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Effect of Vitamin D Supplementation on the Survival of the Metastatic or Advanced Colorectal Cancer Patients: A Systematic Review

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ABSTRACT

Background: Multiple studies have pointed out that low circulating vitamin D level is associated with poor colorectal cancer (CRC) survival. Patients of all stages of CRC were assessed for the benefit of Vitamin D supplementation on the Overall Survival through conducting multiple systematic reviews. By the aid of these reviews, it was found that Vitamin D is effective in early stages with no mention of late stages. Hence, in this review we are assessing whether vitamin D is also effective in advanced or metastatic stages of CRC.

Methods: Our focus is the impact of vitamin D supplementation on the survival outcomes of individuals with metastatic or advanced colorectal cancer. Our search encompassed prominent databases such as PubMed, Cochrane, Google Scholar, clinicaltrials.gov, Scopus and science direct allowing us to gather relevant studies in this field. To ensure the quality and appropriateness of the studies included, we applied specific eligibility criteria for further screening of observational studies and randomized controlled trials (RCTs).

Results: The review comprised seven studies and 1886 patients. Four of the seven studies reported positive results, while the remaining three reported non-significant results. The positive findings indicated a significant increase in overall survival rates for patients with advanced or metastatic colorectal cancer, in addition to improvement in progression-free survival rates. Furthermore, intestinal barrier function related biomarkers CLDN1, OCLD and MUC12 were found to be increased minimally by supplementing a combination of vitamin D and Calcium, increasing the intestinal barrier integrity that further decreased CRC progression.

Conclusion: This systematic review shows clinically significant beneficial effect of vitamin D supplementation on survival outcomes in patients with metastatic or advanced CRC

Keywords: Advanced; Metastatic; Colorectal Cancer; Vitamin D; Overall Survival; Progression Free Survival

Abbreviations: mCRC: Metastatic Colorectal Cancer; EGFR: Antiepidermal Growth Factor Receptor; VGFR: Anti-Vascular Endothelial Growth Factor Receptor; mOS: Median Overall Survival; PFS: Progression Free Survival; ECOG: Eastern Cooperative Oncology Group; RECIST: Response Evaluation Criteria in Solid Tumors; RR: Relative Risk; OS: Overall Survival; NLR: Neutrophil to Lymphocyte Ratio; CEA: Carcinoembryonic Antigen; Cldn1: Caludin1; OCLD: Ocludin; MUC12: Mucin 12; NIH: National Institue of Health; SIGN: Scottish Inter-collegiate Guidelines Network

Introduction

Colorectal cancer (CRC) is one of the most commonly diagnosed cancers worldwide that is characterized by a high mortality rate [1]. Epidemiological and scientific research suggested that the development of CRC is much related to diet and lifestyle factors. Vitamin D, in specific, has been the subject of academic interest as preclinical and epidemiological studies have provided evidence for anti-cancer effects of vitamin D (particularly against CRC [2]). It was demonstrated that higher baseline plasma levels of 25- hydroxy- vitamin D [25(OH) D] are associated with a significant reduction in CRC incidence and that Patients with metastatic CRC (mCRC) tend to be vitamin D deficient and that its supplementation is associated with lower levels of carcinogenesis and enhanced tumor response when compared to anti-cancer therapies only [3]. Multiple proposed explanations of this antineoplastic effect of vitamin D were present. One of the most prominent was its direct effect on cancer cells; as upon binding of vitamin D to its receptor (VDR), this will regulate certain target genes involved in inducing differentiation and apoptosis [4]. Moreover, vitamin D counteracts aberrant WNT-β catenin signaling, which is involved in the etiology of CRC, leading to the inhibition of growth in cell lines, angiogenesis, and metastatic potential [5].

An indirect effect was observed on cancer cells by sparking immune modulatory effects such as anti-inflammatory effects as 1,25-dihydroxyvitamin D inhibits in vitro and in vivo the interferon (IFN)-γ and IL-17 production from T cells, induces the anti- inflammatory cytokine IL-10 from Foxp3+ Treg cells and the antimicrobial IL-22 from type 3 innate lymphoid (ILC3) cells [6]. In this systematic review, we aimed to navigate through the literature and search for the effect of vitamin D supplementation on the survival of metastatic or advanced colorectal cancer patients, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Material and Methods

Eligibility Criteria

Our review was restricted to clinical trials (observational studies and Randomized controlled trials (RCTs)) assessing the effect of vitamin D supplementation on the survival of metastatic or advanced colorectal cancer patients. Our inclusion criteria were limited to articles written in the English language, and original full article that were published between 2003 and 2023. As for the exclusion criteria, we excluded the studies where the outcome is a measure other than survival, the population of interest does not include metastatic or advanced CRC patients or if the study is more concerned with the baseline serum level of vitamin D and not vitamin D supplementation.

Information Sources and Literature Search

Abided by a strict timeline, the search was done using PubMed, Cochrane, Google scholar (first 10 pages), Scopus, science- direct and clinicaltrials.gov databases. To narrow down the search, filters as free full text, articles only published in English, date limitation from 2003 to 2023 with the last date of formal search being 13th August 2023 were used. Example of a utilized Search strategy was [("Vitamin D" OR "1,25-dihydroxycholecalciferol")] AND [("Metastatic colorectal cancer" OR "advanced CRC" OR" stage III CRC" OR "stage IV CRC")]. We also performed relevant citations and reference searches.

Screening and Data Extraction

The First stage of screening the retrieved articles' titles and abstracts was conducted independently by three reviewers (NA, OH, and YR). The second stage of the articles' full text retrieving as well as the assessment for eligibility was achieved through four reviewers (NA,OH,YR,AH). When disagreement arose, a fifth reviewer (MG) settled the disagreement through the guidance of the protocol. The data extraction tools, namely Cochrane Collaboration for randomized Controlled Trials and non-randomized studies was used to extract different fields as author's last name, publication date, sample size, Participant Population, baseline characteristics (median age, gender etc…), intervention, comparator, follow-up duration, and outcome measures.

Quality Assessment

National Institute of Health (NIH) checklist and Scottish Intercollegiate Guidelines Network (SIGN) checklist, which are validated tools, were used to construct a 10-question checklist for assessing the quality of the eligible studies.

Results

Included Studies and Baseline Characteristics

The search strategy yielded 192 articles. This was followed by duplicates removal and then screening for relativity to the search and the eligibility criteria. Afterwards, full texts were screened for the eligibility which resulted in only 7 studies [3,7-12], describing a total of 1886 patients, to be included in the quality assessment (Figure 1). Heterogeneity was seen in the studies in terms of Metastatic CRC patients' survival measures identification and screening (Table 1).

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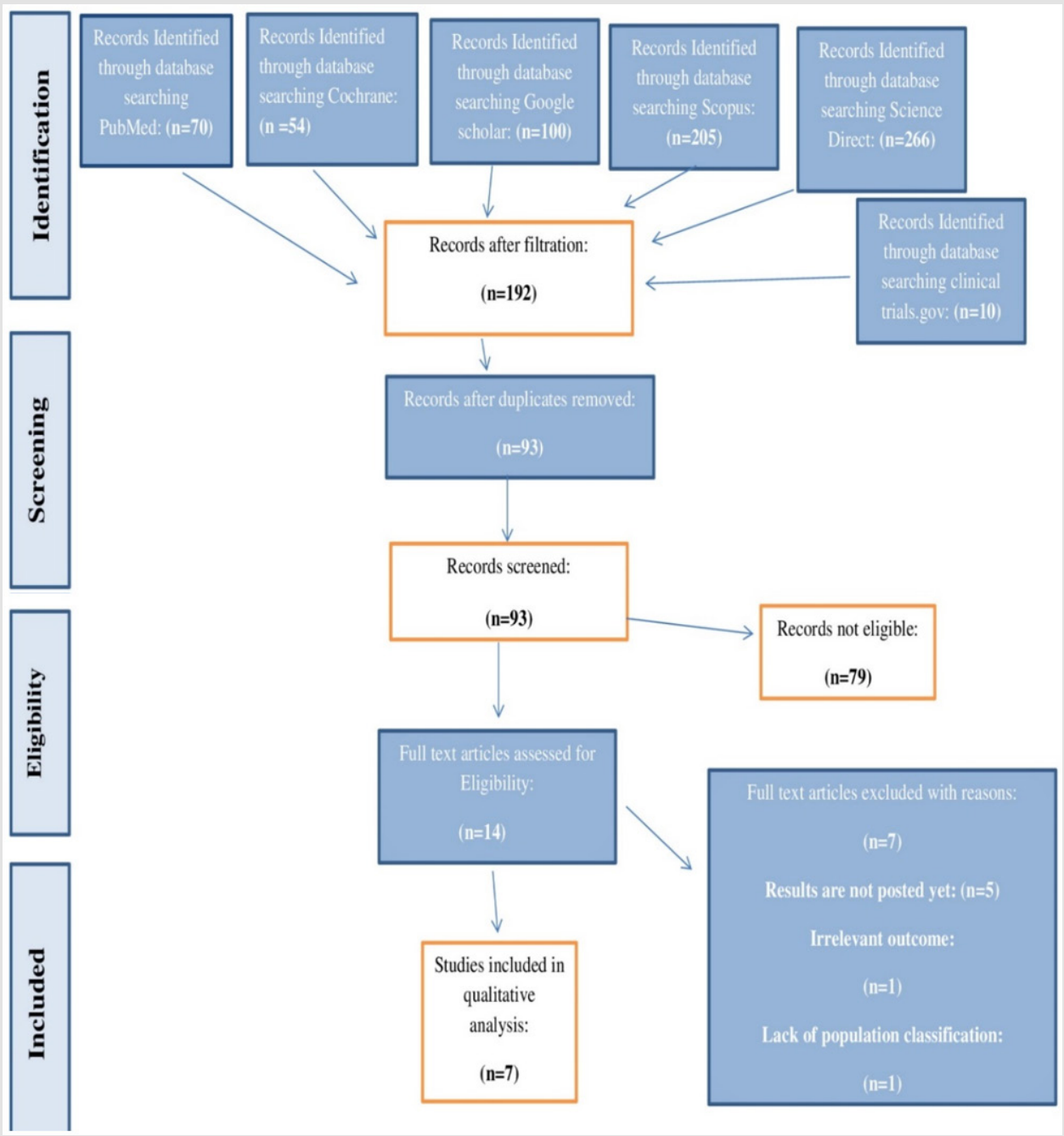

Figure 1: Prisma Flow diagram.

Table 1.

Name of the study	Sample size	Participant Population	Baseline characteristics	Intervention	Comparator	Follow UP duration	Outcome Measures	Key Conclusion	Funding
Golubić, et al. [3]	72	Metastatic CRC	Age Gender: male& female	Chemotherapy (As a first line therapy, FOLFIRI regimen (leu-covorin, fluorouracil, and irinotecan) has been used. (90%) OR Oxaliplatinum or 5 FU-based regimen) With Vitamin D 2,000 IU daily.	Chemotherapy only	46 Months	Among all participants, only one patient was vitamin D deficient. The median 25(OH) D concentration was 33.1 nmol/l. Median PFS for the two groups was 10.5 months during the 46-months follow up. There was no statistically significant differences in mortality between both groups HR D 1.0064, 95% CI =0.3882– 2.609, and P = 0.9895. The median OS in the treatment arm was 39 months, while it was 40 months in the control arm.	The study concluded that the majority of patients with mCRC shows insufficiency in vitamin D levels. In this study, supplementing conventional chemotherapy with 2,000 IU of cholecalciferol per day for two years did not improve OS or PFS.	Conducted at the University Hospital Centre Zagreb as part of the project "The role of predictive and prog- nostic molecular markers in cancer treatment" (project num- ber 108-1080058-0047), supported by the Ministry of Science and Education of the Republic of Croatia.
Morelli, et al. [7]	133	Metastatic CRC	Gender, Age The median 25(OH)D level was 10.8 ng/mL (range 3–53.4 ng/mL), with 60 deficient (<10 ng/mL), 37 insufficient (10–20 ng/mL) and 36 within normal range (>20 ng/mL) levels.	FOLFOX / FOLFIRI + EGFR/VEGF + 400IU/d VitD3	FOLFOX /FOLFIRI + EGFR/ VEGF only	11 Years	Patients with low 25(OH)D levels (< 10 ng/mL) and high neutrophil to lymphocytes ration (NLR) (>3.5) had the shortest survival and patients with 25(OH)D >10 ng/mL and NLR <3.5 had the longest median Overall Survival (mOS) 8.1 and 28.1 months, respectively, HR 3.40 (1.76–6.59), p 0.0004. Besides the significant difference in NLR between 25(OH)D < and > 10 ng/mL patients (mNLR 3.6 vs. 2.9, p 0.03)	This paper concludes how vitamin D levels influence the immune response in patients with mCRC, pinpointing a specific threshold for vitamin D. The analysis highlights the significance of certain blood-related factors, such as the neutrophil-to-lymphocyte ratio, along with the presence of CD4+ T lymphocytes and B-lymphocytes. These factors are closely linked to vitamin D levels and have notable effects on patient survival.	Partially supported by the European Union's Horizon 2020 research and innovation program under grant agreement n°848098.

Ng, et al.[8]	139	Metastatic CRC	Vitamin D<2000 IU/d during last year, Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Age Gender: males and females.	Mfolfox+bevacizumab+4000 IU/d vitD	Mfolfox+bevacizumab+400 IU/d vitD	16 months	High Vitamin D dose (4000IU/d) group had a longer PFS than those who were assigned to Low Vitamin D dose (400IU/d) (12.4 vs. 10.7 months), respectively; log rank P=0.03 for PFS. After multivariate adjustments of prognostic factors, the HR was 0.66 (95% CI, 0.44–.99, 2-sided P=0.04)	SUNSHINE met its pre-specified primary endpoint, with patients randomized to High VitD experiencing longer PFS compared to those randomized to Low VitD. A larger confirmatory phase III randomized trial appears warranted.	No funding mentioned.
Brown, et al. [9]	105	Metastatic or advanced CRC	Age, sex, race and ethnicity, ECOG performance status, primary tumor location, primary tumor resection status, receipt of prior cancer-directed therapy, number of metastatic sites, carcinoembryonic antigen (CEA) concentration, and tumor mutational profile.,	4000 IU/day Vit D3.	400 IU/day Vit D3.	16 weeks	Minimal change in body weight [−0.7 kg; (95% CI: −3.5, 2.0)], body mass index [−0.2 kg/m2; (95% CI: −1.2, 0.7)], muscle area [−1.7 cm2; (95% CI: −9.6, 6.3)], muscle attenuation [−0.4 HU; (95% CI: −4.2, 3.2)], visceral adipose tissue area [−7.5 cm2; (95% CI: −24.5, 9.6)], or subcutaneous adipose tissue area [−8.3 cm2; (95% CI: −35.5, 18.9)] Change in muscle area (nonlinear p = 0.026) and visceral adipose tissue area (nonlinear p = 0.01) were significantly associated with overall survival Change in muscle attenuation (nonlinear p = 0.002) was significantly associated with PFS.	Among patients with advanced or metastatic colorectal cancer, the addition of high-dose vitamin D3, vs standard-dose Vitamin D3, to standard chemotherapy did not result in any differences in body composition. The findings from this exploratory study indicate that the benefits of vitamin D3 on reducing cancer progression and death are unlikely to be mediated by changes in body composition.	Supported by grants from the National Cancer Institute of the National Institutes of Health, the National Institute of General Medicine Sciences of the National Institutes of Health, and from the National Institute of Diabetes and Digestive and Kidney Diseases of the National Institutes of Health. Additional funding was provided by the Gloria Spivak Faculty Advancement Award, Friends of Dana-Farber Cancer Institute Award, Project P Fund, Douglas Gray Woodruff Chair fund, Consano, Pharmavite LLC, and Genentech

Ng, et al. [10]	139	Locally advanced or metastatic adenocarcinoma of the colon or rectum.	Recruited patients (79 Men, 60 Women, Mean Age 56 years) followed an eligibility criteria composing of being pathologically confirmed, having unrespectable locally advanced/metastatic adenocarcinoma of the colon or rectum according to version 1.1 of Response evaluation criteria in solid tumors (RECIST) guidelines. Having taken neo-adjuvant or adjuvant therapy or radiation if the last dose of treatment was 12 months prior to recurrence. ECOG performance status 0 or 1, normal baseline organ function and no hypercalcemia detected.	High dose Vitamin D 4000IU/d	Standard dose Vitamin D 400IU/d	22.9 months	Primary, Progression free survival (PFS) : Median for high dose was 13 months vs. 11 months for standard dose and HR was 0.64 (P value not significant 0.07)	No statistical significance in difference in median PFS was observed among patients with metastatic CRC, where there was an addition of high-dose vitamin D3, vs standard-dose vitamin D3, to standard chemotherapy yet, with a significantly improved supportive hazard ratio. Larger multi-center RCTs are needed for further evaluation of these findings.	No Funding mentioned
Calderwood, et al. [11]	1,121	Advanced Colorectal Adenoma	Eligible participants were age 45–75 years with at least one colorectal adenoma (≥ 0.2 cm) removed in the 4 months prior to study entry and no known remaining polyps in the colon after complete colonoscopy. All participants had blood calcium within the normal reference range, creatinine not exceeding 20% above the upper limit of normal, and 25-hydroxyvitamin D concentrations ≥ 12 ng/ml to ≤ 90 ng/ml at enrollment.	Combination Vit D 1000 IU/d + Ca 1200 mg/d OR Vitamin D3 (1000 IU daily) only.	1200mg calcium	55 ± 15 months	Recurrence (PFS) progression free survival: non- significant value: *3-year follow-up, the relative risk (RRs) (95% confidence intervals) for calcium and vitamin D were 0.98 (0.84–114) and 1.04 (0.90–1.19), respectively. *5-year follow-up, they were 0.90 (0.77–1.05) and 0.93 (0.80–1.08), respectively. 1200 mg calcium per day on risk of advanced adenoma appeared to be more pronounced during the 5 years after active treatment than during the active treatment. (RR 0.65 (0.46-0.93)).	The study do not support an association between supplemental calcium and/or vitamin D3 for 3–5 years and risk of recurrent colorectal adenoma at an average of 4.6 years post-treatment.	Grant support: National Institutes of Health, National Cancer Institute (CA098286, to Dr. Baron).

Mandle, et al. [12]	105	Advanced CRC	Age Male, Female Diet (using the Block Brief 2000 food frequency questionnaire; Nutrition questionnaire, Berkeley, CA). Serum 25-hydroxyvitamin D 125(OH)D] and calcium concentrations were measured at baseline. The mean age of all participants was 59 years, 47% were men, 79% were white, and approximately half held a college degree or higher. Most of the participants were overweight (79%), non-smokers (92%), and consumed less than one drink of alcohol per day on average.	Combination vit D 1000 IU/d + Ca 1200 mg/d OR Vitamin D3 (1000 IU daily) only	Only supplemental calcium (1200 mg, daily)	1 year	Vit D group: Non-significant if vit D only &minimal significance if combinations. Combination relative to Calcium increase expression of tight junction proteins claudin-1(Cldn1) minimally , Occludin (OCLD) by 13%(p=0.26) and mucin 12 (MUc12) by 7% (p=0.50)	The results suggest that calcium may increase biomarkers expression concentrations. No evidence was found for daily supplemental vitamin D3 on the biomarkers, but findings suggested antagonistic effects of co-administered vitamin D3 and calcium on the biomarkers.	Funded by National Cancer Institute, National Institutes of Health; Georgia Cancer Coalition Distinguished Scholar award (to RMB); and the Franklin Foundation (to RMB). Pfizer Consumer Healthcare provided the study agents.

The Main Characteristics of Included Trials are Summarized in (Table 1):

In brief, Golubić, et al. [3], concluded that the majority of patients with metastatic colorectal cancer (mCRC) are vitamin D deficient, where adding 2,000 IU of vitamin D daily for 2 years to standard chemotherapy (As a first line therapy, FOLFIRI regimen (leu- covorin, fluorouracil, and irinotecan) (90%) or bevacizumab oxaliplatinum or 5 FU-based regimen) has not shown any benefit in OS or PFS. Among all participants, only one patient (among a total of 72) was vitamin D deficient. The median 25(OH)D concentration was 33.1 nmol/l. Median PFS for the two groups was 10.5 months. During the 46-months follow up, there was no statistically significant difference in mortality between both groups, HR D 1.0064, 95% CI D 0.3882– 2.609, and P = 0.9895. The median OS in the treatment arm was 39 months, while it was 40 months in the control arm [3]. Morelli et al RCT (2020) found that the lowest survival times were correlated to patients who had low 25(OH)D levels (10 ng/mL) and high neutrophil to lymphocyte ratio(NLR) (>3.5). On the other hand, those who had high 25(OH)D levels (>10 ng/mL) and low neutrophils-to-lymphocyte ratio (NLR) (3.5) had the longest survival times, median overall survival (mOS) 8.1 and 28.1 months, respectively, HR 3.40 (1.76-6.59), p=0.0004; in addition to the substantial difference in NLR between patients who have mNLR 3.6 , the 25(OH)D is <10 And >10 in patient with mNLR 2.9 & p=0.03(7).

The SUNSHINE trial RCT (2017), 139 participants were randomized blindly into two groups.

The first group was assigned to low vitamin D (400IU) plus standard chemotherapy. On the other hand, the second group was assigned to high vitamin D (4000IU) plus standard chemotherapy. Vitamin D capsule compliance was found to be 98%. High Vitamin D dose (4000IU/d) group had a longer PFS than those who were assigned to Low Vitamin D dose (400IU/d) (12.4 vs. 10.7 months), respectively; log rank P=0.03 for PFS. After multivariate adjustments of prognostic factors, the HR was 0.66 (95% CI, 0.44–.99, 2-sided P=0.04).(8) In Brown et al RCT (2020), Only a small change was detected in body weight (-0.7 kg); (95% CI: -3.5, 2.0)), body mass index (-0.2 kg/m2; (95% CI: -1.2, 0.7), muscle area (-1.7 cm2; (95% CI: -9.6, 6.3)), muscle

attenuation (-0.4 HU; (95% CI: -4.2, 3.2)), visceral adipose tissue area [−7.5 cm2; (95% CI: −24.5, 9.6)], and subcutaneous adipose tissue area [−8.3 cm2; (95% CI: −35.5, 18.9)]. In addition, There was a correlation between OS and change in muscle area (nonlinear p = 0.026), also with visceral adipose tissue area (nonlinear p = 0.01). Moreover, muscle attenuation change was more related to PFS (nonlinear p= 0.002] [9]). In SUNSHINE RCT (2019), The median PFS for high-dose vitamin D3(4000IU/d) was 13.0 months (95% CI, 10.1 to 14.7; 49 PFS events) Vs. 11.0 months (95% CI, 9.5 to 14.0; 62 PFS events) for standard-dose vitamin D3(400IU/d) (log-rank P =0.07) among 139 patients (mean age, 56 years; 60 [43%] women) who completed or discontinued chemotherapy and vitamin D3 (median follow-up, 22.9 months) [10].

Post 4.6 years after therapy, Calderwood, et al. [11] found no association between supplemental calcium (1200mg/d) and/or vitamin D3 (1000IU/d) for 3-5 years and the recurrence of colorectal adenoma [11]. Mandle, et al. [12] concluded that vitamin D (1000IU/d) group has shown no prominent changes in claudin 1(CLDNI) expression, only slight increases in ocludin (OCLD) expression in all three-crypt parameters and no change in the expression of mucin 12 (MUC12) in crypt parameters. While for vitamin D (1000IU/d) plus Calcium group(1200mg/d) it has been found that this combination causes small, estimated and non-statistically significant increases in CLDNI expression across all crypt parameters , OCLD expression increases with an estimated 13% (P =0.27), 12% (P = 0.32), and 13% (P = 0.26) in the full length, upper 40%, and lower 60% of crypts, respectively .A minimal increase has been observed with this combination by an estimated 7% (P = 0.50) but didn't show any change in the upper 40% or the lower 60% of crypts . On the other hand, the expression of MUC12, OCLD, and CLDNI all increased in the calcium (1200mg/d) group by 14% (P=0.17), 23% (P=0.11), and 22% (P=0.07), respectively. Furthermore, in all of the treatment groups, no change has been detected in MUC12 expression in the ϕh of the crypts. Hence, it was concluded that the increase of expression of these biomarkers increases the progression free survival significantly [12].

Quality Assessment and Risk of Bias Assessment

The Majority of the studies had high adherence to quality checklist (National Institute of Health and Scottish Intercollegiate Guidelines Network checklists) (Table 2). In addition to that, most of the study participants were not similar before the start of the treatment, differences were observed in the chemotherapy that was given, dosing and baseline characteristics, which suggests a risk of bias.

Table 2: Table summarizing the quality check assessment.

	Ng, et al. [10]	Ng, et al. [8]	Brown, et al. [9]	Morelli, et al. [7]	Golubić, et al. [3]	Calder-wood, et al. [11]	Mandle, et al. [12]
1) The Study addresses an appropriate and clearly focused question	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2) The assignment of subjects to treatment groups is randomized?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
3) Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
4) The only difference between groups is the treatment under investigation?	No	No	Yes	No	No	No	No
5) Were the groups similar at the start of the trial?	No	No	Yes	No	No	No	No
6) Was the eligibility criteria mentioned?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
7) Was Intended Sample size mentioned?	Yes	Yes	Yes	Yes	Yes	Yes	Yes
8) Estimates of diagnostic accuracy and their precision? (such as 95%CI, p value, etc..)	Yes	Yes	Yes	Yes	Yes	Yes	Yes
9) Were study limitations mentioned?	Yes	Yes	No	Yes	Yes	Yes	Yes
10) Were methods for estimating or comparing measures of diagnostic accuracy mentioned?	Yes	Yes	Yes	Yes	Yes	Yes	Yes

Discussion

Post conducting a systematic review to further indulge into the impact of Vitamin D on advanced or metastatic colorectal cancer whilst applying the eligibility criteria, seven papers were identified including 1886 patients. Different outcomes were reached among these papers, four [7-10] reported positive with significant results, while the remaining three [3,11,12] reported non-significant results. The positive findings included a significant increase in OS rates for patients with metastatic colorectal cancer, in addition to an observed improvement in PFS rates. Furthermore, intestinal barrier function related biomarkers CLDN1, OCLD and MUC12 were minimally increased by supplementing vitamin D and Calcium combinations which led to an increase in the intestinal barrier integrity, further decreasing CRC Progression [12] Contrastingly, no prominent difference in OS and PFS rates were observed in the three papers with minimal or non-significant results when Vitamin D was administered to patients with metastatic colorectal cancer [3,11-12]. In another cohort

study, Bao, et al. [13] compared the effect of vitamin D on the survival of stage II and III colorectal cancer patients. The study included a total of 728 patients with stage II-III CRC between 2011 and 2015. Their serum 25-hydroxyvitamin D3 levels were measured. In the primary cohort, the serum 25(OH)D level was positively correlated with the OS of all CRC patients (p= 0.016) and stage III patients (p= 0.009). In the validation cohort, serum 25(OH)D levels were confirmed to have prognostic value for OS for patients with stage III CRC (95% CI 0.080-0.602, p=0.003), and low 25(OH)D levels indicated worse OS for left-sided stage III CRC patients (95% CI 0.075-0.727, p=.012)In conclusion, vitamin D status was found to be positively associated with the survival of CRC patients, especially those with left-sided stage III CRC ,which support our findings and confirms that vitamin D supplementation is of beneficial value even more in Advanced (stage III)CRC patients [13]. In this piece of literature, a number of limitations have surfaced. Our search of literature shows lack of well-designed and adequately powered trials investigating vitamin D supplementation and advanced CRC outcomes. Moreover, the systematic review only studied the positive effect of vitamin D supplementation on the survival of advanced CRC patients without assessing secondary outcomes such as quality of life (Qol) including pain, fatigue and depression. Hence, further clinical trials need to be conducted for the assessment of these components. We acknowledge that the translation of results from supplemental RCTs to a real-life healthcare setting is not always straight forward. Although vitamin D is inexpensive and safe, its intoxication or other adverse effects of supplementation must be considered. Furthermore, the benefit of vitamin D is greatly influenced by poor compliance. The optimal dose for survival benefit remains unclear yet; data from several publications indicates 2000–4000 IU/day to be safe and should be considered for future trials. The effect of vitamin D supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials.

In conclusion, this systematic review demonstrates clinically significant beneficial effect from vitamin D supplementation on survival outcomes in patients with advanced or metastatic CRC, and further large sample trials are needed to fully evaluate the benefit of supplementation which will help in the inclusion of this supplementation in real-life CRC treatment protocols besides the standard chemotherapy.

Author Contributions

MH conceived the idea of the review and formed the team. MG performed the analysis, constructed the tables and figures, and wrote the initial draft. NA conducted the initial search and with YR and OH conducted the screening. NA, YR, AH, and OH extracted the data. The manuscript was then critically reviewed and revised by all the study authors.

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