Acta Scientific CANCER BIOLOGY (ISSN: 2582-4473)

Volume 6 Issue 5 August 2022

Research Article

Dynamical Inflammatory Factors: More Promising Markers in Advanced Tumors

Ziwei Guo and Jun Liang*

Peking University International Hospital, Beijing, China

***Corresponding Author:** Jun Liang, Peking University International Hospital, Beijing, China.

Received: July 12, 2022

Published: July 29, 2022

Abstract

Introduction: Many biomarkers to predict clinical response and prognosis are available but there are still many issues to be further solved. We showed the correlation between dynamical inflammatory factors and clinical response.

Methods: We collected inflammatory factors from patients diagnosed advanced solid tumors. The endpoints were the agreement of therapeutic response, disease control rate, progress-free survival and overall survival.

Results: 41 patients enrolled. AUC was 0.927, 0.957 and 0.160 in dynamic biomarkers ($p < 0.001$) compared with imaging assessment. The disease control rate was 45.2% ($p < 0.05$). Only shorter median progress-free survival can be observed in higher increased neutrophil-to-lymphocyte significantly. The median overall survival was 7 months (95% CI: 4.27-9.73), but no significance.

Conclusion: Dynamical decreased platelet-to-lymphocyte and neutrophil-to-lymphocyte ratio or increased lymphocyte-to monocyte ratio are positively associated with the radiograph assessment, and that lower neutrophil-to-lymphocyte ratio leads to shorter progress-free survival statistically and a trend of shorter overall survival.

Keywords: Dynamic Biomarkers; Immunotherapy; Clinical Benefit; Prognosis

Introduction

It has been several years since programmed cell death/ligand 1 (PD-1/PD-L1) inhibitors brought the remarkable activity in a number of malignancies [1,2]. Considerable efforts are underway to find effective, convenient, and economic biomarkers based on individual characteristics. Several biomarkers are being evaluated, including tumor mutation burden (TMB), microsatellite instability (MSI) status, the overexpression of PD-L1, systematic scoring of multiple immune cells and cytokines in the tumor microenvironment, etc. In recent studies [3-5], we also demonstrated that co-targeting RANKL (TNFSF11), tissue-specific immunosuppressive tumor microenvironments (TMEs), and lack of PD-L1 mediated immunosuppression can play different roles in the development of immunity. For many years, several investigators [6-8] clearly illustrated that a stronger role of higher TMB and more neoantigens can help to explain and understand the mechanism of efficiency.

Although blood TMB ≥ 16 and cutoff ≥ 10 were the promising outcomes in POPLAROAK study [9] and Checkmate 227 [10], the detection of TMB and PD-L1 is not universal. MSI+ showed 46% objective remission rate (ORR) in second line and higher and achieved the characteristic of high tumor mutation burden in a clinical trial of Keynote 016 [11]. The expression of PD-L1≥ 50% was as the first line in 2019 National Comprehensive Cancer Network (NCCN) guideline and in the phase 3 Keynote 042 study [12], in which overall survival (OS) was 20.0 months,17.7 months,16.7 months from PD-L1 tumor proportion score (TPS) ≥ 50% (HR 0.69,95%CI 0.56-0.85), ≥20% (HR 0.77) and ≥1% (HR 0.81). Conversely, PD-L1, a dynamic index, is influenced by numerous factors including therapeutic strategy, the disease itself,

and immune microenvironment. The study of KEYNOTE 001 [6] illustrated the better clinical outcome in the group of the higher expression of PD-L1. However, it was no significance in variable expression levels in Checkmate 057 and 017 [13]. There were obvious limitations and diagnostic inconsistency between the pathologic histology and biopsy. Taken together, although unclear reasons have been identified, emerging biomarkers have to further refine clinical response.

There is growing experience, inflammation as a major driving factor, to promote the development and progression of cancers [14]. As a portion of inflammatory process, platelet reflected the response of inflammation and helped clinical decision in solid cancers [15]. System inflammatory factors of platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte (NLR) and lymphocyte-to monocyte ratio (LMR) strongly established to predict prognosis [16-18]. The published articles [19,20] mainly demonstrated that pre-operative NLR and PLR predicted the disease-free survival (DFS). Few pieces of researches [21,22] showed the shorter progress free survival (PFS) and OS with baseline high NLR. Similarly, NLR was an independent factor in increasing risk of disease progression [23,24]. Unfortunately, there is no conclusive evidence on the dynamic assessment.

In our retrospective study, we collected several different types of tumors to hypothesis dynamic biomarkers to more predict survival outcomes and clinical benefit from a small population who received multi-cycles of immunotherapies. Our findings highlight the potential for clinical response and outcomes as latter lines among advanced and refractory solid cancers.

Materials and Methods

This study was approved by the Institutional Review Boards of Peking University International Hospital (Ethic number 2019-035(BMR)). And written informed consent forms were obtained from all patients. The study conforms to recognized standards of Declaration of Helsinki.

Patient selections

We collected data during immunotherapy in advanced or refractory cancers, including non-small cell lung cancer (NSCLC), extensive-disease small cell lung cancer (ED-SCLC), primary hepatocellular carcinoma (HCC), gastrointestinal cancer and sarcoma, etc. The assessment was performed using computerized tomography (CT) or magnetic resonance (MR) by two independent radiologists. These stages were determined by 2020 National Comprehensive Cancer Network (NCCN) guidelines [25-30]. The inclusion criteria met as follows: patients aged 18-year or older, acceptable serum chemistry tests, measurable target lesion(s), and none of whom used steroid. And exclusion criteria were autoimmune disease, immunosuppressive drugs, previous therapeutic regimen with antibodies or drugs targeting checkpoint pathways, positive test human immunodeficiency virus or interstitial lung disease (patients with a history of pneumonia were not excluded).

Study design

Patients received PD-1 inhibitors as intravenous infusions every three weeks until disease progression or unacceptable toxic events. Therapeutics after progression disease (PD) were permitted if a patient had clinical benefit assessed by oncologists and radiologists (continuing disease or symptom control despite radiographic progression). This decision was based on evidences [31,32] in which some patients might benefit from long-term stabilization in spite of initial evidence of PD. PLR% (dynamic PLR) = PLR*(post-treatment-baseline)/baseline, NLR% (dynamic NLR) = NLR*(post-treatment-baseline)/baseline and LMR% (dynamic LMR) = LMR*(post-treatment-baseline)/baseline. From these patients, 38 patients received ≥ four cycles therapies and 31 specimens had radiographic evaluation. Refractory cancer was defined as either more than third line or the patients in serious medical conditions. These measurable lesions were performed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1) [33]. Clinical data was analyzed from medical records. The endpoints were the consistency of therapeutic response, disease control rate (DCR), ORR, PFS and OS. DCR is considered as the total of disease stabilization plus complete remission as the first or second assessments in all patients of immunotherapy from the analysis. PFS is defined as the time from the first dose of immunotherapy to the date of first documented tumor progression or death from data analysis. And OS was defined as the time from the date of the first dose to the date of death from any cause or last known date alive for patients being alive at the time of analysis. DCR is considered as the total of disease stabilization plus complete remission and partial remission as the first or second assessments in all patients of immunotherapy from the analysis. PFS is defined as the time from the first dose of immunotherapy to the date of first documented tumor progression or death from data analysis. And OS was defined as the time from the date of the first dose to the date of death from any cause or last known date alive for patients being alive at the time of data analysis.

Statistical analysis

Prism 7 (Graphpad Software, San Diego, CA, USA) and IBM SPSS (Version 21.0; SPSS Inc, Chicago, IL, USA) were used for data analysis and graphics. Median follow-up time was six (range 0.8-28) months. Receiver-operating-characteristic (ROC) curves were used by SPSS to analyze PLR%, NLR%, and LMR%. The Youden index (sensitivity + specificity - 1) was the optimal cutoff point. And the p-value of compared ROC curves used Medcalc (v. 19.5.3) software to analyze. Survival curves were estimated using the Kaplan-Meier method, and the log-rank test. $P \leq 5$ was considered significant.

Results

Baseline characteristics of the patients

41 patients received median 4 (range from 1 to 14) cycles of immunological drugs, with median 6 months follow-up time. 11 patients continued immunotherapies, 12 patients progressed and 12 patients died (Figure 1). Nearly half, had two prior systemic therapies and PS≥2. Patients' clinical and pathological characteristics were listed in table 1. The patients had the median 63 years old (range 32-83 aged). And 68% of the patients were men and 100% Asian. 63% patients were active smokers. Tumor types included NSCLC (47%) and gastrointestinal cancer (29%), respectively. Twelve percent spread to central nervous system (CNS) and 29% to at least two lesions in metastases. And the more common lesions are lung (39%) and distant place lymph nodes (32%), respectively.

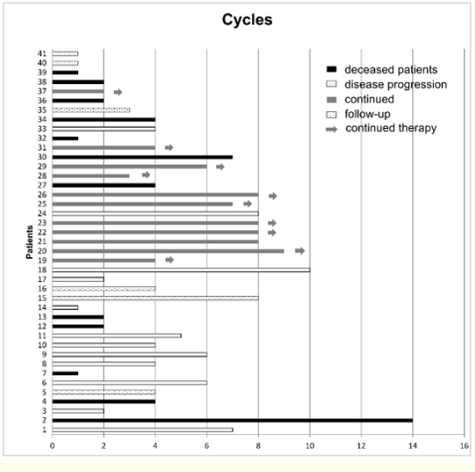


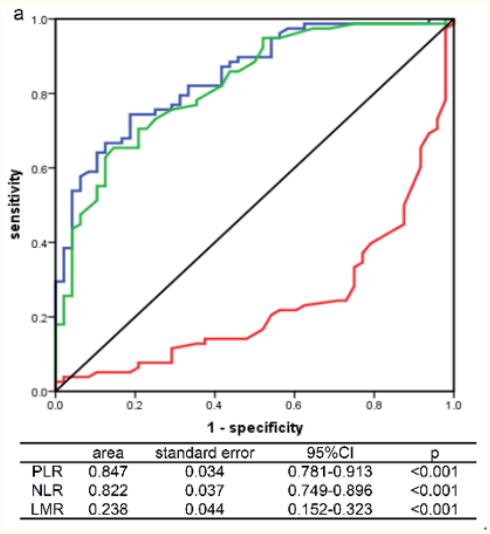
Figure 1: Cycles of immunotherapies in 41 patients. Each bar represented an individual patient. Black bar, deceased patients; light grey bar, patients with disease progression; dark grey with an arrow, patients who continued immunotherapies and dotted bar with follow-up. Arrows were be defined as continued immunotherapy and not progression or intolerant adverse events.

Age at start immunotherapy (years)	**Median**	**63**
	Range	32-83
Gender, n (%)	Female	13(32%)
	Male	28(68%)
ECOG PS*, n (%)	0	2(5%)
	1	20(49%)
	2	9(22%)
	3	10(24%)
Smoking history$^{\phi}$, n (%)	Heavy	26(63%)
	Never/light	15(37%)
Histologic type, n (%)	Non-small cell lung caner	19(47%)
	Small lung cell cancer	5(12%)
	Gastrointestinal cancer	12(29%)
	Hepatocellular cancer	3(7%)
	Soft-tissue cancer	2(5%)
Targetable driver mutations, n (%)	EGFR	2(5%)
	KRAS	4(10%)
	Wild-type	17(41%)
	Unknown	18(44%)
Prior lines of therapy	Median	2
	Range	0 - 6
Site(s) of metastatic disease$^{¤}$, n (%)	Bone	10(24%)
	Brain	5(12%)
	Liver	11(27%)
	Lung	16(39%)
	Soft Tissue	11(27%)
	Lymph nodes$^{\#}$	13(32%)
	Others$^{\&}$	18(44%)
Metastatic sites	>/ = 2	29(71%)
	<2	12(29%)
$^{\phi}$Heavy (≥ 10 pack-years); never/light (< 10 pack-years).		
$^{¤}$Site(s) of metastatic spread present at time of initiation of immunotherapy.		
$^{\#}$Including distant lymph node(s).		
$^{\&}$Including adrenal, pleura, skin, peritoneum, thyroid, ovary.		

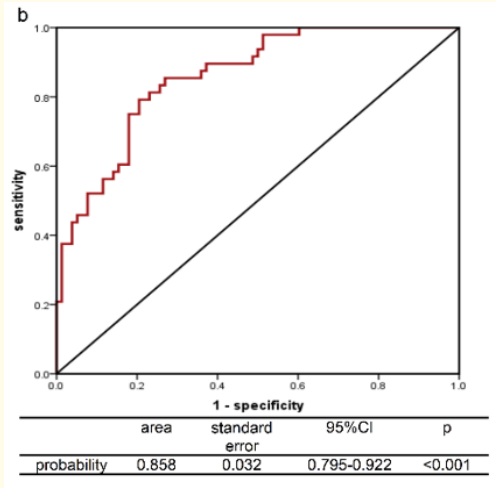
Table 1: Baseline Characteristics (n = 41).

Decreased NLR% is more sensitive on clinical efficiency

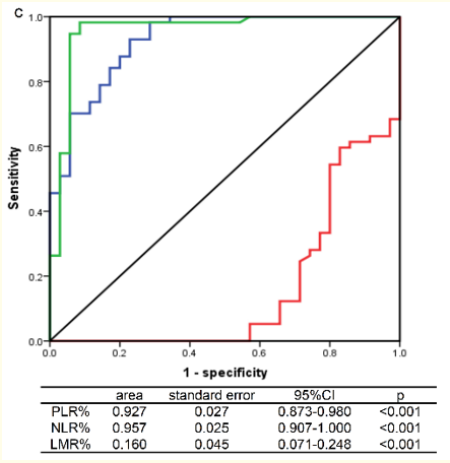
Area under the curve (AUC) of PLR, NLR, and LMR were 0.847, 0.822, and 0.238 (Figure 2 A, $p < 0.001$) and combined diagnosis 0.858 (Figure 2C, $p < 0.001$), respectively. The best cutoff value is 172.8 (sensitivity, 81.25%; specificity, 74.36%), 4.1 (sensitivity, 85.42%; specificity, 65.38%) and 2.7(sensitivity, 72.92%; specificity, 75.64%) on PLR, NLR and LMR. And the AUC was 0.927, 0.957, and 0.160 in the groups of PLR%, NLR%, and LMR% (Figure 2B) and combined diagnosis 0.965 (Figure 2D) compared with imaging assessment, respectively. The optimal cut-off levels were determined to be -1.4 (sensitivity, 77.14%; specificity, 92.98%), -7.1 (sensitivity, 91.43%; specificity, 98.25%) and 14.3 (sensitivity, 65.71%; specificity, 94.74%) for PLR%, NLR% and LMR%. *P*-value was less than 0.001.



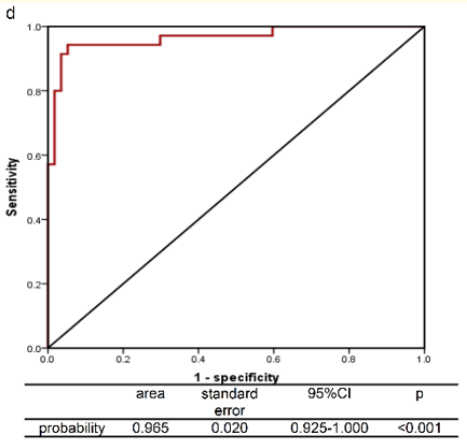
	area	standard error	95%CI	p
PLR	0.847	0.034	0.781-0.913	<0.001
NLR	0.822	0.037	0.749-0.896	<0.001
LMR	0.238	0.044	0.152-0.323	<0.001



	area	standard error	95%CI	p
probability	0.858	0.032	0.795-0.922	<0.001



	area	standard error	95%CI	p
PLR%	0.927	0.027	0.873-0.980	<0.001
NLR%	0.957	0.025	0.907-1.000	<0.001
LMR%	0.160	0.045	0.071-0.248	<0.001



	area	standard error	95%CI	p
probability	0.965	0.020	0.925-1.000	<0.001

Figure 2: ROC curves of PLR, NLR, and LMR (a) and the probability of these parameters (b), NLR%, PLR% and LMR% (c) and the probability of them (d) for advanced solid cancers. Blue lines were PLR% or PLR, green lines were NLR% or NLR, and red lines were LMR% or LMR.

DCR can be significant in each dynamic group

We could find each patient in groups of PLR% (Figure 3a), NLR% (Figure 3b), and LMR% (Figure 3c) and radiographic response (Figure 3d and 3e). The DCR was 45.2% (14 of 31 patients) and the ORR was 9.7% (3 of 31 patients), as illustrated in figure 4a, 4b and 4c. From these, the patients had 3 (10%) cases partial response (PR), 11 (35%) stable disease (SD), and 17 (55%) PD ($p = 0.729$, 0.875 and 0.009 in group of PLR% in figure 4a; $p = 0.403$, 0.585 and 0.001 in group of PLR% in figure 4b; $p = 0.421$, 0.045 and 0.001 in group of PLR% in figure 4c) as the best response on radiographic tests.

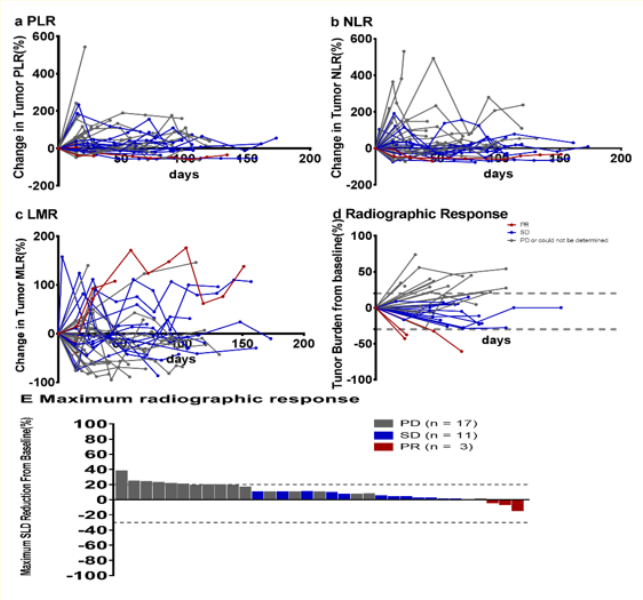


Figure 3: Clinical responses of immunotherapies. The PLR, NLR, and LMR that became Y axes were shown in 3a-3c. Radiograph were shown in 3d-3e. These were measured at regular intervals. The values were the maximum change from the baseline measurements of each measurable tumor. Each line and each bar represented one patient.

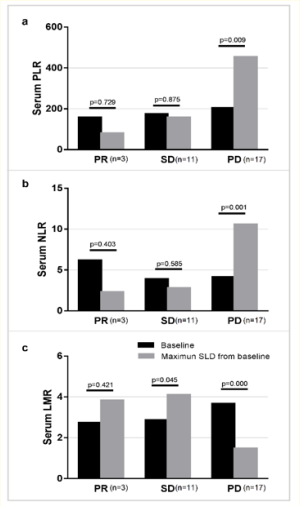
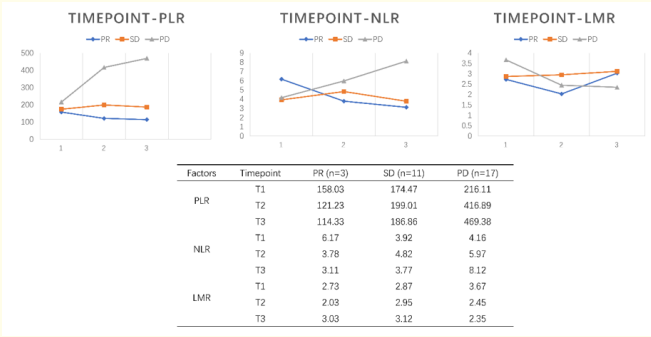


Figure 4: Therapeutic effect and clinical assessment on PLR, NLR, and LMR. PLR, NLR and LMR (a-c) evaluated in baseline (time 1, black) and at tumor re-assessment of maximum SLD from baseline (the first re-assessment or second re-assessment, dark grey) according to clinical response (PR, SD, and PD); P-value is reported on the top of the columns.

Meanwhile, among the 31 patients with malignant cancers and complete PLR, NLR, and LMR data over 3 time points of baseline, first assessment, and second assessment, PR, SD, and PD were predefined. Figure 5 displays the PR, SD, and PD patterns and mean PLR, NLR, and LMR scores by time from immunotherapy. Most patients (n = 17 [55%]) had high PLR and NLR scores throughout (always high), whereas 3 patients (10%) had low PLR and NLR scores throughout (always low). In addition, 11 (35%) patients with SD had high fatigue that resolved (high then resolves) in group of PLR and NLR, The opposite trend of results was observed in the LMR group (Figure 5).



Factors	Timepoint	PR (n=3)	SD (n=11)	PD (n=17)
PLR	T1	158.03	174.47	216.11
	T2	121.23	199.01	416.89
	T3	114.33	186.86	469.38
NLR	T1	6.17	3.92	4.16
	T2	3.78	4.82	5.97
	T3	3.11	3.77	8.12
LMR	T1	2.73	2.87	3.67
	T2	2.03	2.95	2.45
	T3	3.03	3.12	2.35

Figure 5: Assessment patterns over 3 time points with a data table (n = 31). Mean PLR (a), NLR (b), LMR (c) scores for each assessment pattern (PR, SD, PD) are colored. T1, time 1 - baseline; T2, time 2 - first assessment; T3, time 3 - second assessment.

Decreased NLR% got longer PFS and a trend of better OS.

The five-month PFS was 22.0% (9 of 41 patients, 95% CI: 2.892 to 5.108) and 23.7% (9 of 38 patients, 95%CI: 2.934 to 5.066) in the groups of PLR%, NLR%, and LMR% (Figure 6). The median follow-up time was 6 months (range from 0.8 to 28). Each case was followed for six months at least. Only low NLR% can get longer PFS statistically. Moreover, the median PFS was 5 vs. 4 months, 5 vs. 3 months, and 4 vs. 5 months on low vs. high PLR%, NLR% and LMR% (hazard ratio by the log-rank test: 0.76, 95%CI: 0.32-1.79, p = 0.352; HR: 0.49, 95%CI: 0.23-1.06, p = 0.019; HR: 1.61, 95% CI: 0.68-3.80, p = 0.106) (Figure 6). However, we did not see the longer PFS in PLR, NLR or LMR. The OS at seven months was 39.0% (16 of 41 patients, 95%CI: 4.266-9.734) from figure 7A and 36.8% (14 of 38 patients, 95%CI: 5.206-8.794) from figure 7B-7D. For 41 patients, the mOS was 7 months (95% CI: 4.27-9.73, standard error

1.39, figure 7A), but in the group of PLR%, NLR% and LMR%, the mOS was not reached statistical outcome (p = 0.226, 95%CI:0.251-3.045, HR 0.875 in figure 7B; p = 0.099, 95%CI:0.185-1.515, HR 0.530 in figure 7C; p = 0.369, 95%CI:0.200-3.826, HR 0.875 in figure 7D, respectively). Low NLR% was associated with longer PFS and a trend towards longer OS.

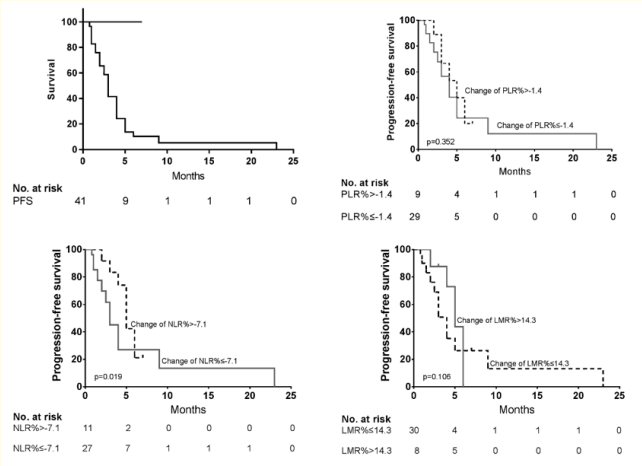


Figure 6: PFS was shown in the groups of PLR%, NLR%, and LMR%.

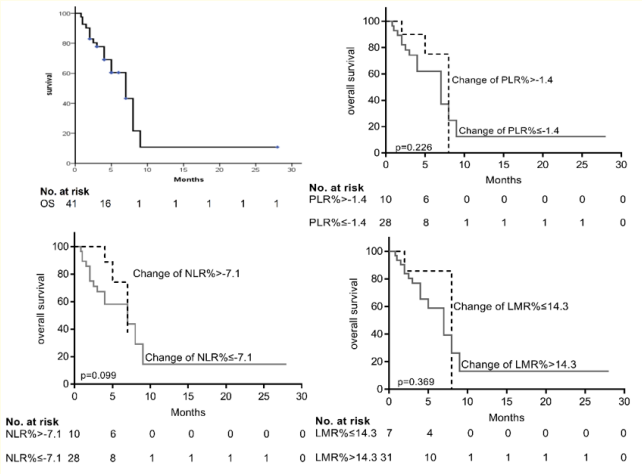


Figure 7: OS was shown in the groups of PLR%, NLR%, and LMR%.

Discussion

In our study, we showed that the low NLR% predicted the longer PFS and higher DCR for patients on the latter lines of advanced or refractory tumors. Besides, a trend towards longer OS was observed in low PLR%. Recent work [3-12] highlighted the importance of immune response with an emphasis on a research hotspot for predictive biomarkers such as TMB, MSI+, PD-L1, co-targeting RANKL, Tissue-specific TMEs and Lacking of PD-L1 mediated immunosuppression. With the progression of malignant diseases, inflammatory factors have been applied to predict clinical outcomes for patients who underwent surgical resection and received anti-PD-1 therapies in different types of tumors of few studies [19,20,34,35]. Despite these successful researches, it has remained a challenge clinically. Based on these observations, the study aimed to perform clinical response and prognosis in groups of PLR %, NLR%, and LMR%.

Firstly, PLR and NLR are strongly associated with clinical responses on the latter lines of immunotherapies. Different studies [19,22,24] had demonstrated that high NLR was associated with low response rate (OR for log (NLR) = 0.17, 95%CI: 0.04-0.68, p = 0.013). High PLR is a poor predictor for PFS and OS of endometrial cancer [34], older patients with metastatic colorectal [29], soft-tissue sarcoma [35], metastatic melanoma [24], etc. However, there is little study to explore the value of dynamical NLR. We found that decreased PLR% and NLR% was positively associated with the radiograph assessment. Nevertheless, this point was different from previous reports because we explore the dynamical monitoring during immunotherapy. Unfortunately, The ORR get no significance compared with previous studies [19,24]. The reason may be samples collection, different antibodies, different cut-off points in our study.

Interestingly, it was obvious that high LMR predicted a good clinical outcome. Few researches [34,36] illustrated that a low LMR before operation had statistically worse 5-year OS (72% high vs 83% low based on cut-off 0.19). Also, low LMR (2-year OS; 58% vs 80%, log-rank p = 0.007) was associated with poor OS in older adults of age ≥65 with solid cancers [37]. Conversely, A study [38] indicated that high LMR (cutoff 0.22) was connected by shorter OS in advanced gastric cancer. In the above studies, there was debate about the correlation between LMR and clinical outcomes. And, there was no correlation between LMR and clinical prognosis

during immunotherapies. In our research, the optimal cut-off level of LMR was similar to these previous researches [34,36,37]. And the correlation of high LMR and longer survival also was similar to previous articles [36,37]. We extend the high LMR connecting with longer PFS and OS in radiographic assessment.

Furthermore, we got longer PFS statistically in decreased NLR% and with a trend towards shorter PFS in increased PLR% and decreased LMR%. But there is no OS difference between these factors. A retrospective analysis [24] of 97 consecutive patients reported that only baseline NLR ≥ 5 was significantly associated with poor prognosis compared with NLR < 5 independently (median PFS: 2 vs.9 months, 95%CI: 1.0-3.0; 2.4-15.6, p< 0.0001; median OS: 2.9 vs.16 months, 95%CI: 1.5-4.3; 7.5-24.5, p < 0.0001). In a very recent publication in "Lung Cancer" [22] was also consistent with reports of melanoma patients in whom high NLR led to worse survival. However, whether and how the dynamic factors, not the baseline alone, affect the clinical outcomes is unknown. Our findings confirmed the positive association of improved PFS in low NLR% not in OS. The plausible explanations for these negative results are the small samples, the timing of treatment, poor performance status, heterogeneous areas, and non-white races, etc.

The biggest limitation we observed in our study was the small samples. The retrospective design was the limitation and had inability to examine proper and regular examinations. The time to complete blood count within each specimen was also a limiting factor. While an effort was made, each sample became an integral follow-up and data for detailed information. This finding could have predictive clinical response and prognosis but also need additional confirmation.

The important strengths of our study included the setting within integrated therapeutic models with meticulous follow-up data. Thus, we performed a historic cohort of patients. Also, we were able to get reliable indications for radiographic assessment and complete blood routine, which is the simple, rapid, accurate, and affordable test.

Conclusion

In conclusion, the low NLR% and high LMR predict the better clinical response and the longer survival for patients. The inflammatory factors are rapidly available biomarkers (low PLR% and NLR%) to help clinical assessment. Further investigation in a large sample is warranted to develop and confirm the clinical benefit.

Acknowledgments

None.

Conflict of Interest Statement

The author reports no conflicts of interest in this work.

Funding Statement

The work was supported by Peking University International Hospital YN2018QN09.

Data Availability Statement

I do not intend to share the data because our data was made without the informed consent of all patients about the section of data sharing in an electronic medical record system.

Ethical Statement

Ethics and informed consent to participate were obtained from all participants in the study. The consent was written and can be found in every medical history. The study conforms to recognized standards of Declaration of Helsinki.

Bibliography

1. Herbst RS., *et al*. "Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients". *Nature* 515.7528 (2014): 563-567.

2. Brahmer JR., *et al*. "Safety and activity of anti-PD-L1 antibody in patients with advanced cancer". *The New England Journal of Medicine* 366.28 (2012): 2455-2465.

3. Amanda JO., *et al*. "Tissue-specific tumor microenvironments influence responses to immunotherapies". *Clinical and Translational Immunology* 8.11 (2019): 1094.

4. William CD., *et al*. "Dual targeting of RANKL and PD-1 with a bispecific antibody improves anti-tumor immunity". *Clinical and Translational Immunology* 8.10 (2019): 1081.

5. David GW., *et al*. "Impact of pre-therapy glioblastoma multiforme microenvironment on clinical response to autologous CMV-specific T-cell therapy". *Clinical and Translational Immunology* 8.11 (2019): 01088.

6. Shavedian N., *et al*. "Previous radiotherapy and the clinical activity and toxicity of pembrolizumab in the treatment of non-small-cell lung cancer: a secondary analysis of the KEYNOTE-001 phase 1 trial". *Lancet Oncology* 18.11 (2017): 865-903.

7. Antonia SJ., *et al*. "Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): A multicentre, open-label, phase1/2 trail". *Lancet Oncology* 17.7 (2016): 883-895.

8. Hellmann MD., *et al*. "Nivolumab plus ipilimumab as first-line treatment for advanced non-small-cell lung cancer (CheckMate 012): Results of an open-label, phase 1, multicohort study". *Lancet Oncology* 2017;18 (1): 31-41.

9. Gandara DR., *et al*. "Blood-based tumor mutational burden as a predictor of clinical benefit in non-small-cell lung cancer patients treated with atezolizumab". *Nature Medicine* 24.9 (2018): 1441-1448.

10. Hellamnn MD., *et al*. "Nivolumab plus Ipimumab in Lung Cancer with a High tumor Mutational Burden". *The New England Journal of Medicine* 378.22 (2018): 2093-2104.

11. Le DT., *et al*. "PD-1 Blockade in Tumors with Mismatch-Repair Deficiency". *The New England Journal of Medicine* 372.26 (2015): 2509-2520.

12. Lopes G., *et al*. "Pembrolizumab vs Platinum-Based Chemotherapy as First-Line Therapy for advanced/ Metastastic NSCLC with a PD-L1 TPS≥1%: Open-Label, Phase 3 KEYNOTE-042 Study". *Lancet* 393.10183 (2019): 1819-1830.

13. Horn L., *et al*. "Nivolumab versus docetaxel in previously treated patients with advanced non-small-cell lung cancer: Two-year outcomes from two randomized, open-label, phase III trials (CheckMate017 and CheckMate 057)". *Journal of Clinical Oncology* 35.35 (2017): 3924-3933.

14. Diakos Cl., *et al*. "Cancer-related inflammation and treatment effectiveness". *Lancet Oncology* 15.11 (2014): 493-503.

15. RL Stone., *et al*. "Paraneoplastic thrombocytosis in ovarian cancer". *The New England Journal of Medicine* 366.7 (2012): 610-618.

16. Templeton AJ., *et al*. "Prognostic role of platelet to lymphocyte radio in solid tumors: a systematic review and meta-analysis". *Cancer Epidemiology, Biomarkers and Prevention* 23.7 (2014): 1204-1212.

17. Duan J., *et al*. "Preoperative elevated neutrophil-to-lymphocyte ratio (NLR) and derived NLR are associated with poor prognosis in patients with breast cancer: A meta-analysis". *Medicine (Baltimore)* 97.49 (2018): 13340.

18. Zhang H., *et al*. "Clinical significance of preoperative neutrophil-lymphocyte vs platelet-lymphocyte radio in primary operable patients with non-small cell lung cancer". *American Journal of Surgery* 210.3 (2015): 526-535.

19. Deng Q., *et al*. "Prognostic value of pre-operative inflammatory response biomarkers in gastric cancer patients and the construction of a predictive model". *Journal of Translational Medicine* 13 (2015): 66.

20. Giakoustidis A., *et al*. "Identifying the role of neutrophil-to-lymphocyte radio and platelets-to-lymphocyte radio as prognostic markers in patients undergoing resection of pancreatic ductal adenocarcinoma". *Annals of Hepato-Biliary-Pancreatic Surgery* 22.3 (2018): 197-207.

21. Ferrucci PF., *et al*. "Baseline neutrophils and derived neutrophil-to-lymphocyte radio: prognostic relevance in metastatic melanoma patients receiving ipilimumab". *Annals of Oncology* 27.4 (2016): 732-738.

22. Diem S., *et al*. "Neutrophil-to-Lymphocyte radio (NLR) and Platelet-to-Lymphocyte radio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab". *Lung Cancer* 111 (2017): 176-181.

23. Rochet NM., *et al*. "The prognostic role of the preoperative absolute lymphocyte count and absolute monocyte count in patients with resected advanced melanoma". *American Journal of Clinical Oncology* 38.3 (2015): 252-258.

24. Capone M., *et al*. "Baseline neutrophil-to-lymphocyte ratio and derived NLR could predict overall survival in patients with advanced melanoma treated with nivolumab". *Journal of Immunotherapy Cancer* 6.1 (2018): 74.

25. Ettinger DS., *et al*. "NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 1. 2020". *Journal of the National Comprehensive Cancer Network* 17.12 (2019): 1464-1472.

26. Kalemkerian GP., *et al*. "NCCN Guidelines Insights: Small Cell Lung Cancer, Version 2. 2018". *Journal of the National Comprehensive Cancer Network* 16.10 (2018): 1171-1182.

27. von Mehren M., *et al*. "NCCN Guidelines Insights: Soft Tissue Sarcoma, Version 1.2021". *National Comprehensive Cancer Network* 18.12 (2020): 1604-1612.

28. Qiu H and Zhou Z. "Updates and interpretation on NCCN clinical practice guidelines for gastric cancer 2017 version 5". *Zhonghua Wei Chang Wai Ke Za Zhi* 21.2 (2018): 160-164.

29. Provenzale D., *et al*. "NCCN Guidelines Insights: Colorectal Cancer Screening, Version 2.2020". *National Comprehensive Cancer Network* 18.10 (2020): 1312-1320.

30. Covey AM. "Hepatocellular Carcinoma: Updates to Screening and Diagnosis". *National Comprehensive Cancer Network* 16.5S (2018): 663-665.

31. Gettinger SN., *et al*. "Overall Survival and Long-term safety of nivolumab (Anti-Programmed Death 1 Antibody, BMS-936558, ONO-4538) in patients with Previously Treated Advanced non-small cell lung cancer". *Journal of Clinical Oncology* 33.18 (2015): 2004-2012.

32. Wolchok JD., *et al*. "Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria". *Clinical Cancer Res* 15.23 (2009): 7412-7420.

33. Eisenhauer EA., *et al*. "New response evaluation criteria in solid tumours: revised RECIST guideline (version 1. 1)". *European Journal of Caner* 45.2 (2009): 228-247.

34. Cummings M., *et al*. "Preoperative neutrophil:lymphocyte and platelet:lymphocyte radios predict endometrial cancer survival". *British Journal of Caner* 113.2 (2015): 311-320.

35. Que Y., *et al*. "Preoperative platelet-lymphocyte ratio is superior to neutrophil-lymphocyte ratio as a prognostic factor for soft-tissue sarcoma". *BMC Cancer* 15 (2015): 648.

36. Yuan C., *et al*. "Elevated pretreatment neutrophil/white blood cell radio and monocyte/lymphocyte ratio predict poor survival in patients with curatively resected non-small cell lung cancer: Results from a large cohort". *Thoracic Cancer* 8.4 (2017): 350-358.

37. Nishijima TF., *et al*. "Inflammatory markers and overall survival in older adults with cancer". *Journal of Geriatric Oncology* 10.2 (2019): 279-284.

38. Song SB., *et al*. "Derived neutrophil to lymphocyte radio and monocyte to lymphocyte radio may be better biomarkers for predicting overall survival of patients with advanced gastric cancer". *OncoTargets and Therapy* 10 (2017): 3145-3154.