Correlation of Peripheral Blood CD4/CD8 Ratio with Efficacy and Prognosis in Patients with Non-Small Cell Lung Cancer Receiving PD-1/PD-L1 Inhibitors

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ABSTRACT

The aim of this study was to investigate the predictive role of the peripheral blood CD4/CD8 ratio in patients with non-small cell lung cancer (NSCLC) treated with PD-1/PD-L1 inhibitors therapy. Cochrane, Embase, Medline, PubMed, and Web of Science were searched until November 2023. Data were analysed using Stata MP 17.0 software. Outcome indicators included progression-free survival (PFS) and overall survival (OS). A total of five studies of the baseline CD4/CD8 ratio in peripheral blood strictly met the inclusion criteria. The pooled outcome indicator showed that high level of peripheral blood CD4/CD8 ratio in patients with NSCLC receiving PD-1/PD-L1 inhibitors was associated with better PFS (HR = 0.62, 95% CI: 0.49-0, 79, p <0.001), rather than OS (HR = 0.90, 95% CI: 0.53-1.51, p = 0.679). The results from this meta-analysis demonstrated that in patients with NSCLC receiving PD-1/PD-L1 inhibitors, a high baseline CD4/CD8 ratio in peripheral blood can predict better PFS.

Key Words: *CD4-CD8 Ratio, Immune checkpoint inhibitors, Non-small cell lung cancer, Peripheral blood, Prognosis, Survival*.

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In the past decade, the clinical use of immune checkpoint inhibitors (ICIs) dominated by programmed cell death 1 (PD-1) inhibitors and programmed cell death ligand 1 (PD-L1) inhibitors has resulted in favourable effects and remarkably improved clinical outcomes in patients with non-small cell lung cancer (NSCLC). Nevertheless, the unpredictability of efficacy has become a bottleneck in the use of PD-1/PD-L1 inhibitors. There is a need to explore predictive biomarkers of immunotherapy efficacy and prognosticacy in patients with NSCLC, in order to provide early intervention for ongoing treatment strategies. In the past, only a few studies have explored the clinical significance of the CD4/CD8 ratio, and these studies have produced inconsistent results, limiting the clinical application of this. Hence, the authors searched for data from the most recent clinical studies and systematically combined the data to elucidate the prognostic value of peripheral blood CD4/CD8 ratios in NSCLC patients treated with PD-1/PD-L1 inhibitors.

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This study followed the PRISMA checklist, and the project has been registered in PROSPERO (No: CRD42023454866). For Cochrane, Embase, Medline, PubMed, and Web of Science, searches were conducted from the time they were created to November 2023. To analyse the pooled data, the authors used Stata version 17.0 MP (Stata Corporation, College Station, TX, USA). The pooled hazard ratio (HR) and corresponding 95% confidence interval (CI) were utilised to compute the effect size of progression-free survival (PFS) and overall survival (OS). For all combined analyses, the result was considered statistically significant when the p-value was less than 0.05.

Five studies of the baseline CD4/CD8 ratio in peripheral blood ultimately met the eligibility criteria.[1-5] For patients with NSCLC receiving PD-1/PD-L1 inhibitors, the pooled results showed that those with high baseline CD4/CD8 ratios had better PFS, not OS. The pooled results of five studies showed that patients with a high CD4/CD8 ratio had a higher PFS than those with a low CD4/CD8 ratio (HR = 0.62, 95% CI: 0.49-0, 79, p <0.001, Figure 1A). The pooled results of two studies reported that a high CD4/CD8 ratio in these patients trended towards improved OS (HR = 0.90, 95% CI: 0.53-1.51, p = 0.679), although not to a statistically significant level (Figure 1B). For the pooled analysis of PFS ($I^2 = 0\%$, p = 0.494) or OS ($I^2 = 0\%$, p = 0.437), no significant heterogeneity was observed.

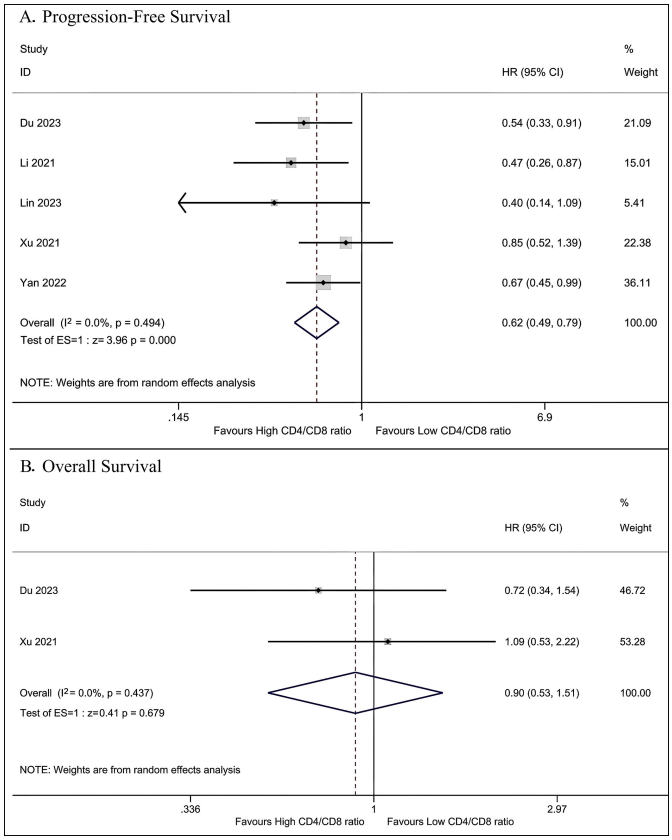

Figure 1: Forest plot showing the HR of high CD4/CD8 ratio *versus* low CD4/CD8 ratio in peripheral blood for PFS and OS in patients with NSCLC treated with PD-1/PD-L1 inhibitors. (A) Combined HR of PFS; (B) Combined HR of OS.

In recent years, immunotherapy has become another better option for the treatment of systemic cancer. The PD-1/PD-L1 axis is an important immune checkpoint axis. By binding to immune checkpoints, PD-1/PD-L1 inhibitors can reactivate the immune response of T-cells, inhibit immunosuppressed regulatory T-cells, and further stimulate the host's immune system to recognise an attack and eliminate tumour cells. Although the use of ICIs has produced some beneficial outcomes for patients with NSCLC, reliable biomarkers for predicting treatment outcomes are still limited. Based on this, the study explores the predictive effect of the CD4/CD8 ratio for patients with NSCLC treated with PD-1/PD-L1 inhibitors, which suggests that a high ratio of baseline CD4/CD8 in peripheral blood may be used as a valid biomarker to predict a better prognosis for these patients.

Tumour patients are often accompanied by certain immunodeficiencies, among which cellular immunodeficiency is more obvious. T lymphocyte-mediated cellular immunity has potent anti-tumour effects in antimalignant immunity. Among the T-lymphocytes of the blood, CD4+ helper T-cells and CD8+ cytotoxic T-cells act as an important part in immunomodulation. Yan *et al*. found that compared with the baseline group, the proportion of CD4+ T cells increased in the immunotherapy effective group and did not change significantly in the ineffective group, indicating that patients in the effective group achieved a durable anti-tumour response, suggesting that peripheral blood continued to recruit anti-tumour T cells.[5] Moreover, higher CD4+ T cells in peripheral blood prior to immunotherapy are associated with better efficacy and prognosis. In the course of immunotherapy, dynamic monitoring of CD4+ T cells may be helpful in assessing patient outcomes and screening patient populations that may be particularly beneficial. As another crucial component of anti-tumour immunity, CD8+ T cells could amplify and differentiate into CTLs, migrate through the peripheral blood to expand tumours and directly destroy tumour cells. Some investigators have found that the number of CD8+ T cells in the peripheral blood of the immunotherapy effective group was significantly lower compared to the baseline.[5]

In normal status, CD4+ T cells and CD8+ T cells balance each other to maintain immunity. In people with malignant tumours, the ratio is often disrupted, and both the number and function of T lymphocytes show different degrees of abnormalities, which in turn affects the immune function of cells, resulting in low immune function and promoting the occurrence and development of tumours. Decreased or inverted CD4/CD8 ratios often indicate cellular immune dysfunction, including abnormal immune activation and immune ageing, so cellular immune function *in vivo* can be assessed by the CD4/CD8 ratio. Organisms can maintain the dynamic balance of CD4/CD8 by regulating the number and ratio of Th1, Th2, Tc1, and Tc2 cells, thus keeping the cellular immune function of the organism in a relatively stable state. If Th1 is converted to Th2 and Tc1 is converted to Tc2, this is known as drift, which has been found in various malignant organisms. At this time, the T lymphocyte subpopulation in peripheral blood has also undergone certain changes, which specifically manifested that the ratio of CD3+ CD4+ T lymphocytes decreased, while the ratio of CD3+ CD8+ T lymphocytes increased. Decreased CD4/CD8 ratios are often thought to lead to increased immune tolerance and increased immunosuppression.

In fact, the peripheral blood CD4/CD8 ratio of lymphocytes is an ancient marker for many diseases, and it is becoming a predictor of different pathologies and treatments, including cardiovascular disease, human immunodeficiency virus infection, and malignancy. The CD4/CD8 ratio is also relevant to lung cancer risk. Low CD4/CD8 ratio in peripheral blood is associated with high-risk types of lung cancer, and similar conclusions were confirmed in tumour tissue. Peripheral blood CD4/CD8 ratio decreased with the increase of NSCLC clinical stage.[5] Du *et al*. and Li *et al*. found that a high CD4/CD8 T cell ratio predicts good anti-tumour immune response.[1,2] Low CD4+/CD8+ ratio predicted a better prognosis in patients with NSCLC receiving stereotactic ablative radiotherapy. For CD4/CD8 ratio not in peripheral blood, a higher CD4/CD8 pleural effusion ratio predicted better survival in lung cancer patients receiving ICIs. Using CD8+/CD4+ TIL ratio in tumour biopsy can predict the response of metastatic melanoma and NSCLC to PD-1/PD-L therapy.[6] These findings point to the need to explore the clinical significance of the CD4/CD8 ratio.

Overall, this study preliminarily suggested that a high baseline CD4/CD8 ratio in peripheral blood was associated with a favourable prognosis in patients with NSCLC receiving PD-1/PD-L1 inhibitors. In particular, patients with a high CD4/CD8 ratio had

better PFS than those with a low CD4/CD8 ratio. This suggests that the baseline peripheral blood CD4/CD8 ratio can be considered as a reliable marker. In future work, more standardised and larger sample sizes are needed to further explore the predictive value of CD4/CD8 ratio in certain subgroups. There is also an urgent need to address coordinated methods and techniques for finding the optimal critical value of the ratio. In addition, on the basis of a single biomarker, researchers should also focus on combining the CD4/CD8 ratio with other qualified markers to further enhance its predictive reliability.

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AUTHORS' CONTRIBUTION:
QMZ, GXL: Design, acquisition, analysis and interpretation of data, and manuscript writing.
YYL, YPW, MZ: Result interpretation and discussion.
ZGS: Design of the study and agreement to be accountable for all aspects of the work.
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