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Meta-Analysis of the Efficacy and Safety of HER2-ADC in the Treatment of Advanced Gastric Cancer

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Abstract: This meta-analysis aims to assess the efficacy and safety of HER2-targeted antibody-drug conjugates (ADCs) in patients with advanced gastric cancer (AGC), providing evidence-based references for the clinical utilization and safety evaluation of HER2-targeted ADCs. Comprehensive search was performed across multiple Chinese and English databases, including Embase, PubMed, Cochrane Library, Web of Science, WanFang, CNKI, VIP, as well as abstracts from major international conferences, up to February 20, 2023. Meta-analysis was conducted using STATA12 software, with pooled rates, means, and 95% confidence intervals (CIs) used to summarize the efficacy and safety of HER2-targeted ADCs in AGC treatment. A Seven studies, involving a total of 671 AGC patients treated with HER2-targeted ADCs, were included. The pooled objective response rate (ORR) of HER2-targeted ADCs was 31.3% (95%CI: 21.4%-41.2%), with a disease control rate (DCR) of 72.5% (95%CI: 57.8%-87.1%). The median overall survival (OS) was 9.91 months (95%CI: 7.71-12.21 months), and the median progression-free survival (PFS) was 4.20 months (95%CI: 3.28-5.11 months). The incidence of any grade adverse events (AEs) was 99.8% (95%CI: 98.5%-100.0%), while the incidence of grade 3 or higher AEs was 59.1% (95%CI: 43.7%-74.6%). The most frequent grade 3 or higher AEs were anemia (22.2%, 95%CI: 19.1%-25.5%) and interstitial pneumonia (1.9%, 95%CI: 1.0%-3.3%). The incidence of serious adverse events (SAEs) was 30.3% (95%CI: 20.2%-40.4%). Sensitivity analysis showed robust findings with a low risk of publication bias.HER2-targeted ADCs demonstrate moderate efficacy in AGC treatment, with a generally manageable safety profile.

1. Introduction

Gastric cancer is a prevalent malignancy with a significant global incidence and mortality burden. According to the GLOBOCAN global cancer statistics, gastric cancer ranks as the fifth most commonly diagnosed cancer worldwide. In 2020, there were approximately 1.09 million new cases of gastric cancer globally, leading to 770,000 deaths, making it the third leading cause of cancer-related deaths. In China, gastric cancer accounts for over 40% of the global incidence and mortality, ranking the highest in the world [1-3]. Gastric cancer is a broadly defined term that includes various

cancers originating from the stomach, as well as gastroesophageal junction (GEJ) adenocarcinoma, which occurs at the junction between the stomach and esophagus. The prognosis for advanced gastric cancer remains poor, with a 5-year survival rate of only 5% [3]. Although conventional chemotherapy remains the primary treatment option for advanced gastric cancer, its efficacy is limited. Human epidermal growth factor receptor 2 (HER2), also referred to as ERBB2, is encoded by the ERBB2 gene and is a member of the epidermal growth factor receptor (EGFR) tyrosine kinase family. HER2 is a membrane-bound receptor capable of forming dimers or multimers with other family members, subsequently activating downstream signaling pathways via its intrinsic tyrosine kinase activity. This receptor plays a key role in various cellular processes, including proliferation, growth, differentiation, and survival[4-8]. The HER2 gene is expressed at low levels in normal human cells, but in certain tumors, HER2 gene amplification or abnormal overexpression leads to a significant increase in protein levels, resulting in abnormal proliferation and metastasis of tumor cells. HER2 serves as a critical therapeutic target in several cancers, most notably in breast and gastric cancers[9]. Research indicates that around 12% to 20% of gastric cancer patients display HER2 overexpression or gene amplification, which is closely associated with the initiation and progression of the disease[10]. Trastuzumab-based combination therapy is now the recommended standard of care for the treatment of HER2-positive advanced gastric cancer[11, 12]. In comparison with paclitaxel, pembrolizumab did not show a survival benefit in second-line therapy, with an objective response rate of only 12% and a median survival of 6 months in third-line treatment. Moreover, nivolumab failed to improve overall survival in first-line therapy for patients with unknown PD-L1 expression, as demonstrated in the ATTRACTION-4 trial[13]. Finally, chemotherapy remains the mainstay of treatment in the last-line setting[14]. Currently, there is a significant gap in the development of biologics for gastric cancer in China, underscoring the need for safer and more effective therapies. Antibody-drug conjugates (ADCs) have shown promise in clinical trials as targeted treatments, combining monoclonal antibodies with cytotoxic agents to selectively kill cancer cells. Trastuzumab deruxtecan has been approved for HER2-positive breast cancer, and more HER2-targeted ADCs are under investigation. However, the efficacy and safety of these ADCs in advanced gastric cancer remain uncertain. This study conducts a meta-analysis to evaluate the clinical research on HER2-targeted ADCs in advanced gastric cancer, synthesizing existing data to provide evidence for clinical practice.

2. Materials and Methods

2.1. Inclusion and Exclusion Criteria

2.1.1. Types of Studies

This study includes randomized controlled trials (RCTs), non-randomized controlled trials, and single-arm studies. Eligible studies must report on the efficacy and safety outcomes of HER2-targeted antibody-drug conjugates in patients with advanced gastric cancer.

2.1.2. Study Population

The study population consists of patients with histologically confirmed advanced gastric cancer. There are no restrictions on patient age, gender, or ethnicity for inclusion.

2.1.3. Interventions

The interventions involve the treatment of advanced gastric cancer patients with HER2-targeted antibody-drug conjugates (e.g., T-Dxd, RC48, ARX788, TDM-1, among others).

2.1.4. Outcome Measures

The studies must report data on both antitumor efficacy and safety outcomes, including the following: objective response rate (ORR), disease control rate (DCR), median overall survival (OS), progression-free survival (PFS), incidence of any-grade adverse events (AEs), incidence of grade 3 or higher adverse events, and incidence of serious adverse events (SAEs).

2.1.5. Exclusion Criteria

The following studies will be excluded: (1) Reviews, meta-analyses, and other forms of secondary research； (2) Case reports or studies lacking sufficient data；(3) Unfinished clinical trials or studies with incomplete data；(4) Duplicate publications.

2.2. Literature Search Strategy

Following the guidelines and recommendations of PRISMA and the Cochrane Collaboration, this study performed a comprehensive and systematic search of relevant English databases, including PubMed, Web of Science, Cochrane Library, Embase, and ClinicalTrials.gov. Chinese databases such as CNKI, VIP, and WanFang were also included. Additionally, major conference abstracts from the American Society of Clinical Oncology (ASCO), European Society for Medical Oncology (ESMO), American Association for Cancer Research (AACR), and Chinese Society of Clinical Oncology (CSCO) were reviewed. The search was conducted up to February 20, 2023, and used Boolean logic with the following search terms and their combinations. The strategy utilized “OR” to connect synonymous subject terms and free terms, and “AND” to combine different search concepts. The search terms included: “gastric cancer,” “stomach cancer,” “antibody-drug conjugate,” “T-Dxd,” “DS-8201,” “trastuzumab deruxtecan,” “DS-8201a,” “ENHERTU®,” “RC48,” “Aidixi,” “Disitamab Vedotin,” “RC48-ADC,” “ARX788,” “TDM-1,” “Ado Trastuzumab Emtansine,” “Trastuzumab Emtansine,” “Kadcyla,” “Trastuzumab DM1 Conjugate,” and “Trastuzumab DM1.”

2.3. Literature Screening and Data Extraction

Following the predefined inclusion and exclusion criteria, titles and abstracts were screened. Full texts were reviewed for studies that passed this step, and a standardized framework was used to extract data such as study design, drug usage, patient demographics, and outcomes like ORR, DCR, OS, PFS, and adverse events (AEs). ORR and DCR were evaluated using RECIST 1.1, and AEs were assessed according to CTCAE 5.0. In cases of incomplete data, authors were contacted, and discrepancies were resolved through final review.

2.4. Quality Assessment of Literature

The quality of the included randomized controlled trials (RCTs), non-randomized controlled trials, and single-arm studies was evaluated based on version 5.1.0 of the Cochrane Handbook for Systematic Reviews of Interventions and the Methodological Index for Non-Randomized Studies (MINORS) scale[15][16]. For RCTs, the primary evaluation criteria included randomization, allocation concealment, blinding, outcome data reporting, selective reporting of outcomes, and other potential biases. Study quality was categorized as "low risk," "unclear risk," or "high risk." In addition, non-randomized controlled trials and single-arm studies were assessed using the MINORS scale, which covers 12 factors such as study objectives, patient inclusion criteria, data collection protocols, outcome measures, follow-up duration, loss-to-follow-up rates, study size, control groups,

baseline comparability, and statistical analysis methods. The scoring system allows for a maximum of 24 points for comparative studies and 16 points for non-comparative studies.

2.5. Statistical Methods

As most studies in this analysis are single-arm without control groups, data from patients treated with HER2-targeted antibody-drug conjugates for advanced gastric cancer were extracted. Outcome measures and standard errors were analyzed, focusing on seven key metrics: objective response rate (ORR), disease control rate (DCR), median overall survival (OS), progression-free survival (PFS), incidence of any-grade adverse events (AEs), grade 3 or higher AEs, and serious adverse events (SAEs). Meta-analysis of single-group proportions (ORR, DCR, AEs) was conducted using Stata's metaprop command, with prevalence (95% CI) as the effect size. For OS and PFS, forest plots were generated via the metan command, using the median (95% CI) as the effect estimate. A random-effects model was applied where necessary, with heterogeneity assessed by Cochran's Q test and the I^2statistic[15]. Significant heterogeneity was defined as Q p-value < 0.05 or $I^2 > 50\%$. A leave-one-out sensitivity analysis was performed to assess each study's influence on the overall results[17]. If heterogeneity was attributable to a specific study, a fixed-effects model was applied after excluding that study. Otherwise, if heterogeneity remained unexplained but within acceptable limits, a random-effects model was retained. If $p \geq 0.05$ or $I^2 \leq 50\%$, a fixed-effects model was used. Although minimal heterogeneity does not necessitate sensitivity or publication bias analyses, these were conducted to ensure robustness. Egger's test and funnel plots were used to assess publication bias[18].

3. Results

3.1. Literature Screening Results and Basic Information of Included Studies

A total of 1,228 articles were initially identified, with 1,205 duplicates and irrelevant studies removed using EndNote. Screening of titles and abstracts further reduced the count to 23 articles. After a full-text review, 16 studies were excluded for incomplete data, case reports, meta-analyses, and reviews. Ultimately, 7 studies (2 randomized controlled trials and 5 non-randomized trials) were included in the analysis. The screening and analysis were conducted using EndNote and Revman 5.4, as shown in Figure 1 and summarized in Table 1.

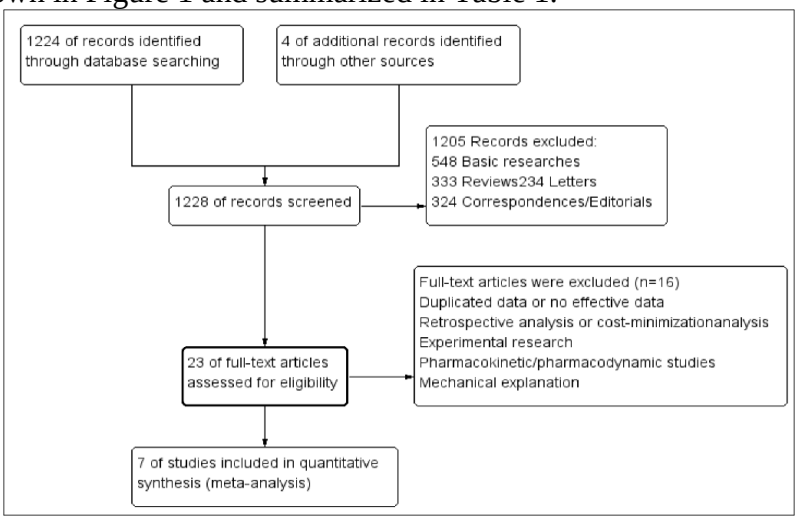


Figure 1: Literature Search Flowchart

Table 1: Basic Characteristics of the Included Studies

Study	Country	HER2-targeted ADC	Design	Treatment	Follow-up, months
Peng, Z 2021	China	RC48	phase 2	2.5 mg/kg, iv.every 2 weeks	7.6 (0.8-23.7)
Shitara, K 2019	Japan, USA	Trastuzumab deruxtecan	phase 1	5.4 or 6.4mg/kg, iv.every 3 weeks	5.5 (2.8, 13.1)
Shitara, K 2020	Japan, South Korea	Trastuzumab deruxtecan	phase 2	6.4mg/kg, iv.once every 3 weeks	NR
Thuss-Patience, P 2017	Global	Trastuzumab emtansine	phase 2/3	2.4mg/kg weekly	17.5/15.4
van Cutsem, E 2021	USA, Europe	Trastuzumab deruxtecan	phase 2	6.4mg/kg, given iv.once every 3 weeks	5.7 (0.7-15.2)
Yamaguchi, K 2023	Japan, South Korea	Trastuzumab deruxtecan	phase 2	6.4mg/kg, given iv.once every 3 weeks	≤14
					≤14
Zhang, Y 2022	China	ARX788	phase 1	1.3, 1.5 or 1.7 mg/kg Q3W	10 (6.5, 15.9)

ADC, antibody-drug conjugate; M, male; F, female; ECOG PS, Easter Cooperative Oncology Group performance status; NR, not reported; RCT, randomized controlled tiral

This meta-analysis included 7 studies [11, 19-24], with a total of 672 patients. Four studies evaluated Trastuzumab Deruxtecan [19, 20, 22, 24], while one study each Evaluated Trastuzumab emtansine [11], Disitamab Vedotin [23], and ARX788 [21].

3.2. Quality Assessment of Included Studies

The included studies were evaluated using the Cochrane Handbook for RCTs and the MINORS criteria for single-arm studies. This meta-analysis included 2 RCTs and 6 single-arm studies. Bias risk for the RCTs is shown in the figures, with both having a low risk, particularly Shitara, K (2019) (Table 2). The single-arm studies exhibited relatively higher risks of bias (Table 3). Overall, the quality of the included studies was high.

Table 2: Quality Evaluation of Randomized Controlled Trials

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall
Shitara, K 2020	Low	Low	Unclear	Unclear	Low	Low	Low	Low
Thuss-Patience, P 2017	Low	Low	Unclear	Unclear	Low	Low	Low	Low

Table 3: Quality Evaluation of Non-Randomized Controlled Trials

Included Studies	Peng, Z 2021	Shitara, K 2019	van Cutsem, E 2021	Yamaguchi, K 2023	Zhang, Y 2022
Are the research objectives clearly defined	2	2	2	2	2
Were the patients enrolled consecutively	0	0	0	0	0
Was the data collection process appropriate	2	2	2	2	2
Were the outcome measures	2	2	2	2	2

suitable					
Were the outcome measures assessed objectively	0	1	0	0	0
Was the follow-up period sufficient	2	2	2	1	2
Was the loss-to-follow-up rate under 5%	1	2	2	2	2
Was a sample size calculation performed	2	2	0	2	0
Was the control group selected appropriately	-	-	-	-	-
Was the control group recruited concurrently	-	-	-	-	-
Is there baseline comparability between groups	-	-	-	--	-
Were the statistical methods properly applied	-	-	-		-
Score	11	13	10	11	10

3.3. Meta-Analysis Results

3.3.1. Objective Response Rate

This meta-analysis included 7 studies, comprising data from 640 patients. Using the metaprop command in Stata12, P-values, confidence intervals, and weights for each study were calculated. The heterogeneity test indicated an I^2 value of 86.05% and a Q-test p-value of $p < 0.001$, suggesting significant heterogeneity across the included studies. Consequently, a random-effects model was employed for the meta-analysis. The pooled ORR of HER2-targeted antibody-drug conjugates in the treatment of advanced gastric cancer was 31.3%, with a 95% confidence interval of 21.4%-41.2%, as illustrated in Figure 2.

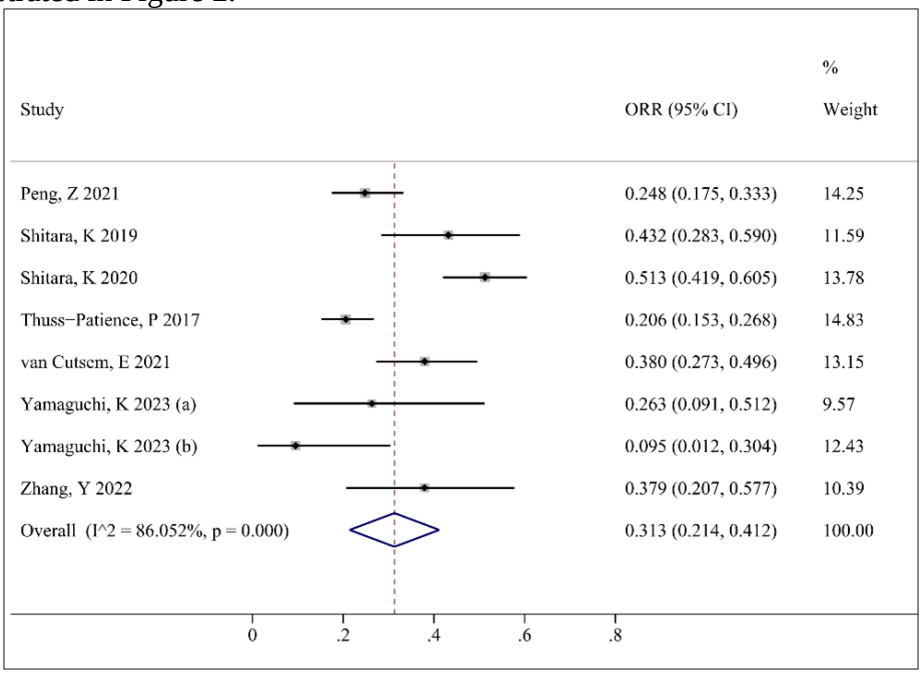


Figure 2: Forest Plot of the Objective Response Rate

3.3.2. Disease Control Rate

Six clinical studies were included, yielding disease control rate data for 436 patients. The heterogeneity test indicated an I^2 of 92.45% and a Q-test p-value of $p < 0.001$, suggesting significant heterogeneity among the selected studies. A random-effects model was applied, and the pooled DCR of HER2-targeted antibody-drug conjugates in the treatment of advanced gastric cancer was 72.5%, with a 95% confidence interval of 57.8%-87.1%, as shown in Figure 3.

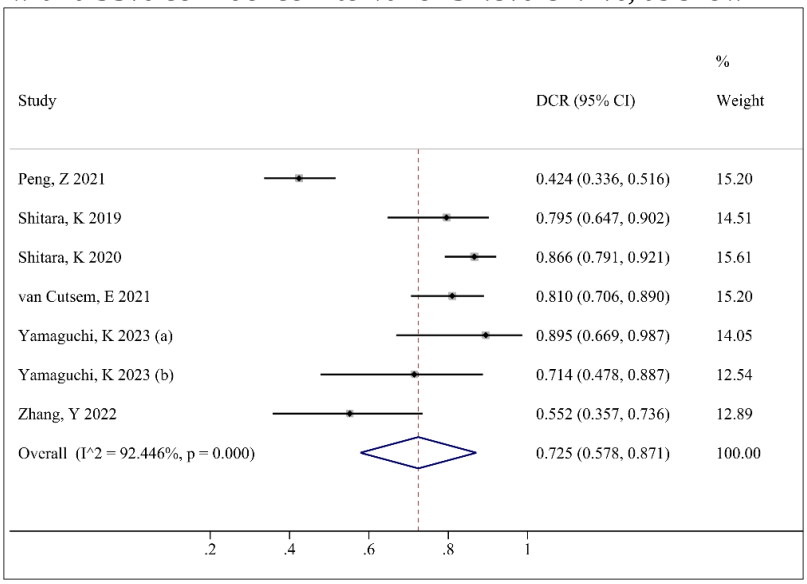


Figure 3: Forest Plot of the Disease Control Rate

3.3.3. Overall Survival

This analysis included overall survival (OS) data from four clinical studies, encompassing 518 patients. The heterogeneity test showed an I^2 value of 85.9% and a Q-test p-value of $p < 0.001$, indicating significant heterogeneity among the included studies. A random-effects model was applied for the meta-analysis (Figure 4), yielding a pooled median OS of 9.91 months for HER2-targeted antibody-drug conjugates in the treatment of advanced gastric cancer, with a 95% confidence interval of 7.71 to 12.21 months.

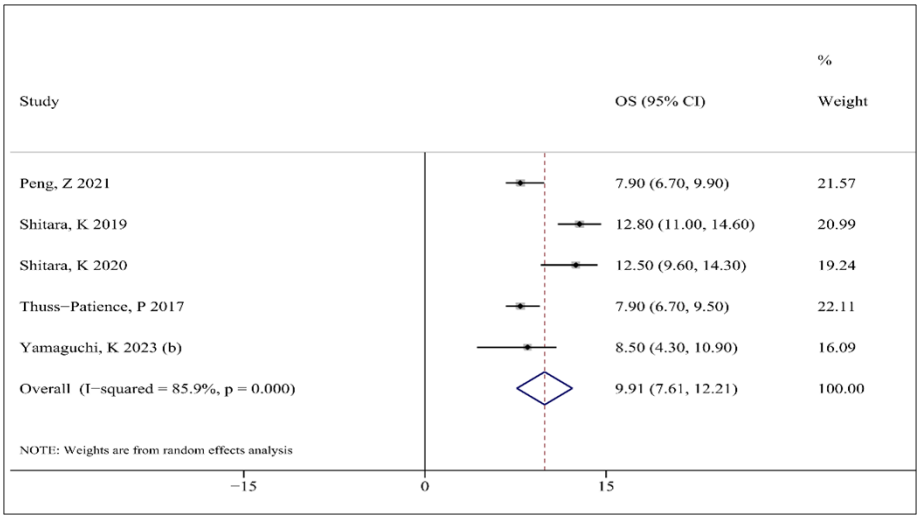


Figure 4: Forest Plot of Overall Survival

3.3.4. Progression-Free Survival

A total of 7 studies were included, with progression-free survival (PFS) data from 640 patients. The meta-analysis indicated significant heterogeneity with $I^2 = 78.0\%$ and $p < 0.001$. Therefore, a random-effects model was applied for the statistical analysis (Figure 5). The pooled PFS was 4.20 months (95% CI: 3.28-5.11).

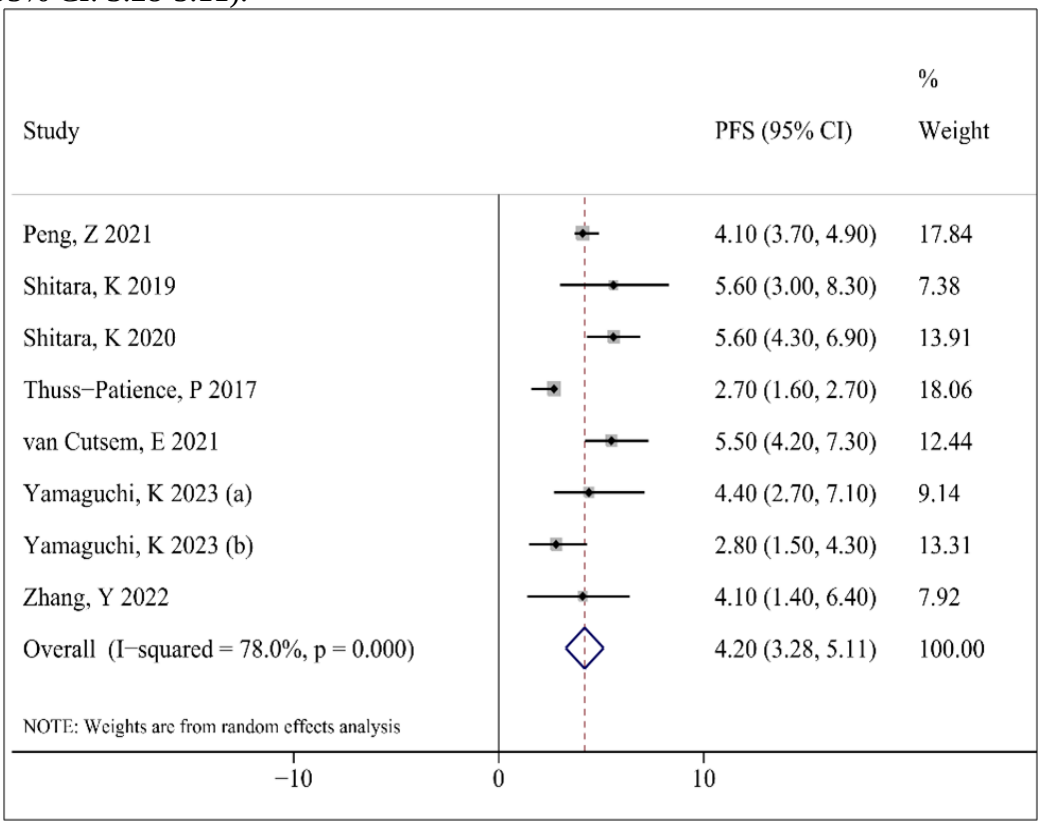


Figure 5: Forest Plot of Progression-Free Survival

3.3.5. Adverse Event Incidence

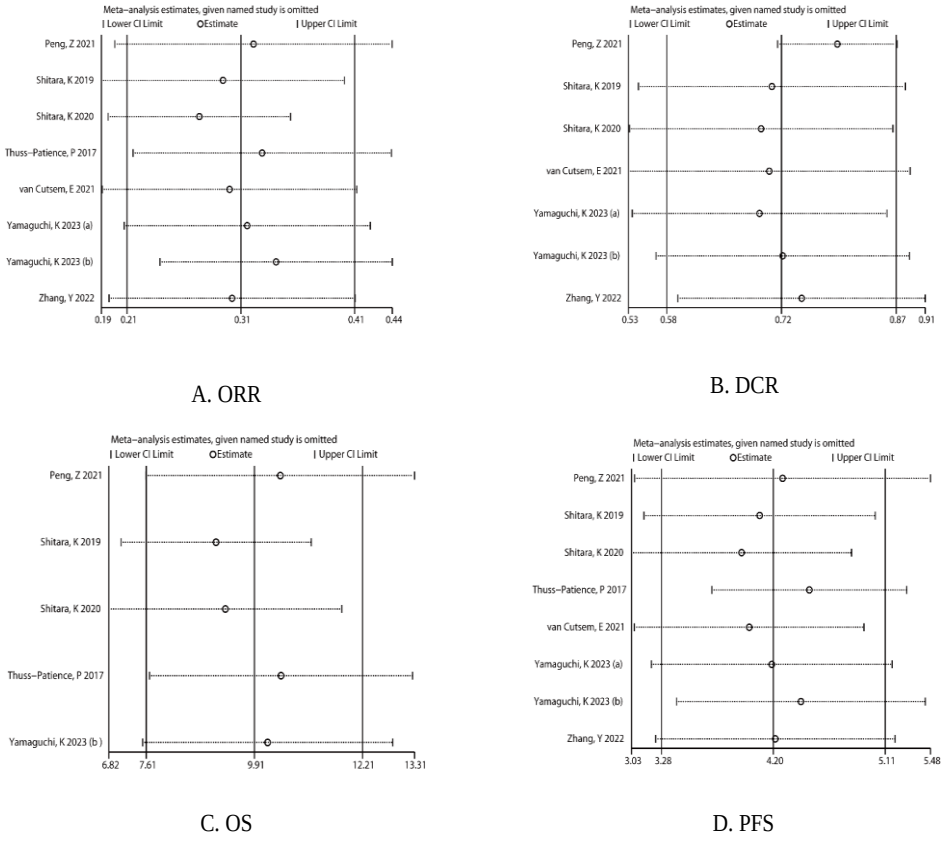
This study included 671 patients, of whom 663 experienced adverse events of any grade. The meta-analysis indicated $I^2 = 43.94\%$, $p = 0.086$, and thus a fixed-effects model was applied for statistical analysis (as shown in Table 4). The pooled incidence of any-grade adverse events (AEs) was 99.8% (95% CI, 98.5%-100.0%). A total of 407 patients experienced grade 3 or higher adverse events. The meta-analysis showed $I^2 = 94.70\%$, $p < 0.001$, suggesting significant heterogeneity among the included studies. A random-effects model was therefore used, and the combined incidence of grade 3 or higher adverse events was 59.1% (95% CI, 43.7%-74.6%).

Table 4: Meta-analysis of Adverse Event (AE) Incidence

Adverse Event Types	Included studies	Heterogeneity		Effect model	Meta-analysis	
		I^2 value (%)	*P*-value		RD(95%CI)	*P*-value
Incidence of any-grade adverse events	7	43.94	0.086	Fixed-effects	0.998 (0.985, 1.000)	0.00001
Incidence of grade 3 or higher adverse events	7	94.70%	0.00001	Random-effects	0.591(0.437,0.746)	0.00001

3.4. Sensitivity Analysis

Sensitivity analysis was performed on the 7 included studies for objective response rate (ORR), disease control rate (DCR), overall survival (OS), and progression-free survival (PFS). The results showed that no individual study significantly influenced the meta-analysis outcomes. This indicates that the stability of this meta-analysis is high, with a strong degree of reliability. For detailed sensitivity analysis results, see Figure 6.



A. ORR

B. DCR

C. OS

D. PFS

Figure 6: Sensitivity Analysis Plot for Each Outcome Indicator

3.5. Publication Bias Analysis

Stata version 12.0 was used to assess publication bias for the objective response rate (ORR) in the 7 included clinical studies. Although the funnel plot showed some asymmetry in the scatter points, Egger's test result indicated $p = 0.438 > 0.05$, suggesting no significant publication bias (see Figure 7). The publication bias analyses for the other outcome measures yielded similar results to those of the ORR.

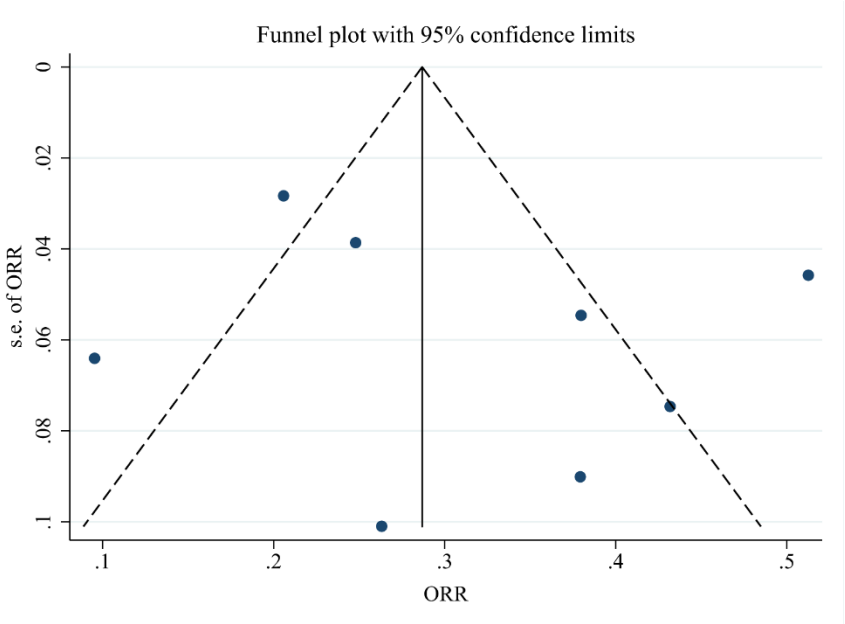


Figure 7: Funnel Plot of Objective Response Rate

4. Discussion

Gastric cancer remains a global health challenge, particularly in China, where incidence and mortality are high. While early-stage gastric cancer responds well to treatment, advanced gastric cancer offers limited options, resulting in poor survival rates. Despite progress in first-line therapies like immunotherapy combined with chemotherapy, limitations persist. Approximately 24% of gastric cancer patients overexpress HER2, but effective targeted treatments are lacking. Pembrolizumab has shown no survival benefit in second-line therapy, and third-line treatment offers an ORR of just 12% with a median survival of 6 months. Nivolumab has also failed to improve overall survival in patients with unknown PD-L1 expression, leaving chemotherapy as the standard for later lines of therapy. In China, there remains a gap in biologic drug development, though HER2-targeted ADCs have shown potential in clinical trials.

This meta-analysis included data from 7 studies involving 671 patients with advanced gastric cancer treated with HER2-targeted ADCs. The pooled ORR was 31.3%, with a median PFS of 4.20 months and median OS of 9.91 months. Compared to the ToGA study, which reported higher ORR (47%) and longer PFS (6.7 months) and OS (13.8 months) in patients receiving trastuzumab, the efficacy of HER2-targeted ADCs appears slightly lower. Safety analysis indicated a high incidence of adverse events (99.8%) with 59.1% experiencing grade 3 or higher AEs, most commonly anemia and neutropenia. Interstitial pneumonia, while rare (1.9%), led to one death in the Shitara2020 study, underscoring the need for careful monitoring of this serious side effect. Although this meta-analysis showed promising results, significant heterogeneity was observed, likely due to differences in study design, statistical methods, and HER2 expression levels. Publication bias was not detected, but further research is required to validate these findings, particularly given the limited number of randomized controlled trials (RCTs). The incidence of gastric cancer varies by geographic region, with East Asia having a high incidence and Europe and the Americas having lower rates [25, 26]. Additionally, advanced gastric cancer patients from different racial backgrounds exhibit differences in tumor immune characteristics and prognosis [27, 28].

5. Conclusion

This meta-analysis suggests that HER2-targeted ADCs offer moderate efficacy and manageable safety profiles in advanced gastric cancer patients. However, only two RCTs were included, and the remaining studies were single-arm or non-randomized trials, limiting the strength of the evidence. Additional RCTs and more detailed HER2 expression data are necessary to fully assess the potential of HER2-targeted ADCs in this population.

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