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Correlation between Serum Interleukin-8, Interleukin-6 Levels, and the Response to Anti-PD-1/PD-L1 Inhibitor in Patients with Malignant Tumors: A Prospective Observational Study

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ABSTRACT

Background: Interleukin (IL)-6 and IL-8 are associated with cancer cell behaviors.

Objective: This study explored the association between serum IL-8 and IL-6 and response to anti-PD-1/PD-L1 inhibitors in patients with malignant tumors.

Methods: This prospective observational study enrolled patients diagnosed with malignant tumors at Shanghai Huadong Hospital between September 2019 and December 2021.

Results: Eighty participants were enrolled (53.8% male, median age 62). Among responders, the median serum IL-8 levels at best response (BR) were reduced compared with baseline [11.6 (9.4, 32.6) vs. 34.6 (26.9, 65.2); P<0.001] and increased in progressive disease (PD) [79 (44.55, 107.7) vs. 11.6 (9.4, 32.6), P<0.001]. Among non-responders, participants who developed PD had significantly increased serum IL-8 levels compared with baseline [80.95 (68.45, 117.25) vs. 30.5 (24.6, 77.5); P<0.001]. Changes in serum IL-8 levels were associated with response to anti-PD-1/PD-L1 inhibitor [responders: -38.6 (-47.2, -11.8); non-responders: 44.5 (3.5, 59.8), P<0.001]. Among non-responders, PD participants had increased serum IL-6 levels compared with baseline [15.9 (7.3, 23.3) vs. 7.9 (4.5, 17.2), P=0.03]. The early changes (2-4 weeks after the first dose) in serum IL-6 levels were not associated with anti-PD-1/PD-L1 inhibitor response (P=0.059).

Conclusions: Serum IL-8 and IL-6 could be effective and easy-to-assess biomarkers for evaluating the response to immune checkpoint inhibitors.

Keywords: Immune Checkpoint Inhibitors; Malignant Neoplasms; Serum Interleukin-6; Serum Interleukin-8; Disease Progression

Abbreviations: PD-1: Programmed Cell Death; ICIs: Immune Checkpoint Inhibitors; TMB: Tumor Mutation Burden; PS: Performance Status; BR: Best Response; PD: Progressive Disease; CR: Complete Response; PR: Partial Response; SD: Stable Disease; ROC: Receiver Operating Characteristic

Introduction

The programmed cell death (PD-1) receptor and its ligand (PD-L1) are involved in an important immune checkpoint that helps keep the body›s immune responses in check [1]. Cancer cells can express PD-L1 and PD-L2, which can inhibit immune-modulatory T-cell activation and facilitate disease progression by targeting the PD-1 receptor [2-4]; thus, blocking either PD-1 or PD-L1 can prevent PD-1 activation, attenuating the immune tolerance and improving T cell-mediated killing of cancer cells [5,6]. So far, several immune checkpoint inhibitors (ICIs) have been approved by the FDA,

including nivolumab, pembrolizumab, cemiplimab (PD-1 inhibitors), atezolizumab, avelumab, and durvalumab (PD-L1 inhibitors) [7-10]. Tumor response to ICIs is usually seen within 12 weeks of treatment. Still, 15% of the patients can display a pseudo progression that manifests as an index tumor enlarged by >25% or the appearance of novel lesions; still, histopathological biopsies have shown that pseudo progression is not true tumor progression as it is not confirmed on subsequent imaging [11,12]. Treatment beyond tumor progression is still debatable [12]. A tumor biopsy is still the best way to determine the nature of a progression [13]. Yet, it is an invasive procedure, the amount of tissue obtained from a needle biopsy may not be sufficient for some patients, and some lesions can be inaccessible. Recent studies have suggested that decreased circulating tumor DNA levels can help confirm the nature of the progression [14]; however, this test is costly and not widely available.

Biomarkers for the monitoring of ICI efficacy include PD-L1, tumor mutation burden (TMB), and microsatellite instability (MSI); however, they all have various disadvantages such as high price, affected by tumor heterogeneity, tumor tissues are required for the test, and different results caused by different reagent and platform [15,16]. Interleukin (IL)-6 is usually expressed at high levels in the tumor microenvironment and is upregulated by almost all cancers [17]. High amounts of serum IL-6 represent the inflammatory state of the tumor microenvironment. Serum IL-6 promotes cancer cells› biological behavior, including apoptosis, survival, proliferation, angiogenesis, invasion, metastasis, and metabolism [18,19]. It also promotes cell protection mechanisms against therapy-induced DNA damage, oxidative stress, and apoptosis [20,21] and thus can be used to monitor cancer activity [17] and predict response to treatments [22,23]. In addition, serum IL-8 is upregulated in tumor cells [24,25] and has direct and indirect protumoral activity [26,27]. Therefore, studies have suggested that serum IL-8 can be used to monitor the tumor response to ICIs [28]. The major advantages of using serum IL levels to monitor ICIs include low price, minimally invasive procedure, and good repeatability. This study explored the correlation between serum IL-8 and IL-6 and response to anti-PD-1/PD-L1 inhibitors in patients with malignant tumors.

Methods

Study Design and Participants

This prospective observational study recruited patients diagnosed with malignant tumors in the Department of Oncology of Shanghai Huadong Hospital between September 2019 and December 2021. The inclusion criteria were:

1. ≥18 years of age;
2. Pathologically confirmed with a malignant tumor;
3. Treated with anti-PD-1/PD-L1 inhibitor therapy;
4. Measurable lesions for efficacy evaluation.

The exclusion criteria were:

1. Acute infectious diseases;
2. Requiring long-term glucocorticoid therapy;
3. A second primary tumor;
4. Receiving solid organ transplants or bone marrow transplants.

The study was approved by the Medical Ethics Committee of Shanghai Huadong Hospital. The participants or their guardians signed the informed consent form for the study.

Treatment

The participants were treated with PD-1 or PD-L1 inhibitor therapy. PD-1 inhibitors included pembrolizumab (2 mg/kg, once every 3 weeks), nivolumab (3 mg/kg, once every 2 weeks), sintilimab (200 mg, once every 3 weeks), camrelizumab (200 mg, once every 3 weeks), and toripalimab (3 mg/kg, once every 2 weeks). Inhibitors of PD-L1 included atezolizumab (1200 mg, once every 3 weeks).

Sample Collection and Testing

Fasting peripheral blood (3 mL) was collected from the participants at baseline, 2-4 weeks after starting treatment, and at each follow-up. Serum IL-8 and IL-6 levels were measured using commercial enzyme-linked immunosorbent assay kits (sandwich ELISA) (Xinyu Biotechnology Co., LTD, Shanghai).

Data Collection and Definition

The clinical data, including sex, age, tumor type, treatment drugs, performance status (PS) score, disease stage, and PD-L1 expression, were also collected from all participants. Levels of serum IL-8 and IL-6 at baseline and at each follow-up, time of best response (BR), progressive disease (PD), participant outcome status, and survival time were analyzed. PD-L1 ≥ 1% was considered a positive PD-L1 expression. The time of BR was defined as the best evaluation result in the efficacy assessment. According to the criteria reported by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1) [29], the best efficacy reaching complete response (CR), partial response (PR), and stable disease (SD) were defined as responders; the best efficacy reaching PD was defined as non-responders. PD was defined as at least a 20% increase in the sum of the largest diameters of the target lesions or the appearance of new lesions.

Statistical Analysis

SPSS 25.0 (IBM Corp., Armonk, NY, USA) was used for statistical analysis. Continuous data with a normal distribution were presented as mean ± standard deviation (mean ± SD), while continuous data with a non-normal distribution were presented as median (interquartile range), and the Mann-Whitney U test was used for comparison between the two groups. The Wilcoxon signed-rank test was used to compare different time points. The categorical data were presented

as n (%). The survival rate and survival curve were performed by the Kaplan-Meier method, and the log-rank test was used to compare the groups. Receiver operating characteristic (ROC) curve analysis was performed to determine the predictive value of changes in serum IL-8 and IL-6. Two-sided P-values <0.05 were considered statistically significant.

Results

Characteristics of the Participants

As shown in Figure 1, 88 patients met the inclusion criteria. Among those, four had acute infectious diseases (two cases of pneumonia, one of acute urinary system infection, and one of gastroenteritis), two were taking long-term oral glucocorticoids, and two with a second primary tumor (one case of nasopharyngeal carcinoma with lung cancer, and one colon cancer with breast cancer) were excluded. Ultimately, 80 participants were enrolled in the study. The baseline data of the participants are shown in Table 1. There were 43 males and 37 females; the median age was 62 years. There were 30 cases of nasopharyngeal carcinoma, 9 with esophageal carcinoma, 13 with gastric cancer, and 28 cases with lung cancer.

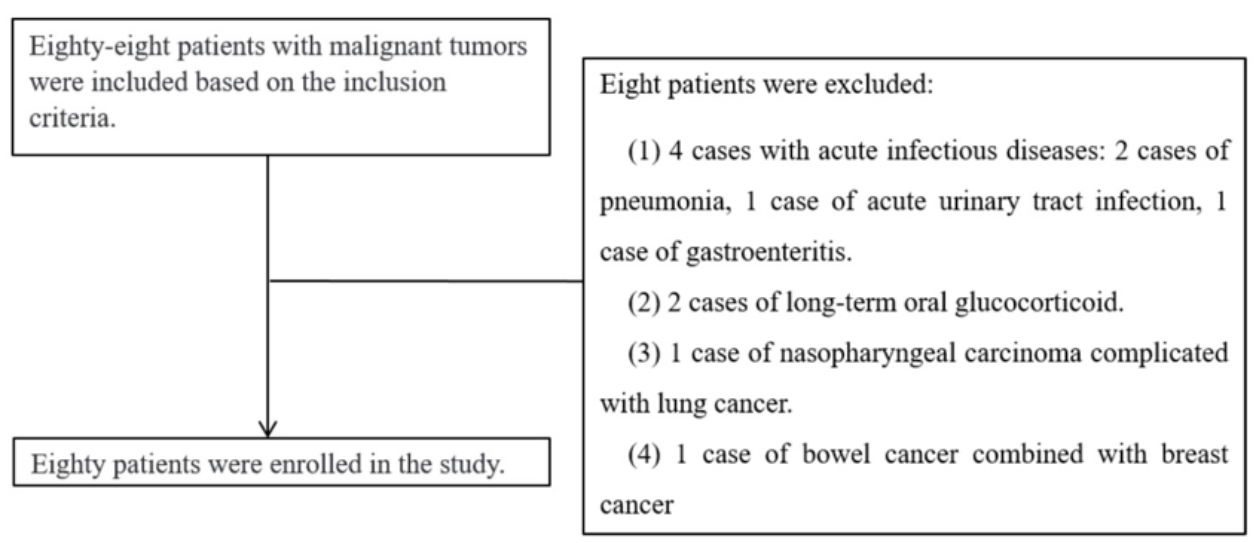

Figure 1: Study flowchart and patient enrollment.

Table 1: Characteristics of the participants.

Variables	Values (n=80)
Age, years, mean ± SD	59.4 ± 12.3
Sex, n (%)	
Male	43 (53.8)
Female	37 (46.3)
PS score, n (%)	
0	31 (38.8)
1	46 (57.5)
2	3 (3.8)
Disease stage, n (%)	
III	9 (11.3)
IIIB	2 (2.5)
IV	69 (86.3)
Tumor type, n (%)	
Nasopharyngeal cancer	30 (37.5)
Lung cancer	28 (35.0)
Esophageal cancer	9 (11.3)
Gastric cancer	13 (16.2)
Treatment drugs, n (%)	
Pembrolizumab	27 (33.8)
Nivolumab	21 (26.3)
Atezolizumab	1 (1.3)
Camrelizumab	13 (16.3)
Sintilimab	11 (13.8)
Toripalimab	7 (8.8)
PD-L1expression, n (%)	
Positive	18 (22.5)
Negative	34 (42.5)
Unknown	28 (35.0)
Survival state, n (%)	
Dead	14 (17.5)
Alive	66 (82.5)
Survival time, month	20.3±3.8

Serum IL-8 levels

The relationship between serum IL-8 changes and tumor response is shown in Figure 2. Among responders, the median serum IL-8 levels in BR were significantly reduced compared with baseline [baseline: 34.6 (26.9, 65.2), BR: 11.6 (9.4, 32.6); P<0.001], and significantly increased in PD [BR: 11.6 (9.4, 32.6), PD: 79 (44.55, 107.7), P<0.001] (Figure 2A). Among non-responders, participants who developed PD had significantly increased serum IL-8 levels compared with baseline [baseline: 30.5 (24.6, 77.5), PD: 80.95 (68.45, 117.25); P<0.001] (Figure 2B). The relationship between the percent changes in serum IL-8 and tumor response is shown in Figure 3. Early changes (2-4 weeks after the first dose) in serum IL-8 levels were associated with response to PD-1/PD-L1 therapy [responders: -38.6 (-47.2, -11.8); non-responders: 44.5 (3.5, 59.8), P<0.001] (Figure 3A). Based on -8.85% as the cutoff value of the percentage changes between serum IL-8 levels at baseline and that at 2-4 weeks, the area under the curve (AUC) was 0.913 (95% CI: 0.853-0.973) (P<0.001), specificity was 80.9% (95% CI: 66.7%-90.9%), and sensitivity was 87.9% (95% CI: 71.8%-96.6%) (Figure 3B).

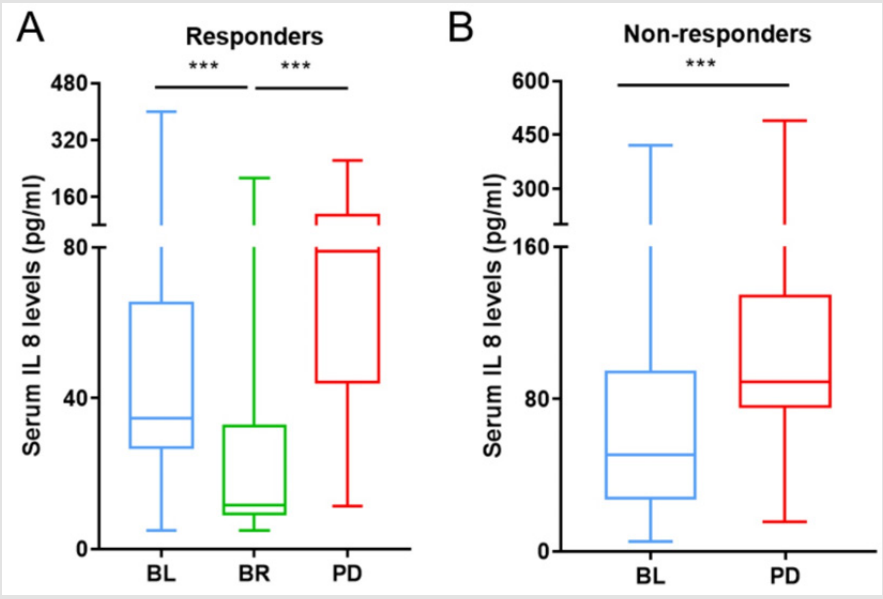

Figure 2: Changes in serum IL-8 levels between responders
A. And non-responders
B. BL: baseline; BR: best response; PD: progressive disease.

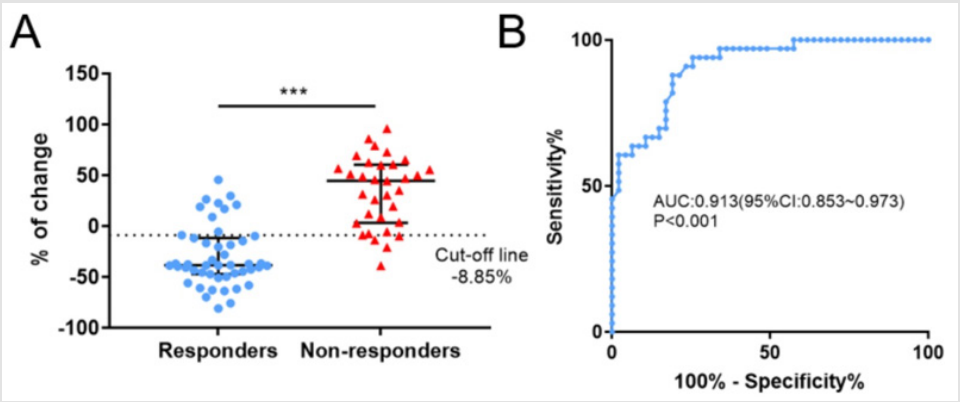

Figure 3: Correlation between the early changes (2-4 weeks after the first dose) in serum IL-8 level and treatment response.
A. Comparison of the percentage change in serum IL-8 levels between responders and non-responders.
B. Receiver operating characteristics (ROC) curve of the correlation between change in serum IL-8 level and treatment response.

The survival of the participants is shown in Figure 4. There were four deaths in the < -8.85% change group and 10 deaths in the ≥ -8.85% change group. The cumulative survival rate at 24 months in the < -8.85% change group was significantly higher than in the ≥ -8.85% change group (85.1% vs. 70.2%, P=0.025). The risk of death in the ≥ -8.85% change group was 3.392 times that in the < -8.85% change group (HR: 3.392, 95% CI: 1.175-9.789).

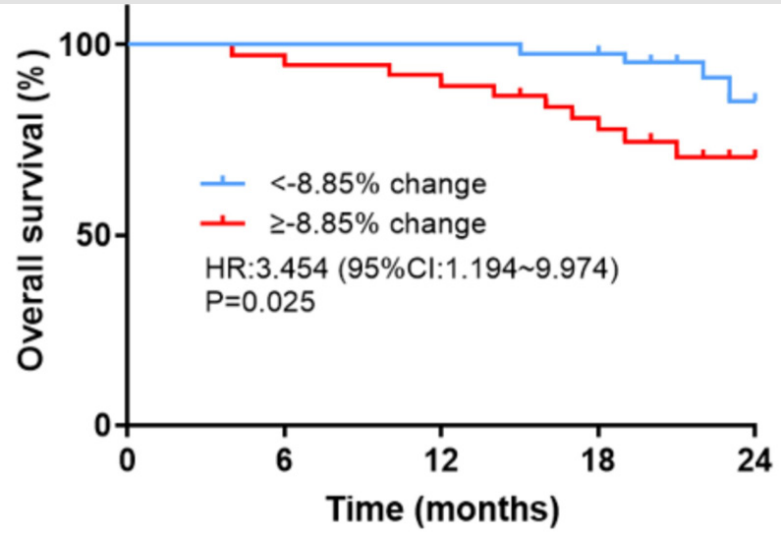

Figure 4: Survival curve analysis of the serum IL-8 change and total survival of patients.

Serum IL-6 levels

The relationship between serum median serum IL-6 changes and tumor response is shown in Figure 5. Among responders, serum IL-6 levels were significantly increased in PD compared with BR [BR: 4.3 (2.6-8.8), PD: 11.4 (4.7-25.3), P<0.001] (Figure 5A). Among non-responders, PD participants had significantly increased serum IL-6 levels compared with baseline [BL: 7.9 (4.5-17.2), PD: 15.9 (7.3-23.3), P=0.03] (Figure 5B). The changes in serum IL-6 levels were not associated with anti-PD-1 response [median change: response: -0.12% (-0.39, 0.27); nonresponse: 0.05% (-0.13, 0.20), P=0.059] (Figure 6).

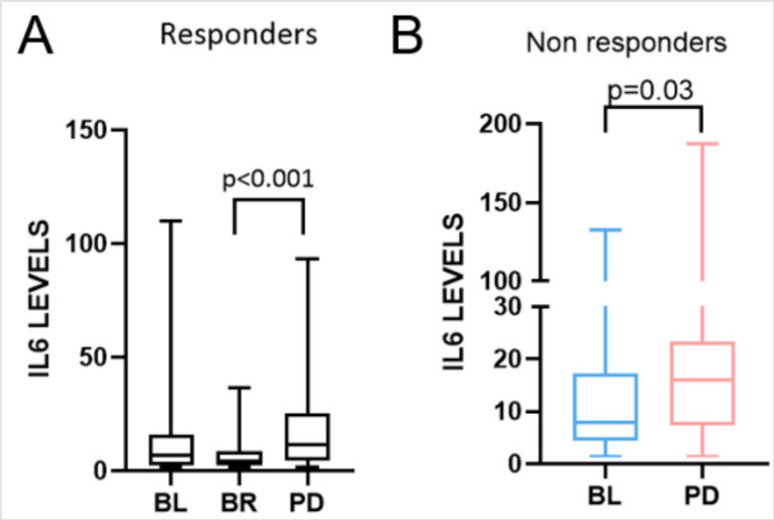

Figure 5: Changes in serum IL-6 levels between responders
A. And non-responders
B. BL: baseline; BR: best response; PD: progressive disease.

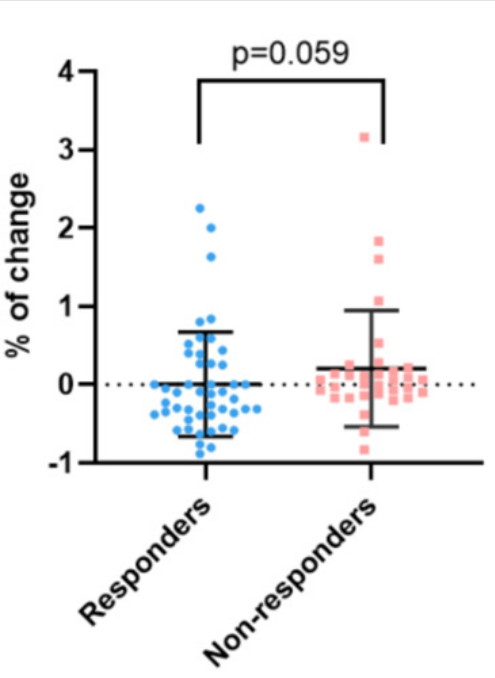

Figure 6: Comparison of the percentage changes in serum IL-6 levels between responders and non-responders.

Discussion

The results suggest that changes in serum IL-8 and IL-6 levels are associated with response to anti-PD-1/PD-L1 inhibitor therapy in patients. Serum IL-8 and IL-6 could be effective and easy-to-assess biomarkers for responding to anti-PD-1/PD-L1 inhibitors in patients with solid tumors. The major advantages of this method are low price, minimally invasive procedure (a simple blood draw), and good repeatability. Previous studies have shown that serum IL-8 levels are high in the tumor microenvironment [24,25,30], exerting various protumoral activities [26,27]. The IL-8-CXCR1/2 axis is also involved in tumor progression, metastasis [31], and angiogenesis [31]. Moreover, high serum IL-8 levels are associated with poor survival [32,33]. These levels are reflected by the serum IL-8 levels, representing the tumor burden [34], and can be used to assess the response to anti-PD-1/PD-L1 inhibitors [28]. Schalper, et al. [35] showed that high baseline serum IL-8 levels could predict a reduced benefit from the anti-PD-1/PD-L1 inhibitors. In the present study, serum IL-8 levels were significantly lower in responders than non-responders and lowered in participants with BR than PD. Decreases in serum IL-8 levels greater than 8.85% could predict BR and were also associated with better survival. Although the present study did not discriminate between pseudoprogression and true progressions, it has been suggested that serum IL-8 levels could be helpful in discrimination.

During pseudoprogression, immune infiltration and immune reaction increase tumor volume, but in reality, the tumor burden decreases, which is reflected in levels of serum IL-8 [28]. During this phase, detecting the cell composition of a mass by imaging is not possible. Thus, biomarkers like serum IL-8 can be used. Future studies should closely examine this crucial issue with anti-PD-1/PD-L1 inhibitors. Hardy-Werbin, et al. [32] showed that lower serum IL-6 levels were associated with better survival in patients treated with ipilimumab, which is also supported by Laino, et al. [36]. On the other hand, Tsuka-Moto and colleagues [37] showed that elevated serum IL-6 levels in melanoma patients treated with nivolumab were associated with poor response. Notably, anti-IL-6 treatment combined with anti-PD-1/PD-L1 inhibitor improves the response rates to anti-PD-1/PD-L1 inhibitor [37-39]. There were no significant changes from baseline in participants with BR or PD in the present study, but the serum IL-6 levels were lower in participants with BR than with PD, which could be due to the small sample size. The present study has limitations. It is a single-center study with a relatively small sample size. Moreover, anti-PD-1/PD-L1 inhibitors may lead to a different response in participants with different types of cancer. Among the non-responders, no confirmation was made regarding the cases of pseudoprogression. Pseudoprogressions remain an important issue with anti-PD-1/PD-L1 inhibitors. Furthermore, the adverse events and the immune-related adverse events were not considered.

Since serum IL-6 and IL-8 are inflammatory markers, immune-related adverse events could influence their effect. Finally, other cytokines could predict the response to anti-PD-1/PD-L1 inhibitors, including tumor necrosis factor-α, interferon-γ, tumor growth factor-β, and other ILs [40]. In conclusion, serum IL-8 and IL-6 could be biomarkers for evaluating the response to anti-PD-1/PD-L1 inhibitors in participants with solid tumors. Serum IL-8 showed predictive value for BR, with high sensitivity and specificity. In addition, serum IL-6 levels were different between participants with BR and PD, but the changes from baseline were similar between responders and non-responders. Future studies should look into models to predict BR to anti-PD-1/PD-L1 inhibitor. Future studies should also discriminate between pseudo progression and true progressions.

Declarations

Data Availability Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval

The study was approved by the Medical Ethics Committee of Shanghai Huadong Hospital. The participants or their guardians signed the informed consent form for the study.

Funding

None.

Conflict of Interest

None.

Author Contributions

Jiayan Chen and Ting Zhao carried out the studies, participated in collecting data, and drafted the manuscript. Jiayan Chen and Ting Zhao performed the statistical analysis and participated in its design. Fei Liu and Xi Chen participated in the acquisition and analysis. Jingwen Wang and Zhan Shi participated in the interpretation of data and drafted the manuscript. All authors read and approved the final manuscript.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

NA.

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