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RESEARCH

Association of lymphocyte subsets percentage with prognosis for recurrent or metastatic nasopharyngeal carcinoma patients receiving PD-L1 inhibitors

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Abstract

Background Immune checkpoint inhibitors (ICIs), particularly PD-1/PD-L1 inhibitors, have demonstrated significant survival benefits in treating recurrent or metastatic nasopharyngeal carcinoma (R/M-NPC). While baseline peripheral blood lymphocyte subsets have been identified as prognostic biomarkers in various cancers treated with ICIs, their relevance in R/M-NPC has not been extensively studied.

Methods This post hoc analysis used data from 153 R/M-NPC patients treated with PD-L1 inhibitor monotherapy in the phase 2 trial KL167-2-05-CTP. The lymphocyte subsets, including total T cells, CD4/CD8 ratio, helper T cells, suppressor cytotoxic T cells, NK cells, and B cells, were tested by flow cytometry. These subsets were grouped using optimal cutoff values identified by the Maximally Selected Log-rank Statistic. Overall survival (OS) and progression-free survival (PFS) were assessed using Kaplan–Meier and Cox regression analysis, and logistic regression analysis evaluated the associations with objective response rate (ORR) and disease control rate (DCR).

Results Patients with lower NK cell percentages showed significantly longer OS (26.3 vs. 12.1 months, $p < 0.001$) and PFS (5.5 vs. 3.7 months, $p < 0.001$) compared to those with higher NK cell percentages. No significant differences in OS or PFS were observed for other lymphocyte subsets. High NK cell percentages were identified as risk factors for shorter OS (HR, 2.49) and PFS (HR, 1.62). There were no significant differences in ORR and DCR between high and low lymphocyte subsets.

Conclusion Lower baseline NK cell percentages are associated with improved OS and PFS in R/M-NPC patients undergoing PD-L1 inhibitor therapy.

Keywords Lymphocyte subsets · Immune checkpoint inhibitors · PD-L1 inhibitor · Nasopharyngeal carcinoma · Prognosis

Introduction

Nasopharyngeal carcinoma (NPC) shows geographical difference in its incidence and mortality worldwide, with Asia accounting for 83.3% of global NPC cases and 83.6% of mortality [1, 2]. Early-stage NPC patients (stages I and II, AJCC staging system) have a 5-year overall survival rate of 94.0%, which drops to 89.2% for stage III and 73.7% for stage IV [3]. Given the shorter survival time of R/M-NPC patients, several clinical trials were conducted and demonstrated that chemotherapy combining ICIs can significantly prolong PFS. Compared to placebo group, Camrelizumab (median PFS: 9.7 months vs. 6.9 months; HR, 0·54 [95% CI, 0·39–0·76]; $p = 0.0002$) and Tislelizumab (median PFS: 9.2 months vs. 7.4 months; HR, 0.52 [95% CI, 0.38–0.73]; $p < 0.0001$) both achieved longer PFS [4, 5]. In the phase 2 clinical trial KL167-2-05-CTP, patients with R/M-NPC

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received KL-A167 (PD-L1 inhibitor) monotherapy and achieved 2.8 months for median PFS [6]. PD-L1 inhibitors have demonstrated both effective outcomes and acceptable safety profiles. A network meta-analysis for recurrent/metastatic head and neck carcinoma (R/M HNSCC) indicates no statistically significant difference in clinical efficacy between PD-1 inhibitor and PD-L1 inhibitor (PD-1 vs. PD-L1: HR, 0.90 [95% CI, 0.78–1.04]; $p = 0.96$) [7]. Additionally, PD-1 inhibitors are associated with a higher incidence of grade 3 or higher adverse reactions (AEs) compared to PD-L1 inhibitors (OR, 1.58 [95% CI, 1.00–2.54]) [8]. The lower incidence of AEs with PD-L1 inhibitors could be due to their selective blocking of PD-L1 only, whereas PD-1 inhibitors block signals from both PD-L1 and PD-L2, increasing the risk of the potential autoimmune reactions [9, 10].

In the previous study (KL167-2-05-CTP) of PD-L1 inhibitors treating R/M-NPC, for full analysis set (FAS) population, ORR was 26.5% (95% CI, 19.2–34.9%) and DCR was 56.8% (95% CI, 47.9–65.4%) [6]. Given the significant heterogeneity in patient prognosis, identifying novel biomarkers to predict the efficacy of PD-L1 inhibitor therapy is crucial. PD-L1 inhibitors can reactivated TILs and remodel lymphocyte differentiation in tumor microenvironment (TME) [11, 12]. Lymphocytes in peripheral blood can eventually infiltrate the TME, providing insights into the efficacy of PD-L1 inhibitor therapy [13]. Therefore, peripheral blood lymphocyte subsets may have potential value in predicting outcomes of PD-L1 inhibitors therapy. Similarly, some studies have demonstrated that peripheral blood lymphocyte subsets can predict the prognosis of patients receiving immunotherapy with other cancers, including NSCLC [14], metastatic genitourinary cancer [15] and melanoma [16]. However, its prognostic value of peripheral blood lymphocyte subsets remains unreported in NPC. To investigate the predictive value of peripheral blood lymphocyte subsets as biomarkers, we conducted this study using the largest cohort of R/M-NPC patients treated with PD-L1 inhibitors to date.

Methods

The design and results of the KL167-2-05-CTP study have been published previously. This phase 2, open-label, multicenter, single-arm trial evaluating KL-A167 in patients with R/M-NPC across 42 hospitals in China. Our retrospective prognostic study protocol received approval from the independent ethics committees of each participating center and was conducted following the Declaration of Helsinki [17]. Study participants obtained the written informed consent.

Patients

Patients with histologically confirmed non-keratinizing R/M-NPC were eligible. All participants were required to have stage IVb R/M-NPC, as classified by the eighth edition of the American Joint Committee on Cancer/International Union Against Cancer staging system. Eligibility required that patients had experienced treatment failure with at least two lines of chemotherapy, including a platinum-based regimen as part of their first-line treatment. Additional eligibility criteria included being 18 years or older, having at least one measurable lesion per RECIST v1.1, an ECOG performance status of 0 or 1, an estimated life expectancy of at least 12 weeks and sufficient organ function. Key exclusion criteria included prior immune checkpoints inhibitors (ICIs) usage, anti-tumor antibody therapy within 12 weeks before treatment initiation, receiving any anti-tumor therapy within 4 weeks prior to the first dose of KL-A167, using immunosuppressive medications within 14 days before treatment initiation, and active central nervous system metastases. Between February 26, 2019, and January 13, 2021, a total of 231 patients with R/M-NPC were evaluated for eligibility across 42 hospitals in China and 153 of them were enrolled. The data cutoff date is July 13, 2021.

Procedures

OS was defined as the duration from the first dose until death. Secondary endpoints included PFS, ORR and DCR. PFS was defined as the period from the first dose to the first occurrence of disease progression or death. ORR, determined according to RECIST v1.1, defined as the percentage of patients with confirmed complete response (CR) and partial response (PR). DCR was defined as the percentage of patients achieving CR, PR and stable disease (SD). Patients received KL-A167 at 900 mg via intravenous infusion every 2 weeks until confirmed disease progression. Progressive disease (PD) was be determined by assessment at least 4 weeks or longer when it reached the criteria for response for the first time, as determined by the investigators. Response assessments took place every 6 weeks during the initial 24 months, then every 12 weeks until disease progression or therapy discontinuation. The baseline peripheral blood lymphocyte subsets percentage were determined in the laboratory at each research center at the time of response assessment. Measured lymphocyte subsets include Total T cells percentage, CD4/CD8 T cells percentage, helper T cells percentage, suppressor cytotoxic T cells percentage, NK cells percentage and B cells percentage. NK cells were characterized based on CD56

expression, and B cells were defined by CD19 expression. For T cells, we classified them as CD3 + and further differentiated into CD4 + and CD8 + populations. Some centers did not detect the lymphocyte subsets percentage in full, leading to missing data that we excluded from our analysis. We analyzed these six biomarkers to investigate their prognostic value. The grouping in the study was not randomized. Data of each biomarker were divided into two groups according to the calculated cutoff value, and the best cutoff value was calculated using maximally selected log-rank statistic method. Then, we conducted Kaplan–Meier survival curve and Cox regression analysis to evaluate OS and PFS. COX regression analysis on continuous lymphocyte subsets percentage was also conducted. The odds rates (OR) and 95%CIs for ORR and DCR were computed using logistic regression analysis. Finally, we explored the correlation of lymphocyte subsets with each other by generating heat maps.

Statistical analysis

We aimed to explore the association of lymphocyte subsets and the prognosis of PD-L1 inhibitor therapy. A two-tailed $p < 0.05$ was considered to statistical significance. Pearson's chi-squared test was used for analyzing categorical variables. Continuous variables conforming to a normal distribution were subjected to t tests, while variables which do not follow a normal distribution were subjected to the Mann–Whitney test. The cutoff value was determined by using maximally selected log-rank statistic method. Survival curves were generated using the Kaplan–Meier method, with comparisons made using the log-rank test. Cox regression analysis was used to calculate hazard rate (HR) and 95%CIs. The odds rates (OR) and 95%CIs for ORR and DCR were computed using logistic regression analysis. R, version 4.3.2 was used for our analyses.

Results

Patient cohort

Overall, 153 patients (125 men [81.7%]; average age, 47.6 years [SD, 9.8 years]) participated in the phase 2 clinical trial of KL-A167 (anti-PD-L1 monotherapy) for R/M-NPC (Table 1). The median follow-up time was 21.7 months. The median OS was 15.2 months. The median PFS was 4.2 months. Table 2 shows patients' baseline peripheral blood lymphocyte subsets.

Table 1 Characteristics of patients

Characteristic	Patients, No. (%) (N = 153)
Age (mean (SD))	47.6 (9.8)
Gender	
Male	125 (81.7)
Female	28 (18.3)
ECOG PS[a]	
0	59 (38.6)
1	94 (61.4)
T Stage	
T0-2	103 (67.3)
T3-4	50 (32.7)
N stage	
N0-2	127 (83.0)
N3	26 (17.0)
Liver metastasis	
Yes[b]	59 (38.6)
No	94 (61.4)
Smoke	
Yes	98 (64.1)
No	55 (35.9)
Alcohol	
Yes	111 (72.5)
No	42 (27.5)
Lactate dehydrogenase U/L (median [IQR])	232.0 [176.0, 403.0]
EBV DNA copies/mL (median [IQR])	1865.0 [421.5, 12275.0]
Body mass index (median [IQR])	21.6 [19.1, 23.5]

a: ECOG PS, Eastern Cooperative Oncology Group Performance Status

b: This includes both patients with no metastasis and those with metastasis to other sites but without liver involvement

Association between lymphocyte subsets percentage and OS, PFS

We conducted the analysis of the association continuous lymphocyte subsets percentage and groups of high and low lymphocyte subsets percentage and OS and PFS. We found that OS and PFS were not significantly different in the two groups of CD4/CD8 ratio in both univariate analysis and multivariate analysis (Table 3). The differences in OS and PFS between two groups of total T cells were not significant in univariate and multivariate analysis (Table 3). In multivariate analysis of helper T cells, patients in low helper T cells percentage group had longer OS than those in high helper T cells percentage group [HR, 2.08(95% CI, 1.11–3.89); $p = 0.022$] (Table 3). In multivariate analysis of suppressor cytotoxic T cells, patients in high suppressor cytotoxic T cells percentage group had longer OS than those in low suppressor cytotoxic T cells percentage group [HR, 0.51(95% CI, 0.28–0.93); $p = 0.029$] (Table 3). Patients in the high baseline NK cells percentage

Table 2 Baseline lymphocyte subsets percentage of patients

Baseline Lymphocyte Subsets Percentage	Patients, No. (%) ($N=153$)
NK cells (mean (SD))	28.4 (12.1)
NK cells (median [IQR])	26.6 [19.8, 35.9]
NK cells group	
≤25.57%	42 (47.7)
>25.57%	46 (52.3)
CD4/CD8 ratio (mean (SD))	3.0 (10.9)
CD4/CD8 ratio (median [IQR])	0.8 [0.6, 1.2]
CD4/CD8 ratio group	
≤0.43%	16 (17.6)
>0.43%	75 (82.4)
Total T cells (mean (SD))	58.0 (13.3)
Total T cells (median [IQR])	58.5 [48.7, 67.0]
Total T cells group	
≤65.08%	68 (68.0)
>65.08%	32 (32.0)
Helper T cells (mean (SD))	23.6 (7.8)
Helper T cells (median [IQR])	22.0 [17.1, 29.4]
Helper T cells group	
≤22.1%	49 (51.6)
>22.1%	46 (48.4)
Suppressor cytotoxic T cells (mean (SD))	30.7 (11.7)
Suppressor cytotoxic T cells (median [IQR])	29.7 [21.4, 39.4]
Suppressor cytotoxic T cells group	
≤38.47%	69 (72.6)
>38.47%	26 (27.4)
B cells (mean (SD))	9.4 (5.5)
B cells (median [IQR])	8.3 [5.1, 12.6]
B cells group	
≤15.1%	76 (88.4)
>15.1%	10 (11.6)

Cutoff value of baseline lymphocyte subsets percentage is calculated by the maximally selected log-rank statistic method

group had significantly shorter median OS than those in the low baseline NK cells percentage group (12.1 months vs. 26.3 months, $p<0.001$) (Fig. 1). In the analysis of NK cells, patients in high NK cells percentage group had an increased risk of death compared with patients in low NK cells percentage group [HR, 2.49 (95% CI, 1.39–4.47); $p=0.002$] (Table 3). The results were consistent in the multivariate analysis of OS [HR, 3.14 (95% CI, 1.47–6.75); $p=0.003$] (Table 3). Patients in low NK cells percentage group also had longer PFS than those in high NK cells percentage group (5.5 months vs. 3.7 months, $p<0.001$) (Fig. 1). Patients in low NK cells percentage group had lower risk of progression than those in high NK cells percentage group in univariate [HR, 1.62 (95% CI, 1.02–2.57); $p=0.041$] (Table 3) and multivariate [HR, 2.04 (95% CI, 1.16–3.59); $p=0.013$] (Table 3) analysis of PFS. It was found that higher continuous NK cells percentage is significantly associated with higher risk of death [HR, 1.04 (95% CI, 1.01–1.08); $p=0.019$] and progression [HR, 1.03 (95% CI, 1.01–1.05); $p=0.010$] (Table 3). Higher continuous B cells were associated longer OS [HR, 0.93 (95% CI, 0.86–0.99); $p=0.032$] (Table 3). However, in multivariate analysis, no significant differences in OS and PFS were demonstrated between high and low B cells groups.

A, C, E, G, I, K OS analysis in NK cells percentage groups, CD4/CD8 ratio percentage groups, total T cells percentage groups, helper T cells percentage groups, suppressor cytotoxic T cells percentage groups and B cells group. B, D, F, H, J, L PFS analysis in NK cells percentage groups, CD4/CD8 ratio percentage groups, total T cells percentage groups, helper T cells percentage groups, suppressor cytotoxic T cells percentage groups and B cells group.

Association between lymphocyte percentage and ORR, DCR

We performed logistics regression analysis to explore the relationship between lymphocyte subsets and ORR, DCR. However, we found no significant difference in other analysis of lymphocyte percentage and ORR, DCR between low and high two groups (eFig. 1). The results were consistent in the analysis of continuous lymphocyte subsets percentage (eFig. 1).

Characteristics of patients grouped by NK cells and correlation of NK cells and other lymphocyte

Given the good prognostic predictive ability of NK cells percentage, we additionally analyzed the characteristics of patients in high and low NK cell percentage groups (eTable 4). We also explored the correlation of NK cells percentage and other lymphocyte subsets percentage. There is a negative linear correlation between NK cells percentage and B cells percentage ($r=-0.179$; $p<0.001$) (eFig. 1). NK cells percentage also had a negative linear correlation with total T cells percentage ($r=-0.795$; $p<0.001$) (eFig. 1), helper T cells percentage (r=-0.397; $p<0.001$) (), suppressor cytotoxic T cells percentage ($r=-0.555$; $p<0.001$) (eFig. 1). However, we did not see a linear correlation between NK cells and CD4/CD8 percentage ($r=0.258$; $p>0.05$) (eFig. 1).

Discussion

With the increasing application of ICIs in various tumors, the era of immunotherapy for RM-NPC has arrived. Previous studies on ICIs for other cancers have demonstrated the

Table 3 Cox analysis for association between lymphocyte subsets percentage and survival outcomes for patients with R/M-NPC receiving anti-PD-L1 monotherapy

		OS				PFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
CD4/CD8 ratio	Continuous	0.99 (0.96–1.03)	0.742	0.99 (0.96–1.02)	0.616	1.02 (1.00–1.04)	0.035	1.02 (1.00–1.04)	0.047
	Low vs. high	2.50 (0.92–4.53)	0.078	1.48 (0.63–3.51)	0.368	1.17 (0.65–2.08)	0.605	1.07 (0.65–2.00)	0.832
Total T cells	Continuous	1.00 (0.98–1.02)	0.823	0.99 (0.97–1.02)	0.648	1.00 (0.66–1.01)	0.662	0.99 (0.97–1.01)	0.305
	Low vs. high	0.69 (0.38–1.20)	0.187	0.86 (0.44–1.65)	0.644	0.76 (0.48–1.21)	0.246	0.71 (0.43–1.20)	0.200
Helper T cells	Continuous	1.01 (0.97–1.04)	0.645	1.02 (0.97–1.06)	0.448	1.00 (0.97–1.03)	0.816	1.02 (0.98–1.04)	0.519
	Low vs. high	1.62 (0.96–2.73)	0.072	2.08 (1.11–3.89)	**0.022**	1.24 (0.80–1.92)	0.329	1.51 (0.92–2.48)	0.099
Suppressor cytotoxic T cells	Continuous	1.00 (0.98–1.02)	0.782	1.00 (0.98–1.02)	0.912	0.97 (0.94–1.00)	0.008	0.98 (0.96–1.00)	0.103
	Low vs. high	0.67 (0.37–1.23)	0.198	1.33 (0.84–2.10)	0.222	0.41 (0.18–0.93)	0.032	0.51 (0.28–0.93)	**0.029**
NK cells	Continuous	1.01 (0.98–1.03)	0.518	1.04 (1.01–1.08)	0.019	1.01 (0.99–1.03)	0.241	1.03 (1.01–1.05)	**0.010**
	Low vs. high	2.49 (1.39–4.47)	**0.002**	3.14 (1.47–6.75)	**0.003**	1.62 (1.02–2.57)	**0.041**	2.04 (1.16–3.59)	**0.013**
B cells	Continuous	0.97 (0.92–1.02)	0.249	0.93 (0.86–0.99)	**0.032**	0.98 (0.94–1.03)	0.419	1.00 (0.94–1.05)	0.875
	Low vs. high	0.37 (0.11–1.19)	0.096	0.45 (0.12–1.62)	0.220	0.85 (0.41–1.77)	0.659	1.03 (0.44–2.42)	0.944

In multivariate analysis, we adjusted for age, gender, ECOG PS, *T* stage, *N* stage, liver metastasis, serum LDH

value of peripheral blood lymphocyte subsets in predicting prognosis [13]. For example, in NSCLC patients receiving PD-1 blockade treatment, researchers found that higher T cell factor 1 (TCF1) frequency in effector-memory (CCR7–) CD8 + T cells correlated with longer PFS (17 months vs. 3 months; HR, 0.39; $p = 0.019$) [18]. Similarly, in metastatic pancreatic cancer, higher baseline circulating CD4 + T central memory cells were associated with longer survival following treatment with nivolumab combined with chemotherapy (20 months vs. 10 months; $p = 0.037$) [19]. In melanoma patients receiving PD-1 inhibitors, peripheral blood B cells were found to correlate with prognosis [20]. However, up to now, the data on the association between the lymphocyte subsets percentage and the prognosis of RM-NPC patients receiving PD-1 inhibitors are limited.

In our study, we thoroughly explored the predictive value of baseline lymphocyte subset percentages in peripheral blood for OS and PFS by analyzing data from a clinical trial with the largest cohort of R/M-NPC patients treated with PD-L1 inhibitor monotherapy [6]. These patients had received two lines of chemotherapy, which can suppress immune function and reduce lymphocyte counts, creating an immune desert status. Despite the compromised immune status following extensive chemoradiotherapy, it was found that patients with higher baseline NK cells percentage had a significantly shorter median OS (12.1 months vs. 26.3 months) and shorter median PFS (3.7 months vs. 5.5 months) after analyzing six lymphocyte subsets percentage. This result suggests that the percentage of NK cells in peripheral blood may serve as a valuable biomarker for predicting outcomes in patients with R/M-NPC receiving anti-PD-L1 therapy. It was observed that CD4/CD8 ratio, total T cells, helper T cells and suppressor cytotoxic T cells were not significantly associated with prognosis of R/M-NPC patients who received PD-1 inhibitors treatment.

The role of NK cells percentage as a biomarker for predicting the prognosis of patients receiving immunotherapy remains uncertain due to limited data. There are currently studies investigating the relationship between baseline lymphocyte subsets percentages in peripheral blood and prognosis in other types of cancer. For instance, in NSCLC patients receiving nivolumab, lower baseline NK cell levels were associated with longer OS [14]. This aligns with our findings that high levels of circulating NK cells predict a worse outcome. Moreover, there have been no similar studies in the field of NPC to date.

NK cells can induce target cell death by releasing cytotoxic granules containing perforin and granzymes, as well as by activating death receptor-mediated pathways [21]. NK cells have multiple anti-tumor function. Many cancer cells can evade detection by cytotoxic CD8 T cells by downregulating the expression of MHC I molecules. However, NK cells can identify the cells of low expression of MHC I molecules and cause the lysis of the cancer cells [22]. ADCC is also a key function of NK cells to kill cancer cells. Given its anti-tumor function, NK cells also play an important role in cancer immunotherapy. In cancer mouse models, it is found that activated NK cells can express PD-1 and PD-1 engagement by PD-L1 on tumor cells can suppress anti-tumor mediated by NK cells [23]. In a study of human body specimens, Wang et al. had

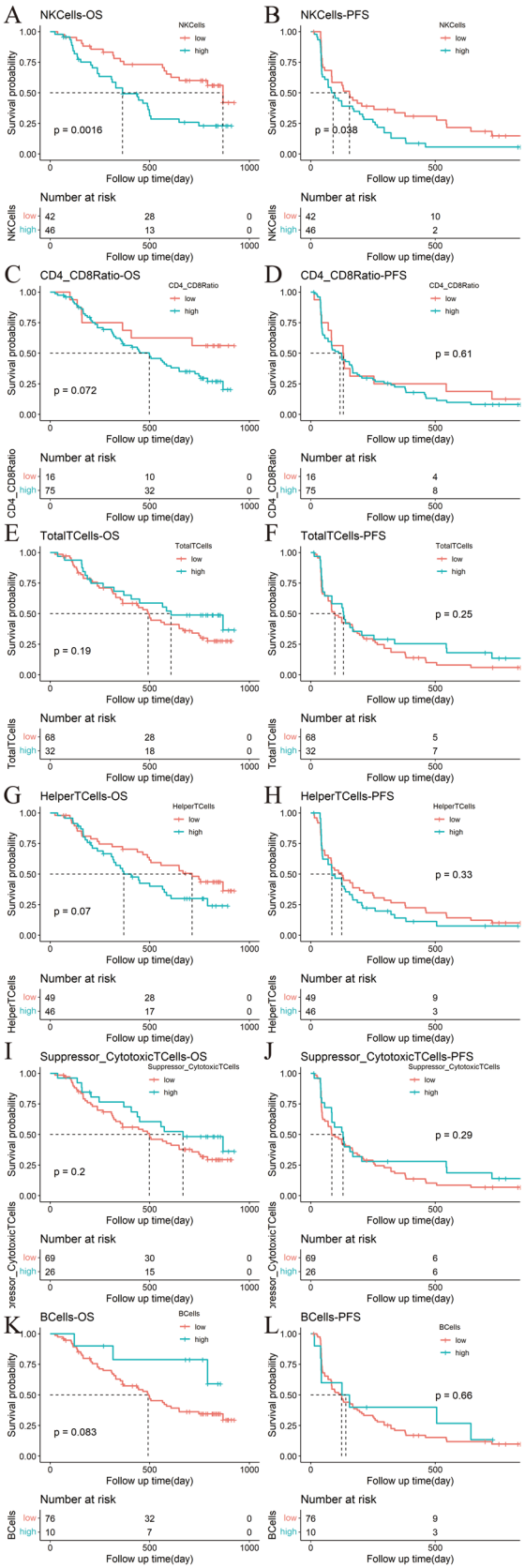

Fig. 1 OS and PFS analysis in different lymphocyte subsets

reported that a high density of NK cells within the tumor or stroma indicates longer OS and PFS [24]. Chen et al. also reported that patients with high NK cells had a longer PFS in a single-cell transcriptomics study [25]. Tumor-infiltrating NK cells were proven to serve as prognostic factors for patients with nasopharyngeal carcinoma receiving immunotherapy, but measuring NK cells in specimens is not easily achievable. Based on the expression of surface CD56, human NK cells can be divided into $CD56^{bright}$ and $CD56^{dim}$ subsets. $CD56^{bright}$ cells make up only about 10% of peripheral blood NK cells but dominate in tissues. They have low cytotoxic activity but secrete cytokines, mainly IFN-γ and TNF-α. $CD56^{dim}$ NK cells are primarily found in peripheral blood, are consistently CD16 positive and exhibit strong cytotoxic activity [26]. The traffic of NK cells from circulation to tissues and lymphoid organs is regulated by chemokines and chemokine receptors, guiding specific NK cell subsets to distinct locations. In the tumor microenvironment of NPC, NK cells may become exhausted and their cytotoxicity suppressed [27]. Low peripheral blood NK cell counts could indicate that more NK cells have been recruited into the tumor immune microenvironment, where PD-L1 blockade can more effectively reverse NK cell inhibition, enabling them to exert anti-tumor effects. Additionally, NK cells with immunoregulatory properties, such as PD-1-expressing NK cells, may be more abundant in tumors with high NK infiltration, leading to immune suppression in these patients. Hence, studying the relationship between NK cells in peripheral blood and prognosis of patients with cancer receiving immunotherapy is significantly important.

There are some limitations in this study. There might be selection bias present because the study used data from a clinical trial, potentially limiting the generalizability of the findings to the broader population. Some research centers did not test all types of lymphocytes resulting in incomplete data for some types of lymphocytes, which resulted in a smaller amount of data being available for analysis. Due to limitations in the detection technology, we were unable to cytotoxic NK cells and differentiate between antigen-presenting NK cells, helper NK cells, and regulatory NK cells in the peripheral blood NK cell population. Our study focused on baseline peripheral blood lymphocyte subsets percentage, and the relationship between changes in peripheral blood lymphocyte subsets percentage during treatment and OS may require further investigation in future studies.

Conclusions

This study suggests that baseline low peripheral blood NK cells percentage is associated with better OS and PFS of R/M-NPC patients who will have prolonged survival with PD-L1 inhibitor therapy.

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Data availability No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval Ethical approval for the collection of human data was obtained from the Institutional Review Board (HX-IRB-AF-12-V4.0) of West China Hospital.

Informed consent Prior to enrollment, all participants provided written informed consent. Registry and the Registration No. of the study/trial: KL-A167 clinical trial (NCT03848286).

Human and animal rights N/A.

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