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Efficacy and safety of antibody drug conjugate therapy in patients with human epidermal growth factor receptor 2-positive non-small cell lung cancer: A single-arm systematic review and meta-analysis

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Abstract. Antibody drug conjugates (ADCs) have demonstrated high levels of efficacy in treating non-small cell lung cancer (NSCLC). Thus, the present study aimed to explore the efficacy and adverse effects of different types of ADCs targeting human epidermal growth factor receptor 2 (HER-2). PubMed, Web of Science, Embase and Cochrane Library were exhaustively searched for articles and conference abstracts describing ADC clinical trials that focused on HER-2. Notably, all articles were published before December 30, 2024. The present study aimed to investigate objective response rate (ORR), disease control rate (DCR), median progression-free survival (PFS) and adverse event (AE) incidence in targeted NSCLC. The results of the present study revealed that the ORR for HER-2 NSCLC was 41.8%. Furthermore, the ORR was 26.0, 38.1 and 57.3% for the Ado-trastuzumab emtansine (T-DM1), trastuzumab rezetecan (SHR-A1811) and trastuzumab deruxtecan (T-DXd) subgroups, respectively. Results of the present study revealed that the DCR of HER-2-positive NSCLC following treatment with ADC was 91.6%. Moreover, the PFS time following treatment with ADC was 2.6, 9.5 and 10.5 months in the T-DM1, SHR-A1811 and T-DXd subgroups, respectively. These results were more optimal than those obtained using alternative agents, such as HER-2-tyrosine kinase inhibitor (TKI)-targeted therapy, humanized monoclonal antibodies and trastuzumab-based therapy, with ORRs of 22.0, 23.0 and 26.0%, DCRs of 59.0, 39.0 and 63.0%, and PFS times of 5.5, 3.1 and 4.6 months, respectively. The results of the present study also indicated that the total incidence of AEs was 96.1%, and the incidence of AEs at grade 3 or higher was 42.4%. Notably, the incidence of AEs in the TDM-1, SHR-A1811 and T-DXd subgroups was 20.0, 47.0 and 47.2%, respectively. In conclusion, the present study revealed that the efficacy of ADCs was superior to that of HER-2-TKI-targeted therapies, humanized monoclonal antibodies and trastuzumab-based therapies. AEs were manageable, with a low incidence of AEs at grade 3 or higher. Notably, T-DXd demonstrated the highest level of antitumor activity. In conclusion, the results of the present study may assist clinicians in selecting the optimal therapeutic option for the treatment of NSCLC.

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Introduction

Lung cancer is the leading cause of cancer-related death worldwide, with non-small cell lung cancer (NSCLC) accounting for >80% of all lung cancer cases. At present, treatment of lung cancer includes surgery, radiation and chemotherapy, with surgery and radiotherapy often used to treat localized tumors (1). Notably, numerous patients experience tumor recurrence and destruction of the immune system following chemotherapy, due to a lack of selectivity. Moreover, patients may experience adverse events (AEs) following chemotherapy, or develop high levels of drug resistance (2). Immunotherapy is a novel treatment option that utilizes the human immune system to inhibit the growth of cancer cells. However, results of a previous study revealed that this treatment option may cause a variety of autoimmune diseases, such as autoimmune hepatitis (3). At present, research is focused on the use of precision-targeted therapy in the treatment of lung cancer, which exhibits higher levels of efficacy and a greater tolerability than traditional cytotoxic drugs (4). Targeted therapies using tyrosine kinase inhibitors (TKIs) effectively inhibit tumor growth, and these are associated with fewer AEs than chemotherapy. However, drug resistance may still develop following treatment with a target therapeutic option (5). Thus, the development of novel drugs with high levels of target binding and toxin activity is required, as these may lead to fewer AEs and improved antitumor effects.

Driver genes for common mutations in NSCLC include epidermal growth factor receptor (EGFR), mesenchymal-epithelial transition factor, B-Raf proto-oncogene, ROS proto-oncogene 1, RET proto-oncogene, anaplastic lymphoma kinase and neurotrophic receptor kinase. Human epidermal growth factor receptor (HER)-2 is a member of the ERBB family, which consists of EGFR (ERBB1), HER-2 (ERBB2), HER-3 (ERBB3) and HER-4 (ERBB4). Notably, there are few HER-2 molecules on the surface of healthy cells, and HER-2 overexpression leads to dimerization of ligands through binding. In turn, this leads to increased heterodimer formation and stimulation of intracellular pathways, which ultimately results in the efficient activation of downstream signaling, increased levels of cellular signaling, enhanced responsiveness to growth factors and malignant growth. ERBB family members play an important role in the development of several solid tumors, leading to the widespread use of inhibitors targeting ERBB. Targeted therapeutic agents that are available for the treatment of HER-2-positive NSCLC include TKIs such as afatinib, and monoclonal antibodies, such as trastuzumab deruxtecan (T-DXd) and antibody drug conjugates (ADCs). Notably, ADCs exhibit the hightest levels of efficacy, with few associated AEs and lower levels of resistance (6). Thus, further investigations focused on the efficacy of such therapies are key for the optimization of thearapeutic options.

ADCs are a novel form of antitumor drug, consisting of a monoclonal antibody and a cytotoxic drug combined with a stable linker. The mechanism of action is complex, as the antibody specifically binds to the target antigen and accurately localizes the cytotoxic drug to the tumor cell, triggering receptor-mediated endocytosis. Subsequently, the cancer cell internalizes and ingests the ADC, and transports to the lysosome through intracellular transport. At this point, the linker is either broken down by the enzymes present within the lysosome, or chemically cleaved, leading to the release of the cancer cell. Therapeutic options associated with high levels of cytotoxicity penetrate cancer cells and exert cytotoxic effects through numerous mechanisms, including the inhibition of DNA synthesis, the disruption of microtubule formation, apoptosis and interference of cell signaling pathways. This complex process results in the death of cancer cells (7).

Notably, ADCs have been used to treat numerous types of advanced or metastatic solid tumors, including NSCLC, with three main types of ADCs targeting HER-2. Ado-trastuzumab emtansine (T-DM1) (8), is supported by the National Comprehensive Cancer Network guidelines for the treatment of patients with HER-2 mutant NSCLC. Trastuzumab deruxtecan (T-DXd), also known as DS-8201 (9), was approved by the U.S. Food and Drug Administration in May 2020. This treatment is considered an option for patients with HER-2 mutant NSCLC following a lack of response to platinum-based therapy. Notably, another ADC, trastuzumab rezetecan (SHR-A1811), consists of trastuzumab and a novel topoisomerase I inhibitor associated via a cleavable linker (10). The present study aimed to investigate the efficacy and safety of ADC therapy in patients with HER-2-positive NSCLC.

Materials and methods

Search strategy. Pubmed (https://pubmed.ncbi.nlm.nih.gov/), Web of Science (https://www.webofscience.com/), Embase (https://www.embase.com/) and Cochrane Library (https://www.cochranelibrary.com/) were searched using the following key words, 'non-small cell lung cancer', 'antibody drug conjugates', 'HER-2' and 'clinical trials'. Databases were screened for all clinical trials published from inception of the database to December 30, 2024.

Selection criteria. Published articles were included in the study according to the following criteria: i) ADCs that are on the market at present; ii) patients who received monotherapy or combination therapy with ADCs; iii) clinical trials that reported on the objective response rate (ORR), disease control rate (DCR), progression-free survival (PFS) time, incidence of AEs and incidence of AEs at grade 3 or higher; iv) prospective clinical studies comparing the efficacy and safety of ADCs with other targeted drugs in the treatment of HER-2-positive NSCLC (randomized controlled trials and single-arm studies); and v) studies published in the English language. The exclusion criteria were as follows: i) Reviews, case reports, animal experiments, meta-analyses, news articles, comments and letters; ii) trials that failed to disclose the efficacy and safety of ADC medications; iii) duplicate published studies and a lack of full text or data; and iv) studies with <10 participants.

Study selection. Following review of published abstracts and titles, duplicate articles and published articles without the full text readily available were eliminated. The full text was screened to select eligible trials and justification for exclusion was noted. The primary criteria for selection were the efficacy and safety of monotherapy or combination therapy of ADC in patients with solid tumors, including NSCLC.

Data extraction. Two authors independently reviewed all studies that met the eligibility criteria. Uncertainties in study inclusion were resolved through consensus with a third author. The characteristics of the included studies are summarized as follows: i) First author's name and year of publication; ii) clinical phase; iii) clinical trial number; iv) intervention; v) cancer type; vi) HER-2 expression (or none); vii) sample size; viii) outcome parameters (clinical responses, including ORR, DCR, median PFS time and adverse reactions).

Quality assessment. The methodological quality of the single-arm studies was assessed using the Methodological Indicators of Non-Randomised Studies (11). The following eight items were assessed: i) The presence of a clear objective; ii) the inclusion of consecutive patients; iii) perspective on data collection; iv) whether the endpoints were appropriate to the study; v) whether there was an unbiased assessment of endpoints; vi) whether the follow-up period was adequate; vii) loss to follow-up <5%; and viii) whether there was a prospective calculation of the study size. Each aforementioned item was rated on a scale of 0-2, where 0 was indicative of 'not reported', 1 was indicative of 'reported but inadequate', and 2 was indicative of 'reported and adequate'. The total score was 16, with ≥9 being a high-quality study and <9 being a low-quality study. The Cochrane Collaboration tool (RoB 2, version 2019), accessed via www.riskofbias.info. was used to assess the risk of bias for randomized controlled studies. Trials were assessed to be at low, high or unclear risk in terms of random sequence generation, allocation concealment, blinding of participants, personnel, outcome assessors, incomplete outcome data and selective outcome reporting.

Statistical analysis. The statistical software Stata (version 18.0; StataCorp LP) was used for the single-arm meta-analysis. I^2 and P-values were used to detect heterogeneity, and included studies were considered heterogeneous if P<0.1 and/or I^2>50%. A random-effects model was used for the pooled analysis, and I^2≤50% and/or P≥0.1 indicated the absence of heterogeneity. All meta-analyses were performed using a random-effects model regardless of heterogeneity test results, as recommended by the Cochrane Handbook for Systematic Reviews (12). Sensitivity analyses using the one-by-one exclusion method and subgroup analyses were used to determine sources of heterogeneity. Forest plots were used to represent the combined results. ORR, DCR, PFS time, incidence rate of AEs and incidence rate of AEs at grade 3 or higher were used as continuous variables. Moreover, additional subgroup analyses were performed to explore the efficacy and safety of ADC in the treatment of HER-2-positive NSCLC.

Results

Study selection. The preliminary search yielded a total of 176 relevant studies, and 151 documents were obtained following the elimination of duplicates. Based on the initial screening of titles and abstracts, 71 studies were excluded, and these included reviews (n=44), systematic evaluations (n=2), commentaries, animal experiments, case reports (n=3), conference abstracts (n=1), books (n=2) and other literature (n=19). The remaining 80 articles were screened for the inclusion of full text, and 40 articles were excluded. Further articles were removed if accurate data could not be obtained during review; as a result 31 of the articles were included in the present study. Following a review of the full texts, 9 published articles were included in the present study. Notably, 1 study was divided into two independent studies due to different cohorts (13); namely, T-DXd 5.4 mg/kg and T-DXd 6.4 mg/kg groups. Another study also documented PFS in immunohistochemistry (IHC)2^+ and IHC3^+ cohorts. The screening process used in the present study is displayed in Fig. 1.

Literature characteristics. A total of 9 studies involving 439 patients were included in the present study, and all studies were published from 2018-2024. In terms of ADC type, T-DM1 was evaluated in 4 studies (n=104), SHR-A1811 in 1 study (n=63) and T-DXd in 4 studies (n=272). Details of the study characteristics and quality evaluation results of the included literature are displayed in Table I. Among the 9 studies, there was 1 randomized control trial and 8 single-arm studies, with 2 phase I studies, 1 phase I/II study and 6 phase II studies.

Quality assessment. In the present study, quality assessment was performed by two independent investigators. When a consensus could not be reached, an additional investigator was included. A total of 8 single-arm studies (14-21) and 1 randomized controlled study (13) were included. In total, 8 studies exhibited consistency in included patients, objectivity of endpoint evaluation and adequate follow-up time. Moreover, a total of 4 studies did not conduct prospective data collection, 2 studies did not meet the loss-to-follow-up rate of <5%, 7 studies were unclear regarding whether the sample size was estimated, and overall, all studies were of high quality. Only 1 randomized controlled study was considered a high-quality study and no studies were excluded due to low quality. Significant statistical heterogeneity was obtained using the following outcomes: A high heterogeneity in ORR (I^2=85.1%; P<0.001) and PFS (I^2=88.6%; P<0.001) of ADC for HER-2-positive NSCLC, which was assessed using subgroup analyses, grouped by drug class. The results of the present study revealed that there was significant heterogeneity in DCR (I^2=63.5%; P=0.012). Notably, a sensitivity analysis was used to assess the stability of the results, and one study was removed at a time. The results demonstrated that a statistically significant change in I^2 occurred, and random-effects modeling analyses were re-run following study exclusion. A random-effects model analysis was selected due to heterogeneity in the incidence of grade 3 or higher AEs (I^2=85.3%, P<0.001). All data are displayed in Table II.

ORR. Assessment of heterogeneity revealed I^2=85.1%, which was >50%, and P<0.0001, which was <0.1, for the Q-test, indicative of a significant heterogeneity between the articles selected in the present study. Notably, a high degree of heterogeneity is useful for meta-analysis with a random-effects model, and analyses can also be continued to examine the causes of heterogeneity. Based on the results of the present study, the source of heterogeneity was considered to be an inconsistency in drug types, and the subsequent subgroup analysis based on drug types revealed that none of them were heterogeneous. Considering drug type as a source of heterogeneity, it can be assumed that the ORR of ADC treatment are stable at 41.8% [95% confidence interval (CI), 5.0-83.5%]. An ORR of 26.0% (95% CI, 0.0-90.3%) was observed when the analysis was limited to subgroup T-DM1, a group ORR of 38.1% (95% CI, 0.0-97.5%) was observed when the analysis was limited to subgroup SHR-A1811 and an ORR of 55.6% (95% CI, 2.9-100.0%) was observed when the analysis was limited to subgroup T-DXd (Figs. 2 and 3).

DCR. Following the exclusion of documents with no data records, assessment of heterogeneity revealed I^2=63.5%, which was >50%, and P=0.012, which was <0.1, for the Q-test, indicative of significant heterogeneity between the nine documents selected. Notably, a high degree of heterogeneity is useful for meta-analysis with a random-effects model, and can also be continued to examine the causes of heterogeneity. Results of the present study revealed that the study by Iwama *et al* (15) (2022) may have caused the high level of heterogeneity. Thus, the analysis was repeated following the exclusion of this document. Results of the present study revealed no heterogeneity, with I^2=0%, which was <50%, and P=0.680, which was >0.1, in the Q-test. Results of the random-effects model revealed that the treatment of HER-2 NSCLC exhibited a DCR value of 92.0% (95% CI, 89.0-95.0%) following treatment with ADC (Figs. 4 and 5).

PFS. No overall PFS data were available in the third study [Peters *et al* (16) (2019)], which was analyzed in two groups using IHC following the exclusion of articles with no data

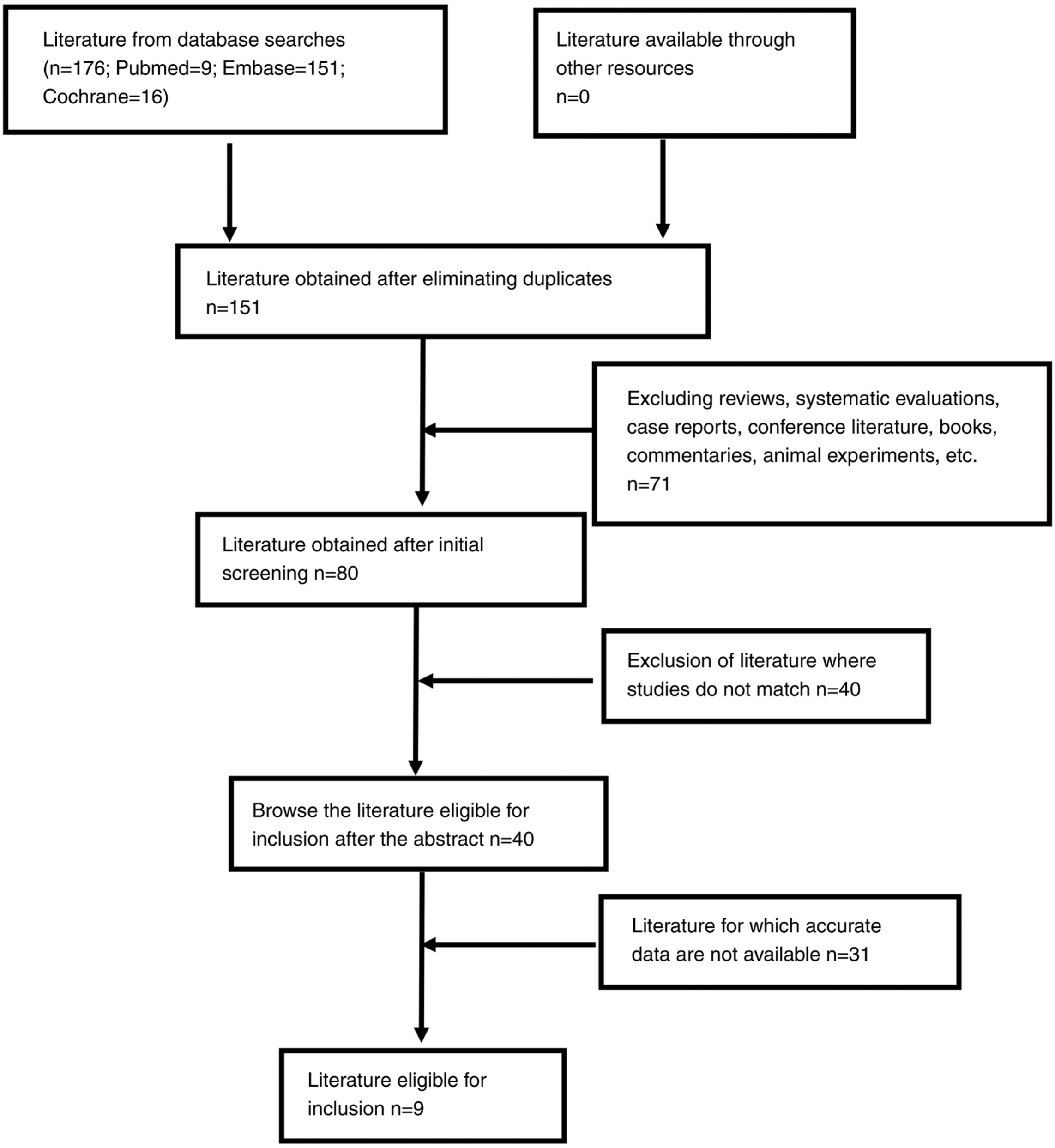

Figure 1. Flow chart depicting the literature screening and selection process.

recorded. Results of the Q-test revealed I^2=88.6%, which was >50%, and P<0.0001, which was <0.1, indicative of significant heterogeneity between the literature selected. In this case, the source of heterogeneity was considered to be due to inconsistency in drug classes. A subsequent subgroup analysis based on drug classes revealed significant heterogeneity between groups, with no heterogeneity within any of the groups. Collectively, these results were indicative of differences in PFS between ADC treatment categories. The results of the present study also highlighted a PFS value of 2.6 months (95% CI, 2.0-3.2 months) when limited to subgroup T-DM1, and a PFS value of 9.5 months (95% CI, 7.2-11.8 months) and 10.5 months (95% CI, 7.6-13.3 months) when limited to subgroups SHR-A1811 and T-DXd, respectively (Figs. 6 and 7).

AE incidence. A total of five articles were tested for heterogeneity, and results of the Q-test highlighted I^2=27.1%, which was <50%, and P=0.241, which was >0.1. Collectively, these results demonstrated that there was no heterogeneity between the articles selected for analysis in the present study. A random-effects model was selected for subsequent meta-analyses and this yielded a pooled incidence of 96.1% for AEs (95% CI range, 93.0-99.0%). Notably, the incidence of adverse reactions in patients treated with ADCs was 96.1% (Fig. 8).

Grade 3 or higher AE incidence. A total of 6 articles were tested for heterogeneity, and results of the Q-test highlighted I^2=85.3%, which was >50%, and P<0.001, which was <0.1. These results were indicative of heterogeneity between the studies selected for the present study. Subgroup analysis by drug type revealed no heterogeneity; thus, it was assumed that the incidence of AEs of grade 3 or higher was stable in patients treated with ADCs (42.4%; 95% CI, 0.4-93.2%). The incidence of AEs in the TDM-1, SHR-A1811 and T-DXd subgroups were

Table I. Study characteristics and quality evaluation.

First author/s, year	Samples, n	County	ORR, %	DCR, %	PFS time, months	AE, %	≥3 AEs, %	Trial no.	Type	HER-2-positive	Cancer type	Score	(Refs.)
Goto *et al*, 2023 (1)	101	RCT phase II	49.0	93.1	9.9	100.0	52.5	NCT04644237	T-DXd	HER-2 mutant	NSCLC	High	(13)
Goto *et al*, 2023 (2)	50	RCT phase II	56.0	92.0	15.4	100.0	66.0	NCT04644237	T-DXd	HER-2 mutant/ upregulation	NSCLC	High	(13)
Li *et al*, 2018	18	Single arm phase II	44.0	-	5.0	-	-	NCT02675829	T-DM1	HER-2 mutant	NSCLC	12	(14)
Iwama *et al*, 2022	22	Single arm phase II	38.1	52.4	2.8	-	-	JapicCTI-194620	T-DM1	HER-2 mutant	NSCLC	13	(15)
Peters *et al*, 2019	49	Single arm phase II	20.0	-	2.6; 2.7	92.0	20.0	NCT02289833	T-DM1	HER-2 mutant/ upregulation	NSCLC	11	(16)
Hotta *et al*, 2018	15	Single arm phase II	6.7	-	2.0	-	-	-	T-DM1	HER-2 mutant/ upregulation	NSCLC	13	(17)
Li *et al*, 2024	63	Single arm phase I/II	38.1	90.5	9.5	100.0	47.0	NCT04818333	SHR-A1811	HER-2 mutant/ upregulation	NSCLC	12	(18)
Tsurutani *et al*, 2020	18	Single arm phase I	55.6	83.3	11.3	100.0	11.1	NCT02564900	T-DXd	HER-2 mutant	NSCLC	12	(19)
Tsurutani *et al*, 2018	12	Single arm phase I	62.5	75.0	-	-	25.0	-	T-DXd	HER-2 mutant/ upregulation	NSCLC	10	(20)
Li *et al*, 2022	91	Single arm phase II	55.0	92.0	8.2	97.0	46.0	NCT03505710	T-DXd	HER-2 mutant	NSCLC	14	(21)

ORR, objective response rate; DCR, disease control rate; PFS, progression-free survival; AE, adverse event; HER-2, human epidermal growth factor receptor 2; RCT, randomized controlled trial; NSCLC, non-small cell lung cancer; T-DM1, Ado-trastuzumab emtansine; SHR-A1811, trastuzumab rezetecan; T-DXd, trastuzumab deruxtecan; NCT, National Clinical Trial.

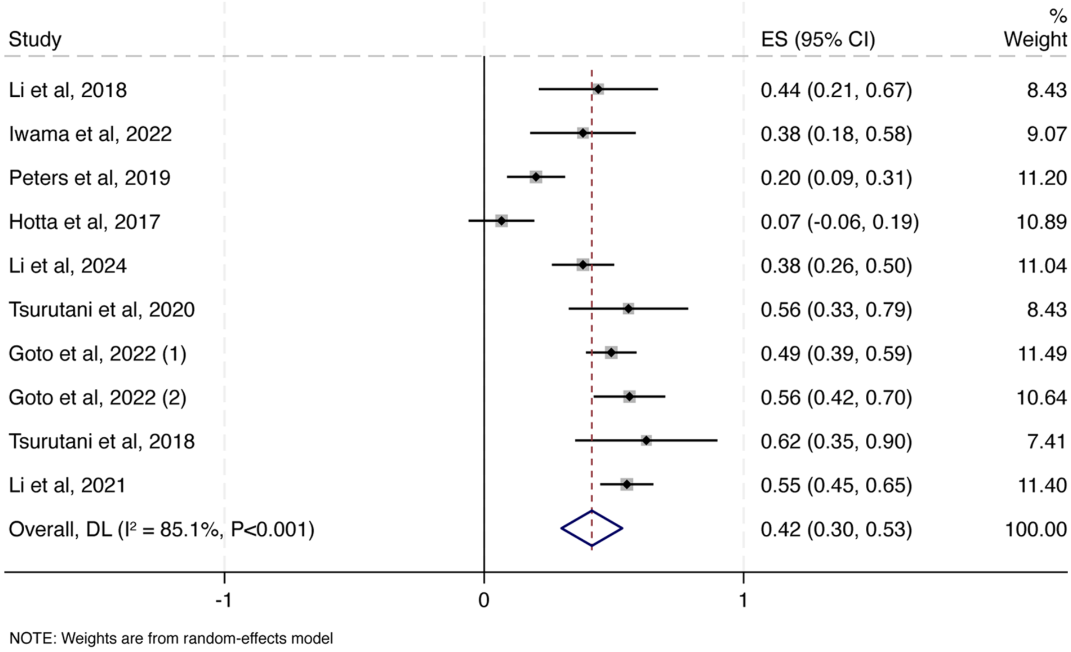

Figure 2. Forest plot of objective response rate among patients treated with human epidermal growth factor receptor 2-targeted antibody drug conjugate. ES, effect size (objective response rate); CI, confidence interval.

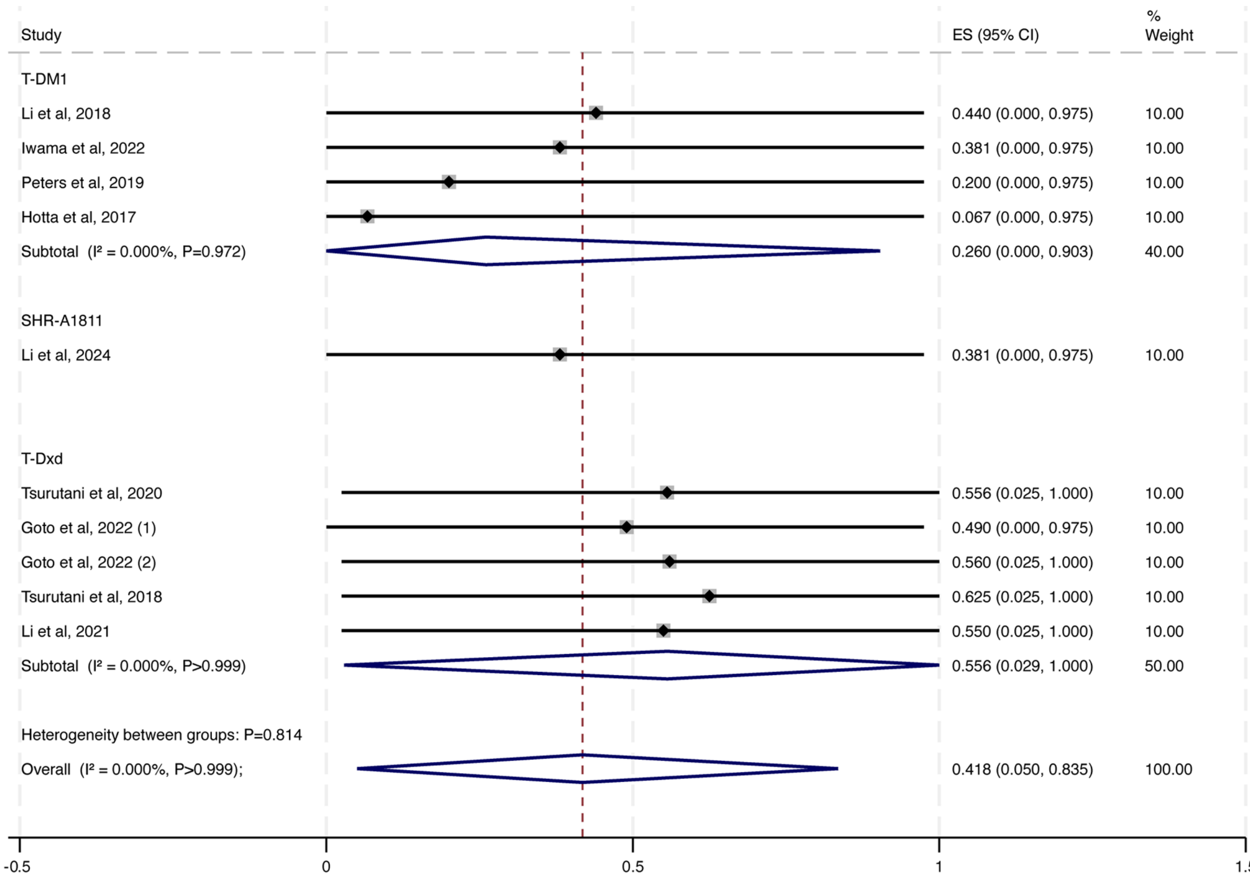

Figure 3. Forest plot of objective response rate subgroup analysis based on drug types. X-axis label: ORR. Events, number of patients achieving objective response; ORR, objective response rate; ES, effect size (ORR); CI, confidence interval; T-DM1, Ado-trastuzumab emtansine; SHR-A1811, trastuzumab rezetecan; T-DXd, trastuzumab deruxtecan.

20.0% (95% CI, 0.0-97.5%), 47.0% (95% CI, 0.0-97.5%) and 47.2% (95% CI, 0.0-99.9%), respectively (Figs. 9 and 10).

Types of adverse reactions. ADCs carry monoclonal antibodies and cytotoxic drugs via the linker, and the payloads often

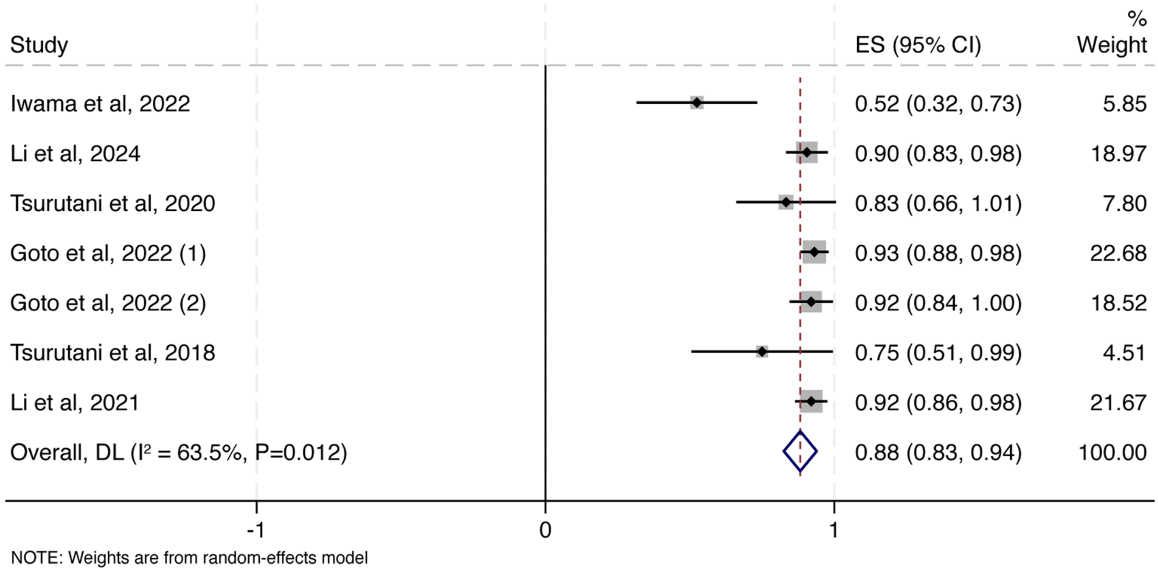

Figure 4. Forest plot of disease control rate among patients treated with human epidermal growth factor receptor 2-targeted antibody drug conjugate. ES, effect size (disease control rate); CI, confidence interval.

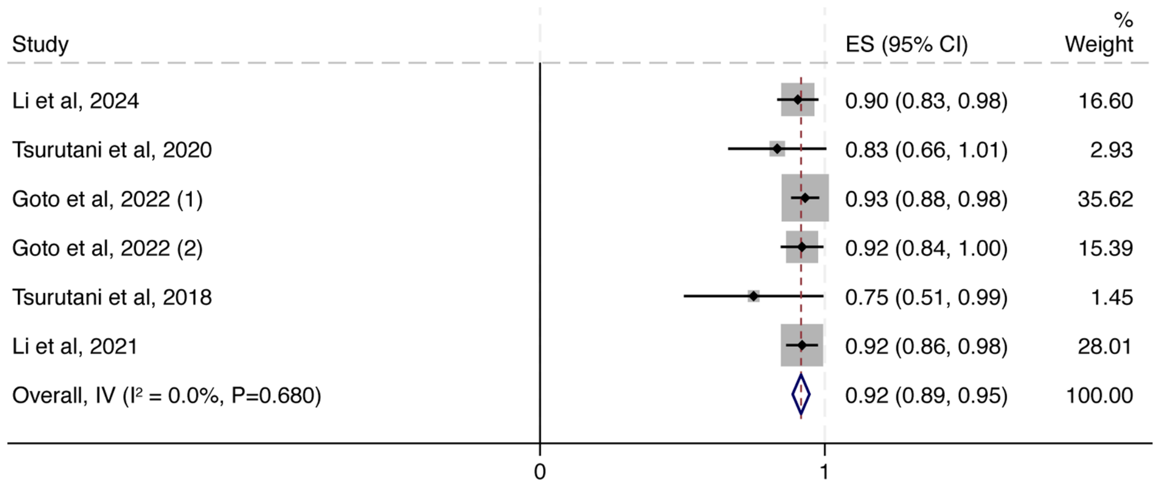

Figure 5. Forest plot of disease control rate sensitivity analysis. ES, effect size (disease control rate); CI, confidence interval.

include two types, microtubule protein inhibitors and DNA damaging agents (22). The results of the present study revealed that the adverse reactions experienced were consistent with the toxicity spectrum of the chemotherapeutic drugs carried. Results of previous analyses revealed that the most common adverse reactions were digestive and hematological toxicity, and digestive toxicity. The main manifestations included nausea, vomiting, diarrhea, decreased appetite, constipation and liver function abnormalities. Moreover, hematological toxicity was mainly characterized by neutropenia, anemia, leukopenia, thrombocytopenia and lymphocytopenia. All data are displayed in Table III.

Discussion

The results of the present study revealed that the ORR for the treatment of NSCLC was stable at 41.8%, and the association with drug type was low. Although the SHR-A1811 subgroup was based on only 1 study with 63 participants, the ORR analysis showed no heterogeneity in the subgroup analyses regardless of whether the study was excluded or not, and the ORR values did not differ significantly, at 42.2% (95% CI, 4.0-85.7%) and 41.8% (95% CI, 0.5-83.5%), respectively. The DCR analysis was repeated following the exclusion of a document (Iwama *et al*, 2022) (15) and the results of the present study revealed no heterogeneity. The DCR value of ADC for HER-2-positive NSCLC was 92%. As for the PFS after subgroup analysis was performed, the heterogeneity between groups was strong, and a subsequent subgroup analysis based on drug classes revealed significant heterogeneity between groups, with no heterogeneity within any of the groups. The results of the present study revealed that the PFS of different types of ADCs for HER-2-positive NSCLC varied, with the T-DXd subgroup exhibiting the highest duration at 10.5 months, compared with 2.6 months for the T-DM1 subgroup and 9.5 months for the SHR-A1811 subgroup. Since the subgroup of SHR-A1811 was

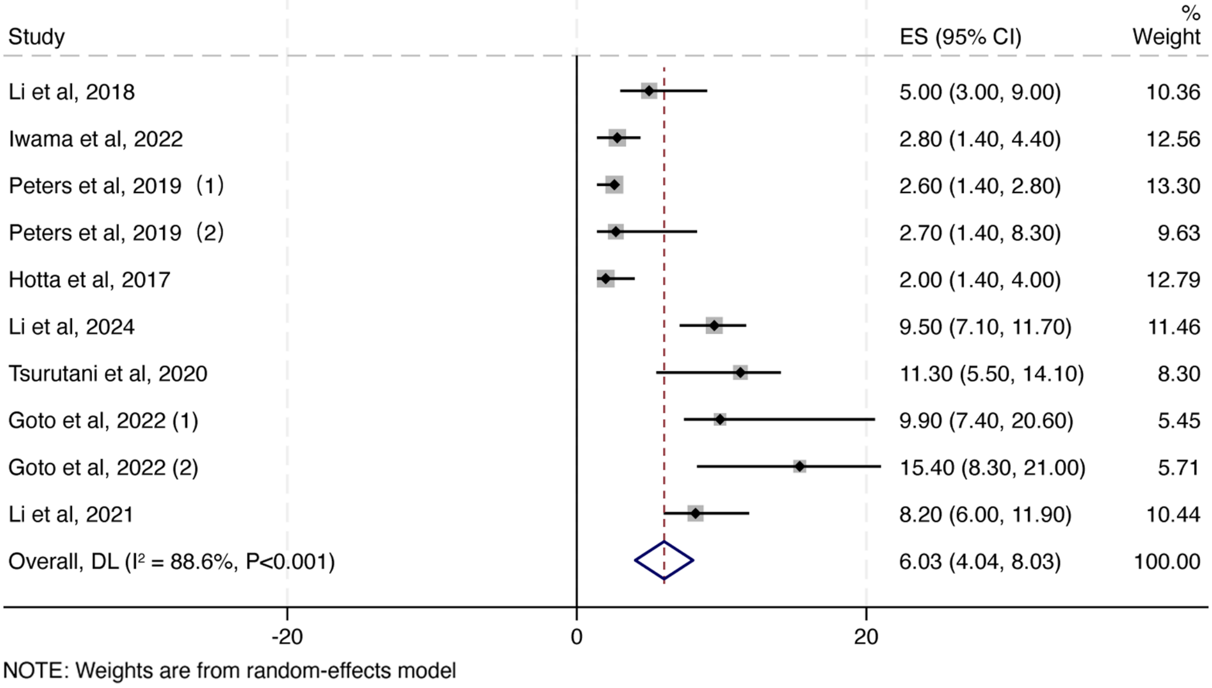

Figure 6. Forest plot of progression-free survival among patients treated with human epidermal growth factor receptor 2-targeted antibody drug conjugate. ES, effect size (progression-free survival); CI, confidence interval.

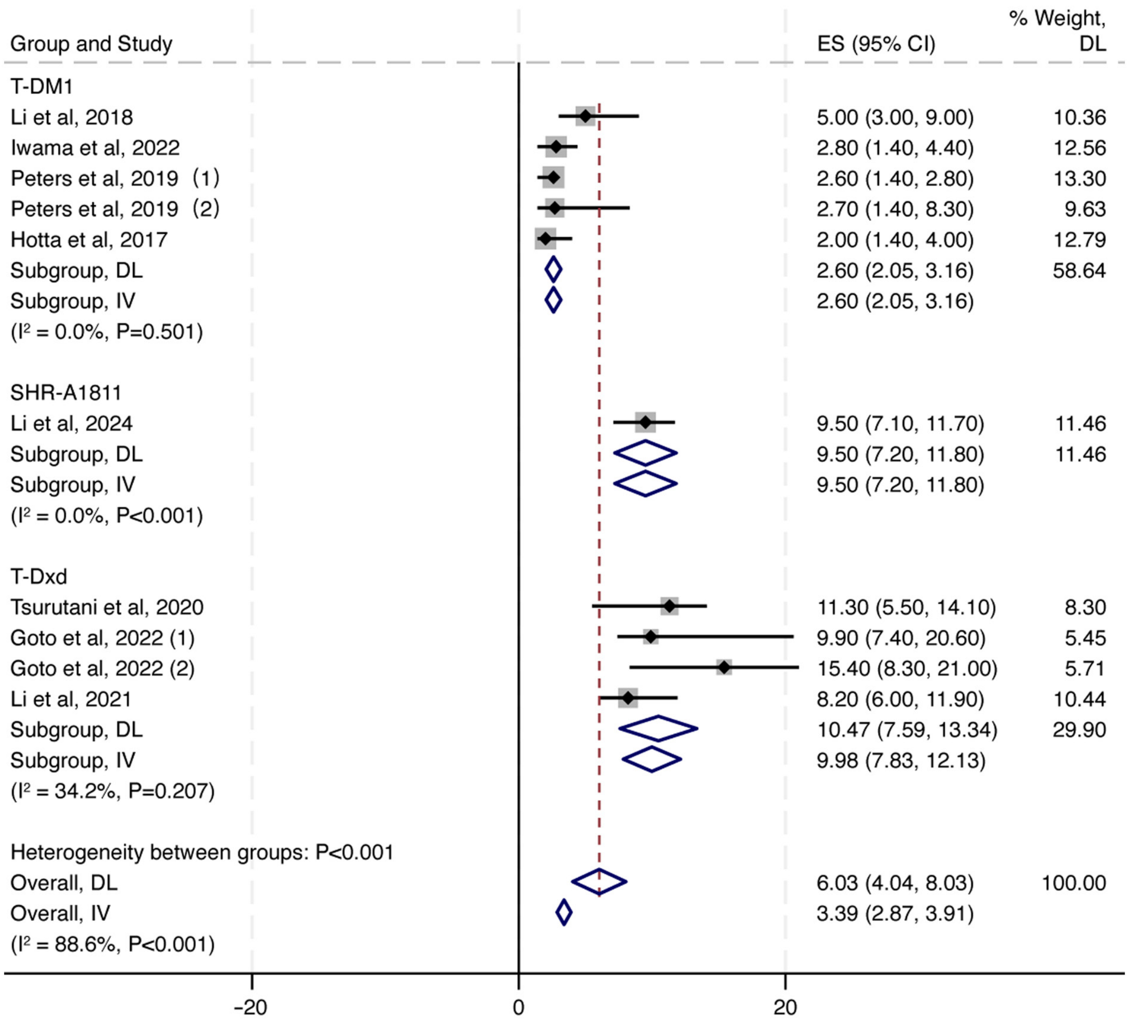

Figure 7. Forest plot of progression-free survival subgroup analysis based on drug types. ES, effect size (progression-free survival); CI, confidence interval.

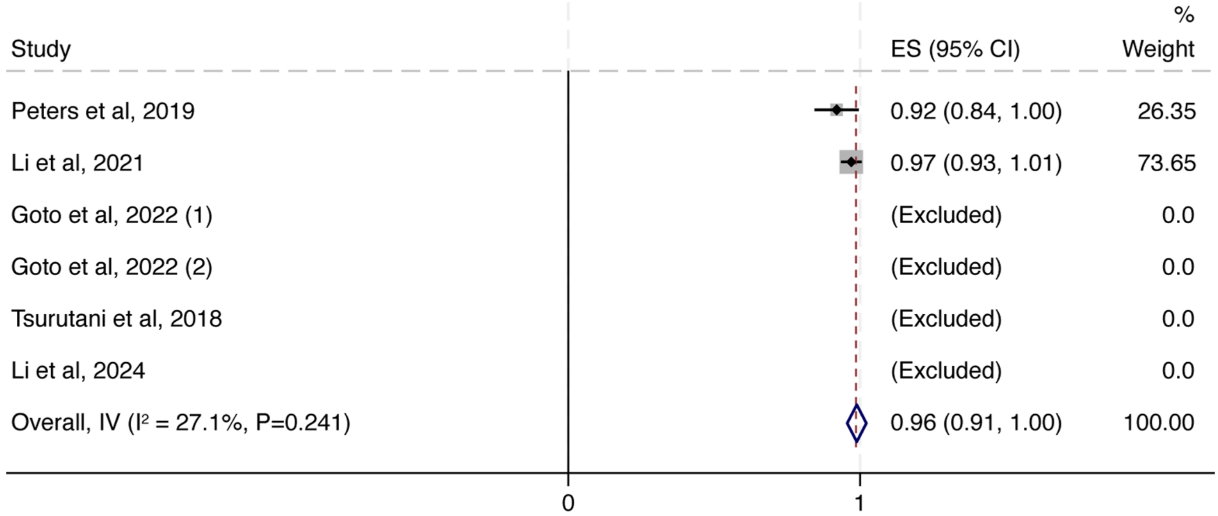

Figure 8. Forest plot of adverse event incidence among patients treated with human epidermal growth factor receptor 2-targeted antibody drug conjugate. ES, effect size (AE incidence); CI, confidence interval.

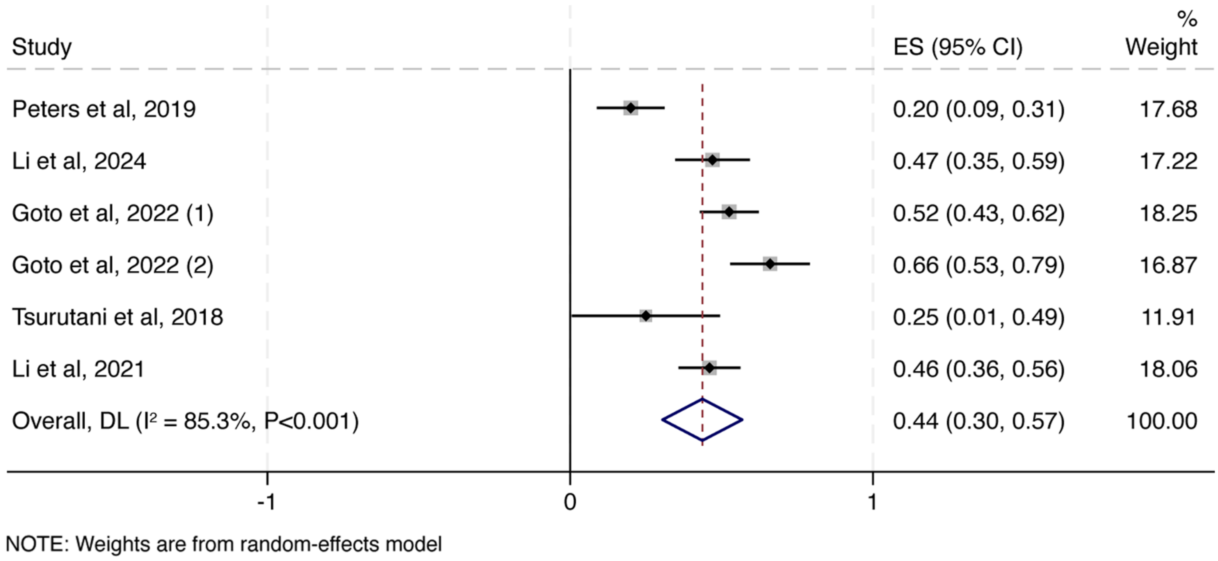

Figure 9. Forest plot of incidence of adverse events at grade 3 or higher among patients treated with human epidermal growth factor receptor 2-targeted antibody drug conjugate. ES, incidence of adverse events at grade 3 or higher; CI, confidence interval.

involved in only 1 study, the results of the subgroup analysis were not markedly different from the previous one after the group was removed and the subgroup analysis was performed again. We hypothesized that T-DXd may be more efficacious than T-DM1 in the treatment of NSCLC, and this may be associated with the structure of ADCs. For example, different classes of payload include the main microtubule protein inhibitor and DNA damaging agent. Notably, T-DM1 consists of an anti-HER-2 monoclonal antibody and a microtubule inhibitor through a linker. Both TDX-d and SHR-A1811 consist of a HER-2 antibody and a topoisomerase inhibitor (23,24). The results of the study revealed that the efficacy of ADCs may be higher than that of HER-2-TKI-targeted therapy, humanized monoclonal antibodies and trastuzumab-based therapy (ORR, 22.0, 23.0 and 26.0%, respectively; DCR, 59.0, 39.0 and 63.0%, respectively; PFS, 5.5, 3.1 and 4.6 months, respectively) (25). This may also be associated with the structure of the ADC, as cytotoxic chemotherapy and targeted therapy inhibit tumor cells, while minimizing toxicity to healthy cells, increasing efficacy while reducing adverse reactions. Thus, efficacy may be improved. Drug-to-antibody ratio (DAR), which refers to the number of payload molecules that are carried by each antibody, is a notable factor associated with ADC activity. Too low a DAR reduces efficacy, while too high a DAR increases *in vitro* potency but also disrupts structural stability, leading to increased toxicity. By contrast, an increase in DAR may indicate more payload carried, leading to enhanced antitumor effects. T-DXd exhibits a DAR of 7-8, and this is ~2-fold higher than that of T-DM1 (DAR, 3-4) (6). In addition, the results of a previous study demonstrated that T-DXd may activate the antitumor ability of the immune system to improve efficacy (26). However, the efficacy of ADCs cannot be considered in isolation due to differences in the inclusion criteria and the prior treatment regimens of patients in different clinical trials.

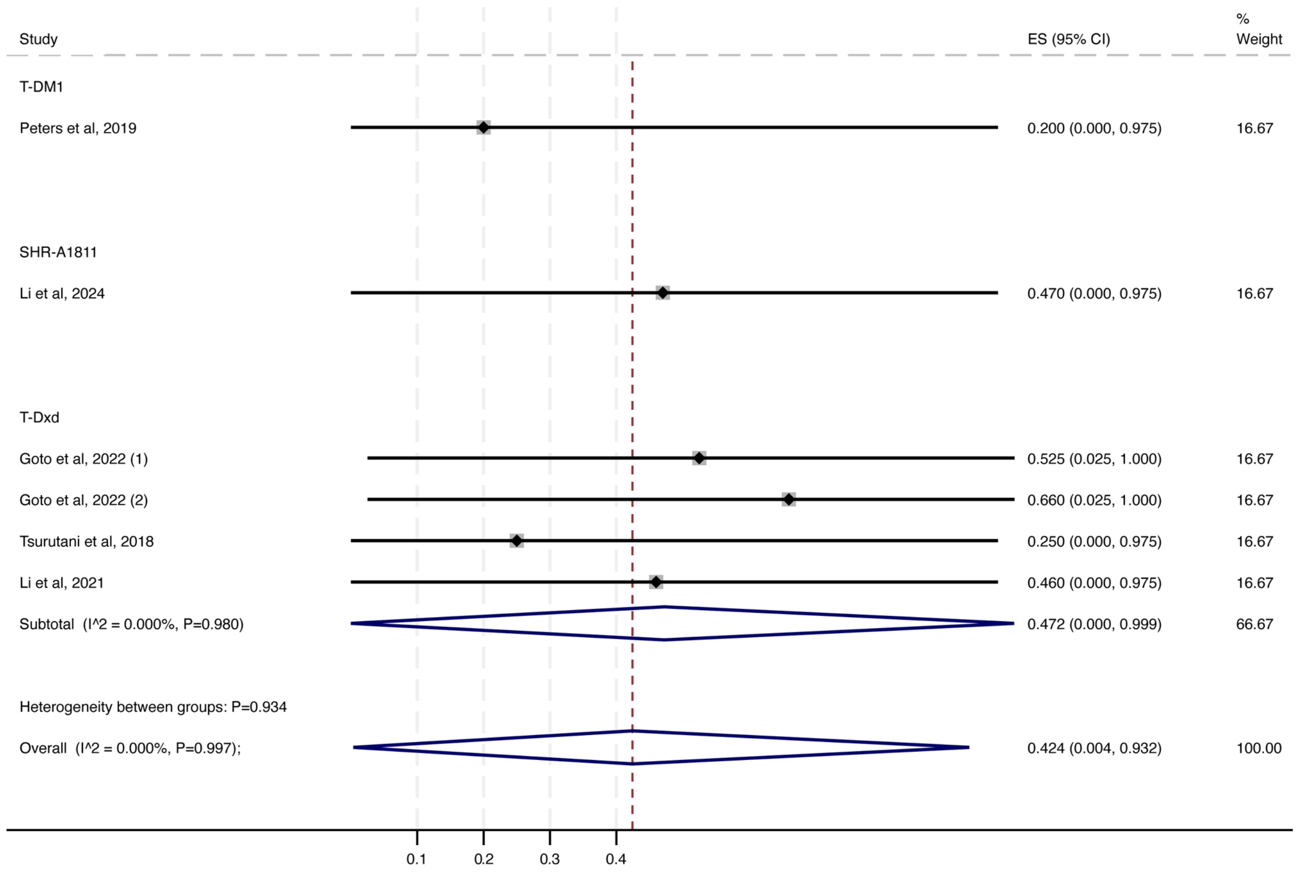

Figure 10. Forest plot of incidence of adverse events at grade 3 or higher by subgroup based on drug types. ES, incidence of adverse events at grade 3 or higher; CI, confidence interval.

The results of the present safety analysis revealed that patients using ADC experienced significant adverse reactions, with an incidence of 96.1%, and the majority of AEs were grade 1-2. Notably, the majority of adverse reactions were controllable. The incidence of AEs at grade 3 or higher was 36.4%, and these mainly manifested as gastrointestinal toxicity and various types of blood cell reduction. The results of the present study revealed that the toxicity profile of the chemotherapeutic agent to which the payload belongs was consistent, highlighting that the adverse reactions were consistent with the payload category (27). The two main types of payloads, namely, microtubule protein inhibitors and DNA damaging agents, cause cell cycle blockades. This may result in typical chemotherapeutic toxicity once separated from the monoclonal antibody, diffusing into the extra-tumoral healthy tissues. This further confirms that off-target effects may lead to the occurrence of adverse reactions (28). In addition, adverse reactions may be associated with the payload and the stability of the linker (29). Ideally, the linker must be stable in the somatic circulation, and efficiently cleaved in tumor cells through lysosomal degradation or physiological conditions *in vivo*. This results in the release of cytotoxic drugs. Notably, unstable linkers may be more prone to non-specific cleavage, which can release the payload prematurely and cause off-target effects (7). The occurrence of AEs is also associated with the choice of target antigen. The main adverse effects of ADCs targeting HER-2 are concentrated in the digestive and hematological systems, and the targeting of trophoblast cell-surface antigen is prone to inducing skin rashes and mucosal inflammation when it is expressed in some healthy epithelial tissues (30). In healthy cells, other mechanisms of adverse reactions include non-specific endocytosis of ADCs and the interaction of antibodies with receptors expressed by immune cells. These mechanisms may result in receptor-mediated endocytosis, and the antibody component of ADCs may also promote toxicity through interaction with immune cells (31).

For nausea and vomiting, anti-emetic medications are recommended in addition to lifestyle interventions. Patients with diarrhea can be treated with hydration and electrolytes, antidiarrheal medications and dietary modifications, while it is also essential to identify the etiological basis and administer antibiotics when necessary. For myelosuppression, thrombocytopenia and leukopenia, prophylactic medications may require that the subsequent chemotherapy session is performed in a timely manner, to avoid injury or infection. Neutropenia requires reduction of the risk of infections and the use of antimicrobials in the case of fever. Patients with anemia require oral supplementation with nutrients and hematopoietic materials, such as iron supplements. ADC treatment for interstitial pneumonitis should be adjusted or stopped depending on clinical symptoms. Moreover, glucocorticoids should be used or antibiotics should be used empirically, and immunosuppressive drugs should be considered if no improvement in the condition is observed. Predictors of adverse reactions are crucial, and regular review, real-time monitoring and timely management of the occurrence of adverse reactions should be prioritised.

Table II. Quality assessment.

Study	Clearly stated study purpose	Consecutive inclusion of patients	Prospective data collection	Endpoints appropriate to study purpose	Unbiased assessment of endpoints	Adequate follow-up period	Loss to follow-up <5%	Sample size estimation	Total Score (max=16)
Li *et al*, 2018 (14)	2	2	0	2	2	2	2	0	12
Iwama *et al*, 2022 (15)	2	2	1	2	2	2	2	0	13
Peters *et al*, 2019 (16)	2	2	1	2	2	2	0	0	11
Hotta *et al*, 2018 (17)	2	2	1	2	2	2	2	0	13
Li *et al*, 2024 (18)	2	2	0	2	2	2	2	0	12
Tsurutani *et al*, 2020 (19)	2	2	0	2	2	2	2	0	12
Goto *et al*, 2023 (13)	2	2	0	2	2	2	2	0	12
Tsurutani *et al*, 2018 (20)	2	2	0	2	2	2	0	0	10
Li *et al*, 2022 (21)	2	2	1	2	2	2	2	1	14

Table III. Types of adverse reactions.

A, All levels

Adverse reaction	n
Nausea	247
Neutropenia	153
Fatigue	151
Decreased appetite	146
Anemia	145
Vomiting	128
Leukopenia	113
AST or ALT increased	112
Alopecia	112
Thrombocytopenia	100
Constipation	90
Diarrhea	82
ILD/pneumonia	38

B, Grade 3 or higher

Adverse reaction	n
Neutropenia	71
Anemia	45
Thrombocytopenia	39
Leukopenia	38
Fatigue	16
Nausea	12
Decreased appetite	11
AST or ALT increased	9
Vomiting	6
Diarrhea	5
ILD/pneumonia	5
Lymphopenia	3

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ILD, interstitial lung disease.

In conclusion, the results of the present study revealed that the efficacy of ADCs was superior to that of HER-2-TKI-targeted therapies, humanized monoclonal antibodies and trastuzumab-based therapies. AEs were manageable, with a low incidence of AEs at grade 3 or higher. Notably, the present study exhibits numerous limitations. For example, the majority of included studies described single-arm trials, and tumor stage and treatment lines were different in each patient. The quality of analysis may have been reduced due to the lack of a control group. The following biases may exist: i) Time effect bias: Inability to distinguish between the natural progression of disease and the intervention effect; and ii) selection bias: Single-arm trials often include highly screened populations with differences in inclusion criteria. Future randomized controlled trials are needed to validate these findings. Moreover, the small sample size of the included studies resulted in limited applicability of traditional publication bias tests; the SHR-A1811 subgroup was based on only 1 study with 63 participants, which may affect the robustness of the results. In addition, some of the included studies had very few subjects, which may have led to selection bias. Further investigations with larger samples are required to validate the current findings. The present study was also limited as the studies analyzed included those focused on both combination therapies and monotherapies. Notably, the order or dose of treatment may have contributed to outcome bias. Results of the heterogeneity test revealed that there was considerable heterogeneity in the pooling of certain effect values. Despite subgroup analyses, specific sources of heterogeneity remain to be fully elucidated. Certain unobserved confounders may have hindered the accuracy of the results, which may limit the reliability of the results due to the small sample size. The sample size imbalance may exaggerate the heterogeneity, and the current subgroup analysis is a preliminary exploratory result, which needs to be validated by more studies, and later larger cohort studies are needed to validate the results in the future.

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Availability of data and materials

The data generated in the present study are included in the figures and/or tables of this article.

Authors' contributions

FZ was responsible for conceptualization, methodology and statistical analysis. FZ and YZ were responsible for data collation, writing the original manuscript, and reviewing and editing of the final manuscript. TN and GH were responsible for statistical analysis and validation of the results. CH was responsible for making substantial contributions to the study's conception and design and supervising and revising it critically for important intellectual content. FZ and CH confirm the authenticity of all the raw data. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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