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Clinical, Prognostic, and Survival Implications of Vitamin B12 Levels in Cancer Patients Following Chemo- or Radiotherapy

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Abstract

Cancer is widely accepted as a metabolic disease. Cancer treatment with chemotherapy and radiotherapy has significant toxicity that can impair prognosis and survival. Vitamin B12 is a cofactor in one-carbon metabolism essential for DNA synthesis and genomic stability. It has been proposed as a potential biomarker for cancer prognosis and survival, but its trends after chemotherapy or radiotherapy remain ambiguous. This systematic review investigated the potential of vitamin B12 levels as biomarkers in patients with cancer and whether levels, and changes after chemotherapy or radiotherapy, are connected with clinical outcomes, cancer prognosis, and survival.

This systematic review followed the 2020 PRISMA guidelines. PubMed, ScienceDirect, Europe PMC, Directory of Open Access Journals (DOAJ), and HubMed were searched using combinations of terms related to vitamin B12, cancer, chemotherapy, radiotherapy, prognosis, and survival, supplemented by MeSH terms in PubMed. Observational studies (2005-2025) in adult cancer patients reporting vitamin B12 changes after chemotherapy/radiotherapy or their clinical, prognostic, or survival associations were included. Two reviewers independently screened records; quality was assessed using the Newcastle-Ottawa Scale for case-control/cohort studies and the JBI Critical Appraisal Checklist for cross-sectional studies. Due to heterogeneity, findings were synthesized narratively rather than meta-analytically.

Of 1,074 records identified, eight studies representing seven distinct cohorts (1,477 patients) met inclusion criteria: one case-control, six cohort, and one cross-sectional study, spanning lung, breast, oesophageal, colorectal, hepatic, cervical cancers and diffuse large B-cell lymphoma. Seven studies evaluated chemotherapy and one, radiotherapy. Earlier chemotherapy studies generally showed no significant or only modest changes in vitamin B12 levels during or after treatment. However, a recent prospective study from Gaza demonstrated a significant decrease in serum vitamin B12 following chemotherapy, accompanied by increased methylmalonic acid and homocysteine, suggesting worsening functional vitamin B12 status. The same cohort demonstrated an association between worsening functional vitamin B12 status and chemotherapy-induced peripheral neuropathy. In contrast, the single radiotherapy study found significantly lower vitamin B12 levels and impaired cobalamin status 6-12 years after pelvic radiotherapy, with 20% of survivors meeting deficiency criteria. Lower baseline vitamin B12 was associated with greater anxiety severity during chemotherapy in one study, while another found lower baseline levels associated with significantly better overall survival and time to progression.

In conclusion, chemotherapy does not appear to consistently alter circulating vitamin B12 levels, although recent evidence suggests it may be associated with a significant decline in vitamin B12 and worsening functional status in some populations. Pelvic radiotherapy may cause long-term vitamin B12 deficiency. While vitamin B12 status may hold clinical and prognostic value in some cancers, the limited number of studies and heterogeneity in the current literature preclude firm conclusions. Further high-quality prospective studies incorporating functional vitamin B12 biomarkers are needed to clarify the relationship between cancer therapy, vitamin B12 status, and clinical outcomes before routine clinical use can be recommended.

Categories: Therapeutics, Oncology, Internal Medicine
Keywords: cancer patients, cancer prognosis, cancer survival, chemotherapy (ct), clinical implication, radiotherapy (rt), serum vitamin b12

Introduction And Background

Cancer, both solid and hematological, is a metabolic disease that results in increasing numbers of abnormal cells, stealing nutrition from surrounding normal cells, ultimately causing their death. As cancer cells

metastasize to other areas of the body, treatment can become futile once a certain point is reached. Cancer remains one of the most common causes of death in the world. According to the WHO, the most common types of cancers in 2024 were lung and breast, followed by colon and rectum, and prostate cancers [1]. Various factors are responsible for cancer deaths. Some of the most prominent include tobacco smoking, air pollution, high body-mass index (BMI), low fruit and vegetable intake, alcohol use, and low physical activity. Chemotherapy and radiotherapy are major treatment methodologies used to inhibit cancer growth and stop its multiplication through complex biochemical processes.

As cancer can be regarded as a metabolic disease, it is expected that vitamins involved in metabolic processes are also affected. One such vitamin is vitamin B12, as its co-enzymatic activity is needed in many body functions

It is biologically plausible that vitamin B12 may have a role in cancer because of its central role in ensuring genomic stability and the regulation of cellular proliferation. It plays an important role as a cofactor in deoxyribonucleic acid (DNA) synthesis. It also supports DNA repair, functional regulation, as well as cell division [2].

Changes in vitamin B12 levels can significantly impact biological functioning. Low levels lead to a shortage in DNA synthesis, which could further lead to genomic instability. On the other hand, raised vitamin B12 levels show more prominent DNA methylation activity. It has been speculated that raised levels reflect, or influence, a stage in tumorigenesis. These mechanisms may help to explain the associations observed between vitamin B12 and cancer occurrence, prognosis, and/or treatment outcome, as shown in Figure *1*.

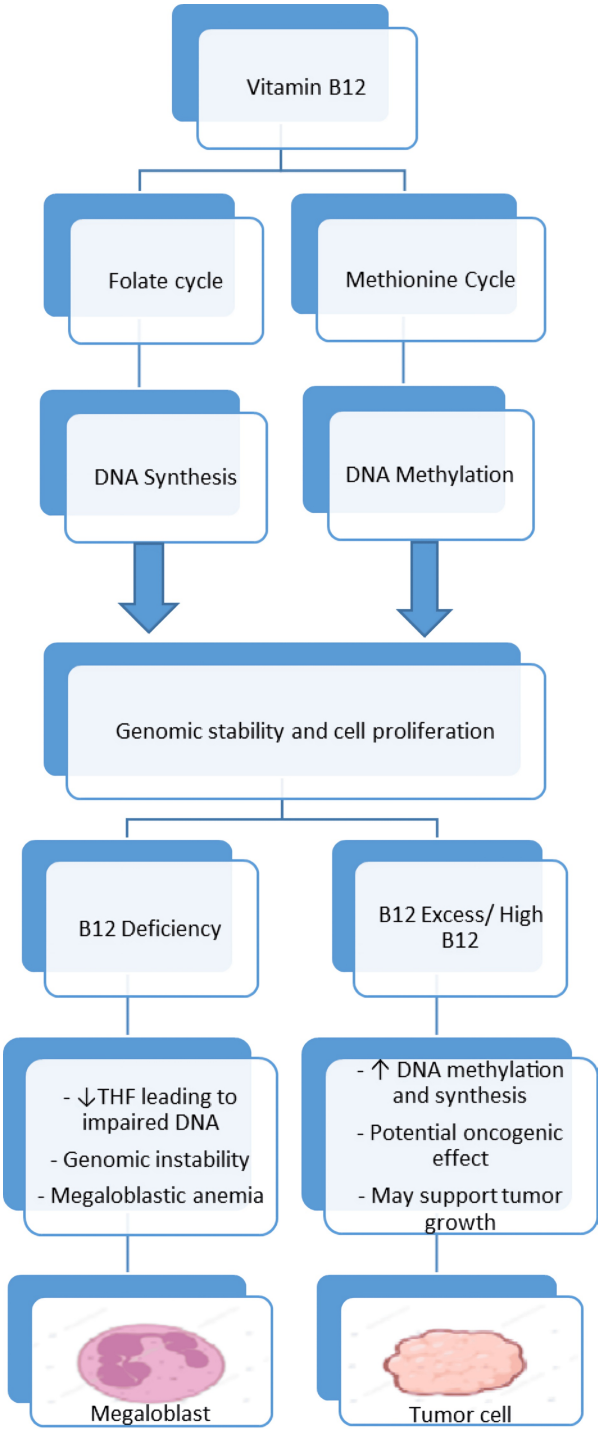


FIGURE 1: Mechanism by which vitamin B12 maintains genomic stability and regulates cellular proliferation.

Image credits: Hala Majeed. The figure was created using BioRender (BioRender Inc., Toronto, Canada) and Microsoft Word (Microsoft Corporation, Redmond, USA).

THF = tetrahydrofolate.

The link of vitamin B12 to cancer has therefore intrigued researchers and clinicians. According to studies evaluating persistently elevated levels of vitamin B12 in certain patients, a link with the presence of solid neoplasms and metastasis has been shown [3,4]. On the contrary, vitamin B12 has been reported to decrease as a result of radiotherapy in some cancers [5].

The use of chemotherapy and radiotherapy in cancer treatment, although effective at improving prognosis

in several neoplasms, has significant toxicity and adverse effects that can affect prognosis and the quality of overall survival in patients. Treatment and intervention decisions are based on certain parameters by which prognosis and chances of survival are determined. Considering this and potential enhancement to quality of life, the decision to refer a patient for specialist care is not taken lightly. For some, symptomatic treatment is preferable. A pertinent question is therefore whether vitamin B12 could be a valuable key in predicting cancer prognosis and survival. The fact that hematological parameters, such as mean corpuscular volume (MCV), and C-reactive protein (CRP) have been linked to cancer prognostication [6-8] makes this an important question to answer. Although researchers have monitored vitamin B12 levels both before and after chemotherapy and radiotherapy with different types of cancer, so far, no explicit study has determined whether increased or decreased levels can be used as effective biomarkers of clinical outcomes, prognostic indicators, or predictors of survival. This study aims to determine whether vitamin B12 levels, particularly trends in these levels after chemotherapy or radiotherapy, are connected with clinical outcomes, cancer prognosis, and survival.

Review

Methods

The current systematic review was conducted following the 2020 version of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [9]. This systematic review was not registered in PROSPERO, OSF, or INPLASY, and no a priori review protocol was written.

Search Sources and Strategy

We searched for relevant literature in PubMed, ScienceDirect, Europe PMC, Directory of Open Access Journals (DOAJ), and HubMed. Due to lack of institutional access to subscription-based conventional databases, these freely available databases were used to increase coverage and strengthen the search. HubMed was used as a supplementary source. A combination of terms relating to vitamin B12, cancer, chemotherapy, radiotherapy, prognosis, and survival prospects was used using Boolean operators ‘AND’ and ‘OR’ to search all databases. In PubMed, however, in addition to these key terms, Medical Subject Headings (MeSH) were also used to maximise the identification of relevant studies. We independently conducted multiple searches using different combinations of MeSH terms and various keywords related to chemotherapy, radiotherapy, prognosis, and survival. In addition, we also conducted targeted searches in the PubMed Advanced Search Builder for studies on cancer prognosis and survival outcomes. Four targeted searches combining vitamin B12 levels with cancer prognosis or survival and chemotherapy or radiotherapy (Searches 3-6 in Table *1*) were initially performed in PubMed but yielded no results. These search combinations were subsequently performed in ScienceDirect, DOAJ, and Europe PMC as supplementary searches to maximize the retrieval of potentially relevant literature. Remaining databases utilized corresponding keyword-based search strategies as well.

Serial No.	Keyword/Search Strategy	Database Used	Number of Results
1.	“ Vitamin B12 levels” AND cancer AND Chemotherapy	PubMed	9
	“ Vitamin B12 levels” AND cancer AND Chemotherapy	Science Direct	199
	“ Vitamin B12 levels” AND cancer AND Chemotherapy	HubMed	13
	“ Vitamin B12 levels” AND cancer AND Chemotherapy	DOAJ	9
	“ Vitamin B12 levels” AND cancer AND Chemotherapy	Europe PMC	417
2.	“Vitamin B12 levels” AND cancer AND radiotherapy	PubMed	2
	“Vitamin B12 levels” AND cancer AND radiotherapy	Science Direct	89
	“Vitamin B12 levels” AND cancer AND radiotherapy	HubMed	2
	“Vitamin B12 levels” AND cancer AND radiotherapy	DOAJ	1
	“Vitamin B12 levels” AND cancer AND radiotherapy	Europe PMC	178
3.	“Vitamin B12 levels” AND “cancer prognosis” AND chemotherapy	Science Direct	7

	“Vitamin B12 levels” AND “cancer prognosis” AND chemotherapy	DOAJ	4
	“Vitamin B12 levels” AND “cancer prognosis” AND chemotherapy	Europe PMC	16
4.	“Vitamin B12 levels” AND “cancer survival” AND chemotherapy	Science Direct	7
	“Vitamin B12 levels” AND “cancer survival” AND chemotherapy	DOAJ	4
	“Vitamin B12 levels” AND “cancer survival” AND chemotherapy	Europe PMC	25
5.	“Vitamin B12 levels” AND “cancer prognosis” AND radiotherapy	Science Direct	5
	“Vitamin B12 levels” AND “cancer prognosis” AND radiotherapy	DOAJ	0
	“Vitamin B12 levels” AND “cancer prognosis” AND radiotherapy	Europe PMC	12
6.	“Vitamin B12 levels” AND “cancer survival” AND radiotherapy	Science Direct	5
	“Vitamin B12 levels” AND “cancer survival” AND radiotherapy	DOAJ	1
	“Vitamin B12 levels” AND “cancer survival” AND radiotherapy	Europe PMC	21
7.	("Vitamin B 12/blood"[Mesh] OR "Vitamin B 12/immunology"[Mesh] OR "Vitamin B 12/radiation effects" [Mesh]) AND ("Neoplasms"[Mesh] OR "National Cancer Institute (U.S.)"[Mesh] OR "Chemotherapy, Cancer, Regional Perfusion"[Mesh] OR "Cancer Survivors"[Mesh]) AND ("Drug Therapy"[Mesh])	PubMed MESH	3
8.	((("Vitamin B 12"[Mesh]) AND ("Vitamin B 12/analysis"[Mesh] OR "Vitamin B 12/physiology"[Mesh] OR "Vitamin B 12/radiation effects"[Mesh])) AND ("Neoplasms/complications"[Mesh] OR "Neoplasms/diagnosis"[Mesh] OR "Neoplasms/drug therapy"[Mesh] OR "Neoplasms/radiotherapy"[Mesh])) AND ("Radiotherapy/adverse effects"[Mesh] OR "Radiotherapy/mortality"[Mesh] OR "Radiotherapy/trends" [Mesh])	PubMed MESH	0
9.	((cancer prognosis) AND (vitamin b12 levels)) AND (chemotherapy or radiotherapy)	PubMed advanced search	31
10.	((cancer survival) AND (vitamin b12 levels)) AND (chemotherapy or radiotherapy)	PubMed advanced search	14
	Total number of research papers identified		1074
	Number of articles after removing duplicates		427

TABLE 1: Keywords/search strategy used and the number of identified papers.

Searches 3 to 6 were initially performed in PubMed but yielded zero results. These searches were subsequently performed in ScienceDirect, DOAJ, and Europe PMC as supplementary searches.

DOAJ = Directory of Open Access Journals.

Database interface filters: In PubMed, filters were applied to restrict the results to studies published between 2005 and 2025, in English, including humans and adults aged ⩾19 years, with free full-text articles. The filter for Article Type was applied to limit results to observational studies. In ScienceDirect, criteria for publication years (2005-2025), English language, Open Access, and Open Archive were used. In Europe PMC, we limited our search to full-text publications published between 2005 and 2025. In DOAJ, the year of publication was limited to 2005-2025. HubMed was searched using the free full-text filter.

All the search records were exported, merged, and duplicates were removed before the screening. The different databases used and the identified number of papers from each database are summarised in Table *1*.

Inclusion Criteria

Only adult cancer populations with exposure to chemotherapy and/or radiotherapy were included. Studies from all geographic locations and ethnic populations were eligible. Outcomes included were changes in vitamin B12 levels following therapy and/or associations between vitamin B12 levels and their prognostic and survival implications. Only observational study designs and full-text articles in the English language that could be retrieved were included for review. Because of the limited number of studies examining the changes in vitamin B12 after chemotherapy or radiotherapy, evidence available for a period of 20 years from 2005 to 2025 was selected.

Exclusion Criteria

Studies with research that focused on benign neoplasms, pediatric population, patients who underwent surgery as part of cancer treatment, or vitamin B12 levels as a diagnostic indicator of cancer were excluded. Patients who underwent surgery were excluded because gastrectomy and ileal resection remove the site of intrinsic factor secretion and vitamin B12 absorption, respectively. Hence, surgically treated patients would confound any treatment-attributable change in vitamin B12. Other studies that were excluded included papers whose full text could not be obtained, gray literature, pre-published articles, papers presented at conferences, editorial articles, letters, reviews, research involving animals, and research conducted in a lab.

Selection Process

After searching the databases, the retrieved articles were transferred to EndNote (Clarivate Plc, London, UK) and duplicate records were removed. Each article was independently screened by two authors based on titles and abstracts. Relevant articles were subsequently assessed for eligibility after full-text availability was confirmed. Studies that met the predetermined inclusion and exclusion criteria were selected for final analysis. Any disagreement between authors in the screening process was resolved by discussion. The literature search was restricted to studies published between 2005 and 2025, consistent with the predefined publication-year eligibility criteria. Screening and eligibility assessment were completed in July 2026; studies published in 2026 were therefore not considered eligible because they fell outside the prespecified publication-year range.

Quality Assessment of the Studies

The assessment of the shortlisted articles was made using relevant quality appraisal tools. The appraisal was done by two independent authors, and any disagreements were resolved through discussion. Case-control and cohort studies were evaluated for quality using the Newcastle-Ottawa Scale (NOS) [10], while cross-sectional studies were evaluated using the JBI Critical Appraisal Checklist [11]. The threshold for quality interpretation of studies evaluated using NOS was set by the authors. Studies that scored ⩾7 were considered good quality, 5-6 were considered fair quality, and ⩽4 were considered poor quality. The quality of the studies was judged and factored into the interpretation of findings. Assessment scores of quality were not the sole reason for exclusion. The certainty of the body of evidence was not assessed using GRADE (Grading of Recommendations, Assessment, Development and Evaluations) due to the limited number and heterogeneity of the studies included.

Data Collection Process

Data extraction was conducted after the articles for the systematic review were finalized. We used a standardized, systematic approach to extract data from each study. Data extraction was done by one reviewer and independently checked by a second reviewer. Disagreements were resolved through discussion. The variables extracted included first author, year, study design, cancer type, sample size, treatment modality, chemotherapy and/or radiotherapy, vitamin B12 levels at baseline and follow-up, and major findings on vitamin B12 levels with prognostic or survival implications.

Vitamin B12 levels were presented in the units reported by the individual studies. Definitions of vitamin B12 deficiency were extracted as reported by the individual studies rather than applying a uniform threshold across all studies. Study authors were not contacted for unclear or missing data.

Data Synthesis

The eight studies selected for the systematic review were too heterogeneous to permit a quantitative meta-analysis. As a result, we summarized and analyzed the evidence tables, which contained the results of vitamin B12 levels after chemotherapy and/or radiotherapy. Comparison of consistencies and variation in vitamin B12 levels between various studies based on type of cancer, type of treatment, sample size, and their relevance to the review question was done. When interpreting and synthesizing the results, due consideration was also given to study quality and risk of bias.

Results

Study Identification and Selection

We found a total of 1,074 relevant articles after using five databases. Before conducting a more thorough search, 647 duplicates were removed. Upon reviewing the titles and abstracts, 86 articles were identified for full-text retrieval. After performing quality appraisal and evaluating for eligibility on the shortlisted articles, eight articles were reviewed. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart in Figure 2 illustrates the selection process for the studies.

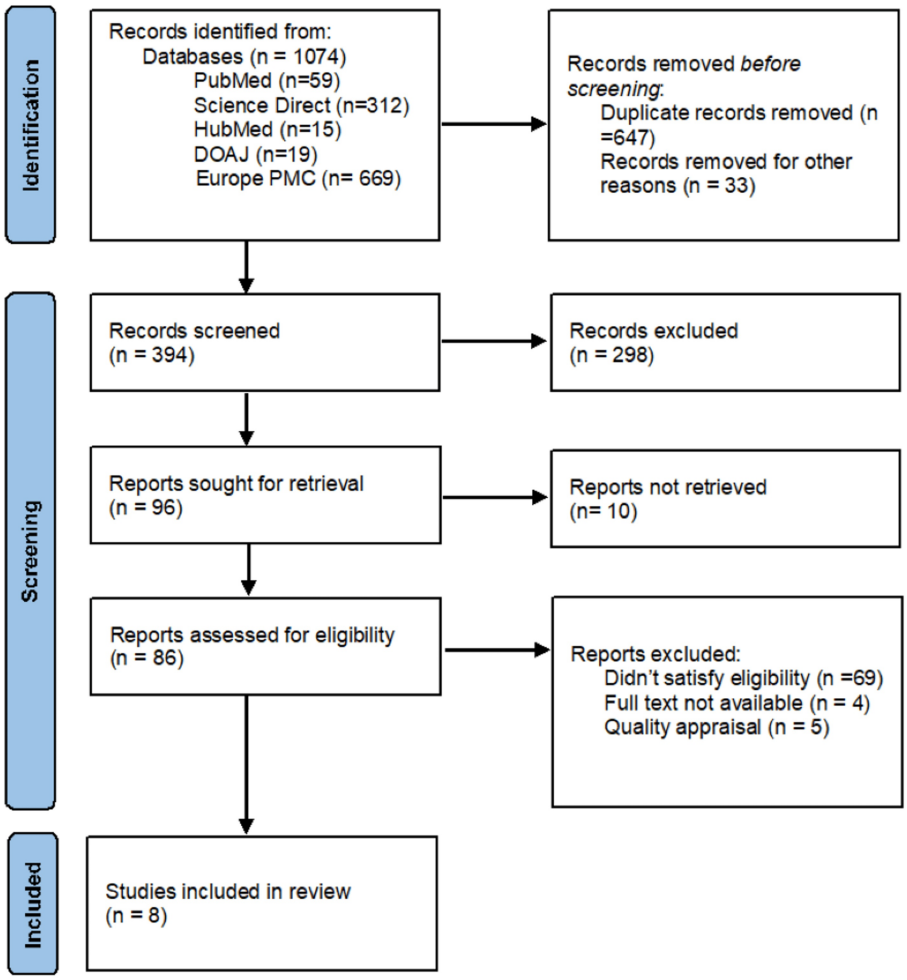


FIGURE 2: PRISMA 2020 flow diagram for new systematic reviews that included searches of databases and registers only

PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; DOAJ = Directory of Open Access Journals.

The articles were finalised after going through quality appraisal using the relevant quality appraisal tools [10,11]. Table 2 and Table 3 show the results of the quality appraisal.

Study	Selection	Comparability	Outcome	Quality
EL-Najjar et al. 2025 [12]	3 stars	0 stars	2 stars	5/9: Fair
EL-Najjar et al. 2025 [13]	3 stars	0 stars	2 stars	5/9: Fair
Kacar et al. 2023 [14]	4 stars	1 star	2 stars	7/9: Good
Liang et al. 2021 [15]	3 stars	1 star	2 stars	6/9: Fair
Liang et al. 2021 [16]	3 stars	1 star	2 stars	6/9: Fair
Cao et al. 2020 [17]	3 stars	1 star	2 stars	6/9: Fair
Bystrom et al. 2009 [18]	4 stars	1 star	1 star	6/9: Fair

TABLE 2: Quality appraisal of case-control and cohort studies using the Newcastle-Ottawa Scale.

The threshold set by the authors for interpreting the quality of the studies through scores is as follows: ≥7: Good, 5-6: Fair, ≤4: Poor.

Newcastle-Ottawa Scale [10].

Serial Number	JBI Question	Assessment
1.	Were the criteria for inclusion in the sample clearly defined?	Yes
2.	Were the study subjects and setting described in detail?	Yes
3.	Was the exposure measured in a valid and reliable way?	Yes
4.	Were objective, standard criteria used for measurement of the condition?	Yes
5.	Were confounding factors identified?	Yes
6.	Were strategies to deal with confounding factors stated?	Yes
7.	Were the outcomes measured in a valid and reliable way?	Yes
8.	Was appropriate statistical analysis used?	Yes

TABLE 3: Quality appraisal of cross sectional study using the JBI Critical Appraisal Checklist.

JBI Critical Appraisal Checklist [11].

Outcomes Measured

The final research papers mainly reported levels of vitamin B12 after chemotherapy or radiotherapy, prognosis, and survival of cancer patients. The second outcomes assessed included metabolic effects due to treatment and quality of life after chemotherapy or radiotherapy.

Study Characteristics

We reviewed a total of 1,477 cancer patients in eight study papers. Of these confirmed studies, one was a case-control study, six were cohort studies, and one was a cross-sectional study. All studies included cancer patients who received chemotherapy or radiotherapy without surgical procedures as part of their treatment regimen for cancer. The cancer types analysed in the study were lung cancer, oesophageal cancer, adenocarcinoma of the colon, cervical cancer, and diffuse large B-cell lymphoma (DLBCL). The type of cancer was unspecified in one study. In cohort studies, blood measures of vitamin B12 levels were taken before and after treatment or at baseline to examine their association with subsequent clinical outcomes. The included studies did not uniformly report chemotherapy regimens. Only one study involved treatment with radiotherapy and was a cross-sectional study.

The studies which were selected for the review are summarized below in Table *4*.

Authors and year of publication	Type of study	Purpose of the study	Number of participants	Vitamin B12 findings	Relevance to Review
EL-Najjar et al. 2025 [12]	Prospective cohort	To explore baseline vitamin B12 and related metabolite levels in newly diagnosed cancer patients pre- and post-chemotherapy regimen at European Gaza Hospital, along with its association with chemotherapy-induced peripheral neuropathy (CIPN).	64 enrolled patients, of whom pre- and post-chemotherapy data of vitamin B12 and related metabolite levels were available for 45 patients.	Serum vitamin B12 levels significantly decreased following chemotherapy (median 355.0 to 219.0 pg/mL; $p < 0.001$), accompanied by significant increases in methylmalonic acid and homocysteine. The findings were consistent with worsening functional vitamin B12 status following chemotherapy.	Direct evidence of chemotherapy leading to a significant decrease in vitamin B12 status and worsening functional B12 biomarkers post treatment and possible clinical relevance to chemotherapy induced peripheral neuropathy (CIPN).
EL-Najjar et al. 2025 [13]	Prospective cohort	To evaluate nutritional status of newly diagnosed cancer patients before and after chemotherapy, along with biochemical evaluation of vitamin B12 and related metabolites.	64 enrolled patients, of whom pre- and post-chemotherapy data of vitamin B12 and related metabolite levels were available for 45 patients.	Serum vitamin B12 levels significantly decreased following chemotherapy (median 355.0 to 219.0 pg/mL; $p < 0.001$), accompanied by significant increases in methylmalonic acid and homocysteine. The findings were consistent with worsening functional vitamin B12 status following chemotherapy.	Direct evidence of chemotherapy leading to a significant decrease in vitamin B12 status and worsening functional B12 biomarkers post-treatment, providing clinical evidence of altered Vitamin B12 status in relation to chemotherapy-induced nutritional decline.
Kacar et al. 2023 [14]	Case-control	The study aimed to evaluate the relationship between serum vitamin D and B12 levels, nutritional status, and psychological factors (depression and anxiety) in adult cancer patients before and after chemotherapy.	The study included 44 cancer patients undergoing chemotherapy and 44 age- and gender-matched healthy controls.	Serum vitamin B12 levels showed no statistically significant difference during chemotherapy or compared with controls (first cure: 311.7 ± 127.1 pg/mL; last cure: 313.7 ± 151.3 pg/mL; controls: 342.8 ± 150.4 pg/mL; $p = 0.421$). Lower serum vitamin B12 levels were independently associated with increased anxiety severity during chemotherapy ($\beta = -0.406$, $p = 0.006$)	Direct chemotherapy-related evidence assessing serum vitamin B12 status and its clinical implications during treatment.
Liang et al. 2021 [15]	Retrospective cohort	To investigate the status of multiple vitamins in EC patients during chemo and assess if they are clinically significant.	203 EC patients aged 37-78 years who were receiving chemotherapy were enrolled in the study.	Serum vitamin B12 levels did not significantly change following chemotherapy in esophageal cancer patients (pre-chemotherapy median 557.219 pg/mL vs post-chemotherapy median 546.789 pg/mL; $Z = -0.326$, $p = 0.745$), and no vitamin B12 deficiency was detected during chemotherapy	Direct chemotherapy-related evidence evaluating longitudinal changes in serum vitamin B12 and nutritional status in esophageal cancer patients undergoing chemotherapy.
Liang et al. 2021 [16]	Retrospective cohort	To investigate changes in serum concentration of multiple vitamins, including Vitamin B12, in patients undergoing chemo	178 lung cancer patients were	Serum vitamin B12 levels did not significantly change following two cycles of chemotherapy in lung cancer patients (pre-chemotherapy median 536.719 pg/mL vs post-chemotherapy median 542.221 pg/mL; Z =	Direct chemotherapy-related evidence evaluating longitudinal serum vitamin B12 changes and

		for lung cancer and identify if any clinical values and influencing factors exist.	enrolled in the study.	−0.101, p = 0.920), and no vitamin B12 deficiency or excess was observed during chemotherapy.	nutritional implications in lung cancer patients undergoing chemotherapy.
Cao et al. 2020 [17]	Prospective cohort	To investigate the clinical significance of B vitamins and SNPs on OCM-related genes in diffuse large B-cell lymphoma receiving chemo and immunotherapy	322 newly diagnosed DLBCL patients.	Serum vitamin B12 levels showed no significant association with treatment response, progression-free survival, or overall survival (CR p=0.722 and 0.623; PFS p=0.396 and 0.127; OS p=0.462 and 0.338).	Chemotherapy-based prognostic study assessing baseline serum vitamin B12 and survival/ treatment outcomes in DLBCL patients receiving R-CHOP immuno-chemotherapy; provides negative evidence regarding prognostic significance of vitamin B12.
Bystrom et al. 2009 [18]	Retrospective cohort	To compare serum vitamin B12, folate, and homocysteine values of ACRC patients before and during chemotherapy treatment and to detect possible deficiencies and relate them to outcome and toxicity in a retrospective analysis.	567 patients	Serum vitamin B12 levels showed only modest changes during chemotherapy (baseline mean 421 pmol/L, median 368 pmol/L; after 2 months mean 409 pmol/L, median 354 pmol/L). No correlation was observed between vitamin B12 levels and objective response, anemia, or severe chemotherapy toxicity. However, patients with subclinically low baseline vitamin B12 levels (<300 pmol/L) demonstrated significantly improved overall survival (p = 0.0002) and time to progression (p = 0.03) compared with patients with higher vitamin B12 levels.	Direct chemotherapy-based study evaluating longitudinal vitamin B12 status before and during treatment and its association with toxicity, treatment response, progression, and survival in advanced colorectal cancer patients.
Vistad et al. 2009 [6]	Cross-sectional	To investigate association between pelvic radiotherapy (RT) and markers of intestinal absorption in cervical cancer survivors.	55	Vitamin B12 levels were significantly lower in cervical cancer survivors 6–12 years after pelvic radiotherapy compared with the reference population (median 213 vs 337 pmol/L; p < 0.001). Serum methylmalonic acid levels were significantly higher (median 0.20 vs 0.14 µmol/L; p < 0.001), and 20% of survivors (11/55) met criteria for cobalamin deficiency.	Direct radiotherapy-related study demonstrating long-term vitamin B12 deficiency and impaired cobalamin status in cervical cancer survivors following pelvic radiotherapy.

TABLE 4: Summaries and characteristics of all included studies.

Studies are identified by the first author's surname and the year of publication.

EC = esophageal cancer; SNPs = single nucleotide polymorphisms; OCM = one-carbon metabolism; DLBCL = diffuse large B-cell lymphoma; PFS = progression-free survival; OS = overall survival; CR = complete response; R-CHOP = rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; ACRC = advanced colorectal cancer.

Discussion

Out of eight reports representing seven distinct study cohorts covered in this review, seven reports assessed chemotherapy and one report evaluated radiotherapy. The two recent reports from Gaza were derived from the same prospective cohort and therefore represent complementary findings rather than independent populations [12,13]. The earlier chemotherapy studies generally showed no statistically significant or only modest changes in vitamin B12 levels during or after therapy [14-18]. However, the recent prospective study from Gaza demonstrated a significant decrease in serum vitamin B12 following chemotherapy, accompanied by significant increases in methylmalonic acid (MMA) and homocysteine (Hcy), consistent with worsening functional vitamin B12 status [12,13]. Though the studies varied greatly in cancer type and

chemotherapeutic regimen, these findings suggest that the effect of chemotherapy on vitamin B12 status may not be uniform and may depend on patient population, nutritional status, treatment regimen, and the method used to assess vitamin B12 status [18,19,20]. In contrast to our findings, a study conducted by Vistad et al. (2009), which was the only one to assess radiotherapy, revealed significantly lower vitamin B12 levels and impaired cobalamin status between 6 and 12 years after pelvic radiotherapy [5]. This finding shows that cancer survivors receiving pelvic irradiation may sustain vitamin B12 deficiency for the long term [5]. Further evaluation of vitamin B12 status is warranted in this population. Future research should evaluate clinical implications of deficiencies more and whether targeted screening or supplementation strategies improve outcomes.

The findings from the recent Gaza studies should, however, be interpreted with caution. Although 64 patients were enrolled, paired vitamin B12 and related metabolite measurements were available for only 45 patients [12,13]. The relatively small sample size may limit the precision and generalizability of the observed changes. In addition, the cohort included different cancer types and chemotherapy regimens, making it difficult to determine whether the observed reduction in vitamin B12 was directly attributable to chemotherapy or was influenced by other factors [10]. The concurrent study in the same cohort also showed a decline in nutritional status after chemotherapy, indicating that nutritional deterioration may have played a role in the observed reduction in vitamin B12 [13]. Thus, the decrease in vitamin B12 should be interpreted in the light of both exposures to chemotherapy and nutritional status.

The first Gaza report that specifically evaluated chemotherapy-induced peripheral neuropathy (CIPN) provides further support for the clinical relevance of these findings [12]. The study found that the increase in MMA after chemotherapy was significantly associated with the severity of CIPN, and this association remained significant after multivariable adjustment [12]. This suggests that worsening functional vitamin B12 status may have clinical neurological implications during chemotherapy [12]. However, this finding should be interpreted cautiously because platinum compounds were the most commonly used chemotherapy agents in the Gaza cohort (46.9%), followed by taxanes (28.1%), and these chemotherapy classes are well recognized causes of peripheral neuropathy [21,22]. Therefore, the observed association between worsening functional vitamin B12 status and CIPN may be influenced by the neurotoxic effects of the chemotherapy regimens themselves [21,22,12]. Nevertheless, the finding provides an important potential clinical link between altered vitamin B12 status and chemotherapy-related neurological toxicity that warrants further investigation.

Another important consideration is the way in which vitamin B12 status is assessed. Most of the studies included in this review measured serum vitamin B12 levels alone [14-18]. However, serum vitamin B12 alone may underestimate functional vitamin B12 deficiency, since metabolic markers such as MMA may be more sensitive to detecting impaired cobalamin status [23]. The recent Gaza studies assessed vitamin B12 together with related metabolites and demonstrated significant increases in MMA and Hcy following chemotherapy [12,13]. This raises the possibility that studies relying only on serum vitamin B12 may fail to identify some functional changes following chemotherapy [23]. Although this possibility cannot be established retrospectively, it should be considered when interpreting the lack of significant changes observed in some of the other chemotherapy studies. Future studies should therefore consider assessing serum vitamin B12 together with functional biomarkers such as MMA when evaluating changes in vitamin B12 status following cancer treatment.

While chemotherapy generally did not appear to consistently change vitamin B12 concentrations, three studies found clinically relevant associations with vitamin B12 status [6,14,12,13]. Kacar et al. found that lower vitamin B12 levels were independently associated with greater severity of anxiety during chemotherapy. This suggests that vitamin B12 status may have implications not only for hematologic and neurologic functions but also for psychological well-being [14]. Likewise, the recent Gaza study showed that the decline in functional vitamin B12 status, which was indicated by the rise in MMA after chemotherapy, was significantly associated with chemotherapy-induced peripheral neuropathy [12]. Similarly, Byström et al. observed that patients with lower baseline vitamin B12 levels exhibited significantly better overall survival and a longer time to progression compared with those with higher baseline levels [18]. This finding is corroborated by earlier studies which indicated that high levels of circulating vitamin B12 were associated with worse prognosis, increased tumor burden, and metastatic disease in patients with solid cancers [3,4]. One theory holds that elevated serum vitamin B12 signals increased production of cobalamin-binding proteins by tumor or inflammatory cells, not improved nutritional status [24]. These results may indicate that vitamin B12 levels during chemotherapy may not consistently change, although some populations may experience significant declines. Nevertheless, baseline vitamin B12 status may have prognostic and clinical value in cancer patients [25, 26].

A high level of vitamin B12 is consistently linked with the presence of solid tumors. This link is more pronounced for metastatic disease compared with non-metastatic disease, even after accounting for known causes of elevated vitamin B12 [3,4]. Most cancers of the pancreas, colon and rectum, lung, prostate, urothelium, bone, and liver are associated with these elevations, and these have also been linked with worse cancer outcomes [3,4]. These findings overall suggest the potential prognostic relevance of vitamin B12 in oncology.

Current evidence remains predominantly observational. Elevated vitamin B12 levels may not be an independent prognostic biomarker [27, 28]. It is unclear whether it merely reflects tumor burden, systemic inflammation, hepatic dysfunction, or something else [3,4]. Consequently, the possible use of making multiple measurements of vitamin B12 post-treatment needs further exploration. Future studies are needed to determine if vitamin B12 changes can predict disease progression, recurrence, or survival and whether vitamin B12 monitoring should be routinely implemented into clinical practice because of its meaningful benefit to patients.

Several strengths and limitations of the evidence should be kept in mind when interpreting the findings of this review. One strength was that the majority of the included reports were cohort studies, which can provide robust longitudinal data on vitamin B12 status over time in relation to treatment exposure [29]. The designs firstly enabled assessment of subjects' vitamin B12 status over time in relation to treatment exposure. Secondly, such designs minimize the potential risk for recall bias [30]. In addition, the cross-sectional study by Vistad et al. (2009) could provide information from a longer follow-up since they evaluated vitamin B12 status after 6-12 years of having pelvic radiotherapy [5]. They could provide information about late toxicities.

Still, many limitations were found. Only one study of patients on radiotherapy was available for evaluation; therefore, comparison between effects of chemotherapy and radiotherapy on vitamin B12 was not possible. Only a small number of distinct study cohorts met the inclusion criteria, indicating that the overall evidence base was also small. The two recent Gaza reports originated from the same underlying prospective cohort and should not be considered independent evidence. Furthermore, only 45 of the 64 enrolled patients had paired biochemical measurements in this cohort, which limits the strength and generalizability of the findings [12,13]. Moreover, certain subscription-based databases that required institutional access, such as Embase, Scopus, Web of Science, and The Cochrane Library, could not be used. This is due to the unavailability of subscriptions and thus may have resulted in missing some relevant studies. In addition, there were no included studies for several common cancers (gastric, renal, hepatic), which makes it difficult to generalize the findings to these patients. Another shortcoming was the absence of information on vitamin B12 status before diagnosis, which made it hard to know whether vitamin B12 levels reflected treatment or inherent differences in patients. Furthermore, none of the studies that were included assessed use of combined chemo-radiotherapy. This is used widely in current days [31]. Most studies ultimately assessed vitamin B12 levels either during treatment or shortly after treatment, with little long-term data. Consequently, the long-term impact of chemotherapy on vitamin B12 status is still not fully understood.

The exclusion of patients who underwent surgery as part of cancer treatment was intended to reduce confounding of treatment-related changes in vitamin B12. Gastrectomy can impair vitamin B12 absorption through reduced intrinsic factor availability, while ileal resection can impair vitamin B12 absorption by removing part of the principal site of absorption. Therefore, including patients who underwent such procedures could make it difficult to distinguish changes attributable to chemotherapy or radiotherapy from changes caused by altered gastrointestinal anatomy and absorption [32]. However, exclusion of surgically treated patients may also limit generalizability of the findings, as surgical treatment is part of the multimodal treatment for many cancer patients. Future studies should therefore clearly document the type and timing of cancer surgery and consider its possible effects on vitamin B12 status when assessing the effects of chemotherapy or radiotherapy.

Another limitation is that the recent Gaza cohort had a relatively high proportion of patients receiving platinum-based chemotherapy, which was the most common chemotherapy class in the cohort [12,13]. Since platinum-based agents are independently associated with peripheral neuropathy, this may have influenced the observed association between worsening functional vitamin B12 status and CIPN [21,22]. Future studies should therefore account for individual chemotherapy agents and cumulative treatment exposure when evaluating the relationship between vitamin B12 status and chemotherapy-related neurological outcomes.

This review's findings propose several important directions for future research. More extensive prospective cohort studies are needed to better characterize changes in vitamin B12 status across cancers, which are currently limited in number and vary across heterogeneous cancer types and treatment modalities. With more evidence being available, meta-analyses may help further estimate more accurately the effects of chemotherapy and radiotherapy on vitamin B12 concentrations in cancers. Future studies should also include larger and more representative populations, standardized assessment of nutritional status, detailed reporting of chemotherapy regimens, and paired assessment of serum vitamin B12 and functional biomarkers such as MMA and Hcy.

More studies are warranted, as previous studies have linked high serum vitamin B12 levels with advanced oncologic outcomes including advanced stage of disease, increased burden of metastasis, and survival disadvantage in those with solid tumours [3,4]. Nevertheless, the relevance of raised levels of vitamin B12 during or after chemotherapy and radiotherapy is debatable, as it could merely reflect the severity of disease.

Future studies should thus evaluate the prognostic value of serial vitamin B12 measurements in cancer patients and whether certain thresholds are associated with clinically meaningful outcomes. The findings

may help clarify whether vitamin B12 assists in risk stratification and treatment decisions, but its role in treatment decisions is uncertain.

Conclusions

In conclusion, the available information suggests that the effect of chemotherapy on circulating vitamin B12 levels is inconsistent. While several studies showed no substantial change or only modest reductions, the recent prospective Gaza cohort demonstrated a significant decline in serum vitamin B12 accompanied by worsening functional vitamin B12 biomarkers following chemotherapy. However, the relatively small sample size, incomplete paired biochemical data, heterogeneous cancer population and chemotherapy regimens, and the fact that the two recent reports originated from the same cohort limit the strength and generalizability of this finding. Pelvic radiation may contribute to the pathogenesis of long-term vitamin B12 deficiency in cancer survivors. Evidence of clinical implications of vitamin B12 status is limited, such as a possible relationship of low baseline vitamin B12 with increased anxiety severity during chemotherapy and an association between worsening functional vitamin B12 status and chemotherapy-induced peripheral neuropathy. However, the latter finding should be interpreted cautiously because platinum-based chemotherapy, which was the most common treatment in the Gaza cohort, is itself associated with peripheral neuropathy. However, current evidence on the relationship between vitamin B12 levels and cancer prognosis as well as survival is limited and inconsistent. The use of serum vitamin B12 alone may also fail to identify functional abnormalities, highlighting the potential value of incorporating biomarkers such as MMA in future studies. Meta-analysis was not feasible due to the small number of studies, heterogeneity in cancer types, treatment regimens, period of follow-up, and outcome variables, and these findings have limited generalizability. Thus, routine clinical use of vitamin B12 as a biomarker cannot be recommended at present. Further well-designed prospective studies are needed to clarify the relationship between cancer therapy, vitamin B12 status, functional B12 biomarkers, nutritional status, chemotherapy-related neurological toxicity, and clinically relevant outcomes including prognosis and survival.

Additional Information

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All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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