BMC Gastroenterology

SYSTEMATIC REVIEW

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Efficacy and safety of pembrolizumab in advanced gastric and gastroesophageal junction cancer: a systematic review and meta-analysis

Xiaoying Ji[1], Guoping Wang[1], Dandan Pan[1], Shanxia Xu[2] and Xinming Lei[3*]

Abstract

Background Pembrolizumab, a PD-1 inhibitor, has shown potential for treating advanced gastric and gastroesophageal junction (GEJ) cancer. This meta-analysis evaluates its efficacy and safety, alone or combined with chemotherapy, in this population.

Methods A systematic review and meta-analysis were conducted in accordance with PRISMA guidelines. Databases including PubMed, Embase, the Cochrane Central Register of Controlled Trials, and Web of Science were searched up to October 31, 2024. Twelve studies comprising 4,069 patients were included. The primary outcomes were overall survival (OS) and progression-free survival (PFS); secondary outcomes included objective response rate (ORR), adverse events (AEs), and grade ≥ 3 AEs. Effect sizes were calculated using mean differences (MDs) and odds ratios (ORs) with 95% confidence intervals (CIs).

Results Pembrolizumab combined with chemotherapy significantly improved OS (MD = 1.92 months; 95% CI: 0.94 to 2.91) and ORR (MD = 11.05%; 95% CI: 6.29 to 15.82) compared to chemotherapy alone. Pembrolizumab monotherapy did not show a significant effect on OS (MD = 0.24 months; 95% CI: −1.15 to 1.63) and was associated with a significant reduction in PFS (MD = −2.28 months; 95% CI: −2.85 to −1.71) compared to chemotherapy alone. For safety, pembrolizumab monotherapy significantly reduced the risk of AEs (OR = 0.68; 95% CI: 0.57 to 0.81) and grade ≥ 3 AEs (OR = 0.39; 95% CI: 0.30 to 0.51) compared to chemotherapy. Pembrolizumab combined with chemotherapy did not significantly alter the risk of AEs (OR = 1.01; 95% CI: 0.90 to 1.13) or grade ≥ 3 AEs (OR = 1.12; 95% CI: 0.99 to 1.27) compared to chemotherapy alone.

Conclusion Pembrolizumab combined with chemotherapy improves survival and response rates with a manageable safety profile in advanced gastric and GEJ cancers. Monotherapy shows limited efficacy, highlighting the need for combination strategies and patient selection.

Keywords Pembrolizumab, Gastric cancer, Gastroesophageal junction cancer, Meta-analysis, Immunotherapy, Adverse events

*Correspondence:
Xinming Lei
1542620591@qq.com
Full list of author information is available at the end of the article

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Introduction

Advanced gastric cancer (GC) and gastroesophageal junction (GEJ) cancer remain significant global health challenges, with high mortality rates and frequent diagnosis at late stages, contributing to their substantial clinical burden [1, 2]. Despite being the fifth most commonly diagnosed cancer worldwide, gastric cancer is the third leading cause of cancer-related deaths, with over one million new cases and approximately 769,000 deaths reported in 2020 alone [3, 4]. This represents a considerable strain on healthcare systems, with profound impacts on morbidity, mortality, and healthcare costs [5].

Although current treatment strategies for advanced GC and GEJ cancers—including surgery, chemotherapy, and targeted therapies—have led to some improvements in patient outcomes [6], these modalities often show limited efficacy in advanced stages and are associated with significant toxicity [7]. In response to these challenges, immunotherapy has emerged as a key therapeutic approach, leveraging the body's immune system to combat malignancies [8]. Pembrolizumab, a monoclonal antibody targeting the programmed death-1 (PD-1) pathway, has shown promise in enhancing anti-tumor immune activity, offering an innovative mechanism for treating advanced cancers [9].

Recent clinical trials have demonstrated pembrolizumab's potential to prolong overall survival (OS) and progression-free survival (PFS) in patients with advanced GC and GEJ cancers [10–12]. However, its toxicity profile, particularly when used in combination with chemotherapy, requires careful evaluation [13]. Additionally, emerging data suggest that combining pembrolizumab with standard chemotherapy may generate synergistic effects, enhancing treatment efficacy while highlighting the importance of balancing efficacy with safety in clinical decision-making [14]. Notably, the combination approach has shown promise in reducing immune-related adverse events (irAEs) such as hearing loss, which, though rare, have become an area of concern in immune checkpoint inhibitor (ICI) therapies [15–17]. This evolving landscape of combination therapies warrants further exploration, especially as pembrolizumab is increasingly integrated into earlier treatment lines and adjuvant settings.

Despite growing clinical interest, existing meta-analyses in this field exhibit critical limitations. For instance, Yang et al. focused exclusively on pembrolizumab monotherapy, omitting combination regimens and biomarker-stratified outcomes [18], while Jiang et al. excluded single-arm studies, thereby overlooking real-world efficacy in PD-L1-selected populations [19]. Moreover, prior syntheses often conflated toxicity profiles, failing to differentiate irAEs from chemotherapy-related adverse events in combination therapies. These gaps hinder the development of personalized treatment protocols and underscore the need for a comprehensive evaluation of pembrolizumab's role across therapeutic contexts.

Therefore, this systematic review and meta-analysis synthesizes data from randomized controlled trials (RCTs) and single-arm studies to critically assess pembrolizumab's efficacy and safety, both as monotherapy and in combination with chemotherapy, for patients with advanced, unresectable GC or GEJ cancer. This effort not only provides evidence-based guidance for clinical decision-making but also outlines key areas for further investigation in oncologic research, particularly in optimizing treatment regimens and managing irAEs associated with ICI therapies.

Methods

This pre-registered systematic review and meta-analysis was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [20], and the study is registered with the PROSPERO database under registration number CRD42024621468.

Search strategy

A comprehensive systematic literature search was performed in PubMed, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science from their inception to October 31, 2024, without language restrictions. The detailed search strategy, including the following specific search terms: 'pembrolizumab', 'gastric cancer', 'gastroesophageal junction cancer', 'chemotherapy', 'immunotherapy', and 'adverse events', is provided in Supplementary File 1. Additionally, the reference lists of relevant articles and reviews were manually searched to identify further studies. Two researchers independently screened the titles and abstracts of all identified articles, followed by full-text assessments of potentially eligible studies. Discrepancies were resolved through discussion, and if consensus was not reached, a third researcher was consulted for arbitration.

Study selection

Two independent reviewers systematically evaluated all screened abstracts against predefined inclusion criteria to select eligible studies. Studies were included if they met the following criteria:

a) Population: Patients diagnosed with advanced gastric cancer or gastroesophageal junction cancer.
b) Intervention: Pembrolizumab administered alone or in combination with chemotherapy.

c) Comparison: Placebo, chemotherapy alone, or no comparator for single-arm trials or retrospective cohort studies.
d) Outcomes: Reported efficacy and safety outcomes.
e) Study Design: RCTs, single-arm trials, or retrospective cohort studies. Retrospective cohort studies were included to ensure a comprehensive understanding of pembrolizumab's real-world efficacy and safety, especially when randomized trials were unavailable.

Studies were excluded if:

a) Population: Patients had other cancers or significant comorbidities (e.g., cardiovascular disease, autoimmune diseases, or severe infections) to minimize confounding factors affecting survival outcomes or adverse event (AE) incidence.
b) Intervention: Included other immunotherapies besides pembrolizumab.
c) Data: Data were incomplete or insufficient for analysis.
d) Publication Type: The study was a review, meta-analysis, abstract, letter, or communication.
e) Duplicate Data: Multiple studies derived from the same patient population or dataset; in such cases, only the study with the longest follow-up or most comprehensive data was included to avoid duplication.

Potentially relevant full-text articles were retrieved and further evaluated. Disagreements during the selection process were resolved through discussion, or if necessary, by consultation with a third reviewer to reach a consensus.

Data extraction

All eligible studies retrieved from the specified databases were managed using EndNote X9 software. Two researchers independently extracted relevant data, and any discrepancies were resolved through consensus. Extracted information included study characteristics (e.g., author names, title, publication year, journal), participant demographics (e.g., age, gender, baseline performance status), intervention details (e.g., type of intervention, dosage, treatment duration), and outcomes. For quantitative data, standard deviations (SDs) were calculated from standard errors (SEs) using the formula: $SD = SE \times \sqrt{n}$. When SDs or SEs were unavailable, SDs were estimated using alternative metrics such as confidence intervals, t-values, quartiles, ranges, or p-values, following the guidelines in Sect. 7.7.3 of the Cochrane Handbook. In cases of missing critical data, the original authors were contacted up to four times over six weeks to request additional information.

Outcomes

The primary outcomes of this study included both efficacy and safety indicators. Efficacy outcomes focused on OS, PFS, objective response rate (ORR), complete response (CR), and partial response (PR). Safety outcomes included the incidence of adverse events (AEs) and grade ≥ 3 AEs. These outcomes were used to comprehensively evaluate the impact of pembrolizumab, either alone or in combination with chemotherapy, compared with placebo or chemotherapy alone in patients with gastric cancer or gastroesophageal junction cancer.

Risk of bias

For included RCTs, the Cochrane Risk of Bias Assessment Tool was used to evaluate the risk of bias across key domains: selection bias, performance bias, detection bias, attrition bias, and reporting bias. Each study was assessed in these domains and categorized as having a low, unclear, or high risk of bias. For non-randomized studies, the ROBINS-I tool was employed to assess the risk of bias. This tool evaluates several key dimensions: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selective reporting. The overall risk of bias for each study was classified as low, moderate, serious, or critical.

Data synthesis

Heterogeneity among the included studies was assessed using the I2 statistic and categorized as follows: $I2 < 25\%$ indicated very low heterogeneity; $25\% \leq I2 < 50\%$ low heterogeneity; $50\% \leq I2 < 75\%$ moderate heterogeneity; and $I2 \geq 75\%$ high heterogeneity [21]. A fixed-effects model was used when $I2 > 0.1$, indicating low heterogeneity; otherwise, a random-effects model was employed.

OS, PFS, and ORR were treated as continuous variables, with effect sizes calculated as mean differences (MDs). CR, PR, AEs, and grade ≥ 3 AEs were considered categorical variables, with effect sizes calculated as odds ratios (ORs).

All statistical analyses were performed using STATA software (version 13.0; StataCorp LP, College Station, TX, USA). A two-sided p-value ≤ 0.05 was considered statistically significant. Potential publication bias was assessed using funnel plots and Egger's test, with $p < 0.05$ indicating significant publication bias [22], thereby enhancing the reliability of the results.

Results

Characteristics of included studies

An initial electronic search identified 945 records. After removing duplicates, 477 records underwent title and abstract screening, and 67 articles were assessed for full-text eligibility. Ultimately, 11 articles comprising 12 studies involving a total of 4069 patients were included in this meta-analysis (Fig. 1) [10, 11, 23–31]. These studies primarily focused on patients with advanced, unresectable gastric or gastroesophageal junction cancers. Sample sizes ranged from 14 to 1579 participants, with a median of 140. Patient ages varied from 61 to 70 years, with a median age of 62. The included studies were published between 2016 and 2023, with a median publication year of 2021.

Among the included studies, eight were RCTs [10, 11, 24, 26, 29–31], of which six compared pembrolizumab monotherapy with chemotherapy, and four compared pembrolizumab combined with chemotherapy against chemotherapy alone. Four single-arm studies were included: one assessed pembrolizumab combined with radiotherapy, while the remaining three evaluated pembrolizumab monotherapy [23, 25, 27, 28]. Detailed characteristics of the included studies are provided in Supplementary File 2.

Risk of bias

The risk of bias in the seven included RCTs was assessed using the Cochrane Risk of Bias Assessment Tool (See supplementary file 3, supplementary Fig. 3.1). All studies demonstrated low risk in the areas of random sequence generation, selective reporting, and other biases. One study was rated with some concerns for allocation concealment, four studies showed some concerns in the blinding of outcome assessment, and one study had some concerns regarding incomplete outcome data. Two studies were classified as high risk for blinding of participants, while four studies showed some concerns in this domain.

The four non-RCT studies were assessed using the ROBINS-I tool, with all studies being rated with a moderate overall risk of bias (See supplementary file 3, supplementary Table 3.1). Common concerns across these studies included moderate issues with confounding, selection of participants, and missing data, along with some concerns related to deviations from intended interventions. Detailed assessments are available in Supplementary File 3.

Assessment of heterogeneity and inconsistency

High heterogeneity was observed across most outcomes, except for grade ≥ 3 AEs in RCTs and overall AEs in single-arm studies. This heterogeneity may stem from differences in patient populations, including age, disease stage,

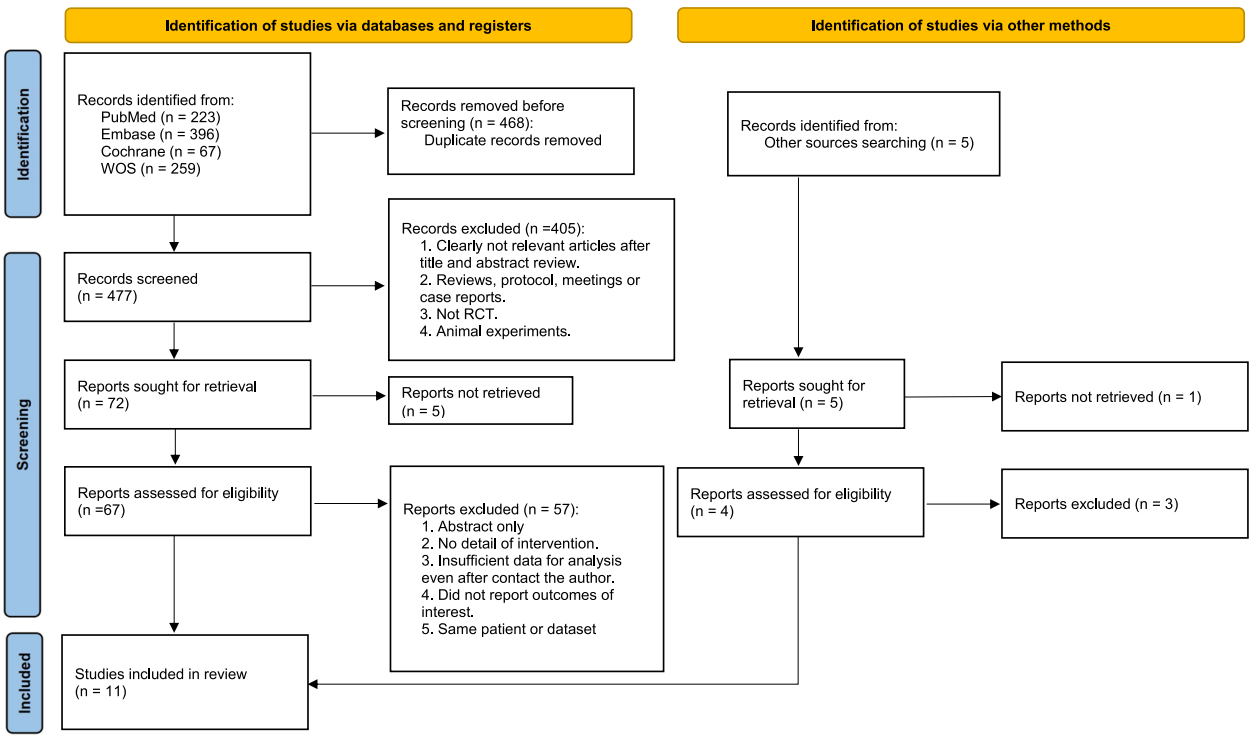

Fig. 1 PRISMA Flow diagram of the search process for studies. *RCT* randomized controlled trials

prior treatments, and performance status, as well as inconsistencies in pembrolizumab dosage, combination chemotherapy regimens, and timing of administration. Variations in study design, such as follow-up duration and outcome criteria, likely contributed further. Sensitivity analyses, excluding individual studies, indicated no outliers, with results consistently centered around the mean effect size. These potential sources of heterogeneity should be considered when interpreting the findings.

Funnel plots (Supplementary File 4) showed symmetrical distributions for most outcomes, indicating minimal publication bias. Supplementary Figs. 4.1 and 4.9 demonstrated uniform distributions, while supplementary Figs. 4.3, 4.6, 4.10, 4.13, and 4.14 displayed notable asymmetry, suggesting significant bias. Egger's test revealed no small-study effects for most outcomes ($P > 0.05$), except for grade ≥ 3 AEs in RCTs. Results for this outcome should be interpreted with caution.

The results of meta-analysis

Efficacy RCT studies A total of 10 studies involving 3808 patients evaluated the impact of pembrolizumab on OS. The pooled analysis demonstrated a statistically significant improvement in OS with pembrolizumab (Fig. 2a) (MD = 2.16, 95% CI: 0.70, 3.63), though with substantial heterogeneity ($I^2 = 74.8\%$, $p < 0.001$). Among individual studies, 4/10 showed significant OS benefits, while 6/10 reported non-significant trends. Subgroup analysis by treatment modality revealed that pembrolizumab combined with chemotherapy (4 studies, 2544 patients) provided a homogeneous OS benefit (MD = 1.92, 95% CI: 0.94, 2.91, $p < 0.001$; $I^2 = 0\%$, $p = 0.658$), whereas monotherapy (6 studies, 1264 patients) showed no significant effect (MD = 2.11, 95% CI: -0.92, 5.15, $p = 0.74$) but high heterogeneity ($I^2 = 83.7\%$, $p < 0.001$).

For PFS, 10 studies (3808 patients) showed no pooled benefit with pembrolizumab (Fig. 2b) (MD = 0.83, 95% CI: -1.70, 3.36; $I^2 = 99.3\%$, $p < 0.001$). Subgroup analysis highlighted divergent results: pembrolizumab monotherapy significantly reduced PFS (MD = -2.28, 95% CI: -2.85, -1.71; $I^2 = 55.5\%$, $p = 0.047$), driven by consistent worsening in 6/6 studies, while combination therapy showed no effect (MD = 5.80, 95% CI: -0.79, 12.38; $I^2 = 99.4\%$, $p < 0.001$).

Nine studies involving 3004 patients assessed the ORR. The meta-analysis showed no significant improvement in ORR with pembrolizumab compared to control groups (Fig. 2c) (MD = 1.18, 95% CI: -4.43, 6.79; $I^2 = 89.6\%$, $p < 0.001$). Among the individual studies, 2/9 studies showed significant improvement in ORR with pembrolizumab, while 1 study showed a significant reduction, and

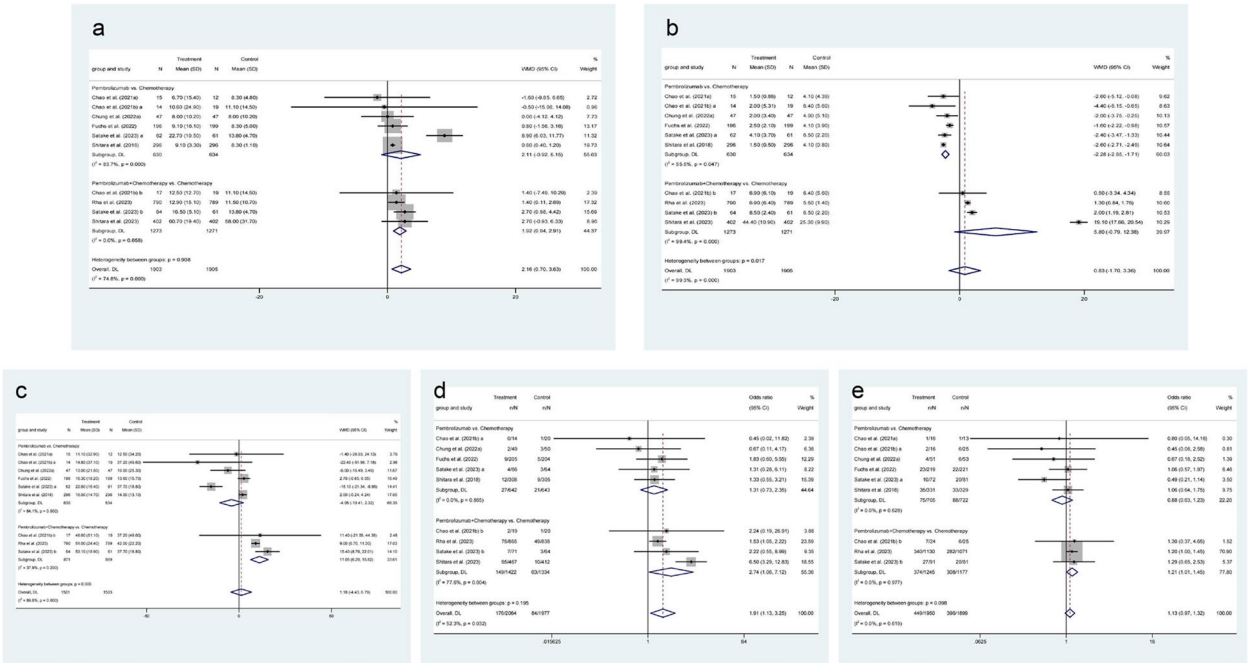

Fig. 2 Forest plots of the efficacy of pembrolizumab in gastric or gastroesophageal junction cancer (RCTs): (**a**) overall survival (OS); (**b**) progression-free survival (PFS); (**c**) objective response rate (ORR); (**d**) complete response (CR); and (**e**) partial response (PR). The black square represents the effect size of each study. The black solid line indicates the 95% CI for the effect size. The red dashed line shows the overall pooled effect, and the diamond represents the pooled effect size with the corresponding CI

6/9 studies showed no significant difference. Subgroup analysis indicated that pembrolizumab monotherapy (6 studies, 1264 patients) showed no significant effect on ORR compared to chemotherapy alone (MD = -4.05, 95% CI: -10.41, 2.32; $I^2 = 84.1\%$, $p < 0.001$), whereas pembrolizumab combined with chemotherapy (3 studies, 1740 patients) significantly improved ORR (MD = 11.05, 95% CI: 6.29, 15.82; $I^2 = 37.9\%$, $p = 0.200$).

For CR, nine studies (4041 patients) demonstrated that pembrolizumab significantly improved CR compared to control groups (OR = 1.91, 95% CI: 1.13, 3.25; $I^2 = 52.3\%$, $p = 0.032$, Fig. 2d). Among the individual studies, 2/9 studies showed significant improvement in CR, while 7/9 studies showed no significant difference. Subgroup analysis showed no significant effect for pembrolizumab monotherapy (5 studies, 1285 patients) (OR = 1.31, 95% CI: 0.73, 2.35; $I^2 = 0\%$, $p = 0.865$), whereas pembrolizumab combined with chemotherapy (4 studies, 2756 patients) significantly increased CR (OR = 2.74, 95% CI: 1.06, 7.12; $I^2 = 77.6\%$, $p = 0.004$).

For PR, nine studies (3849 patients) showed no significant improvement in PR with pembrolizumab compared to control groups (Fig. 2e) (OR = 1.13, 95% CI: 0.97, 1.32, $I^2 = 0\%$, $p = 0.619$). Among the individual studies, 1/9 study showed significant improvement, while 8/9 studies showed no significant difference. Subgroup analysis indicated that pembrolizumab monotherapy (6 studies, 1427 patients) showed no significant effect on PR compared to chemotherapy (OR = 0.88, 95% CI: 0.63, 1.23; $I^2 = 0\%$, $p = 0.628$), whereas pembrolizumab combined with chemotherapy (3 studies, 2422 patients) significantly increased PR (OR = 1.21, 95% CI: 1.01, 1.45; $I^2 = 0\%$, $p = 0.977$).

Single-arm studies Pooling data from four single-arm studies revealed a median OS of 8.83 months (95% CI: 4.61, 13.06) and a median PFS of 1.93 months (95% CI: 1.49, 2.37) for advanced gastric and gastroesophageal junction cancer. The median ORR was 31.06% (95% CI: 13.58, 48.54). Median CR and PR were 2% (95% CI: 1, 4) and 30% (95% CI: 7, 53), respectively (see Fig. 3).

Safety RCT studies Seven studies (7143 patients) evaluated AEs associated with pembrolizumab treatment. The meta-analysis showed no significant difference in AE risk between pembrolizumab and control groups (OR = 0.85, 95% CI: 0.71, 1.03; Fig. 4a). Heterogeneity among studies was moderate ($I^2 = 64.4\%$, $p = 0.010$), suggesting variability in AE reporting, possibly due to differences in patient populations and treatment regimens. Subgroup analysis indicated that pembrolizumab monotherapy (4 stud-

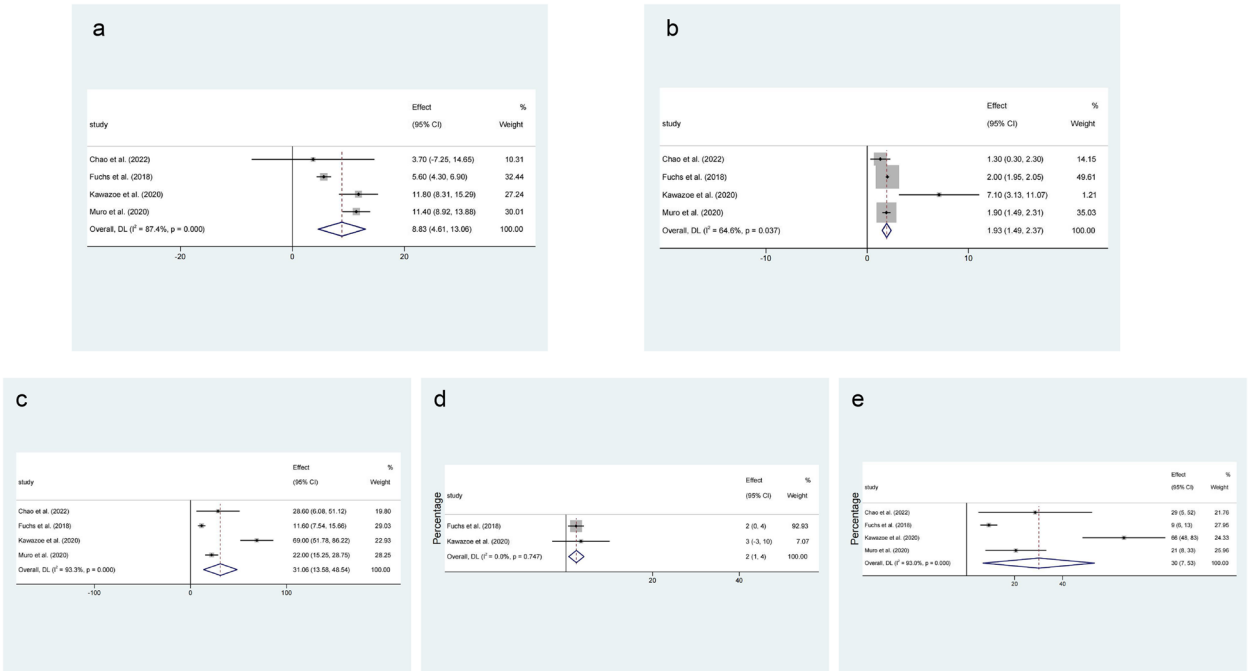

Fig. 3 Forest plots of the efficacy of pembrolizumab in gastric or gastroesophageal junction cancer (single-arm studies): (**a**) overall survival (OS); (**b**) progression-free survival (PFS); (**c**) objective response rate (ORR); (**d**) complete response (CR); and (**e**) partial response (PR). The black square represents the effect size of each study. The black solid line indicates the 95% CI for the effect size. The red dashed line shows the overall pooled effect, and the diamond represents the pooled effect size with the corresponding CI

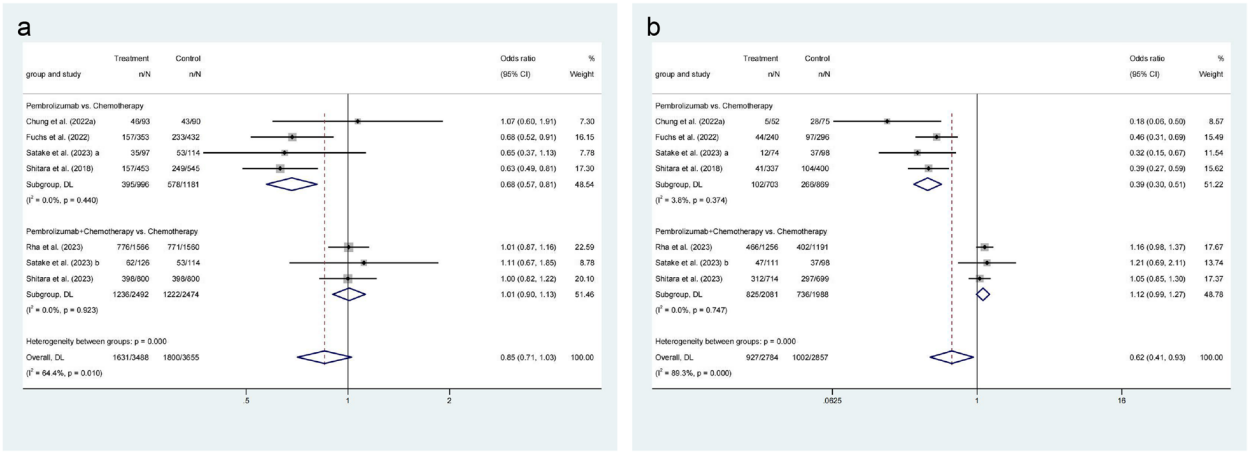

Fig. 4 Forest plots of the safety of pembrolizumab in gastric or gastroesophageal junction cancer (RCTs): (**a**) overall survival (OS); (**b**) progression-free survival (PFS); (**c**) objective response rate (ORR); (**d**) complete response (CR); and (**e**) partial response (PR). The black square represents the effect size of each study. The black solid line indicates the 95% CI for the effect size. The red dashed line shows the overall pooled effect, and the diamond represents the pooled effect size with the corresponding CI

ies, 2177 patients) significantly reduced the risk of AEs (OR = 0.68, 95% CI: 0.57, 0.81; $I^2 = 0\%$, $p = 0.440$), while pembrolizumab combined with chemotherapy (3 studies, 4966 patients) showed no significant difference compared to control groups (OR = 1.01, 95% CI: 0.90, 1.13; $I^2 = 0\%$, $p = 0.923$).

For grade ≥ 3 AEs, seven studies (5641 patients) demonstrated that pembrolizumab significantly reduced the risk compared to controls (OR = 0.62, 95% CI: 0.41, 0.93; Fig. 4b). The I^2 for this analysis was 89.3%, indicating moderate heterogeneity, likely due to varying definitions of grade ≥ 3 AEs across studies. Subgroup analysis showed that pembrolizumab monotherapy (4 studies, 1572 patients) significantly reduced the risk of grade ≥ 3 AEs (OR = 0.39, 95% CI: 0.30, 0.51; $I^2 = 3.8\%$, $p = 0.374$), whereas pembrolizumab combined with chemotherapy (3 studies, 4069 patients) showed no significant difference compared to controls (OR = 1.12, 95% CI: 0.99, 1.27; $I^2 = 0\%$, $p = 0.747$).

Single-arm studies Data from two single-arm studies revealed a median AE rate of 41% (95% CI: -11, 92) and a median grade ≥ 3 AE rate of 30% (95% CI: -5, 64) for advanced gastric and gastroesophageal junction cancer (see Fig. 5).

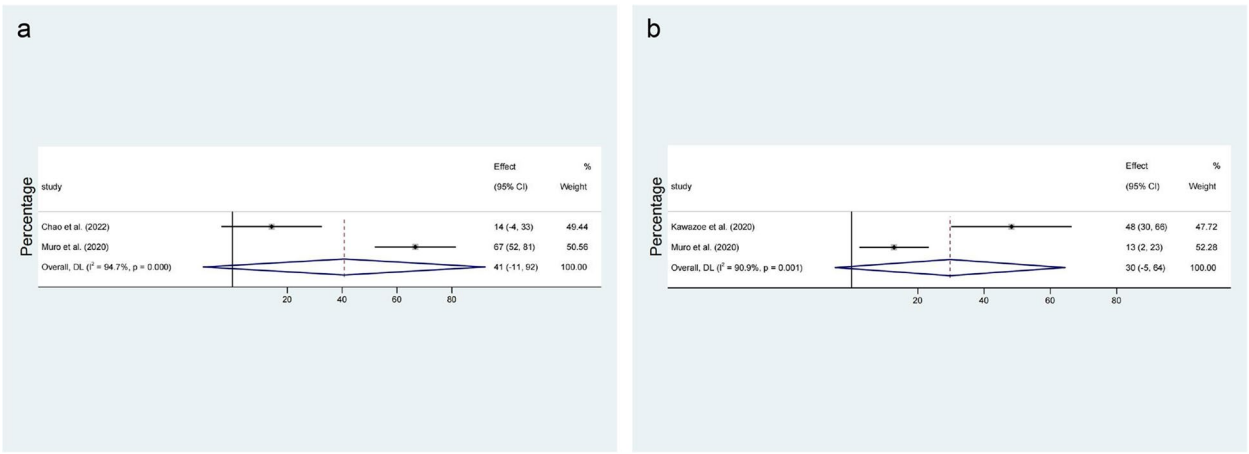

Fig. 5 Forest plots of the safety of pembrolizumab in gastric or gastroesophageal junction cancer (single-arm studies): (**a**) overall survival (OS); (**b**) progression-free survival (PFS); (**c**) objective response rate (ORR); (**d**) complete response (CR); and (**e**) partial response (PR). The black square represents the effect size of each study. The black solid line indicates the 95% CI for the effect size. The red dashed line shows the overall pooled effect, and the diamond represents the pooled effect size with the corresponding CI

Discussion

This comprehensive meta-analysis, encompassing 11 articles and 12 studies with a total of 4069 patients with advanced unresectable gastric or GEJ cancer, systematically evaluated the efficacy and safety of pembrolizumab interventions. The main findings are as follows: First, pembrolizumab combined with chemotherapy significantly improved OS and ORR compared to chemotherapy alone, underscoring its potential to enhance prognosis in advanced disease. These results suggest a synergistic effect when pembrolizumab is incorporated into standard chemotherapy regimens. Second, pembrolizumab monotherapy did not demonstrate significant improvements in OS, PFS, ORR, or PR compared to chemotherapy alone. In fact, pembrolizumab monotherapy was associated with a significant reduction in PFS, highlighting its limited efficacy as a standalone treatment in this patient population and emphasizing the necessity of combination strategies to achieve optimal outcomes. Third, pembrolizumab combined with chemotherapy did not significantly reduce or increase the risk of AEs or grade ≥ 3 AEs compared to chemotherapy alone, suggesting a manageable safety profile when used in combination regimens. Additionally, single-arm studies reported a median OS of 8.83 months, a median PFS of 1.93 months, and a median ORR of 31.06%, further supporting the potential of pembrolizumab in specific patient populations.

Pembrolizumab, an immune checkpoint inhibitor targeting the PD-1 receptor, enhances the immune system's ability to recognize and eliminate cancer cells. This mechanism has introduced a novel therapeutic avenue for patients with advanced gastric and GEJ cancers, conditions historically associated with limited treatment options and poor prognoses. In our study, pembrolizumab combined with chemotherapy significantly improved OS and ORR compared to chemotherapy alone, demonstrating its potential to enhance clinical outcomes in advanced disease. However, pembrolizumab monotherapy failed to show significant benefits in OS, PFS, ORR, or PR and was even associated with a reduction in PFS, suggesting limited efficacy as a standalone treatment. These findings align with prior research on immunotherapy in oncology. For instance, the KEYNOTE-062 trial demonstrated that pembrolizumab combined with chemotherapy significantly improved OS in patients with advanced gastric and GEJ cancers, particularly in those with a combined positive score (CPS) ≥ 10 [12]. Similarly, the KEYNOTE-059 trial reported that pembrolizumab, when added to standard chemotherapy, enhanced both PFS and OS in biomarker-selected populations [29]. These results underscore the value of pembrolizumab as part of combination regimens, particularly in patients with programmed death-ligand 1 (PD-L1)–positive tumors or microsatellite instability-high (MSI-H) status.

The potential of pembrolizumab, particularly in combination with chemotherapy, underscores a significant shift in the therapeutic landscape for advanced gastric and GEJ cancers. This study highlights the synergistic effects of pembrolizumab, reinforcing the importance of combination strategies in overcoming the immunosuppressive tumor microenvironment. However, important knowledge gaps remain, particularly regarding patient selection criteria. The variability in treatment responses based on biomarkers, such as PD-L1 expression or MSI-H, calls for a more personalized approach. Further research is required to identify reliable biomarkers that predict which patients are most likely to benefit from pembrolizumab, both as a monotherapy and in combination with other agents. Moreover, while pembrolizumab is associated with a manageable safety profile, the occurrence of irAEs such as pneumonitis and colitis suggest that a deeper understanding of these toxicities is essential to optimize treatment protocols and improve patient outcomes [32].

The lack of efficacy observed with pembrolizumab monotherapy may be attributed to several biological and clinical factors. As a monotherapy, pembrolizumab relies on pre-existing immune activation to elicit antitumor effects [33]. In advanced gastric and GEJ cancers, the tumor microenvironment is often highly immunosuppressive, characterized by elevated levels of regulatory T cells, myeloid-derived suppressor cells, and inhibitory cytokines, which can attenuate the effectiveness of immune checkpoint inhibitors [34]. In contrast, the combination of pembrolizumab with chemotherapy addresses these challenges by modulating the tumor microenvironment. Chemotherapy-induced immunogenic cell death releases tumor-associated antigens, promoting dendritic cell maturation and T-cell priming [35, 36]. This process amplifies the immune response and enhances the efficacy of pembrolizumab. Furthermore, chemotherapy can reduce the population of immunosuppressive cells within the tumor microenvironment, creating conditions more favorable for immune activation [37]. The synergistic effects observed with pembrolizumab and chemotherapy highlight the importance of combination strategies in the treatment of advanced gastric and GEJ cancers. These findings provide a robust rationale for incorporating pembrolizumab into standard chemotherapy regimens and emphasize the need for further investigation into biomarkers and patient selection criteria to optimize therapeutic outcomes.

Looking ahead, we anticipate that the landscape of immunotherapy in gastric and GEJ cancers will continue to evolve rapidly. In the next five years, we expect

to see more robust combination regimens that integrate pembrolizumab with novel immunotherapies, targeted therapies, or precision medicine approaches. Advances in biomarker identification will allow for better patient stratification, ensuring that treatments are tailored to the individual's tumor characteristics and immune profile. Additionally, as our understanding of immune-related toxicities deepens, strategies to mitigate these side effects, such as early detection and personalized management plans, will likely improve the overall safety and tolerability of immunotherapy. As we continue to explore combination therapies, particularly those targeting both the immune system and tumor biology, we may see transformative changes in the prognosis of patients with advanced gastric and GEJ cancers.

The analysis of single-arm studies provided valuable insights into the efficacy of pembrolizumab, particularly in real-world scenarios or for patients who may not meet the stringent eligibility criteria of RCTs. In this meta-analysis, single-arm studies reported a median OS of 8.83 months, a PFS of 1.93 months, and an ORR of 31.06%. These findings highlight the potential clinical benefits of pembrolizumab, especially in biomarker-selected or heavily pretreated populations. The observed ORR of 31.06% is consistent with results from pivotal trials such as KEYNOTE-059, which reported similar response rates in patients with PD-L1–positive tumors [38]. This suggests that pembrolizumab monotherapy may provide meaningful clinical benefits in a subset of patients, particularly those with specific biomarkers such as high PD-L1 expression or MSI-H status. However, the relatively short PFS observed in the single-arm studies indicates that the durability of pembrolizumab's efficacy may be limited when used as monotherapy, reinforcing the necessity of combination strategies to achieve more robust and sustained therapeutic outcomes. Variability in response rates across single-arm studies can be attributed to differences in patient populations, including variations in prior treatments, biomarker expression, and tumor microenvironment characteristics. For example, patients with MSI-H or high tumor mutational burden (TMB) tumors tend to respond better to immune checkpoint inhibitors due to increased neoantigen presentation and heightened immune recognition [39]. In contrast, patients with low PD-L1 expression or non-immunogenic tumors are less likely to benefit from pembrolizumab monotherapy, as these tumors often exhibit immune evasion mechanisms that diminish the efficacy of immune checkpoint blockade [40].

Safety is a critical consideration in the treatment of advanced gastric or GEJ cancer, given the fragility of these patients due to disease progression, comorbidities, and the cumulative burden of prior treatments. Effective therapies must not only improve survival outcomes but also maintain an acceptable safety profile to ensure patients can tolerate treatment without compromising quality of life. In this study, pembrolizumab demonstrated a manageable safety profile across RCTs. Overall, pembrolizumab monotherapy significantly reduced the risk of AEs and grade ≥ 3 AEs compared to chemotherapy alone. Subgroup analysis revealed that monotherapy was particularly advantageous in minimizing the incidence of severe toxicities, such as hematological and gastrointestinal AEs commonly associated with traditional chemotherapy regimens. In contrast, pembrolizumab combined with chemotherapy did not significantly increase or decrease the risk of overall AEs or grade ≥ 3 AEs compared to chemotherapy alone, suggesting it is a tolerable addition to standard chemotherapy regimens. These findings are consistent with prior studies, including the KEYNOTE-061 trial, which reported that pembrolizumab had a significantly lower toxicity burden compared to chemotherapy, particularly regarding grade ≥ 3 AEs such as neutropenia and nausea [10]. Our study adds new evidence by highlighting that pembrolizumab combined with chemotherapy does not exacerbate chemotherapy-related toxicities, making it a feasible option for combination regimens. Similarly, real-world studies have corroborated that pembrolizumab's immune-related adverse events (irAEs), such as pneumonitis, colitis, and hepatitis, are less frequent but manageable when detected and addressed early [41]. The favorable safety profile of pembrolizumab monotherapy and its neutral effect when combined with chemotherapy can be attributed to its immune-specific action. Unlike chemotherapy, which indiscriminately targets dividing cells and causes systemic toxicity, pembrolizumab activates the immune system more selectively by blocking the PD-1 pathway, enabling T cells to identify and eliminate tumor cells [42]. However, the occurrence of irAEs reflects an overstimulated immune response, often localized to specific organs [43]. When combined with chemotherapy, pembrolizumab may share overlapping toxicity profiles without introducing additive toxicity, as chemotherapy-induced immunogenic cell death enhances antigen presentation and immune activation without significantly altering pembrolizumab's toxicity profile [44].

The analysis of single-arm studies further elucidates the safety profile of pembrolizumab, offering insights into its tolerability in less controlled, real-world scenarios. In these studies, the median AE rate was 41%, and the median grade ≥ 3 AE rate was 30%. These findings indicate that pembrolizumab's toxicity profile in single-arm studies is comparable to that reported in RCTs, reinforcing its consistency across diverse clinical settings. The AE

and grade ≥ 3 AE rates observed reflect pembrolizumab's immune-related toxicity spectrum, including events such as colitis, pneumonitis, and hepatitis. These toxicities are immune-mediated and typically manageable with early intervention, such as corticosteroid administration [45]. Notably, the grade ≥ 3 AE rate of 30% is lower than that typically associated with cytotoxic chemotherapy in this patient population, which often exceeds 50% in clinical trials [46]. This highlights pembrolizumab's favorable toxicity profile compared to traditional treatments, particularly for patients who may not tolerate the cumulative toxicities of chemotherapy. The consistency of AE rates across single-arm and RCT data suggests that pembrolizumab's safety is not significantly influenced by differences in trial design, further supporting its broad applicability.

This meta-analysis has several notable strengths. First, it is one of the most comprehensive evaluations to date, incorporating data from 11 articles and 12 studies with a total of 4069 patients, thereby providing robust and generalizable evidence on the efficacy and safety of pembrolizumab in advanced gastric and GEJ cancers. The inclusion of RCTs and single-arm studies allows for a balanced perspective on pembrolizumab's clinical performance in both controlled and real-world settings. Second, the study employed rigorous statistical methodologies, including subgroup analyses, enhancing the robustness of the conclusions and providing a deeper understanding of pembrolizumab's differential effects based on treatment modality and patient characteristics. However, several limitations must be acknowledged. First, the considerable heterogeneity among the included studies poses a significant challenge. Variations in pembrolizumab dosage, treatment duration, biomarker status, and patient populations can influence the comparability of results. While subgroup analyses partially mitigate these issues, residual variability remains a concern, particularly given the wide range of treatment regimens and inclusion criteria across studies. Second, the relatively short follow-up durations of many included studies limit the ability to assess long-term outcomes such as survival beyond the study periods and the impact of late-onset adverse events. This restricts the evaluation of pembrolizumab's durability and long-term safety profile, which remains a critical aspect in cancer treatment. Third, while Egger's test indicated no significant publication bias for most outcomes, funnel plot asymmetry was observed for grade ≥ 3 AEs and ORR in single-arm studies, suggesting potential underrepresentation of negative or neutral findings. The pooled benefits of pembrolizumab combined with chemotherapy-particularly for survival and response rates-may be modestly overestimated if smaller studies with unfavorable outcomes remain unpublished. For instance, single-arm trials reporting lower ORR in biomarker-unselected populations might be underrepresented, inflating the perceived efficacy of monotherapy in real-world settings. Additionally, industry-sponsored trials, which constituted a notable proportion of included studies, may prioritize reporting favorable safety profiles, potentially understating rare but severe immune-related toxicities. These biases disproportionately affect outcomes reliant on small-sample or industry-funded studies, necessitating cautious interpretation of pembrolizumab's risk–benefit ratio in clinical practice.

Conclusion

This meta-analysis, encompassing 12 studies and 4069 patients, highlights that pembrolizumab combined with chemotherapy significantly improves OS and ORR in advanced gastric or gastroesophageal junction cancer, offering a synergistic effect with manageable safety. In contrast, pembrolizumab monotherapy failed to demonstrate significant benefits in OS, PFS, or ORR, suggesting limited efficacy as a standalone treatment. Safety analysis revealed that pembrolizumab combined with chemotherapy neither significantly increased nor decreased the risk of AEs or grade ≥ 3 AEs compared to chemotherapy alone. These findings emphasize the value of pembrolizumab in combination regimens for appropriately selected patients. Future research should prioritize biomarker-guided treatment, long-term outcomes, and protocol standardization to further refine its clinical application. Pembrolizumab combined with chemotherapy represents a targeted and effective strategy for improving outcomes in this challenging patient population.

Abbreviations

GEJ	Gastroesophageal junction
OS	Overall survival
PFS	Progression-free survival
ORR	Objective response rate
AEs	Adverse events
MDs	Mean differences
Ors	Odds ratios
Cis	Confidence intervals

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12876-025-03754-w.

Supplementary Material 1.

Acknowledgements

Not applicable.

Authors' contributions

Xiaoying Ji: Data curation, Formal Analysis, Methodology, Software, Writing – original draft. Guoping Wang, Dandan Pan: Data curation, Software, Writing

– original draft. Shanxia Xu: Formal Analysis, Methodology, Writing – original draft. Xinming Lei: Conceptualization, Supervision, Validation, Visualization, Writing – review & editing. All authors contributed to the manuscript and approved the final version for submission.

Funding
No funding.

Data availability
All data generated or analysed during this study are included in this published article and its supplementary information files.

Declarations

Ethics approval and consent to participate
This is a systematic review and meta-analysis, ethics approval is not applicable.

Consent for publication
The manuscript does not include the participant's identification image or other personal or clinical details.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Pharmacy, Yiwu Central Hospital, Yiwu, Zhejiang 322000, China. [2]Quzhou Zhong Da Lang Yuan Nursing Home, Quzhou, Zhejiang 324000, China. [3]The Quzhou Afliated Hospital of Wenzhou Medical University, Quzhou People's Hospital, Quzhou, Zhejiang 324000, China.

Received: 26 November 2024 Accepted: 3 March 2025
Published online: 14 March 2025

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