph.edu.cn; cnxwdoc@163.com Departmental sources					
Background: Material/Methods:		We sought to determine the effect of pre-operative hemoglobin (HGB) and platelet (PLT) levels on the clinical features and prognosis of early-stage squamous cervical carcinoma (SCC). We performed a retrospective analysis of 380 patients with SCC who underwent hysterectomy and pelvic lymph- adenectomy. SCC was confirmed post-operatively by pathological diagnosis. The relations between HGB and PLT levels and clinicopathological characteristics were observed, and a Cox regression analysis was performed					
Results:		to determine their influence on survival. There were significant differences in tumor staging, tumor diameter, and lymphatic metastasis between the 69 patients with PLT levels >300×10 ⁹ /L and the 311 patients with PLT levels \leq 300×10 ⁹ /L (<i>P</i> <0.05). Tumor stag- ing, extent of differentiation, and lymphatic metastasis were significantly different between 134 patients with HGB levels <120 g/L and 246 patients with HGB levels \geq 120 g/L (<i>P</i> <0.05). The overall survival rate in the group with PLT levels >300×10 ⁹ /L was lower than that in the group with PLT levels \leq 300 × 10 ⁹ /L, but this difference was not significant. The overall survival rate in the group with HGB levels <120 g/L was significantly lower than that in the group with HGB levels \geq 120 g/L (<i>P</i> <0.05), and the overall survival rate in the group with PLT levels >300×10 ⁹ /L and HGB levels <120 g/L (<i>P</i> <0.05). According to Cox regression analysis, a pre-operative HGB level <120 g/L was considered a separate risk factor affecting prognosis					
Conclusions:		Close attention must be paid to pre-operative PLT and HGB levels, and anemia should be remedied to facilitate the treatment of cervical carcinoma.					
MeSH Ke	MeSH Keywords: Carcinoma, Squamous Cell • Hemoglobin A • Platelet Count						
Full-t	ext PDF:	http://www.medscimonit.com/abstract/index/idArt/895016					



Background

Thrombocytosis and anemia are 2 factors adversely affecting prognosis for patients with malignant cervical tumors [1–4]. Thrombocytosis in patients with malignant tumors may be related to the invasion and metastasis of the tumor and can produce a series of biological responses related to thrombocytosis [1,5]. Most patients with malignant tumors have anemia primarily because of variations in iron metabolism due to the insufficiency of endogenous hematopoietin and blood loss. Anemia and hypoxemia can enhance angiopoiesis, promote tumor cell proliferation and metastasis, reduce the response of tumor cells to apoptotic cell signals, and influence curative effects [6].

A host of current, related studies have focused on the relations among platelet (PLT) or hemoglobin (HGB) level, the curative effects of cervical carcinoma treatment, and prognosis, with particular focus on advanced cervical carcinoma [1,7–9]. However, there have been few studies focusing on the relations among combined PLT-HGB levels, clinical features, and prognosis of early-stage cervical carcinoma [10]. Here, we aimed to study the relations between pre-operative PLT and HGB levels and the clinical features and prognosis of patients with earlystage squamous cervical carcinoma (SCC).

Material and Methods

General data

We carried out a retrospective analysis of 380 patients with SCC treated from June 2000 to July 2013. This study was conducted in accordance with the Declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Peking University People's Hospital. Written informed consent was obtained from all participants before the operation. All patients underwent radical hysterectomy with pelvic lymphadenectomy, and SCC was verified by post-operative pathological diagnosis. Tumor staging was based on the 2009 International Federation of Gynecology and Obstetrics (FIGO) staging system. We retrospectively reviewed pre-operative HGB and PLT levels, age, tumor stage, tumor differentiation, lymphatic metastasis, depth of tumor invasion into the cervical mesenchyme, parametrial metastasis, vessel infiltration, and tumor size. No patient had acute or chronic liver or kidney injury, bleeding, thromboembolic disease, heart disease, or other infectious diseases. Those who took anticoagulant or coagulant drugs within the preceding month or with a previous history of malignant tumor, radiotherapy, chemotherapy, or immunological therapy were excluded. All patients were followed for 12 to 175 months, with a median follow-up period of 62 months and a lost-to-follow-up rate of 3.4%.

Statistical methods

SPSS 16.0 (SPSS Inc., Chicago, IL, USA) was used for data processing. All tests were 2-sided, with significance set at p<0.05. The measurement data are presented as means \pm standard deviation, and inter-group comparisons were performed with the Student's *t*-test. Enumerated data are presented as cases (constituent ratio), and inter-group comparisons were performed with the Pearson chi-squared test or Fisher exact test. The logrank test was used for the single-factor analysis of the influence of pre-operative PLT, HGB, and combined PLT-HGB levels on the post-operative long-term survival of patients, and the Kaplan-Meier method was used to determine survival curves. Cox regression analysis of pre-operative PLT and HGB levels on the post-operative long-term survival of patients with SCC was also performed.

Clinical grouping

Patients with PLT levels > 300×10^{9} /L were classified as having thrombocytosis [11], and patients were divided into 2 groups based on this PLT level for comparison of clinical features and 5-year survival rates. Patients with HGB levels <120 g/L were classified as having anemia, and patients were divided into 2 groups based on this HGB level for comparison of clinical features and 5-year survival rates. Based on the survival analysis, the effects of PLT, HGB, and combined PLT-HGB levels on the prognosis of cervical carcinoma were then evaluated.

Results

This study involved 380 patients with SCC, aged 51.01 ± 8.71 years. We obtained the pre-operative PLT and HGB levels of all 380 patients. Before the initial treatment, the mean PLT level was (242.87±69.00)×10⁹/L and the mean HGB level was 123.35±15.02 g/L.

Relations between PLT level and the clinical features of cervical carcinoma

Patients with PLT levels >300×10⁹/L accounted for 18.2% (69/380) of the study group, and, compared with patients with PLT levels \leq 300×10⁹/L, had a more advanced tumor stage (*P*<0.05), larger tumor size (*P*<0.05), and higher incidence of positive lymph node (*P*<0.05). There was no statistical difference between these 2 groups in terms of age, extent of differentiation, depth of cervical invasion, existence of cancer embolus in the vessel, parametrial positivity, or 5-year survival rate (Table 1).

Table 1. Relations between PLT and the clinical features of cervical carcinoma.

Influencing Factor	PLT ≤30 (n:	00×10° g/L =311)	PLT >300×10° g/L (n=69)		P value
Age	52.75		4	3.13	0.474
FIGO stage					0.033
IA	46	(14.8%)	20	(29.0%)	
IB	137	(44.1%)	27	(39.1%)	
IIA	51	(16.4%)	11	(15.9%)	
IIB	77	(24.8%)	11	(15.9%)	
Tumor differentiation					0.524
G1	79	(25.2%)	15	(21.7%)	
G2–G3	232	(74.8%)	54	(78.3%)	
Tumor diameter					0.015
≻4 cm	73	(23.3%)	26	(37.7%)	
≤4 cm	238	(76.7%)	43	(62.3%)	
Lymphatic metastasis					0.017
Positive	48	(15.3%)	19	(27.5%)	
Negative	263	(84.7%)	50	(72.5%)	
Depth of tumor invasion into the	0.161				
<1/2	182	(58.8%)	34	(49.3%)	
≥1/2	129	(41.2%)	35	(50.7%)	
Cancer embolus in vessel					0.117
Positive	100	(32.3%)	29	(42.0%)	
Negative	211	(67.7%)	40	(58.0%)	
Parametrial					0.697
Negative	301	(96.8%)	68	(98.6%)	
Positive	10	(3.2%)	1	(1.4%)	
5-year survival rate	12	0/156	24/35		0.300

Relations between HGB level and clinical features of cervical carcinoma

There were 134 patients with HGB levels <120 g/L. Compared with patients with HGB levels >120 g/L, they had a more advanced tumor stage (P<0.05), worse differentiation (P<0.05), higher incidence of positive lymph node (P<0.05), and a higher 5-year survival rate (P<0.05). There were no statistical differences between these 2 groups in terms of age, depth of cervical invasion, existence of cancer embolus in the vessel, or parametrial positivity (Table 2).

Relations between PLT, HGB, and combined PLT-HGB levels and overall survival rate

The log-rank test was performed for the single-factor analysis of the influence of pre-operative PLT, HGB, and combined PLT-HGB levels on the post-operative long-term survival of patients, while the Kaplan-Meier method was used to determine the survival curves. The overall survival rate of the group with PLT levels $>300 \times 10^9$ /L was lower than that of the group with PLT levels $\leq 300 \times 10^9$ /L (Figure 1), but this difference was not significant. The overall survival rate of the group with HGB levels

Table 2. Relations between HGB and the clinical features of cervical carcinoma.

Influencing Factor	Influencing Factor HB <12 g/L (n=134)		HB : (n	≥12 g/L =246)	P value
Age	44.30		5	54.67	0.333
FIGO stage					0.023
IA	14	(10.4%)	50	(20.3%)	
IB	55	(41.0%)	110	(44.7%)	
IIA	29	(21.6%)	35	(14.2%)	
IIB	36	(26.9%)	51	(19.8%)	
Tumor differentiation					0.012
G1	23	(17.2%)	71	(28.9%)	
G2–G3	111	(82.8%)	175	(71.1%)	
Tumor diameter					0.587
>4 cm	32	(23.9%)	65	(26.4%)	
≤4 cm	102	(76.1%)	181	(73.6%)	
Lymphatic metastasis					0.018
Positive	32	(23.9%)	35	(14.6%)	
Negative	102	(76.1%)	210	(85.4%)	
Depth of tumor invasion into the cervical mesenchyme					0.087
<1/2	69	(51.5%)	149	(60.6%)	
≥1/2	65	(48.5%)	97	(39.4%)	
Cancer embolus in vessel					0.776
Positive	51	(38.1%)	90	(36.6%)	
Negative	83	(61.9%)	156	(63.4%)	
Parametrial					0.753
Negative	131	(97.8%)	238	(96.7%)	
Positive	3	(2.2%)	8	(3.3%)	
5-year survival rate 44/66		4/66	100/125		0.042

<120 g/L was significantly lower than that of the group with HGB levels \geq 120 g/L (*P*<0.05) (Figure 2). The overall survival rate of the group with PLT levels >300×10⁹/L and HGB levels <120 g/L was significantly lower than that of the group with PLT levels \leq 300×10⁹/L and HGB levels \geq 120 g/L (*P*<0.05) (Figure 3).

Relations between PLT and HGB levels and cervical carcinoma prognosis

Cox regression analysis of the factors with the potential to influence prognosis of patients with SCC revealed that age,

tumor differentiation, tumor size, lymphatic metastasis, and FIGO stage were the independent risk factors for patients' survival and that HGB level was a protective factor (Table 3).

Relations between combined PLT-HGB level and cervical carcinoma prognosis

The Cox regression analysis with combined PLT-HGB level as a factor influencing tumor prognosis revealed that combined preoperative anemia and thrombocytosis and pre-operative anemia were independent risk factors for patients' survival (Table 4).

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Figure 1. Applying Kaplan-Meier method to draw the survival curves for different PLT levels.



Figure 2. Applying Kaplan-Meier method to draw the survival curves for different HGB levels.

Discussion

Relations between PLT and HGB levels and cervical carcinoma clinical features

According to the literature, patients with thrombocytosis account for 14–38% of all patients with malignant tumors [12]. Malignant cells often produce cytokines and growth factors able to induce platelets, which in turn can secrete growth factors that stimulate cancer cell proliferation, angiogenesis, and distant progression [1,5,13]. Platelets are a rich source of both



Figure 3. Applying Kaplan-Meier method to draw the survival curves for different PLT-HGB combined levels.

platelet-derived growth factor, which is a potent mitogen, and thrombospondin, which supports the adhesion of tumor cells to the endothelium through an increased expression of urokinase-type plasminogen activator [5,13]. Hernandez et al. [1] performed an analysis of 294 patients with stage IIB-IVA cervical carcinoma who had no aortic lymph node metastasis and did not undergo standard radiotherapy or chemotherapy with hydroxyurea or misonidazole. Compared with the patients with normal PLT levels, the patients with thrombocytosis had tumors with a greater volume and were more likely to have bilateral parametrial infiltration, tumors fixed to the pelvic wall, and positive cavum pelvis lymph nodes. Zhao's [14] research on the influence of PLT level on early-stage cervical carcinoma showed that 25.5% of patients had thrombocytosis; thrombocytosis had positive correlations with tumor staging, tumor size, and tumor recurrence rate; and thrombocytosis tended to occur among patients with advanced cervical carcinoma. Thus, there appears to be a negative correlation between thrombocytosis and tumor characteristics [15,16].

In this study, 18.1% of patients had pre-operative thrombocytosis, in line with the rate reported in the literature. Our results show that a higher PLT level is associated with later clinical stages, greater tumor volume, and a higher positive lymph node rate; however, thrombocytosis was not significantly associated with 5-year survival rate, perhaps related to unmeasured difference in the patients, as well as the sample size. This non-significant result is in contrast to results from the study noted above.

For patients with cervical carcinoma, anemia can directly influence the effects of radiotherapy [3]. About 30% of patients Anemia

0.001

Indicator	Hazard ratio (95%	Cl) P value
Age	2.843 (1.136–7.1	11) 0.026
Tumor differentiation (G2–G3 vs. G1)	1.744 (1.034–2.9	42) 0.037
Tumor size (>4 cm <i>vs</i> . ≤4 cm)	1.704 (1.070–2.7	16) 0.025
Lymph node (positive vs. negative)	1.895 (1.179–3.0	46) 0.008
FIGO staging		0.000
IB vs. Ia	1.415 (0.605–3.3	14) 0.423
lla <i>vs</i> . la	2.712 (1.114–6.6	01) 0.028
llb vs. la	2.937 (1.215–7.1	03) 0.011
Thrombocythemia	0.663 (0.380–1.1	58) 0.149

2.200

Table 3. Factors influencing prognosis of the cervical carcinoma patients [1].

Table 4. Factors influencing prognosis of the cervical carcinoma patients [2].

Indicator	Hazard ratio (95%Cl)		P value
Tumor differentiation (G2–G3 vs. G1)	2.595	(1.114–6.045)	0.027
Tumor size (>4 cm vs. ≤ 4cm)	2.674	(1.152–6.210)	0.022
Lymph node (positive vs. negative)	3.543	(1.472–8.528)	0.005
FIGO staging			0.002
IB vs. Ia	1.494	(0.638–3.500)	0.356
lla vs. la	3.088	(1.272–7.496)	0.013
llb vs. la	3.103	(1.278–7.534)	0.012
Anemia (–) + Thrombocytosis (–)			0.000
Anemia (+) + Thrombocytosis (–)	1.683	(1.082–2.615)	0.021
Anemia (–) + Thrombocytosis (+)	0.758	(0.319–1.800)	0.530
Anemia (+) + Thrombocytosis (+)	3.715	(2.111–6.540)	0.000

(1.375 - 3.521)

with cervical carcinoma have pre-operative anemia [17]. In this study, 35.3% of patients had pre-operative anemia. The present research showed that such actions as blood transfusion prior to the operation would not improve the prognosis for patients with cervical carcinoma, indicating that the tumor has a highly invasive nature among patients with anemia, and may imply poor prognosis. Therefore, anemia may indicate high tumor risk [18].

Relations between PLT and HGB levels and survival of cervical carcinoma

A meta-analysis by Yu et al. showed that 12 out of 14 studies confirmed a negative correlation between thrombocytosis and the 5-year survival rate [7]. The results of Hernandez et al. [1]

showed that, among patients with advanced cervical carcinoma with negative cavum pelvis lymph nodes, there was a negative correlation between thrombocytosis and survival rate. In contrast, a study by Gadducci et al. [8] showed that pre-operative PLT and HGB levels were unrelated to the 5-year survival rate of the patients. Shin's [19] research showed that patients with anemia had a lower survival rate compared with that of patients without anemia, but the difference was not significant. The present study indicated that pre-operative HGB level was significantly correlated with the overall survival rate, although there was no significant association between preoperative PLT level and overall survival, despite the fact that the overall survival was lower for the group with PLT levels >300×10⁹/L compared with that for the group with PLT levels \leq 300×10⁹/L. We found that overall survival for the group

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with both PLT levels >300×10⁹/L and HGB levels <120 g/L was significantly lower than that for the group with both PLT levels \leq 300×10⁹/L and HGB levels \geq 120 g/L (P<0.05). However, at present, no other reported study has evaluated the overall survival rate with the combined PLT-HGB levels as the predictor; therefore, a larger study is needed to confirm these results.

Relations between PLT and HGB levels and cervical carcinoma prognosis

Several studies have confirmed that the pre-operative PLT level is an independent factor influencing cervical carcinoma prognosis [1,20]; however, some studies have also denied it [14,21]. The present study showed that the pre-operative PLT level was not an independent factor that influenced prognosis. Many recent studies indicate that, among patients with cervical carcinoma undergoing new adjuvant chemotherapy and radical hysterectomy, HGB level could influence prognosis [9,18]; however, there are conflicting reports as to whether it is an independent factor that influences prognosis. According to Choi's report [22], a low pre-operative HGB level was an independent factor that influences the prognosis of some patients with advanced cervical carcinoma. The research of Shin et al. showed that a low HGB level was an independent factor influencing the survival rate of patients with early-stage cervical carcinoma [19]. However, the research of Angiolo et al. denied this association. The present study showed that preoperative HGB level might be an independent factor that influences prognosis. The reason for the reported differences

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may be due to differences in the participants, different tumor staging, or different therapeutic methods.

This study also analyzed the combined pre-operative PLT-HGB level as a potential factor influencing prognosis and revealed that PLT levels > 300×10^{9} /L combined with HGB levels <120 g/L may be an independent factor influencing prognosis, although there has been no similar previous research and the results remain to be verified in a study with a larger sample size.

Conclusions

Measuring the HGB and PLT levels of patients pre-operatively is a simple and affordable means to predict disease stage and recurrence. In particular, the HGB level could be an independent factor that influences prognosis in early-stage cervical carcinoma. Therefore, attention should be paid to the preoperative PLT and HGB levels and to correcting any observed anemia, which may have a positive effect in the treatment of cervical carcinoma. The study did not investigate the impact on the clinical features and prognosis by means of correcting anemia or/and thrombocytosis in the preoperative setting, which needs further research.

Conflicts of interest

All of the authors declare that they have no conflicts of interest regarding this paper.

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