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REVIEW

Predictive value of serum cytokines in patients with non-small-cell lung cancer receiving anti-PD-1 blockade therapy: a meta-analysis

Qian Liu[1,2,3,4] · Zakari Shaibu[5] · Aiguo Xu[6] · Fang Yang[1,2,3,4] · Ruoxue Cao[1,2,3,4] · Fumeng Yang[1,2,3,4]

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Abstract

Non-small cell lung cancer (NSCLC) is a leading cause of cancer-related deaths worldwide. Immunotherapy, particularly PD-1 inhibitors, has revolutionized the treatment landscape for NSCLC. However, the predictive biomarkers for PD-1 inhibitor therapy are still limited. Serum cytokines have emerged as potential biomarkers for predicting treatment outcomes. This meta-analysis aims to investigate the predictive value of serum cytokines in PD-1 inhibitor therapy for NSCLC. We conducted a comprehensive literature search in major databases, including PubMed, Google scholar, Embase, and Cochrane database, with a focus on literature published up until October 22, 2024. Studies investigating the association between serum cytokine levels and treatment outcomes in NSCLC patients receiving PD-1 inhibitor therapy were included. The primary outcomes were progression-free survival (PFS) and overall survival (OS). The meta-analysis revealed that elevated IL-6 levels were significantly associated with poorer PFS in NSCLC patients (HR = 2.30, 95% CI [1.39–3.80], $P = 0.001$). Additionally, high IL-10 expression was related to poorer PFS in NSCLC after therapy (HR = 2.45, 95% CI [1.26–4.76], $P = 0.009$). In contrast, no significant associations were found between OS and the expression of various cytokines, including IL-4, IL-5, IL-6, IL-8, IL-10, IFN-γ, IL-1β, TNF-α, and IL-12p70. This meta-analysis demonstrates that elevated IL-6 and IL-10 levels are significantly associated with poorer PFS in NSCLC patients receiving PD-1 inhibitor therapy. These findings suggest that serum cytokine levels may serve as predictive biomarkers for treatment outcomes. Further studies are needed to validate these results and explore the underlying mechanisms.

Keywords PD-1 inhibitor · Non-small cell lung cancer · Serum cytokines · Predictive biomarkers · Immunotherapy response · Cytokine biomarkers

✉ Fumeng Yang
yfm31095018@163.com

Qian Liu
15805125083@163.com

Zakari Shaibu
Zakarishaibu76@outlook.com

Aiguo Xu
rsysz@163.com

Fang Yang
yfhwd@sina.com

Ruoxue Cao
caoruoxue9490@163.com

1 Department of Laboratory Medicine, Lianyungang Clinical College Jiangsu University & the Second People'S Hospital of Lianyungang, 41 East Hailian Road, Lianyungang 222006, Jiangsu, China

2 Department of Laboratory Medicine, Lianyungang Clinical College Xuzhou Medical University & the Second People'S Hospital of Lianyungang, Lianyungang 222006, Jiangsu, China

3 Department of Laboratory Medicine, The Second People'S Hospital of Lianyungang Affiliated with Kangda College of Nanjing Medical University, Lianyungang 222006, Jiangsu, China

4 Department of Laboratory Medicine, Lianyungang Clinical College, Bengbu Medical University & the Second People'S Hospital of Lianyungang, Lianyungang 222006, Jiangsu, China

5 School of Medicine, Jiangsu University, Zhenjiang 212013, Jiangsu, China

6 Department of Oncology, The Second People'S Hospital of Lianyungang, Lianyungang 222006, Jiangsu, China

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Abbreviations

NSCLC	Non-small cell lung cancer
IL	Interleukins
IFN	Interferon
ICI	Immune checkpoint inhibitors
PD-1	Program death-1
PD-L1	Program death ligand
OS	Overall survival
PFS	Progression-free survival
OR	Odd ratio
HR	Hazard ratio
CI	Confidence interval
MD	Mean difference
RD	Risk difference
GDF-15	Growth differentiation factor 15

Introduction

Non-small cell lung cancer (NSCLC) poses a significant threat to global health, contributing to considerable cancer-related morbidity and mortality worldwide [1]. Despite various advancements in treatment, patients with NSCLC often face a poor prognosis, especially in late-stage disease, where third-generation platinum-based chemotherapy has historically been the primary first-line treatment due to limited response to targeted therapies [2]. While maintenance therapies like pemetrexed and bevacizumab have improved survival outcomes for non-squamous NSCLC, the 5-year overall survival (OS) rate for advanced disease remains low [3]. The emergence of immune checkpoint inhibitors (ICIs) has transformed cancer therapy by leveraging the immune system, with agents such as PD-1/PD-L1 and CTLA-4 inhibitors reactivating dormant immune responses, leading to sustained clinical outcomes and reduced toxicity [4]. However, the efficacy of single-agent PD-1 therapy is disappointingly limited, as demonstrated by clinical trials where response rates barely exceed 20% and established biomarkers like tumor PD-L1 expression and tumor mutation burden fail to reliably predict treatment responses [5–7]. For instance, the KEYNOTE-024 trial indicated that many NSCLC patients with high PD-L1 expression did not benefit significantly from PD-1 therapy, reflecting the complexity of underlying biological mechanisms. While high PD-L1 expression can identify patients who benefit from pembrolizumab over standard chemotherapy [8], studies indicate that an elevated neutrophil-to-eosinophil ratio correlates with poorer OS and progression-free survival (PFS), suggesting its utility as a non-invasive prognostic marker [9]. There is a pressing need for large-scale clinical trials to compare chemoimmunotherapy and ICI monotherapy as first-line treatments in these patients [10]. Additionally, most cases of ICI-related hearing loss are reversible, underscoring the importance of monitoring and managing immune-related adverse events [11].

Numerous studies have shown that ICIs can enhance survival and induce antitumor responses in lung cancer, whether used alone or in combination therapies [12–14]. Some ICIs have also been applied in adjuvant and neoadjuvant treatment settings [15–17]. However, the clinical outcomes are not consistently positive, as resistance remains a persistent challenge. Primary resistance occurs when a patient does not respond at all to immunotherapy from the outset, while some individuals who initially benefit from ICIs may eventually experience acquired resistance. The mechanisms underlying both primary and acquired resistance share certain similarities. For instance, the CheckMate 032 randomized trial reported an objective response rate of only 12% for nivolumab as a standalone treatment and 21% for the combination of nivolumab and ipilimumab, indicating that over half of the participants did not respond to therapy [18]. Currently, the reasons for these disappointing outcomes are not fully understood. Additionally, there is still no agreement on a definitive set of biomarkers that can reliably predict responses to ICI therapy. As a result, considerable interest exists in identifying predictive biomarkers that would facilitate the selection of suitable therapies, thereby improving survival rates and minimizing unnecessary treatment-related adverse effects [4].

Cytokines, which are small proteins crucial for cell signaling and the regulation of immune responses, have gained increasing attention in recent research as potential prognostic markers. These molecules are key players in modulating immune activities, inflammation, and tissue repair [19]. In the context of immunotherapy, numerous studies have investigated their role. Cytokines help shape the tumor microenvironment, influencing tumor growth, metastasis, and overall disease progression [20]. Depending on the specific type of cancer and accompanying conditions, cytokines can either promote or inhibit antitumor immune responses [21]. For example, higher pre-treatment levels of interleukin (IL)−6 and IL-8 have been linked to unfavorable prognoses in patients receiving ICI therapies [22, 23]. Additionally, tracking long-term changes in cytokine levels may assist in predicting patient outcomes, especially when differentiating between true progression and pseudoprogression [24, 25]. However, the connection between plasma cytokine concentrations and the effectiveness of anti-PD-1 therapies has not yet been thoroughly investigated.

Despite the promise of PD-1 inhibitors, there is an ongoing need for reliable biomarkers to predict treatment response and improve patient outcomes. This study aims to investigate the predictive value of serum cytokines concerning PFS and OS in patients with NSCLC who received anti-PD-1 inhibitors.

Materials and method

Ethics statement

The present study drew exclusively from existing literature, thereby eliminating the need for ethics committee approvals or patient consent forms, as no original data collection or human subject participation was involved. The meta-analysis followed the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement to ensure accurate and thorough reporting [26]. No human tissues or animal subjects were utilized in this investigation, exempting it from ethics committee oversight.

Data sources and searches

In this study, a systematic and extensive search strategy was performed across well-known scholarly databases, including PubMed, Google scholar, Embase, and Cochrane database. A query strategy was carefully developed, using a combination of search terms such as Search 1: ((((cytokines) AND (predictive response)) AND (PD-1 inhibitor)) AND (immune checkpoint inhibitor)) AND (non-small cell lung cancer).Search:2 (((((cytokine level) AND (survival outcome)) AND (prognosis)) AND (immune checkpoint inhibitor)) AND (PD-1 inhibitor)) AND (Non-small cell lung cancer), with a specific focus on identifying English language publications up until October 22, 2024. Furthermore, in addition to searching the databases, a thorough search of the reference lists of all included articles in the final analysis, as well as relevant previous reviews, was conducted to ensure a comprehensive exploration of the existing literature on the investigated topic. Study Registration: Prospero ID: CRD42025630975.

Study selection

Prior to conducting the literature search, we established specific inclusion and exclusion criteria. To be included in this meta-analysis, a study had to meet the following criteria: (1) Patients diagnosed with NSCLC; (2) It had to evaluate cytokine levels in serum samples of patients diagnosed with NSCLC who were receiving treatment with PD-1 treatment; (3) It had to report median survival outcomes after treatment in NSCLC patients; 4) It had to investigate the relationship between cytokine levels and prognosis in NSCLC patients. Studies were excluded if they: (1) Did not focus on NSCLC patients or did not evaluate cytokine levels in relation to prognostic outcomes. (2) Did not involve the administration of immunotherapy. (3) Were reviews, letters, editorials, conference abstracts, or case reports. (4) Had insufficient data or inadequate reporting of methodology; (5) Had a small sample size that might not yield reliable results; and (6) Did not provide clear outcomes related to prognosis.

Data extraction

We used Endnote 20 software to cite and reference the studies. Two researchers (Z.S and F.Y) independently screened each article based on the title and abstract. They assessed whether the research relied on clinical data, reported cytokine levels, and had accessible full texts. Any conflicts were resolved through additional discussions. We gathered information from selected studies, excluding those that lacked detailed descriptions of cytokine levels and outcomes such as OS and PFS following treatment with PD-1 inhibitor. The core data collected for the meta-analysis included author identity, publication year, methodology, number of patients, and outcomes, as outlined in Table 1. Results of the outcomes in each included studies are displayed in Table 2.

Quality assessment

To evaluate the methodological quality of the trials included in this study, we employed the Cochrane Handbook for Systematic Reviews of Interventions (Version 5.1) risk of bias assessment tool. A comprehensive evaluation was conducted, focusing on key aspects such as random sequence generation, allocation concealment, blinding, data completeness, selective reporting, and potential sources of bias. Trials were subsequently classified into one of three categories: 'high risk' of bias (presence of bias in one or more critical domains), 'low risk' of bias (minimal risk of bias across all essential domains), or 'unclear' risk of bias (uncertain bias status). The results of this risk of bias assessment are presented in a visual format in Figs. 1 and 2.

Statistical analysis

Statistical analysis was conducted using Review Manager version 5.4.1. We calculated odds ratios (ORs) along with 95% confidence intervals (CIs) for dichotomous data, employing a fixed effect (FE) model based on the Mantel–Haenszel (M-H) statistical method. For survival data, such as OS and PFS was assessed using the hazard ratios (HRs) and 95% CIs. To assess heterogeneity among the studies, we utilized the Q statistic and I^2 statistic. Considerable variability was detected, as indicated by an I^2 statistic above 50% [27]. We employed a fixed-effects approach when I^2 was 50% or less and a random-effects approach when it exceeded 50%. Funnel plots were used to mitigate publication bias. Statistical significance was set at $P < 0.05$.

Table 1 Characteristics of included studies

Author	Year	Design	Total no. patients	Method	Cytokine type (pg/ml)	Outcomes
Hongyu Liu et al. [28]	2024	RS	60	CORPLEX	IL-4, IL-5, IL-6, IL-8, IL- 10, IL-12P70, IFN-g, IL-1b and TNF-α	OS, PFS
Yusuke Inoue et al. [35]	2023	RS	200	IHC	IL-4, IL-6, IL-7, IL-10, IL-18, IFN-γ	OS, PFS
Sanmamed et al. [36]	2017	RS	29	ELISA	IL-8	OS
Yuequan Shi et al. [29]	2021	RS	60	EasyMagPlex	IL-2, IL-4, IL-5, IL-6, IL-8, IL- 10, IL-12P70, IFN-g, IL-1b and TNF-α	PFS
Qiu Zhao et al. [31]	2021	RS	40	Flow cytometry	IL-5 and IFN-γ	PFS
Chengming Liu et al. [32]	2022	RS	45	Flow cytometry	IL-6	
Chong Chen et al. [33]	2023	RS	100	–	IL-6	PFS
Diego Kauffman-Guerrero et al. [34]	2021	RS	29	Human Cytokine-Inflammation (9-plex)	IL-6, TNF-α	
Yun Peng et al. [30]	2023	RS	35	Flow cytometry	IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IFN-α, IFN -γ, TNF-α	OS, PFS

Results

A systematic search of multiple databases yielded an initial 850 studies, which were then subjected to a rigorous deduplication process. This resulted in the removal of 455 duplicate studies, leaving a total of 395 unique records for further evaluation. Following a meticulous screening process, 117 studies were deemed potentially eligible for inclusion in the meta-analysis. However, upon closer examination, 108 studies were excluded due to non-alignment with predefined criteria. Ultimately, a stringent selection process culminated in the inclusion of nine studies that met the eligibility criteria, as illustrated in Fig. 3.

Progression free survival

The analysis focusing on PFS yielded intriguing results. Three studies [28–30] examining IL-4 expression found no significant difference in PFS after treatment, with a HR of 1.03 (95% CI [0.85–1.26], I2 = 0%, $P = 0.75$) (Fig. 4a). Similarly, four studies [28–31] investigating IL-5 expression revealed no impact on PFS, with an HR of 0.91 (95% CI [0.48–1.71], I2 = 0%, $P = 0.76$) (Fig. 4b).

In contrast, seven studies [28–30, 32–35] demonstrated a significant difference in IL-6 expression on PFS after treatment. Elevated IL-6 levels were associated with poorer PFS, with an HR of 2.30 (95% CI [1.39–3.80], $I^2 = 91\%$, $P = 0.001$) (Fig. 4c). Four studies [28–30, 34] examining IL-8, IL-10, and IFN-γ expression found that IL-8 had no significant difference in PFS impact, with an HR of 2.03 (95% CI [0.88–4.71], $I^2 = 96\%$, $P = 0.10$) (Fig. 4d). However, high IL-10 expression was related to poorer PFS in NSCLC after therapy, with an HR of 2.45 (95% CI [1.26–4.76], $I^2 = 75\%$, $P = 0.009$) (Fig. 4e). IFN-γ expression showed no significant difference in PFS impact, with an HR of 2.83 (95% CI [0.27–29.50], $I^2 = 99\%$, $P = 0.38$) (Fig. 4f).

Three studies [28–30] investigating IL-1β expression found no significant difference in NSCLC patients' PFS after treatment, with an HR of 0.88 (95% CI [0.55–1.42], $I^2 = 34\%$, $P = 0.61$) (Fig. 4g). Four studies [28–30, 34] examining TNF-α expression revealed no difference in PFS impact, with an HR of 2.08 (95% CI [0.72–6.00], $I^2 = 95\%$, $P = 0.18$) (Fig. 4h).

Lastly, three studies [28–30] investigating IL-12p70 expression showed no significant difference in PFS impact, with an HR of 1.12 (95% CI [0.82–1.50], $I^2 = 0\%$, $P = 0.47$) (Fig. 4i). These findings suggest that the expression of IL-6 and IL-10 may be significantly associated with PFS in NSCLC patients, while the expression of other cytokines may not have a significant impact.

Overall survival

The meta-analysis revealed no significant differences in OS for various cytokines in NSCLC patients. Specifically, two studies [28, 29] examining IL-4 and IL-5 expression reported no significant difference in OS, with HRs of 0.87 (95% CI [0.57–1.34], $I^2 = 0\%$, $P = 0.52$) and 0.81 (95% CI [0.32–2.06], $I^2 = 65\%$, $P = 0.66$), respectively (Fig. 4a and 4b).

Four studies [28, 29, 32, 35] investigating IL-6 expression also found no significant difference in OS, despite a seemingly elevated HR of 3.30 (95% CI [0.92–11.18], $I^2 = 98\%$, $P = 0.07$) (Fig. 4c). Additionally, three studies [28, 29, 36] examining IL-8 expression showed no significant difference

Table 2 Cytokine expression in NSCLC and survival outcomes

Authors		95%CI								
		IL-4	IL-5	IL-6	IL-8	IL-10	IFN-g	IL-1b	TNF-a	IL-12p70
Hongyu Liu et al	PFS	0.84–1.29	1.15–3.13	1.03–1.08	0.99–1.03	1.03–1.83	0.82–3.40	0.56–7.41	0.99–1.12	0.75–1.58
	OS	0.57–1.49	0.66–2.29	1.02–1.09	0.99–1.04	0.88–1.74	0.42–2.85	0.05–11.53	0.92–1.16	0.49–1.93
Yusuke Inoue et al	PFS	–	–	1.31–2.33	–	–	–	–	–	–
	OS	–	–	1.99–3.85	–	–	–	–	–	–
M.F. Sanmamed et al	OS	–	–	–	1.0–90.1	–	–	–	–	–
Yuequan Shi et al	PFS	0.408–1.686	0.395–1.650	1.012–4.189	0.744–3.398	0.997–5.418	0.289–1.193	0.277–1.209	0.913–3.823	0.480–1.970
	OS	0.268–1.794	0.185–1.192	0.744–4.776	0.699–4.718	0.435–3.097	0.180–1.204	0.107–0.989	0.510–3.332	0.260–1.740
Qiu Zhao et al	PFS	–	0.1802–1.016	–	–	–	0.1877–1.036	–	–	–
Chengming Liu et al	PFS	–	–	2.49–5.85	–	–	–	–	–	–
	OS	–	–	13.32–34.81	–	–	–	–	–	–
Chong Chen et al	PFS	–	–	2.152–18.304	–	–	–	–	–	–
Diego Kauffman–Guerrero et al	PFS	–	–	0.95–9.33	2.71–5.29	2.86–20.57	30.79–49.22	–	5.50–16.50	–
Yun Peng et al	PFS	0.5837–2.334	0.4087–1.634	1.111–4.663	0.5904–2.361	1.079–4.515	0.7907–3.235	0.5063–2.024	0.5063–2.024	0.6941–2.775

in OS, with an HR of 1.57 (95% CI [0.68–13.63], $I^2 = 62\%$, $P = 0.29$) (Fig. 4d).

Furthermore, two studies [28, 29] each were collected for IL-10, IFN-γ, IL-1β, TNF-α, and IL-12p70, and the analysis revealed no significant differences in OS for these cytokines. The HRs and corresponding CIs were as follows: IL-10, HR = 1.23 (95% CI [0.89–1.70], $I^2 = 0\%$, $P = 0.21$) (Fig. 4e); IFN-γ, HR = 0.71 (95% CI [0.36–1.40], $I^2 = 35\%$, $P = 0.32$) (Fig. 4f); IL-1β, HR = 0.37 (95% CI [0.13–1.03], $I^2 = 0\%$, P = 0.06) (Fig. 4g); TNF-α, HR = 1.04 (95% CI [0.92–1.16], $I^2 = 0\%$, $P = 0.54$) (Fig. 4h); and IL-12p70, HR = 0.86 (95% CI [0.49–1.49], $I^2 = 0\%$, $P = 0.59$) (Fig. 4i).

Publication bias

An assessment of publication bias in the analysis of IL-6 expression and PFS outcomes in NSCLC patients treated with PD-1 blockade revealed no significant asymmetry. The funnel plot showed all studies within the 95% CI limits. Statistical evaluation using the Egger test confirmed the absence of publication bias, with results indicating significant heterogeneity (Tau2 = 0.35; $Chi^2 = 67.58$, df = 6, $P < 0.00001$; $I^2 = 91\%$). The overall effect test yielded a Z-score of 3.24, corresponding to a P value of 0.001 (Fig. 6).

Discussion

Understanding the interplay between serum cytokines and treatment response is vital for enhancing cancer therapy outcomes. This meta-analysis offers critical insights into the prognostic value of serum cytokines for patients with NSCLC undergoing anti-PD-1 blockade therapy. Our results indicate that increased levels of IL-6 and IL-10 are significantly linked with reduced PFS among NSCLC patients, implying their potential utility as predictive biomarkers for treatment efficacy (Figs. 5 and 6).

IL-6 is a pro-inflammatory cytokine frequently associated with tumor promotion in chronic inflammatory contexts and various malignancies [22, 37, 38]. The IL-6/JAK/STAT3 signaling pathway is well-recognized for its crucial immunoregulatory functions in numerous disease states, including cancer [39]. In terms of antitumor immunity, IL-6 has been found to diminish the production of IFNγ derived from CD4 + T cells and can influence PD-1/PD-L1 interactions in tumor-associated macrophages [40]. Additionally, IL-6 facilitates tumor angiogenesis [41] and supports tumor growth through apoptosis inhibition [42]. It has also been shown that cancer cells undergoing chromosomal instability may rely on a cGAS-mediated inflammatory response, making IL-6 a key player in this process [43]. Multiple studies confirm that elevated serum IL-6 levels correlate with poor prognosis across various cancers, both in patients who were

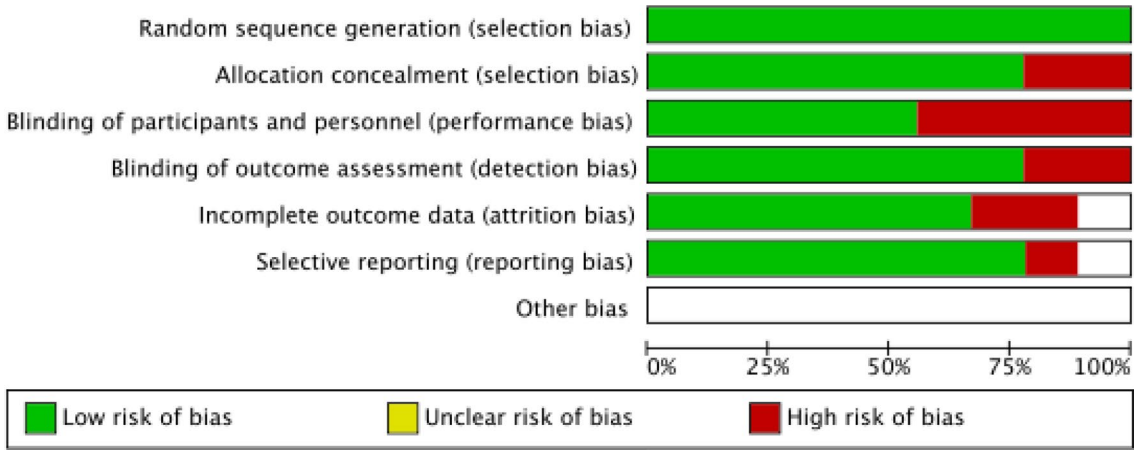

Fig. 1 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

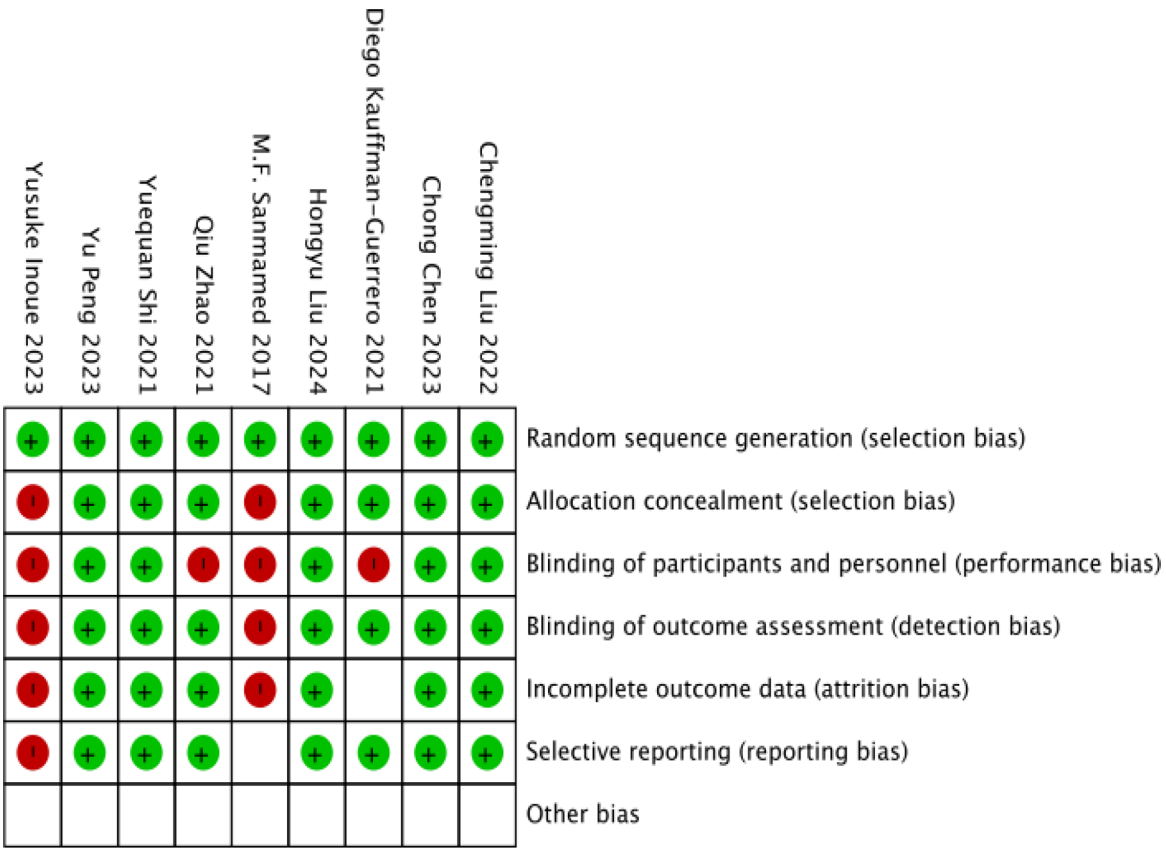

Fig. 2 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

treated with ICIs [22, 32, 34, 44, 45] and those who were not [46–48]. These findings, along with our own, support the notion that targeting IL-6 in conjunction with ICIs specifically PD-1 blockade could offer therapeutic advantages [40, 49]. The association of IL-6 with diminished PFS corroborates earlier research indicating that this cytokine contributes to tumor proliferation and immune suppression [29, 35]. Similar to our findings, Kang et al. showed that baseline serum IL-6 levels negatively impacted response predictions to ICIs in NSCLC patients [44], although methodological differences in sample collection exist. Further, Keegan et al. found that pre-treatment IL-6 levels did not correlate with survival in their categorization of 47 patients but noted that increases in plasma IL-6 were associated with poorer PFS

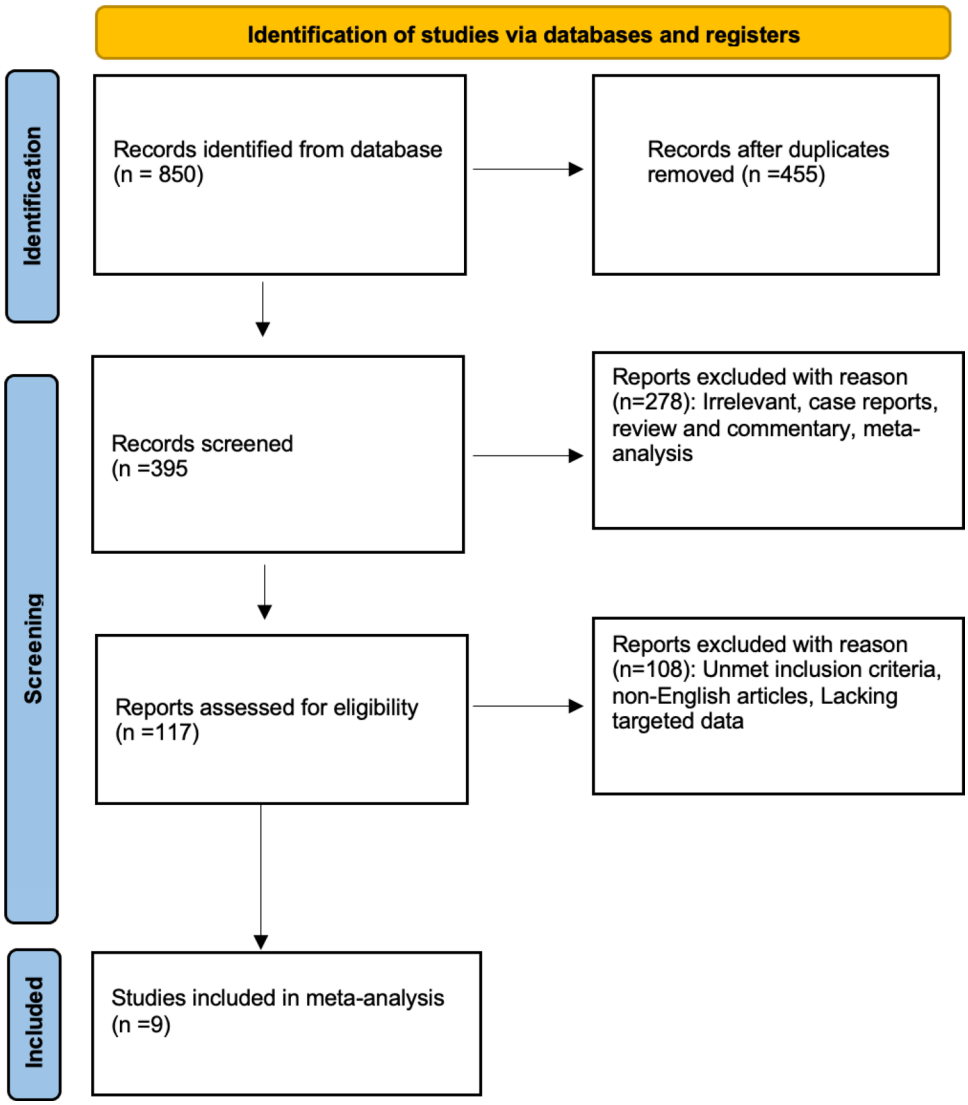

Fig. 3 Prisma selection of included studies

among those treated with PD-1 inhibitors [24]. Variability in grouping methods and small sample sizes may account for differences between studies, along with variations in racial demographics among participants. Additionally, the negative predictive role of baseline plasma IL-6 levels has been documented in melanoma and pancreatic cancer patients receiving immunotherapy [22, 40].

Recent studies have highlighted the role of growth differentiation factor 15 (GDF-15) in immune modulation and as a marker of cancer-related cachexia [50]. GDF-15 contributes to immune evasion by inhibiting T-cell activity within the tumor microenvironment, potentially diminishing the efficacy of ICIs [50, 51]. Similarly, interleukin-6 (IL-6), a pro-inflammatory cytokine, has been studied as an immune biomarker, but its role in modulating responses to ICIs remains to be fully elucidated [24, 52]. Elevated IL-6 levels have been associated with poorer outcomes in cancer patients, but its specific role in modulating responses to ICIs remains unclear. Several studies have examined the prognostic value of IL-6 in cancer therapy; yet, its relationship with biomarkers such as GDF-15 has not been fully explored [53]. Although both biomarkers have been studied independently, the relationship between serum GDF-15 and IL-6 levels in predicting immunotherapy response has not been comprehensively evaluated. Furthermore, considering the global disparities in access to immunotherapy, particularly in low- and middle-income countries, identifying biomarkers like GDF-15 to prioritize patients most likely to benefit from these therapies is of both clinical and economic significance [54].

IL-10 is another significant inflammatory cytokine that influences both immune suppression and stimulation. It plays a critical role during inflammation by inhibiting the activity of Th1 and Th2 cells, as well as B lymphocytes, thereby reducing pro-inflammatory cytokine production and downregulating the inflammatory cascade. Prior studies have

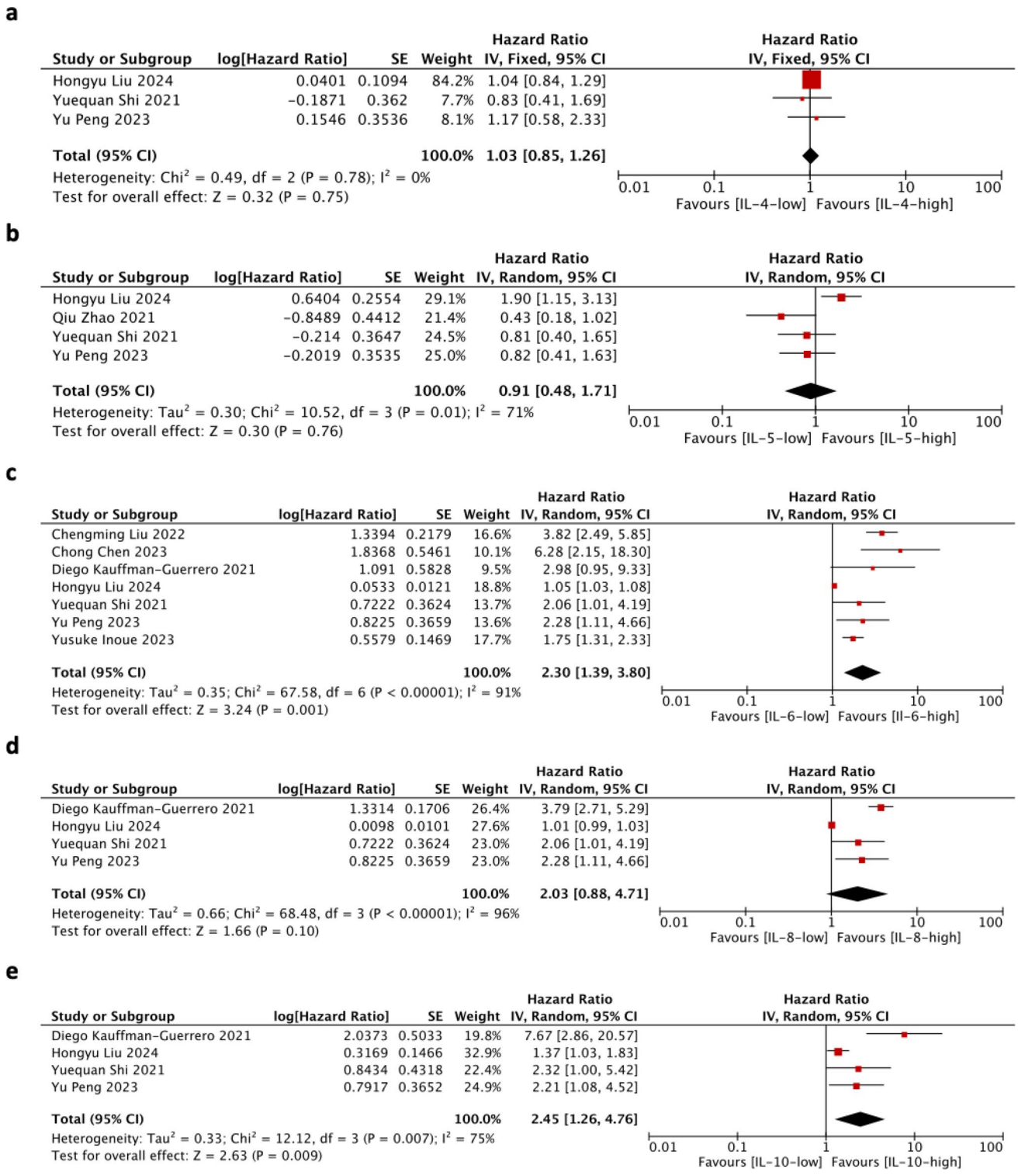

Fig. 4 Forest plot of PFS associated with cytokine expression in NSCLC patients treated with PD-1 Inhibitors: **a** IL-4, **b** IL-5, **c** IL-6, **d** IL-8, **e** IL-10, **f** IFN-γ, **g** IL-1β, **h** TNF-α, and **i** IL-12p70. Note: The forest plot displays the HR and 95% CI for PFS associated with each cytokine

indicated a correlation between IL-10 expression levels and tumor size in lung cancer tissues of NSCLC patients, with elevated serum IL-10 levels linked to poorer prognosis. Furthermore, IL-10 may contribute to tumor resistance against ICIs by undermining the efficacy of IFN-γ in modulating the PD-1/PD-L1 signaling axis [55]. This aligns with

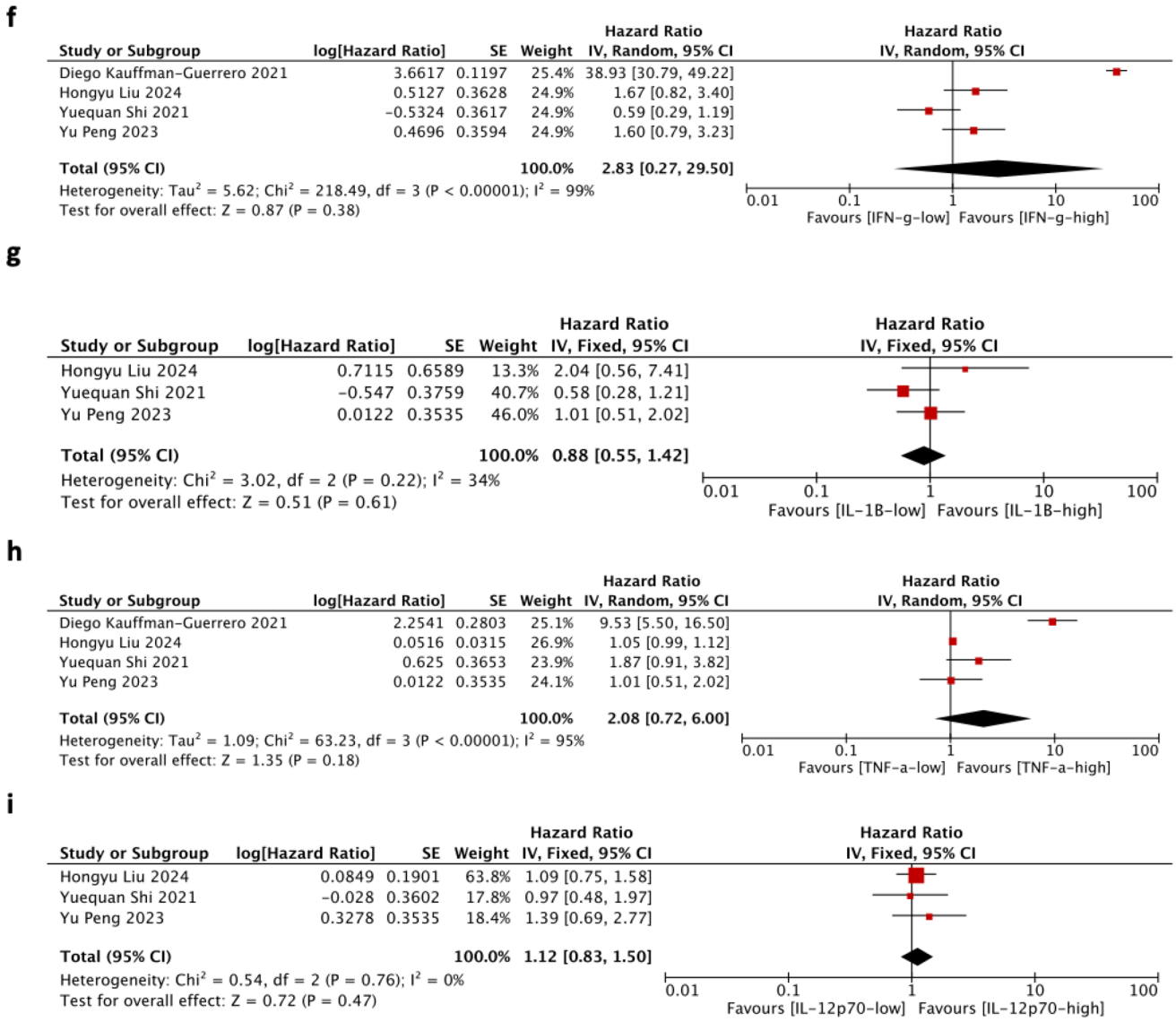

Fig. 4 (continued)

our findings where IL-10 was associated with reduced PFS. Additional research supports the notion that high IL-10 levels could signal an increased likelihood of adverse clinical outcomes [30]. However, recent studies indicate that elevated IL-10 can also encourage the activation and proliferation of CD8 + T cells, facilitating antitumor responses [56]. Conversely, the results of another study showed a positive correlation between higher baseline cytokine levels and improved PFS in patients with advanced NSCLC undergoing immunotherapy [57].

Our analysis revealed that, in contrast to IL-6 and IL-10, there were no significant associations between other cytokines, such as IL-4, IL-5, IL-8, IFN-γ, IL-1β, TNF-α, and IL-12p70, and treatment outcomes related to PFS and OS in patients with NSCLC. This lack of significant correlation is not entirely surprising, given the complex interactions between cytokines, tumor biology, and the tumor microenvironment. Factors contributing to these findings may include the possibility that dominant oncogenic pathways mask the effects of cytokines, the inherent heterogeneity of NSCLC tumors, and the timing of cytokine measurements. Furthermore, the study's sample size and the demographics of the patient population may not have been adequate to detect subtle cytokine-mediated effects. For instance, previous work documented a lack of significant associations between baseline serum levels of IL-8 and responses to anti-PD-1 monoclonal antibodies [36, 58]. Intriguingly, early changes in serum IL-8 levels following treatment have been shown to correlate with patient responses, indicating that IL-8 may reflect critical shifts in

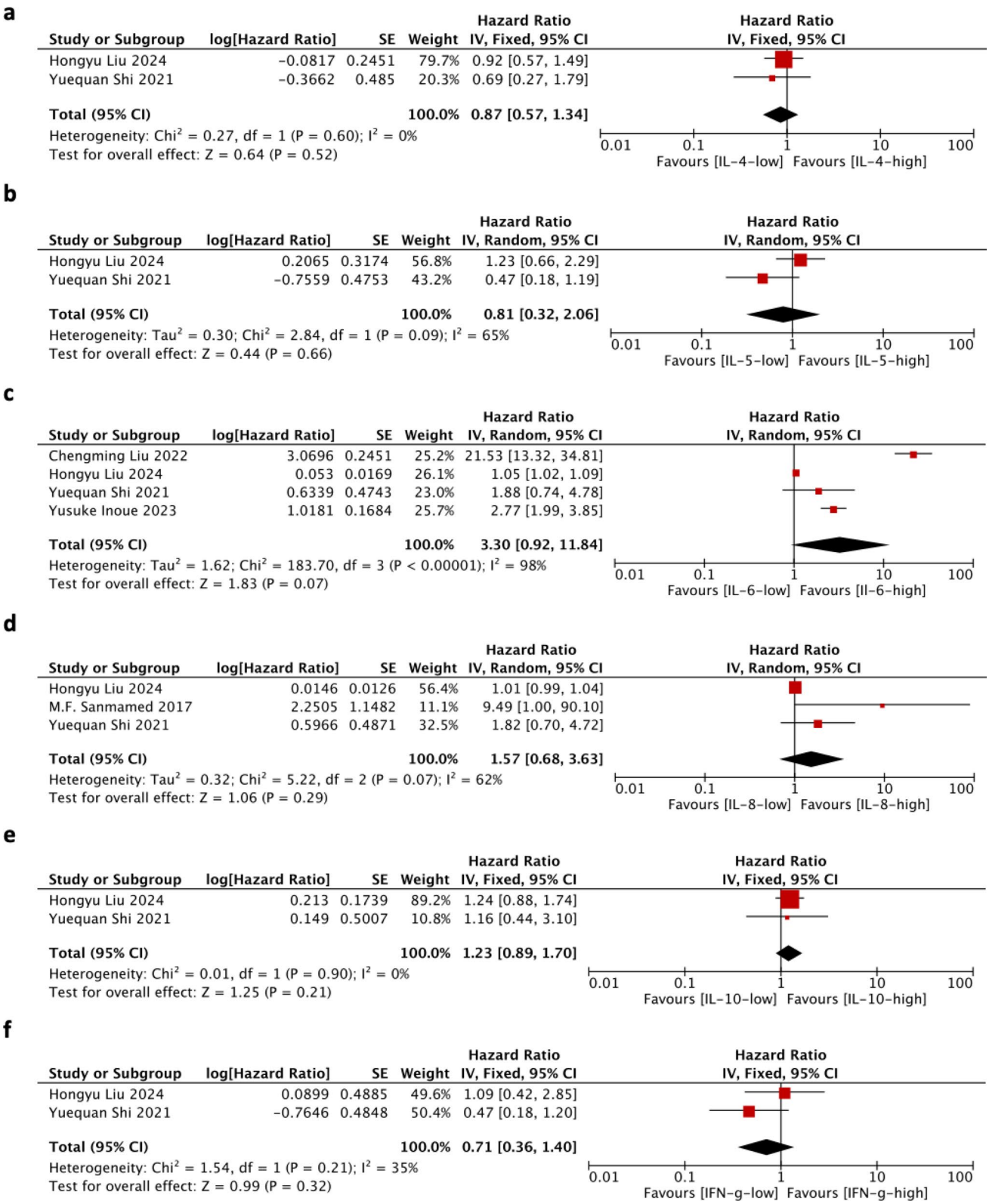

Fig. 5 Forest plot of OS associated with cytokine expression in NSCLC patients treated with PD-1 inhibitors: **a** IL-4, **b** IL-5, **c** IL-6, **d** IL-8, **e** IL-10, **f** IFN-γ, **g** IL-1β, **h** TNF-α, and **i** IL-12p70. Note: The forest plot displays the HR and 95% CI for OS associated with each cytokine

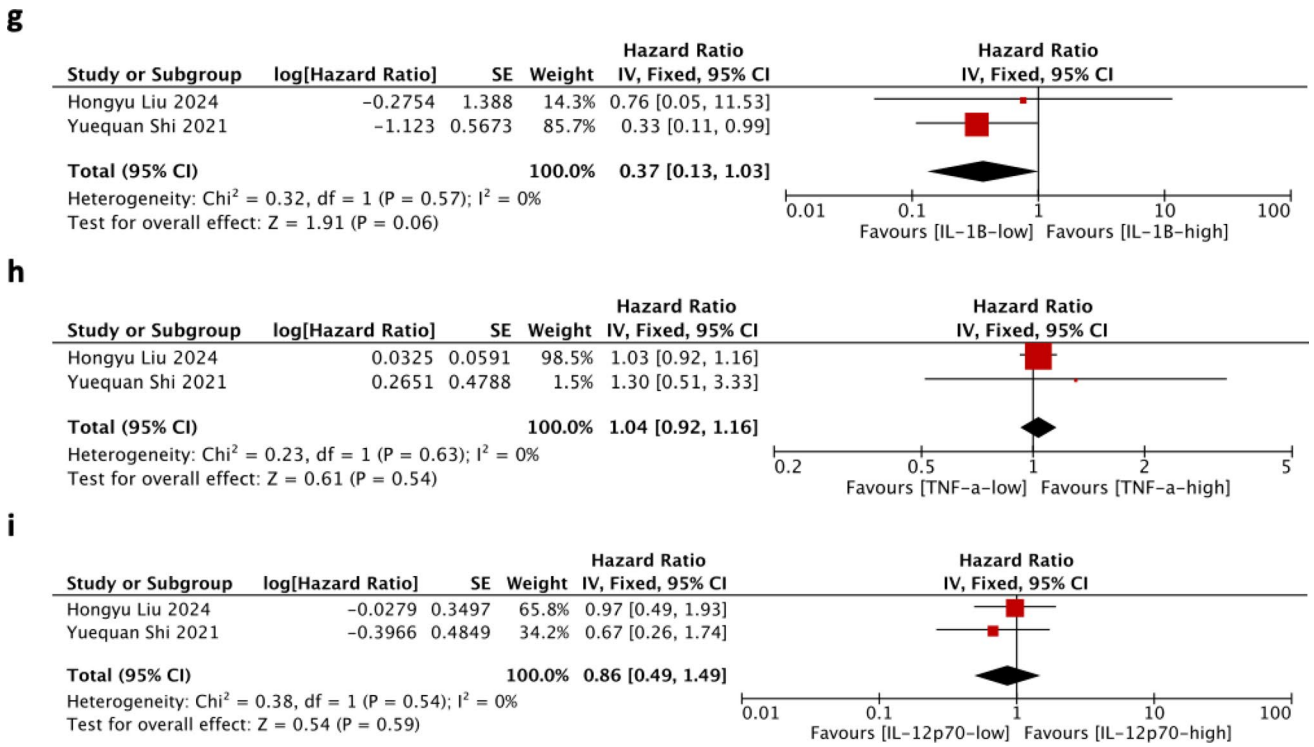

Fig. 5 (continued)

the tumor microenvironment after PD-1 blockade, rather than merely serving as a marker of tumor burden. Additionally, IL-4 has been recognized as an immunosuppressive cytokine that can contribute to tumor growth and metastasis [59]. Its lack of significant association with PFS and OS in our study suggests that while IL-4 may play a role in shaping the tumor microenvironment, it does not appear to be a reliable predictor of treatment outcomes in NSCLC.

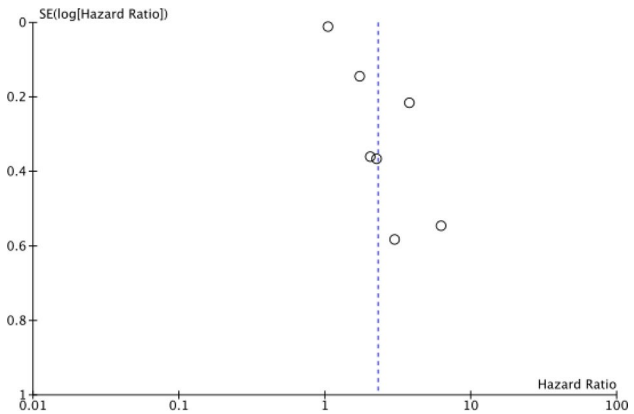

Fig. 6 Funnel plot of PFS for IL-6 in NSCLC patients treated with PD-1 inhibitors. The funnel plot is used to assess publication bias and asymmetry. The horizontal axis represents the standard error of the HR, and the vertical axis represents the HR. The dashed line indicates the overall HR. Symmetry of the plot suggests low risk of publication bias

Conversely, research by Boutsikou et al. illustrated that elevated levels of various cytokines, such as IFN-γ, TNF-α, IL-1β, IL-2, IL-4, IL-5, IL-6, IL-8, IL-10, and IL-12 were associated with enhanced responses to anti-PD-1 therapy and increased survival durations, providing insights into patient selection for immunotherapy [58]. Supportively, another study suggested that higher levels of Th1 cytokines, including IFN-γ and TNF-α, as well as Th2 cytokines like IL-5, IL-4, and IL-10, present in patients with NSCLC could reliably predict clinical responses to PD-1 blockade therapies. Additionally, there was a positive correlation between elevated baseline cytokine levels and improved PFS among patients with advanced NSCLC receiving immunotherapy [57]. Moreover, increased levels of IFNγ have been recognized as strong predictors of effective and enduring responses to ICIs, potentially due to IFNγ's role in amplifying the activity of tumor-infiltrating lymphocytes (TILs) [60]. IFNγ supports a lymphocyte-driven immune response, indicating a possible synergistic effect when combined with ICI therapy. Several studies have similarly identified a positive relationship between high IFNγ levels and improved outcomes with ICI treatment [61, 62]. Nonetheless, additional research is needed to define a precise cutoff for IFNγ levels. Furthermore, another investigation revealed a correlation between serum IL-5 and IFNγ levels and the efficacy of

anti-PD-1 therapy in metastatic gastric cancer and NSCLC patients. Remarkably, early variations in serum levels of IL-5 and IFNγ could predict PFS for NSCLC patients on anti-PD-1 monoclonal antibody treatment [31]. In contrast, previous studies found that elevated levels of IL-5, IL-8, and TNF-α, as well as low levels of IL-4, were linked with shorter PFS, with higher IL-5 levels correlating to worse PFS outcomes. Additionally, patients with high baseline levels of IL-8 and TNF-α or low IL-4 levels experienced shorter OS. The findings indicated that increasing TNF-α levels were associated with poorer treatment responses, while higher levels of IL-5 and IFNγ corresponded with more favorable treatment outcomes [28].

These combined findings point to unique roles for IL-6 and IL-10 in the tumor microenvironment and their differential impact on treatment outcomes. The implications of this meta-analysis are significant for the clinical management of NSCLC patients undergoing anti-PD-1 therapy. Levels of serum cytokines, especially IL-6 and IL-10, show promise as biomarkers for predicting treatment responses and identifying patients who may benefit from alternative or combination therapeutic strategies. The identification of IL-6 and IL-10 as predictive biomarkers has significant clinical implications. Elevated levels of these cytokines may indicate a reduced likelihood of response to anti-PD-1 therapy, allowing clinicians to consider alternative or combination therapeutic strategies. For instance, patients with high IL-6 and IL-10 levels may benefit from therapies targeting the IL-6/JAK/STAT3 pathway or immune-modulating agents that can mitigate the suppressive effects of these cytokines. Furthermore, the use of IL-6 and IL-10 as biomarkers could guide treatment selection and personalized medicine approaches. By stratifying patients based on their cytokine profiles, clinicians can optimize treatment outcomes and minimize unnecessary toxicity. This personalized approach may also enable clinicians to identify patients who are more likely to benefit from combination therapies or novel immunotherapeutic agents.

The findings of this meta-analysis should be interpreted in the context of several limitations. Firstly, the included studies exhibited variability in sample sizes, study designs, and laboratory techniques, which may have contributed to heterogeneity in the results. Additionally, the majority of the studies reviewed were observational, which may restrict causal inferences. Furthermore, our analysis focused solely on studies reporting associations between serum cytokine levels and treatment outcomes for NSCLC patients on anti-PD-1 blockade therapy, which may not represent the broader spectrum of ICIs treatments. Finally, the lack of standardized cutoff values for serum cytokine levels and the timing of cytokine measurements may limit the generalizability of our findings. Future studies should aim to validate our findings in larger, prospective cohorts and explore other potential predictive biomarkers. Future research directions may also include investigating the association between serum cytokines and the mechanism of PD-1 inhibitor therapy. Elucidating the biological mechanisms underlying the prognostic value of serum cytokines may provide valuable insights into the development of novel therapeutic strategies.

Conclusion

In summary, this meta-analysis indicates that serum cytokine levels, particularly IL-6 and IL-10, are predictive of poorer progression-free survival in NSCLC patients undergoing anti-PD-1 blockade therapy. These findings are crucial for the clinical management of NSCLC patients and underline the necessity for further investigation into the underlying mechanisms and potential therapeutic applications.

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Availability of Data and Material No datasets were generated or analyzed during the current study.

Declarations

Conflict of interest The authors declare no competing interests.

Approval by institutional review board (IRB) This systematic review used studies that are published in several medical databases. Ethics approval was not required for this study.

Consent for publication Not applicable.

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