Nutrición Hospitalaria

Vitamina D y cáncer gástrico: revisión sistemática y metaanálisis

Vitamin D and gastric cancer — A systematic review and meta-analysis

10.20960/nh.04410

06/13/2023

OR 4410

Vitamin D and gastric cancer — A systematic review and meta-analysis

Vitamina D y cáncer gástrico: revisión sistemática y metaanálisis

Xi Zhao[1], Jie Wang[2], Long Zou[1]

[1]Sichuan Mental Health Center. The Third Hospital of Mianyang. Mianyang, People's Republic of China. [2]Graduate Division. North Sichuan Medical College. Nanchong, People's Republic of China

Received: 29/08/2022
Accepted: 08/03/2023
Correspondence: Long Zou. Sichuan Mental Health Center. The Third Hospital of Mianyang. MianYang 621000, People's Republic of China
e-mail: zl08163697@163.com

Ethical statement: the authors respond for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately considered and resolved.

Availability of data and materials: this publication is backed by multiple datasets, which are openly available at locations cited in the reference section. Additional data for this article have been supplied as supplementary files. There is no additional unpublished data.

Competing interests: all authors have completed the ICMJE uniform disclosure form. The authors do not have any conflicts of interest to declare.

Statement: the manuscript has been both read and approved by all the authors.

Publication history: posted history: this manuscript was previously posted on Research Square: doi: 10.21203/rs.3.rs-1067367/v1

ABSTRACT

Objective: to explore the association between serum vitamin D level and the occurrence and pathological grade of gastric cancer.

Material a nd methods: search PubMed, Embase, Web of Science, Cochrane and Chinese database; all articles about the association between serum vitamin D levels and gastric cancer published before July 2021.

Results: 10 trials with 1159 cases of gastric cancer patients and 33,387 cases of regular control patients were analyzed. The serum vitamin D level of the gastric cancer group (15.56 ± 7.46 ng/ml) was lower than in the control group (17.60 ± 1.61 ng/ml), and the difference was statistically significant. The patients with gastric cancer, clinical stage III/IV (16.19 ± 8.04 ng/ml) had lower vitamin D levels than those with stage I/II (19.61 ± 9.61 ng/ml), and the patients with low differentiation of gastric cancer (17.5 ± 9.5 ng/ml) had lower levels than those with well- or moderately-differentiated cancer (18.04 ± 7.92 ng/ml). The patients with lymph node metastasis (19.41 ± 8.63 ng/ml) had lower vitamin D levels than the patients without lymph node metastasis (20.65 ± 7.96 ng/ml), and the difference was statistically significant.

Conclusion: vitamin D levels were negatively associated with gastric cancer. Vitamin D levels were significantly associated with different clinical stages, degrees of differentiation, and lymph node metastasis, suggesting that low vitamin D levels might predict poor prognosis in gastric cancer.

Keywords: Stomach neoplasm. Vitamin D. Meta-analysis.

RESUMEN

Objetivo: investigar la asociación entre los niveles de vitamina D en suero y la carcinogénesis gástrica y su clasificación patológica.

Material y métodos: se buscaron en las bases de datos PubMed, Embase, Web of Science, Cochrane y China todos los artículos sobre la asociación entre los niveles séricos de vitamina D y el cáncer gástrico publicados antes de julio de 2021.

Resultados: se analizaron diez datos de 1159 pacientes con cáncer gástrico y 33.387 pacientes normales de control. El nivel de vitamina D en suero del grupo (15,56 ± 7,46 ng/ml) de cáncer gástrico era inferior al del grupo de control (16,19 ± 8,04 ng/ml), y la diferencia era estadísticamente significativa. En los pacientes con cáncer gástrico en estadio clínico III/IV (16,19 ± 8,04 ng/ml) era inferior al de los pacientes en estadio I/II (19,61 ± 9,61 ng/ml) y en los pacientes con cáncer de estómago poco diferenciado (17,5 ± 9,5 ng/ml) era menor que en los pacientes con cáncer bien o moderadamente diferenciado (18,04 ± 7,92 ng/ml); en los pacientes con metástasis en ganglios linfáticos (19,41 ± 8,63 ng/ml) era inferior al de los pacientes sin metástasis en ganglios linfáticos (20,65 ± 7,96 ng/ml), siendo la diferencia estadísticamente significativa.

Conclusión: los niveles de vitamina D se correlacionaron negativamente con el cáncer gástrico. Los niveles de vitamina D se asociaron significativamente a los diferentes estadios clínicos, el grado de diferenciación y la metástasis en ganglios linfáticos, lo que sugiere que los niveles bajos de vitamina D pueden ser un factor de predicción de mal pronóstico en el cáncer gástrico.

Palabras clave: Tumores gástricos. Vitamina D. Metaanálisis.

INTRODUCTION

Gastric cancer is the fifth most common cancer and the third most common cause of cancer death globally (1). According to statistics, there were about 1 million newly diagnosed cases of gastric cancer in 2018 (2); approximately 784,000 people died of stomach cancer (1). The incidence and mortality of gastric cancer has plummeted in recent years, partly due to broader population screening and increased awareness of the treatment of *Helicobacter pylori* infection (3).However, cancer is still a major health problem affecting Chinese people and people all over the world. According to the latest statistics, there are 319,000 newly diagnosed cases of gastric cancer and 390,000 cases died of gastric cancer in China (3). Although interventions have been made to reduce the burden of cancer, the first task is to identify possible risk factors related to cancer risk (4). Therefore, we urgently need predictors of early gastric cancer that are easy to identify, obtain, and improve.

Recently, the role of vitamin D in gastric cancer has been gradually explored. Vitamin D is a precursor of the steroid hormone calcitriol. It mainly binds to vitamin D receptors to regulate gene expression, thereby inhibiting the growth of gastric cancer cells (5,6). It is known that vitamin D has the effects of inhibiting proliferation, promoting apoptosis, and inhibiting inflammation and angiogenesis (6). Recently, it has been discovered that it can also overcome the resistance of chemotherapy drugs by reversing or reducing EMT (epithelial-mesenchymal transition) and cancer cell stemness (7). There is currently no human randomized controlled trial to clearly support the beneficial effects of vitamin D; however, some clinical research results strongly indicate that vitamin D deficiency will increase the incidence of cancer, and supplementing vitamin D may be an economical and safe method to reduce the incidence of cancer

and improve the prognosis of cancer (8). This study collects relevant clinical studies and conducts systematic reviews and meta-analyses to clarify the correlation between serum vitamin D levels and the occurrence of gastric cancer and different clinicopathological characteristics. Moreover, it also provides relevant evidence for the role of vitamin D in the primary prevention and long-term prognosis of gastric cancer.

METHODS

Inclusion and exclusion criteria

Inclusion criteria: 1) all articles related to vitamin D and gastric cancer published before July 2021, the language type is limited to English and Chinese, including cross-sectional studies, case-control studies; 2) at least one parameter required by this research can be extracted, including the serum vitamin D levels of the experimental group and the control group, the serum vitamin D levels of patients with different clinical grades, degrees of differentiation, and distant metastasis; 3) hematological indicators of all subjects were collected before radiotherapy, chemotherapy or surgery.

Exclusion criteria: 1) repetitive literature, literature reviews, graduation theses, case reports, etc.; 2) animal experiments or basic research; 3) documents for which the full text cannot be obtained; 4) documents for which the required data is not available or cannot be obtained; 5) do not clearly state the status of vitamin D supplementation before obtaining serological specimens.

Search strategy

Our search database of PubMed, Embase, Web of Science, Cochrane, and Chinese database before July 2021. The search terms mainly include: "vitamin D", "gastric cancer", "stomach neoplasm", etc. The search languages are limited to Chinese and English. In addition, a manual search was conducted on the references of the subject-

related articles to expand the search scope. Taking Embase, which has the most documents, as an example, the search terms were as follows: ((((((((((((((((("Stomach Neoplasm") OR "Neoplasms, Stomach") OR "Gastric Neoplasms") OR "Gastric Neoplasm") OR "Neoplasm, Gastric") OR "Neoplasms, Gastric") OR "Cancer of Stomach") OR "Stomach Cancers") OR "Gastric Cancer") OR "Cancer, Gastric") OR" Cancers, Gastric") OR "Gastric Cancers") OR "Stomach Cancer") OR "Cancer, Stomach') OR" Cancers, Stomach") OR "Cancer of the Stomach") OR "Gastric Cancer, Familial Diffuse")) AND ((((((vitamin D) OR ((((((Ergocalciferols) OR Calciferols) OR Vitamin D 2) OR Vitamin D2) OR "D2, Vitamin") OR Ergocalciferol)) OR ((((((Cholecalciferol) OR Calciol) OR "(3 beta,5Z,7E)-9,10-Secocholesta-5,7,10(19)-trien-3-ol) OR Vitamin D 3) OR Vitamin D3) OR Cholecalciferols)) OR ((((((((((((((((((((((((((((((Calcitriol) OR 1 alpha,25-Dihydroxyvitamin D3) OR 1 alpha,25 Dihydroxyvitamin D3") OR "D3, 1 alpha,25-Dihydroxyvitamin") OR "1,25-Dihydroxyvitamin D3") OR "1,25 Dihydroxyvitamin D3") OR" D3, 1,25-Dihydroxyvitamin") OR" 1 alpha,25-Dihydroxycholecalciferol") OR "1,25-Dihydroxycholecalciferol") OR "1,25 Dihydroxycholecalciferol") OR "Bocatriol) OR Calcijex") OR "Calcitriol KyraMed") OR" KyraMed, Calcitriol") OR "Calcitriol-Nefro") OR "Calcitriol Nefro") OR Decostriol) OR "MC1288") OR "MC-1288") OR "MC 1288") OR Osteotriol) OR Renatriol) OR Rocaltrol) OR Silkis) OR Sitriol) OR Soltriol) OR Tirocal) OR '20-epi-1alpha,25-dihydroxycholecaliferol") OR "1,25-dihydroxy-20-epi-Vitamin D3') OR "1,25 dihydroxy 20 epi Vitamin D3") OR" D3, 1,25-dihydroxy-20-epi-Vitamin") OR "1,25(OH)2-20epi-D3") OR "1 alpha, 25-dihydroxy-20-epi-Vitamin D3")))).

Literature quality assessments

The Newcastle-Ottawa Quality Assessment Scale (NOS) was used to assess the case-control studies' quality. NOS includes three aspects, selection, comparability, and exposure or results. The total score is 9 points. The total score of included studies is ≥ 6 points, considered

high quality (9). Research scores included in this study are all ≥ 6 points, and the total average score is 8 points. Evaluation of 2 cross-sectional studies using the cross-sectional study evaluation criteria recommended by the Agency for Healthcare Research and Quality (AHRQ) (10). The entire score is 11 points, and the two studies are 9 points (11) and 8 points (12), both of which are high-quality articles. The scoring results are shown in table I.

Data collection

According to the inclusion and exclusion criteria, the first author's name, publication time, research location, number of cases and parameters (including patient age and gender, smoking, and drinking history, gastric mucosal tissue type, lymph node metastasis, and pathological grading are recorded). The two authors independently extracted the data (Zhao X, Wang J), and the differences were resolved through discussion. When the extracted serum vitamin D concentration unit is inconsistent, it is uniformly adjusted to ng/ml.

Statistical method

The RevMan5.4 provided by the Cochrane Library's official website and Stata 14 statistical software were used for the meta-analysis, and the Q statistic test and I^2 test were used to analyze the heterogeneity of the included studies. If there was significant heterogeneity between studies ($p < 0.1$, $I^2 \geq 50\,\%$), then the source of heterogeneity was analyzed. Apparent clinical heterogeneity was processed by analysis or sensitivity analysis that eliminates each study to determine the potential source of heterogeneity. After excluding the factors that affect heterogeneity, the combined analysis of the research results adopted the random effects model analysis; if heterogeneity was not significant, the fixed effects model analysis was adopted. All measurement data used mean difference (MD) as the effect indicator, and each effect size is given with its 95 % confidence interval (CI). A forest map was plotted and

compared the count data among multiple groups of the single-factor analysis. When the difference of p was smaller than 0.05, it was statistically significant. The Egger test was used to evaluate publication bias. When $p < 0.1$, it was considered statistically significant, and there was publication bias.

RESULTS

Basic characteristics and quality evaluation

Seven hundred ninety-three related documents were first detected, and 27 duplicate documents were found. After reading the title and abstract, 746 articles were excluded. After reading the complete text, ten articles were finally included (11-20); the screening flowchart is shown in figure 1, including 1159 cases of gastric cancer patients and 33,387 cases of regular control patients. The literature screening process and results are shown in figure 1, including 8 case-control studies (13-20), and 2 cross-sectional studies (11,12), all coming from India, Iran, Turkey, South Korea, China and other Asian countries. The essential characteristics and the quality evaluation of the literature are shown in table I.

Statistical analysis

Comparison of serum vitamin D levels between gastric cancer group and the healthy control group

Among the included ten studies, only seven studies (11-17) compared the serum vitamin D levels of the gastric cancer experimental group and the normal control group, comparing 730 cases of gastric cancer with 33,387 cases of normal individuals, and conducted a meta-analysis of seven studies. Significant heterogeneity was found during the analysis ($I^2 = 99$ %, $p < 0.00001$). We found no significant heterogeneity among subgroups of different vitamin D determination methods and publication years (before or after 2018). After the sensitivity analysis, it was finally found that

there was no significant change in heterogeneity after excluding any one of the studies. The analysis showed that the vitamin D level of the gastric cancer group was significantly lower than that of the standard group, and the difference was statistically significant (MD = -8.28, 95 %CI (-14.32 to -2.23), $p = 0.007$), as shown in figure 2.

Vitamin D and clinical stage

Six studies (12,14,17-20) reported the serum vitamin D levels of patients with different clinical stages of gastric cancer. A total of 650 patients with gastric cancer were analyzed, including 429 patients with stage III/IV and 221 with stage I/II. The results show significant heterogeneity ($I^2 = 80$ %, $p = 0.0002$). After submitting each study one by one, it was found that there was no heterogeneity ($I^2 = 0$ %, $p = 0.89$) after excluding Li Qiang's research, considering that Li Qiang's research subjects are older adults aged 62-83, and the sample size is small. Not including Li Qiang's research, the results showed that the vitamin D level of patients with stage III/IV was lower than that of patients with stage I/II, and the difference was statistically significant (MD = -3.57, 95 % CI (-4.21 to -2.92), $p < 0.00001$), as shown in figure 3.

2.2.3 Vitamin D and degree of differentiation

Six studies (12,13,17-20) reported a total of 677 patients with differently differentiated gastric cancer patients with serum vitamin D levels, and the results suggest severe heterogeneity ($I^2 = 80$ %, $p = 0.0002$). The sensitivity analysis suggests there is no significant improvement in heterogeneity after excluding any one study. The poorly differentiated serum vitamin D level or other differentiated gastric cancer patients was significantly lower than that of well or moderately-differentiated gastric cancer patients. The difference was statistically significant (MD = -2.59, 95 % CI (-4.85 to -0.66), $p = 0.03$), as shown in figure 4.

Vitamin D and lymph node metastasis and distant metastasis

Three studies (18-20) reported 404 cases of gastric cancer, including 191 cases of N0/N1 gastric cancer and 213 cases of N2/N3 gastric cancer. The analysis demonstrated that there was no heterogeneity (I^2 = 0 %, p = 0.72) . The serum vitamin D level of patients with lymph node metastasis N2/N3 is lower than that of patients with N0/N1, and the difference is statistically significant (MD = -0.55, 95 % CI (-0.77 to -0.32), p < 0.00001), as shown in figure 5. Four studies (17-20) reported 392 patients with gastric cancer, including 62 patients with gastric cancer with distant metastasis and 330 patients with gastric cancer without distant metastasis. The difference was not statistically significant (MD = -2.57, 95 % CI (-6.73-1.58), p = 0.23). In addition, we also analyzed the differences in serum vitamin D levels by age, gender, smoking habit, drinking habit, and time of onset (whether more than four months), and the results showed no statistical significance.

Publication bias and sensitivity analysis

We performed the Egger test to evaluate publication bias on seven articles (11-17) that included control of gastric cancer and regular patients and finally found no obvious publication bias (p = 0.395). We included six articles on different clinical stages of gastric cancer patients(12,14,17-20) and the Egger test to evaluate publication bias, and no obvious publication bias was found (p = 0.685). Evaluation of 6 articles with different degrees of differentiation (12,13,17-20) found the difference was statistically significant (P=0.055), suggesting a publication bias, as shown in figure 6.

DISCUSSION

Our study concluded that decreased vitamin D levels increased the risk of gastric cancer and were significantly associated with different clinical grades, degrees of differentiation, and lymph node metastases.

Vitamin D is a fat-soluble vitamin. The two main active forms are

vitamin D3 (cholecalciferol) and vitamin D2 (ergocalciferol). Vitamin D3 is the only form of vitamin D that naturally occurs in animals. It can produced from 7-dehydrocholesterol in the skin through sunlight exposure. The synthesis of vitamin D3 in the skin is the most important source of vitamin D, but vitamin D2 and vitamin D3 have no biological activity, and both must be activated by 25-hydroxylase in the liver and 1,25-dihydroxylase in the kidney to $1,25(OH)_2D3$ (calcitriol) (6). Calcitriol is a potent steroid hormone that regulates gene expression in most tissues after binding to vitamin D receptors (8).

The current anti-tumor research of vitamin D mainly includes the effect on cancer cell apoptosis and proliferation. Recently, it has also been found that vitamin D also has a certain effect on the tumor microenvironment and drug resistance in chemotherapy. Studies have shown that $1,25(OH)_2D_3$ can re-encode the cancer-associated fibroblast (CAF) genes to reduce the malignant phenotype of colon cancer and directly inactivate CAF to achieve the prevention and protection of colon cancer. It can also affect immune cells and endothelial cells by stimulating CAF to secrete signal factors (21). Vitamin D may participate in the resistance of multiple drugs through different mechanisms, but the existing molecular mechanisms mainly involve reversing or reducing the epithelial-mesenchymal transition (EMT), and the inhibition of cancer cell stemness. EMT is a cellular program that leads tumor cells to have other characteristics of malignant tumors, such as decreased apoptosis. The latest research has found that it can cause tumors to develop resistance to chemotherapy, radiotherapy and immunotherapy(7). Therefore, a large number of studies have suggested that inhibition of EMT can effectively improve tumor drug resistance. Studies have shown that EMT has occurred after long-term use of the EGFR inhibitor erlotinib to treat non-small cell lung cancer. Treatment with $1,25(OH)_2D3$ can reverse EMT and restore sensitivity through inhibition of TGF-β by EMT induction of cancer cells (22). In addition, by inhibiting the

expression of LCN2 and phosphorylation of Nf-kB, oral cancer cells can be sensitized to cisplatin again (23). In in vitro studies, human colorectal cancer cells treated with vitamin D analog PRI-2191 and imatinib had significantly down-regulated their expression of stemness-related genes, indicating that vitamin D plays a crucial role in controlling to initiate cancer recurrence of residual colon cancer cells (24).

The study's results showed that the serum vitamin D level of patients with gastric cancer was lower than that of normal individuals. It can be seen that adequate vitamin D levels have a certain preventive effect on the occurrence of gastric cancer. In the study of gastric cancer patients in different clinical stages, it was found that the serum vitamin D level of patients with stage III/IV gastric cancer was significantly lower than that of patients with stage I/II. It can be seen that vitamin D has a certain effect on the prognosis of gastric cancer. There are two studies (18,19) analyzing the survival data of patients with gastric cancer, and the results suggest that patients with high vitamin D levels have a longer survival time than patients with lower levels. The result of Wang (18) suggest that the median survival time of patients with vitamin D > 20 ng/ml is 52.4 ± 4.98 months, and that of patients with ≤ 20 ng/ml is 29.8 ± 5.15 months. Li Q's research (19) showed that the progression-free survival period of gastric cancer patients with vitamin D greater than 20 ng/ml was 19 months (95 % CI: 14.1-23.8 months), and the progression-free survival period of patients with ≤ 20 ng/ml was 10 months (95 % CI: 7.8-12.1 months), the difference being statistically significant. Therefore, vitamin D levels may affect the survival of patients with gastric cancer. However, few studies report related outcomes, and many clinical studies are still needed to confirm these findings.

Although some studies suggest that vitamin D is likely to play a role in the neoadjuvant treatment or even in chemotherapy prevention (18), existing studies have not confirmed that vitamin D supplementation can improve the occurrence and prognosis of

tumors. Urashima M first proposed that vitamin D supplementation does not improve 5-year recurrence-free survival rate for patients with gastrointestinal tumors (25). Interestingly, the research team found that vitamin supplementation in high-grade differentiation, signet ring-cell carcinoma, and squamous-cell carcinoma cannot improve relapse-free survival (RFS), but vitamin D supplementation can improve RFS in poorly differentiated cancers (26). At the same time, they found that low levels of bioavailable 25-hydroxyvitamin D (vitamin D that is not bound to vitamin D binding protein) in gastric cancer patients with vitamin D supplementation can significantly improve 5-year RFS (27). It is undeniable that this study has certain limitations: the sample size of each study is small, and some analyses only include three documents, which may be biased; Egger test results included in this article may show publication bias in some indicators of the study, considering most published articles have positive results and negative effects may be missed; different determination methods of serum vitamin D levels in the included studies may also bias the results. In general, vitamin D measurement methods can be divided into two main approaches: strategies based on immunoassays (CLIA, ECLIA, RIA, and ELISA), and chromatographic methods including HPLC and liquid chromatography-tandem mass spectrometry (LC-MS). The disadvantages of immunoassays are the non-specificity of the used antibodies and significant interference. Chromatographic techniques are also burdened with certain limitations and drawbacks, especially the complex technical equipment and the time-consuming preparation and evaluation of samples (28). The analytical performance is highly variable, creating rules for defining regular vitamin D status ranges (29). Vitamin D levels are affected by the intensity of ultraviolet rays. Vitamin D status varies across all continents and countries. Vitamin D status usually is adequate in Latin America and Australia but, in contrast, it is deficient in the Middle East and some countries in Asia. Therefore, our study only

analyzed Asian countries, and the results are limited (30). Although the studies are all from Asia, the effects of ultraviolet radiation intensity and sunshine duration at different latitudes are not considered. Vitamin D is also affected by many factors, such as other diets, absorbability, clothing styles, sunscreen use, where you live, etc. (30). Therefore, we must design more rigorous randomized controlled studies to verify the final results.

In conclusion, serum vitamin D level is correlated with the occurrence, development and prognosis of gastric cancer. The reduction of vitamin D increases the risk of gastric cancer. At the same time, vitamin D levels are significantly related to different clinical stages, degrees of differentiation, and lymph node metastasis. Therefore, serum vitamin D levels may be an essential factor in the prevention and prognosis of gastric cancer. There is no apparent correlation between the patient's age, gender, smoking and drinking history, onset time, and distant metastasis. Paying attention to serum vitamin D levels may become a clinical trend and make a specific contribution to the early detection and treatment of gastric cancer. However, according to the quality and sample size of the included articles, we need more rigorously designed, meticulous, high-quality, large-sample prospective randomized controlled studies to verify this conclusion.

REFERENCES

1. Smyth EC, Nilsson M, Grabsch HI, van Grieken NC, Lordick F. Gastric cancer. Lancet 2020;396(10251):635-48. DOI: 10.1016/S0140-6736(20)31288-5
2. Arnold M, Abnet CC, Neale RE, Vignat J, Giovannucci EL, McGlynn KA, et al. Global Burden of 5 Major Types of Gastrointestinal Cancer. Gastroenterology 2020;159(1):335-49.e15. DOI: 10.1053/j.gastro.2020.02.068
3. Feng RM, Zong YN, Cao SM, Xu RH. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 2019;39(1):22. DOI: 10.1186/s40880-019-0368-6
4. Cao M, Li H, Sun D, Chen W. Cancer burden of major cancers in China: A need for sustainable actions. Cancer Commun (Lond) 2020;40(5):205-10. DOI: 10.1002/cac2.12025
5. Carlberg C, Muñoz A. An update on vitamin D signaling and cancer. Semin Cancer Biol 2022;79:217-30. DOI: 10.1016/j.semcancer.2020.05.018
6. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: Metabolism, Molecular Mechanism of Action, and Pleiotropic Effects. Physiol Rev 2016;96(1):365-408. DOI: 10.1152/physrev.00014.2015
7. Dongre A, Weinberg RA. New insights into the mechanisms of epithelial-mesenchymal transition and implications for cancer. Nat Rev Mol Cell Biol 2019;20(2):69-84. DOI: 10.1038/s41580-018-0080-4
8. Feldman D, Krishnan AV, Swami S, Giovannucci E, Feldman BJ. The role of vitamin D in reducing cancer risk and progression. Nat Rev Cancer 2014;14(5):342-57. DOI: 10.1038/nrc3691
9. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25(9):603-5. DOI:

10.1007/s10654-010-9491-z

10. Zeng X, Zhang Y, Kwong JS, Zhang C, Li S, Sun F, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8(1):2-10. DOI: 10.1111/jebm.12141
11. Kwak JH, Paik JK. Vitamin D Status and Gastric Cancer: A Cross-Sectional Study in Koreans. Nutrients 2020;12(7):2004. DOI: 10.3390/nu12072004
12. Kevin A, Anandhi A, Lakshminarayanan S, Sureshkumar S, Kamalanathan S. Association between serum 25-hydroxy vitamin D level and gastric adenocarcinoma - a cross sectional study. Prz Gastroenterol 2021;16(2):155-60. DOI: 10.5114/pg.2020.100659
13. Zeng Y, Chu Y, Sun J. Relationship Between Serum 25-(OH) D3, Ca2+ And Gastric Carcinoma. Cancer Research On Prevention And Treatment 2015;04:369-72.
14. Bao AY. Clinical Significance Of Serum 25-Hydroxyvitamin D Level Of Gastric Cancer Patients. Journal Of Modern Laboratory Medicine 2016;0(2).
15. Eom SY, Yim DH, Kim DH, Yun HY, Song YJ, Youn SJ, et al. Dietary vitamin D intake and vitamin D related genetic polymorphisms are not associated with gastric cancer in a hospital-based case-control study in Korea. J Biomed Res 2018;32(4):257-63. DOI: 10.7555/JBR.32.20170089
16. Durak Ş, Gheybi A, Demirkol Ş, Arıkan S, Zeybek ŞÜ, Akyüz F, et al. The effects of serum levels, and alterations in the genes of binding protein and receptor of vitamin D on gastric cancer. Mol Biol Rep 2019;46(6):6413-20. DOI: 10.1007/s11033-019-05088-9
17. Hedayatizadeh-Omran A, Janbabaei G, Alizadeh-Navaei R, Amjadi O, Mahdavi Izadi J, Omrani-Nava V. Association between pre-chemotherapy serum levels of vitamin D and

clinicopathologic findings in gastric cancer. Caspian J Intern Med 2020;11(3):290-4. DOI: 10.22088/cjim.11.3.290

18. Wang XL, Fan CG, Yang LI, Guo-Li LI. Correlations Between Serum 25(OH) Vitamin D Levels And The Prognosis Of Advanced Gastric Cancer Patients With Neoadjuvant Chemotherapy. Parenteral & Enteral Nutrition 2019;26(1).
19. LI Qiang SUY, Wei-Guo R. Clinical Significance Of Serum 1,25-(OH)2D3 Level In Elderly Patients With Gastric Cancer. Chin J Mult Organ Dis Elderly 2014;13(5).
20. Ren C, Qiu MZ, Wang DS, Luo HY, Zhang DS, Wang ZQ, et al. Prognostic effects of 25-hydroxyvitamin D levels in gastric cancer. J Transl Med 2012;10:16. DOI: 10.1186/1479-5876-10-16
21. Ferrer-Mayorga G, Gómez-López G, Barbáchano A, Fernández-Barral A, Peña C, Pisano DG, et al. Vitamin D receptor expression and associated gene signature in tumour stromal fibroblasts predict clinical outcome in colorectal cancer. Gut 2017;66(8):1449-62. DOI: 10.1136/gutjnl-2015-310977
22. Liu C, Shaurova T, Shoemaker S, Petkovich M, Hershberger PA, Wu Y. Tumor-Targeted Nanoparticles Deliver a Vitamin D-Based Drug Payload for the Treatment of EGFR Tyrosine Kinase Inhibitor-Resistant Lung Cancer. Mol Pharm 2018;15(8):3216-26. DOI: 10.1021/acs.molpharmaceut.8b0030
23. Huang Z, Zhang Y, Li H, Zhou Y, Zhang Q, Chen R, et al. Correction: Vitamin D promotes the cisplatin sensitivity of oral squamous cell carcinoma by inhibiting LCN2-modulated NF-κB pathway activation through RPS3. Cell Death Dis 2020;11(3):190. DOI: 10.1038/s41419-020-2389-0
24. Kotlarz A, Przybyszewska M, Swoboda P, Neska J, Miłoszewska J, Grygorowicz MA, et al. Imatinib inhibits the regrowth of human colon cancer cells after treatment with 5-FU and cooperates with vitamin D analogue PRI-2191 in the downregulation of expression of stemness-related genes in 5-

FU refractory cells. J Steroid Biochem Mol Biol 2019;189:48-62. DOI: 10.1016/j.jsbmb.2019.02.003

25. Urashima M, Ohdaira H, Akutsu T, Okada S, Yoshida M, Kitajima M, et al. Effect of Vitamin D Supplementation on Relapse-Free Survival Among Patients With Digestive Tract Cancers: The AMATERASU Randomized Clinical Trial. JAMA 2019;321(14):1361-9. DOI: 10.1001/jama.2019.2210
26. Yonaga H, Okada S, Akutsu T, Ohdaira H, Suzuki Y, Urashima M. Effect Modification of Vitamin D Supplementation by Histopathological Characteristics on Survival of Patients with Digestive Tract Cancer: Post Hoc Analysis of the AMATERASU Randomized Clinical Trial. Nutrients 2019;11(10):2547. DOI: 10.3390/nu11102547
27. Urashima M, Okuyama M, Akutsu T, Ohdaira H, Kaji M, Suzuki Y. Effect of Vitamin D Supplementation on Survival of Digestive Tract Cancer Patients with Low Bioavailable 25-Hydroxyvitamin D levels: A Post Hoc Analysis of the AMATERASU Randomized Clinical Trial. Cancers (Basel) 2020;12(2):347. DOI: 10.3390/cancers12020347
28. Máčová L, Bičíková M. Vitamin D: Current Challenges between the Laboratory and Clinical Practice. Nutrients 2021;13(6):1758. DOI: 10.3390/nu13061758
29. Altieri B, Cavalier E, Bhattoa HP, Pérez-López FR, López-Baena MT, Pérez-Roncero GR, et al. Vitamin D testing: advantages and limits of the current assays. Eur J Clin Nutr 2020;74(2):231-47. DOI: 10.1038/s41430-019-0553-3
30. Lips P, de Jongh RT, van Schoor NM. Trends in Vitamin D Status Around the World. JBMR Plus 2021;5(12):e10585. DOI: 10.1002/jbm4.10585

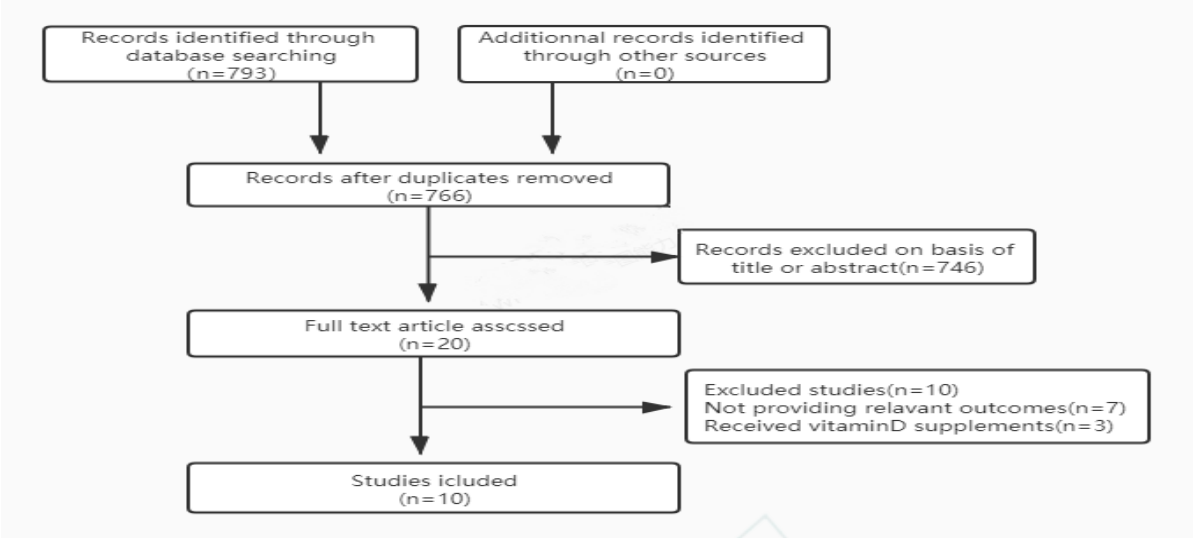

Figure 1. The literature screening process and results

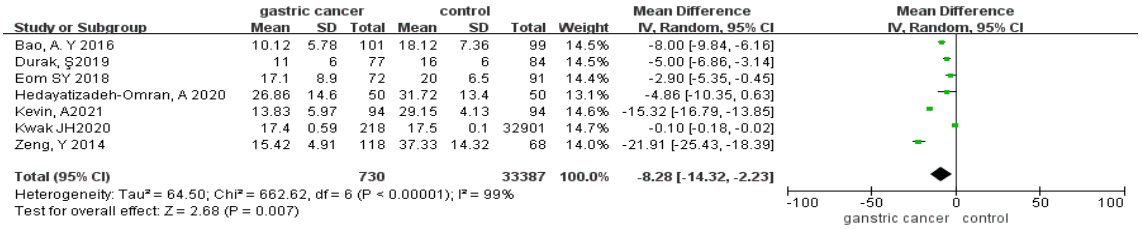

Figure 2. Serum vitamin D levels between the gastric cancer group and healthy control group. The analysis showed that the vitamin D level of the gastric cancer group was significantly lower than that of the normal group.

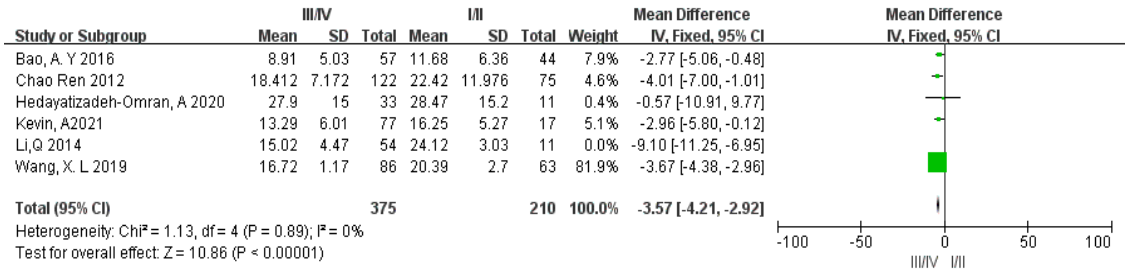

Figure 3. Serum vitamin D levels between different clinical stages. The vitamin D level of patients with stage III/IV was lower than that of patients with stage I/II.

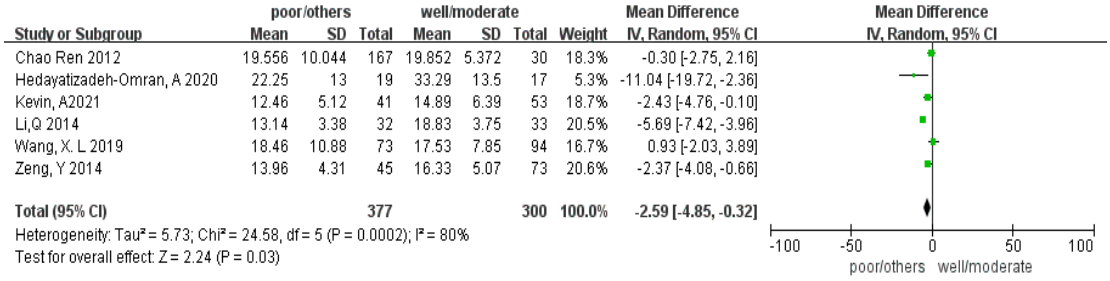

Figure 4. Serum vitamin D levels between different degrees of differentiation. The serum vitamin D level of poorly differentiated or other differentiated gastric cancer patients was significantly lower than that of well- or moderately-differentiated gastric cancer patients.

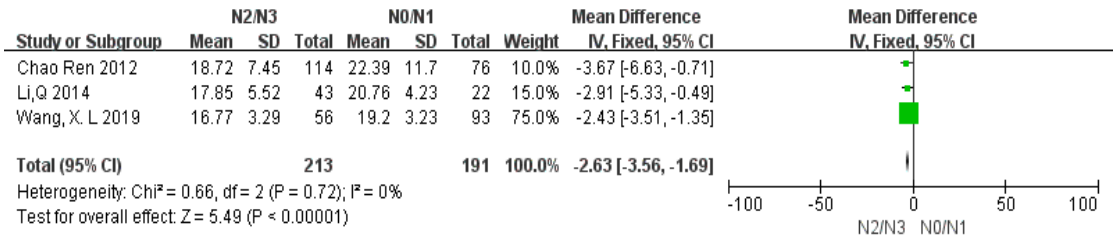

Figure 5. Serum vitamin D levels between lymph node metastases. The serum vitamin D level of patients with lymph node metastasis N2/N3 is lower than that of patients with N0/N1.

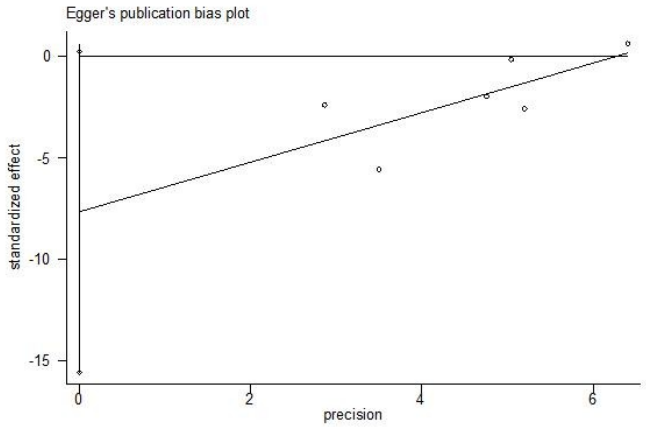

Figure 6. The publication bias. No obvious publication bias was found.

Table I. Basic characteristics and quality evaluation

Name	**Country**	**Year**	**Study type**	Test	Gastric cancer		Conrol		**NOS AHRQ***
					n	Mean ± SD	*n*	Mean ± SD	
Zeng, Y (13)	China	2014	Case-control study	ELISA	118	15.42 ± 4.91	68	37.33 ± 14.32 14.32	9
Bao, AY (14)	China	2016	Case-control study	ECLI	101	10.12 ± 5.78	99	18.12 ± 7.36	10
Eom, SY (15)	Korea	2018	Case-control study	ELISA	72	17.1 ± 8.9	91	20 ± 6.5	9
Durak, Ş (16)	Turkey	2019	Case-control study	HPLC	77	11 ± 6	84	16 ± 6	9
Hedayatizadeh-Omran, A (17)	Iran	2020	Case-control study	ELISA	50	26.86 ± 14.6	50	31.72 ± 13.4	9
Kwak, JH (11)	Korea	2020	Cross- sectional study	RIA	218	17.4 ± 0.59	32901	17.5 ± 0.1	9*
Kevin, A (12)	India	2021	Cross- sectional study	-	94	13.83 ± 5.97	94	29.15 ± 4.13	8*
Wang, XL	China	2019	Case-control study	ELISA	167	18.94 ± 9.47	-	-	7

(18)									
Li , Q (19)	China	2014	Case-control study	ELISA	65	18.26 ± 4.13	-	-	8
Chao, R (20)	China	2012	Case-control study	ELISA	197	19.94 ± 9.47	-	-	6

*AHRQ evaluation standard. HPLC: high-pressure liquid chromatography; RIA: radioimmunoassay; ECLI: electro-chemiluminescence immunoassay.