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Efficacy and safety of different drugs in patients with HER2-positive gastric cancer: network meta-analysis

Jie Zhang[1,2], Chunluan Yuan[1*] and Xiao Ma[2*]

Abstract

Background In the past decade, there has been a significant advancement in targeted therapy and immunotherapy, leading to the discovery of new drugs and changes in the treatment approach for patients with HER2-positive gastric cancer. Although several drugs are available for treating these patients, there is still no consensus on their selection, and there has been limited direct or indirect comparison among them.

Objective To address this gap, a network meta-analysis was conducted to assess the efficacy and safety of different drugs used in the treatment of HER2-positive gastric cancer.

Methods By searching through databases such as PubMed, Embase, Web of Science, and Cochrane Library, we identified 16 randomized controlled trials that involved a total of 4485 patients and utilized 9 different intervention measures.

Results Based on the current evidence, compared with chemotherapy alone, the hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) in gastric cancer patients treated with nivolumab were [hazard ratio (HR): 2.61 95%confidence interval (CI) (1.51, 4.51)] and [hazard ratio (HR): 2.01 95% confidence interval (CI) (1.18, 3.42)], respectively. Compared with chemotherapy alone, the hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS) in gastric cancer patients treated with trastuzumab deruxtecan were [hazard ratio (HR): 1.7 95% confidence interval (CI) (1.13, 2.56)] and [hazard ratio (HR): 2.13 95% confidence interval (CI) (1.42, 3.22)], respectively. It is suggested that nivolumab and trastuzumab deruxtecan can effectively prolong overall survival (OS) and progression-free survival(PFS) in patients with HER2-positive gastric cancer, while also reducing the risk of adverse events to some extent. Therefore, these two regimens, nivolumab and trastuzumab deruxtecan, are considered to be effective and safe options for the treatment of patients with HER2-positive gastric cancer.

Conclusions In previous studies, trastuzumab-based chemotherapy has been a common treatment for HER2-positive gastric cancer. To a certain extent, our study provides a reliable direction for future treatment options for HER2-positive gastric cancer.

Systematic review registration PROSPERO CRD42023420941

Keyword Gastric cancer, Network meta-analysis, Efficacy, Safety

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Introduction

Gastric cancer, a common malignant tumor of the digestive system, is currently the second leading cause of cancer-related death worldwide due to its high mortality rate. Although there has been a decrease in incidence and mortality in recent years, it still remains the primary burden of cancer globally [1, 2]. Chemotherapy remains the cornerstone of treatment for gastric cancer. Consequently, early detection and identification of treatment regimens that are both effective and have minimal side effects are of utmost importance. Unfortunately, detecting gastric cancer in its early stages is challenging, resulting in most patients being diagnosed with advanced gastric cancer accompanied by metastasis, thus eliminating the possibility of surgical treatment. As a result, chemotherapy has become the primary traditional palliative treatment approach.

In recent years, there has been a shift in the tumor treatment model towards individualized care, leading to rapid development in the precision treatment of tumors. As a result, the effectiveness of immune checkpoint inhibitors (ICIs) in combating tumors has become increasingly evident [3, 4]. Numerous targeted and immunotherapeutic drugs have been utilized for patients with HER2-positive gastric cancer [5, 6]. Trastuzumab, a recombinant humanized anti-HER2 monoclonal antibody, has shown significant improvements in overall survival (OS) for patients with HER2-positive metastatic gastric cancer or gastroesophageal junction carcinoma when incorporated into chemotherapy. Additionally, no safety concerns were identified [7, 8]. Previous meta-analyses have shown that trastuzumab combined with chemotherapy has a favorable safety and efficacy profile compared to chemotherapy alone[9]. Trastuzumab deruxtecan, a HER2 antibody–drug conjugate, has demonstrated lower risks of death or disease progression in patients who have previously received trastuzumab. However, it is important to note that there have been limited adverse reactions, primarily associated with interstitial pneumonia [10]. Lapatinib, due to its low rate of cardiotoxic events, has emerged as an alternative to trastuzumab [11]. Furthermore, a combination of pertuzumab, trastuzumab, and chemotherapy has shown improved survival rates for patients with HER2-positive tumors [12]. Pertuzumab in combination with trastuzumab and chemotherapy may be a potential treatment option [13]. Afatinib, on the other hand, can be used as a novel targeted therapy for patients who are resistant to trastuzumab [14]. A multicenter study revealed that the combination of nivolumab and chemotherapy significantly enhanced the progression-free survival (PFS) for patients with gastric cancer or gastroesophageal junction carcinoma. Additionally, through its complementary mechanism of action, the cytotoxic T lymphocyte antigen-4 (CTLA-4) inhibitor ipilimumab can enhance antitumor T cell function and induce de novo antitumor T cell responses [15]. Pembrolizumab, whether used as monotherapy or in combination with chemotherapy, has demonstrated favorable antitumor activity [16]. Finally, the bispecific antibody MM-111, which binds to both HER2 and HER3 to obstruct downstream signaling, shows promise as a treatment for patients with HER2-positive gastric cancer [17].

It is clear that chemotherapy is still the basis of existing treatments. Nevertheless, there are many options for the treatment of HER2-positive gastric cancer. There is a lack of consensus and systematic comparison, with treatment primarily relying on clinical experience. Furthermore, the efficacy of immune checkpoint inhibitor treatment can be influenced by factors such as albumin levels and liver function [18, 19]. Hence, our objective is to assess the superiority of different antitumor regimens through meta-analysis. Traditional meta-analysis only allows for direct comparison between two treatment regimens within a limited scope, which may not accommodate the need to compare various treatment options. Network meta-analysis, on the other hand, overcomes the limitations of traditional meta-analysis by enabling both direct and indirect comparisons. Through this study, we aim to resolve the aforementioned disputes using network meta-analysis and provide robust evidence to aid clinical decision-makers in selecting the most effective treatment regimen.

Materials and methods

Registration

This network meta-analysis was reported according to the Systematic Review and Meta-Analysis Protocol and has been registered in the International Prospective Register of Systematic Reviews (PROSPERO), with the registration number CRD42023420941.

Literature search

Databases including PubMed, Embase, Cochrane Library, and Web of Science were searched as of March 17, 2023. Subject words and free words were used, such as (trastuzumab) OR (pertuzumab) OR (pembrolizumab) OR (Trastuzumab deruxtecan) OR (nivolumab) OR (ipilimumab) OR (afatinib) OR (lapatinib) AND (HER2-positive) AND (Stomach Neoplasms). The specific search strategies are shown in Supplementary S1.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) patients over 18 years old, diagnosed with gastric cancer or gastroesophageal junction carcinoma and histologically

HER2-positive (centrally assessed immunohistochemistry [IHC] 3 + or [IHC] 2 + /in situ hybridization [ISH]-positive) according to The National Comprehensive Cancer Network (NCCN) guidelines; (2) targeted or immunotherapy regimen with or without chemotherapy was used in the case group, and placebo therapy with or without combined chemotherapy was used in the control group, regardless of previous chemotherapy situations. (3) Primary prognosis indicators: progression-free survival (PFS), overall survival (OS), objective response rate (ORR), disease control rate (DCR); secondary prognostic indicators: adverse events (AE) and number of adverse events with grade ≥ 3; (4) Randomized controlled trials.

Exclusion criteria were (1) meeting abstracts, protocols, letters, systematic reviews, animal experiments; (2) repeated publications, unsatisfactory results, no data available; (3) non-randomized controlled studies; (4) ongoing clinical trials.

Data extraction

Literature screening and data extraction were conducted by two independent evaluators. They reviewed literature titles, abstracts, and full texts to identify relevant studies, excluding any irrelevant ones directly. Afterward, the full texts of the remaining studies were downloaded and carefully examined to select eligible ones. In case of any disagreements, a third investigator intervened to resolve them. Throughout the process, strict adherence to the predefined inclusion and exclusion criteria was ensured. During the data extraction phase, the observation indicators were carefully examined and cross-checked to maintain consistency in the extracted data. The extracted data primarily included the name of the first author, publication year, country of origin, sample size, gender distribution, age range, intervention and control measures, follow-up duration, and outcome indicators.

Quality evaluation

Two investigators independently assessed the quality of the included studies using the bias analysis assessment tool provided in Cochrane Handbook for Systematic Reviews 5.1.0 [20]. The assessment covered seven domains: random sequence generation (selection bias), allocation concealment (selection bias), blinding of performers and participants (performance bias), blinding of outcome assessors (observation bias), integrity of data results (follow-up bias), selective reporting of study results (reporting bias), and other sources of bias. If the original study fully adhered to the above criteria, its quality would be classified as "low risk", indicating a low overall risk of bias and high study quality. If the original study only partially met the criteria, its quality would be classified as "unclear risk", indicating a moderate possibility of bias. If the original study did not meet any of the above criteria, its quality would be classified as "high risk", indicating a high risk of bias and low study quality.

Data analysis

To conduct network meta-analysis and generate visualizations such as network diagrams, rankograms, line charts, and funnel plots, we utilized the GeMTCpackage (R 4.2.3) software along with Just another Gibbs sampler (JAGS) software. The effect size was assessed using point estimation and interval estimation. The Bayes-Markov-Monte Carlo random-effects model was employed to pool the data, employing 5 chains for simulation with 5000 prior iterations and 20,000 iterations. As there were no closed loops in the network, it was not possible to evaluate the inconsistencies between direct and indirect comparisons. The prioritization of different intervention measures was based on Surface Under the CumulativeR-Ankingcurve (SUCRA) values.

The efficacy of different drugs in terms of PFS and OS was assessed by calculating the HR value and 95% CI. An HR value of less than 1 suggests that a particular treatment regimen is more likely to reduce the risk of death or slow disease progression compared to another regimen. On the other hand, an HR value greater than 1 indicates that a treatment regimen is more likely to increase the risk of death or accelerate disease progression. If the 95% CI includes the value 1, it suggests that there is no significant difference between the treatments. For binary variables such as ORR, DCR, and AE, the effect size was measured using the OR along with its corresponding 95% CI. An OR value of less than 1 suggests that one drug treatment may be less effective than another. Conversely, an OR value greater than 1 suggests that one drug treatment may be more effective. If the 95% CI contains the value 1, it indicates that there is no significant difference between the treatments.

Publication bias and heterogeneity

All the included studies were assessed for risk of bias. Publication bias in ORR, DCR, and AE was assessed using funnel plots. The asymmetry of the corrected funnel plots indicated a high possibility of publication bias in the above indicators. When there is heterogeneity, the effect size is synthesized by random effects.

Result

Literature search

A preliminary search was conducted on PubMed, Embase, Cochrane Library, and Web of Science databases, yielding a total of 1644 studies. After removing 414 duplicate articles, further screening of titles and abstracts resulted in the removal of 982 studies. Finally, a full-text

review was conducted, and 16 studies met the inclusion criteria. Please refer to Fig. 1 for a detailed illustration of the screening process.

Basic characteristics of included literature

The included studies were published from 2013 to 2023. A total of 16 [21–35randomized controlled studies were included, involving 4487 patients and 9 intervention measures, including chemotherapy (che), lapatinib combined with chemotherapy (lap_che), nivolumab (niv), trastuzumab (trz), trastuzumab combined with chemotherapy (trz_che), trastuzumab deruxtecan (trz_dex), trastuzumab combined with nivolumab with ipilimumab (trz_niv_ipi), trastuzumab combined with pertuzumab with chemotherapy (trz_pez_che), MM-111 combined with trastuzumab with chemotherapy (MM111_trz_che). In the included studies, the experimental group involved 2401 people, and the control group 2084 people. The experimental group ranged in age from 19 to 89 years and the control group from 22 to 84 years. The specific characteristics of the included studies are shown in Table 1.

Assessment of risk of bias

All 16 studies included in the analysis provided detailed descriptions of their methods for random sequence generation. The majority of them employed either the random data table method or the computer-generated random number table method, indicating a low risk of bias in this aspect. However, there were potential biases related to imperfect allocation concealment and the lack of blinding of patients and trial personnel. The assessment of the risk of bias in the included studies is displayed in Figs. 2 and 3.

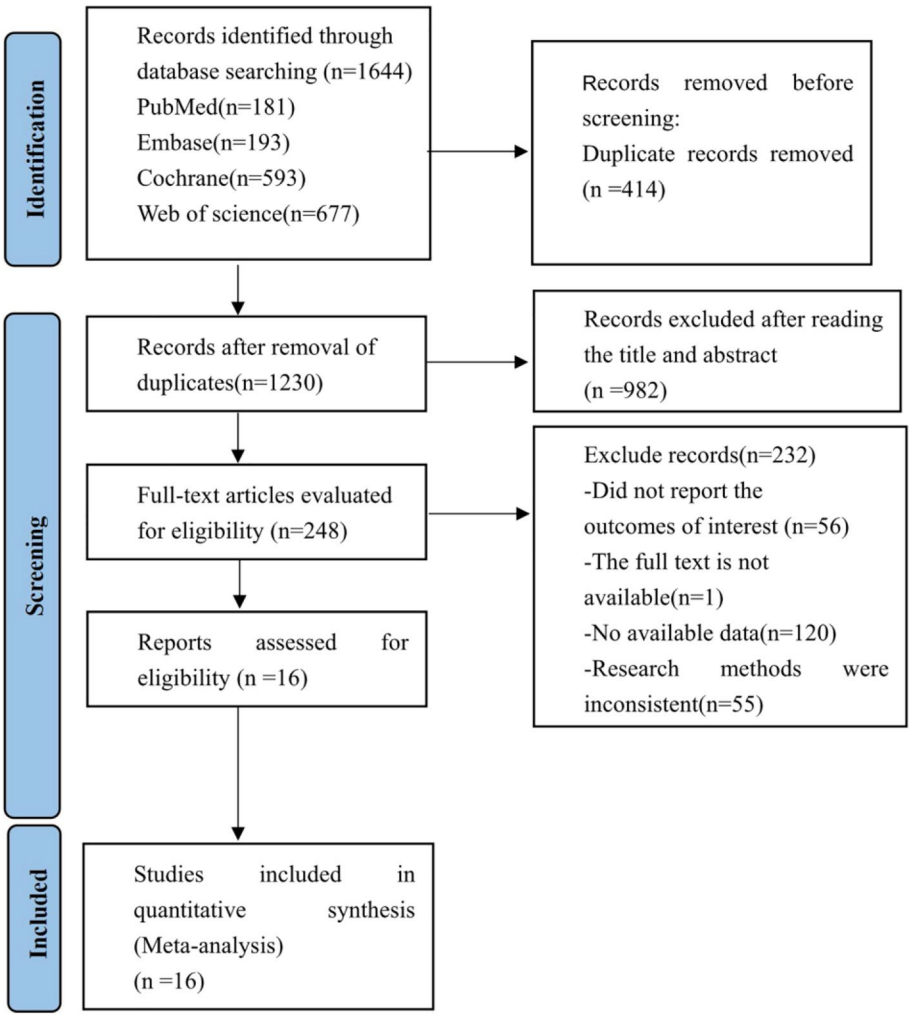

Fig. 1 Literature flow chart

Table 1 Characteristics of included studies

Study	Study design	Country	Sample size		Gender (M/F)	Age (years) M (SD)		Intervention		Follow-up (M)	Outcome
			EG	CG		EG	CG	EG	CG		
Akitaka Makiyama 2020 [21]	RCT	Japan	44	45	71/18	65(50–89)	67(33–81)	trz + che	che	10	F1; F2;F3; F4; F5
Alexander Stein 2022 [22]	RCT	Germany	44	44	70/18	63(42–80)	60 (41–79)	trz + niv + ipi	che	14.3	F3; F4; F5; F6
Elizabeth C. Smyth 2019 [23]	RCT	UK	22	24	35/11	64(56–69)	64(56–69)	lap + che	che	–	F5
J. Randolph Hecht 2016 [24]	RCT	USA	249	238	365/122	61(19–86)	59(27–84)	lap + che	che	23	F3; F4; F5;
Hofheinz 2022 [30]	RCT	Germany	40	41	64/17	59.5(36–83)	61(24–77)	che + trz/pez	che	22	F1; F3; F5
Josep Tabernero 2018 [25]	RCT	Spain	388	392	617/163	62(54.5–69)	61(54–68)	pez + trz + che	che	25	F3; F4; F5; F6
Bang 2010 [34]	RCT	Korea	294	290	444/140	59.4	58.5	trz + che	che	18.6	F1; F2; F3; F4; F5; F6
Manish A. Shah 2018 [28]	RCT	USA	228	117	–	–	–	trz	che	17.5	F3; F4
Tianshu Liu 2019 [33]	RCT	China	82	81	130/33	59(25–78)	59(23–73)	pez + trz + che	che	22	F1; F3; F4; F5; F6
Merrimack: A study of MM-111 and paclitaxel with trastuzumab in patient-sHER2 positive carcinomas of the distal esophagus, gastroesophageal (GE)junction and stomach, unpublished	RCT	USA	42	42	77/7	63.5(31–78)	62.5(35–81)	MM-111 + trz + che	che	–	F4; F5
Taroh Satoh 2019 [32]	RCT	Japan	59	22	67/14	62(23–83)	62.5(33–77)	niv	che	14	F1; F2; F3; F4; F5
Taroh Satoh 2014 [31]	RCT	Japan	132	129	207/54	61(32–79)	62(22–80)	lap + che	che	–	F1; F3; F4; F5;F6
Lin Shen 2013 [35]	RCT	China	36	48	67/17	58.7(48.2–69.2)	58.2(47.7–68.7)	trz + che	che	15.2	F1; F2; F3; F4; F5; F6
K. Shitara 2020 [27]	RCT	Japan	125	62	142/45	65(34–82)	66(28–82)	trx_dex	che	6	F1; F2; F3; F4; F5
Josep Tabernero 2023 [26]	RCT	Spain	388	392	617/163	–	–	pez + trz + che	che	46.1	F1; F2; F3; F4; F5; F6
Thuss-Patience 2017 [29]	RCT	Germany	228	117	272/73	62(19–79)	62(27–80)	trz	che	17.5	F1; F3; F4; F5; F6

RCT randomized controlled trial, *EG* experimental group, *CG* control group, *F1* ORR, *F2* DCR, *F3* OS, *F4* PFS, *F5* adverse events, *F6* adverse events grade > = 3, *che* chemotherapy, *lap* lapatinib, *niv* nivolumab, *trz* trastuzumab, *trz_dex* trastuzumab deruxtecan, *pez*pertuzumab, *MM111* MM-111

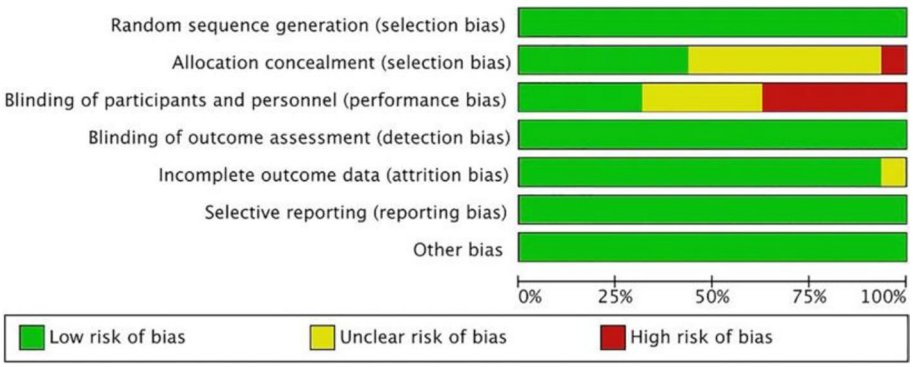

Fig. 2 Risk bias of graph

Network diagram

The network relationship diagram for 9 intervention measures including che, lap_che, niv, trz, trz_che, trz_dex, trz_niv_ipi, trz_pez_che, and MM111_trz_che is shown in Supplementary S2. A dot signifies a specific intervention, with the dot size reflecting the number of patients utilizing that intervention. A straight line denotes the presence of direct comparative evidence between two interventions, with the thickness of the line corresponding to the number of studies involved in comparing the two interventions.

Network analysis results

Overall survival (OS)

OS was reported in 14 studies, involving 4,355 patients and 8 treatment regimens, including che, lap_che, niv, trz, trz_che, trz_dex, trz_niv_ipi, and trz_pez_che. The network meta-analysis generated a total of 28 direct or indirect comparisons, and patients receiving niv, trz_dex, and trz_pez_che had longer OS than those receiving che (as shown in Supplementary S3). The results of the ranking of SUCRA showed that patients receiving niv had the longest OS and patients receiving che had the shortest OS (as shown in Table 2). The cumulative probability showed that patients receiving niv had the longest OS (as shown in Fig. 4).

Progression-free survival (PFS)

A total of 13 studies reported PFS, involving 4358 patients with 8 treatment regimens, including che, lap_che, niv, trz, trz_che, trz_dex, trz_niv_ipi, and trz_pez_che. A total of 28 direct or indirect comparisons were generated through network meta-analysis, and patients receiving lap_che, niv, trz_che, trz_dez, and trz_pez_che had longer PFS than those receiving che (as shown in Supplementary S3). The results of ranking according to SUCRA showed that patients receiving trz_dex had the longest PFS and patients receiving trz_niv_ipi had the shortest PFS (as shown in Table 2). According to the cumulative probability, patients receiving trz_dex had the longest PFS (as shown in Fig. 5).

Objective response rate (ORR)

ORR was discussed in 10 studies, involving 2655 patients and 7 treatment regimens, including che, lap_che, niv, trz, trz_che, trz_dex, and trz_pez_che. A total of 21 direct or indirect comparisons were generated through network meta-analysis, and patients receiving trz, trz_che, and trz_pez_che had higher ORR than those receiving lap_che (as shown in Supplementary S3). The results of ranking according to SUCRA showed that patients receiving niv had the highest ORR and patients receiving che had the lowest ORR (as shown in Table 2). According to the cumulative probability, patients receiving niv had the highest ORR (as shown in Fig. 6).

Disease control rate (DCR)

A total of 6 studies reported DCR, involving 1805 patients and 5 treatment regimens, including che, niv, trz_che, trz_dex, and trz_pez_che. A total of 10 direct or indirect comparisons were generated through network meta-analysis, and the DCR of trz_che was lower than that of che (as shown in Supplementary S3). The results of ranking according to SUCRA showed that trz_dex had the highest DCR and che had the lowest DCR (as shown in Table 2). According to the cumulative probability, trz_dex had the highest DCR (as shown in Fig. 7).

Adverse event (AE)

A total of 11 studies reported recurrence, involving 4140 patients and 7 treatment regimens, including che, lap_che, trz, trz_che, trz_dex, trz_pez_che, and MM111_trz_che. A total of 21 direct or indirect comparisons were generated through network meta-analysis, and lap_che, MM111_trz_che, and trz_dex had a

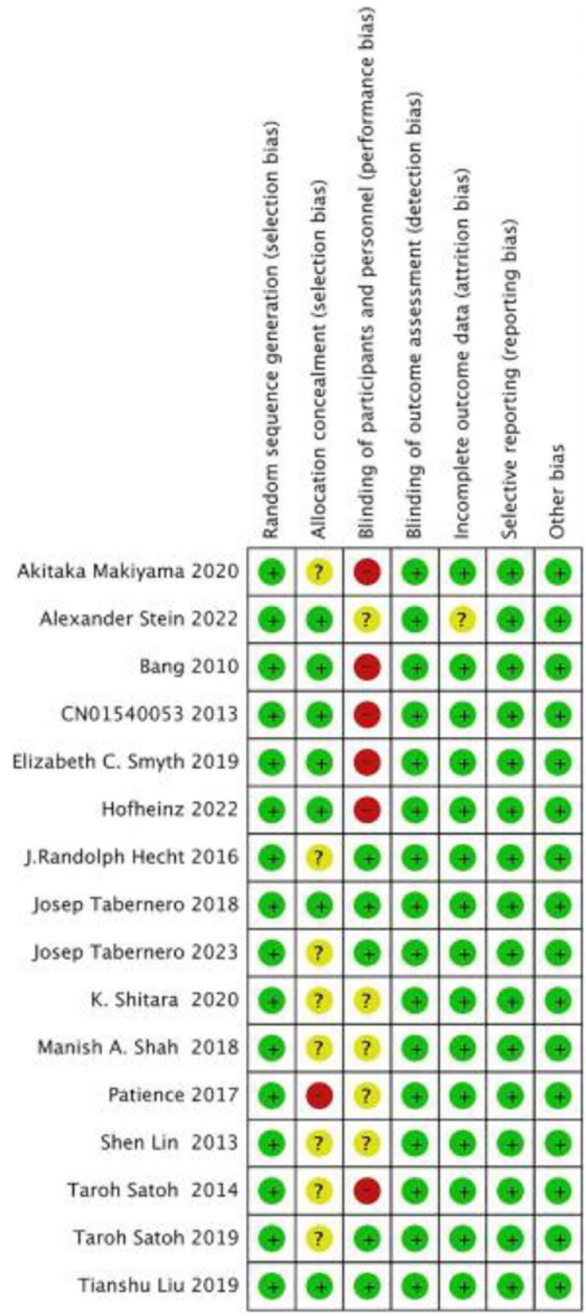

Fig. 3 Risk bias of summary

lower incidence of adverse events than che (as shown in Supplementary S3). The results of ranking according to SUCRA showed that trz_dex had the lowest incidence of adverse events, and che had the highest incidence of adverse events (as shown in Table 2). According to the cumulative probability, trz_dex had the lowest incidence of adverse events (as shown in Fig. 8).

Adverse event grade> = 3

A total of 8 studies were included, involving 3085 patients and 6 treatment regimens, including che, lap_che, trz, trz_che, trz_niv_ipi, and trz_pez_che. A total of 15 direct or indirect comparisons were generated through network meta-analysis, and patients receiving lap_che and trz_pez_che had a higher probability of AE grade ≥ 3 than those receiving che (as shown in Supplementary S3). The results of ranking according to SUCRA showed that patients receiving lap_che had the lowest probability of AE grade ≥ 3, and patients receiving che had the highest probability of AE grade ≥ 3 (as shown in Table 2). According to the cumulative probability, patients receiving che had the highest probability of AE grade ≥ 3 (as shown in Fig. 9)

Publication bias and heterogeneity

The publication bias of ORR, DCR, and AE was assessed using a funnel plot, and the corrected funnel plot was asymmetric, suggesting a high possibility of publication bias for the above indicators (as shown in Supplementary S4).

Discussion

Many molecular markers have been discovered with the advancement of precision therapy for gastric cancer. In the TCGA database, gastric cancer has been classified into four subtypes based on different molecular targets: EBV type, MSI type, GS type, and CIN type [36]. Among these subtypes, HER2 is the most common biomarker that holds definitive clinical significance. As a member of the EGFR family, HER2 plays a crucial role in regulating cell proliferation and differentiation. Overexpression or amplification of the HER2 receptor leads to its dense distribution on the cell surface, activating multiple intracellular signaling pathways. It promotes cell proliferation, angiogenesis, survival, and metastasis by activating PI3K/Akt, Ras/MEK/ERK, and JAK/STAT pathways [37]. Activation of the PI3K/AKT/mTOR pathway in patients with HER2-positive breast cancer is associated with acquired resistance to multiple drugs [38]. Overexpression of HER2/neu can activate Ras/Raf/MEK/ERK pathway, resulting in decreased expression of wild p53 protein [39]. This may be the molecular mechanism that leads to poor prognosis and non-response to treatment in HER2/neu overexpressed breast cancer patients. The positive rate of HER2 in gastric cancer ranges from 12 to 20% [40]. Despite this, the 5-year survival rate for HER2-positive gastric cancer remains significantly low, ranging from 5 to 20% [41], indicating its highly malignant nature. Therefore, conducting research on gastric cancer with HER2 amplification and overexpression is of

Table 2 Overall ranking of SUCRA

Rank	che	lap_che	niv	trz	trz_che	trz_dex	trz_niv_ipi	trz_pez_che	MM111_trz_che
OS	0.23	0.44	0.97	0.08	0.60	0.82	0.31	0.54	NA
PFS	0.27	0.44	0.89	0.14	0.68	0.93	0.05	0.61	NA
ORR	0.07	0.69	1.00	0.14	0.43	0.81	NA	0.36	NA
DCR	0.08	NA	0.55	NA	0.56	0.97	NA	0.35	NA
AE	0.82	0.50	NA	0.79	0.38	0.02	NA	0.79	0.20
AE grade > = 3	0.59	0	NA	0.88	0.48	NA	0.83	0.22	NA

che chemotherapy, *lap_che* lapatinib+chemotherapy, *niv* nivolumab, *trz* trastuzumab, *trz_che* trastuzumab+chemotherapy, *trz_dex* trastuzumab deruxtecan, *trz_niv_ipi* trastuzumab+nivolumab+ipilimumab, *trz_pez_che* pertuzumab+trastuzumab+chemotherapy, *MM111_trz_che* MM-111+trastuzumab +chemotherapy

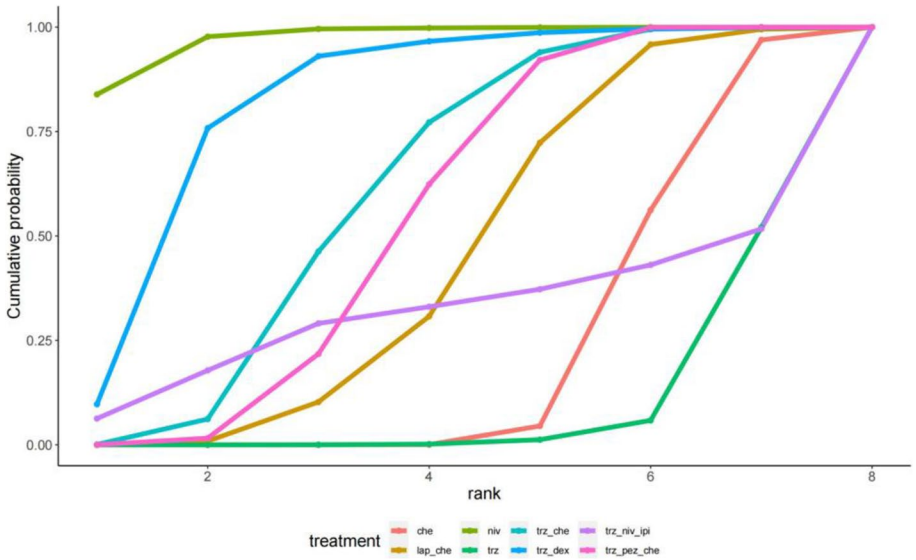

Fig. 4 OS cumulative probability plot. che: chemotherapy; lap_che: lapatinib+chemotherapy; niv: nivolumab; trz: trastuzumab; trz_che: trastuzumab+chemotherapy; trz_dex: trastuzumab deruxtecan; trz_niv_ipi: trastuzumab+nivolumab+ipilimumab; trz_pez_che: pertuzumab+trastuzumab+chemotherapy

utmost importance. In recent years, various drugs such as chemotherapy, targeted therapy, immunotherapy, and anti-angiogenic therapy have been progressively utilized in the medical treatment of HER2-positive gastric cancer. However, there is still a need for a comprehensive evaluation of these treatment approaches.

Currently, there are various treatment options available for HER2-positive gastric cancer, each with distinct mechanisms of action. One of these options is antibody conjugate drugs (ADCs), which combine HER2-specific antibodies with potent cytotoxic drugs via a specific linker. This enables the targeted delivery of cytotoxic drugs to tumor cells, effectively killing them through chemotherapy [42]. Tumor immunotherapy, on the other hand, relies on the activation of T cells to eliminate tumor cells. The interaction between the PD-1 ligand on the surface of tumor cells and the PD-1 receptor on T cells plays a crucial role in this process. By sending inhibitory signals to immune cells, this interaction leads to T cell inactivation and immune tolerance [43]. Immunosuppressive agents function by blocking the interaction between tumor cells and immune cells, enhancing the immune response against tumors. However, the lack of unified standards and systematic comparison poses a challenge in this field, hindering further advancements in our knowledge. To the best of our knowledge, this is the first network meta-analysis comparing 9 treatment regimens for HER2-positive gastric cancer, including che, lap_che, niv, trz, trz_che, trz_dex, trz_niv_ipi, trz_pez_che, and MM111_trz_che. This study has identified that the use of chemotherapy alone and targeted therapy with trastuzumab alone does not significantly extend survival and even leads to higher rates of adverse reactions. On the other hand, the combination of targeted

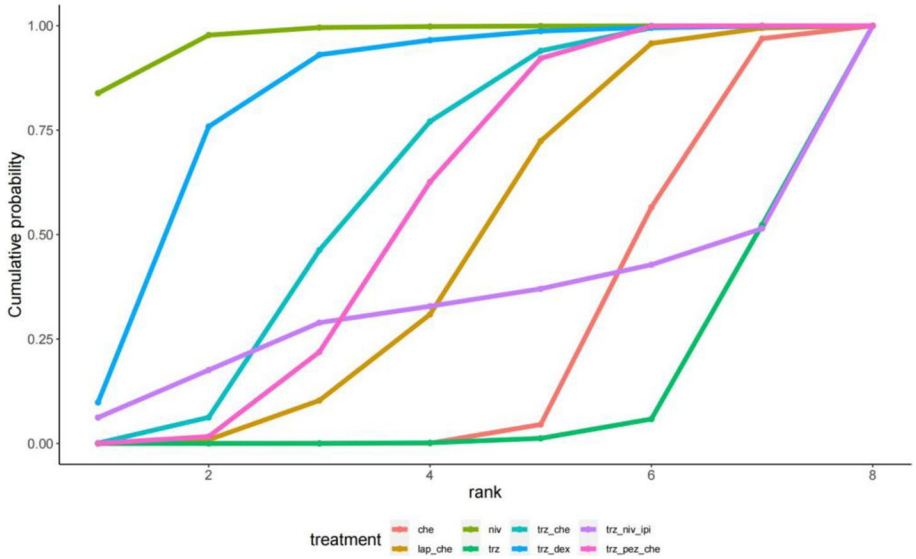

Fig. 5 PFS cumulative probability plot. che: chemotherapy; lap_che: lapatinib + chemotherapy; niv: nivolumab; trz: trastuzumab; trz_che: trastuzumab + chemotherapy; trz_dex: trastuzumab deruxtecan; trz_niv_ipi: trastuzumab + nivolumab + ipilimumab; trz_pez_che:pertuzumab + trastuzumab + chemotherapy

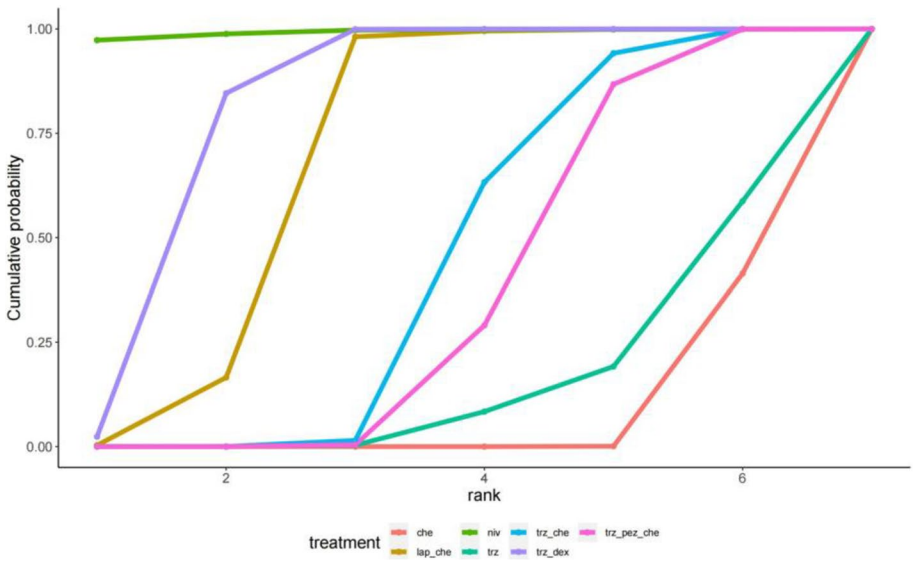

Fig. 6 ORR cumulative probability plot. che: chemotherapy; lap_che: lapatinib + chemotherapy; niv: nivolumab;trz: trastuzumab; trz_che: trastuzumab + chemotherapy; trz_dex: trastuzumab deruxtecan; trz_pez_che:pertuzumab + trastuzumab + chemotherapy

therapy and chemotherapy, as well as targeted therapy and immunization, has shown slightly improved efficacy and safety compared to single therapies. Importantly, the use of trastuzumab deruxtecan and nivolumab has demonstrated a significant prolongation of overall survival (OS) and progression-free survival (PFS) in patients with HER2-positive gastric cancer. Notably, nivolumab has shown an almost 100% ORR (objective response rate) with a lower incidence of adverse events. These findings are supported by the results of the ATTRACTION-2 clinical trial [44], which evaluated the use of nivolumab and placebo in patients with advanced gastric cancer. The 3-year follow-up data showed that the median OS in the nivolumab group was 26.7 months, with a 3-year survival rate of 35.5%. Additionally, a Phase I study investigating the efficacy of neoadjuvant nivolumab

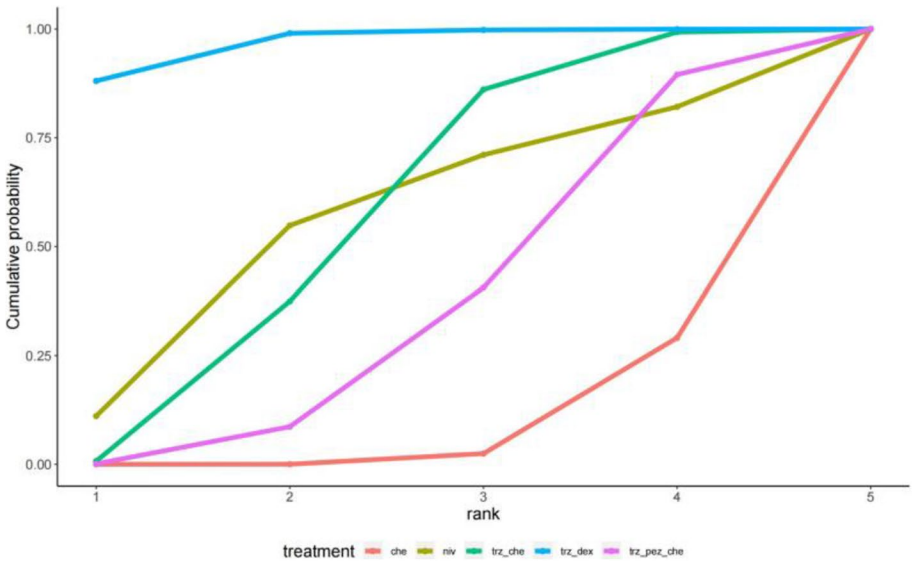

Fig. 7 DCR cumulative probability plot. che: chemotherapy; lap_che: lapatinib + chemotherapy; niv: nivolumab; trz_che: trastuzumab + chemotherapy;trz_dex: trastuzumab deruxtecan; trz_pez_che:pertuzumab + trastuzumab + chemotherapy

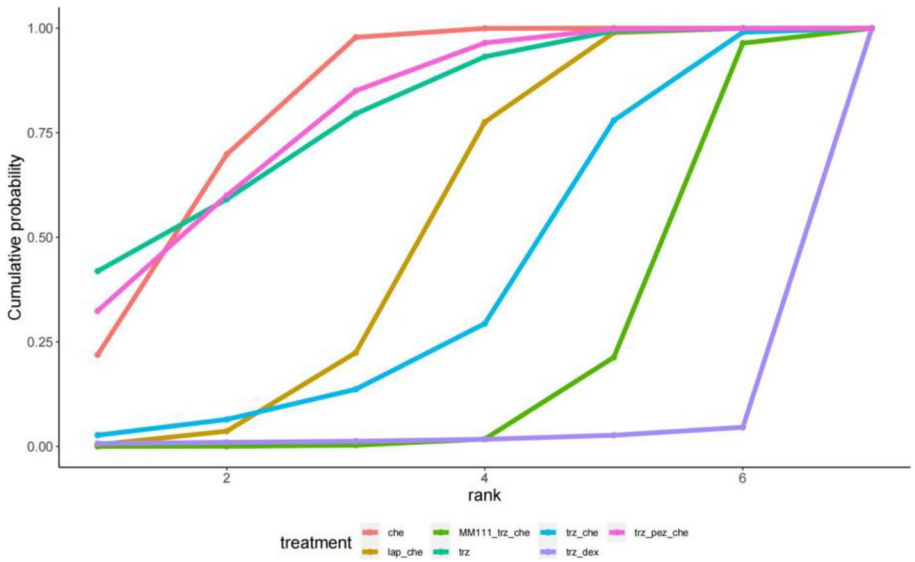

Fig. 8 AE cumulative probability plot. che: chemotherapy; lap_che: lapatinib + chemotherapy;trz: trastuzumab; trz_che: trastuzumab + chemotherapy; trz_dex: trastuzumab deruxtecan; trz_pez_che:pertuzumab + trastuzumab + chemotherapy; MM111_trz_che: MM-111 + trastuzumab + chemotherapy

monotherapy for gastric cancer [45] reported a low rate of treatment-related adverse events (0–6%) and the ability of nivolumab to induce major pathological responses in some patients with resectable gastric cancer. These findings are consistent with the results of our study.

Currently, trastuzumab deruxtecan has received approval in the United States for second-line or late-line treatment. Trastuzumab deruxtecan is an antibody–drug conjugate that consists of an HER2 antibody, a cytotoxic topoisomerase I inhibitor, and a lysable tetrapeptide ligand. In a Phase II study comparing the efficacy of trastuzumab deruxtecan with chemotherapy, over half of the patients in the trastuzumab deruxtecan group experienced objective responses [46]. The OS rate was found to be 12.5 months, and the common adverse reactions mainly included neutropenia,

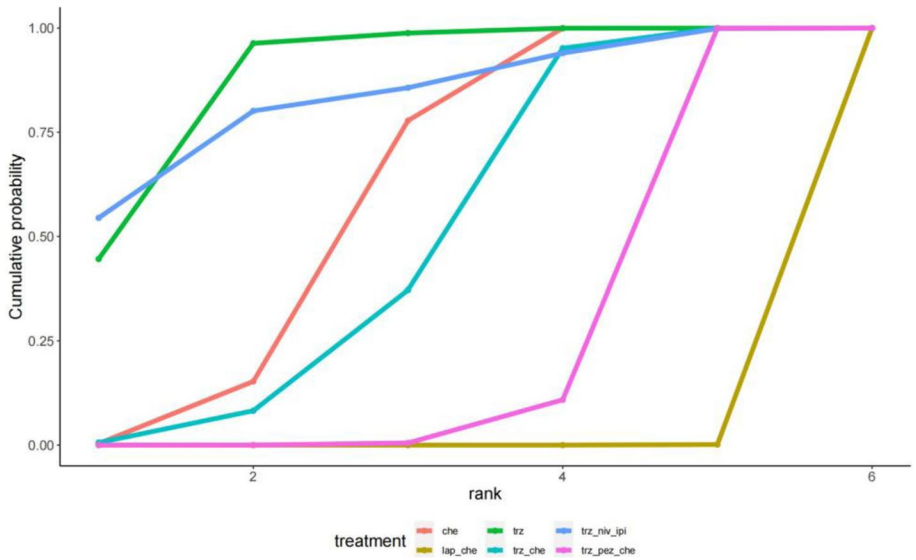

Fig. 9 AE grade ≥ 3 cumulative probability plot. che: chemotherapy; lap_che: lapatinib + chemotherapy; trz: trastuzumab; trz_che: trastuzumab + chemotherapy; trz_niv_ipi: trastuzumab + nivolumab + ipilimumab; trz_pez_che: pertuzumab + trastuzumab + chemotherapy

anemia, and leukopenia. Trastuzumab deruxtecan has several unique advantages compared to trastuzumab, most notably a high drug antibody ratio of 8:1 and a bystander antitumor effect. Previous studies have shown significant antitumor activity in heavily pretreated patients with HER2-positive breast cancer and gastric cancer. A Phase Ib study revealed that out of 44 patients treated with varying doses of trastuzumab deruxtecan, 43.2%25 (19/44) showed an objective response rate, and 79.5% 25 (35/44) had disease control [47]. Based on these results and 16 randomized controlled studies, it was found that the adverse reactions to trastuzumab deruxtecan mainly included nausea, decreased neutrophil count, and anemia. Due to its lower incidence of adverse reactions, trastuzumab deruxtecan is expected to have promising prospects in the future. Additionally, the use of MM-111 bispecific antibody therapy is considered a potential alternative treatment for HER2-positive gastric cancer [48]. However, in this study, the combination of MM-111 with trastuzumab and chemotherapy was associated with a higher risk of adverse reactions compared to trastuzumab deruxtecan monotherapy. Furthermore, the lack of data on survival and response rates prevents a meaningful comparison between the two treatments. In conclusion, immunotherapy, targeted therapy, and chemotherapy all provide benefits to patients with HER2-positive gastric cancer to a certain extent. Monotherapy or combination therapy using drugs that can prolong OS and PFS, improve response rates, and reduce the incidence of adverse reactions have the potential to offer patients a better prognosis. We remain optimistic that the use of drugs will lead to better treatment outcomes and fewer side effects for patients with gastric cancer in the next 5 years. This advancement is expected to benefit a larger population of patients. Moving forward, it is crucial to conduct additional well-designed randomized controlled trials to validate the effectiveness and safety of different drugs in treating HER2-positive gastric cancer.

However, this study still has several limitations. First, the quality of included studies is medium with unbalanced proportion, and some studies lacked sufficient allocation concealment and blinding methods, which are potential sources of bias. Second, HER2-positive gastric cancer of different stages affected the comparability. Third, some studies did not report data on survival and response rate, resulting in the incomplete results of some treatment regimens. Fourth, the follow-up time was 1 to 46 months with varied results. In addition, although our study confirmed that nivolumab and trastuzumab deruxtecan have low adverse reactions and efficacy in terms of ethical considerations for treatment options, the potential socioeconomic costs of nivolumab and Trastuzumab are much higher than those of traditional treatments, which may also hinder patients' choice of treatment options. In the future, better randomized controlled clinical trials can be designed to include more patients with HER2-positive gastric cancer, with extended follow-up to confirm or expand these results.

Conclusion

In summary, the administration of nivolumab and trastuzumab deruxtecan has proven to be both efficacious and well-tolerated in the management of patients diagnosed with HER2-positive gastric cancer.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13643-025-02777-4.

Supplementary Material 1. Specific search strategies.

Supplementary Material 2. The network relationship diagram for 9 intervention measures.

Supplementary Material 3. The network meta-analysis.

Supplementary Material 4. The publication bias of ORR, DCR, and AE.

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Not applicable

Authors' contributions
Conceptualization: Xiao Ma and Chunluan Yuan. Methodology: Jie Zhang. Formal analysis and investigation: Jie Zhang. Writing—original draft preparation: Xiao Ma. Writing—review and editing. Xiao Ma. Funding acquisition: Xiao Ma. Resources: Jie Zhang. Supervision: Jie Zhang and Chunluan Yuan. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability
All relevant data are within the manuscript and its additional files.

Declarations
Ethics approval and consent to participate.
Not applicable.

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