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ORIGINAL ARTICLE

Prognostic value of inflammatory and nutritional indexes among advanced NSCLC patients receiving PD-1 inhibitor therapy

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Abstract

Though immunotherapy has to some extent improved the prognosis of patients with advanced non-small cell lung cancer (NSCLC), only a few patients benefit. Furthermore, immunotherapy efficacy is affected by inflammatory and nutritional status of patients. To investigate whether dynamics of inflammatory and nutritional indexes were associated with prognosis, 223 patients were analysed retrospectively. The inflammatory indexes of interest were neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII) while prognostic nutritional index (PNI) and the haemoglobin, albumin, lymphocyte and platelet (HALP) score were considered as nutritional indexes. Patients were divided into high and low groups or into 'increase' and 'decrease' groups based on pre-treatment cut-off values and index dynamics after 6-week follow-up respectively. High pre-treatment PLR (OR = 2.612) and increase in NLR during follow-up (OR = 2.516) were significantly associated with lower objective response rates. Using multivariable analysis, high pre-treatment PLR (HR, 2.319) and increase in SII (HR, 1.731) predicted shorter progression-free survival, while high pre-treatment NLR (HR, 1.635), increase in NLR (HR, 1.663) and PLR (HR, 1.691) and decrease in PNI (HR, 0.611) predicted worse overall survival. The nomogram's C-index in inside validation was 0.718 (95% CI: 0.670–0.766). Our results indicated both nutritional and inflammatory indexes are associated with survival outcomes. Inflammatory indexes were additionally linked to treatment response. Index dynamics are better predictors than baseline values in predicting survival in advanced NSCLC patients receiving PD-1 inhibitor combined with chemotherapy as first-line.

KEYWORDS
dynamic, immunotherapy, inflammatory indexes, non-small cell lung cancer (NSCLC), nutritional indexes

1 | INTRODUCTION

Immune checkpoint inhibitors (ICIs) treatment, represented by programmed cell death protein-1 (PD-1) inhibitors, has greatly improved the prognosis of patients with advanced non-small cell lung cancer (NSCLC) compared to traditional chemotherapy,[1] leading to major reformation of treatment patterns. ICIs, combined with chemotherapy therapy, have become the standard first-line treatment for advanced NSCLC with negative driver gene. However, only about 10%–40% patients benefit from durable responses from immunotherapy, with some even going through hyper-progression or fatal toxicity.[2–5] To date, tumour tissue PD-L1 expression and tumour mutation burden (TMB) have been the most widely accepted predicting biomarkers approved by the Food and Drug Administration (FDA). Nevertheless, considerable inconsistency exists in many different cases.[6,7] As for other reported biomarker candidates, including tumour neoantigen burden (TNB), deficient mismatch repair (dMMR), high microsatellite instability (MSI-high), T-cell receptor clonality, tumour-infiltrating lymphocytes (TIL), DNA damage and repair genes (DDR), effector T-cell gene signature and intestinal microbiota,[8–10] the invasive nature and high cost would be the additional concerns besides the unacceptable inaccuracy in identifying patients who may benefit from immunotherapy. Therefore, finding an inexpensive prognostic biomarker of clinical response to immunotherapy remains urgently required.

Patient conditions, including inflammatory and nutritional status, is likely to impact immune responses and yet this is not fully understood. Recently, peripheral blood indexes representing inflammation or nutrition have been increasingly studied in predicting treatment responses to immunotherapy among patients with NSCLC.[11–13] The majority of the studies have focused on single haematological indexes, such as white blood cell (WBC), neutrophils, lymphocytes, platelets, haemoglobin and albumin, while the prognostic value of a single index is relatively low. Although there were studies exploring combined peripheral blood indexes, the patients recruited were mostly heterogeneous or only baseline indicators were evaluated.[14–17]

In this study, we carried out a retrospective analysis to examine the capacity of combined peripheral blood indexes in predicting the response and survival of patients in a dynamic pattern. The combined peripheral blood indexes were divided into inflammatory markers, including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune-inflammation index (SII); and nutritional indicators, including prognostic nutritional index (PNI) and the haemoglobin, albumin, lymphocyte and platelet (HALP) score. The present study was initiated to investigate whether the two categories of indexes are associated with clinically prognostic values and a new nomogram with relatively high accuracy was developed for assessment.

TABLE 1 Baseline characteristics of the patients

Characteristics	No. of patients	%
Total	223	100.0
Age		
≤60	109	48.9
>60	114	51.1
Sex		
Male	189	84.8
Female	34	15.2
ECOG-PS		
0 score	113	50.7
1 score	110	49.3
Histology		
LUAD	133	59.6
LUSC	90	40.4
Stage		
IIIB/IIIC	28	12.6
IV	195	87.4
Metastatic sites		
Lung	59	26.5
Pleura	51	22.9
Liver	11	4.9
Bone	87	39.0
CNS	18	8.1
Adrenal gland	8	3.6
Distant lymph node metastasis	22	9.9
PD-L1 expression		
Negative	45	20.2
Positive	73	32.7
Unknown	105	47.1
Baseline index		
NLR, M (IQR)	3.18	(2.33–4.32)
PLR, M (IQR)	144.37	(106.32–196.27)
SII, M (IQR)	792.07	(570.01–1247.30)
PNI, M (IQR)	50.50	(47.25–54.60)
HALP, M (IQR)	39.33	(26.54–53.27)

Abbreviations: CNS, central nervous system; ECOG, Eastern Cooperative Oncology Group; HALP, haemoglobin, albumin, lymphocyte and platelet; IQR, interquartile range; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand 1; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; PS, performance status; SII, systemic immune-inflammation index.

2 | RESULTS

2.1 | Clinical characteristics of patients

A total of 223 patients were included in this study. Their characteristics are summarized in Table 1. The average age at the time of diagnosis was 60.4 years. Most patients were male (84.8%, $n = 189$). Every subject had an Eastern Cooperative Oncology Group Performance Status (ECOG-PS) score of 0 or 1. Lung adenocarcinoma accounted for most cases (59.6%; $n = 133$), while lung squamous cell carcinoma was observed in 40.4% ($n = 90$) of patients. About 87.4%

TABLE 2 Relationships between indexes and objective response rate (ORR)

	PR group (N)	Non-PR group (N)	ORR (%)	χ2	p
Total	118	105			
Clinical indexes					
Age					
≤60	62	47	56.9	1.346	0.246
>60	56	58	49.1		
Sex					
male	98	91	51.9	0.562	0.453
female	20	14	58.8		
ECOG-PS					
0 score	69	44	61.1	6.103	0.013
1 score	49	61	44.5		
Histology					
LUAD	76	57	57.1	2.364	0.124
LUSC	42	48	46.7		
Stage					
IIIB/IIIC	18	10	64.3	1.662	0.197
IV	100	95	51.3		
PD-L1 expression					
Negative	18	27	40.0	125.348	<0.001
Positive	47	26	64.4		
Unknown	53	52	50.5		
Pre-treatment indexes					
NLR					
Low	67	46	59.3	3.379	0.053
High	51	59	46.4		
PLR					
Low	74	38	66.1	15.632	<0.001
High	44	67	39.6		
SII					
Low	69	43	61.6	6.824	0.009
High	49	62	44.1		
PNI					
Low	49	63	43.8	7.585	0.006
High	69	42	62.2		
HALP					
Low	47	65	42.0	10.829	0.001
High	71	40	64.0		
Variance indexes					
NLR					
Decrease	76	49	60.8	7.098	0.008
Increase	42	56	42.9		
PLR					
Decrease	58	56	50.9	0.389	0.533
Increase	60	49	55.0		
SII					
Decrease	64	52	55.2	0.495	0.482
Increase	54	53	50.5		
PNI					
Decrease	59	53	52.7	0.005	0.943
Increase	59	52	53.2		
HALP					
Decrease	75	56	57.3	2.397	0.122
Increase	43	49	46.7		

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HALP, haemoglobin, albumin, lymphocyte and platelet; LUAD, Lung adenocarcinoma; LUSC, Lung squamous cell carcinoma; NLR, neutrophil-to-lymphocyte ratio; PD-L1, programmed cell death ligand 1; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; PR, partial response; PS, performance status; SII, systemic immune-inflammation index.

of the cases ($n = 195$) were in Stage IV. The number of patients with Kirsten rat sarcoma viral oncogene homologue (KRAS) mutation, v-RAF murine sarcoma viral oncogene homologue B1 (BRAF) mutation, human epidermal growth factor receptor-2 (HER2) mutation and epidermal growth factor receptor gene exon 20 insertion (EGFR-20ins) mutation were 9, 2, 2 and 3 respectively. The number of patients with positive and negative PD-L1 expression were 76 and 43 respectively, and there were 104 patients for whom the PD-L1expression was unknown.

All subjects received anti-PD1 therapy combined with chemotherapy as first-line treatment with a median follow-up of 20.4 months (95% confidence interval [CI]: 14.5–26.3). The median progression-free survival (PFS) and overall survival (OS) for all patients were 12 months (95% CI, 10.674–13.326) and 20 months (95% CI, 18.536–21.464), respectively. The cut-off values for NLR, PLR, SII, PNI and HALP were 3.18, 144.37, 792.07, 50.50 and 39.33, respectively.

2.2 | Correlation of treatment response with pre-treatment values and dynamics of inflammatory and nutritional indexes

Better objective response rate (ORR) was observed in patients with lower levels of pre-treatment PLR (66.1%) and SII (61.6%) and higher levels of pre-treatment PNI (43.8%) and HALP (42.0%), compared with respective counterpart groups (39.6% for PLR, 44.1% for SII, 62.2% for PNI and 64.0% for HALP), with the p value of $p < 0.001$, 0.009, 0.006 and 0.001 respectively. It is also the case for patients with an ECOG-PS score of 0 in contrast to those with an ECOG-PS score of 1 (61.1% and 44.5% respectively, $p = 0.013$).

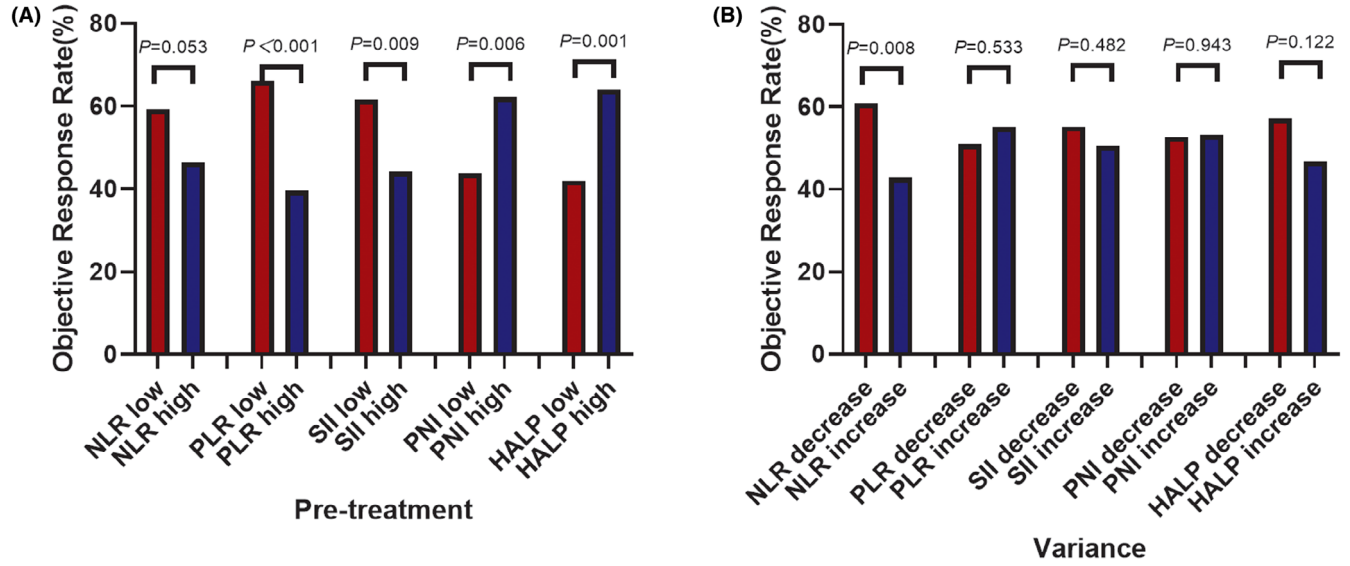

FIGURE 1 Different tumour responses of patients with advanced non-small cell lung cancer (NSCLC) patients who received death protein-1 (PD-1) inhibitor combined with chemotherapy as first-line according to inflammatory/nutritional indexes. (A) Pre-treatment, (B) variance. HALP, haemoglobin, albumin, lymphocyte and platelet; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune-inflammation index.

Patients with positive PD-L1 expression has higher ORR (64.4%) than those with negative PD-L1 expression (40.0%) ($p = 0.010$). There was no difference between patients with unknown PD-L1 expression and those with negative or positive PD-L1 expression ($p = 0.239$ or 0.066, respectively). Age, sex, histology, stage and pre-treatment NLR levels were not associated with ORR (Table 2, Figure 1A).

Higher ORR could be observed in subjects demonstrating a decline in NLR (76/125, 60.8%) compared with those in NLR-increase group (42/98; 42.9%, $p = 0.008$). But it was not the case for other indexes (Figure 1B).

In the multivariate logistic regression analysis, high pre-treatment PLR (OR = 3.557, 95% CI: 1.993–6.350, $p = 0.000$) and dynamic increase in NLR (OR = 2.626, 95% CI: 1.466–4.703, $p = 0.003$) were significantly associated with inferior ORR.

2.3 | Relationships of patient outcomes with pre-treatment values and dynamics of inflammatory and nutritional indexes

The median PFS values of patients with higher pre-treatment levels of NLR (low group, 14 months vs. high group, 9 months; hazard ratio [HR], 1.571; [95% CI, 1.151–2.144]; $p = 0.004$), PLR (low group, 14 months vs. high group, 10 months; HR, 1.716; [95% CI, 1.264–2.329]; $p = 0.001$), SII (low group, 13 months vs. high group, 10 months; HR, 1.371; [95% CI, 1.012–1.857]; $p = 0.042$) were shorter than those at the lower pre-treatment level. Low ECOG-PS score (0 score, 13 months vs. 1 score, 9 months; HR, 1.619; [95% CI, 1.193–2.198]; $p = 0.002$) was linked to longer PFS (Table 3). No associations were found between PFS with baseline levels of the two nutritional indexes, PNI and HALP (Figure 2). Our data only support a role for the pre-treatment levels of the NLR score (low group, 21 months vs. high group, 19 months; HR, 1.587; [95% CI, 1.110–2.268]; $p = 0.011$) (Figure 2), and the ECOG-PS scores (0 score, 21 months vs. 1 score, 17 months; HR, 1.639; [95% CI, 1.162–2.312]; $p = 0.005$) in predicting the OS of patients. PD-L1 expression was not associated with PFS and OS (Table 3).

As shown in Figure 3 and Table 3, patients demonstrating an increase in NLR (decrease group, 14 months vs. increase group = 9 months, HR, 2.000, [95% CI, 1.463–2.735], $p < 0.001$), PLR (decrease group = 13 months vs. increase group = 11 months, HR, 1.384, [95% CI, 1.022–1.875], $p = 0.036$) and SII (decrease group = 14 months vs. increase group = 10 months, HR, 1.667, [95% CI, 1.230–2.260], $p < 0.001$) suffered from shorter PFS than those showing a decline pattern. In comparison, patients demonstrating an increase in PNI (decrease group = 11 months vs. increase group = 13 months, HR, 0.642, [95% CI, 0.472–0.873], $p = 0.005$) were associated with longer PFS. No significant difference was observed between the decrease and the increase group for HALP (11 months vs. 13 months respectively, HR, 0.863, [95% CI, 0.635–1.174], $p = 0.348$).

The dynamics of NLR (decrease group, 23 months vs. increase group, 17 months; HR, 2.261; [95% CI, 1.586–3.223]; $p < 0.001$), PLR (decrease group , 22 months vs. increase group, 19 months; HR, 1.539; [95% CI, 1.092–2.169]; $p = 0.014$), SII (decrease group, 21 months vs. increase group, 18 months; HR, 1.607; [95% CI, 1.142–2.262]; $p = 0.007$) and PNI (decrease group, 17 months vs. increase group, 26 months; HR, 0.449; [95% CI, 0.315–0.640]; $p < 0.001$) were closely associated with OS. The median OS tended to be longer in patients showing an increasing pattern for HALP

TABLE 3 Univariate Cox regression analysis of PFS and OS

	PFS				OS			
	median m	HR	(95% CI)	*p*	median m	HR	(95% CI)	*p*
Clinical indexes								
Age(y)								
≤60	13				20			
>60	11	1.096	0.809–1.484	0.555	19	1.057	0.751–1.486	0.752
Sex								
Female	13				26			
Male	11	1.296	0.859–1.955	0.217	19	1.575	0.997–2.489	0.051
ECOG-PS								
0 score	13				21			
1 score	9	1.619	1.193–2.198	0.002	17	1.639	1.162–2.312	0.005
Histology								
LUSC	12				20			
LUAD	11	0.799	0.586–1.089	0.155	20	0.832	0.589–1.176	0.298
Stage								
IIIB/IIIC	14				22			
IV	12	1.477	0.868–2.514	0.151	19	0.948	0.551–1.630	0.847
PD-L1 expression								
Negative	10				19			
Positive	11	0.830	0.536–1.286	0.405	21	0.682	0.426–1.093	0.111
Unknown	13	0.827	0.546–1.251	0.369	19	0.827	0.533–1.283	0.395
Pre-treatment indexes								
NLR								
Low	14				21			
High	9	1.571	1.151–2.144	0.004	19	1.587	1.110–2.268	0.011
PLR								
Low	14				20			
High	10	1.716	1.264–2.329	0.001	19	1.382	0.978–1.951	0.066
SII								
Low	13				20			
High	10	1.371	1.012–1.857	0.042	19	1.140	0.808–1.610	0.455
PNI								
Low	10				20			
High	13	0.898	0.661–1.221	0.492	19	0.959	0.680–1.353	0.813
HALP								
Low	10				20			
High	13	0.771	0.569–1.045	0.093	19	0.996	0.709–1.401	0.493
Variance indexes								
NLR								
Decrease	14				23			
Increase	9	2.000	1.463–2.735	<0.001	17	2.261	1.586–3.223	<0.001
PLR								
Decrease	13				22			
Increase	11	1.384	1.022–1.875	0.036	19	1.539	1.092–2.169	0.014

TABLE 3 (Continued)

	PFS				OS			
	median m	HR	(95% CI)	*p*	median m	HR	(95% CI)	*p*
SII								
Decrease	14				21			
Increase	10	1.667	1.230–2.260	0.001	18	1.607	1.142–2.262	0.007
PNI								
Decrease	11				17			
Increase	13	0.642	0.472–0.873	0.005	26	0.449	0.315–0.640	<0.001
HALP								
Decrease	11				19			
Increase	13	0.863	0.635–1.174	0.348	21	0.736	0.519–1.045	0.087

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HALP, haemoglobin, albumin, lymphocyte and platelet; HR, hazard ratio; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; PS, performance status; SII, systemic immune-inflammation index.

compared to those demonstrating a decline pattern (decrease group, 19 months vs. increase group, 21 months; HR, 0.736; [95% CI, 0.519–1.045]; $p = 0.087$).

Results from multivariate Cox regression analysis showed that ECOG-PS score (HR, 1.460; 95% CI, 1.064–2.005; $p = 0.019$), pre-treatment PLR (HR, 2.319; 95% CI, 1.496–3.595; $p < 0.001$) and dynamics of SII (HR, 1.731; 95% CI, 1.063–2.819; $p = 0.027$) were independently associated with PFS. As for OS, the ECOG-PS score (HR, 1.442; 95% CI, 1.014–2.052; $p = 0.042$), pre-treatment NLR (HR, 1.635; 95% CI, 1.121–2.386; $p = 0.011$), as well as dynamics of NLR (HR, 1.663; 95% CI, 1.064–2.599; $p = 0.026$), PLR (HR, 1.691; 95% CI, 1.068–2.677; $p = 0.025$) and PNI (HR, 0.611; 95% CI, 0.415–0.900; $p = 0.013$) were found to be the independent predicting factors (Table 4).

2.4 | Nomogram and predictive models using R

The five independent risk factors (i.e., ECOG-PS score, pre-treatment NLR as well as dynamics of NLR, PLR and PNI) determined with the multivariate Cox regression analysis were used in developing a predictive nomogram for NSCLC patients treated with received PD-1 inhibitor combined with chemotherapy as first-line treatment. The resulting nomogram (see Figure 4) yielded an internal verification C-index of 0.718 (95% CI, 0.670–0.766), indicating that the model has excellent prediction accuracy.

3 | DISCUSSION

In this study, we found that both pre-treatment values and dynamics of inflammatory indexes were related to ORR, PFS and OS, while only the dynamics of nutritional indexes correlated with OS. Our study also showed dynamics of these clinical indexes were much stronger than pre-treatment values in predicting survival of patients. To our knowledge, we are among the first to comprehensively explore the prognostic value of dynamic variations in a series of inflammatory and nutritional indexes in NSCLC treated with chemo immunotherapy as first-line treatment and develop a nomogram to help clinicians identify potential unfavourable factors in order to adopt appropriate intervention measures.

Inflammation is crucial in all stages of tumour development and progression. It also impacts the tumour immune microenvironment and treatment response.[18,19] High neutrophil count is related to the release of tumour-promoting substances (e.g., reactive oxygen species, arginase, inflammatory cytokines, tumour or vascular growth factors, metalloproteinases) and may lead to cancer progression and spread.[20] The mouse model of subcutaneous mesothelioma demonstrates that neutrophils promote the growth of tumour cells by inhibiting $CD8^+$ T cells.[21] Low lymphocyte counts are associated with aggrieved anti-tumour response, $CD8^+$ T-cell cytotoxicity and $CD4^+$ helper T-cell functions.[22] Platelets play an important and multifaceted role in cancer progression, releasing many cytokines, such as platelet-derived growth factor and platelet-reactive protein, which may promote haematogenous spread and invasion.[23] In our study, patients in the NLR-decrease group (60.8%) had a higher ORR than in the NLR-increase group (42.9%), and high pre-treatment values of and a dynamic increase in NLR were independent risk factors predicting a shorter OS. Multiple retrospective studies and meta-analyses have suggested that low pre-treatment PLR and SII may be a potential prognostic biomarker favouring the survival of cancer patients.[12,24–29] These were consistent with our results.

Given an important role for nutritional status in tumour immunotherapy, accumulating studies have explored the link between nutritional status-related factors and prognosis.[30,31] The scarcity of essential nutrients, such as amino acids, glucose and fatty acids, can induce altered metabolic reprogramming and functions in immune cells.[32] Some immune cells may lose their anti-tumour functions, while

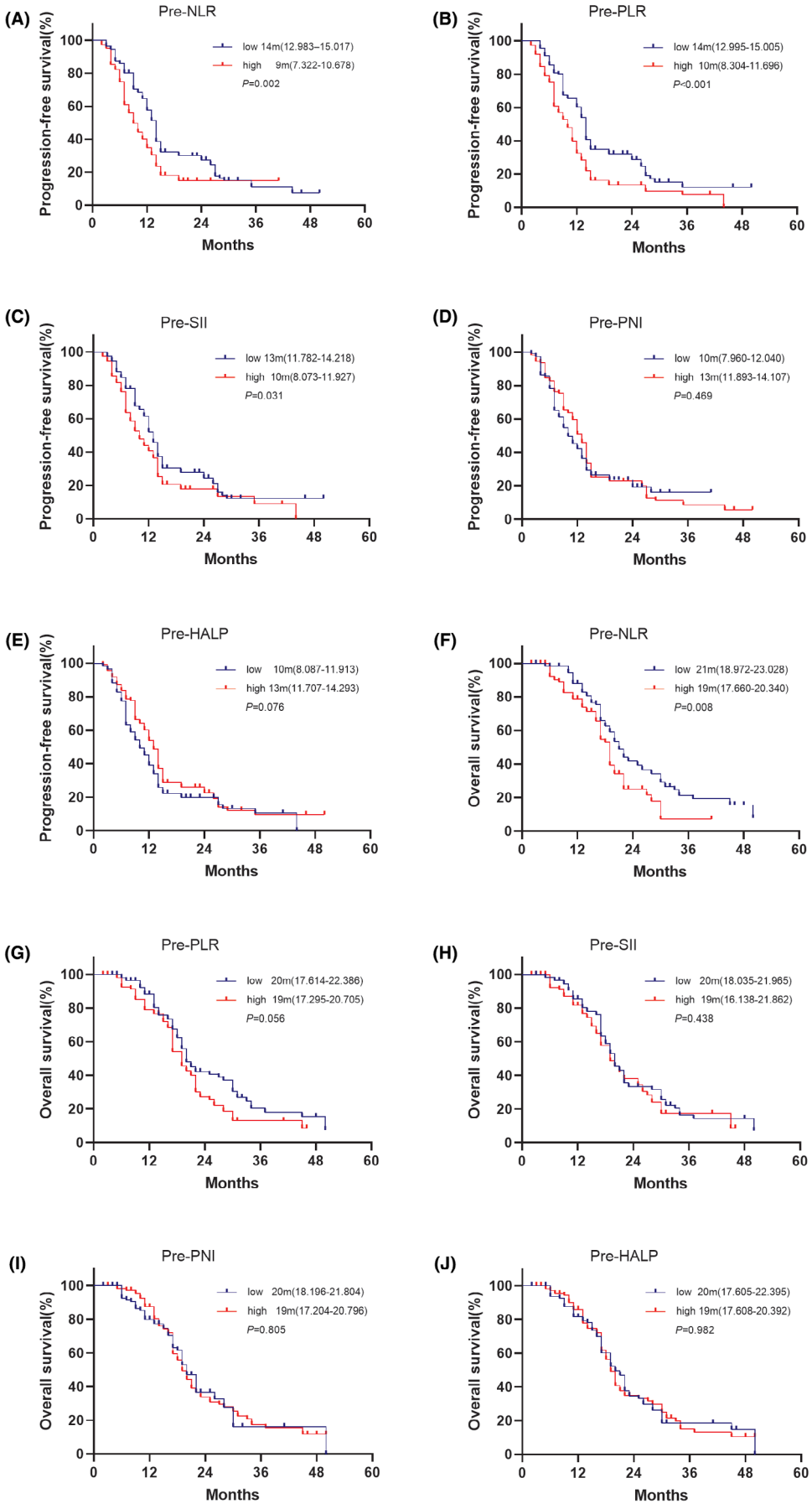

FIGURE 2 Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) comparing patients with advanced non-small cell lung cancer (NSCLC) patients who received death protein-1 (PD-1) inhibitor combined with chemotherapy as first-line according to pre-treatment inflammatory/nutritional indexes. (A, F) PFS and OS stratified by the baseline neutrophil-to-lymphocyte ratio (NLR) index, (B, G) PFS and OS stratified by the baseline platelet-to-lymphocyte ratio (PLR) index, (C, H) PFS and OS stratified by the baseline systemic immune-inflammation index (SII) index, (D, I) PFS and OS stratified by the baseline prognostic nutritional index (PNI) index, (E, J) PFS and OS stratified by the baseline haemoglobin, albumin, lymphocyte and platelet (HALP) index.

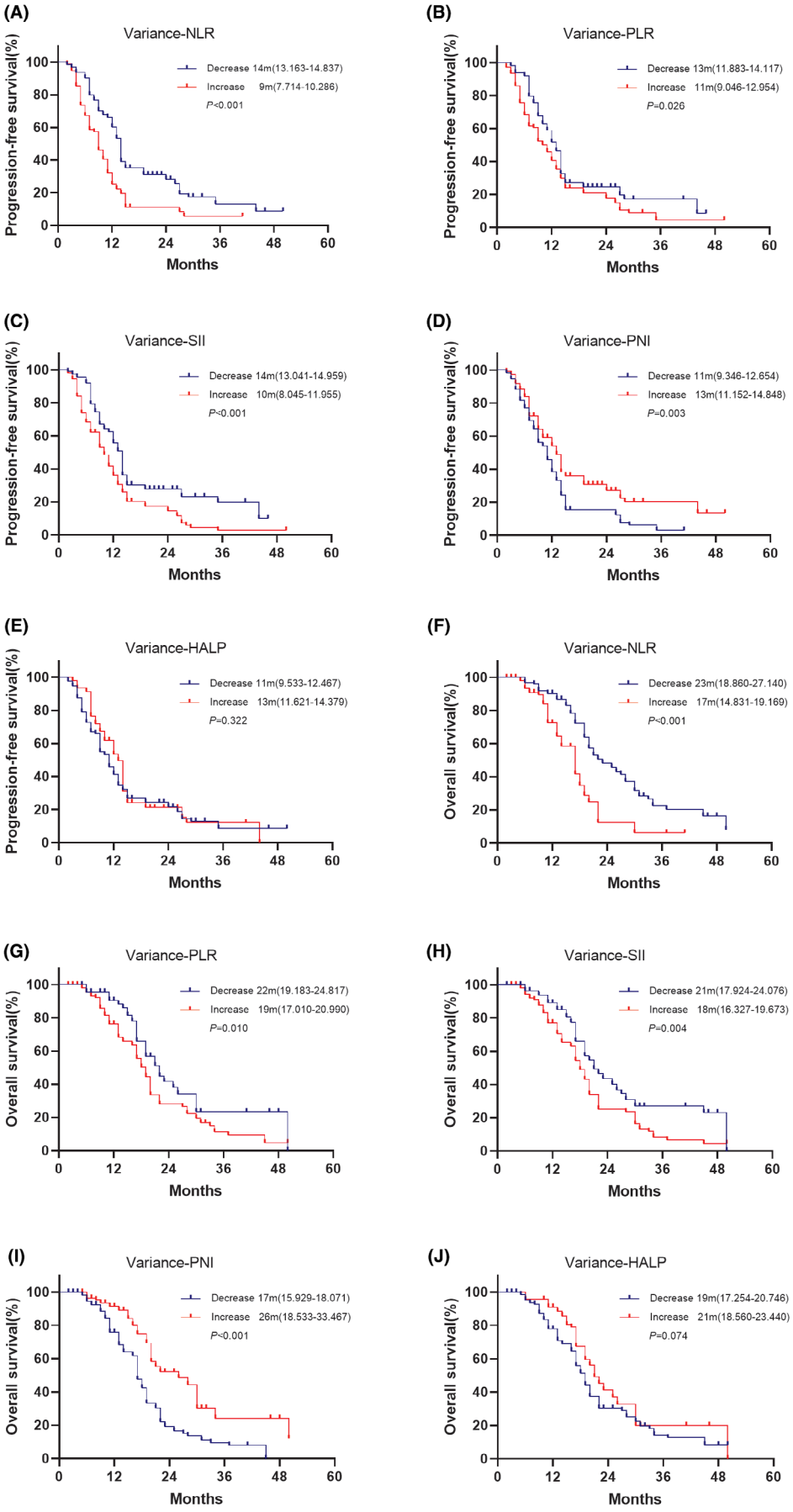

FIGURE 3 Kaplan–Meier curves for progression-free survival (PFS) and overall survival (OS) comparing patients with advanced non-small cell lung cancer (NSCLC) patients who received death protein-1 (PD-1) inhibitor combined with chemotherapy as first-line according to variances of inflammatory/nutritional indexes. (A, F) PFS and OS stratified by the baseline neutrophil-to-lymphocyte ratio (NLR) index, (B, G) PFS and OS stratified by the baseline platelet-to-lymphocyte ratio (PLR) index, (C, H) PFS and OS stratified by the baseline systemic immune-inflammation index (SII) index, (D, I) PFS and OS stratified by the baseline prognostic nutritional index (PNI) index, (E, J) PFS and OS stratified by the baseline haemoglobin, albumin, lymphocyte and platelet (HALP) index.

TABLE 4 Multivariate Cox regression analysis of PFS and OS

	PFS				OS		
	HR	(95% CI)	p		HR	(95% CI)	p
ECOG-PS				ECOG-PS			
0 score				0 score			
1 score	1.460	1.064–2.005	0.019	1 score	1.442	1.014–2.052	0.042
Pre-treatment indexes				Pre-treatment indexes			
NLR				NLR			
Low				Low			
High	1.326	0.893–1.970	0.162	High	1.635	1.121–2.386	0.011
PLR							
Low							
High	2.319	1.496–3.595	0.000				
SII							
Low							
High	0.964	0.606–1.532	0.876				
Variance indexes				Variance indexes			
NLR				NLR			
Decrease				Decrease			
Increase	1.421	0.956–2.110	0.082	Increase	1.663	1.064–2.599	0.026
PLR				PLR			
Decrease				Decrease			
Increase	1.397	0.900–2.167	0.136	Increase	1.691	1.068–2.677	0.025
SII				SII			
Decrease				Decrease			
Increase	1.731	1.063–2.819	0.027	Increase	0.936	0.579–1.513	0.787
PNI				PNI			
Decrease				Decrease			
Increase	0.904	0.641–1.275	0.566	Increase	0.611	0.415–0.900	0.013

Abbreviations: ECOG, Eastern Cooperative Oncology Group; HR, hazard ratio; OS, overall survival; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; PLR, platelet-to-lymphocyte ratio; PNI, prognostic nutrition index; PS, performance status; SII, systemic immune-inflammation index.

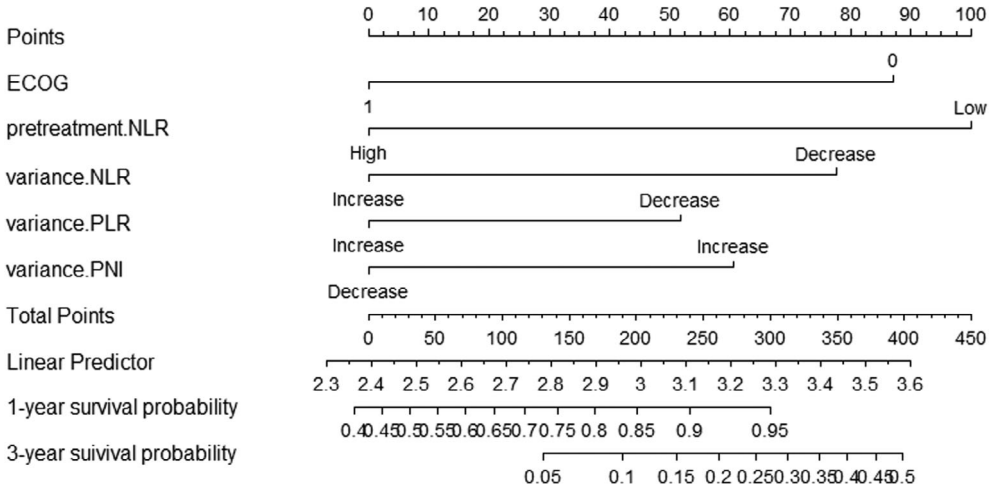

FIGURE 4 Nomogram for predicting advanced non-small cell lung cancer (NSCLC) patients who received death protein-1 (PD-1) inhibitor combined with chemotherapy as first-line. ECOG, Eastern Cooperative Oncology Group; NLR, neutrophil-to-lymphocyte ratio; PNI, prognostic nutritional index

others may differentiate or polarize into immunosuppressive phenotypes. Dysfunctional metabolism can also affect immune responses and lead to an immunosuppressive tumour microenvironment (TME).[33] As a sign of malnutrition, low levels of albumin and haemoglobin were associated with unfavourable clinical outcomes, but they were not predictors for disease control.[34–37] The HALP score has

been shown to be a prognostic indicator[38,39] for NSCLC patients who have undergone surgery[14] and adjuvant chemotherapy.[40] However, there are no recent studies looking into the relationship of the HALP score with prognoses of NSCLC patients treated with immunotherapy. In this study, we did not find the association between HALP and patient survival. Previous studies suggested that a low pre-treatment PNI score is an independent risk factor for the survival of advanced NSCLC patients receiving PD-1 inhibitor treatment,[41,42] which is confirmed by a recent meta-analysis.[43] Our results demonstrated significant improvement in the survival of patients showing a dynamic increase in PNI but without association with treatment efficacy.

Patients with advanced cancer are prone to malnutrition, which, in turn, leads to various complications, severe toxicity and shortened survival. Patients with good nutritional status may have better tolerance to following treatments, after the failure of first-line treatment. Nutritional status may be more relevant to long-term survival. Nutritional interventions should thus be considered for malnourished patients.

However, the prognostic value of pre-treatment indexes was questionable. For instance, Suh et al. found no difference in PFS between patients with NLR < 5 and NLR ≥ 5 at baseline among NSCLC patients treated with anti-PD-1 antibody.[44] These conflicting results may derive from differences in characters of recruited patients, such as age, sex and race. Maybe it is not proper to set a fixed cut-off value for NLR. Some research found reduced NLR after 6 or 12 weeks of treatment was connected to higher survival rates in two reports.[12,13] And in another study, NLR levels of non-responders increased by 6.6 compared to responders after two courses of nivolumab treatment.[45] NLR was also found to decrease by 0.09 every month among patients who had response to complete response/partial response (CR/PR) when receiving PL-(L)1 inhibitors.[46] Consistently, our study found decreased NLR was associated with higher ORR, while no correlation was found between pre-treatment NLR and ORR. In addition, dynamic changes in PLR, SII and PNI were found to be related to PFS and the OS, while it was not the case for baseline scores. It thus appears that dynamics rather than baseline levels of the clinical parameters could accurately predict the survival outcomes.

In this study, we used a nomogram to estimate the 1 and 3-year survival rates of advanced NSCLC patients who received PD-1 inhibitor combined with chemotherapy. We then conducted internal verification to check the nomogram and found the C-index to be 0.718 (95% CI, 0.670–0.766), indicating that the accuracy of the prediction model is high.

PD-L1 expression and tumour mutational burden (TMB) are approved by the FDA as indicators for predicting the efficacy of immunotherapy in NSCLC. However, the failure of Checkmate 026 indicates PD-L1 expression may not predict prognosis accurately in all patients.[6] The ORRs of NSCLC patients with positive PD-L1 expression were 38.3%–46.1% when receiving first-line monotherapy with PD-1/PD-L1 inhibitors.[2,47,48] Estimation of TPS by pathologists may lead to intra/inter-observer bias. Heterogeneity may exist in different regions of the tumour tissues, and the dynamic changes in the expression of PD-L1 in tumours have been documented.[49] In our study, although PD-L1 positive patients tended to be associated with better PFS and OS, the differences failed to reach statistical significance, which may arise from missing values. For TMB, the ORR in NSCLC patients with high TMB treated with nivolumab plus ipilimumab was only around 33%–48%.[7,50] Lack in standard test methods and high cost limit application of TMB in clinical settings. In 2017, FDA approved Pembrolizumab for the treatment of all patients with MSI-H/dMMR, regardless of tumour type. But it may not be the case in lung cancer patients, because of low incidence.[51] It is thus indispensable to build a multidimensional predicting model for individual immunotherapy, not only due to complex interactions between tumour cells and TME, but also nutritional and inflammatory state of hosts.

Our study has several limitations that should be considered when evaluating the research results. First, the study was a single-centre retrospective study with a limited sample size. Multi-centre prospective studies are needed to confirm our results. Second, single chemotherapy may cause changes in peripheral blood indexes, suggesting only patients receiving chemotherapy should be included in the positive control group. Unfortunately, in our study we could not recruit these patients for the positive control group because chemotherapy alone as first-line treatment is rare in current clinical practice. Third, the standard cut-off values for these indexes have not been confirmed. While some authors selected the median values, others only chose the values previously reported by previous studies. Finally, data were missing from a large portion of patients, since the detection of PD-L1 expression is not necessary before initiation of first-line chemotherapy combined with immunotherapy.[52]

While inflammatory and nutritional indexes could serve as independent predictors of long-term survival, inflammatory indexes are additionally linked to treatment response. Dynamics of the explored clinical parameters were stronger than baseline values in predicting survival in advanced NSCLC patients receiving PD-1 inhibitor combined with chemotherapy as first-line.

4 | METHODS

4.1 | Patients

We performed a retrospective analysis of consecutive patients with advanced NSCLC at the Shanghai Pulmonary Hospital from March 2017 to March 2019. Patients were eligible for inclusion in this study if they had received anti-PD-1 antibody combined with chemotherapy treatment as first-line treatment. Combination chemotherapies were based on platinum doublet chemotherapies, including paclitaxel/nab-paclitaxel, and pemetrexed in accordance with the tumour histology. All study participants had to meet the criterion: (i) at least 18 years old; (ii) histologically or cytologically confirmed unresectable NSCLC (based on the International Association for the Study of Lung Cancer guidelines, 8th edition); (iii) driver-genes including epidermal growth factor receptor (EGFR)/ROS proto-oncogene 1 (ROS1)/anaplastic lymphoma kinase (ALK) wildtype; (iv) ECOG-PS <3; and (v) exhibited

disease progression after receiving therapy once every 3 weeks for at least two courses.

Patient clinical information was obtained from the patients' electronic medical records and the following were included: age at diagnosis, sex, baseline ECOG-PS score, pathology type, stage, sites of distant metastases, types of driver mutations, treatment regimen, best response to treatment, date of progression, date of death, and date of the last follow-up. Routine blood test results and the blood biochemical index scores at baseline and 6 weeks after treatment (0 weeks, 6 weeks) were also collected. Data of PD-L1 expression of the tumour sample at diagnosis detected by immunohistochemistry according to standard practice (clone 22C3; DAKO) was collected. Considering the percentage of viable tumour cells with partial or complete membrane staining, the tumour proportion score (TPS) of ≥1% was defined as PD-L1 positive. Patients were accordingly divided into three groups according to the PD-L1 expression: positive, negative and unknown. This study was approved by the Institutional Ethical Review Board of the Shanghai Pulmonary Hospital and permitted waiver of the written informed consents because of the retrospective and anonymous study design.

4.2 | Definition of inflammatory and nutritional indexes

The inflammatory markers are defined as follows: NLR = the ratio of neutrophil count to lymphocyte count(10^9/L); PLR = the ratio of platelet count(10^9/L) to lymphocyte count(10^9/L); SII = platelet count (10^9/L) × NLR; The PNI = sum of albumin value (g/L) and five times lymphocyte count (10^9/L); HALP = Haemoglobin (g/L) × Albumin (g/L) × Lymphocytes(10^9/L)/Platelets (10^9/L). For all indexes, the median value was calculated and used as the cut-off value and handled as binary variables in the analysis. Based on the difference between the baseline scores and the score at 6 weeks (after two treatment cycles) collected before anti-PD-1 antibody treatment, patients were clustered into two groups (increase and decrease).

4.3 | Assessment

According to the immune response evaluation criteria in solid tumours (iRECIST) guidelines, the ORR is defined as the percentage of patients with the best overall response of CR or PR. PFS is defined as the time from PD-1 inhibitor treatment until disease progression or death. OS is defined as the time from the disease onset until death from any cause or the last follow-up, whichever came first.

4.4 | Statistical analysis

Categorical variables were summarized as numbers and percentages and were statistically measured using the chi-square or Fisher's exact test. Continuous variables with non-normal distribution were shown as median and interquartile range (IQR). The relationship between the dependent variable and multiple independent variables was explored using binary logistic regression. The Kaplan–Meier method was used to draw the survival curves to estimate the PFS and OS probabilities. The Cox regression analysis was used to analyse the prognostic factors. Lastly, the nomogram and the prediction model were generated using the R programming language. All tests were two-sided, and the statistical significance was set at $p < 0.05$. IBM SPSS 22.0 (IBM Corp., Armonk, NY, USA), R (version x64 4.2.0) and GraphPad Prism 9.0.0 were used for the statistical analyses and display.

AUTHOR CONTRIBUTIONS

Conceptualization: Qiyu Fang, Jie Zhang and Caicun Zhou; methodology: Qiyu Fang, Wei Li, Jia Yu and Bin Chen; Formal analysis and investigation: Wei Li, Jia Yu, Jie Luo, Qinfang Deng; Writing—original draft preparation, Qiyu Fang; Writing—review and editing, Qiyu Fang, Yayi He and Jie Zhang; Resources: Jie Zhang; Supervision Jie Zhang and Caicun Zhou; All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The datasets used and/or analysed during the current study are available from the corresponding authors on reasonable request.

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