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Review

Effects of Circulating 25(OH)D Status in Advanced Colorectal Cancer Patients Undergoing Chemotherapy: A Systematic Review

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Abstract. *Background/Aim: Colorectal cancer (CRC) is a disease of poor prognosis. An advantageous connection between vitamin D supplementation and prognostic improvement was depicted in CRC patients. However, the effects of circulating vitamin D on cancer outcomes are unclear for advanced CRC patients, especially for those receiving chemotherapy. Materials and Methods: The review was registered on PROSPERO (register number: CRD42021243547). PUBMED, EMBASE, Cochrane Library, and Web of Science were searched for English-language publications using relevant keywords. Two reviewers independently selected articles, assessed quality, and extracted data. We applied RevMan5.4 and Stata14 for meta-analysis. Results: We included an RCT and three prospective cohort studies, which were of high overall quality. Higher circulating 25(OH)D level was related with better disease outcomes in advanced CRC patients undergoing chemotherapy: progression-free survival (HR=0.85, 95% CI=0.71-0.99; I^2=34.4%), overall survival (OR=0.56, 95% CI=0.38-0.82; I^2=0%). Conclusion: High circulating 25(OH)D content is beneficial for improving prognosis of advanced CRC receiving chemotherapy.*

Colorectal cancer (CRC) is the third most wide-ranging cancer globally, with the second-highest mortality rate (1). Its global disease burden is predicted to rise more than 2.2 million new cases and 1.1 million deaths by 2030 (2). Among patients with CRC, less than half of patients could be diagnosed at an early stage, and the survival rates decline to 14% for metastatic CRC (3). Standard therapy for CRC includes surgery, radiotherapy, and adjuvant therapy with anticancer drugs (4). Chemotherapy is a primary therapeutic strategy for advanced or metastatic CRC patients (5, 6).

Vitamin D has been demonstrated to inhibit cancer cell progression (7). Recent studies have shown that vitamin D supplementation increased progression-free survival (PFS) in CRC patients under chemotherapy regimens, even in an advanced status (8-10). Moreover, accumulating evidence has depicted that vitamin D, when used with chemotherapy, increased the effect of antineoplastic drugs such as gemcitabine (11), cisplatin (11), and doxorubicin (12). Similarly, calcitriol has been found to reduce inflammation and retard tissue damage following 5-fluorouracil (5-FU) infusion (13) and to be beneficial to good health *via* enhancing the protective effects of the innate immune response (14), especially for older patients with cancer (14). A higher level of vitamin D has been suggested to improve response to neoadjuvant treatment (15). In addition, vitamin D plays a meaningful role in decreasing chemotherapy-induced intestinal mucositis (16). Also, patients with adequate vitamin D concentration were more likely to complete the whole chemotherapy process (17). However, CRC patients tend to be diagnosed with vitamin D deficiency (8, 18-20). The study demonstrated an exceptionally high rate of vitamin D deficiency in advanced CRC (3). Meanwhile, chemotherapy has been related to increase in vitamin D deficiency risk (21).

Several studies have shown a relationship between higher circulating vitamin D levels and better prognosis among CRC patients (19, 22-25). However, the effects of vitamin D on cancer progression and survival are still unclear for advanced CRC patients, as well as for CRC patients undergoing chemotherapy. Hence, we conducted a systematic review to explore the potential impact of high circulating

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Key Words: Advanced colorectal cancer, chemotherapy, 25-hydroxyvitamin D, progression-free survival, overall survival, review.

25(OH)D levels on the prognosis of advanced CRC patients receiving chemotherapy treatment.

Materials and Methods

We performed this systemic review according to the Preferred Reporting Items of Systematic reviews and Meta-Analyses (PRISMA) guidelines (26). The study was registered on PROSPERO (register number: CRD42021243547) in March 2021, after the initial literature search. Moreover, we updated the literature search in June 2021.

Search strategy. We implemented a thorough literature search in PUBMED, EMBASE, Web of Science, and Cochrane Library initially in Match 2021 and then updated in June 2021. We used an appropriate search strategy that combined Medical Subject Heading terms and text words. Additionally, references from the selected literature were screened for potentially included studies.

Eligibility and exclusion criteria. *Inclusion criteria:* (i) research participants to be advanced or metastatic CRC patients undergoing any chemotherapy; (ii) circulating vitamin D levels [25(OH)D] as exposure; (iii) CRC survival as outcome; (iv) observational or interventional studies; (v) at least one year of follow-up; (vi) adult participants; (vii) odd ratios (OR), risk ratios (RR) or hazard ratios (HR) and their respective 95% confidence intervals (CIs) as a measure of effect estimators; (viii) published in English.

Exclusion criteria: (i) no use of a standard and precise method to measure circulating vitamin D level; (ii) no report of any advanced or metastatic CRC outcomes; (iii) reviews, case reports, conference abstracts, letters, comments, or other types of publications that did not report complete data.

Study selection. Two reviewers (XFZ and LYZ) independently assessed the titles and abstracts of all publications to confirm possible relevant studies. Then, full-text censoring was conducted when either reviewer considered that the article needed further exploration. In case of a discrepancy, an additional rater was consulted (XLH).

Data extraction. Two reviewers (XFZ and LYZ) independently extracted the following information from the included studies: the basic information of literature (author, publication year, country), study design, follow-up duration, study size, patient characteristics (cancer type, age), chemotherapy content, circulating 25(OH)D concentration, PFS and overall survival (OS). In case of a discrepancy, an additional rater was consulted (XLH).

Quality assessment. Two reviewers (XFZ and LYZ) independently assessed the quality of prospective cohort studies using the Newcastle-Ottawa Scale (NOS) (18) and RCTs by the Cochrane risk of bias tool. Disagreement was resolved by the third reviewer (XLH). The NOS has a range of 0-9 points, with ≥7 points seen as high quality, 4-6 points as moderate quality, and <4 as low quality. For RCTs, we evaluated the production of random sequence; concealment for allocation sequence; blinding of participants, conductors, collectors, and reviewers; missing outcome data (we defined a low risk of bias if the rate of lost data was less than 10%); and other possible sources of bias. Any RCT with a large proportion of lost elements (>50%) would be excluded from the quantitative assessment because of the high risk of bias. Since our included studies<10, we did not apply a funnel plot to observe publication bias.

We applied the GRADE system to appraise our meta-analysis outcomes (27, 28). Evidence was upgraded by one level from "low quality" for "moderate quality" (or by two levels for "high quality"): significant effect, plausible confounding would not change the effect and dose-response gradient. Two reviewers (XFZ and LYZ) independently assessed outcomes and used the GRADE profiler to create "Summary of findings" tables. In case of a discrepancy, an additional rater was consulted (XLH).

Data analysis. We used RevMan5.4 and Stata14 software to perform the meta-analysis. We obtained a pooled OR and 95% CI using a fixed-effects model for dichotomous outcomes. Moreover, subgroup analyses were implemented based on country or location.

The Mantel–Haenszel chi-square test, with significance set at $p<0.1$, and the I^2 statistic was used to evaluate heterogeneity between included studies. I^2 values greater than 25% were considered as low heterogeneity, 50% as moderate, and 75% as high heterogeneity (29). Sensitivity analysis was performed by excluding each included study, one at a time.

Results

Selected studies. The initial search results showed 1,451 records; after duplications were removed, there were 1,191 records remained. After we screened the titles and abstracts of the 1,191 records, 1,163 irrelevant articles were excluded. We included 28 articles for full-text assessment. Twenty-three publications were excluded for various reasons. As a result, 5 studies (3, 8, 18, 30, 31) were included in the systematic review and four studies (3, 8, 18, 31) in the meta-analysis. The details of study selection and reasons for exclusion are depicted in Figure 1. There were no additional eligible studies produced through our review of the references.

Study and patient characteristics. The critical characteristics of included studies are summarized in Table I. Most of the studies were from North America. Included studies were 2 RCTs and 3 prospective cohort studies. The study samples varied from 71 to 416, with a total of 968 participants. The follow-up time was more than or close to 2 years. All patients that were included received chemotherapy.

In the SUNSHINE trial (8), 70% of advanced CRC patients initially had an inadequate circulating 25(OH)D level. However, 4000 IU/day supplementation increased median 25(OH)D from 16.1 to 34.8 ng/ml with a growing PFS from 11.0 to 13.0 months in advanced patients (HR=0.64; 95% CI=0-0.90). Golubic *et al*. (30) reported no function of vitamin D supplementation on reducing negative outcomes in stage IV patients (2,000 IU/day for 46 months; survival HR=1.01; 95% CI=0.39-2.61). Yuan *et al*. (3) found that, compared to patients with lower 25(OH)D levels (<10.8 ng/ml), patients with higher levels (>24.1 ng/ml) had an HR of 0.66 (95% CI=0.53-0.83) for OS and 0.81 (95% CI=0.66-1.00) for PFS.

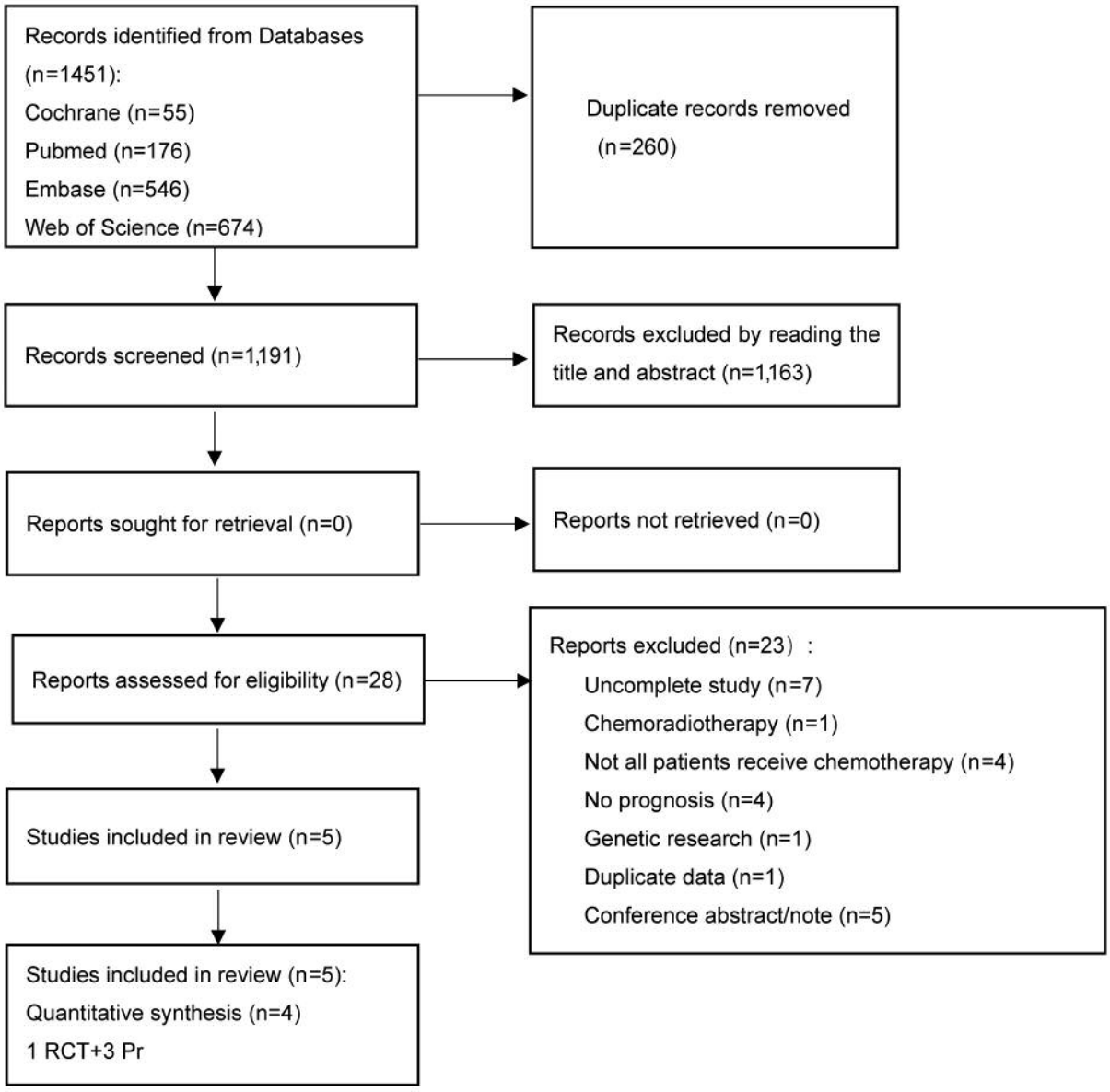

Figure 1. *Flowchart depicting the process of study selection and reasons for exclusions.*

Abrahamsson *et al*. (31) found that among the T4 CRC patients, those with circulating 25(OH)D level <50 nmol/l presented higher risk of cancer advancement (PFS: HR=3.09; 95% CI=1.01-9.45) than those with 25(OH)D level >50 nmol/l. Ng *et al*. (18) found that baseline plasma 25(OH)D levels did not affect CRC patient outcomes.

Circulating 25(OH)D assessment. In the SUNSHINE trial (8), Yuan *et al*. (3) study and Ng *et al*. (18) study, 25(OH)D concentrations were measured by radio-immunoassay. For the SUNSHINE trial (8), median 25(OH)D content in the intervention group was 34.9 ng/ml (range=24.9-44.7), and in the control group was 18.7 ng/ml (range=13.9-23.0). Regarding the Yuan *et al*. (3) study, patients in the high grade (>24.1 ng/ml) were defined as the experimental group and lower degree of 25(OH)D (<10.8 ng/ml) as the control group. Similarly, in Ng *et al*. study (18), >27.1 ng/ml was defined as the experimental group, and <13.2 ng/ml as the control group. In the study by Abrahamsson *et al*. (31), 25(OH)D was measured based on liquid chromatography-mass spectrometry; >20 ng/ml was defined as the experimental group, and <20 ng/ml as the control group. In the study of Golubic *et al*., the

Table I. *Study and patient characteristics.*

Authors, year (ref)	Country	Study design	Follow-up	Population characteristics		Chemotherapy
				Males, n (%)	Age, years (mean, range)	
Golubić *et al*., 2018 (30)	Croatia	RCT	46 m	71 (51%)	Metastatic, 69 (24-79)	FOLFIRI/ oxaliplatinum/5-FU
Yuan *et al*., 2019 (3)	North America	Prospective cohort	5.6 y	416 (52%)	Advanced/ metastatic, 59	mFOLFOX6/ FOLFIRI
Abrahamsson *et al*., 2019 (31)	Norway	Prospective cohort	74.5 m	84 (60%)	T2-T4CRC, 58.5 (30-73)	FLOX+oxaliplatin+ capecitabine
Ng *et al*., 2011 (18)	North America	Prospective cohort	5.1 y	258 (59%)	IV stage, 61 (26-85)	IFL/FOLFOX/IROX
Ng *et al*., 2019 (8)	USA	RCT	22.9 m	139 (57%)	Metastatic, 56	mFOLFOX6+ bevacizumab

RCT: Randomized controlled trial; m: months; y: years; FOLFIRI: leucovorin, fluorouracil, and irinotecan; 5-FU: 5-fluorouracil; mFOLFOX6: leucovorin, fluorouracil, and oxaliplatin; CRC: colorectal cancer; FLOX: oxaliplatin, 5-fluorouracil and folic acid; IFL: fluorouracil, leucovorin, and irinotecan; FOLFOX: fluorouracil, leucovorin and oxaliplatin; IROX: irinotecan and oxaliplatin.

Table II. *The quality of the three prospective cohort studies.*

Authors, year (ref)	Selection				Comparability	Outcome		
	Representation	Patients were from the same cohort	Measurement of vitamin D was uniform	Outcomes were not present at study initiation[d]	Cofounders controlled	Outcome assessment	Follow-up long enough[f]	Completeness of follow-up
Yuan *et al*., 2019 (3)	0[a]	1	1	1	2	1	1	1
Abrahamsson *et al*., 2019 (31)	0[b]	1	1	1	0[e]	1	1	1
Ng *et al*., 2011 (18)	0[c]	1	1	1	2	1	1	1

[a]Participants were predominantly individuals of European descent; [b]age limitations; [c]only included a population who consent to plasma biomarker protocol; [d]a prospective cohort study; [e]no description; [f]follow-up >2 years.

circulating 25(OH)D concentration was evaluated by the competitive electrochemiluminescence binding assay, and there was nothing mentioned on circulating 25(OH)D concentration.

Study quality. The quality of every single cohort study is shown in Table II. The total quality of the 3 cohort studies was high, holding an average NOS of 7. Two of them were of high quality with a score of 8 (3, 18); the remaining 1 was of moderate quality with a score of 6 (31). Regarding the two RCTs, the SUNSHINE trial was of low risk of bias. On the contrary, we noticed that the trial by Golubic *et al*. was not a random, placebo-controlled, blinded trial, without enough description. Hence, we believed that the Golubic *et al*. trial was at high risk of bias and decided to exclude it from the meta-analysis (Figure 2).

Meta-analysis of high circulating 25(OH)D levels and survival outcomes. Overall meta-analysis of 4 trials, consisting of 897 patients, indicated a beneficial effect of high circulating 25(OH)D level on PFS in advanced CRC patients undergoing chemotherapy (OR=0.64; 95% CI=0.43-0.96; p=0.03; Figure 3). A low to moderate heterogeneity was observed across these pooled studies (p-value for heterogeneity 0.13, I^2=46%). Moreover, we created a forest plot (Figure 4) of the regression analysis results from three studies (due to insufficient data, the study by Abrahamsson *et al*. (31) was excluded). Figure 4 demonstrated a favorable effect of higher circulating 25(OH)D status, which was consistent with Figure 3. More specifically, CRC progression was reduced by 15% (HR=0.85, 95% CI=0.71-0.99; p-value for heterogeneity 0.218, I^2=34.4%).

The pooled OR from our included studies was 0.56 (95% CI=0.38-0.82) for OS (Figure 5), which suggested that high circulating vitamin D level was beneficial for OS. In addition, no heterogeneity was found over the pooled studies (p-value for heterogeneity 0.68, I^2=0%).

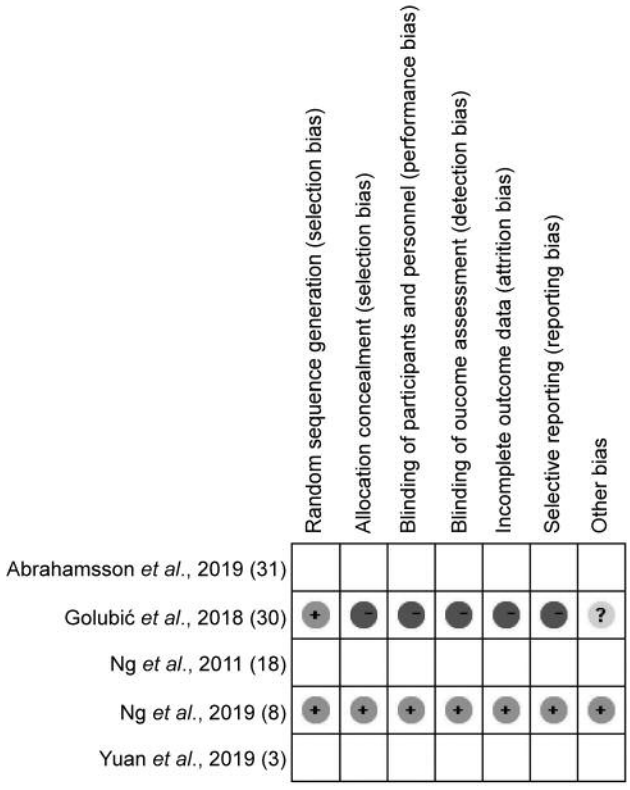

Figure 2. *Risk of bias of the two random controlled trials.*

Subgroup meta-analysis. We carried out a subgroup analysis of OS according to the locations of patients. We noticed that three of the four included studies are located in North America. Therefore, we divided the included studies into the following two subgroups: North America, Norway (Figure 5). We found that subgroup analysis did not change the statistical significance: North America: OR=0.60, 95% CI=0.40-0.90, p=0.01; and Norway: OR=0.33, 95% CI=0.11-1.05, p=0.06.

Sensitivity analysis. We noticed a low to moderate heterogeneity in the pooled PFS (I^2=46%). To find the reason, we used the method of excluding studies one by one to test the heterogeneity. Results showed that when Ng *et al*. (18) study was excluded, there was no heterogeneity in the synthesized data (p-value for heterogeneity 0.65, I^2=0%). Moreover, the meta-analysis result was not quantitatively changed (OR=0.44, 95%CI=0.26-0.75) (Figure 6).

Quality of the evidence. We used the GRADE profiler to evaluate the quality of the evidence (Table III). It showed that our outcomes were of moderate quality. Since we only included one RCT study, when we run the GRADE profiler, we set the study design as "observational studies". We upgraded the outcomes from low quality to moderate quality due to comparatively larger effects.

Discussion

Our study is the first systematic review and meta-analysis to investigate the influence of a higher circulating 25(OH)D concentration on the prognosis of advanced CRC patients undergoing chemotherapy. Through this meta-analysis, we have drawn the following conclusion: high circulating 25(OH)D levels are beneficial for advanced CRC patients undergoing chemotherapy. It was shown that a higher 25(OH)D level was related to better PFS and OS outcomes; specifically, there was a 15% reduction in CRC progression in this cancer population. We have noticed that the OS results of the North America group and the Norway group were consistent in reporting outcomes in OS. We noted a low to moderate heterogeneity in the pooled PFS (p-value for heterogeneity 0.13, I^2=46%). When we exclude the Ng *et al*. study, there was no heterogeneity in the synthesized data. We rechecked this paper and found that only one-tenth of the cohort participants showed a 25(OH)D concentration of more than 33 ng/ml. Due to the uneven distribution of 25(OH)D concentration in the study, higher circulating 25(OH)D status was not crucial for improving total PFS. The heterogeneity might be caused by too few individuals with a high 25(OH)D status in the cohort.

On the other hand, we only broadly proved that high circulating 25(OH)D levels are beneficial for patients with advanced CRC undergoing chemotherapy, while not proposed a specific 25(OH)D concentration that can produce favorable results. This was due to two reasons: (i) most of the studies we included are observational studies; (ii) there were different cut-offs of high and low circulating 25(OH)D levels. In the SUNSHINE trial (8), high 25(OH)D levels were >24.9 ng/ml and low ranged from 13.9 to 23.0 ng/ml. Yuan *et al*. (3) categorized 25(OH)D levels >24.1 ng/ml as high and <10.8 ng/ml as low. In the study by Ng *et al*. (18), high and low levels were defined as >27.1 ng/ml and <13.2 ng/ml, respectively, while in the study by Abrahamsson *et al*. (31) as >20 ng/ml and <20 ng/ml, respectively. Therefore, we propose that in future studies, high-quality RCTs are needed and a unified standard to categorize vitamin D levels should be followed. There is still a long way to clarify suitable cutoff values in future studies. However, these trials still have an essential value because they have investigated the significance of a higher 25(OH)D concentration in the treatment of advanced CRC patients receiving chemotherapy.

A large number of studies have shown that CRC patients are generally deficient in vitamin D. The main reasons for low 25(OH)D status are reduced sun exposure, use of sunscreen, a decrease in physical activity, and rise of obesity rates (32). In the study by Yuan *et al*. (3), participants with

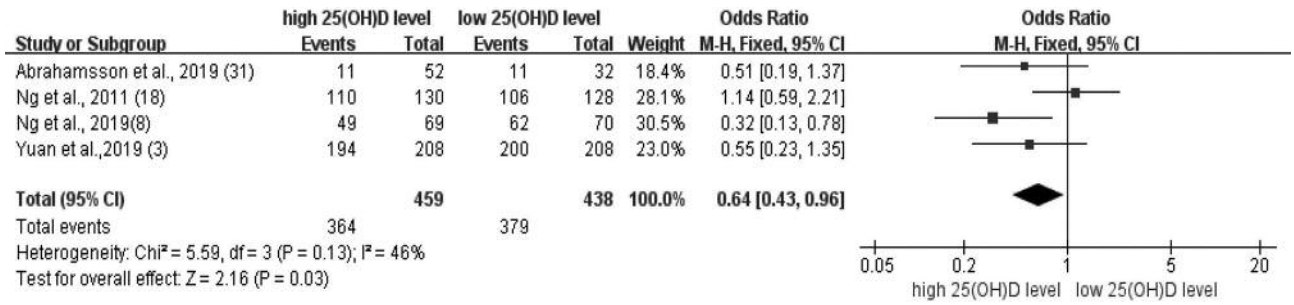

Figure 3. *The progression-free survival of the included studies (OR=0.64; 95% CI=0.43-0.96). M-H: Mantel–Haenszel; OR: odds ratio.*

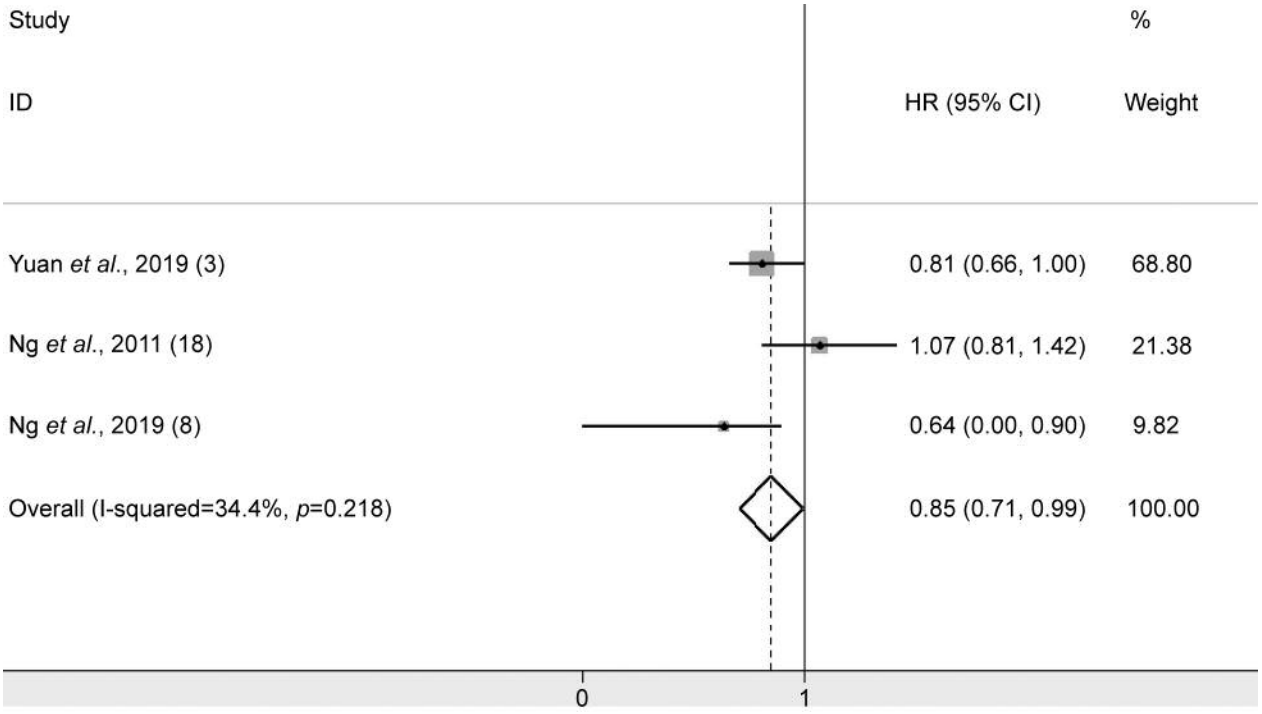

Figure 4. *The progression-free survival of our included studies (HR=0.85, 95% CI=0.71-0.99).*

advanced CRC had lower 25(OH)D levels, with an average level of less than 20 ng/ml.

Initially, we included two RCTs, one of which was excluded due to a lack of essential data. In addition, three high- or medium-quality prospective cohort studies were eligible that reduced the likelihood of biases. In the meta-analysis, four studies were included, totaling 897 patients, suggesting a benefit of high circulating 25(OH)D levels on the overall survival in advanced CRC patients undergoing chemotherapy (OR=0.56; 95% CI=0.38-0.82; p=0.003).

Our study has several limitations. First, the enrolled patients in this meta-analysis may not represent the population at large. The included literatures were mainly from North America, including mainly white people, thus our results cannot be generalized to different regions and populations. Additional studies in other populations are warranted. The second limitation is that the number of studies and patients is relatively small. Our study only included one RCT and three prospective cohort studies, although the total quality of the included studies is high. Large-scale, high-quality RCTs are needed in future

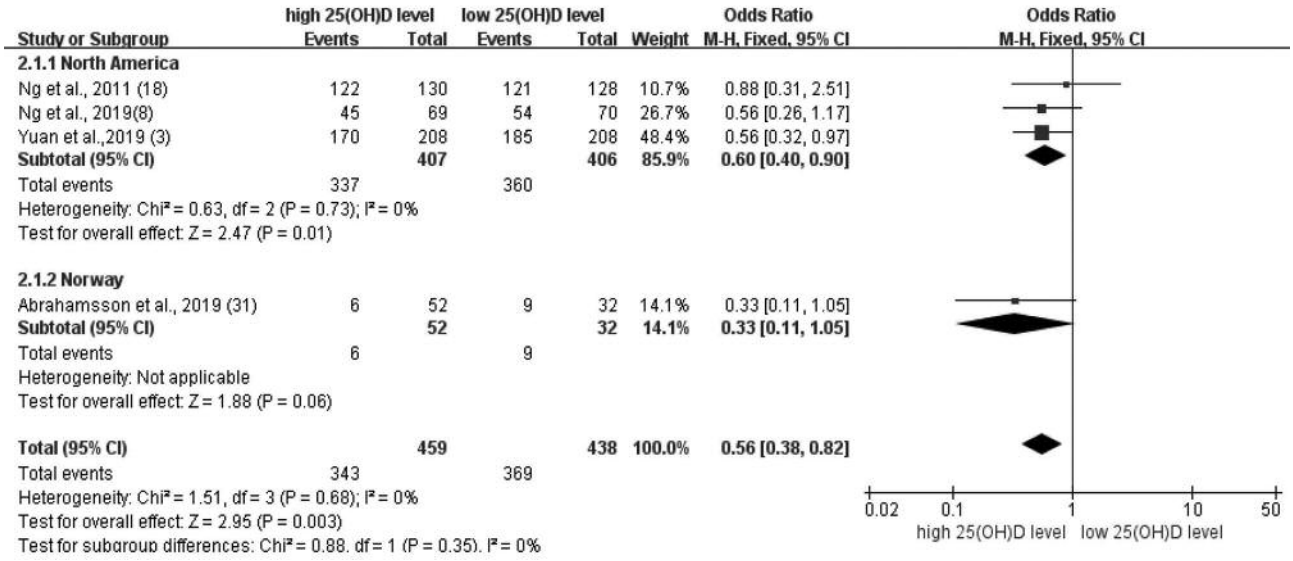

Figure 5. *Forest plot of the overall survival in the included studies. Total OR=0.56, 95% CI=0.38-0.82, p-value for heterogeneity=0.68, I^2=0%; indicating that there was a beneficial relationship between high 25(OH)D and OS, and no heterogeneity among studies. Subgroup analysis did not change the statistical significance: North America: OR=0.60, 95% CI=0.40-0.90, p=0.01; Norway: OR=0.33, 95% CI=0.11-1.05, p=0.06. Between 2 subgroups, there was no heterogeneity (p-value for heterogeneity=0.35, I^2=0%). M-H: Mantel–Haenszel; OR: odds ratio.*

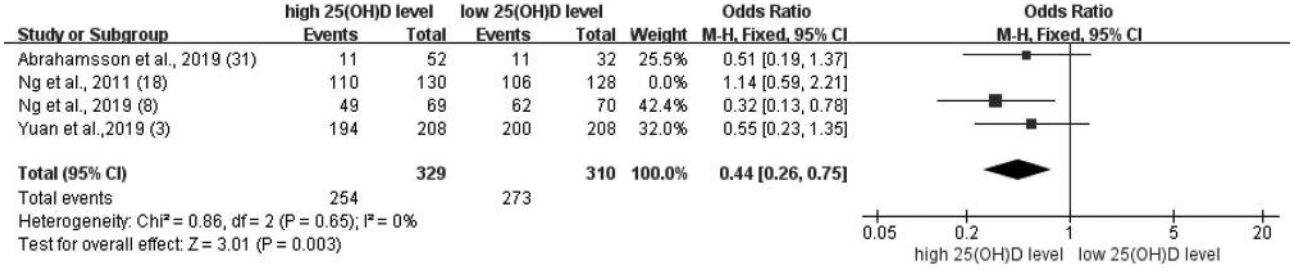

Figure 6. *Forest plot of sensitivity analysis of the included studies. The study by Ng et al. (18) was excluded.*

research. Third, the study by Abrahamsson *et al*. (31) included not only advanced CRC but also T2-T4 stages CRC patients. However, the sample size of this study is small, and the non-advanced patients cannot have a significant influence on the outcome. Fourth, most patients had a single 25(OH)D measurement, while the time of blood sample collection was also different. For future RCTs, circulating 25(OH)D levels should be measured more than once by using a standardized method like liquid chromatography-tandem mass spectrometry. Finally, we must consider that chemotherapy regimens and cycles were inconsistent among included studies (Table I).

An analysis of 304 patients with CRC indicated that the advantage of a high circulating 25(OH)D level might be more apparent among participants with advanced CRC than those in earlier stages (22). In a study on breast cancer patients undergoing chemotherapy, participants with vitamin D supplementation had better PFS than those without (33). More RCTs are needed to evaluate the impact of high 25(OH)D levels on OS, in advanced CRC patients undergoing chemotherapy.

An ongoing RCT is investigating whether the combination of vitamin D3 and standard chemotherapy is beneficial in patients with mCRC (34). The study shows that vitamin D3 supplementation along with chemotherapy might function better in contracting tumor volume. Another RCT currently being conducted explores the therapeutic effect of traditional chemotherapy regimens plus vitamin D3 *vs*. traditional chemotherapy regimens alone in untreated advanced CRC (35).

Table III. *Quality of the evidence*.

Higher 25(OH)D level for advanced CRC patients receiving chemotherapy

Patient or population: Patients with advanced CRC and receiving chemotherapy
Settings: Intervention: higher 25(OH)D level

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk control	Corresponding risk higher 25(OH)D level				
PFS (HR) and OS (OR)	Study population		OR=0.64	897	⊕ ⊕ ⊕ ⊝	
Follow-up: mean 4.5 years	865 per 1,000	804 per 1,000 (734 to 860)	(0.43-0.96)	(4 studies)	moderate[1]	
	Moderate					
	857 per 1,000	793 per 1,000 (720 to 852)				
Sensitivity analysis	Study population		OR=0.44	639	⊕ ⊕ ⊕ ⊝	
Follow-up: mean 4 years	881 per 1,000	765 per 1,000 (657 to 847)	(0.26-0.75)	(3 studies)	moderate[2]	
	Moderate					
	886 per 1,000	774 per 1,000 (669 to 854)				

*The basis for the assumed risk (*e.g.*, the median control group risk across studies) is provided in footnotes. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). CI: Confidence interval; OR: odds ratio; [1]total patients 897; [2]total patients 639. GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: We are very uncertain about the estimate.

If we can obtain survival profit by supplementing vitamin D in advanced CRC patients undergoing chemotherapy, it will be of great significance because vitamin D is safe and low-cost. Similar findings have been reported by Maalmi *et al*. for CRC patients (36). Currently, the most commonly used form for vitamin D supplements is vitamin D3. However, the side effects of vitamin D3 limit its application as an anti-CRC treatment (37). Thus, it is necessary to create more non-calcemic vitamin D3 analogs in the future (38).

Conclusion

This systematic review demonstrated that high circulating 25(OH)D content improves the prognosis of advanced CRC patients receiving chemotherapy. Most of these patients tend to be 25(OH)D deficient. Exogenous vitamin D supplementation might serve as a way to improve the prognosis of patients with advanced CRC receiving chemotherapy. Future well-designed, multicenter, and large-scale RCTs are warranted to consolidate the evidence.

Conflicts of Interest

The Authors declare no conflicts of interest.

Authors' Contributions

X.Z.: conception, methodology, article research, formal analysis, writing the draft, revising the review, and editing the final manuscript. L.Z.: methodology, article research, formal analysis, and writing the draft. S.J.: conception, revisions and editing of the final manuscript. T.L.: methodology and writing the draft. G.L.: revision and editing the final manuscript. J.Y.: supervision, revision of the review. X.H.: conceptualization, project administration, supervision, revisions and editing the final manuscript.

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