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REVIEW

Cytokine profiles as predictive biomarkers for treatment outcomes in advanced gastric cancer patients undergoing PD-1 blockade immunochemotherapy: a meta-analysis

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Abstract

Immunotherapy, specifically PD-1 blockade, is a promising treatment for advanced gastric cancer (AGC). However, predicting patient response is challenging. Cytokines, key immune response regulators, could be important biomarkers for forecasting patient outcomes and susceptibility to PD-1 blockade immunochemotherapy in AGC. This meta-analysis aims to evaluate the potential of cytokine profiles as predictive biomarkers for treatment outcomes in patients with AGC undergoing immunochemotherapy. Meta-analysis. Original studies on the evaluation of various serum samples of cytokines in AGC patients after immunochemotherapy were searched in PubMed, Google Scholar, Embase, Cochrane Library, and Web of Science, with a focus on literature published up to October 31, 2023. Data from multiple studies were pooled to analyze the impact of IL-2, IL-4, IL-6, IL-8, IL-10, and IFN-γ expression on treatment outcomes using RevMan 5.4.1. Prospero ID: CRD42024557837. Five studies were included. In AGC patients receiving immunochemotherapy, high levels of IL-4 were correlated with enhanced PFS following therapy. In contrast, there were no significant differences observed in the expression of IL-2, IL-6, IL-10, and IFN-γ for PFS in AGC after treatment. Notably, elevated IL-6 expression was significantly associated with poorer OS in AGC patients undergoing immunochemotherapy. The findings suggest that expression levels of cytokines, particularly IL-4 and IL-6, play a significant role in predicting treatment outcomes in AGC patients undergoing immunochemotherapy. Further research is warranted to validate these results and elucidate the underlying mechanisms driving these associations.

Keywords Cytokines · Interleukins · Immune checkpoint inhibitors · PD-1 · Stomach neoplasm

Abbreviations

AGC	Advanced gastric cancer
GC	Gastric 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

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Introduction

The incidence of gastrointestinal cancer is on the rise, and so is the age-standardized rate of diagnosis. There is a significant global variation, with the highest rates found in South America, Eastern Asia, and Central and Eastern Europe [1, 2]. Globally, gastric cancer (GC) ranks among the most common and deadly cancers, holding the fifth position in terms of incidence

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and the fourth in mortality rates [3, 4]. It poses a substantial public health challenge, responsible for approximately 44.0% of new GC diagnoses and 48.6% of deaths associated with the disease worldwide [5, 6]. Unfortunately, patients with AGC have a poor prognosis, with an average survival of only about one year, due to limited treatment options and delays in treatment [7]. The main treatments for GC include radiation therapy, chemotherapy, and targeted therapy. The treatment plan is determined by factors such as the stage of the disease, the presence of biomarkers, and the recommendations of the treating physician [8].

In recent years, our understanding of the molecular mechanisms of GC has greatly improved, leading to significant advancements in novel therapies [9]. Immune checkpoint inhibitors (ICIs) have been particularly effective in killing cancer cells by activating the immune response. Examples of ICIs include antibodies that target the cytotoxic T-lymphocyte antigen CTLA-4 and immunotherapies that target the pathways of programmed cell death 1 (PD-1) and programmed death ligand 1 (PD-L1). These developments have revolutionized the treatment of various solid tumors [10]. Several PD-1 inhibitors, such as Nivolumab, Pembrolizumab, Sintilimab, Camrelizumab, and Tislelizumab, have been approved for use in cancer therapy and have shown promising results in the treatment of various cancers, including lung, melanoma, and gastroesophageal cancers [11]. However, a significant number of patients with GC who receive ICIs do not experience any therapeutic effect [12].

Recent studies have shed light on the processes involving infection, inflammation, innate immunity, and cancer [13]. The cytokines produced by activated immune cells play a crucial role in these processes. In addition to stimulating the antitumorigenic properties of T cells, pro-inflammatory cytokines such as IL-1β, IL-8, IL-12, TNF-α, and IFN-γ also contribute to the malignant transformation, growth, invasion, and metastasis of tumors [14]. Cytokines can both promote the growth, invasion, and metastasis of tumors and stimulate the antitumorigenic properties of T cells [15]. Despite advancements in treatment modalities, the prognosis of patients with AGC remains dismal. Cytokines are known to play a critical role in modulating the immune response, and their interaction with PD-1 blockade immunochemotherapy may have implications for treatment efficacy and prognosis in patients with AGC.

The goal of the study is to assess the predictive value of cytokines combined with PD-1 blockade immunochemotherapy in predicting prognosis susceptibility in patients diagnosed with AGC.

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 [16]. No human tissues or animal subjects were utilized in this investigation, exempting it from ethics committee oversight. The study's methodology was preregistered in the PROSPERO database (CRD42024557837), an international repository of systematic review protocols, to promote research integrity and replicability.

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, Cochrane Library, and Web of Science. A query strategy was carefully developed, with a specific focus on identifying English-language publications up until October 31, 2023. The full search strategy, including database-specific queries, is shown in Table 1 for transparency and reproducibility. 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 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 AGC; (2) It had to evaluate cytokine levels in serum samples of patients diagnosed with AGC who were receiving combination of PD-1 treatment and chemotherapy; (3) It had to report 5 years survival outcomes after treatment in AGC patients; (4) It had to investigate the relationship between cytokine levels and prognosis in AGC patients. Studies were excluded if they: (1) Did not focus on AGC 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

Table 1 Search Strategy

Database	Search Terms
Pubmed	((cytokine profile) OR (cytokine levels)) OR cytokine biomarkers)) AND (gastric cancer)) OR (stomach cancer)) OR (advanced gastric cancer)) AND (PD-1 blockade)) OR (PD-1 inhibitor)) OR (pembrolizumab)) OR (nivolumab)) OR (immunotherapy)) OR (immunochemotherapy)) AND (treatment outcomes)) OR (prognostic biomarkers)) OR (predictive biomarkers)) OR ("response rate)) OR (survival outcomes)
Google Scholar	(Cytokine biomarkers or cytokine profiles) AND (immunochemotherapy OR PD-1 blockade) AND (predictive biomarkers OR treatment outcomes) AND (gastric cancer OR stomach cancer)
Embase	(cytokine profile OR cytokine levels OR cytokine biomarkers) AND (gastric cancer OR stomach cancer OR advanced gastric cancer) AND (PD-1 blockade OR PD-1 inhibitor OR pembrolizumab OR nivolumab OR immunotherapy OR immunochemotherapy) AND (treatment outcomes OR prognostic biomarkers OR predictive biomarkers OR response rate OR survival outcomes)
Cohrane Library	(cytokine profile OR cytokine biomarkers) AND (gastric cancer OR stomach cancer) AND (PD-1 blockade OR immunochemotherapy) AND (treatment outcomes OR predictive biomarkers)
Web of Science	(cytokine profile OR cytokine levels OR cytokine biomarkers) AND (gastric cancer OR stomach cancer OR advanced gastric cancer) AND (PD-1 blockade OR PD-1 inhibitor OR pembrolizumab OR nivolumab OR immunotherapy OR immunochemotherapy) AND (treatment outcomes OR prognostic biomarkers OR predictive biomarkers OR response rate OR survival outcomes)

reports. (4) Had insufficient data or inadequate reporting of methodology; (5) Had a small sample size that might not yield reliable results; (6) Did not provide clear outcomes related to prognosis.

Data extraction

We used Endnote 20 software to cite and reference the studies. Two researchers 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 immunochemotherapy. The core data collected for the meta-analysis included author identity, publication year, nationality, Methodology, number of patients, patient age, and hazard ratio (HR) estimations, as shown in Table 2. Supplementary data included the outcome and types of cytokines featured in each study, shown in Table 3.

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% [17]. 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 $p < 0.05$.

Results

During the comprehensive search conducted across various databases, a total of 100 relevant studies were meticulously identified. Upon careful scrutiny, 57 studies were identified as duplicates and subsequently removed from consideration. This left a refined pool of 43 unique records for meticulous

Table 2 Characteristics of selected studies

First author	Year	Country	Study Design	Patients	Method	HR estimation
Qiufeng Qi et al [18]	2022	China	RS	52	Immunofluorescence	HR for PFS
Yidan Hou et al [19]	2023	China	RS	41	–	HR for OS, PFS
Xiao Ning Li et al [21]	2022	China	–	205	Immunohistochemistry	HR for OS, PFS
Wei-Chih Liao et al [22]	2008	Taiwan	RS	155	ELISA	HR for OS
Zhenzhan Zhang et al [20]	2022	China	RCT	135	–	HR for OS, PFS

Table 3 Outcomes of Cytokines expressions after Immunochemotherapy

Authors	Cytokines HR 95%CI				
	IL-2	IL-4	IL-6	IL-10	IFN-g
Qiufeng Qi et al [18]	PFS (0.6646–1.971)	PFS (0.3304–0.9807)	PFS (0.6233–1.849)	PFS (0.4985–1.479)	PFS (0.5157–1.529)
Yidan Hou et al [19]	PFS; 0.702 (0.294–1.674)	PFS; 0.73 (0.333–1.599)	OS; 3.018 (1.367–6.666), PFS; 1.882 (0.866–4.089)	PFS; 0.668 (0.311–1.437)	PFS; 0.79 (0.372–1.677)
Xiao Ning Li et al [21]	–	–	OS; 1.806(1.124–2.901)	–	–
Wei-Chih Liao et al [22]	–	–	OS;1.77(1.07–2.92)	–	–
Zhenzhan Zhang et al [20]	–	–	OS; 2.67 (1.06–6.72), PFS; 2.98 (1.11–7.98)	–	PFS; 1.93 (0.91–4.07)

screening. Following a thorough screening process, 12 studies emerged as potentially eligible for inclusion in the meta-analysis. However, after a detailed assessment, 9 studies were excluded due to specific reasons that did not align with the predefined criteria. Ultimately, a careful selection process led to the inclusion of three studies that met the stringent eligibility criteria and were thereby included in the final meta-analysis, as shown in Fig. 1.

Comparison of cytokines in AGC prognosis after with immunochemotherapy

In two studies [18, 19] conducted on patients with AGC undergoing immunochemotherapy, it was found that there was no significant difference in the expression of IL-2 for PFS (HR: 1.00; 95% CI: 0.63–1.58; $P = 0.99$) Fig. 2a. However, high expression of IL-4 was associated with improved PFS after the therapy, with pooled data from two studies [18, 19] showing a significant correlation (HR: 0.62; 95% CI: 0.39–0.96; $P = 0.03$) Fig. 2b. Fixed-effect models were used due to the absence of significant heterogeneity observed in these studies ($I^2 = 0\%$, $P = 0.69$).

The expression of IL-6 collected from two studies [18–20] for PFS in AGC after treatment showed no significant difference (HR: 1.49; 95% CI: 0.99–2.23; $P = 0.06$) Fig. 2c. Similarly, the expression of IL-10 retrieved from two studies [18, 19] did not show a significant difference in AGC (HR: 0.83; 95% CI: 0.50–1.39; $P = 0.49$) Fig. 2d. Also no significant variation was seen in PFS after analyzing three studies [18–20] for the expression of IFN-g in AGC after treatment (HR: 1.05; 95% CI: 0.72–1.54; $P = 0.79$) Fig. 2e.

In terms of OS in AGC after therapy, two studies [19–22] focused on IL-6 expression. The combined data revealed that high IL-6 expression was significantly associated with poor OS in AGC (HR: 2.01, 95% CI: 1.49–2.71; $P < 0.00001$) Fig. 3.

Quality assessment

We utilized the Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1, and risk of bias tool to systematically assess the quality of the trials in this study. We scrutinized various aspects such as sequence generation, allocation concealment, blinding, incomplete data, selective reporting, and other potential biases. We categorized trials as'high risk'if they exhibited biases in one or more critical domains,'low risk'if bias risks were minimal across all essential domains, and'unclear'if the bias status was uncertain. These categorizations are visually depicted in Figs. 4 and 5.

Publication bias

Figure 6 and 7 presents a funnel plot illustrating the expression of IL-6 in GC patients treated with PD-1 blockade, with a focus on OS and PFS outcomes. The plot displays a symmetrical distribution of studies around the median axis, with all studies falling within the expected funnel-shaped region. This visual representation suggests that publication bias is unlikely to be a significant concern in this analysis, as the studies appear to be evenly distributed and free from overt asymmetry.

Discussion

In recent years, immunotherapy has been increasingly used to treat various tumors. Researchers have found certain blood indicators that can reflect the immune status of patients. These indicators, such as PD-1 + CD8 + T cells [23], $CD4^+$ T cells [24], circulating tumor cells [25], and cytokines [26], can help predict how patients will respond to immunotherapy. However, there is still a lack of research on using peripheral blood parameters to predict the effectiveness of first-line ICIs in patients with AGC. Therefore, this

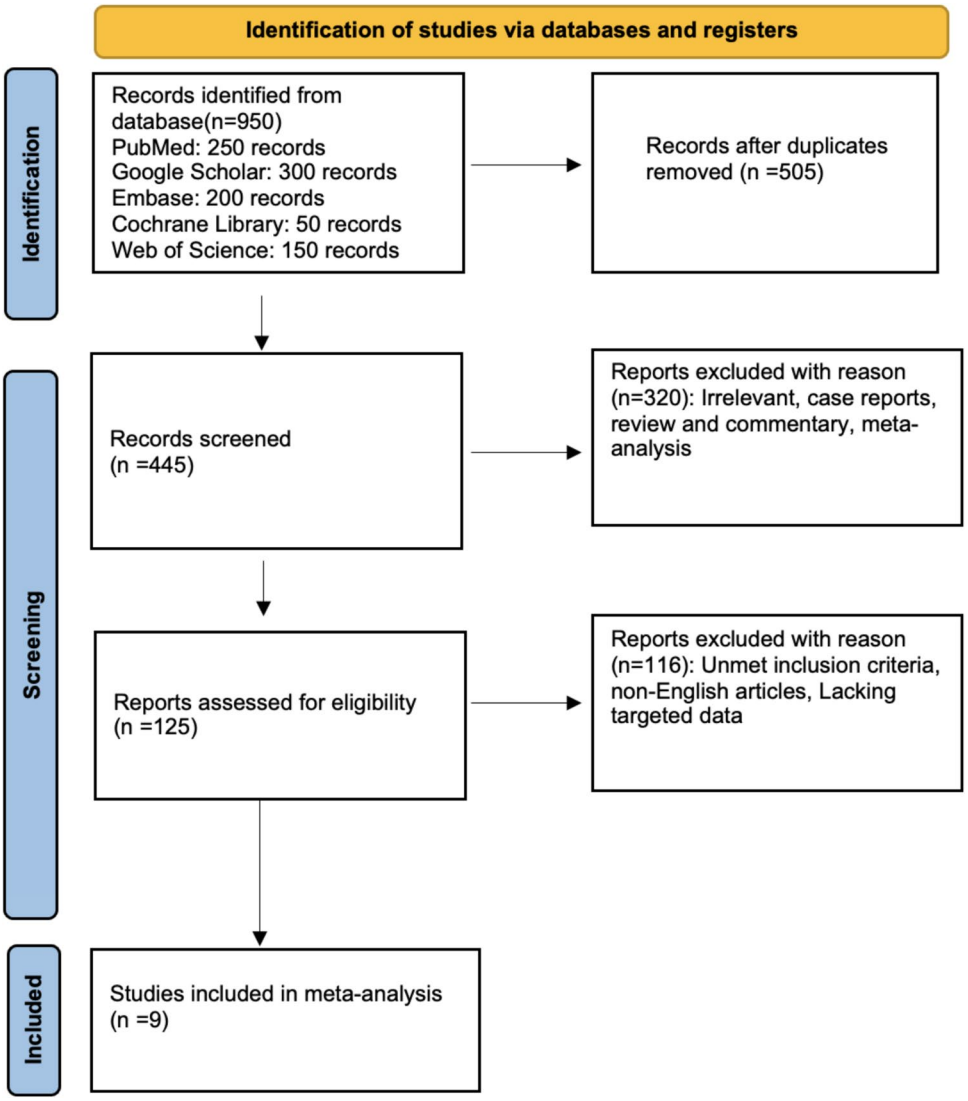


Fig. 1 Prisma flow of included studies

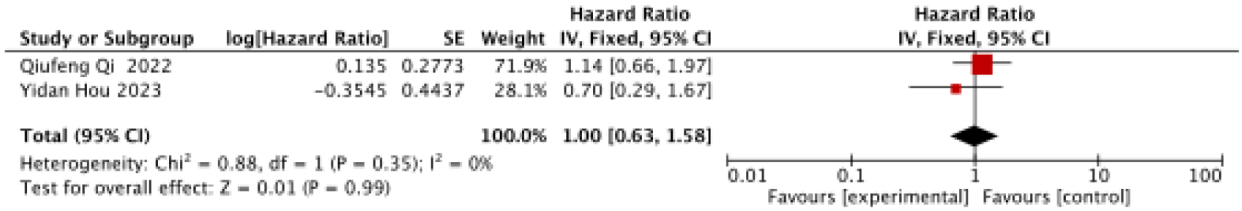
study aims to analyze the correlation between post-treatment cytokine levels in the blood and prognosis of AGC patients who received immunochemotherapy. By comparing the cytokine profiles of AGC patients who benefited from PD-1 therapy with those who did not, we aim to identify potential biomarkers that are associated with treatment response and outcomes in this group of patients.

The findings of this study shed light on the interplay between cytokine expression and PD-1 blockade immunochemotherapy in patients with AGC and provide valuable insights into potential biomarkers for treatment outcomes. In addition, this study has provided valuable insights into the contrasting effects of specific cytokines on PFS and OS in AGC patients undergoing immunochemotherapy. The study findings highlight the positive impact of IL-4 on PFS and the negative association of elevated IL-6 levels with OS, underscoring the potential role of these cytokines as prognostic indicators in the treatment of AGC. Importantly, the identification of IL-4 as a potential predictive biomarker for treatment response in AGC patients post therapy represents a significant contribution to our understanding of cytokine-mediated immune responses in cancer treatment. By clarifying the beneficial effects of IL-4 in enhancing antitumor immunity and treatment outcomes, our study serves as a pioneering effort in advancing our knowledge of cytokine profiling in PD-1 inhibitor therapy for AGC.

Elevated levels of IL-4 have been commonly observed in various types of cancers. However, the role of IL-4, whether it is pro- or anti-tumoral, remains uncertain. This role is dependent on the levels of IL-4 and its interaction with other immunological modulators [27]. A recent study found that patients treated with ipilimumab showed increased IL-4 levels. Importantly, those patients with higher IL-4 levels demonstrated better outcomes, which supports our findings [28]. The positive impact of IL-4 on PFS following PD-1 therapy in AGC patients may be due to its potential

Progression free survival

a



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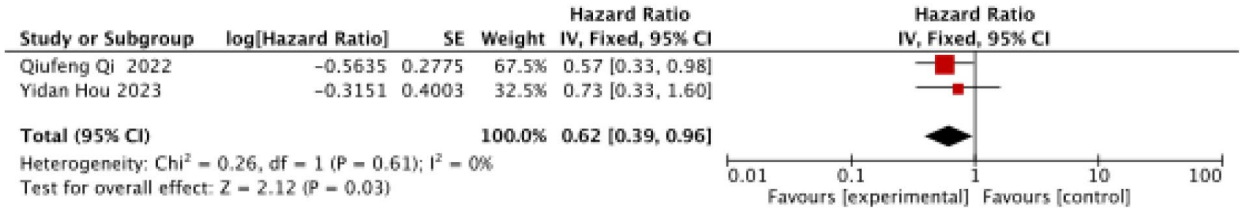

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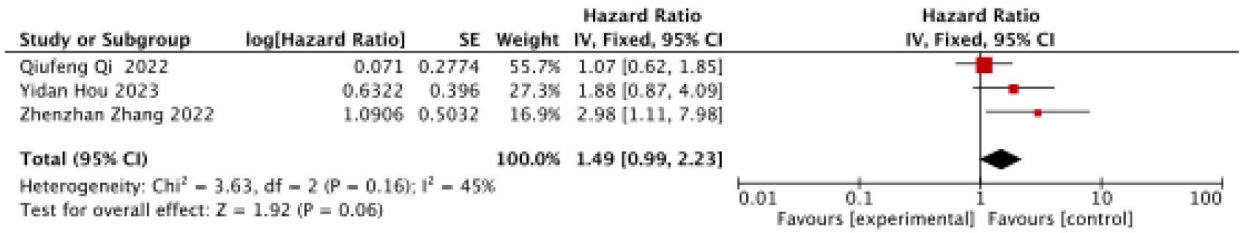

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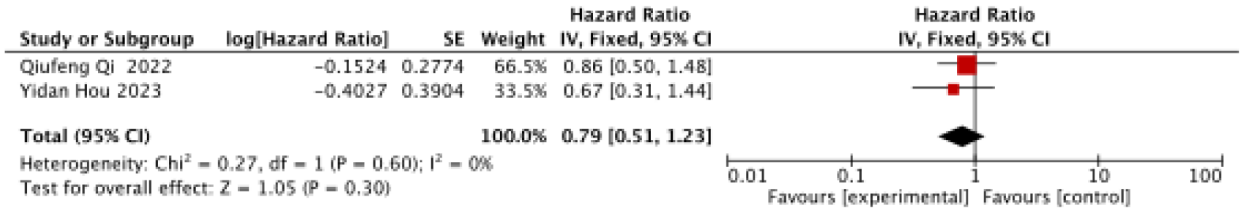

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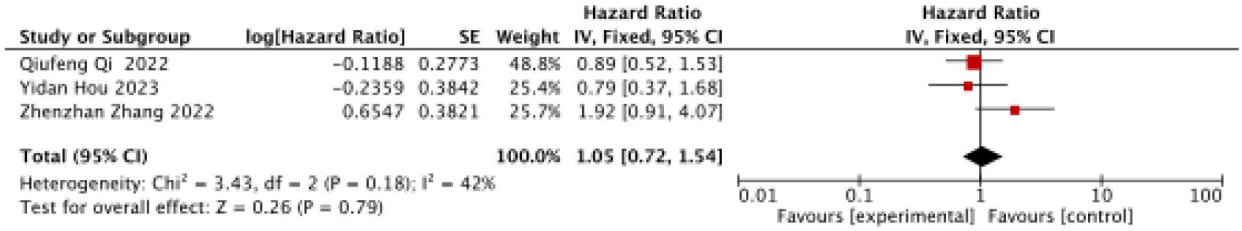

Fig. 2 Forest plot of PFS for; **a**: IL-2; **b**: IL-4; **c**: IL-6; **d**:IL-10; **e**: IFN-g

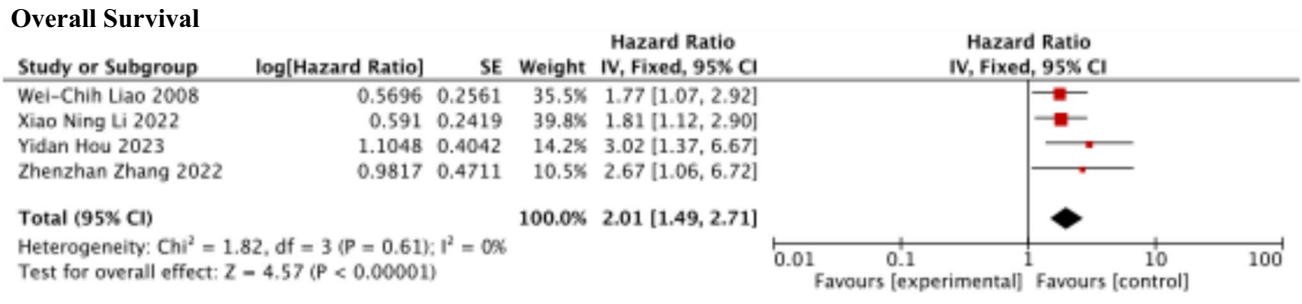

Fig. 3 Forest plot of OS for IL-6

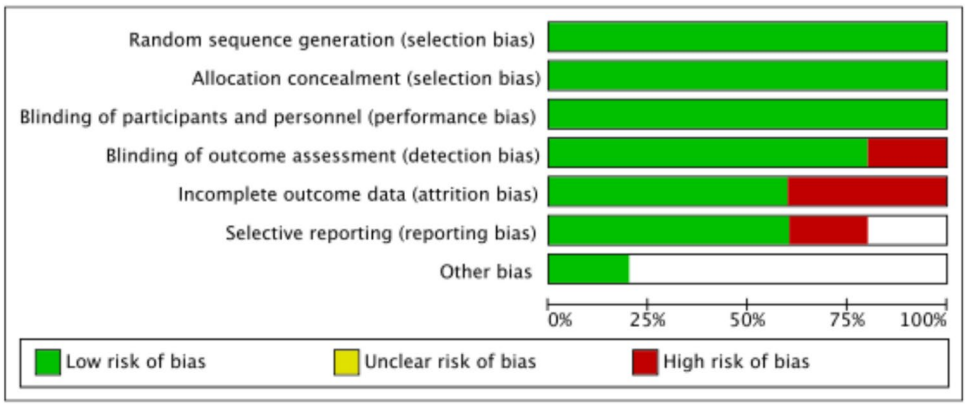

Fig. 4 Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

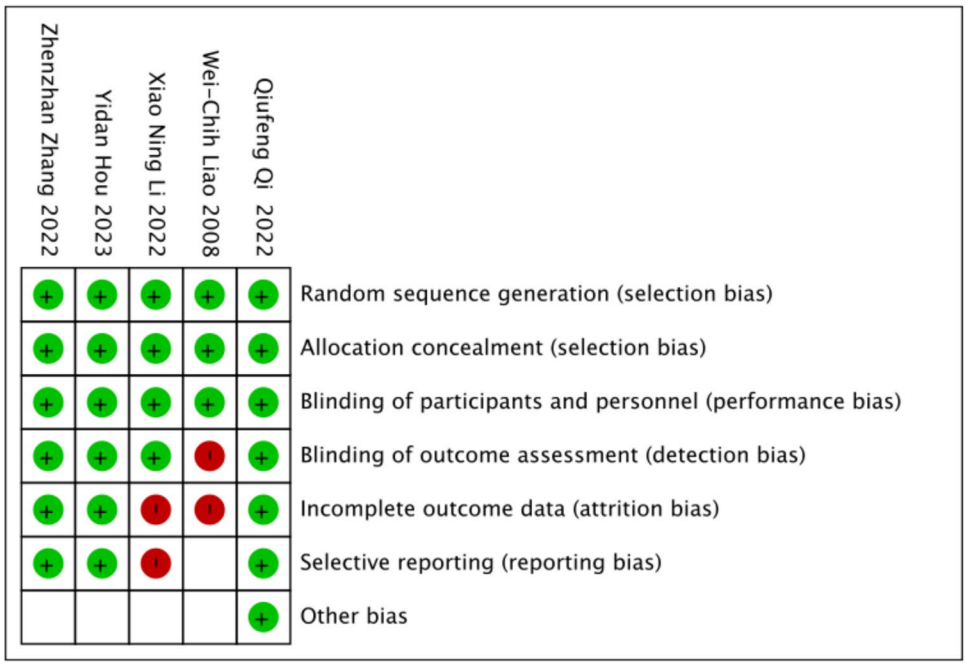

Fig. 5 Risk of bias summary: review authors' judgements about each risk of bias item for each included study

antitumor and immune-stimulatory effects. IL-4 has been shown to enhance immune responses against tumors and inhibit tumor growth. Additionally, IL-4 may enhance the effectiveness of immunotherapy by influencing the immune microenvironment and promoting the activation of immune cells to target cancer cells. Further research is needed to reveal the mechanisms underlying the beneficial effects of IL-4 in cancer treatment, which could lead to the

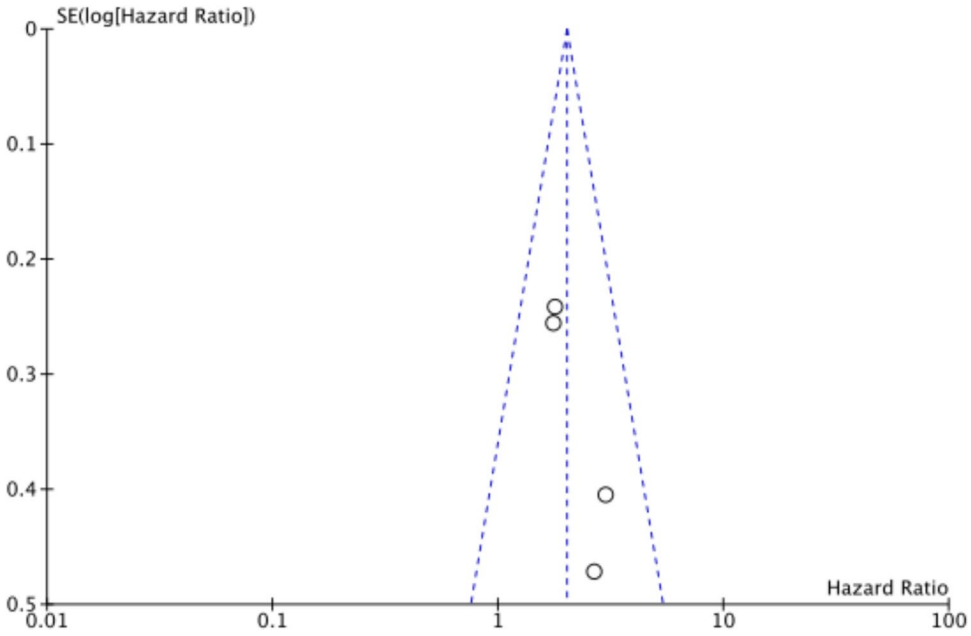

Fig. 6 Funnel plot of IL-6 (OS)

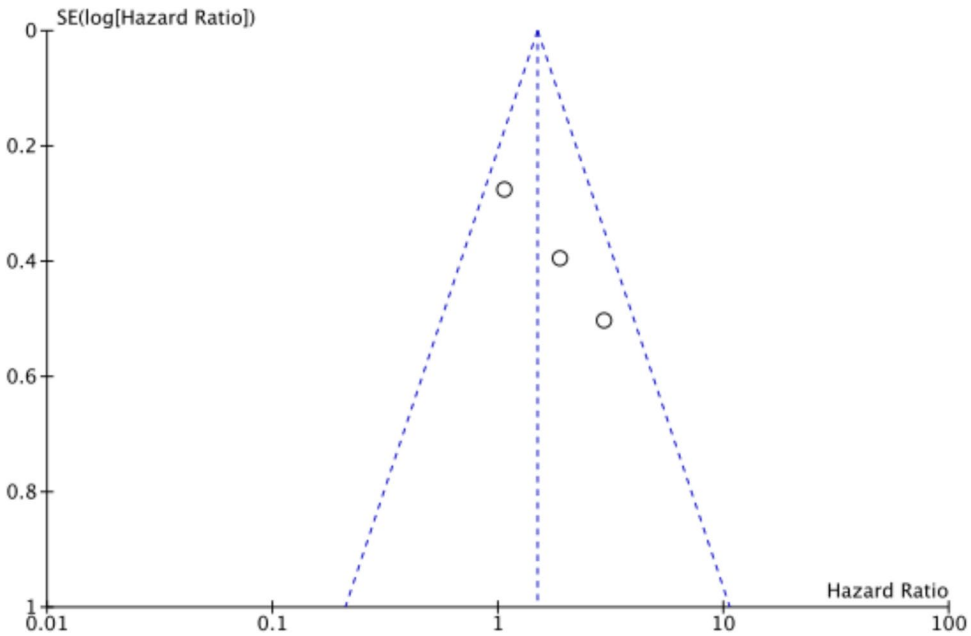

Fig. 7 Funnel plot of IL-6(PFS)

development of novel therapeutic strategies targeting IL-4 to enhance immune responses and improve outcomes in cancer patients undergoing immunotherapy.

Elevated levels of IL-6 have been found in the serum of various solid tumors, including lung, breast, pancreatic, and GC [29]. Another study confirmed our findings by demonstrating that patients with stomach cancer had significantly higher levels of IL-6. However, it is important to note that, IL-6 levels were negatively correlated with OS after treatment [30]. Furthermore, Jiameng Liu et al. reported that responsive patients exhibited a decreasing pattern in IL-6 levels over the course of the immunochemotherapy, a trend notably absent in nonresponsive patients [31]. The pro-inflammatory and immunosuppressive effects of IL-6 may explain this, but further research is needed to fully understand the underlying mechanisms. However, another study has shown that decreased IL-6 signaling is linked to a decreased risk of GC. These findings present opportunities to develop preventive and therapeutic strategies to fight against this disease. Furthermore, IL-6 shows promise as a prognostic biomarker for GC [32]. Study findings reveal that in responsive patients, tumor tissues regress gradually,

leading to a decline in IL-6 serum levels and reduced immune system activation. In nonresponsive patients, however, tumor progression persists, maintaining high immune system activation. Monitoring IL-6 levels could serve as a quick indicator of the effectiveness of PD-1 blockade in the short term [31]. Another study found that after two cycles of immunochemotherapy, elevated levels of IL-6 were significantly associated with a poorer prognosis [18]. Max et al. also discovered a correlation between high IL-6 levels and resistance to immunochemotherapy [33]. Patients with higher levels of IL-6 had significantly worse OS, suggesting that IL-6 may be a predictor of resistance to ICIs. These observations are consistent with a study by Yu et al., who reported that increased circulating levels of IL-6 are linked to poor outcomes in liver cancer patients receiving therapy with PD-1 inhibitors [34]. IL-6 has also been associated with tumor progression and treatment resistance in lung cancer [35, 36]. In some studies, increased levels of IL-6 in the serum have been associated with metastasis and poor prognosis in prostate, ovarian, and gastrointestinal cancers [37–39]. Tsukamoto et al. suggested that increased IL-6 levels could indicate reduced efficacy of PD-1 blockade in melanoma patients, and blocking IL-6 enhances PD-L1 expression on tumor cells [40]. The reason IL-6 can distinguish between effective and ineffective treatment may be due to the non-specific nature of PD-1 blockade, as indicated by our findings [41]. The consistent findings regarding the association of elevated IL-6 levels with poor prognosis, treatment resistance, and reduced efficacy of PD-1 inhibitors in various cancers emphasize the potential significance of IL-6 as a predictive biomarker for patient outcomes in immunotherapy. Further research is warranted to fully understand the underlying mechanisms by which IL-6 impacts the immune response and tumor microenvironment, leading to resistance to ICIs and poorer treatment outcomes. These findings underline the importance of investigating cytokine profiles, such as IL-6, to better predict treatment responses and personalize therapeutic strategies for cancer patients undergoing immunotherapy. Furthermore, our results revealed no significant differences in IL-2, IL-6, IL-10, and IFN-g levels in AGC patients receiving PD-1 therapy, suggesting the need for additional confirmation through larger-scale studies.

The identification of IL-4 and IL-6 as potential biomarkers for treatment outcomes in patients undergoing immunochemotherapy, particularly in AGC, holds significant clinical implications. IL-4 demonstrates promising impacts on PFS post immunochemotherapy, potentially attributing to its antitumor and immune-stimulatory effects. Conversely, elevated levels of IL-6 correlate with poor prognosis, indicating resistance to ICIs and reduced treatment efficacy. These insights underscore the importance of cytokine profiling in predicting response to immunotherapy and guiding personalized treatment strategies for cancer patients. Further research is needed to interpret the underlying mechanisms influencing the contrasting effects of IL-4 and IL-6, emphasizing the significance of investigating cytokine profiles to enhance treatment outcomes and improve patient care in the management of AGC and other cancers undergoing immunotherapy. Additionally, the complex interplay between various cytokines and their implications on treatment response and survival outcomes necessitates a comprehensive exploration to optimize therapeutic approaches and advance understanding in the field of cancer immunotherapy.

Limitations

Firstly, this meta-analysis is constrained by the inclusion of only three studies, which limits the robustness and generalizability of the conclusions drawn. Secondly, variability among the studies in design, timing of sample collection, and the cycles of immunochemotherapy administered may impact the validity of the findings. Different treatment protocols and the specific immunotherapy regimens utilized can influence cytokine expression, potentially leading to inconsistencies in treatment outcome assessments. Additionally, the measurement methods for cytokine levels varied across studies, with some employing ELISA, while others used multiplex assays, potentially contributing to heterogeneity in the data and complicating cross-study comparisons. Moreover, the relatively small sample sizes might heighten the risk of bias and affect the reliability of the observed associations. There is also the potential for publication bias, as studies with positive outcomes may be more likely to be published than those yielding negative or inconclusive results. Addressing these limitations in future research is essential to solidify the evidence supporting cytokine profiles as predictive biomarkers in AGC.

Conclusion

In conclusion, the evaluation of cytokine expression, particularly IL-4 and IL-6, appears to have a notable impact on treatment outcomes in patients with AGC undergoing treatment with PD-1 therapy. These findings underscore the potential prognostic value of cytokine profiles in predicting therapeutic responses and outcomes in AGC patients receiving PD-1 inhibitors. Further research efforts are essential to validate these results and deepen our understanding of the underlying mechanisms governing these associations.

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Author contributions Fumeng Yang and Zakari Shaibu wrote the main manuscript text and prepared figures. Qian Liu and Wei Zhu oversaw the research project, securing funding and providing comprehensive guidance throughout the study. All authors reviewed the manuscript.

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

Declarations

Conflict of interest The authors declare no competing interests.

Ethical approval 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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