Original Article

Increasing serum complement component 1q is associated with worse prognosis in advanced non-small cell lung cancer treated with immune checkpoint inhibitors: a single-center, retrospective study

Jiazhuo Tang[1], Yang Fu[2], Yuxiao Song[1], Jiaxin Yin[2], Jun Wang[3], Hugo Arasanz[4,5], Bicheng Zhang[1]

[1]Cancer Center, Renmin Hospital of Wuhan University, Wuhan, China; [2]Department of Oncology, Xiangyang Hospital, Hubei University of Chinese Medicine, Xiangyang, China; [3]Department of Oncology, The First Affiliated Hospital of Shandong First Medical University, Jinan, China; [4]Department of Medical Oncology, Hospital Universitario de Navarra, Navarra Medical Research Institute (IdiSNA), Pamplona, Spain; [5]Oncobiona Group, Navarrabiomed, Navarra Medical Research Institute (IdiSNA), Pamplona, Spain

Contributions: (I) Conception and design: B Zhang; (II) Administrative support: B Zhang, J Wang; (III) Provision of study materials or patients: J Yin, Y Song; (IV) Collection and assembly of data: J Tang, Y Fu; (V) Data analysis and interpretation: J Tang; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Bicheng Zhang, Ph.D. Cancer Center, Renmin Hospital of Wuhan University, 99 Zhangzhidong Road, Wuhan 430061, China. Email: bichengzhang@hotmail.com.

Background: There is a lack of readily available clinical markers of non-small cell lung cancer (NSCLC) immunotherapy efficacy. Previous studies have found that overexpressed complement component 1q (C1q) promotes macrophage M2 polarization and an immunosuppressive tumor microenvironment. This study aimed to evaluate the association between serum C1q and the efficacy of immune checkpoint inhibitors (ICIs) in patients with advanced NSCLC.

Methods: A total of 168 patients with advanced NSCLC who received ICIs in the Renmin Hospital of Wuhan University were included in this study. Serum C1q levels were collected before and 3 weeks after immunotherapy treatment, together with other data on clinical and demographic characteristics. The primary outcome was overall survival (OS) (months from first dose of ICIs to death, censored at date of last follow-up). Secondary outcome was progression-free survival (PFS) [defined as months from first dose of ICIs to clinical or radiographic progression by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) or death, censored at date of last follow-up] and objective response rate (ORR) which was defined as rate of complete response (CR) or partial response (PR) at best response by RECIST 1.1.

Results: A total of 168 patients were included in this study, including 127 males (75.60%) and 41 females (24.40%). Thirty-nine patients achieved objective response (2 CR, 37 PR), and 111 patients (66.07%) had stable disease (SD) as best response. The ORR was 23.21% and the disease control rate was 89.28%. The upward trends of serum C1q levels between baseline and post-treatment were strongly associated with the shorter PFS [hazard ratio (HR) =1.554, 95% confidence interval (CI): 1.07–2.10, P=0.01] and OS (HR =1.444, 95% CI: 1.01–1.98, P=0.03). Moreover, taking the median OS 18.9 months as the cut-off of prognosis, receiver operating characteristic (ROC) analysis showed that serum baseline C1q yielded an area under the ROC curve of 0.785 (95% CI: 0.711–0.869). The optimal serum baseline C1q cut-off point to predict immunotherapy prognosis was 216.2 mg/L.

Conclusions: These findings suggested that elevated serum C1q after ICIs treatment was related to a worse prognosis in NSCLC. Monitoring the baseline and dynamic data of C1q during hospitalization showed the potential to predict the prognosis of NSCLC patients.

Keywords: Complement component 1q (C1q); non-small cell lung cancer (NSCLC); immune checkpoint inhibitors (ICIs); survival; Eastern Cooperative Oncology Group performance status (ECOG-PS)

Submitted Apr 09, 2024. Accepted for publication May 10, 2024. Published online May 24, 2024.
doi: 10.21037/jtd-24-304
View this article at: https://dx.doi.org/10.21037/jtd-24-304

Introduction

Lung cancer is one of the malignant tumors with the highest morbidity and mortality all over the world, of which about 85% are non-small cell lung cancer (NSCLC). Immune checkpoint inhibitors (ICIs), represented by programmed cell death protein-1 (PD-1)/programmed cell death ligand-1 (PD-L1) antibodies and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) antibodies, have become the first-line standard treatment for patients with advanced NSCLC and significantly improve survival (1). Unfortunately, most of the patients do not respond to the treatment and no accurate biomarkers able to identify these patients have been discovered yet. There are three main prognostic markers in NSCLC treated with ICIs, including clinical characteristics, blood-based biomarkers and genetic markers. Clinical characteristics such as Eastern Cooperative Oncology Group performance status (ECOG-PS) and age which predict efficacy have been extensively studied. Patients with ECOG-PS score ≥2 showed limited benefit from ICIs treatment, but the association between old age and efficacy of ICIs remains controversial (2-4). Studies investigating predictive blood-based biomarkers are insufficient (5,6). Moreover, blood-based biomarkers such as lactate dehydrogenase (LDH), C-reactive protein (CRP) and neutrophils to leukocytes ratio (NLR) are dynamic, the optimal time and frequency of measurements are also controversial (7-9). In terms of genetic markers, although markers represented by PD-L1 are effective in predicting the efficacy of ICIs, the detection method is difficult to be quantified and standardized (10). In addition, the detection is costly and some require tumor tissue, which is invasive (11). Therefore, a large number of clinical studies and transformational research are still needed to figure out easily accessible, cost-effective and standardized biomarkers (12,13).

Previous studies have shown that the function of anti-tumor immune cells [such as natural killer (NK) cells and $CD8^+$ T cells] is significantly inhibited in advanced lung cancer patients because the tumor microenvironment (TME) contains a large number of immunosuppressive cells such as tumor-associated macrophages (TAMs) and regulatory T cells (Tregs) (14,15). Our former research revealed that TAMs in lung adenocarcinoma (LUAD) could secrete a large amount of complement component 1q (C1q) (16), a small protein involved in inflammatory and immunological responses, suggesting that a high levels of C1q may be related to worse prognosis of such patients. Besides, Iyer *et al.* (17) demonstrated that C1q has an association with the efficacy of immunotherapy in patients with advanced lung cancer. In addition, considering the easy availability of serum C1q in clinical practice, the use of serum C1q for the prediction of efficacy is a promising approach. In esophageal cancer, serum baseline and post-treatment C1q have been shown to be associated with the efficacy of combined immunotherapy (18). Nevertheless, there is still a lack of studies investigating the association between serum C1q and the prognosis of NSCLC immunotherapy. This present study discovered that increasing serum C1q may be related to a worse prognosis of ICIs treatment in advanced NSCLC. We present this article in accordance with the REMARK reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-304/rc).

Highlight box

Key findings

- Elevated serum complement component 1q (C1q) after immune checkpoint inhibitors (ICIs) treatment was related to a worse prognosis in non-small cell lung cancer (NSCLC). Moreover, baseline serum C1q levels showed the potential to predict NSCLC immunotherapy prognosis.

What is known and what is new?

- In esophageal cancer, serum baseline and post-treatment C1q have been proven to be associated with the efficacy of immunotherapy. However, the relationship between serum C1q, the prognosis of NSCLC and the efficacy of immunotherapy remains unclear.
- We collected clinical data from our center to retrospectively analyze the prognostic and predictive value of serum C1q in patients with advanced NSCLC treated with ICIs.

What is the implication, and what should change now?

- Our results provide insight into the efficacy of immunotherapy in advanced NSCLC. The serum C1q may be a novel biomarker for predicting the prognosis of patients with advanced NSCLC treated with ICIs.

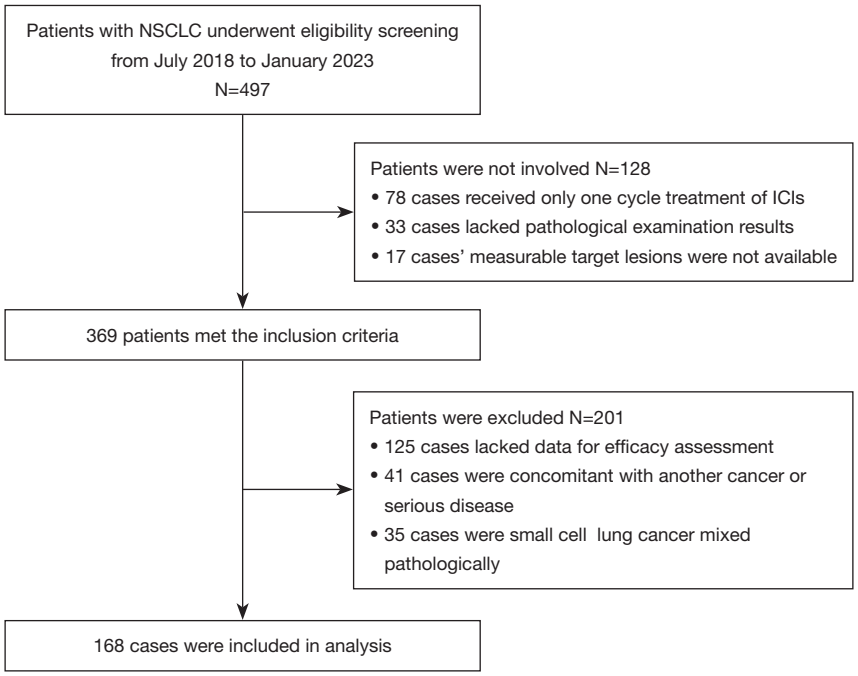

Figure 1 Flow chart of immune checkpoint inhibitors in the treatment of patients with advanced NSCLC. NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors.

Methods

Study design and eligibility criteria

A retrospective study of patients with advanced NSCLC in Renmin Hospital of Wuhan University, China was conducted from July 2018 to May 2023. The inclusion criteria included: (I) pathological diagnosis of NSCLC; (II) clinical staging of IIIb–IV; (III) patients treated with ICIs, such as anti-PD-1 or PD-L1 antibody, for at least two cycles; (IV) at least one measurable target lesion. The exclusion criteria were as follows: (I) concomitant with another cancer or serious disease; (II) data of efficacy assessment was not available; (III) mixed small cell lung cancer (SCLC) histology. This study was performed in accordance with the principle of the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University dated on 2022-02-18. Individual consent for this retrospective analysis was waived.

Active and passive methods were used to collect follow-up data. The active method means that patients went to the outpatient clinic or hospitalization department for follow-up regularly, and the passive method means that we followed up patients by telephone, text message, etc. To maintain accurate surveillance information, data fields relating to patient vital status, date of last contact, treatment, and recurrence were updated. Patients were followed until the date of death or the last date of follow-up (May 31, 2023). Patients who were lost to follow-up were permitted for survival analysis. A flow chart of the present study is illustrated in *Figure 1*. Eventually, a total of 168 patients with advanced NSCLC were enrolled in this study.

Data collection and outcome

Baseline characteristics, including demographic characteristics (age and sex), smoking status, ECOG-PS, metastasis (brain, bone and liver), histology type, driver gene mutation, previous treatment, and immunotherapy regimen, were collected. Blood was drawn from the patient's periphery vein and the blood samples were sent to the hospital laboratory for testing. The data of CRP, neutrophils, and lymphocytes were collected from routine blood tests. The whole blood was centrifuged to separate the serum for the detection of C1q, albumin, globulin, and LDH. Data of C1q at baseline and 3 weeks after ICIs treatment, baseline albumin to globulin ratio (AGR), NLR, LDH, and CRP were recorded and calculated. The primary outcome was overall survival (OS) (months from first dose of ICIs to death, censored at date of last follow-

up). Secondary outcome was progression-free survival (PFS) [defined as months from first dose of ICIs to clinical or radiographic progression by Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) or death, censored at date of last follow-up] and objective response rate (ORR) which was defined as rate of complete response (CR) or partial response (PR) at best response by RECIST 1.1.

Response assessments

Tumor response efficacy was determined as CR, PR, stable disease (SD), or progressive disease (PD). The overall response rate (ORR) consisted of CR and PR. The disease control rate (DCR) was composed of CR, PR, and SD in 3 months after ICIs were administered. PFS was defined as the time from the first day of immunotherapy treatment to disease progression. The OS was the time from the date on which advanced NSCLC was confirmed and first-line treatment began to the date of death, or the date of death in line with the last follow-up by the families.

Clinical data during the immunotherapy were recorded to evaluate the efficacy. All ICIs and targeted regimens were administered in standard doses, based on Chinese Society of Clinical Oncology (CSCO) guidelines. The response was assessed according to RECIST 1.1. Before analysis, efficacy was evaluated by two oncologists according to RECIST 1.1 criteria based on chest computed tomography (CT) every 4–8 weeks, and positron emission tomography (PET)/CT was also referred to if existed during the evaluation.

Statistical analysis

The normality of continuous variables was assessed using the Shapiro-Wilk test. Normally distributed continuous variables were presented as means ± standard deviations and analyzed using Student's *t*-test. For non-normally distributed continuous variables, medians [interquartile ranges (IQRs)] were presented and analyzed using the Mann-Whitney *U* test. Categorical variables were expressed as frequency (percentage, %) and analyzed using Fisher's exact test. OS and PFS were estimated based on Kaplan-Meier methods, and compared using log-rank test. Univariate and multivariate Cox regression models were performed to analyze the correlation between clinical factors and PFS and OS, through which hazard ratio (HR) and related 95% confidence intervals (CIs) were estimated. All statistical analyses were performed in SPSS version 25.0 (IBM Corp., Armonk, NY, USA). A two-sided P values <0.05 were considered statistically significant.

Data availability

The data generated in this study are not publicly available due to information that could compromise patient privacy but are available upon reasonable request from the corresponding author.

Results

Baseline characteristics

A total of 168 patients with advanced NSCLC were included in the study, including 127 males (75.60%) and 41 females (24.40%). Thirty-five (20.83%) were ≥75 years old at the beginning of the first ICIs treatment, 51 (30.36%) had a previous history of smoking, 109 (64.88%) had LUAD, 57 (33.93%) had lung squamous cell carcinoma (LUSC), and 2 (1.19%) had NSCLC not otherwise specified (NSCLC-NOS). The results of the driving gene test in 91 patients (54.17%) could be traced back, including 46 patients with driving gene mutation and 45 patients with wild type. The details of the baseline characteristics of the patients are shown in *Table 1*.

Response to immunotherapy treatment

The median follow-up period was 17.1 months (IQR, 7.7–21.2 months). A total of 168 patients were accessible to clinical and imaging data for efficacy evaluation. Thirty-nine patients (23.21%) achieved an objective response (2 cases of CR, 37 cases of PR), and 111 patients (66.07%) had SD as best response. DCR of 3 months was 89.28%. In addition, of 83 patients receiving first-line ICIs-based therapy, 23 patients (27.71%) achieved an objective response (1 cases of CR, 22 cases of PR), and 55 patients (66.27%) had the best efficacy of SD, thus DCR was 93.98%.

Association of serum C1q levels and patient survival

The patients were classified into the C1q increased group and the C1q decreased group according to the trend of serum C1q after ICIs treatment. Both median PFS (mPFS) (P=0.01) and median OS (mOS) (P=0.03) of patients in C1q increased group were significantly shorter compared with those in C1q decreased group (*Figure 2*). Taking the mOS 18.9 months as the cutoff of prognosis and the

Table 1 Baseline characteristics of involved patients with advanced NSCLC treated with ICIs

Characteristics	N (%)
Sex	
Male	127 (75.60)
Female	41 (24.40)
Age (years)	
≥75	35 (20.83)
<75	133 (79.17)
Smoking history	
Ever/current	51 (30.36)
Never	117 (69.64)
ECOG-PS	
0–1	147 (87.50)
≥2	21 (12.50)
Brain metastasis	
Yes	30 (17.86)
No	138 (82.14)
Bone metastasis	
Yes	67 (39.88)
No	101 (60.12)
Liver metastasis	
Yes	18 (10.71)
No	150 (89.29)
Histology type	
LUAD	109 (64.88)
LUSC	57 (33.93)
NSCLC-NOS	2 (1.19)
Driver gene mutation	
Wild	45 (26.79)
Mutant	46 (27.38)
Unknown	77 (45.83)
Treatment line	
First line	83 (49.40)
Second line	50 (29.76)
Third or further line	35 (20.84)
Combination therapy	
Yes	155 (92.26)
No	13 (7.74)

NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; ECOG-PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NOS, not otherwise specified.

patients were divided into over mOS group and below mOS group, receiver operating characteristic (ROC) analysis showed that baseline serum C1q yielded an area under the ROC curve (AUC) of 0.785 (95% CI: 0.711–0.869) (*Figure 3*). The optimal serum baseline C1q cut-off point to predict immunotherapy prognosis was 216.2 mg/L, which gave a sensitivity of 66.7% and a specificity of 84.9% (P<0.001).

The levels of baseline AGR, NLR, LDH, and CRP were compared in the above groups reflecting mPFS or mOS, respectively. The results of 158 samples for blood routine and biochemical examination were collected, among which 152, 152, 150, and 150 pieces of data were used for AGR, NLR, LDH, and CRP analysis respectively, and none of them was found to be correlated with prognosis (Figure S1).

Correlation between clinicopathological characteristics and survival

Until 3 May 2023, a total of 91 patients presented progression or death. Subgroup analysis based on clinical characteristics showed that the mPFS of patients whose age was <75 years (8.4±0.8 *vs.* 6.7±1.5 months, P=0.02) or ECOG-PS score 0–1 (8.5±0.7 *vs.* 4.8±2.2 months, P=0.001) was significantly longer than that of the corresponding control group. There was no significant difference in mPFS between patients with or without smoking history (P=0.39) or brain metastasis (P=0.89) (Table S1). The mOS of patients whose ECOG-PS 0–1 was significantly longer than those whose ECOG-PS ≥2 (P<0.001), the mOS of patients without brain metastasis was significantly longer than that of patients with brain metastasis (P=0.03). The mOS of patients whose age <75 years (P=0.09) tended to be prolonged. There was no significant difference in mOS among different sex groups (P=0.58) or bone metastasis (P=0.72) (Table S2).

Univariate and multivariate Cox proportional regression models were performed to analyze the PFS and OS. The multivariate Cox regression analyses showed that ECOG-PS ≥2 was significantly related to shorter PFS (P=0.001) (Table S3) and OS (P=0.001) (Table S4) of the patients with advanced NSCLC. Previous chemotherapy was an independent prognostic factor for OS of advanced NSCLC treated with ICIs (P=0.03).

Discussion

Our study focused on exploring C1q leading to diminished

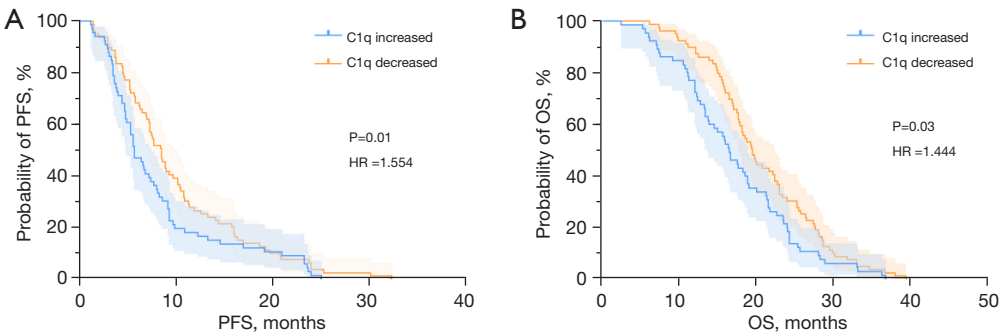

Figure 2 Correlation between serum C1q levels trends and survival of patients with advanced NSCLC treated with immunotherapy. (A) PFS of patients whose serum C1q decreased (mPFS =8.6 months, 95% CI: 7.8–9.4) or increased (mPFS =5.6 months, 95% CI: 4.6–6.6) after ICIs treatment. Patients whose serum C1q level increased after ICIs treatment showed shorter mPFS (HR =1.554, 95% CI: 1.07–2.10, P=0.01); (B) OS of patients whose serum C1q decreased (mOS =19.5 months, 95% CI: 17.7–21.3) or increased (mOS =16.5 months, 95% CI: 14.5–18.5) after ICIs treatment. Patients whose serum C1q level increased after ICIs treatment showed shorter mOS (HR =1.444, 95% CI: 1.01–1.98, P=0.03). PFS, progression-free survival; OS, overall survival; HR, hazard ratio; C1q, complement component 1q; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; mPFS, median PFS; mOS, median OS.

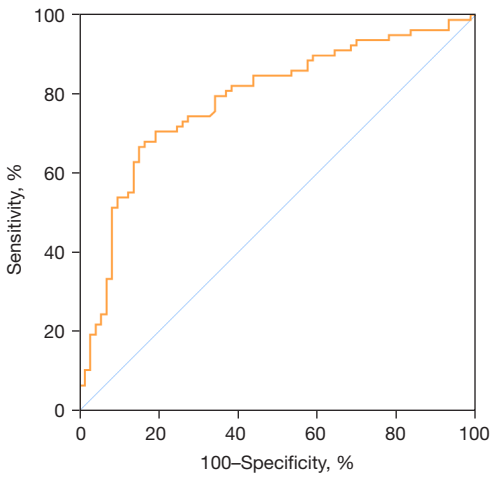

Figure 3 Ability of baseline C1q level to predict OS of patients with advanced NSCLC to immunotherapy. The AUC is 0.785; the 95% CI is 0.711 to 0.869; and the difference is statistically significant (P<0.001). The cut-off value of baseline C1q is 216.2 mg/L; the corresponding sensitivity is 66.7%; and the specificity is 84.9%. C1q, complement component 1q; OS, overall survival; NSCLC, non-small cell lung cancer; AUC, area under the curve; CI, confidence interval.

efficacy of ICIs in patients with advanced NSCLC. C1q in TME can act as a tumor promoter by promoting cancer cell adhesion, migration, and proliferation in NSCLC, melanoma, and colon cancer (19), and can influence the efficacy of ICIs in multiple ways. C1q can lead to immunotherapy resistance by enhancing signaling pathways. The overexpression of C1q in malignant pleural mesothelioma induces the production of immunosuppressive TME, leading to immunotherapy resistance (20). C1q enhances MAPKs, and PI3K/AKT signaling and makes hepatocellular carcinoma cells more aggressive (21). Our previous study suggests that overexpressed C1q in TAMs promotes macrophages M2 polarization and induces and maintains immunosuppressive TME by up-regulating nucleotide-binding leucine-rich repeat-containing receptor 12 (NLRP12) expression and activating nuclear transcription factor-kappa B (NF-κB) pathway (16). Meanwhile, a bioinformatics study explored common differentially expressed genes in NSCLC through multiple publicly available databases and showed that elevated C1q expression levels are associated with poorer prognosis in NSCLC patients (22). However, it is not clinically feasible to detect C1q in TME. Given the convenience of detecting peripheral blood, we endeavored to determine whether C1q in peripheral blood is as worthwhile as C1q in TME for predicting prognosis.

Our study found that serum C1q levels may be a useful predictor of the efficacy of ICIs. We retrospectively analyzed the efficacy of ICIs in 168 patients with advanced NSCLC, showing that ICIs showed a good clinical effect, with ORR of 23.21%, DCR of 89.28%, mPFS of 8.1 months, and mOS of 18.9 months. By comparing the relationship between serum C1q levels and survival in advanced NSCLC patients receiving ICIs treatment, the

results revealed that patients with elevated serum C1q levels had poorer survival. In addition, baseline serum C1q levels showed the potential to predict NSCLC immunotherapy prognosis. Individual studies focused on the relationship between C1q and the prognosis of malignant tumor patients treated with ICIs successively emerged in recent years. This study aimed to explore the correlation between serum C1q levels and the efficacy of ICIs in real-world patients with advanced NSCLC. Our study concluded that the higher the C1q level was, the more limited the benefit of ICIs for NSCLC patients. Thus, we came up that monitoring the baseline and dynamic data of C1q during hospitalization and performing a comprehensive analysis of its changing trend may be helpful in judging the prognosis of patients.

Our study also discovered that age and ECOG-PS score also had a significant impact on the prognosis of NSCLC patients. The PFS of patients ≥75 years old was significantly shorter than that of those <75 years old. The PFS and OS of patients whose ECOG-PS 0–1 were significantly longer than those of patients whose ECOG-PS ≥2. Mezquita *et al.* (23) found that patients with advanced NSCLC with an ECOG-PS score of 0–1 had better survival outcomes. The age stratification results of the KEYNOTE-010 and KEYNOTE-042 studies showed that the benefit from ICIs treatment in NSCLC patients ≥75 years old was significantly lower than that in patients <75 years old (4). A retrospective study of higher age stratification showed that the OS of advanced NSCLC patients >80 years old after ICIs treatment was only 3.62 months, whereas that of people <80 years old was more than 12.92 months (2). Our study also found that there was a relationship between ECOG-PS and PFS/OS, however, the relationship between age and survival was not clear. In this study, age ≥75 years old was significantly related to shorter PFS, but was not related to OS. It might be because the sample was not large enough or the follow-up time was not long enough. Although many studies have implied the correlation between old age and shorter PFS/OS, it is still controversial whether patients with older age tend to achieve worse survival.

Conclusions

In summary, our research showed that a high level of serum C1q may be related to worse efficacy of NSCLC immunotherapy. This study presents several limitations, including the small sample size. Besides, our sample came from a single center, so the generalizability of our findings to other patient populations needs to be confirmed. In the future, prospective clinical studies of large scale are still needed to further verify the relationship between serum C1q level and survival of ICIs in patients with NSCLC.

Acknowledgments

Funding: This work was supported by the National Natural Science Foundation of China (No. 82272928); CSCO-BMS Cancer Immunotherapy Research Foundation (No. Y-BMS2019-003); Knowledge Innovation Program of Wuhan-Basic Research (No. 2022020801010475), and Medical Youth Outstanding Talents Project of Hubei Province (No. EWT2019-48).

Footnote

Reporting Checklist: The authors have completed the REMARK reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-304/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-304/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-304/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-304/coif). H.A. receives consulting fees from Astra Zeneca, payment for lectures from Takeda, gets support for attending meetings from MSD, Roche, Angelini Pharma, BMS, and takes charge of clinical trial coordination for Ferrer, outside this study. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was performed in accordance with the principle of the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Renmin Hospital of Wuhan University dated on 2022-02-18. Individual consent for this retrospective analysis was waived.

References

1. Corke L, Sacher A. New Strategies and Combinations to Improve Outcomes in Immunotherapy in Metastatic Non-Small-Cell Lung Cancer. Curr Oncol 2021;29:38-55.
2. Lichtenstein MRL, Nipp RD, Muzikansky A, et al. Impact of Age on Outcomes with Immunotherapy in Patients with Non-Small Cell Lung Cancer. J Thorac Oncol 2019;14:547-52.
3. Voruganti T, Soulos PR, Mamtani R, et al. Association Between Age and Survival Trends in Advanced Non-Small Cell Lung Cancer After Adoption of Immunotherapy. JAMA Oncol 2023;9:334-41.
4. Nosaki K, Saka H, Hosomi Y, et al. Safety and efficacy of pembrolizumab monotherapy in elderly patients with PD-L1-positive advanced non-small-cell lung cancer: Pooled analysis from the KEYNOTE-010, KEYNOTE-024, and KEYNOTE-042 studies. Lung Cancer 2019;135:188-95.
5. Liang S, Wang H, Tian H, et al. The prognostic biological markers of immunotherapy for non-small cell lung cancer: current landscape and future perspective. Front Immunol 2023;14:1249980.
6. Weber S, van der Leest P, Donker HC, et al. Dynamic Changes of Circulating Tumor DNA Predict Clinical Outcome in Patients With Advanced Non-Small-Cell Lung Cancer Treated With Immune Checkpoint Inhibitors. JCO Precis Oncol 2021;5:1540-53.
7. Zhang Z, Li Y, Yan X, et al. Pretreatment lactate dehydrogenase may predict outcome of advanced non small-cell lung cancer patients treated with immune checkpoint inhibitors: A meta-analysis. Cancer Med 2019;8:1467-73.
8. Iivanainen S, Ahvonen J, Knuuttila A, et al. Elevated CRP levels indicate poor progression-free and overall survival on cancer patients treated with PD-1 inhibitors. ESMO Open 2019;4:e000531.
9. Lim JU, Kang HS, Yeo CD, et al. Predictability of early changes in derived neutrophil-to-lymphocyte ratio and neutrophil-to-lymphocyte ratio in patients with advanced non-small cell lung cancer treated with immune checkpoint inhibitors. J Thorac Dis 2021;13:2824-32.
10. Brueckl WM, Ficker JH, Zeitler G. Clinically relevant prognostic and predictive markers for immune-checkpoint-inhibitor (ICI) therapy in non-small cell lung cancer (NSCLC). BMC Cancer 2020;20:1185.
11. Uehara Y, Hakozaki T. Immune checkpoint inhibitors for patients with gene-rearranged non-small cell lung cancer. Transl Lung Cancer Res 2023;12:6-10.
12. Tang S, Qin C, Hu H, et al. Immune Checkpoint Inhibitors in Non-Small Cell Lung Cancer: Progress, Challenges, and Prospects. Cells 2022;11:320.
13. Roulleaux Dugage M, Albarrán-Artahona V, Laguna JC, et al. Biomarkers of response to immunotherapy in early stage non-small cell lung cancer. Eur J Cancer 2023;184:179-96.
14. Gong Z, Jia Q, Chen J, et al. Impaired Cytolytic Activity and Loss of Clonal Neoantigens in Elderly Patients With Lung Adenocarcinoma. J Thorac Oncol 2019;14:857-66.
15. Erbe R, Wang Z, Wu S, et al. Evaluating the impact of age on immune checkpoint therapy biomarkers. Cell Rep 2021;36:109599.
16. Song Y, Fu Y, Wang J, et al. Complement C1q induces the M2-polarization of tumor-associated macrophages in lung adenocarcinoma. Genes Dis 2024;11:101093.
17. Iyer A, Xu W, Reid RC, et al. Chemical Approaches to Modulating Complement-Mediated Diseases. J Med Chem 2018;61:3253-76.
18. Wen J, Zhao Y, Fang CX, et al. Association between serum baseline C1q and IgG levels and the efficacy of combined immunotherapy in patients with esophageal squamous cell carcinoma: a retrospective study. Immunopharmacol Immunotoxicol 2023;45:83-8.
19. Bulla R, Tripodo C, Rami D, et al. C1q acts in the tumour microenvironment as a cancer-promoting factor independently of complement activation. Nat Commun 2016;7:10346.
20. Balduit A, Vidergar R, Zacchi P, et al. Complement protein C1q stimulates hyaluronic acid degradation via gC1qR/HABP1/p32 in malignant pleural mesothelioma. Front Immunol 2023;14:1151194.
21. Lee JH, Poudel B, Ki HH, et al. Complement C1q stimulates the progression of hepatocellular tumor through the activation of discoidin domain receptor 1. Sci Rep 2018;8:4908.
22. Kou W, Li B, Shi Y, et al. High complement protein C1q levels in pulmonary fibrosis and non-small cell lung cancer

associated with poor prognosis. BMC Cancer 2022;22:110.
23. Mezquita L, Auclin E, Ferrara R, et al. Association of the Lung Immune Prognostic Index With Immune Checkpoint Inhibitor Outcomes in Patients With Advanced Non-Small Cell Lung Cancer. JAMA Oncol 2018;4:351-7.

Cite this article as: Tang J, Fu Y, Song Y, Yin J, Wang J , Arasanz H, Zhang B. Increasing serum complement component 1q is associated with worse prognosis in advanced non-small cell lung cancer treated with immune checkpoint inhibitors: a single-center, retrospective study. J Thorac Dis 2024;16(5):3251-3259. doi: 10.21037/jtd-24-304

Supplementary

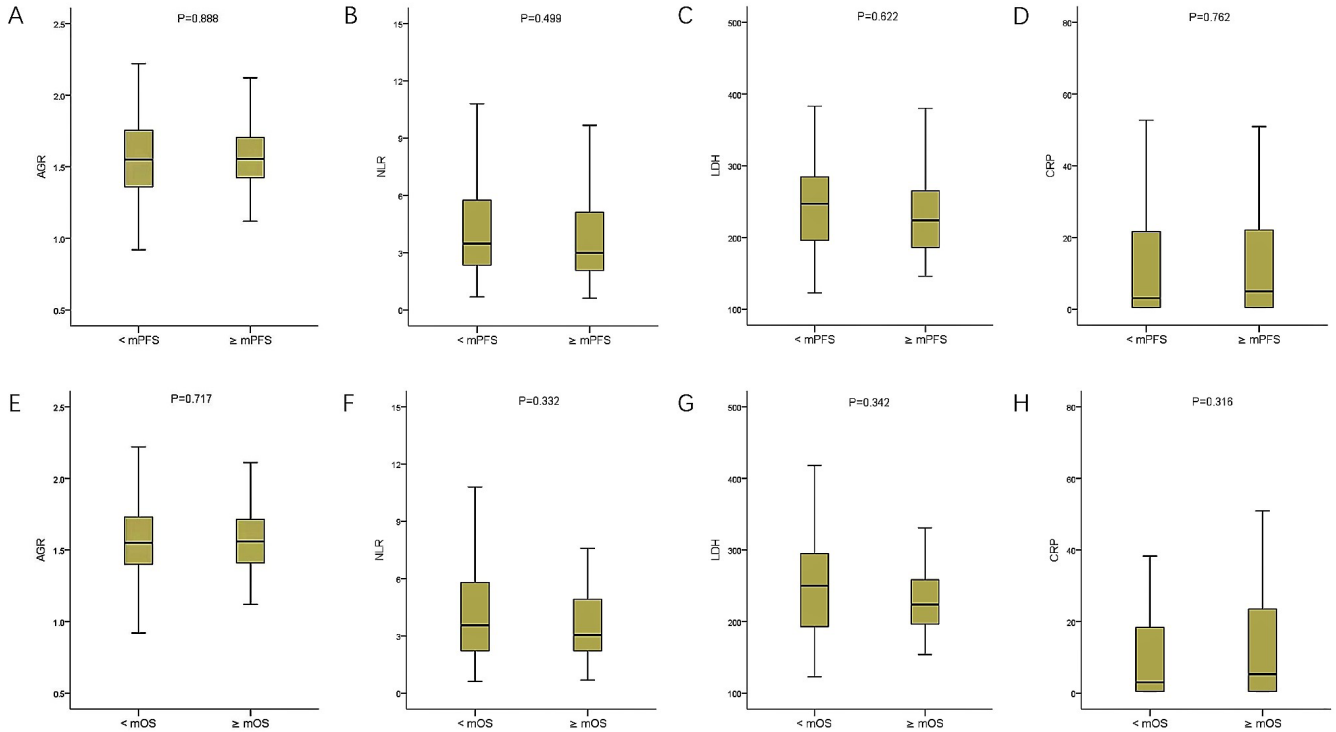

Figure S1 Correlation between laboratory results and survival of patients with advanced NSCLC. (A) Levels of AGR between different PFS groups; (B) levels of NLR between different PFS groups; (C) levels of LDH between different PFS groups; (D) levels of CRP between different PFS groups; (E) levels of AGR between different OS groups; (F) levels of NLR between different OS groups; (G) levels of LDH between different OS groups; (H) levels of CRP between different OS groups. No significant difference was found. AGR, albumin to globulin ratio; NLR, neutrophils to leukocytes ratio; LDH, lactate dehydrogenase; CRP, C-reactive protein; PFS, progression-free survival; mPFS, median PFS; OS, overall survival; mOS, median OS; NSCLC, non-small cell lung cancer.

https://dx.doi.org/10.21037/jtd-24-304

Table S1 Subgroup analysis of PFS in patients with advanced NSCLC receiving ICIs treatment

Group	N	Median PFS (95% CI) (months)	P value
Sex			0.081
Male	120	8.1 (6.8, 9.4)	
Female	41	7.6 (6.2, 9.0)	
Age (years)			0.022*
≥75	33	6.7 (5.2, 8.2)	
<75	128	8.4 (7.6, 9.2)	
Smoking history			0.390
Yes	48	6.9 (5.0, 8.8)	
No	113	8.5 (7.5, 9.5)	
ECOG-PS			0.001*
0–1	140	8.5 (7.8, 9.2)	
≥2	21	4.8 (2.6, 7.0)	
Histology type			0.272
LUAD	106	8.3 (7.4, 9.2)	
LUSC	53	8.1 (5.6, 10.7)	
NSCLC-NOS	2	5.3 (–)	
Brain metastasis			0.895
Yes	35	7.7 (5.7, 9.7)	
No	126	8.3 (7.3, 9.3)	
Bone metastasis			0.688
Yes	67	8.5 (7.2, 9.8)	
No	94	7.7 (6.2, 9.2)	
Liver metastasis			0.641
Yes	17	8.4 (3.8, 13.0)	
No	144	8.0 (7.0, 9.0)	
Previous surgery			0.613
Yes	27	9.2 (8.0, 10.4)	
No	134	7.8 (6.7, 8.9)	
Previous targeted therapy			0.346
Yes	43	8.4 (6.7, 10.1)	
No	118	7.9 (6.7, 9.1)	
Combination therapy			0.397
Yes	138	7.8 (6.7, 8.9)	
No	23	8.5 (7.4, 9.6)	
Treatment line			0.936
First line	77	7.2 (5.1, 9.2)	
Second or further line	84	8.4 (7.7, 9.1)	

*, P value <0.05. PFS, progression-free survival; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NOS, not otherwise specified.

https://dx.doi.org/10.21037/jtd-24-304

Table S2 Subgroup analysis of OS in patients with advanced NSCLC receiving ICIs treatment

Group	N	Median OS (95% CI) (months)	P value
Sex			0.588
Male	126	18.3 (16.4, 10.2)	
Female	41	18.9 (17.2, 20.6)	
Age (years)			0.097
≥75	35	18.2 (15.7, 20.8)	
<75	132	18.9 (17.5, 20.3)	
Smoking history			0.112
Yes	51	18.9 (16.2, 21.6)	
No	116	18.8 (17.3, 20.3)	
ECOG-PS			<0.001*
0–1	146	19.5 (17.7, 21.4)	
≥2	21	12.8 (10.9, 14.7)	
Histology type			0.124
LUAD	108	18.3 (16.3, 20.3)	
LUSC	57	18.9 (17.6, 20.2)	
NSCLC-NOS	2	13.9 (–)	
Brain metastasis			0.036*
Yes	35	15.9 (14.5, 17.3)	
No	132	19.5 (18.1, 20.9)	
Bone metastasis			0.727
Yes	67	20.1 (17.8, 22.4)	
No	100	18.2 (17.2, 19.2)	
Liver metastasis			0.615
Yes	17	19.6 (12.0, 25.2)	
No	150	18.9 (17.6, 20.2)	
Previous surgery			0.763
Yes	29	18.1 (15.3, 20.9)	
No	138	18.9 (17.5, 20.3)	
Previous targeted therapy			0.204
Yes	43	19.9 (15.2, 24.6)	
No	124	18.6 (17.4, 19.8)	
Combination therapy			0.720
Yes	143	18.9 (17.6, 20.2)	
No	24	16.5 (14.6, 18.4)	
Treatment line			0.372
First line	83	18.8 (17.9, 19.7)	
Second or further line	84	19.5 (16.5, 22.5)	

*, P value <0.05. OS, overall survival; NSCLC, non-small cell lung cancer; ICIs, immune checkpoint inhibitors; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; NOS, not otherwise specified.

https://dx.doi.org/10.21037/jtd-24-304

Table S3 Univariate and multivariate Cox regression models of clinical characteristics and PFS in patients with NSCLC

Group	Univariate Cox regression analyses		Multivariate Cox regression analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male *vs.* female)	0.725 (0.503, 1.044)	0.084	–	–
Age (≥75 *vs.*<75 years)	1.574 (1.063, 2.332)	0.024*	1.407 (0.915, 1.896)	0.120
Smoking history (yes *vs.* no)	0.394 (0.826, 1.625)	0.394	–	–
ECOG-PS (≥2 *vs.* 0–1)	2.246 (1.402, 3.598)	0.001*	2.317 (1.411, 3.806)	0.001*
Histology type (LUSC *vs.* LUAD)	0.813 (0.583, 1.135)	0.224	–	–
Brain metastasis (yes *vs.* no)	0.975 (0.667, 1.426)	0.895	–	–
Bone metastasis (yes *vs.* no)	1.067 (0.777, 1.464)	0.690	–	–
Liver metastasis (yes *vs.* no)	1.127 (0.679, 1.868)	0.644	–	–
Previous surgery (yes vs no)	0.899 (0.593, 1.364)	0.617	–	–
Previous targeted therapy (yes *vs.* no)	1.183 (0.832, 1.683)	0.350	–	–
Previous chemotherapy (yes *vs.* no)	0.820 (0.599, 1.124)	0.218	–	–
Combination therapy (yes *vs.* no)	1.211 (0.774, 1.896)	0.402	–	–
Treatment line (second or further line *vs.* first line)	0.987 (0.724, 1.347)	0.936	–	–

*, P value <0.05. PFS, progression-free survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma.

Table S4 Univariate and multivariate Cox regression models of clinical characteristics and OS in patients with NSCLC

Group	Univariate Cox regression analyses		Multivariate Cox regression analyses	
	HR (95% CI)	P value	HR (95% CI)	P value
Sex (male vs female)	0.907 (0.634, 1.295)	0.590	–	–
Age (≥75 *vs.* <75 years)	1.375 (0.941, 2.007)	0.099	–	–
Smoking history (yes *vs.* no)	1.160 (0.834, 1.614)	0.379	–	–
ECOG-PS (≥2 *vs.* 0–1)	2.325 (1.456, 3.713)	<0.001*	2.325 (1.397, 3.869)	0.001*
Histology type (LUSC *vs.* LUAD)	0.706 (0.503, 0.991)	0.044*	0.764 (0.510, 1.144)	0.192
Brain metastasis (yes *vs.* no)	1.491 (1.023, 2.173)	0.038*	1.259 (0.831, 1.909)	0.277
Bone metastasis (yes *vs.* no)	0.946 (0.691, 1.294)	0.728	–	–
Liver metastasis (yes *vs.* no)	0.879 (0.531, 1.456)	0.617	–	–
Previous surgery (yes *vs.* no)	0.940 (0.629, 1.407)	0.764	–	–
Previous targeted therapy (yes *vs.* no)	1.256 (0.882, 1.787)	0.207	–	–
Previous chemotherapy (yes *vs.* no)	0.726 (0.531, 0.994)	0.046*	0.664 (0.453, 0.973)	0.036*
Combination therapy (yes *vs.* no)	0.924 (0.598, 1.426)	0.721	–	–
Treatment line (second or further line *vs.* first line)	1.115 (0.845, 1.565)	0.375	–	–

*, P value <0.05. OS, overall survival; NSCLC, non-small cell lung cancer; HR, hazard ratio; CI, confidence interval; ECOG-PS, Eastern Cooperative Oncology Group performance status; LUSC, lung squamous cell carcinoma; LUAD, lung adenocarcinoma.

https://dx.doi.org/10.21037/jtd-24-304