Effectiveness of immune checkpoint inhibitors in combination with tyrosine kinase inhibitors in patients with advanced or metastatic colorectal carcinoma with either mismatch repair proficient or metastatic microsatellite stable disease: A systematic review and meta-analysis

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Abstract. Immune checkpoint inhibitors (ICIs) have limited efficacy in mismatch repair proficient (pMMR) or metastatic microsatellite stable (MSS) advanced or metastatic colorectal cancer (mCRC). ICIs, in conjunction with tyrosine kinase inhibitors (TKIs) possessing anti-angiogenic properties, serve as a potential strategy for circumventing the resistance exhibited by MSS or pMMR mCRC to immunotherapeutic interventions. The present study aimed to evaluate efficacy and safety of ICIs + TKIs and provide a reference for the treatment of CRC. The present systematic review and meta-analysis was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. PubMed, Embase, Cochrane, Web of Science and ClinicalTrials.gov databases were screened from January 1, 2003 to July 28, 2023. A total of 14 studies were included in qualitative and quantitative analyses, with a total of 819 patients enrolled. The Newcastle-Ottawa scale scores of the 14 cohort studies included were ≥7, indicating they were of a high quality. The objective response rate (ORR) of ICIs + TKIs was 14% [95% confidence interval (CI), 0.08-0.24; P=0.132] in patients with advanced or metastatic MSS/pMMR CRC. The disease control rate (DCR) was 65% (95% CI, 0.58-0.74; P<0.0001). The overall incidence of adverse events of varying severity linked to combination of ICIs and TKIs in patients with advanced or metastatic MSS/pMMR CRC was 64% (95% CI, 0.52-0.78; P<0.0001). The incidence of grade ≥3 adverse reactions was 24% (95% CI, 0.14-0.4; P<0.0001). The sensitivity analysis indicated that the exclusion of individual studies did not yield statistically significant variations in combined analysis results. Based on the examination of publication bias, ORR and DCR, Begg's and Egger's tests had P-values of 0.114 and 0.395, respectively. Overall publication bias overall was absent in the Begg's funnel plot, as there was no apparent asymmetry. Nonetheless, the P-values of the Egger's and Begg's tests for adverse reactions and adverse reactions grade ≥3 were P=0.008 and P=0.048, respectively. The asymmetry of the Begg's funnel plots was evident, suggesting the presence of potential publication bias regarding adverse event results. In conclusion, the combination of ICIs and TKIs demonstrates a favorable effectiveness and notable safety profile in the management of patients with advanced or metastatic MSS/pMMR CRC.

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Introduction

Colorectal cancer (CRC) is the second most prevalent cause of mortality globally and ranks as the third most frequently occurring malignancy (1). The global death rate for CRC is >800,000 individuals annually, with a persistent upward trend in the incidence and fatalities associated with CRC (2).

The treatment of early-stage CRC often involves extensive surgical intervention followed by adjuvant chemotherapy. This comprehensive approach is associated with favorable prognostic outcomes (3). However, due to the absence of readily discernible symptoms during the initial stage of CRC, at the time of diagnosis, a substantial number of individuals have advanced or metastatic (m)CRC. This results in a poor prognosis, characterized by a low 5-year overall survival rate of 5-8% (4).

Chemotherapy is the prevailing therapeutic approach for managing mCRC; however, it is associated with obstacles, including limited selectivity, systemic adverse responses and suboptimal concentration of administered drug at the tumor site (5,6). Immunotherapy has demonstrated positive results in treatment of numerous types of malignant cancer, such as melanoma, renal cell carcinoma and non-small cell lung cancer (7). Research has demonstrated that immune checkpoint inhibitors (ICIs) exhibit favorable effectiveness in individuals with mCRC who possess mismatch repair deficient (dMMR) or microsatellite

instability-high (MSI-H) attributes (8,9), but only in patients with mismatch repair deficient (dMMR) or microsatellite instability-high (MSI-H). However, occurrence of dMMR/MSI-H tumors accounts for only 2-4% of all cases of mCRC (10).

Most individuals diagnosed with CRC demonstrate MMR proficient (pMMR) or MS stable (MSS) status. These molecular characteristics of CRC can lead to a diminished effectiveness of ICIs in combating the malignancy (11,12). According to clinical studies, the combination of anti-angiogenic drugs and ICIs enhances the efficacy of treatment of malignant tumors (13-15). These drugs possess anti-angiogenic properties and can hinder the expression of immunosuppressive molecules; as a result, they contribute to restoration of the immunosuppressive tumor microenvironment (TME) (13). Hence, using ICIs in conjunction with tyrosine kinase inhibitors (TKIs) that possess anti-angiogenic properties may serve as a potential strategy for circumventing resistance exhibited by MSS or pMMR mCRC towards immunotherapeutic interventions.

At present, regorafenib and fruquintinib are the primary TKIs used for the treatment of CRC. In patients with MSS/pMMR mCRC, the combined therapy of nivolumab and regorafenib shows a 33% objective remission rate, according to the findings of a phase 1b clinical trial (16). Recently, avelumab and regorafenib were the subjects of a phase II clinical investigation, where the positive response of patients was limited to achieving a stable disease state (17). Zhang *et al* (18) reported that the combined use of fruquintinib and programmed death cell death protein 1 (PD-1) inhibitors yields notable outcomes in the treatment of advanced MSS CRC. The aforementioned study revealed an objective effective rate of 11.8% and a disease control rate of 70%. These findings indicate favorable therapeutic outcome in the treatment of CRC.

The aforementioned studies indicate that the combination of ICIs and TKIs holds potential as a viable therapeutic approach for individuals with advanced or mCRC who exhibit MSS or pMMR status. However, the number of related studies is relatively small, and this treatment strategy is currently mainly applied to small sample size Phase I or II trials, where patients are usually superselective, and the overall efficacy and safety of these trials are still unknown (16-18). There is lack of agreement about the appropriate therapeutic approach for patients with advanced or metastatic MSS/pMMR CRC. Therefore, the present systematic review and meta-analysis was performed to assess relevant literature with data on the combined use of ICIs and TKIs for the treatment of patients with MSS/pMMR with advanced-stage or invasive CRC. The aim was to determine if the treatment is safe and successful, and to offer guidance for managing CRC.

Materials and methods

Search strategy. The current study aligns with the principles and recommendations in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The systematic review procedure performed in the present study was registered on the International Platform of Registered Systematic Review and Meta-Analysis Protocols (registration no. INPLASY202390019; doi.org/10.37766/inplasy2023.9.0019).

To ensure comprehensive investigation, an extensive search was performed across multiple databases, including Embase (https://www.embase.com/), Web of Science (https://webofscience.clarivate.cn/), Cochrane (https://www.cochranelibrary.com/), PubMed (http://www.ncbi.nlm.nih.gov/pubmed) and ClinicalTrials.gov (clinicaltrials.gov/). Articles published from January 1, 2003 to July 28, 2023 were included study. The articles were searched in all languages and relevant articles were included regardless of language of publication or primary outcomes. The complete search terms used for all databases were: ((((Regorafenib) OR (Fruquintinib)) OR (Tyrosine kinase inhibitors)) AND ((((((((((immune checkpoint inhibitor) OR (PD-1 Inhibitors)) OR (programmed cell death protein 1 inhibitor)) OR (PD-L1 Inhibitors)) OR (Programmed Death-Ligand 1 Inhibitors)) OR (CTLA-4 inhibitors)) OR (PD-1-PD-L1 Blockade)) OR (Nivolumab)) OR (Atezolizumab)) OR (Durvalumab)) OR (Avelumab)) OR (pembrolizumab))) AND ((((((((((((((((Colorectal Neoplasms[Title/Abstract]) OR (Colorectal Neoplasm[Title/Abstract])) OR (Neoplasm, Colorectal[Title/Abstract])) OR (Neoplasms, Colorectal[Title/Abstract])) OR (Colorectal Tumors[Title/Abstract])) OR (Colorectal Tumor[Title/Abstract])) OR (Tumor, Colorectal[Title/Abstract])) OR (Tumors, Colorectal[Title/Abstract])) OR (Colorectal Cancer[Title/Abstract])) OR (Cancer, Colorectal[Title/Abstract])) OR (Cancers, Colorectal[Title/Abstract])) OR (Colorectal Cancers[Title/Abstract])) OR (Colorectal Carcinoma[Title/Abstract])) OR (Carcinoma, Colorectal [Title/Abstract])) OR (Carcinomas, Colorectal[Title/Abstract])) OR (Colorectal Carcinomas[Title/Abstract])).

Inclusion criteria. To assess the suitability of studies, the population (P), intervention (I), comparator (C), outcome (O) and study design (S) framework was used. Utilizing this particular framework resulted in proficient assessment and determination of the suitability and qualification of the studies. The criteria were as follows: P, patients with advanced or metastatic MSS/pMMR CRC; I, TKIs + ICIs; C, patients with CRC before the study started; O, adverse reaction rate, disease control rate (DCR) and objective response rate (ORR); and S, cohort or case-control studies.

Exclusion criteria. Exclusion criteria included: Articles lacking survival data and studies assessing the combination of ICIs + TKIs in primary tumors besides CRC. Studies with individuals diagnosed with CRC or other malignancy that failed to provide separate findings were also excluded. The analysis also excluded letters to the editor, reviews, animal studies, case reports and conference abstracts.

Extraction of data and evaluation of quality. A total of two researchers, JL and YXZ, performed the literature screening process. This involved carefully reviewing the topic, picking relevant articles based on the aforementioned criteria, and evaluating the abstract and full text of the selected articles. To assess the quality of cohort and case-control studies, the Newcastle-Ottawa scale (NOS) was used (19). The NOS is a comprehensive framework of eight items that are further categorized into three domains: Population selection, exposure or outcome evaluation, and comparability. Each item is assigned

a numerical score on a scale ranging from 0-9; scores >5 indicate a high level of quality (19). The following data were separately recorded by two researchers (JL and YXZ): Details of the first author; publication date; country in which the study was performed; type of research; treatment technique; number of patients participating in the research; % male patients; and the median follow-up period of the study. Discussions with a third researcher (SQL) resolved disagreements between the two researchers.

Statistical analysis. The current study performed extensive meta-analysis of pertinent literature to assess a range of clinical outcomes. Meta-analysis was performed using STATA 16.1 statistical software (StataCorp LLC, College Station, TX). DCR, ORR, adverse reaction rate and grade ≥3 adverse reaction rate were assessed. These outcomes and corresponding 95% confidence intervals (CIs) were analyzed. To evaluate inter-study heterogeneity, the statistical measures of the I^2 statistic and Cochran's Q test were used. Values <25% were considered to indicate low levels of heterogeneity; 25-50% indicated moderate levels of heterogeneity and values >50 and <75% were considered to indicate high levels of heterogeneity (20). When values >75%, sensitivity analysis is conducted on the evaluated effect size and research heterogeneity to evaluate the stability of the results, excluding studies with a significant impact on heterogeneity. The random effect model was used for combined analysis. Funnel plots were used to assess publication bias. The identification of potential bias was accomplished by evaluating the asymmetry of the plots, which was assessed using Egger's and Begg's tests. P<0.05 was considered to indicate a statistically significant difference.

Results

Study characteristics. A total of 14 studies, with a sample size of 819 patients, were selected for inclusion after assessing the full-text articles and extracting relevant data. The selection procedure adhered to the guidelines outlined in the PRISMA flowchart (Fig. 1). The present study analyzed cohort studies (16-18,21-31) and the pertinent information on the included research is outlined in Table I.

Quality evaluation of the included studies. The present study used the NOS to evaluate the quality of studies. A score of 5-9 on the NOS suggested a study was of good quality. All 14 studies reviewed obtained scores ≥7, indicating a high level of quality (Table II).

Meta-analysis. The ORR of the combination therapy of ICIs + TKIs was 14% (95% CI, 0.08-0.24; Fig. 2A) in patients diagnosed with advanced or metastatic MSS/pMMR CRC. The DCR was 65% (95% CI, 0.58-0.74; Fig. 2B). The overall incidence of adverse events of varying severity associated with the combination of ICIs + TKIs was 64% (95% CI, 0.52-0.78; Fig. 2C). The incidence of grade ≥3 adverse reactions was 24% (95% CI, 0.14-0.40; Fig. 2D).

Assessment of publication bias. The sensitivity analysis indicated that the exclusion of individual studies did not yield statistically significant variations in combined analysis results

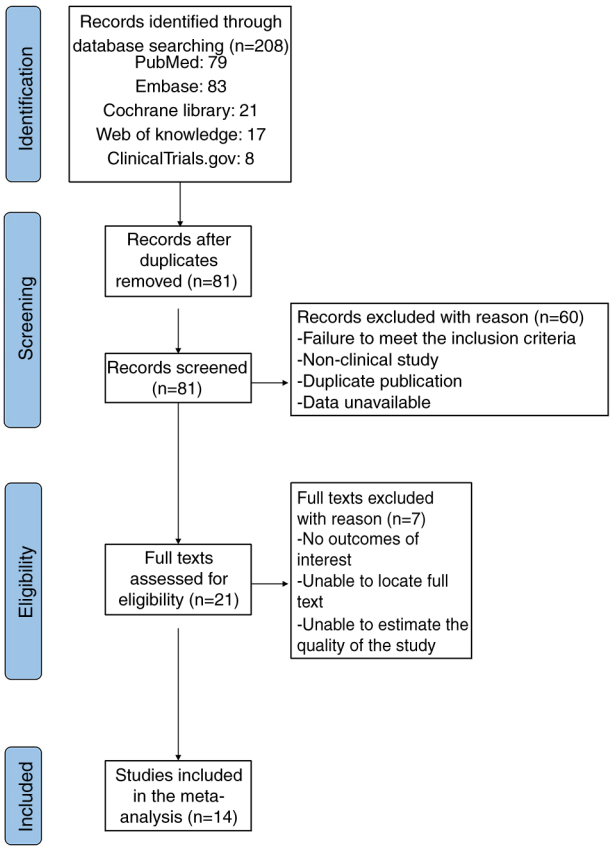

Figure 1. Screening strategy for the included studies.

(Fig. 3A-D). This suggested that the overall results obtained from the present study may be considered valid and reliable. Furthermore, Begg's and Egger's tests for objective response and disease control were 0.114 and 0.395, publication bias was indicated to be absent as there was no apparent asymmetry in the Begg's funnel plot for objective response (Fig. 4A) and disease control (Fig. 4B). P-values obtained from the Begg's and Egger's tests for adverse reactions and adverse reaction grade ≥3 were 0.008 and 0.048, respectively. The asymmetry of the Begg's funnel plot for adverse reactions (Fig. 4C) and adverse reaction grade ≥3 (Fig. 4D) were evident, suggesting presence of potential publication bias.

Discussion

The relevance of immune inhibitors in the clinical setting is underscored by their potent anticancer impact, which extends to several types of solid tumor, such as renal clear cell carcinoma, liver cancer and melanoma (32). The use of ICIs in managing patients with MSI-H or dMMR mCRC has received approval from the United States Food and Drug Administration. This is based on the compelling evidence from multiple clinical trials (33,34). MSI-H/dMMR CRC exhibits enhanced tumor antigen production by elevating tumor mutational burden, which leads to heightened infiltration of T cells into the TME, rendering these tumors more responsive to ICIs (35). Conversely, MSS/pMMR CRC with low tumor mutational burden and minimal infiltration of T cells exhibits resistance to ICIs (35).

Table I. Characteristics of all studies included in the meta-analysis.

First author, year	Country	Enrollment	PD-1/PD-L1 inhibitor	TKI	Patients	Male, %	Median follow-up, months	(Refs.)
Fukuoka *et al*, 2020	Japan	Cohort	Nivolumab	Regorafenib	25	72.00	6.6	(16)
Cousin *et al*, 2021	France	Cohort	Avelumab	Regorafenib	43	74.00	7.2	(17)
Zhang *et al*, 2022	China	Cohort	ICI	Fruquintinib	110	57.30	9.8	(18)
Chen *et al*, 2022	China	Cohort	ICI	Regorafenib	21	37.50	16.2	(21)
Wang *et al*, 2020	USA	Cohort	Nivolumab and pembrolizumab	Regorafenib	18	88.90	7.0	(22)
He *et al*, 2023	China	Cohort	ICI	Regorafenib	84	56.00	14.2	(23)
Kim *et al*, 2022	USA	Cohort	Nivolumab	Regorafenib	40	53.80	7.9	(24)
Li *et al*, 2020	China	Cohort	ICI	Regorafenib	21	69.60	7.9	(25)
Ma *et al*, 2023	China	Cohort	Toripalimab	Fruquintinib	18	63.16	9.2	(26)
Ren *et al*, 2020	China	Cohort	SHR-1210	Apatinib	9	30.00	8.2	(27)
Sun *et al*, 2021	China	Cohort	ICI	Fruquintinib and regorafenib	51	52.90	6.2	(28)
Xu *et al*, 2022	China	Cohort	ICI	Regorafenib	30	46.70	12.0	(29)
Yang *et al*, 2022	China	Cohort	ICI	Regorafenib	82	60.00	5.5	(30)
Yu *et al*, 2021	China	Cohort	Toripalimab	Regorafenib	33	54.54	19.0	(31)

PD-1, programmed cell death protein 1; PD-L1, programmed death ligand 1; TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor.

Table II. Quality assessment using the Newcastle-Ottawa Scale for cohort studies.

	Selection				Comparability	Outcome				
First author, year	Representa-tiveness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of design or analysis	Assess-ment of outcome	Demonstration that follow-up was long enough for outcomes to occur	Adequacy of follow-up	Score	(Refs.)
Fukuoka *et al*, 2020	1	1	1	1	2	1	0	1	8	(16)
Cousin *et al*, 2021	1	1	1	1	2	1	0	1	8	(17)
Zhang *et al*, 2022	1	1	1	1	2	1	0	1	8	(18)
Chen *et al*, 2022	1	1	1	1	2	1	1	1	9	(21)
Wang *et al*, 2020	1	1	1	1	2	1	0	1	8	(22)
He *et al*, 2023	1	1	1	1	2	1	0	1	8	(23)
Kim *et al*, 2022	1	1	1	1	2	1	0	1	8	(24)
Li *et al*, 2020	1	1	1	1	2	1	0	1	8	(25)
Ma *et al*, 2023	1	1	1	1	2	1	0	1	8	(26)
Ren *et al*, 2020	1	1	1	1	2	0	0	1	7	(27)
Sun *et al*, 2021	1	1	1	1	2	1	0	1	8	(28)
Xu *et al*, 2022	1	1	1	1	2	1	1	1	9	(29)
Yang *et al*, 2022	1	1	1	1	2	1	0	1	8	(30)
Yu *et al*, 2021	1	1	1	1	2	1	1	1	9	(31)

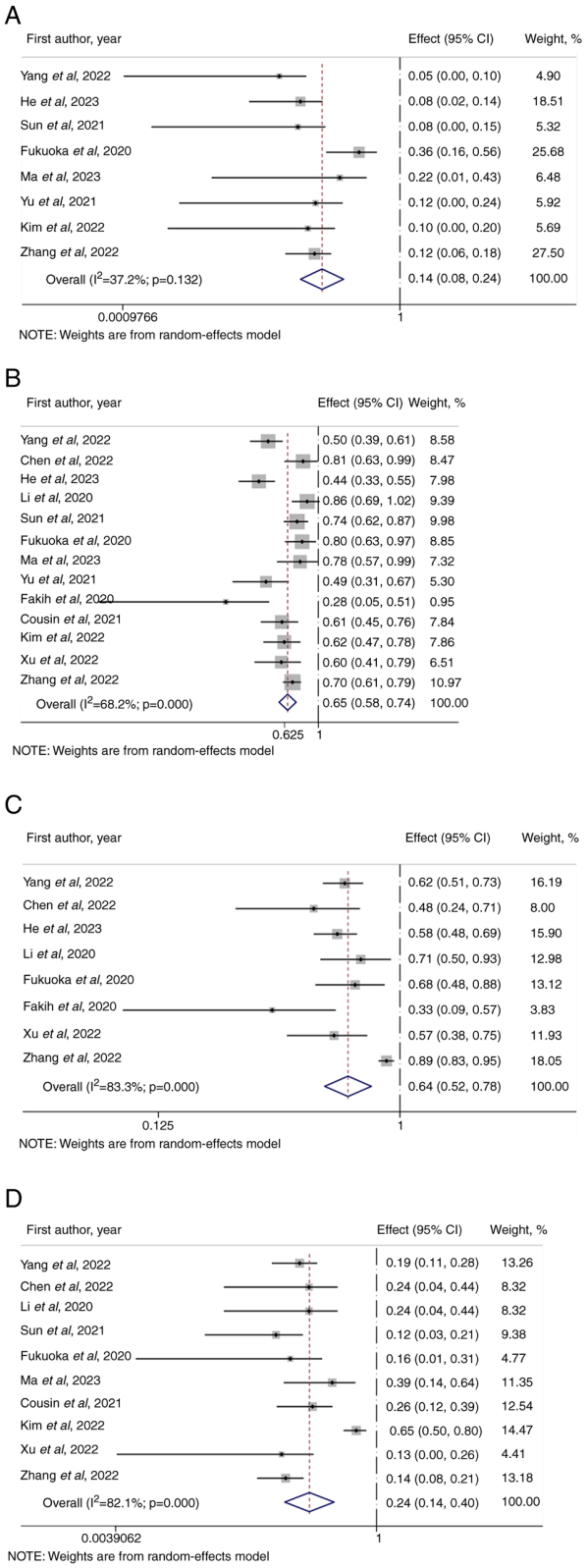

Figure 2. Meta-analyses. Meta-analysis of (A) objective response, (B) disease control and (C) adverse reaction rate, and (D) incidence of grade ≥3 adverse reactions of immune checkpoint inhibitors combined with tyrosine kinase inhibitors in patients with advanced or metastatic metastatic microsatellite stable/mismatch repair proficient colorectal cancer.

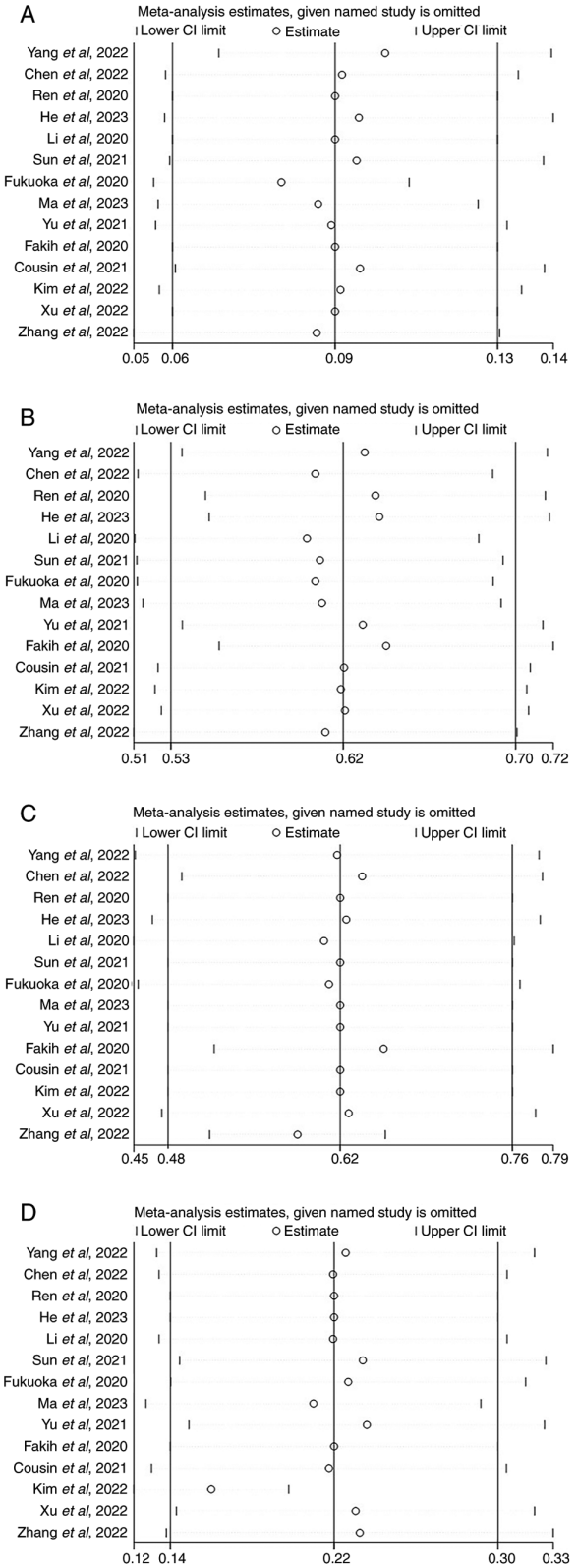

Figure 3. Sensitivity analysis. Sensitivity analysis of (A) objective response, (B) disease control and (C) adverse reaction rate, and (D) incidence of grade ≥3 adverse reactions of immune checkpoint inhibitors combined with tyrosine kinase inhibitors in patients with advanced or metastatic metastatic microsatellite stable/mismatch repair proficient colorectal cancer.

Researchers are investigating combined strategies to reverse the MSS immunosuppressive microenvironment of CRC (12,36), which can lead to benefits from ICI therapy. Clinical study IMblaze 370 reported the combination of atezolizumab (an anti-programmed cell death ligand 1 antibody) and cobiotinib (a mitogen-activated extracellular

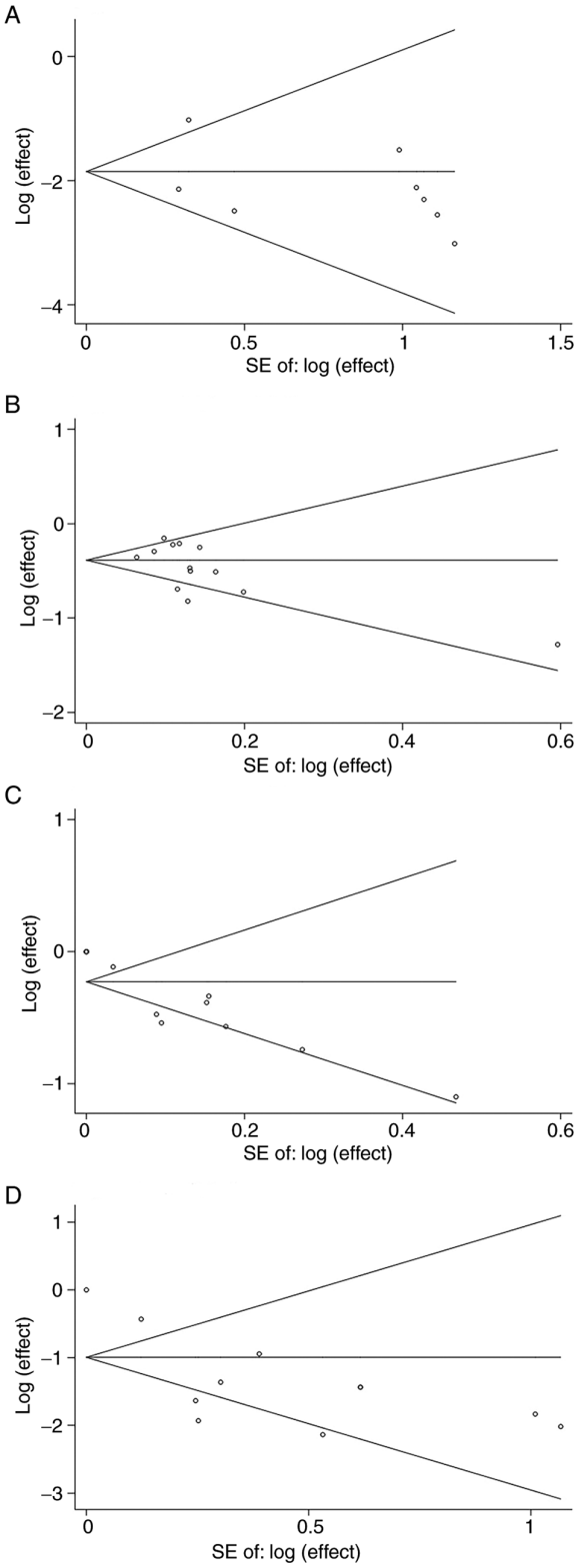

Figure 4. Begg's funnel plots for publication bias test with pseudo 95% confidence limits. (A) objective response, (B) disease control and (C) adverse reaction rate, and (D) incidence of grade ≥3 adverse reactions of immune checkpoint inhibitors combined with tyrosine kinase inhibitors in patients with advanced or metastatic metastatic microsatellite stable/mismatch repair proficient colorectal cancer.

signal-regulated kinase inhibitor), but the results showed that only 3% of patients were effective with this regimen (12). In the study CHECKMATE 142, 1/20 patients diagnosed with MSS/pMMR CRC and treated with a combination of nivolumab and ipilimumab had an objective response (36). Nevertheless, the challenges associated with using ICIs for cancers classified as 'immune rejection' or 'immune desert' cannot be solved by these connected study findings.

There is a need to investigate novel treatment approaches to overcome the immune resistance of MSS/pMMR CRC. Wu *et al* (37) assessed the efficacy of ICIs combined with chemotherapy, anti-VEGF and anti-EGFR in the treatment of pMMR/non-MSI-H mCRC. ICI-based combination therapy was revealed to be promising in the treatment of pMMR/non-MSI-H mCRC with good efficacy and controllable toxicity. Based on this, the present study focused on the therapeutic effect of combining anti-VEGF drugs with ICIs on pMMR/non MSI-H mCRC.

Several studies have demonstrated the potential of combining anti-VEGF therapy with ICIs as a therapeutic approach to address drug resistance in MSS/pMMR CRC (13-15). VEGF promotes angiogenesis, which may result in the proliferation of immune cells that suppress tumor growth, such as regulatory T cells and myeloid-derived suppressor cells. Additionally, VEGF can enhance infiltration of tumor-associated macrophages into the TME (13). Moreover, VEGF has immunosuppressive properties via its ability to hinder the differentiation of progenitor cells derived from $CD4^+$ and $CD8^+$ lymphocytes. Moreover, previous studies have reported that VEGF possesses the ability to augment T-cell exhaustion via the upregulation of several molecules on T cells (14,38). These molecules include cytotoxic T lymphocyte-associated protein 4, PD-1, lymphocyte activation gene 3 and T-cell immunoglobulin and mucin domain-containing protein 3 (38,39). The present study provided a theoretical framework for the combined use of angiogenesis inhibitors and ICIs. In clinical settings, TKIs, such as regorafenib and fruquintinib, are often used as anti-angiogenic pharmaceuticals. These medications have been incorporated into the therapeutic regimen for CRC (28-30). Yang *et al* (30) assessed the combined use of ICIs with regorafenib for treating patients with advanced or metastatic MSS CRC. In terms of ICIs drug selection, 39% of patients used Sintilimab, 20% used nivolumab, and others included: toripalimab (15%), camrelizumab (14%), pembrolizumab (7%) and tislelizumab (4%). The study reported an ORR of 4.9% and a DCR of 50%. Furthermore, Ma *et al* (26) used a combination of toripalimab and fruquintinib, resulting in notable effectiveness: 4/18 patients in the final analysis exhibited partial responses, and 10/18 had stable disease. Nevertheless, further investigation is required to establish the effectiveness and safety of the combined administration of TKIs and ICIs.

The present study aimed to perform a comprehensive review and meta-analysis to assess the efficacy and safety of TKIs used in conjunction with ICIs for individuals diagnosed with advanced or metastatic MSS/pMMR CRC. The study involved integrating analyses with the evaluation of ORR, DCR, incidence of adverse reactions and incidence of grade ≥3 adverse reactions. The findings indicated that combining TKI and ICIs may have a favorable therapeutic outcome and the incidence of grade 3 adverse reactions was satisfactory. Moreover, this is consistent with previous clinical studies in terms of therapeutic effect (16-18), and the therapeutic effect of TKI + ICI combination therapy provides evidential support

for ICIs combined with anti-VEGF therapy for patients with advanced or metastatic MSS/pMMR CRC. In terms of the potential mechanism of the combination therapy, VEGFR and EGFR signaling pathways are related; therefore, the combination of anti-VEGF and ICIs can block several VEGFR- and EGFR-mediated signaling pathways in addition to immunosuppression, thereby inhibiting tumor angiogenesis (25,29). This would circumvent resistance to immunotherapy interventions demonstrated by MSS/pMMR mCRC.

Unlike a previous study (37), the present study explored numerous anti-VEGF drugs in the combination of anti-VEGF and ICI treatment. TKIs combined with ICIs showed satisfactory results and safety, and may be a promising strategy for treatment of pMMR/MSS mCRC. In a study by Fukuoka *et al* (16), when nivolumab and regorafenib were combined, the ORR was 36%, and the incidence of adverse reactions grade >3 was 16%. It was hypothesized that combination of 80 mg regorafenib and nivolumab could increase the antitumor activity with controllable security. Furthermore, Cousin *et al* (17) combined avelumab and regorafenib with a DCR value of <60%, but the incidence of grade 3 adverse reactions was 25.6% and the safety was lower than other combination regimens.

The present study had several limitations. The analysis included a total of 14 studies, excluding individual case reports and ongoing studies, all of which were cohort studies. The selection of subjects, types of drug may have impacted the response of patients to the investigational drug, necessitating a randomized controlled clinical study to mitigate the influence of potential confounding factors. However, the present study used NOS to evaluate the quality of studies; all 14 studies had scores ≥7, indicating the high quality of the studies. Nevertheless, variations in use of TKIs + ICIs across different research studies contributed to the inherent variability.

Regorafenib and fokuntinib are efficacious oral angiogenesis inhibitors; however, regorafenib is a multi-targeted TKI that predominantly exerts its effects on VEGFR2, platelet-derived growth factor receptor and fibroblast growth factor receptor tyrosine kinases (40), whereas fokuntinib is a potent and highly selective VEGFR1/2/3 TKI (41). This suggests that the regulatory mechanism of active binding sites by the two TKIs is distinct. Compared with regorafenib, fruquintinib belongs to a new generation of small molecular TKIs with strong effects. It is highly selective to VEGFR-1, -2 and -3 but has no obvious inhibitory effect on other kinase activity, and it has been reported to maintain target inhibition, minimize toxicity and decrease the incidence of adverse reactions (42,43). Regorafenib targets multiple pathways and can inhibit angiogenesis to a greater extent than fruquintinib and also limit the development of resistance to targeted therapy in tumor cells (44). Therefore, regorafenib may have more notable long-term benefits in combination with ICIs than fruquintinib. In a study by Sun *et al* (28), the therapeutic effects of fruquintinib + ICIs and regorafenib + ICIs were compared. Patients in the fruquintinib group took 3-5 mg oral fruquintinib, whereas patients in the regorafenib group took 80-160 mg oral regorafenib once/day for 21 consecutive days in 28-day cycles. The patients were injected intravenously with PD-1 inhibitors at the recommended dose from the first day of taking molecular targeted drugs: 240 mg toripalimab every 3 weeks; 200 mg nivolumab every 2 weeks and 200 mg sintilimab or camrelizumab every 3 weeks. The study reported that fruquintinib + ICIs had greater short-term survival benefits compared with regorafenib + ICIs, and the c group had a lower incidence of adverse reactions, which is consistent with the present hypothesis. Furthermore, Chen *et al* (21) and Li *et al* (25) reported higher DCRs of 80.9 and 85.7, respectively. In the study by Chen *et al* (21) the TKI used was regenifenib and the ICIs were used according to the recommended doses: 240 mg nivolumab and 200 mg camrelizumab every 2 weeks and 200 mg sinilimab, 240 mg toripalimab, 200 mg pembrolizumab and 200 mg tislelizumab every 3 weeks. Li *et al* (25) used regeorafenib, patients received an anti PD-1 internally starting on day 1 of oral regeorafenib according to its recommended dose response: 240 mg nivolumab every 2 weeks; 200 mg camrelizumab every 2 or 3 weeks and 240 mg toripalimab and 200 mg pembrolizumab and sinilimab every 3 weeks. Wang *et al* (22) did not observe any grade ≥3 adverse reactions with the TKI regorafenib and ICIs nivolumab or pembrolizumab. The aforementioned results indicated that when the TKI drugs used are consistent, different ICIs impact on the efficacy and safety of combination therapy. However, due to differences in administration time, dosage, subject population, and ICIs regimen of regorafenib and fruquintinib in the included studies, the present study did not perform subgroup analyses to further assess the best treatment plan of TKI combined with ICIs.

In conclusion, although the present study had limitations, the systematic review and meta-analysis findings suggested that the combination of immunosuppressants and TKIs exhibited favorable effectiveness and notable safety profiles when used in the management of patients with advanced or metastatic MSS/pMMR CRC. To validate these findings, it is imperative to perform rigorous prospective research and randomized controlled trials in future. These studies should investigate the optimal regimen and dose of TKI + ICIs, potential biomarkers for patient selection, identification of predictive biomarkers and the development of tailored treatments for different subtypes of MSS/pMMR CRC.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

JL and YXZ conceived and designed the study. SQL, YXZ and JXZ collected data and performed the database search. JL and YXZ performed statistical analysis. JL, SQL, YXZ and JXZ drafted the manuscript. JL and SQL confirm the authenticity

of all the raw data. All authors revised the manuscript. All authors have read and approved the final 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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