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Elevated platelet-to-lymphocyte corresponds with poor outcome in patients with advanced cancer receiving anti-PD-1 therapy

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ABSTRACT

Objectives: The purpose of this retrospective analysis was to investigate the prognostic value of PLR for PD-1 inhibitors.

Methods: Patients were divided into different subgroups according to PLR. Univariate survival analysis and a multivariate Cox proportional hazards regression model were used to assess the association between PLR and overall survival (OS) or progression-free survival (PFS).

Results: The optimal cut-off value of baseline PLR was 164. Among the total 85 patients, 34 patients presented with PLR ≥ 164, and 51 presented with PLR < 164, respectively. The median OS for the high PLR group was 7.0 months (95% CI: 4.1–9.9 months), and it was not reached for the low PLR group ($P < 0.001$). The median PFS was 3.0 months (95% CI: 1.9–4.1 months) vs. 9.8 months (95% CI: 6.1–13.5 months) for the high and low PLR groups, respectively ($P < 0.001$). In multivariate analysis, a PLR > 164 and body mass index (BMI) > 24.0 were independently associated with OS (hazard ratio [HR]: 3.549, 95% confidence interval [CI]: 1.901–6.625, $P < 0.001$ and HR: 0.496, 95% CI: 0.260–0.945, $P = 0.033$), meanwhile PLR was also significantly associated with inferior PFS (HR: 2.567, 95% CI: 1.551–4.249, $P < 0.001$). Disease control rate for high and low PLR group was 38.2% and 74.5%, respectively, and it was also correlated with elevated PLR ($P = 0.001$).

Conclusion: This retrospective analysis indicates that PLR could be used as a biomarker to stratify patients who will have a better response to anti-PD-1 agents.

1. Introduction

In recent years, cancer treatment has undergone revolutionary changes, especially with the clinical application of immune check-point inhibitors represented by programmed death-1/programmed death ligand-1 (PD-1/PD-L1) inhibitors. These agents demonstrate dramatic clinical activity and improve overall survival (OS) in a variety of cancers, and have been approved worldwide as a treatment for melanoma, non-small cell lung cancer (NSCLC), hepatocarcinoma, renal cancer and so on [1–5]. However, in an unselected population, the overall response rate to an anti-PD-1 antibody is only approximately 20% [6,7]. When patients are stratified by some biomarkers, such as positive PD-L1 expression, the subsets with high PD-L1 expression determined by an FDA-approved test have a better response to an anti-PD-1 agent [8]. For example, for NSCLC patients with notably positive PD-L1 expression (a tumour proportion score [TPS] ≥ 50%), the response rate can reach 30–40% [8–10], whereas the rate is only 8%–18%, in populations with negative (TPS < 1%) or weak (TPS = 1–49%) PD-L1 expression [10,11].

There are still some limitations to PD-L1 testing. First, PD-L1 expression is biologically heterogeneous, demonstrating a range of expression levels intra-tumour and inter-tumour [12–14]. Its expression in primary tumour and metastases may also be different; in addition, the result of PD-L1 testing may be inconsistent when detected in archival samples, fresh samples or cell samples [15,16]. Second, prior therapies such as chemotherapy or targeted therapy may also influence PD-L1 expression [16]. Thus, the level of PD-L1 expression detected in the initial diagnostic sample may differ from the patient PD-L1 status when a PD-1/PD-L1 inhibitor is introduced. These factors affect the accuracy of PD-L1 detection, so the result may not represent the true status of the tumour. Third, several PD-L1 assays have been developed to label PD-L1 in tumours. In addition to commercial tests, laboratories and

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institutions may create their own assays [17]. These assays target different epitopes on the PD-L1 molecule whether intracellular or extracellular, have various levels of sensitivity and specificity, and use different antibody clones, protocols, scoring systems and cut-off values to define PD-L1 positivity [10,13,18,19]. Thus, current PD-L1 assays are not standardized, leading to a significant reduction in the clinical significance of PD-L1 testing, and may cause inappropriate treatment decisions.

In addition, clinical trials detecting the association between PD-L1 status and outcomes are mainly concentrated in non-squamous NSCLC. In many other primary tumours, the PD-L1 status may also predict benefit from anti-PD-1 treatment, however, no definitive conclusions can be drawn yet. Even in non-squamous patients, the responses may be similar in PD-L1 negative and positive patients in some centers [20], highlighting the challenges with this biomarker. Given the shortcomings of PD-L1 as a predictive index as well as the high treatment costs of PD-1 inhibitors, it is urgent to develop novel, reliable, accessible and inexpensive markers to identify specified patients most likely to benefit from immunotherapies, thereby improving patient response rates and decreasing healthcare costs. These markers may be helpful in treatment decisions and are likely to be meaningful for personalized health care in the context of cancers.

In 1863, Virchow discovered an abnormal inflammatory response in patients with cancer [21]. In recent years, accumulating evidence has confirmed that inflammatory reactions play manifold and enabling roles in cancer initiation, proliferation, angiogenesis, infiltration, and metastasis [22–24]. In addition, the inflammatory response has been negatively associated with prognosis in several cancer types [25,26]. Numerous haematological parameters have been investigated as potential inflammatory biomarkers that reflect patient prognosis, such as the platelet-to-lymphocyte ratio (PLR), which has been demonstrated to be associated with worse outcomes in a variety of cancer patients, including those with melanoma [27], NSCLC [28], colorectal cancer [29] or oesophageal cancer [30]. The PLR is an ideal biomarker, because PLR detection methods are readily available, inexpensive and non-invasive. Currently, for patients treated with PD-1 inhibitors, only a few studies showed that the derived neutrophil-to-lymphocyte ratio (dNLR) and lung immune prognostic index (LIPI, a combination of the baseline dNLR and lactate dehydrogenase levels) are associated with poor outcomes in patients with melanoma or lung cancer [31–34]. Few studies have explored the relationship between the PLR and prognosis in patients undergoing treatment with anti-PD-1 antibodies.

Many studies have focused on PD-L1 expression and the tumour mutational burden, but clinical features such as age, gender, drinking history, smoking history, PLR and BMI are also likely to be associated with the responses to immunotherapy. The purpose of this retrospective study was to investigate the relationship between PLR and the response to anti-PD-1 therapy in patients with advanced cancers, with the hope of providing some guidance for the clinical application of anti-PD-1 antibodies.

2. Methods

2.1. Patients

We conducted a retrospective study of 85 patients with refractory or relapsed advanced cancer. All patients received PD-1 inhibitors (Opdivo, Keytruda or other) after failing multiline treatments at Henan Cancer Hospital between January 1, 2016 and June 30, 2018. For all patients, clinical data including patient demographics, baseline complete blood cell counts (within 3 weeks before PD-1 inhibitor), smoking history, drinking history and Eastern Cooperative Oncology Group Performance Status (ECOG PS) at the initiation of PD-1 inhibitor treatment were collected. Additional enrollment criteria were as follows: (1) Patients received at least 2 cycles of treatment with PD-1 inhibitor. (2) Patients had at least one measurable lesion as defined by the Response Evaluation Criteria in Solid Tumors (RECIST1.1) [35]. (3) All patients had baseline computed tomography (CT) or magnetic resonance imaging (MRI) assessment (within 4 weeks before PD-1 inhibitor). (4) Uncontrolled infection was absent.

2.2. Efficacy assessments

The assessment was performed every 6 weeks or whenever the patients showed obviously advanced symptoms. The evaluation was conducted according to RECIST1.1: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). Overall response rate (ORR) was calculated as follows: (number of CR cases + number of PR cases) / total number of patients × 100%. Disease control rate (DCR) was defined as the (numbers of CR + PR + SD cases) / total number of patients × 100%. Overall survival (OS) time was defined as time from initiation of PD-1 inhibitor until death (event) or last follow-up (censored). Progression-free survival (PFS) time was defined as time from initiation of PD-1 inhibitor until disease progression or death (event), or last follow-up (censored).

2.3. Statistical analysis

The PLR was calculated from the complete blood count and defined as the absolute platelet count/absolute lymphocyte count. The optimal cut-off value for the PLR was assessed using a receiver operating characteristic (ROC) curve. All patients were divided into high or low PLR groups. Descriptive statistics were used to summarize demographic characteristics. Comparisons between patient characteristics were conducted using chi-square test for categorical variables. OS and PFS curves were conducted with the Kaplan-Meier method and the log-rank test was used to compare the differences between groups. Univariate Cox proportional hazards model was used to evaluate factors associated with OS and PFS. Variables with statistical significance (cut-off, $P = 0.10$) in the univariate analysis were included in the final multivariate model. The results are presented as hazard ratios (HR) with 95% confidence intervals (95% CI). Statistical analysis was performed with SPSS version 21.0 (IBM Corp, USA). All statistical tests were two-sided, and significance was set at $P \leq 0.05$.

3. Results

3.1. Patient characteristics

Baseline patient characteristics are shown in Table 1. A total of 85 patients receiving treatment with PD-1 inhibitors, including 42 males and 43 females, were included in this retrospective study. The median follow-up period was 11.0 months (rang, 1.5–28.8 months). Among the patients, there were 40 melanoma patients, 24 renal cell carcinoma patients, 10 Hodgkin lymphoma patients and 11 NSCLC patients.

3.2. Baseline PLR and survival

The optimal cut-off for the PLR was 164. At baseline, 34 patients presented with PLR ≥ 164, and 51 presented with PLR < 164. The PLR value was associated with the number of metastatic sites ($P = 0.003$), but not with other variables (Table 1). For the high PLR group, the median OS was 7.0 months (95% CI: 4.1–9.9 months), and the median OS was not reached for the low PLR group ($P < 0.001$) (Fig. 1a). For the high and low PLR groups, the median PFS was 3.0 months (95% CI: 1.9–4.1 months) vs. 9.8 months (95% CI: 6.1–13.5 months), respectively ($P < 0.001$) (Fig. 1b).

Multivariate analysis showed that the PLR was independently associated with inferior OS and PFS (Table 2). As shown in Table 2, patients with a baseline PLR ≥ 164 had a 3.5-fold increased risk of death (HR: 3.549, 95% CI: 1.901–6.625, $P < 0.001$) and a 2.6-fold increased risk of progression (HR: 2.567, 95% CI: 1.551–4.249, $P < 0.001$). In

Table 1
Patient characteristics and association between PLR and clinical categorical variables.

Variable	NO. of patients (%)			*P* value
	Total NO. *N* = 85 (%)	Low PLR (*N* = 51, 60.0%)	High PLR (*N* = 34, 40.0%)	
Gender				0.723
Male	42 (49.4)	26 (51)	16 (47.1)	
Female	43 (50.6)	25 (49)	18 (52.9)	
Age (years)				0.472
< 65	64 (75.3)	37 (72.5)	27 (79.4)	
≥65	21 (24.7)	14 (27.1)	7 (20.6)	
Smoking history				0.225
Yes	29 (34.1)	20 (39.2)	9 (26.5)	
No	56 (65.9)	31 (60.8)	25 (73.5)	
Alcohol-drinking history				0.516
Yes	18 (21.2)	12 (23.5)	6 (17.6)	
No	67 (78.8)	39 (76.5)	28 (82.4)	
BMI (kg/m^2)				0.593
< 24	47 (55.3)	27 (52.9)	20 (58.8)	
≥24	38 (44.7)	24 (47.1)	14 (41.2)	
Type of inhibitor				0.335
Keytruda	18 (21.2)	11 (21.6)	7 (20.6)	
Opdivo	57 (67.1)	32 (62.7)	25 (73.5)	
Other	10 (11.1)	8 (15.7)	2 (5.9)	
ECOG PS before PD-1 inhibitor therapy				0.152
0–1	71 (83.5)	45 (88.2)	26 (76.5)	
≥2	14 (16.5)	6 (11.8)	8 (23.5)	
NO. of metastatic sites before PD-1 inhibitor therapy				0.003
≤2	49 (57.6)	36 (70.6)	13 (38.2)	
> 2	36 (42.4)	15 (29.4)	21 (61.8)	
Lines of PD-1 inhibitor therapy				0.072
≤3	35 (55.3)	25 (49.0)	10 (29.4)	
> 3	50 (44.7)	26 (51.0)	24 (70.6)	

PLR: platelet to lymphocyte ratio; BMI: body mass index; *N*: number; BMI: body mass index; ECOG PS: Eastern Cooperative Oncology Group performance status; NO.: number; PD-1: programmed death-1.

addition, multivariate analysis also showed that BMI was the only independent protective factor for OS. Patients with BMI ≥ 24.0 kg/m^2 had higher survival rate (HR: 0.496, 95% CI: 0.260–0.945, $P = 0.033$).

In subgroup analyses, the median OS of high PLR group for melanoma patients was 6.0 months (95% CI: 1.0–11.0 months), and the median OS was 17.0 months (95% CI: not reached) for low PLR group ($P = 0.015$) (Fig. 2a); the respective median PFS were 3.0 months (95% CI: 2.2–3.8 months) vs. 6.0 months (95% CI: 0.1–12.0 months) ($P = 0.005$) (Fig. 2b). For renal cell carcinoma patients, the median OS for high PLR group was 7.0 months (95% CI: 2.8–11.2 months), and it was not reached for low PLR group ($P = 0.001$) (Fig. 3a). The median PFS were 2.0 months (1.5–2.5 months) vs. 9.8 months (2.7–16.9 months) for high and low PLR groups, respectively ($P = 0.007$) (Fig. 3b).

3.3. Response

In the low-PLR group, 10 patients had a complete response (CR) (19.6%), 6 patients exhibited a partial response (PR) (11.8%), 22 patients displayed stable disease (SD) (43.1%), and 13 patients showed progressive disease (PD) (25.5%).In the high-PLR group, 2 patients had a CR (5.9%), 3 patients exhibited a PR (8.8%), 8 patients displayed SD (23.5%), and 21 patients showed PD (61.8%) (Table 3). The disease control rate (DCR) was 74.5% (38/51) in the low-PLR group and 38.2% (13/34) in the high-PLR group (Fig. 4). The DCR was also significantly associated with PLR ($P = 0.001$) (Fig. 4).

For 40 melanoma patients, the DCR was 59.1% vs. 33.3% for the low and high PLR groups, respectively, and the ORR was 9.1% vs. 5.5% (Table 4). For 24 renal cell carcinoma patients, DCR was 83.3% vs. 41.7%, and ORR was 33.3% vs. 16.7% for the low and high PLR groups, respectively (Table 5).

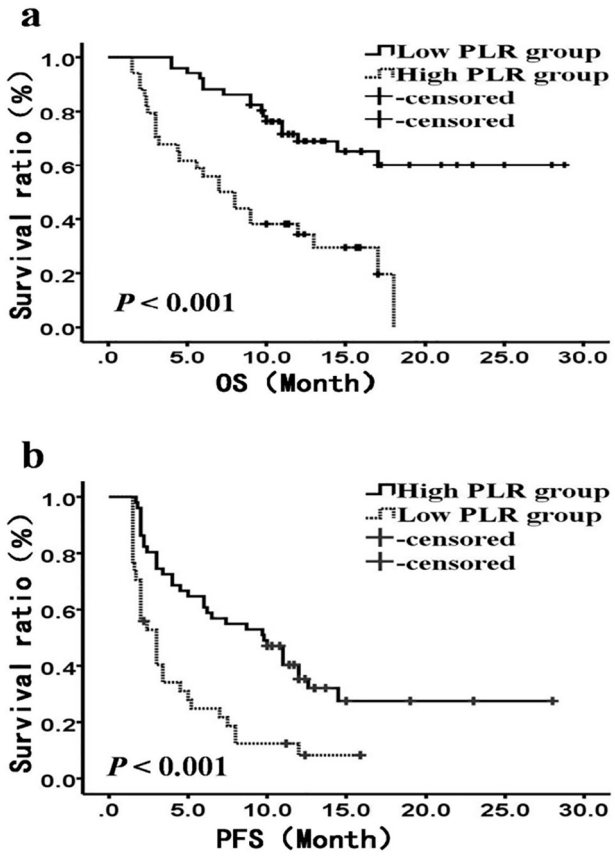

Fig. 1. Kaplan-Meier analysis of OS and PFS for 85 patients. OS curve (a), PFS curve (b).
OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio.

4. Discussion

In recent years, with the clinical application of PD-1/PD-L1 inhibitors, there has been a significant progression in the field of cancer therapy, along with improved response rate and prolonged survival time.

However, most patients are still unable to benefit from the treatment with PD-1/PD-L1 inhibitors, along with frequent adverse effects and high costs. Given these limitations, we need to find an ideal prognostic indicator to screen the populations that are most likely to benefit from this promising therapy.

Hundreds of years ago, inflammation was recognized to have a close association with human tumours, and this finding has been confirmed by an increasing number of studies [21,36,37]. During the development and progression of tumours, including tumour initiation, proliferation, angiogenesis, infiltration, and metastasis, inflammation plays a crucial role [22–24]. Many factors, including various cytokines and chemokines, contribute to these processes [38,39]. As a novel inflammatory marker, PLR has been confirmed to be inversely associated with survival time in a variety of cancers, such as melanoma [27], NSCLC [28], colorectal cancer [29], oesophageal cancer [30], and hepatocellular carcinoma [40].

One of our previous retrospective studies was performed to evaluate the association between pretreatment PLR and clinical outcome in patients with melanoma [27]. The study included 140 patients with stage

Table 2
Univariate and multivariate analysis for overall survival and progression free survival.

Variable		Overall survival				Progression free survival			
		Univariate HR, 95% CI	*P* value	Multivariate HR, 95% CI	*P* value	Univariate HR, 95% CI	*P* value	Multivariate HR, 95% CI	*P*[a] value
Gender	Male	1	0.157	–	–	1	0.982	–	–
	Female	0.647 (0.351–1.194)		–		0.994 (0.608–1.627)		–	
Age (years)	< 65	1	0.175	–	–	1	0.372	–	–
	≥65	1.548 (0.814–2.944)		–		1.273 (0.737–2.198)		–	
Smoking history	Yes	1	0.362	–	–	1	0.899	–	–
	No	0.750 (0.402–1.401)		–		0.968 (0.580–1.617)		–	
Alcohol-drinking history	Yes	1	0.327	–	–	1	0.908	–	–
	No	0.704 (0.345–1.436)		–		0.966 (0.534–1.749)		–	
BMI (kg/m^2)	< 24	1	0.028	1	0.033	1	0.242	–	–
	≥24	0.496 (0.261–0.943)		0.496 (0.260–0.945)		0.751 (0.458–1.232)		–	
ECOG PS	0–1	1	0.021	1	0.104	1	0.587	–	–
	≥2	2.193 (1.099–4.377)		1.786 (0.887–3.598)		1.191 (0.621–2.284)		–	
NO. of metastatic sites	≤2	1	0.553	–	–	1	0.961	–	–
	> 2	0.832 (0.457–1.513)		–		0.988 (0.601–1.623)		–	
Lines of PD-1 inhibitor therapy	≤3	1	0.347	–	–	1	0.566	–	–
	> 3	1.345 (0.720–2.513)		–		1.152 (0.699–1.899)		–	
PLR	< 164	1	< 0.001	1	< 0.001	1	< 0.001	1	< 0.001
	≥164	3.660 (1.961–6.831)		3.549 (1.901–6.625)		2.567 (1.551–4.249)		2.567 (1.551–4.249)	

PLR, platelet to lymphocyte ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group Performance Status; NO., number; PD-1, programmed death-1.

[a] Variables with $P \leq 0.10$ in univariate analysis were included in multivariate model.

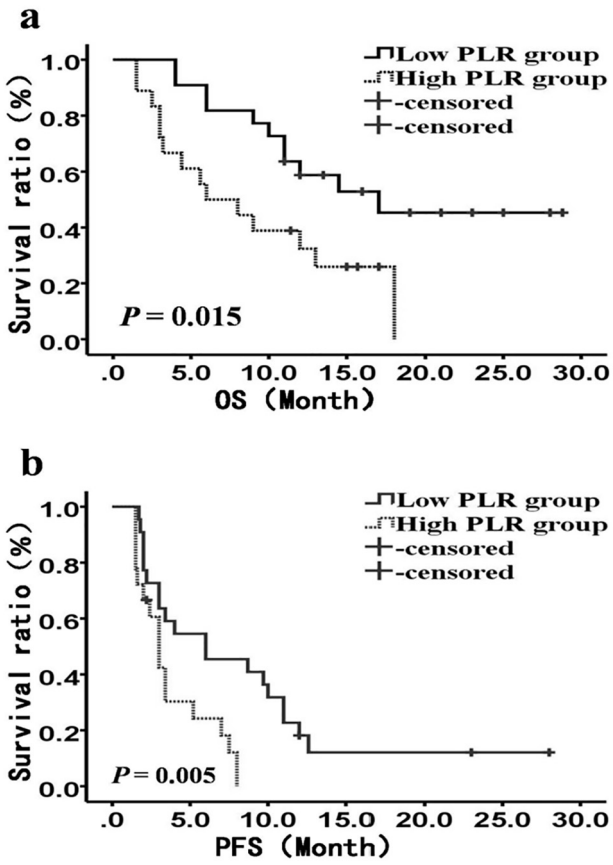

Fig. 2. Kaplan-Meier analysis of OS and PFS for melanoma patients. OS curve (a), PFS curve (b).
OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio.

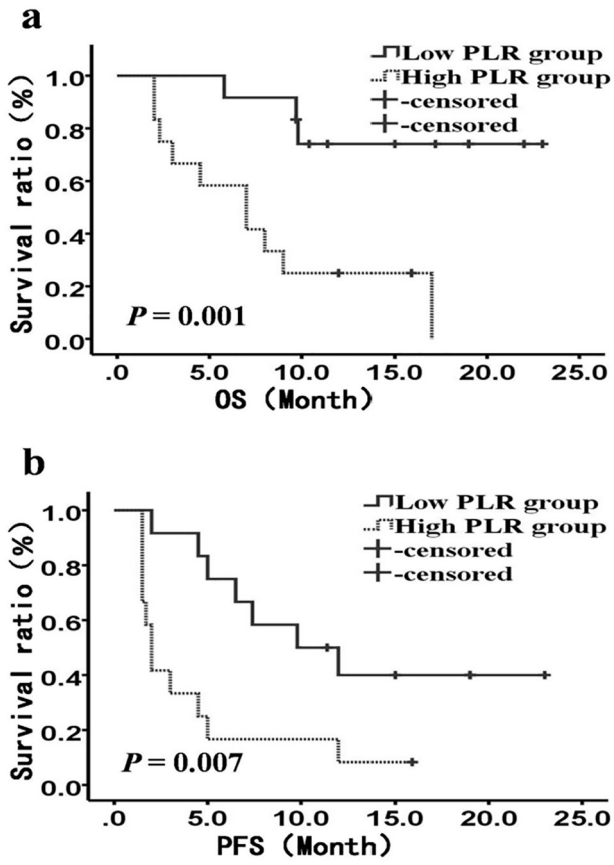

Fig. 3. Kaplan-Meier analysis of OS and PFS for renal cell carcinoma patients. OS curve (a), PFS curve (b).
OS, overall survival; PFS, progression-free survival; PLR, platelet to lymphocyte ratio.

I-IV melanoma and demonstrated that an elevated PLR (≥120.15) was independently associated with a higher risk of death than those with lower PLR level regardless of disease stage. In a meta-analysis [41], a total of 2017 patients from 9 studies were included. The pooled results indicated that an elevated PLR was strongly associated with poor OS and disease-free survival/relapse-free survival in patients with hepatocellular carcinoma. In addition, another meta-analysis enrolled 5314

Table 3
Clinical response according to PLR for 85 patients.

Response	Number (85, %)	Low PLR (*N* = 51, 56.5%)	High PLR (*N* = 34, 43.5%)
CR	12 (14.1)	10 (19.6)	2 (5.9)
PR	9 (10.6)	6 (11.8)	3 (8.8)
SD	30 (35.3)	22 (43.1)	8 (23.5)
PD	34 (40.0)	13 (25.5)	21 (61.8)

PLR, platelet to lymphocyte ratio; *N*, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

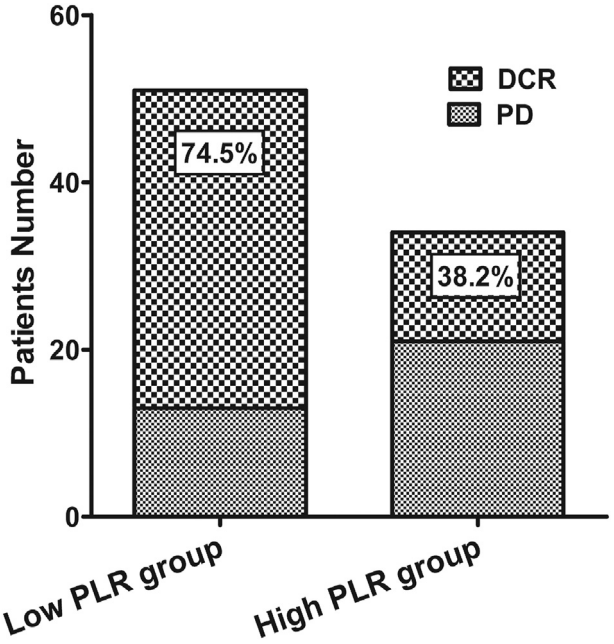

Fig. 4. Comparison of DCR for high and low PLR groups ($P = 0.001$).
DCR, disease control rate; PD, progressive disease; PLR, platelet to lymphocyte ratio.

Table 4
Clinical response according to PLR for melanoma patients.

Response	Number (40, %)	Low PLR (*N* = 22, 55.0%)	High PLR (*N* = 18, 45.0%)
CR	2 (5.0)	2 (9.1)	0 (0.0)
PR	1 (2.5)	0 (0.0)	1 (5.5)
SD	16 (40.0)	11 (50.0)	5 (27.8)
PD	21 (52.5)	9 (40.9)	12 (66.7)

PLR, platelet to lymphocyte ratio; *N*, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 5
Clinical response according to PLR for renal cell carcinoma patients.

Response	Number (24, %)	Low PLR (*N* = 12, 50.0%)	High PLR (*N* = 12, 50.0%)
CR	4 (16.7)	3 (25.0)	1 (8.3)
PR	2 (8.3)	1 (8.3)	1 (8.3)
SD	9 (37.5)	6 (50.0)	3 (25.0)
PD	9 (37.5)	2 (16.7)	7 (58.4)

PLR, platelet to lymphocyte ratio; *N*, number; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

lung cancer patients from 13 studies [42]. The summary results demonstrated that an elevated baseline PLR (> 160) was significantly and independently correlated with an increased risk of death (HR: 1.526, 95% CI: 1.268–1.836, $P < 0.001$) in patients with lung cancer. Notably, this conclusion was applicable to both Asian and Caucasian populations. Although these studies didn't explore the relationship between PLR and outcomes in patients treated with anti-PD-1 antibodies, the studies implied that PLR may become a promising prognostic indicator for cancer patients.

Currently, there are only a few studies reporting the relationship between the baseline PLR and prognosis in patients treated with anti-PD-1 antibodies. One of these two retrospective studies enrolled 52 NSCLC patients treated with nivolumab [43]. In the study, the baseline PLR was confirmed to be an independent marker for clinical outcomes in multivariate analyses. Compared with those with PLR < 262, the patients with high PLR (PLR ≥ 262) had a 4-fold increased risk of death. In addition, a lower overall response rate was also observed for patients with elevated PLR. Another study also involved NSCLC [44]. In nivolumab group, the median OS for patients with high and low PLR were 6.0 and 10.0 months, respectively. Although the difference in OS did not achieve statistical significance, the response rate was significantly reduced in the high-PLR group (8.3% vs. 46.15%, respectively, $P < 0.001$). These studies showed that it was reasonable to use PLR as a prognostic factor for patients treated with PD-1 inhibitors.

To further validate the prognostic value of PLR in advanced cancer patients treated with immunotherapy, we conducted this small retrospective study. All patients received PD-1 inhibitors after failing multiline therapies. The optimal cut-off value for PLR was 164. The patients with an elevated PLR were more likely to have both inferior PFS and OS than those with a low baseline PLR. Despite the small number of patients, the study implied that an elevated PLR was independently and significantly associated with poor survival. This conclusion was maintained in multivariate analysis and was consistent with previous reports. Thus, it is reasonable to stratify patients according to this biomarker to identify populations that will achieve a survival benefit from anti-PD-1 antibodies.

Accumulating evidence has demonstrated that inflammation plays a multifold and important role in tumour initiation and progression [22,45]. However, the exact mechanism is still poorly understood. Several possible explanations have been reported. Platelets, as an important participant in the inflammatory response, promote tumour progression by influencing various stages of tumour development. First, platelets can promote tumour angiogenesis by secreting multiple angiogenic factors, including platelet-derived growth factor (PDGF), fibroblast growth factor (FGF), epidermal growth factor (EGF), transforming growth factor-beta (TGF-β) and vascular endothelial growth factor (VEGF-A, VEGF-C) [46–49]. Second, evidence that suggests the involvement of platelets in tumour cell division and proliferation has accumulated. A variety of factors secreted by platelets and receptors on the surface of platelets, such as TGF-β1, PDGF and P2Y12, are involved in these processes [50,51]. Third, the invasion and dissemination of cancer cells have also been shown to be related to platelets. In this process, epithelial to mesenchymal transition (EMT) plays an important role. Activated platelets can release some regulators, such as VEGF, FGF and TGF-β, inducing EMT directly and indirectly, contributing to the process of tumour metastasis [52,53]. Finally, the role of platelets in tumour immune escape has also been reported. A study showed that platelets impaired nature killer (NK) cell-mediated immune-surveillance of tumour cells though platelet-mediated shedding of natural killer group 2 member D (NKG2D) ligands, protecting tumour cells from natural killer cell lysis [54]. It is also well established that platelets can also transfer major histocompatibility complex (MHC) class I to tumour surface, suppressing the cytotoxic effect of NK cells [55]. In addition, as a by-product during platelet-inflammation interactions, tumour cell-induced platelet aggregation (TCIPA) can protect tumour cells from physical stress and attack by tumour necrosis factor-α (TNF-α), facilitating tumour growth and spreading [56].

Obesity, a major health threat defined by an increased body mass index (BMI, ≥28 kg/m^2) [57], is reaching a pandemic level and was

defined as a disease by the World Health Organization in 1977. A high BMI has been confirmed as a risk factor for numerous complications, and been associated with worse outcomes in several cancers [58,59]. However, a high BMI also demonstrates paradoxical effects, both positive and negative, on cancer treatment responses. In some cancers, a high BMI is associated with improved responses and clinical outcomes [60,61].

In this study, the cut-off value for BMI was 24.0 kg/m^2 based on "The guidelines for prevention and control of overweight and obesity in Chinese adults". This study showed that high BMI was associated with improved OS in patients treated with PD-1 inhibitors, and this relationship remained statistically significant after adjusting for gender, age, smoking history, drinking history, ECOG PS, number of metastatic sites, line of treatment and PLR. In addition, patients with high BMI also had improved PFS, although the differences did not achieve statistical significance, likely due to the small sample size. Although obesity is always accompanied by chronic inflammation, and results in immune dysregulation [62,63], the impact of obesity on immune responses during tumour progression and immunotherapy is poorly understood. Recently, a retrospective, multicohort analysis was carried out to assess the association of BMI with the clinical outcomes of patients with melanoma treated with targeted therapy, immunotherapy, or chemotherapy [64]. In the cohort of 330 patients treated with PD-1 inhibitors, the median OS for male patients with high BMI ($\geq$30 kg/m^2) or normal BMI (18.5–24.9 kg/m^2) was 26.9 and 14.3 months, respectively, and the median PFS was 7.6 and 2.7 months, respectively. This study provides strong evidence supporting the presence of a paradoxical effect of obesity on the treatment of tumours. To investigate the detailed mechanism, Murphy et al. [65] conducted a meaningful study across multiple species, including mice, rhesus macaques and humans, and demonstrated that obesity promoted T cell exhaustion, immune ageing and tumour growth. More importantly, obese models exhibited a significant increase in mean PD-1 expression in the tumour microenvironment driven by leptin, a protein hormone produced by adipose tissue. Obesity results in immune dysfunction and tumour progression but also brings a surprise to cancer patients, improving immune responses and survival after PD-1/PD-L1 inhibitor treatments. These studies remind us of the paradoxical effects, both positive and negative, of obesity on cancer immunotherapy. When developing treatment regimens, it may be reasonable to consider patient-associated factors such as gender, age and BMI. A large prospective cohort of Chinese populations showed that BMI had a "U"-shaped relationship with survival time, and the advantage was limited to overweight and mildly obese patients [66]. Although these studies demonstrated that high BMI had an association with improved survival outcomes in cancer patients who received immunotherapy, whether we should increase patients' weight to obtain a better response is still a question worthy of further study.

This study also has some limitations. First is the retrospective nature of this study and all the patients are from a single center, so there may have been a risk of bias and confounding factors. Second, although all patients received treatment with PD-1 inhibitors, this study included various types of cancer, and the number of patients per disease was limited. In addition, despite applying strict enrollment criteria, we could not completely exclude factors that might influence platelet or lymphocyte levels (such as infection and the use of steroids). In addition, the BMI range in this study was mainly concentrated at 18.0–28.0 kg/m^2 (88%). We divided the patients into only two groups with a threshold of 24.0 kg/m^2, and detailed subgroup analysis was not conducted. Given these limitations, prospective, randomized, large-scale clinical trials are needed in the future to provide more reliable and useful data.

5. Conclusions

This work demonstrates that high pre-treatment PLR is closely related to poor clinical outcomes in patients treated with anti-PD-1 antibodies. Notably, methods to measure the PLR is readily available, non-invasive and easy-to-read, and these tests do not increase the economic burden on patients. These conclusions need to be confirmed by multicenter, prospective clinical trials, and we hope these indexes may become reliable markers used in clinical practice to support clinicians identifying patients who may benefit from immunotherapy and to determine individual treatment regimens, so that protecting patients from unnecessary drug-related toxicities and improving response rates.

Declaration of Competing Interest

The authors declare no potential conflicts of interest.

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