Original Article

The prognostic role of neutrophil-to-lymphocyte ratio and C-reactive protein in metastatic colorectal cancer using regorafenib: a systematic review and meta-analysis

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Background: The application of regorafenib has changed the landscape of subsequent-line treatment in metastatic colorectal cancer (mCRC). Baseline neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP), as two of the most common inflammatory factors, are suggested to be potential prognostic factors for mCRC patients treated with regorafenib, but the results are conflicting. In this study, we conducted a meta-analysis to evaluate the prognostic role of NLR and CRP in mCRC patients treated with regorafenib.

Methods: We searched online databases such as Embase, PubMed, and the Cochrane library up to April 2022, without language limitation, to identify clinical studies evaluating the prognostic role of NLR or CRP in regorafenib treated mCRC patients. The main endpoints were hazard ratio (HR) of overall survival (OS) and progression-free survival (PFS). The associations between NLR, CRP, and the above endpoints were extracted. Review Manager 5.4 was used to conduct the combined analysis. The Newcastle-Ottawa Scale (NOS) was applied for assessing the quality of included studies. Heterogeneity was detected by chi-square-based Q test and I^2 statistic, and publication bias was evaluated by funnel plot asymmetry and Egger's test.

Results: Eight studies involving 1,287 cases were included, with 5 reporting survival outcomes based on NLR level and 4 reporting survival according to CRP level. The results of meta-analysis showed that the calculated HR of OS for subsequent-line regorafenib in mCRC patients with high versus low NLR was 2.52 [I^2=52%, 95% confidence interval (CI): 1.75–3.64; P<0.00001]. The combined HR of PFS with high versus low baseline NLR was 2.11 (I^2=12%, 95% CI: 1.80–2.48; P<0.00001). For patients with a high level of CRP, the OS was significantly shorter when compared with patients with a low level of CRP (I^2=0%, HR =1.88; 95% CI: 1.55–2.29; P<0.00001).

Conclusions: High level of NLR could be associated with OS in mCRC patients treated with regorafenib. It is suggested that the impact of regorafenib on OS may vary according to the baseline NLR.

Keywords: Regorafenib; colorectal cancer (CRC); neutrophil-to-lymphocyte ratio (NLR); C-reactive protein (CRP); biomarker

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Introduction

Colorectal cancer (CRC) is one of the most common colorectal malignancies. The incidence of CRC is increasing yearly (1), and it has poor survival outcomes (2). Currently, the main treatment strategy for CRC is surgery (3-6) with curative intention. However, due to the insidious symptoms of CRC, around 20% of patients are diagnosed with distant metastases, thus losing the opportunity to undergo complete resection of localized disease and/or distant metastases (7). Even for patients who receive surgical resection, it is reported that almost half will present with metastases (7,8).

Currently, the most common treatment regimen for CRC patients with distant metastases is fluorouracil-based systemic chemotherapy combined with anti-vascular targeted therapy (9). Although the short-term outcomes are satisfactory, most patients will develop resistance (10). Regorafenib, a new targeted agent, has shown acceptable toxicity and remarkable efficacy in metastatic CRC (mCRC) patients who are resistant to fluorouracil combined with platinum or irinotecan treatments (11-14). Thus, in recent years, regorafenib has been approved for clinical application in mCRC patients in China (12,15). With increasing clinical use of regorafenib, determining potential biomarkers to assist with effective application of regorafenib in these patients is needed.

A number of retrospective studies focusing on the identification of predictors of regorafenib efficacy have been undertaken (16-20). As previously reported, numerous factors affect tumor prognosis, tumorigenesis, and progression, and inflammatory response plays a vital role in these processes (21,22). Various inflammatory cells and inflammatory factors play different roles in tumor progression (22). Neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) are factors associated with inflammation. Previous studies have reported that baseline NRL and CRP are potential prognostic factors for long-term prognosis of patients with solid cancers (23-26). However, their prognostic values are controversial. A study by Marshall *et al.* evaluated the clinical factors which predict prognosis in HER2-positive gastric cancer who received trastuzumab based chemotherapy (27). The results showed that NLR [hazard ratio (HR) =0.55, 95% confidence interval (CI): 0.29–1.06, P=0.074] was not significant (27). Other studies also suggested a non-significant connection between NLR and overall survival (OS) (28), and CRP and OS (29). It is also not well determined whether NLR (30) or CRP could serve as prognostic factors in mCRC patients treated with regorafenib. In 2015, a study by Del Prete *et al.* assessed the impact on survival of NLR in mCRC patients receiving regorafenib monotherapy (31). They reported that high NLR was related to worse OS (HR =1.70, 95% CI: 1.08–2.68, P=0.024) (31). Later, other studies found similar results in these patients (14,32). However, the study by Watanabe *et al.* found that NLR was not significantly associated with OS (30). One of the major reasons for this conflicting finding may be the sample size. In addition, there is no meta-analysis-based evidence to assess the prognostic role of NLR or CRP in regorafenib treated mCRC patients. Therefore, in this study, we employed meta-analysis to investigate the value of baseline NLR and CRP in long-term prognosis of patients with mCRC. We present the following article in accordance with the MOOSE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-683/rc).

Methods

We searched Chinese and English-language databases, including PubMed, Embase, Cochrane Library, Wanfang, and Chinese National Knowledge Infrastructure for relevant studies published up to April 2022. The main search terms were: colorectal carcinoma, NLR, CRP, and regorafenib. To ensure potential studies were not omitted, reference lists of the included articles were searched manually and relevant reviews were further screened.

Inclusion and exclusion criteria

Inclusion criteria

Patient: patients with pathologically confirmed CRC, and were diagnosed with metastatic disease by tumor/node/metastasis (TNM) staging method. Treatments: patients received regorafenib treatment. Comparisons: baseline NLR or CRP values were presented, and survival benefits of these patients were compared based on NLR or CRP levels. Outcomes: OS and/or progression-free survival (PFS) were reported as the outcome indicators. HR and its 95% CI of OS and/or PFS based on NLR or CRP were reported. There were adequate criteria for defining high and low NLR and CRP in the included studies. Study types were not only limited to cohort or case-control studies, but also other types were included if they met the above criteria.

Exclusion criteria

(I) Reviews, animal cell experiments, conference abstracts

that could not provide sufficient information for inclusion, and articles without the full text available; (II) patients did not receive regorafenib treatment; and (III) multiple reports from the same clinical trial and regarded as the same study.

Data extraction and quality assessment

Two researchers independently screened the literature and extracted data. When there was a disagreement, consensus was reached by discussion. The following information was extracted from the final included studies: first author, publication time, region, study type, treatment modality, sample size, general information of patients, NLR and its cutoff value, CRP and its cutoff value, OS, PFS, and HR of OS and PFS based on NLR and CRP. For study reporting survival outcomes of patients with trifluridine/tipiracil or regorafenib treatments, only the regorafenib related data was extracted.

No included studies were randomized controlled trials (RCTs). For non-RCT studies, the risk of bias of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (33). Out of a maximum possible score of 9, the NOS scores of 7 or higher were considered as high-quality studies. The main limitations lowering the overall quality of the included studies were two aspects: loss to follow-up rate and comparable on confounders.

Statistical analysis

Statistical analysis was performed using Review Manager 5.4 software. HR and 95% CI were obtained from the included studies, and HR values were combined using the Mantel-Haenszel method. HR >1 indicated that NLR was associated with poor prognosis in mCRC. The HR values from the multiple Cox regression analysis were preferred and used as the first option. The data from univariate analysis was also in an additional analysis if sufficient. Heterogeneity was assessed using the I^2 statistic, with $I^2 \geq 50\%$ and $P<0.1$ indicating significant heterogeneity between studies, in which case the random-effects model was used. Otherwise, a fixed-effect model was used. Funnel plot analysis and Egger's test were used to assess risk of publication bias. Subgroup and sensitivity analyses were performed if the heterogeneity caused by baseline characteristics was significant. $P<0.05$ was considered statistically significant.

Results

Literature search results and quality evaluation

A total of 244 articles were retrieved by searching the above databases, and 3 articles were retrieved by manual search of citations, including 216 studies in English and 31 in Chinese. A total of 125 duplicate reports were excluded by Endnote software, and a further 73 articles were excluded after reading the title and abstract. A further 41 articles were excluded after checking the full text. The 3 references retrieved by citation were excluded because they were all from the same clinical trial and did not report detailed data on outcome indicators. Finally, 8 studies (14,30,31,34-38) with a total of 1,287 patients were included in the meta-analysis (*Table 1*). The NOS scores of the included studies were all ≥7 (*Table 2*), indicating that the quality of the studies was good. The study selection process is presented in *Figure 1*. reported the relationship between CRP and OS. The included studies used the receiver operating characteristics curve analysis or upper normal level to determine cut-off values for NLR and CRP. Patients received regorafenib monotherapy, regorafenib in combination with chemotherapy, and regorafenib plus immune checkpoint inhibitors (*Table 1*).

Meta-analysis results

NLR and survival

Five studies reported the association of NLR and OS benefit in mCRC patients after regorafenib treatment, and only 3 studies presented the HR of OS based on NLR. The study of Watanabe *et al.* reported the result based on continuous variable, and was not included in the analysis (30). As reported in their study, the HR was less than one without statistically significance (HR =0.99, P=0.80) (30). For the rest studies, there was significant heterogeneity between the included studies (I^2=52%, P=0.15), and a random-effect model was used (*Figure 2A*). Meta-analysis result based on univariate analyses showed that the high baseline NLR group was associated with poor OS in mCRC (HR =2.52, 95% CI: 1.75–3.64, P<0.00001).

The impact of NLR on PFS in mCRC patients treated with regorafenib was assessed in 4 studies. As indicated by the heterogeneity test, the risk of heterogeneity was considered low (I^2=12%, P=0.32 for pooled HR under

Table 1 Baseline characteristics of included studies

Author	Year	Study type	Number	Region	Sex (male)	Age (years)	Cancer details	Treatment strategy	Treatment details	Line of treatment	NLR cutoff value	CRP cutoff value (mg/L)	Outcomes
Del Prete M	2015	Retrospective	208	Europe	103 (50%)	61	Pretreated colorectal cancer	Regorafenib	Regorafenib monotherapy, 160 mg/d	≥2	0.381	NR	OS, PFS, ORR, DCR, prognostic factors
Moriwaki T	2018	Retrospective	212	Asia	323 (59%)	64	Metastatic colorectal cancer	Regorafenib versus trifluridine/tipiracil	Regorafenib	≥2	NR	NR	OS, PFS, ORR, DCR, prognostic factors
Moriwaki T	2020	Retrospective	489	Asia	291 (60%)	64	Metastatic colorectal cancer	Regorafenib versus trifluridine/tipiracil	Regorafenib	≥2	NR	1	OS, prognostic factors
Chida K	2021	Retrospective	550	Asia	323 (59%)	64	Metastatic colorectal cancer	Regorafenib versus trifluridine/tipiracil	Regorafenib and trifluridine/tipiracil	≥2	NR	1	OS, prognostic factors
Su YL	2021	Retrospective	356	Asia	210 (59%)	60	Metastatic colorectal cancer	Regorafenib	Regorafenib monotherapy, 160 mg/d	≥2	4	NR	OS, prognostic factors
Watanabe D	2021	Retrospective	60	Asia	34 (57%)	66	Metastatic colorectal cancer	Later-line chemotherapy with regorafenib	Later-line chemotherapy with regorafenib	≥2	NA	NA	OS, PFS, ORR, DCR, safety, prognostic factors
Yang K	2022	Retrospective	48	Asia	50 (60%)	63	Advanced or metastatic microsatellite stable colorectal cancer	Regorafenib combined with immune checkpoint inhibitors	Regorafenib combined with immune checkpoint inhibitors	≥2	2	NR	OS, PFS, ORR, DCR, safety, prognostic factors
Erdoğan AP	2022	Retrospective	65	Europe	34 (52%)	NR	Metastatic colorectal cancer	Regorafenib	Regorafenib	≥2	5.87	5	OS, PFS, prognostic factors

NLR, neutrophil-lymphocyte ratio; CRP, C-reactive protein; OS, overall survival; PFS, progression-free survival; ORR, objective response rate; DCR, disease control rate; NR, not reported; NA, not applicable.

Table 2 Quality assessment of included studies using the Newcastle-Ottawa Scale

Author	Year	Selection				Comparability	Outcome			Score
		A	B	C	D	E	F	G	H	
Del Prete M	2015	☆	☆	☆	☆	☆	☆	☆	–	7
Moriwaki T	2018	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Moriwaki T	2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Chida K	2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Su YL	2021	☆	☆	☆	☆	☆	☆	☆	☆	8
Watanabe D	2021	☆	☆	☆	☆	☆	☆	☆	☆	8
Yang K	2022	☆	☆	☆	☆	☆	☆	☆	☆	8
Erdoğan AP	2022	☆	☆	☆	☆	☆	☆	☆	☆	8

"Selection" includes: A, representativeness of cases; B, selection of controls; C, exposure ascertainment; D, no death when investigation began. "Comparability" includes: E, comparable on confounders. "Outcome" includes: F, outcome assessment; G, adequate follow-up; H, loss to follow-up rate. The total score is equal to the total number of stars.

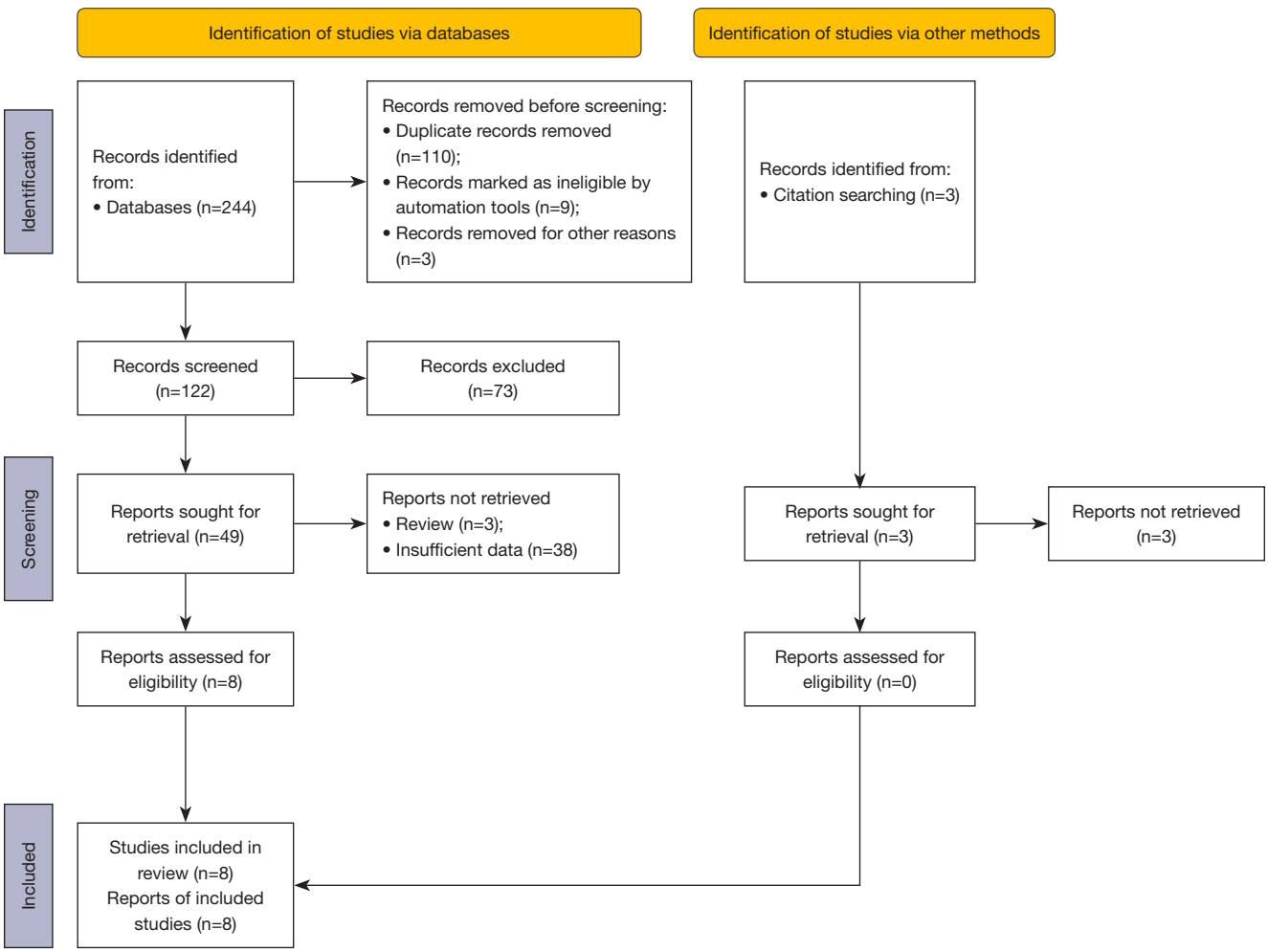

Figure 1 Flow chart of the systematic search and study selection process.

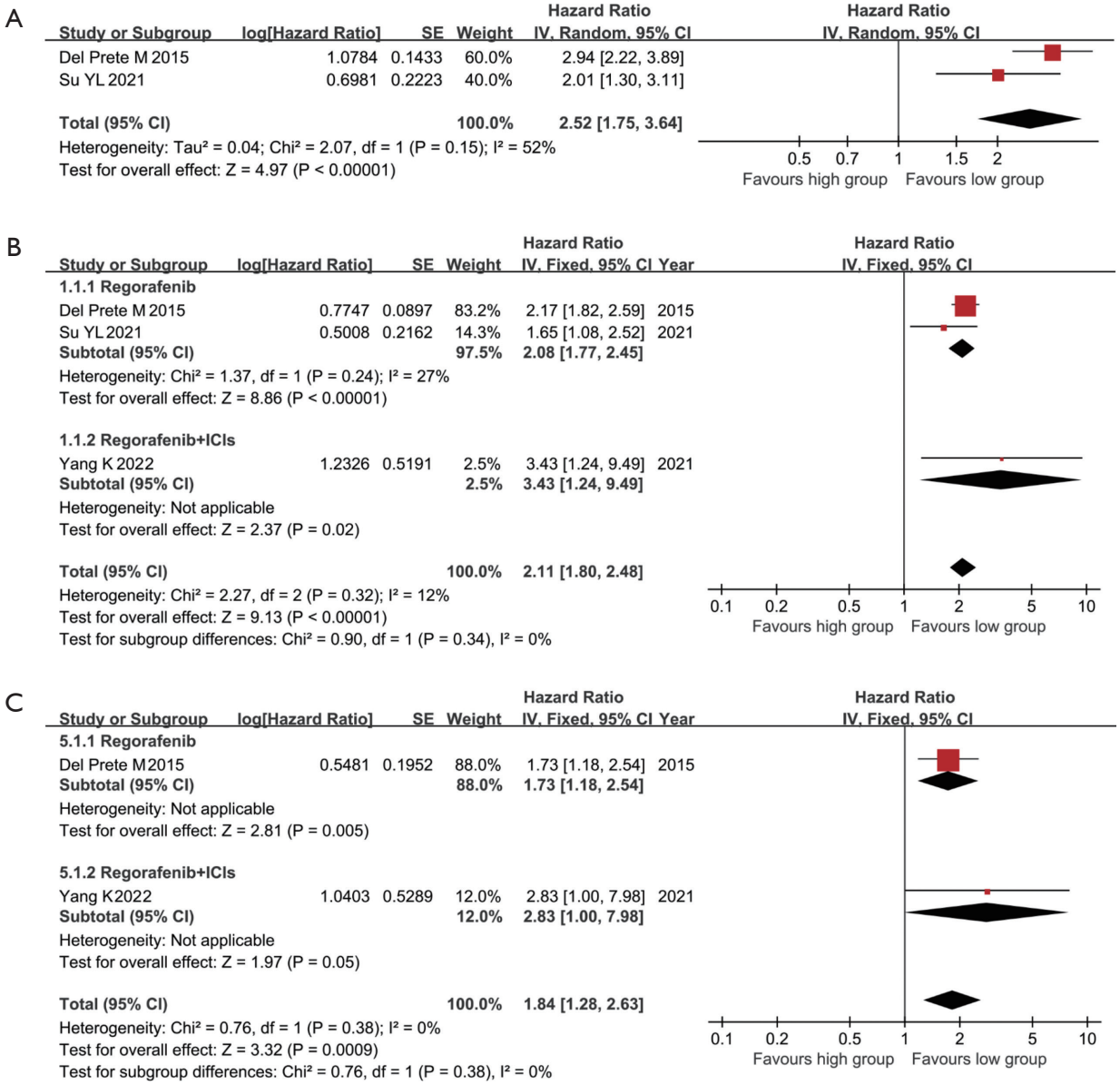

Figure 2 Association between baseline NLR and survival outcomes in mCRC patients treated with regorafenib. (A) The association between OS and NLR based on univariate analysis. (B) The association between PFS and NLR based on univariate analysis. (C) The association between PFS and NLR based on multivariate analysis. CI, confidence interval; mCRC, metastatic colorectal cancer; NLR, neutrophil-to-lymphocyte ratio; OS, overall survival; PFS, progression-free survival; SE, standard error.

univariate analysis; I^2=0%, P=0.38 for pooled HR under multivariate analysis), and thus the fixed-effect model was applied (*Figure 2B,2C*). The combined results showed that patients with high NLR were at a higher risk of disease progression compared to those with low NLR (univariate analysis: HR =2.11, 95% CI: 1.80–2.48, P<0.01; multivariate analysis: HR =1.84, 95% CI: 1.28–2.63, P=0.0009).

CRP and survival

Only 3 studies reported data about the relationship between CRP level and survival in mCRC patients with a treatment history of regorafenib. As there was a study (30) analyzed the impact of continuous CRP on OS, we separately presented the result. A negative association (HR =1.22, P=0.0001) between OS and CRP was observed (30). For

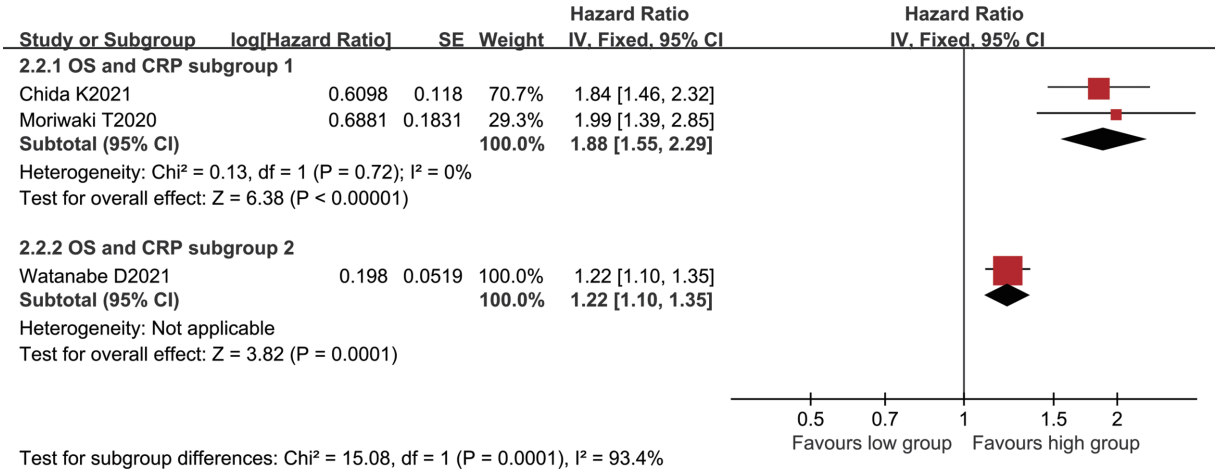

Figure 3 Association between baseline CRP and OS in mCRC patients treated with regorafenib. CI, confidence interval; CRP, C-reactive protein; mCRC, metastatic colorectal cancer; OS, overall survival; SE, standard error.

the other two studies, the heterogeneity test found that there was significant heterogeneity between the included studies (I^2=0%, P=0.72), and a fixed-effects model was used (*Figure 3*). Meta-analysis results showed that the OS of the high CRP group was shorter than that of the low CRP group (HR =1.88, 95% CI: 1.55–2.29, P<0.00001).

Subgroup analysis

For PFS and NLR, we performed a subgroup analysis according to treatment (*Figure 2B,2C*). The results showed that for patients treated with regorafenib, high baseline NLR was associated with higher risk of progression (univariate analysis: HR =2.08, 95% CI: 1.77–2.45, P<0.00001; multivariate analysis: HR =1.73, 95% CI: 1.18–2.54, P=0.005). For patients treated with regorafenib plus immunotherapy regimen, the high NLR group had an increased risk of progression compared with those with low NLR (univariate analysis: HR =3.43, 95% CI: 1.24–9.49, P=0.02; multivariate analysis: HR =2.83, 95% CI: 1.00–7.98, P=0.05).

Publication bias

Funnel plot analysis was used to assess publication bias for OS and PFS. The funnel plots of the included studies showed an asymmetric distribution, indicating low risk of publication bias (*Figure 4*). Furthermore, we did the Egger's test and Begg's test to evaluate the publication bias, and the results showed negative findings (Begg's test for OS, P=0.32; Egger's test for PFS, P=0.95).

Discussion

In recent years, regorafenib has been an important option for the treatment of mCRC, but little is known about potential predictors of regorafenib efficacy. In the present study, we assessed the prognostic value of baseline NLR and CRP in patients with mCRC treated with regorafenib. The results showed that a high level of NLR at baseline was associated with poor OS and PFS. Elevated CRP at baseline was also associated with poor OS. Further subgroup analysis also showed that the predictive effect of NLR was independent of treatment regimen.

NLR has been shown to be predictive of efficacy in a variety of solid tumors receiving different treatment modalities (39). High NLR is usually associated with poor prognosis (39). The findings in this study were consistent with these results. However, there is still disagreement over how the threshold value of NLR is defined. Common methods of obtaining cut-off values include the use of median values and the use of subject workup curves for diagnostic experiments. In this study, the value of NLR was obtained at baseline, but the cut-off values for NLR varied among studies, which may have influenced the predictive value of NLR.

In terms of CRP in evaluating the prognosis of cancer patients undergoing antitumor treatments, several studies

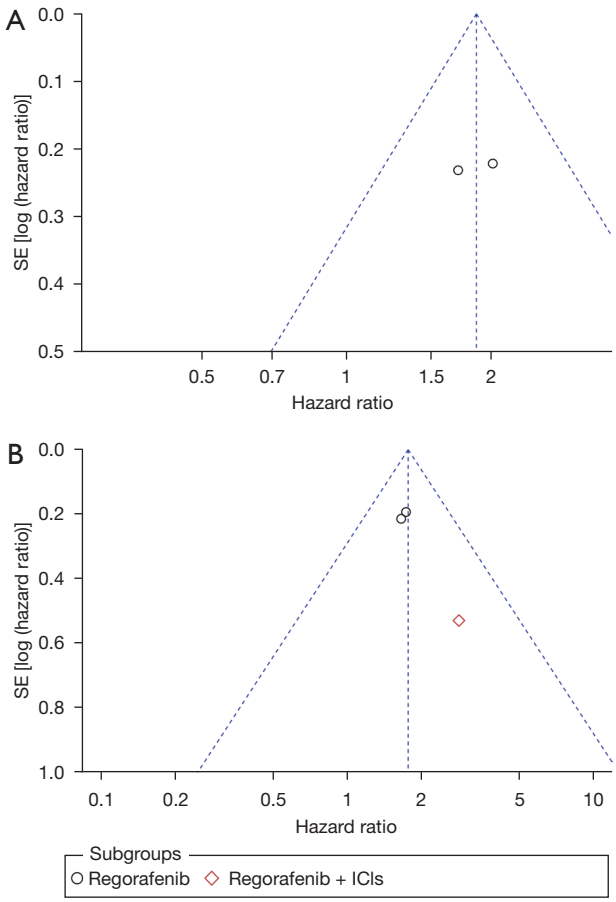

Figure 4 Funnel plot analysis for detecting publication bias. SE, standard error; ICIs, immune checkpoint inhibitors.

have found similar findings (40,41). One meta-analysis investigating the relationship between CRP and prognosis in cancer patients found that increased serum CRP level was associated with 1.48 times the risk of death (42). Another study evaluated the relationship between CRP and postoperative prognosis in 470 gastric cancer patients (43). The study assessed the association between postoperative CRP levels and gastric cancer survival, with the results showing that the mortality rate from relapse of cancer in the high postoperative CRP group was significantly higher than that of the group with low postoperative CRP. Our study showed that increased CRP was correlated with worse OS in patients with mCRC, and patients with low CRP who received regorafenib had a better survival benefit than those with high CRP. However, the optimal cut-off value of this biomarker was also varied across studies. How the cut-off value is obtained remains an important issue and limits the clinical application of these factors.

The included studies in this study were considered high-quality, were comparable in terms of patient age and performance status scores, and had good coherence in terms of outcome indicators, resulting in a low risk of bias. However, this meta-analysis included only 8 studies, which may have influenced our results. The limitations of this study were as follows: (I) the included studies were retrospective and the quantity was limited, which may have introduced bias; (II) differences in previous treatment history may have been the main factor contributing to the heterogeneity of the CRP analysis; (III) although baseline NLR and CRP were obtained, the cut-off values were not consistent across studies. Therefore, more well-designed studies are needed to validate these findings.

In conclusion, NLR and CRP may be potential prognostic indicators for evaluating efficacy of regorafenib in mCRC patients, with the advantage that they are cheap and feasible. It is suggested that the impact of regorafenib on OS may vary according to the baseline NLR.

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Footnote

Reporting Checklist: The authors have completed the MOOSE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-683/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-683/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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