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Platelet-to-lymphocyte ratio in peripheral blood: A novel independent prognostic factor in patients with melanoma

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ABSTRACT

Objectives: This retrospective study aimed to investigate the prognostic value of pre-treatment platelet-to-lymphocyte ratio (PLR), which is an inflammatory indicator, in patients with melanoma.

Methods: Patients in this retrospective analysis were admitted between January 1, 2010 and December 31, 2015 in Henan Cancer Hospital. Receiver operating characteristic (ROC) curve was performed the optimal cut-off value for PLR. The 140 patients were divided into two groups: high PLR group and low PLR group. The relationship between PLR and overall survival (OS) was analyzed. The Kaplan-Meier and Log rank tests were used for univariate survival analysis and Cox proportional hazards regression model for multivariate analysis.

Results: The optimal cut-off value of PLR determined by ROC curve was 120.15. Univariate and Cox multivariate survival analysis all showed that PLR and clinical stage were factors affecting OS in melanoma patients ($P < 0.05$). The overall median OS was 21.0 months (95% confidence interval (CI): 18.1–23.9), for 17.0 months in the high PLR group, and 34.0 months in the low PLR group (hazard ratio: 0.436, 95% CI: 0.291–0.652, $P < 0.001$), respectively. Clinical subgroup analysis showed that PLR was a risk factor in patients with stage II, III, and IV disease ($P < 0.05$).

Conclusion: The elevated PLR was an independent prognostic predictor for OS in patients with melanoma.

1. Introduction

Melanoma is a highly-malignant tumor which occurs in skin, mucosa, and visceral organs frequently. It accounts for 4% of all skin cancers but nearly 75% of skin tumors-related mortality [1]. In addition to providing early diagnosis, determining readily available and reliable biomarkers that can predict patient's prognosis is also an effective measure of improving prognosis.

The systemic inflammatory response to cancer has been firstly described by Virchow in 1863 [2]. In recent years, increasing evidences have demonstrated that the inflammatory response plays a pivotal role in different stages of tumor progression, including initiation, proliferation, invasion, metastasis and angiogenesis [3,4]. Various elements contribute to these responses, including recruitment of T lymphocytes, cytokines (tumor necrosis factor-α (TNF-α), interleukin (IL)-1α and IL-1β), chemokines (monocyte chemoattractant protein-1, -2 and -3 (MCP-1/CCL2, MCP-2/CCL8 and MCP-3/CCL7)), apoptosis inhibition, DNA damage, destruction of the adaptive immune system, and the altering responses to systemic therapies [2,3,5,6]. The inflammatory responses can be represented by lots of biomarkers such as platelet to lymphocyte ratio (PLR), which has been confirmed as an inflammatory index.

Studies have indicated that platelets play multiple roles in inflammatory processes: promoting progression of tumor through facilitation of neoangiogenesis, producing adhesion molecules and increasing early metastasis, etc. [7–11]. Consequently, the amount of platelets shall reflect the invasive potential of cancer cell to some extent [12–14]. Lymphocytes are major components of immune system, involved in cancer surveillance and tumor defense by hindering tumor cell proliferation and metastasis [5].

A number of studies have confirmed that platelet to lymphocyte ratio (PLR) as an inflammatory index is an independent risk prognostic factor of esophageal cancer [15], gastric cancer [16], colorectal cancer [17,18], breast cancer [19], small cell lung cancer [20], and liver cancer [21,22]. Therefore, it is rational to use PLR as a biomarker to predict the prognosis of cancer. Meanwhile, this marker could be easily obtained from routine blood cell testing in clinic, without increasing the financial burden of the patients.

However, to the best of our knowledge, the prognostic value of PLR in melanoma has not yet been reported. The purpose of this study was

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to investigate the relationship between pre-treatment PLR and overall survival (OS) of patients with melanoma.

2. Methods

2.1. Patients

We retrospectively analyzed the clinical data of all the 140 melanoma patients, treated in Henan Cancer Hospital, from January 1, 2010 to December 31, 2015. The inclusion criteria were as follows: (1) Patients with a histopathological or immunohistochemical diagnosis of melanoma; (2) Patients with routine blood tests within one week (blood routine measured by Japan Sysmex XN-2000 automatic blood cell analyzer and ancillary reagents, platelet count by Electrical Impedance Method, lymphocyte count by flow cytometry); (3) Patients without second primary tumors, hematologic diseases, and immune system diseases; (4) Patients with complete clinical and follow-up information, as well as clear outcome events and statuses included. Staging was conducted according to the seventh edition of the American Joint Committee on Cancer Clinical Staging System for Melanoma with imaging examinations, surgical information, and pathological reports. The study was approved by the ethics committee of Zhengzhou University and all patients signed an informed consent.

2.2. Definitions

PLR was calculated as the absolute platelet count divided by absolute lymphocyte count. The OS was calculated from first treatment to death (event) or the last follow-up (censored).

2.3. Statistical analysis

Receiver operating characteristic (ROC) curve was performed to calculate the cut-off value for PLR. The value with the maximal Youden index was chosen as the optimal cutoff point. Categorical variables were compared using chi-square test. Survival analysis was conducted with the Kaplan-Meier method while the log-rank test was used to compare intergroup difference. Univariate analysis was performed using the Cox's proportional hazards model and significant univariate factors were entered into multivariate Cox's proportional hazards model. The hazard ratio (HR) and its 95% Wald confidence interval (95% CI) were estimated by using Cox's proportional hazards model in the univariate analysis. All statistical analysis was conducted using SPSS 21.0 software (IMB Corp, USA), and all tests were two-sided. A P value < 0.05 was considered statistically significant.

3. Results

3.1. Clinical characteristics of the patients

Patients' clinical characteristics are shown in Table 1. A total of 140 patients were recruited in this study, which including 69 males and 71 females, with the median age of 56.4 years, ranged from 22.0 to 81.0 years. The optimal cutoff was 120.15, and the area under the ROC curve (AUC) was 0.806 (95% CI: 0.653–0.958, $P < 0.001$), with a sensitivity of 73% and a specificity of 83% (Fig. 1). The high PLR (≥120.15) group had 44 cases, and the low PLR (< 120.15) group had 96 cases. Clinical staging at presentation was stage I in 2 (1.4%), stage II in 19 (13.6%), stage III in 30 (21.4%), and stage IV in 89 (63.6%). All the characteristics were evenly distributed in high PLR group and low PLR group.

3.2. Survival analysis

The median follow-up period was 21.5 months (1.0–80.0). The median overall survival (mOS) for 140 patients was 21.0 months (95% CI: 18.1–23.9) (Fig. 2 A). The mOS of low and high PLR groups were 34.0 and 17.0 months (HR: 0.436, 95% CI: 0.291–0.652, $P < 0.001$), respectively (Fig. 2 B).

Univariate analysis showed that factors associated with OS were clinical stage and PLR (Table 2). Furthermore, the multivariate analysis indicated that stage (HR, 3.280; 95% CI: 1.869–5.755; $P < 0.001$) and PLR (HR, 2.430; 95% CI: 1.615–3.654; $P < 0.001$) remained meaningful for OS (Table 2).

In subgroup analyses, the respective mOS of low and high PLR groups were 55 and 35 months in stage II (HR: 0.257, 95% CI: 0.078–0.844, $P = 0.017$) (Fig. 2 C); 36 and 28 months in stage III (HR: 0.378, 95% CI: 0.161–0.885, $P = 0.018$) (Fig. 2 D); and 20 and 12 months in stage IV (HR: 0.487, 95% CI: 0.282–0.841, $P = 0.007$) (Fig. 2 E).

OS, overall survival; PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval.

Table 1
The relationship between PLR and clinical characteristics.

Characteristics	Total patients	Low PLR group	High PLR group	χ^2 value	P value
Gender				2.468	0.116
Male	69	26	43		
Female	71	18	53		
Age (years)				0.001	0.981
< 65	102	32	70		
≥65	38	12	26		
Anatomic location				0.002	0.964
Mucosal	41	13	28		
Non-mucosal	99	31	68		
Smoking history				1.252	0.263
Yes	36	14	22		
No	104	30	74		
Drinking history				0.709	0.400
Yes	38	14	24		
No	102	30	72		
Stage				0.510	0.475
I-II	21	8	13		
III-IV	119	36	83		

PLR, platelet to lymphocyte ratio.

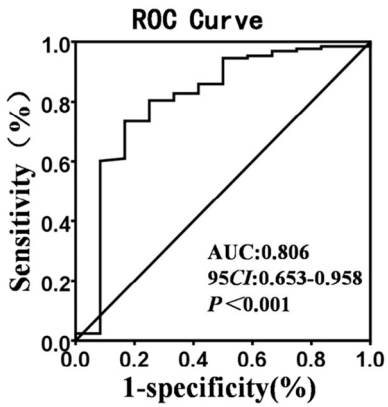

Fig. 1. ROC curve for the PLR with an optimal cut-off value of 120.15 (sensitivity 73%, specificity 83%).
ROC, receiver operating characteristic; PLR, platelet to lymphocyte ratio; AUC, area under the ROC curve; CI, confidence interval.

4. Discussion

A majority of studies have shown that systemic inflammation can increase the risk of multiple tumors and is also associated with poor clinical outcomes [2,3]. PLR, as an inflammatory marker, has proven to be an independent prognostic risk factor in many solid tumors. To the