


# Prognostic Significance of Platelet (PLT) and Platelet to Mean Platelet Volume (PLT/MPV) Ratio During Apatinib Second-Line or Late-Line Treatment in Advanced Esophageal Squamous Cell Carcinoma Patients

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## Abstract

**Background:** Apatinib has a certain efficacy for advanced esophageal squamous cell carcinoma (ESCC). This study aimed to investigate the prognostic significance of platelet (PLT) and platelet to mean platelet volume (PLT/MPV) ratio for advanced ESCC patients with apatinib second-line or late-line treatment. **Methods:** A retrospective study included 80 patients with advanced ESCC who received Apatinib  $\geq 2$  lines targeted therapy. We collected baseline clinical characteristics and blood parameters from the patients. Kaplan–Meier plots and univariate and multivariate analysis were used to find the factors related to progression-free survival (PFS). **Results:** The optimal cut-off values of PLT and PLT/MPV ratio were determined by X-tile software. Kaplan–Meier analysis demonstrated that patients in the high PLT group had better PFS than those in the low PLT group (156 d vs 80 d,  $P < .001$ ), and patients in the high PLT/MPV ratio group had better PFS than those in low PLT/MPV ratio group (157 d vs 85 d,  $P < .001$ ). Univariate analysis revealed pretreatment PLT and PLT/MPV ratio were significantly correlated with PFS. Multivariate analysis revealed high levels of pretreatment PLT/MPV ratio was an independent predictor of longer PFS (HR: 0.257, 95% CI: 0.089-0.743,  $P = .012$ ). **Conclusion:** High levels of baseline PLT and PLT/MPV may indicate a better prognosis in apatinib  $\geq 2$  lines treatment for advanced ESCC patients.

## Keywords

Advanced esophageal squamous cell carcinoma, ESCC, platelet, PLT, platelet to mean platelet volume ratio, PLT/MPV

## Abbreviations

CR, complete response; Lower, lower thoracic esophageal squamous cell carcinoma; Middle, middle thoracic esophageal squamous cell carcinoma; MPV, mean platelet volume; No-ORR group, the first-time evaluation results was SD or PD; ORR, objective response rate; ORR group, the first-time evaluation results was CR or PR; PLT/MPV ratio, total platelet count/mean platelet volume; PR, partial response; PD, progressive disease; PLT, platelet; RY group, patients have the history of radiotherapy; RN group, patients never received radiotherapy; SY group, patients have the history of surgery; SN group, patients never received surgery; SD, stable disease; Upper, upper thoracic esophageal squamous cell carcinoma.

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## Introduction

Among all cancers in the world, esophageal cancer is the sixth leading cause of death. In 2020, there will be approximately 604 000 newly diagnosed esophageal cancer cases worldwide.<sup>1</sup> Esophageal cancer is traditionally divided into esophageal squamous cell carcinoma (ESCC) and adenocarcinoma (EAC) subtypes based on histology. The prevalence of each subtype varies greatly depending on the geographic area.<sup>2,3</sup> In Western countries, the incidence of esophageal squamous cell carcinoma has dropped significantly compared with adenocarcinoma, but squamous cell histology still accounts for approximately 90% of all esophageal cancer cases worldwide. Chemotherapy is the main treatment for esophageal cancer. Currently, KEYNOTE-181,<sup>4</sup> ATTRACTION-03,<sup>5</sup> and ESCORT<sup>6</sup> have established the standard for second-line treatment of advanced esophageal squamous cell carcinoma with PD-1 (programmed cell death receptor 1) inhibitors. However, PD-1 inhibitor was not available at the time of second-line treatment in the patients enrolled in this study, and it is necessary to explore new treatment methods.

Apatinib is a novel small molecule vascular endothelial growth factor receptor-2 (VEGFR-2) tyrosine kinase inhibitor. It strongly inhibits tumor angiogenesis by blocking the signal transduction pathway after vascular endothelial growth factor (VEGF) binds to its receptor, thus exerting an anti-tumor effect. In phase II clinical study,<sup>7</sup> a total of 141 patients with advanced gastric cancer or gastroesophageal junction adenocarcinoma who failed second-line and above chemotherapy were included. The patients were randomly divided into 3 groups: placebo control group, apatinib 850 mg qd group, and apatinib 425 mg bid group. Using the full analysis set (FAS), compared with the control group, apatinib not only has a certain objective response rate (ORR), but also has a survival benefit. Li and Wang<sup>8</sup> applied apatinib for second-line treatment to 62 patients with advanced esophageal squamous cell carcinoma who failed the first-line treatment with platinum-based chemotherapeutics. The results showed that 15 patients had PR, 31 patients had SD, 16 patients had PD, ORR was 24.2%, DCR was 74.2%, median PFS was 115 days, and median OS was 209 days. It also shows that apatinib has a significant effect on advanced esophageal squamous cell carcinoma, and may become a potential second-line treatment for advanced esophageal squamous cell carcinoma. In recent years, some studies have confirmed that apatinib has a certain effect on the second-line and above treatment of esophageal squamous cell carcinoma,<sup>9–11</sup> but how to screen the effective population is one of the most urgent clinical problems.

Some studies have shown that some indicators in the blood reflect inflammatory changes in the tumor microenvironment.<sup>12–14</sup> Neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR), lymphocyte-to-monocyte ratio (LMR), and systemic inflammation index (SII) reflected the level of systemic inflammation in the body.<sup>15,16</sup> Some studies have found the relationship between NLR, PLR,

LMR, SII, and the results of esophageal cancer surgery, radiotherapy, and chemotherapy.<sup>17–22</sup> A study was proved that the baseline NLR value is an independent prognostic factor for patients with metastatic colorectal cancer treated with apatinib. It shows that the prognosis of patients in the high-baseline NLR group was worse than that of the low-baseline NLR group.<sup>23</sup> Another study to evaluate the prognostic value of preoperative PLR in the treatment of transarterial chemoembolization (TACE) combined with apatinib for advanced liver cancer was conducted on 134 patients who received TACE + apatinib (TACE-A) treatment and TACE treatment alone retrospective analysis. The study found that the PLR value can be used to predict the prognosis of patients with advanced liver cancer receiving TACE-A treatment. Patients with advanced liver cancer with a PLR value > 150 may not be suitable for TACE-A treatment.<sup>24</sup> A large number of studies have confirmed that platelets play an important role in the growth and metastasis of tumors.<sup>25</sup> Platelets interact with tumor cells through surface receptors to help tumor metastasis.<sup>26</sup> At the same time, tumor cells will further activate platelets, stimulate platelets to release active substances, and optimize the tumor's growth environment.<sup>27</sup> Platelet volume (MPV) is a new indicator of platelet size and activity and has been thought to be a sign of platelet function and activation.<sup>28</sup> In recent years, studies on platelet activation to promote tumor angiogenesis have attracted widespread attention, and platelet parameters can predict the therapeutic effect of tumors.<sup>29,30</sup> In the targeted therapy of tumors, a study found that MPV is an independent predictor of shorter PFS in the treatment of EGFR-mutant lung adenocarcinoma with EGFR tyrosine kinase inhibitors.<sup>31</sup> Although more and more platelet parameters have been found to be related to anti-tumor efficacy, there is no research on the relationship between platelet parameters and apatinib treatment in advanced esophageal squamous cell carcinoma.

Thus, the purpose of this study was to retrospectively analyze the clinical characteristics of 80 patients with advanced ESCC in Apatinib  $\geq 2$  lines treatment, analyze the effectiveness of apatinib treatment, and explore PLT and PLT/MPV on the prognostic effect in Apatinib  $\geq 2$  lines treatment for advanced ESCC.

## Materials and Methods

### Patients

We retrospectively collected a total of 915 patients diagnosed with advanced ESCC from October 1, 2017, to April 1, 2021, in Anhui Provincial Hospital. A total of 80 patients met the enrollment criteria and had complete follow-up data. The entry criteria are as follows: patients were pathologically diagnosed as progressive or metastatic ESCC; failed after receiving at least the first-line standard treatment; all patients received 250 mg or 500 mg apatinib orally daily treatment for 1 month or more; patients in the combination therapy group

received apatinib in combination with paclitaxel-based or fluorouracil-based chemotherapy; patients had at least one target lesion according to RECIST Standard Version 1.1; patients took a radiological examination to assess therapeutic effect every 2 to 3 months; patients did not receive chemotherapy or radiation therapy for at least 1 month before receiving apatinib; patients did not receive long-term glucocorticoid therapy; patients did not have immune system diseases, hematological diseases, or hepatitis virus infections. We randomly selected 35 patients from the 80 patients as the internal-validation cohort.

### Clinical Data Collection

Clinical data collected including gender, age, the primary site of the tumor, the number of treatment lines, single drug, or combined chemotherapy treatment, previous surgery, previous

**Table 1.** The Clinical Characteristics of 80 Patients With Advanced ESCC.

Clinical characteristics	Cases ( <i>n</i> )	%
Gender		
Female	14	17.5
Male	66	82.5
Age (year)		
< 65	45	56.25
≥ 65	35	43.75
$x \pm s$	62.58 ± 9.44	
Primary site		
Upper	11	13.75
Middle	33	41.25
Lower	36	45.0
Treatment lines		
Second line	40	50.0
After the second line	40	50.0
Therapy		
Monotherapy	23	28.75
Combination therapy	57	71.25
Surgery		
Yes	45	56.25
No	35	43.75
Radiotherapy		
Yes	43	53.75
No	37	45.25
First evaluation results		
CR	0	0
PR	18	22.5
SD	48	60.0
PD	14	17.5
Progress-free survival (days)		50.0
< 135	40	50.0
≥ 135	40	
$x \pm s$	144.46 ± 82.17	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; Upper, upper thoracic esophageal squamous cell carcinoma; Middle, middle thoracic esophageal squamous cell carcinoma; Lower, lower thoracic esophageal squamous cell carcinoma.

radiotherapy, and first evaluation result. Blood parameters were recorded before treatment with apatinib, including total platelet count (PLT), mean platelet volume (MPV), and then the quantitative values of PLT/MPV ratio were calculated. Progression-free survival (PFS) was measured as the time from treatment initiation to the disease progression or death.

### Laboratory Testing

Blood samples were collected in the early morning when patients were at a resting state. All samples were tested by Sysmex XE-5000 automatic blood analyzers within 2 h.

### Statistical Analysis

All statistical analyses and graphs were performed using Graphpad Prism version 9.0 (GraphPad Software Inc., San Diego, CA, USA) and SPSS version 26.0 (IBM Corporation, Armonk, NY, USA) software. The optimal cut-off values of baseline blood parameters were determined using X-tile software version 3.6.1 (Yale University, New Haven CT, USA). The Chi-square or Fisher's exact test was used for comparison of rates, Student's *t*-test was used for the comparison of data with normal distribution. Spearman test was used for the correlation analysis. Survival curves were estimated using the Kaplan–Meier method and the log-rank test was used for statistical comparisons. Cox regression analysis was performed for univariate and multivariate analysis. The difference was considered statistically significant at  $P < .05$ .

### Ethical Approval and Informed Consent

This study was approved by the Ethics Committee of Anhui Provincial Hospital. The requirement for informed consent was waived by the ethics committee because of the study's retrospective nature.

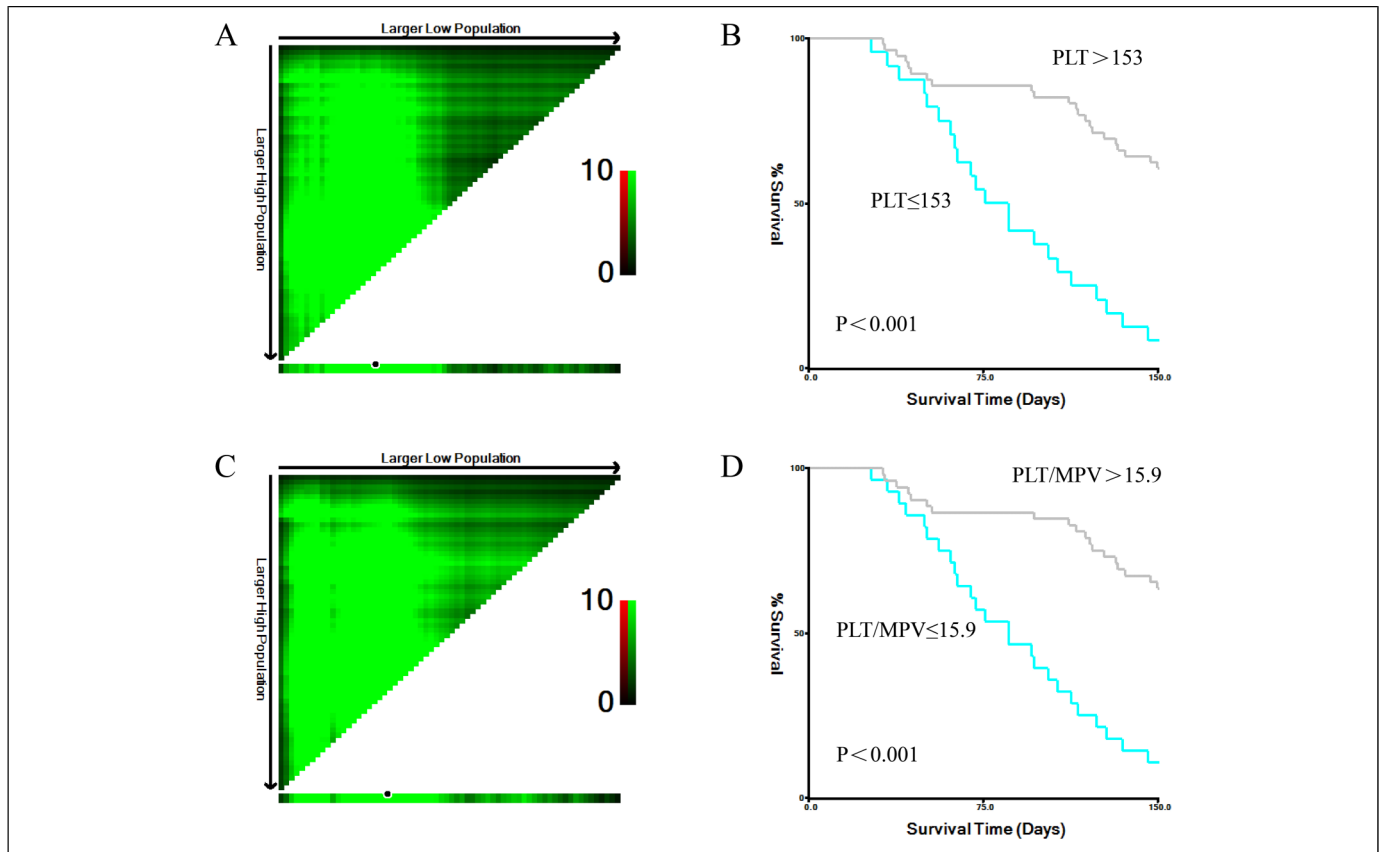
### Statement

We have de-identified all patient details.

## Results

### Baseline Characteristics

The data of 80 patients had been collected. The average age of these patients was 62.58 ± 9.44 years old. All patients had received apatinib ≥ 2 lines treatment. The clinical characteristics of the total patients are shown in Table 1. Among these patients, 40 cases were treated as second-line treatment; 32 cases were treated as third-line treatment; 6 cases were treated as fourth-line treatment; 2 cases were treated as fifth-line treatment. All patients completed the efficacy evaluation, including CR 0 cases (0%), PR 18 cases (22.5%), SD



**Figure 1.** Cut-off values for the pretreatment blood parameters determined by X-tile software. Abbreviations: PLT, platelet (A, B); PLT/MPV ratio, total platelet count/mean platelet volume (C, D).

48 cases (60.0%), PD 14 cases (17.5%), ORR was 22.5%, and DCR was 82.5%.

### The Cut-off Value for PLT and PLT/MPV Ratio

The optimal cut-off value for the PLT and PLT/MPV ratio was analyzed by X-tile software (survival time: cut-off at PFS = 135 days). The optimal cut-off value of PLT was calculated as 153, PLT/MPV ratio was calculated as 15.9. Thus, patients were divided into high PLT group (PLT > 153) ( $n = 56$ ), low PLT group (PLT  $\leq 153$ ) ( $n = 24$ ), high PLT/MPV ratio group (PLT/MPV ratio > 15.9) ( $n = 52$ ), and the low PLT/MPV ratio group (PLT/MPV ratio  $\leq 15.9$ ) ( $n = 28$ ) (Figure 1).

### The Association Between the Baseline Blood Parameters and Clinical Characteristics

The Chi-square test demonstrated the difference between the baseline blood parameters and clinical characteristics. Gender, age, the primary site of the tumor, the number of treatment lines, single drug, or combined chemotherapy treatment, previous surgery, previous radiotherapy, and first evaluation result showed no difference in different blood parameter groups before the treatment ( $P > .05$ ). However, PFS (PFS  $\geq 135$  days

vs PFS < 135 days) showed a significant difference between all different blood parameter groups ( $P < .001$ ) (Table 2).

### Kaplan–Meier Analysis in Blood Parameters

Kaplan–Meier analysis of 80 patients showed that PFS of the high PLT group (PLT > 153) was significantly longer than the low PLT group (PLT  $\leq 153$ ) (156 d vs 80 d,  $P < .001$ ) (Figure 2A), and high PLT/MPV ratio group (PLT/MPV ratio > 15.9) was significantly longer than the low PLT/MPV ratio group (PLT/MPV ratio  $\leq 15.9$ ) (157 d vs 85 d,  $P < .001$ ) (Figure 2B).

### Correlation Analysis Between Blood Parameters and PFS

The correlation between baseline blood parameters and PFS was demonstrated by Pearson test. The results showed that PLT and PLT/MPV are pleasurable correlated with PFS, and it was statistically significant ( $P < .05$ ) (Figure 3).

### The PFS in Patients With Different Clinical and Blood Parameters

The student's *t*-test revealed the differentiation of PFS between different clinical and blood parameter groups. PFS showed no statistical difference in gender, age, the primary site of the tumor, single drug or combined chemotherapy treatment, and previous

**Table 2.** Correlation Between Hematological Parameters and Clinical Features of 80 Patients With Advanced ESCC by Chi-Square Test.

Clinical features		PLT			PLT/MPV		
		≤ 153	>153	<i>P</i> -value	≤ 15.9	> 15.9	<i>P</i> -value
Gender	Female	4	10	1.0	8	6	.109
	Male	20	46		20	46	
Age(year)	<65	10	35	.085	15	30	.723
	≥65	14	21		13	22	
Primary site	Upper	5	6	.717	4	7	1.0
	Middle	11	22		12	21	
	Lower	8	28	.262	4	7	1.0
	Middle	11	22	.302	12	21	.792
Treatment lines	Second line	14	26	.329	14	26	1.0
	After the second line	10	30		14	26	
Therapy	Monotherapy	7	16	.957	9	14	.623
	Combination therapy	17	40		19	38	
Surgery	Yes	13	32	.806	17	28	.555
	No	11	24		11	24	
Radiotherapy	Yes	13	30	.961	17	26	.359
	No	11	26		11	26	
Results of the first evaluation	ORR (CR+PR)	3	15	.161	5	13	.466
	SD+PD	21	41		23	39	
PFS (days)	< 135	21	19	<.001	24	16	<.001
	≥ 135	3	37		4	36	

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PLT, platelet; PLT/MPV ratio, total platelet count/mean platelet volume.

radiotherapy ( $P > .05$ ). But, patients in the second-line treatment group had longer PFS than after the second-line treatment group ( $P = .016$ ), the surgery group had longer PFS than the no-surgery group ( $P = .002$ ), the first-time evaluation results was ORR group had longer PFS than no-ORR group ( $P < .001$ ). In high PLT group (PLT > 153), PFS was longer than low PLT group (PLT ≤ 153) ( $P < .001$ ); meanwhile, in high PLT/MPV ratio group (PLT/MPV ratio > 15.9), PFS was longer than low PLT/MPV ratio group (PLT/MPV ratio ≤ 15.9) ( $P < .001$ ) (Figure 4).

### The Univariate and Multivariate Analysis of Clinical and Blood Parameters

The univariate analysis identified that treatment lines, surgery, results of the first evaluations, pretreatment PLT and PLT/MPV ratio were significantly associated with PFS (Table 3). Multivariate analysis distinctly revealed that the treatment lines (HR: 2.725, 95% CI: 1.452-5.115,  $P = .002$ ), surgery (HR: 3.176, 95% CI: 1.715-5.882,  $P < .001$ ) PLT/MPV ratio (HR: 0.257, 95% CI: 0.089-0.743,  $P = .012$ ) were independent prognostic factors for PFS (Table 4).

### Kaplan–Meier Analysis of Blood Parameters for Internal Validation

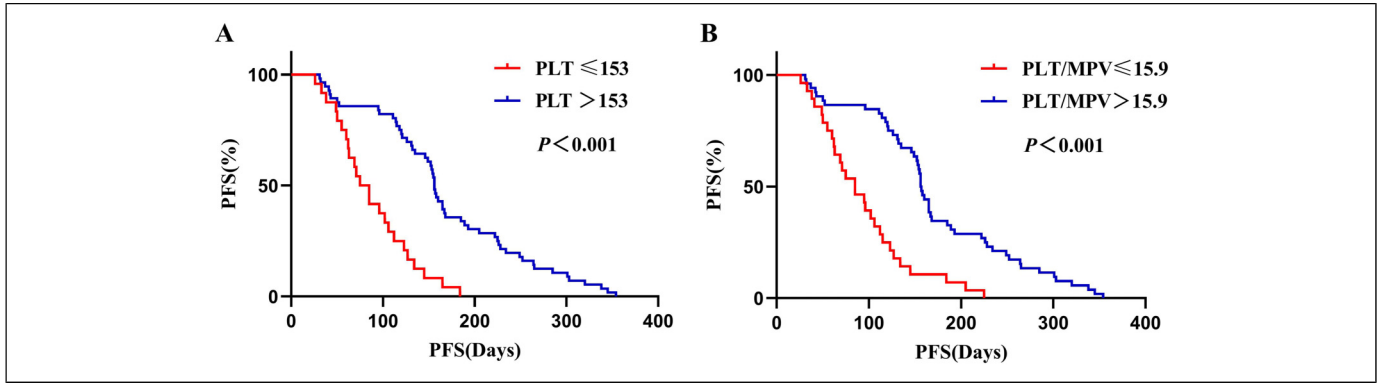
Kaplan–Meier analysis of 35 patients from the internal-validation datasets showed that PFS of the high PLT group

(PLT > 153) was significantly longer than the low PLT group (PLT ≤ 153) (149 d vs 73 d,  $P < .001$ ) (Figure 5A), and high PLT/MPV ratio group (PLT/MPV ratio > 15.9) was significantly longer than the low PLT/MPV ratio group (PLT/MPV ratio ≤ 15.9) (149 d vs 80 d,  $P = .006$ ) (Figure 5B).

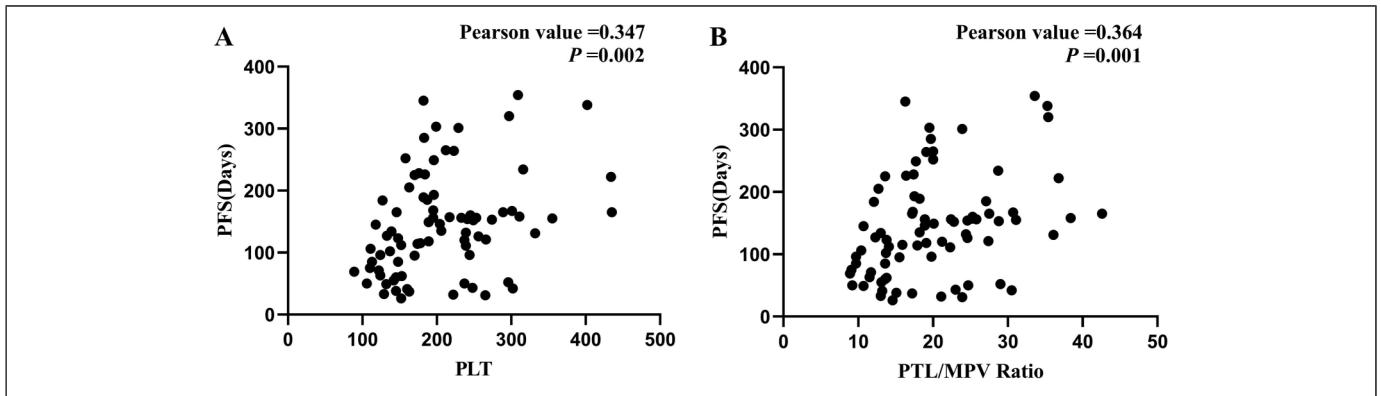
## Discussion

There were some studies about the relationship between blood parameters and esophageal cancer, but most studies reveal the relationship between blood parameters and the results of surgery, radiotherapy, and chemotherapy.<sup>17–22</sup> The relationship between PFS of targeted therapy for advanced ESCC and blood parameters had not been fully uncovered.

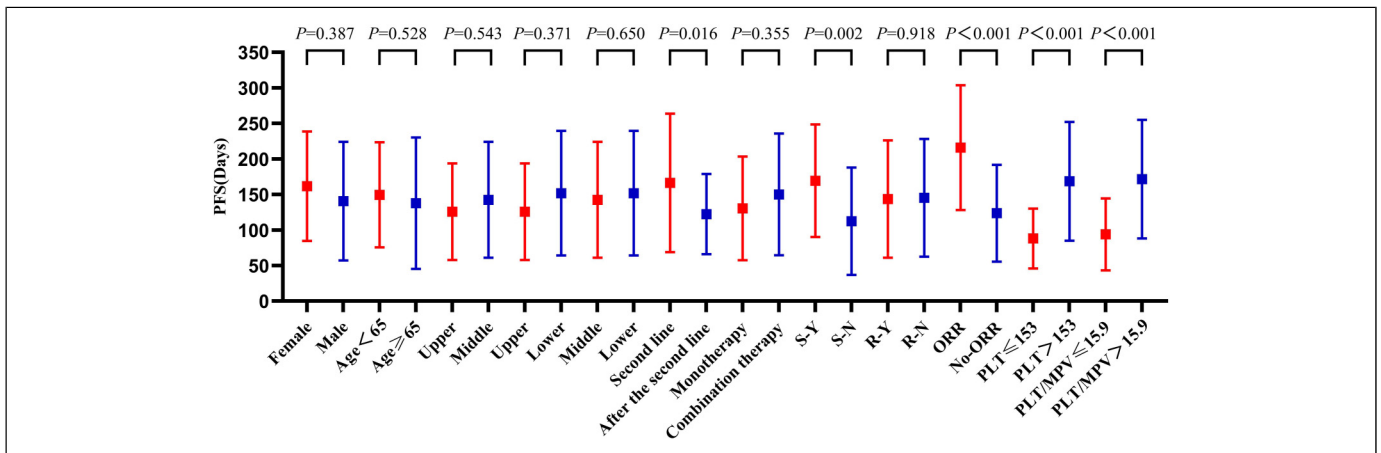
Platelet activation is a common phenomenon in cardiovascular diseases, such as acute ischemic stroke, myocardial infarction, and renal artery stenosis.<sup>32,33</sup> The clinical significance of this process in several malignant tumors has received more attention.<sup>34,35</sup> The 2 main aspects of evaluating platelet activation status are PLT and MPV.<sup>36</sup> As the 2 main indicators of platelet activation, the clinical significance of PLT and MPV in ESCC patients has received increasing attention. Our study demonstrated that the baseline PLT and PLT/MPV ratio had a preliminary prognostic value of PFS in the light of univariate analysis, and we found high PLT group (PLT >153) and high PLT/MPV ratio group (PLT/MPV ratio >15.9) had a superior PFS. Multivariate analysis showed PLT/MPV ratio was the independent factor of PFS. The Chi-square test and student's



**Figure 2.** Kaplan–Meier analysis for progress-free survival (PFS) in 80 patients with advanced ESCC patients. Abbreviations: PLT, platelet (A); PLT/MPV ratio, total platelet count/mean platelet volume (B).



**Figure 3.** Correlation analysis between progress-free survival (PFS) and blood parameters in 80 patients with advanced ESCC patients. Abbreviations: PLT, platelet (A); PLT/MPV ratio, total platelet count/mean platelet volume (B).



**Figure 4.** Student’s *t*-test for PFS between different clinical features and blood parameters. (A) Comparison of mean PFS between the different clinical feature groups; (B) comparison of mean PFS between the different blood parameter groups.

Abbreviations: PFS, progress-free survival; SY group, patients have the history of surgery; SN group, patients never received surgery; RY group, patients have the history of radiotherapy; RN group, patients never received radiotherapy; ORR group, the first-time evaluation results was CR or PR; No-ORR group, the first-time evaluation results was SD or PD; PLT, platelet; PLT/MPV ratio, total platelet count/mean platelet volume.

**Table 3.** Univariate Analysis of PFS in 80 Patients With Advanced ESCC.

Variable		Case (n)	HR (95%CI)	P-value
Gender	Female	14		
	Male	66	1.146 (0.641-2.050)	.645
Age (year)	< 65	45		
	≥ 65	35	0.990 (0.629-1.558)	.967
Primary site	Upper	11		
	Middle	33	0.797 (0.399-1.594)	.521
	Lower	33	0.724 (0.364-1.440)	.357
Treatment lines	Second line	40		
	After the second line	40	2.116 (1.293-3.462)	.003*
Therapy	Monotherapy	23		
	Combination therapy	57	0.757 (0.463-1.240)	.269
Surgery	Yes	45		
	No	35	1.844 (1.170-2.904)	.008*
Radiotherapy	Yes	43		
	No	37	1.021 (0.654-1.595)	.926
Results of the first evaluation	ORR (CR+PR)	7		
	SD+PD	73	2.927 (1.624-5.275)	<.001*
PLT	≤ 153	24		
	> 153	56	0.250 (0.144-0.433)	<.001*
PLT/MPV	≤ 15.9	28		
	> 15.9	52	0.287 (0.172-0.479)	<.001*

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; PLT, platelet; PLT/MPV ratio, total platelet count/mean platelet volume.

\* $P < .05$ , the difference was statistically significant.

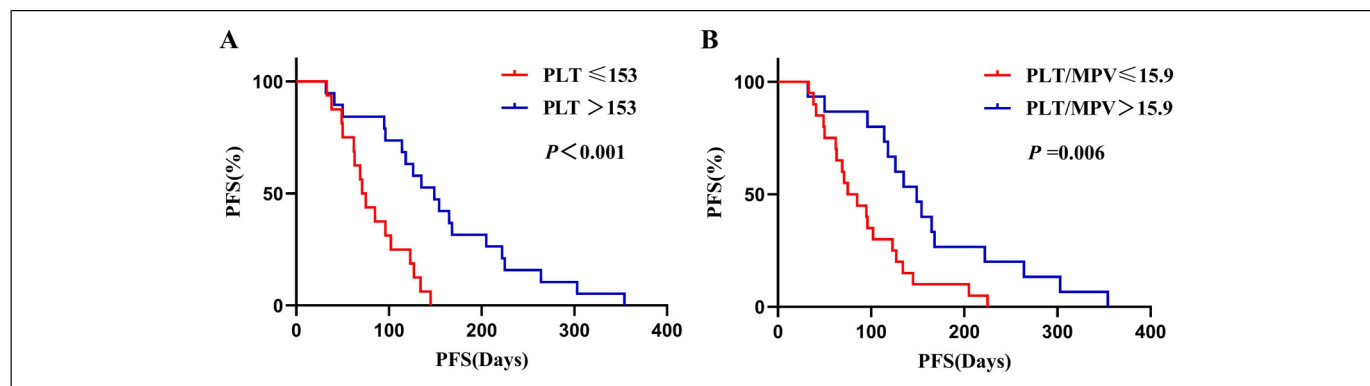
**Table 4.** Multivariate Analysis of PFS in 80 Patients With Advanced ESCC.

Variable	HR (95% CI)	P-value
Gender	2.103 (0.933-4.742)	.073
Age (year)	1.019 (0.595-1.745)	.946
Primary site	0.768 (0.339-1.741)	.527
	0.957 (0.447-2.049)	.910
Treatment lines	2.725 (1.452-5.115)	.002
Therapy	0.761 (0.412-1.408)	.385
Surgery	3.176 (1.715-5.882)	<.001
Radiotherapy	0.726 (0.422-1.251)	.249
Results of the first evaluation	1.389 (0.706-2.733)	.341
PLT	0.605 (0.203-1.803)	.367
PLT/MPV	0.257 (0.089-0.743)	.012

Abbreviations: PLT, platelet; PLT/MPV ratio, total platelet count/mean platelet volume.

*t*-test both revealed that PLT and PLT/MPV ratio of baseline had a relationship with PFS. Kaplan-Meier analysis showed PFS of patients in high PLT group (PLT > 153) was longer than low PLT group (PLT ≤ 153), and high PLT/MPV group (PLT/MPV ratio > 15.9) was longer than low PLT/MPV ratio group (PLT/MPV ratio ≤ 15.9). We did not find the prognostic significance of MPV in the treatment of apatinib for advanced ESCC patients. Zhang et al<sup>37</sup> found that baseline PLT and MPV (COP-MPV) before surgery were independent prognostic factors for DFS and OS, and could be used as an effective predictor of survival for ESCC patients after surgery.

Angiogenesis is an important pathological feature of tumor occurrence and development. It can not only provide oxygen to tumor cells but also deliver proteases and cytokines that help tumor cells penetrate and spread. Tumor angiogenesis is closely related to platelets.<sup>38</sup> Platelets come into contact with prethrombus structures such as collagen in blood vessels, causing changes in blood flow, and endothelial cells release von Willebrand factor to activate platelets. Activated platelets mainly release regulatory factors that promote angiogenesis, such as VEGF and PDGF. It also releases regulatory factors that inhibit angiogenesis, such as endostatin, thrombin sensitive protein 1, etc, and releases TGF-β, which has a bidirectional regulation of angiogenesis. These substances jointly regulate tumor angiogenesis. Most scholars believe that in terms of angiogenesis, the promoting effect of platelets is greater than the inhibiting effect.<sup>39-41</sup> VEGF has high specificity to endothelial cells and is the most effective mitogen inducer to promote angiogenesis. Under hypoxic conditions, it can effectively bind to the VEGF receptor (VEGFR) on the endothelial cell membrane to phosphorylate VEGFR. Phosphorylation of VEGFR activates the mitogen-activated protein kinase signal channel, induces endothelial cells to deform, move, proliferate and divide, and promote capillary angiogenesis. The meta-analysis by Kut et al.<sup>42</sup> found that the level of VEGF in platelets of tumor patients increased significantly compared with healthy controls (413 ng/mL vs 216 ng/mL). Some studies also confirmed that high baseline platelet levels in tumor patients indicate a more significant increase in VEGF levels.<sup>43,44</sup> The angiogenesis effect of VEGF is mainly mediated by VEGFR2, which is highly expressed on vascular endothelial cells.<sup>45</sup> Thus, VEGFR2 has become an



**Figure 5.** Kaplan–Meier analysis for progress-free survival (PFS) in 35 patients from internal-validation cohort. Abbreviations: PLT, platelet (A); PLT/MPV ratio, total platelet count/mean platelet volume (B).

important target for tumor therapy.<sup>46</sup> As an anti-angiogenic drug, apatinib blocks the signal transduction pathway after the binding of VEGF to its receptor and has shown certain efficacy in the treatment of a variety of solid tumors.<sup>47,48</sup> In our study, we speculate that patients in the high PLT group and high PLT/MPV ratio group at baseline have a more significant increase in VEGF levels compared to patients in the low PLT group and low PLT/MPV ratio group, thus having a better effect on the treatment of apatinib.

This study had some limitations. This research was a single-center retrospective study. There might be selection and information bias due to the study design and the sample size of patients included in the study was relatively small. Nowadays, the second-line standard treatment for advanced esophageal squamous cell carcinoma is PD-1 inhibitors, and the use of apatinib may not be appropriate. Thus, multi-center, prospective, and larger population studies are needed to verify these results.

## Conclusions

This study aimed to investigate the prognostic significance of platelet (PLT) and platelet to mean platelet volume (PLT/MPV) ratio for advanced ESCC patients with apatinib second-line or late-line treatment. Baseline PLT and PLT/MPV ratio was a significant predictor of outcome and a high level of baseline PLT and PLT/MPV ratio suggested superior PFS in apatinib  $\geq 2$  lines treatment for advanced ESCC patients.

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## Declaration of Conflicting Interests


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## Supplemental Material

Supplemental material for this article is available online.

## References

- Sung H, Ferlay J, Siegel RL, et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2021;71(3):209–249.
- Abnet CC, Arnold M, Wei WQ. Epidemiology of esophageal squamous cell carcinoma. *Gastroenterology.* 2018;154(2):360–373.
- Zhang Y. Epidemiology of esophageal cancer. *World J Gastroenterol.* 2013;19(34):5598–5606.
- Kojima T, Shah MA, Muro K, et al. Randomized phase III KEYNOTE-181 study of pembrolizumab versus chemotherapy in advanced esophageal cancer. *J Clin Oncol.* 2020;38(35):4138–4148.
- Kato K, Cho BC, Takahashi M, et al. Nivolumab versus chemotherapy in patients with advanced oesophageal squamous cell carcinoma refractory or intolerant to previous chemotherapy (ATTRACTION-3): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2019;20(11):1506–1517.
- Huang J, Xu J, Chen Y, et al. Camrelizumab versus investigator's choice of chemotherapy as second-line therapy for advanced or metastatic oesophageal squamous cell carcinoma (ESCOR): a multicentre, randomised, open-label, phase 3 study. *Lancet Oncol.* 2020;21(6):832–842.
- Li J, Qin S, Xu J, et al. Apatinib for chemotherapy-refractory advanced metastatic gastric cancer: results from a randomized, placebo-controlled, parallel-arm, phase II trial. *J Clin Oncol.* 2013;31(26):3219–3225.
- Li J, Wang L. Efficacy and safety of apatinib treatment for advanced esophageal squamous cell carcinoma. *Onco Targets Ther.* 2017;10:3965–3969.
- Yanwei L, Feng H, Ren P, et al. Safety and efficacy of apatinib monotherapy for unresectable, metastatic esophageal cancer: a



- single-arm, open-label, phase II study. *Oncologist*. 2020;25(10):e1464-e1472.
10. Li J, Jia Y, Gao Y, et al. Clinical efficacy and survival analysis of apatinib combined with docetaxel in advanced esophageal cancer. *Onco Targets Ther*. 2019;12:2577-2583.
  11. Zhao J, Lei J, Yu J, et al. Clinical efficacy and safety of apatinib combined with S-1 in advanced esophageal squamous cell carcinoma. *Invest New Drugs*. 2020;38(2):500-506.
  12. Magdy M, Hussein T, Ezzat A, Gaballah A. Pre-treatment peripheral neutrophil-lymphocyte ratio as a prognostic marker in gastric cancer. *J Gastrointest Cancer*. 2019;50(4):763-768.
  13. Vallard A, Garcia MA, Diao P, et al. Outcomes prediction in pre-operative radiotherapy locally advanced rectal cancer: leucocyte assessment as immune biomarker. *Oncotarget*. 2018;9(32):22368-22382.
  14. Hong YF, Chen ZH, Wei L, et al. Identification of the prognostic value of lymphocyte-to-monocyte ratio in patients with HBV-associated advanced hepatocellular carcinoma. *Oncol Lett*. 2017;14(2):2089-2096.
  15. Yang J, Xu H, Guo X, et al. Pretreatment inflammatory indexes as prognostic predictors for survival in colorectal cancer patients receiving neoadjuvant chemoradiotherapy. *Sci Rep*. 2018;8(1):3044.
  16. Yang J, Guo X, Wang M, Ma X, Ye X, Lin P. Pre-treatment inflammatory indexes as predictors of survival and cetuximab efficacy in metastatic colorectal cancer patients with wild-type RAS. *Sci Rep*. 2017;7(1):17166.
  17. Wang C, Tong J, Tang M, et al. Pretreatment neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio as prognostic factors and reference markers of treatment options for locally advanced squamous cell carcinoma located in the middle and upper esophagus. *Cancer Manag Res*. 2021;13:1075-1085.
  18. Han F, Liu Y, Cheng S, et al. Diagnosis and survival values of neutrophil-lymphocyte ratio (NLR) and red blood cell distribution width (RDW) in esophageal cancer. *Clin Chim Acta*. 2019;488:150-158.
  19. Zhi X, Jiang K, Shen Y, et al. Peripheral blood cell count ratios are predictive biomarkers of clinical response and prognosis for non-surgical esophageal squamous cell carcinoma patients treated with radiotherapy. *J Clin Lab Anal*. 2020;34(10):e23468.
  20. Song Q, Wu JZ, Jiang HF, Wang S, Cai SN. The postoperative lymphocyte to monocyte ratio change predicts poor clinical outcome in patients with esophageal squamous cell carcinoma undergoing curative resection. *Dis Markers*. 2020;2020:1451864.
  21. Li KJ, Xia XF, Su M, Zhang H, Chen WH, Zou CL. Predictive value of lymphocyte-to-monocyte ratio (LMR) and neutrophil-to-lymphocyte ratio (NLR) in patients with oesophageal cancer undergoing concurrent chemoradiotherapy. *BMC Cancer*. 2019;19(1):1004.
  22. Gao Y, Guo W, Cai S, et al. Systemic immune-inflammation index (SII) is useful to predict survival outcomes in patients with surgically resected esophageal squamous cell carcinoma. *J Cancer*. 2019;10(14):3188-3196.
  23. Li A, Wang K, Xu A, et al. Apatinib as an optional treatment in metastatic colorectal cancer. *Medicine (Baltimore)*. 2019;98(35):e16919.
  24. Chen L, Ke Z, Xiong F, et al. Platelet-to-lymphocyte ratio predicts therapy outcomes of transarterial chemoembolization plus apatinib in the treatment of advanced hepatocellular carcinoma. *Anticancer Drugs*. 2020;31(9):966-972.
  25. Li N. Platelets in cancer metastasis: to help the "villain" to do evil. *Int J Cancer*. 2016;138(9):2078-2087.
  26. Walsh TG, Metharom P, Berndt MC. The functional role of platelets in the regulation of angiogenesis. *Platelets*. 2015;26(3):199-211.
  27. Yap ML, McFadyen JD, Wang X, et al. Targeting activated platelets: a unique and potentially universal approach for cancer imaging. *Theranostics*. 2017;7(10):2565-2574.
  28. Lee JH, Park M, Han S, Hwang JJ, Park SH, Park SY. An increase in mean platelet volume during admission can predict the prognoses of patients with pneumonia in the intensive care unit: a retrospective study. *PLoS One*. 2018;13(12):e0208715.
  29. Wang H, Chen WM, Zhou YH, Shi JP, Huang YQ, Wang WJ. Combined PLT and NE to predict the prognosis of patients with locally advanced cervical cancer. *Sci Rep*. 2020;10(1):11210.
  30. Omar M, Tanriverdi O, Cokmert S, et al. Role of increased mean platelet volume (MPV) and decreased MPV/platelet count ratio as poor prognostic factors in lung cancer. *Clin Respir J*. 2018;12(3):922-929.
  31. Watanabe K, Yasumoto A, Amano Y, et al. Mean platelet volume and lymphocyte-to-monocyte ratio are associated with shorter progression-free survival in EGFR-mutant lung adenocarcinoma treated by EGFR tyrosine kinase inhibitor. *PLoS One*. 2018;13(9):e0203625.
  32. Fitzgerald DJ, Roy L, Catella F, FitzGerald GA. Platelet activation in unstable coronary disease. *N Engl J Med*. 1986;315(16):983-989.
  33. Davi G, Patrono C. Platelet activation and atherothrombosis. *N Engl J Med*. 2007;357(24):2482-2494.
  34. Connolly GC, Phipps RP, Francis CW. Platelets and cancer-associated thrombosis. *Semin Oncol*. 2014;41(3):302-310.
  35. Stegner D, Dütting S, Nieswandt B. Mechanistic explanation for platelet contribution to cancer metastasis. *Thromb Res*. 2014;133:S149-S157.
  36. Kamath S, Blann AD, Lip GY. Platelet activation: assessment and quantification. *Eur Heart J*. 2001;22(17):1561-1571.
  37. Zhang CY, Zhang J, Ma YF, Zhe H, Zhao R, Wang YY. Prognostic value of combined analysis of CTLA-4 and PLR in esophageal squamous cell carcinoma (ESCC) patients. *Dis Markers*. 2019;2019:1601072.
  38. Szubert S, Moszynski R, Szpurek D, et al. The expression of platelet-derived growth factor receptors (PDGFRs) and their correlation with overall survival of patients with ovarian cancer. *Ginekol Pol*. 2019;90(5):242-249.
  39. Wojtukiewicz MZ, Sierko E, Hempel D, Tucker SC, Honn KV. Platelets and cancer angiogenesis nexus. *Cancer Metastasis Rev*. 2017;36(2):249-262.
  40. Jiang L, Luan Y, Miao X, et al. Platelet releasate promotes breast cancer growth and angiogenesis via VEGF-integrin cooperative signalling. *Br J Cancer*. 2017;117(5):695-703.

41. Battinelli EM, Markens BA, Italiano JE Jr. Release of angiogenesis regulatory proteins from platelet alpha granules: modulation of physiologic and pathologic angiogenesis. *Blood*. 2011;118(5):1359-1369.
42. Kut C, Mac Gabhann F, Popel AS. Where is VEGF in the body? A meta-analysis of VEGF distribution in cancer. *Br J Cancer*. 2007;97(7):978-985.
43. Ferroni P, Spila A, D'Alessandro R, et al. Platelet activation and vascular endothelial growth factor 165 release in hepatocellular cancer. *Clin Chim Acta*. 2011;412(5-6):450-454.
44. Verheul HM, Hoekman K, Lupu F, et al. Platelet and coagulation activation with vascular endothelial growth factor generation in soft tissue sarcomas. *Clin Cancer Res*. 2000;6(1):166-171.
45. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med*. 2003;9(6):669-676.
46. Peng FW, Liu DK, Zhang QW, Xu YG, Shi L. VEGFR-2 inhibitors and the therapeutic applications thereof: a patent review (2012-2016). *Expert Opin Ther Pat*. 2017;27(9):987-1004.
47. Zhang X, Wang C, Lin Y. Pilot dose comparison of apatinib in Chinese patients with progressive radioiodine-refractory differentiated thyroid cancer. *J Clin Endocrinol Metab*. 2018;103(10):3640-3646.
48. Chen X, Qiu T, Zhu Y, et al. A single-arm, phase II study of apatinib in refractory metastatic colorectal cancer. *Oncologist*. 2019;24(7):883-e407.