Impact of vitamin D level at diagnosis and transplantation on the prognosis of hematological malignancy: a meta-analysis

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Abstract:
Vitamin D deficiency impairs prognosis in many types of cancer; however, its significance in each subtype of hematological malignancies is unclear. In addition, data on the association between pre-transplant vitamin D levels and outcomes of hematopoietic stem cell transplantation (HSCT) are inconsistent. This systematic review and meta-analysis aimed to elucidate the impact of vitamin D levels at diagnosis or pre-HSCT on the prognosis of hematological malignancies. A total of 30 articles and abstracts were extracted from PubMed, Embase, Cochrane Library databases, and conference proceedings. Fixed and random-effect models were used to analyze primary outcomes: overall survival (OS) and progression-free survival (PFS). Lower vitamin D level was significantly associated with poorer OS and PFS in myeloid (hazard ratio [HR]: 1.39, 95% confidence interval [CI] 1.06-1.82; HR: 2.03, 95%CI 1.23-3.32, respectively) and lymphoid malignancies (HR: 2.07, 95%CI 1.79-2.40; HR:1.91, 95%CI 1.61-2.25, respectively), as well as outcomes of several lymphoma subtypes individually. Furthermore, pre-transplant lower vitamin D level was associated with poorer OS in both autologous and allogeneic HSCT (HR: 1.65, 95%CI 1.04-2.61; HR: 1.50, 95%CI 1.03-2.18, respectively). Despite the relatively small number of studies evaluated, these data suggest the importance of vitamin D status in outcomes of hematological malignancies (PROSPERO registration number: CRD42020205821).

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Title

Impact of vitamin D level at diagnosis and transplantation on the prognosis of hematological malignancy: a meta-analysis

Short title for the running head

Vitamin D deficiency in hematological malignancies

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Key Points

・Lower vitamin D level was associated with poorer OS and PFS in myeloid and lymphoid malignancies, as well as several lymphoma subtypes.

・Pre-transplant lower vitamin D level was related to poorer OS in both autologous and allogeneic hematopoietic stem cell transplantation.
Abstract

Vitamin D deficiency impairs prognosis in many types of cancer; however, its significance in each subtype of hematological malignancies is unclear. In addition, data on the association between pre-transplant vitamin D levels and outcomes of hematopoietic stem cell transplantation (HSCT) are inconsistent. This systematic review and meta-analysis aimed to elucidate the impact of vitamin D levels at diagnosis or pre-HSCT on the prognosis of hematological malignancies. A total of 30 articles and abstracts were extracted from PubMed, Embase, Cochrane Library databases, and conference proceedings. Fixed and random-effect models were used to analyze primary outcomes: overall survival (OS) and progression-free survival (PFS). Lower vitamin D level was significantly associated with poorer OS and PFS in myeloid (hazard ratio [HR]: 1.39, 95% confidence interval [CI] 1.06–1.82; HR: 2.03, 95%CI 1.23–3.32, respectively) and lymphoid malignancies (HR: 2.07, 95%CI 1.79–2.40; HR:1.91, 95%CI 1.61–2.25, respectively), as well as outcomes of several lymphoma subtypes individually. Furthermore, pre-transplant lower vitamin D level was associated with poorer OS in both autologous and allogeneic HSCT (HR: 1.65, 95%CI 1.04–2.61; HR: 1.50, 95%CI 1.03–2.18, respectively). Despite the relatively small number of studies evaluated, these data suggest the importance of vitamin D status in outcomes of
hematological malignancies (PROSPERO registration number: CRD42020205821).
Introduction

Vitamin D is produced in sun-exposed skin or taken in the diet, hydroxylated in the liver and the proximal renal tubule to 1,25(OH)$_2$D$_3$, and acts as a steroid hormone by binding to the vitamin D receptor$^1$. It plays an important role not only in skeletal health but also in tumorigenesis by controlling cell proliferation, apoptosis, differentiation, angiogenesis, invasive and metastatic potential, and tumor immunity$^{2-4}$. The association between circulating vitamin D levels and cancer outcomes has been investigated in many types of cancer, and some meta-analyses revealed that higher vitamin D levels result in better outcomes in several cancers, including colorectal$^5$, breast$^5$, prostate cancer$^6$, and melanoma$^7$.

The role of vitamin D in hematological malignancies has also been studied in clinical settings, since in vitro analysis showed the ability of vitamin D to induce differentiation of human acute myeloid leukemia (AML) cells into mature myeloid cells$^8$. Although clinically meaningful data using vitamin D and its analogs as differentiation therapy for AML are limited$^9$, some meta-analyses have revealed that vitamin D deficiency in hematological malignancies was associated with poorer prognosis$^{5,10}$. Hematological malignancies include many different subtypes of myeloid and lymphoid malignancies; thus, the influence of vitamin D on each subtype should be
examined separately, but a detailed analysis to address this issue has not yet been performed.

In addition, the effects of vitamin D levels on autologous and allogeneic hematopoietic stem cell transplantation (HSCT) have been studied in several studies, and the significance still remains controversial\(^\text{11}\); thus, a comprehensive analysis is warranted. Herein, we performed a systematic review and meta-analysis to determine the impact of vitamin D level at diagnosis or pre-HSCT on the prognosis of each subtype of hematological malignancies. This is the first meta-analysis focusing on each subtype of lymphoid malignancies and also looking at transplant outcomes.

**Methods**

**Search strategy**

This study was registered with PROSPERO (CRD42020205821) and conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines\(^\text{12}\). PubMed, EMBASE, and the COCHRANE registry of clinical trials (CENTRAL) databases were searched through February 17\(^\text{th}\), 2021 without language restriction, using the following terms: “vitamin D” AND (“lymphoma” OR “leukemia” OR “myeloma” OR “myelodysplastic syndrome” OR “hematological
malignancy” OR “hematopoietic stem cell transplantation” OR “bone marrow transplantation”) AND (“progression-free survival” OR “overall survival” OR “PFS” OR “OS” OR “survival” OR “prognosis”). We also searched conference proceedings of the American Society of Hematology (ASH) (2004-2020), the American Society of Clinical Oncology (ASCO) (2011-2020), and European Hematology Association (EHA) (2009-2020), and scanned references of identified articles and reviews for further studies.10,11

**Study selection and quality assessment**

Two authors (YI and AH) independently assessed the titles and abstracts of all the identified studies by searching electronic databases. Subsequently, we screened the full texts of the potentially eligible articles. We excluded studies that (1) lacked information needed to evaluate hazard ratios (HRs) of outcomes, (2) were duplicate publications using overlapping patient cohorts, and (3) included many non-malignant patients undergoing allogeneic HSCT (allo-HSCT). Any discrepancies between the authors were resolved through a discussion including a third author (MK), until consensus was reached. The outline of the data extraction is described in Figure 1. The Newcastle-Ottawa scale was used to assess the quality of the non-randomized trials.13
Endpoints

The primary outcomes in this review were HRs of overall survival (OS) and progression-free survival (PFS), alternatively termed event-free, relapse-free, or leukemia-free survival in some articles. Secondary outcomes were time-to-treatment (TTT) for patients with chronic lymphocytic leukemia (CLL), relapse rate, and non-relapse mortality (NRM) for allo-HSCT. When the article reported both univariate and multivariate analyses, multivariate data were preferred. When HR was not available, it was estimated using the methods described by Tierney et al.\textsuperscript{14}. When the cohort was divided into more than two groups according to vitamin D level, the data comparing between groups with the highest and lowest levels were used. With regard to the measurement of vitamin D level, serum 25-hydroxyvitamin D (25(OH)D) is the major circulating vitamin D metabolite, and is used to assess vitamin D status in this meta-analysis. 1 ng/mL of vitamin D corresponds to 2.5 nmol/L.

Statistical analysis

Data were analyzed using the statistical software ‘EZR’\textsuperscript{15}. For each trial, the impact of vitamin D deficiency was calculated using HRs with 95% confidence interval (CI), and
mean HRs and upper 95% CI from each study were input into EZR software for statistical analysis. An HR of more than 1 favored the higher vitamin D arm. We used the random effect model according to the method of Der Simonian-Laird\textsuperscript{16}. When the p value for heterogeneity exceeded 0.10, we preferred the Mantel-Haenszel (fixed-effect) method. We assessed the trial results using the chi-square test of heterogeneity and the I\textsuperscript{2} measure of inconsistency. Heterogeneity was considered statistically significant when the p-value was less than 0.10, or the I\textsuperscript{2} statistic was greater than 50%. Potential sources of heterogeneity were investigated using subgroup analyses. Publication bias was examined using funnel plots, coupled with Egger’s test.

Results

Study selection

The literature search through PubMed, EMBASE, Cochrane Library databases, and three conference proceedings (ASH, ASCO, and EHA) identified 1212 articles after duplicates removed, of which 52 were considered relevant through the evaluation of titles and abstracts. Among them, 30 articles fulfilled the criteria for this meta-analysis: 5 articles on myeloid malignancies\textsuperscript{17–21}, 20 on lymphoid malignancies\textsuperscript{18,22–40}, 3 on autologous HSCT (ASCT)\textsuperscript{41–43}, and 3 on allo-HSCT\textsuperscript{44–46}. A flow diagram of the article
selection process is shown in Figure 1. 22 articles were excluded with the following reasons: (1) duplicate publications from overlapping cohort\textsuperscript{47,48}, (2) insufficient data of primary endpoint\textsuperscript{49–60}, and (3) transplantations including many non-malignancies or unidentified diseases\textsuperscript{61–68}. The characteristics of each study are summarized in Table I.

**Vitamin D level in myeloid malignancies at diagnosis**

The OS data for myeloid malignancies were available in 5 articles\textsuperscript{17–21} that included 573 patients with AML, chronic myeloid leukemia (CML), juvenile myelomonocytic leukemia (JMML), myelodysplastic syndrome (MDS), and primary myelofibrosis (PMF). Patients with lower vitamin D level had significantly poorer OS (HR: 1.39, 95%CI 1.06–1.82) with substantial heterogeneity ($I^2 = 57\%$, $p = 0.03$) (Figures 2A and B). PFS that was analyzed in 384 patients from 3 cohorts\textsuperscript{20,21} was significantly poorer in the group of lower vitamin D status (HR: 2.03, 95%CI 1.23–3.32) without heterogeneity ($I^2 = 0\%$, $p = 0.57$) (Figure 2C).

**Vitamin D level in lymphoid malignancies at diagnosis**

The data on 4502 patients from 14 articles were eligible for the analysis of OS in lymphoid malignancies\textsuperscript{18,22–24,26–28,30–34,36,40}. OS was significantly poorer in the group of
lower vitamin D status (HR: 2.07, 95%CI 1.79–2.40) without heterogeneity (I² = 10%, p = 0.33) (Figure 3A). The funnel plot suggested a publication bias (p = 0.002, Figure 3B). PFS analyzed in 3436 patients from 13 articles was also significantly poorer in patients with lower vitamin D level (HR: 1.91, 95%CI 1.61–2.25) with heterogeneity (I² = 39%, p = 0.04) (Figure 3C). The funnel plot did not show a publication bias (p = 0.69, Figure 3D).

Vitamin D level in diffuse large B cell lymphoma at diagnosis

Next, we analyzed each subtype of lymphoid malignancies. First, for diffuse large B cell lymphoma (DLBCL), data on 1272 patients from 5 articles were eligible for the analysis of OS and PFS. Lower vitamin D status was associated with poorer OS (HR: 2.20, 95%CI 1.70–2.86) and PFS (HR: 2.05, 95%CI 1.47–2.86) (Figures 4A-D).

Vitamin D level in follicular lymphoma at diagnosis

Second, for follicular lymphoma (FL), data on 1065 patients from 3 cohorts were eligible for the analysis of OS. Tracy et al. performed an expanded analysis of their prior cohort, thus we used their expanded data. Lower vitamin D status was also associated with significantly poorer OS (HR: 2.55, 95%CI 1.68–3.88) without
heterogeneity (Figure 5A). The PFS data were available for 423 patients from 2 cohorts\textsuperscript{36}, and lower vitamin D status was associated with significantly poorer PFS (HR: 1.67, 95%CI 1.16–2.42) without heterogeneity (Figure 5B).

**Vitamin D level in mantle cell lymphoma at diagnosis**

Third, for mantle cell lymphoma (MCL), the data on 141 patients from 2 articles were available\textsuperscript{32,34}, which showed no significant association between vitamin D level and OS (HR: 3.10, 95%CI 0.53–18.24) or PFS (HR: 1.98, 95%CI 0.60–6.59) with substantial heterogeneity (Figures 5C and D).

**Vitamin D level in Hodgkin lymphoma at diagnosis**

Fourth, for Hodgkin lymphoma (HL), the OS data were available on 351 patients from only 1 article\textsuperscript{36}, which reported that lower vitamin D status was related to impaired OS (HR: 1.82, 95%CI 1.53–2.15). Furthermore, the data on 427 patients from 2 articles were eligible for the analysis of PFS\textsuperscript{25,36}, which revealed poor PFS in patients with lower vitamin D level (HR: 2.31, 95%CI 1.36–3.93) (Figure 5E).

**Vitamin D level in T cell lymphoma at diagnosis**
Fifth, for T cell lymphoma (TCL), data on 163 patients from 2 articles\textsuperscript{22,32} and 414 patients from 3 articles\textsuperscript{22,32,37} were eligible for the analysis of OS and PFS, respectively. Lower vitamin D status was associated with poor OS and PFS (HR: 2.49, 95\%CI 1.38–4.48; HR: 1.97, 95\%CI 1.38–2.82, respectively) (Figures 5F and G). Kim et al. further divided TCL into peripheral TCL and extranodal NK/T-cell lymphoma (ENKTL)\textsuperscript{37} and showed that vitamin D deficiency in only ENKTL patients had impaired prognosis; thus, further subdivision of TCL may be required for more accurate examination.

**Vitamin D level in CLL at diagnosis**

Sixth, for CLL, the data on 618 patients from 2 articles were eligible for the analysis of OS\textsuperscript{28,31}, which showed that lower vitamin D status was not significantly associated with OS (HR: 2.07, 95\%CI 0.80–5.36) (Figure 5H). There were no papers reporting on PFS, and TTT data were available from 2 articles with 673 patients\textsuperscript{29,31}. TTT was significantly shorter in the group of lower vitamin D status (HR: 1.55, 95\%CI 1.19–2.00) (Figure 5I).

**Vitamin D level in multiple myeloma at diagnosis**

Seventh, for multiple myeloma (MM), only one article was included in our search\textsuperscript{35},
which reported that lower vitamin D status was significantly associated with poor OS (HR: 1.34, p = 0.008). They showed that its impact on OS was only observed in Caucasian patients (HR: 1.45, p = 0.005), but not in African Americans, suggesting a difference between ethnic groups.

**Threshold of vitamin D level in the studies of lymphoid malignancies**

There is no unified definition of vitamin D level cutoff for vitamin D deficiency at present\(^{11}\), and the studies included in this meta-analysis selected various thresholds based on different guidelines as shown in Table I. To examine this discrepancy, we performed subgroup analysis classified by the cutoff value in lymphoid malignancies. First, 8 studies defined 50 nmol/L (20 ng/mL) as a threshold\(^{18,22,24,26,28,34,35,39}\), and patients with vitamin D level less than 50 nmol/L showed poorer OS (HR: 2.83, 95%CI 1.81–4.42) and PFS significantly (HR: 2.48, 95%CI 1.76–3.51) (Supplementary figure 1A and B), without heterogeneity. Second, 3 studies defined 25 nmol/L (10 ng/mL) as a threshold\(^{25,26,37}\) and vitamin D level less than 25 nmol/L was associated with poorer PFS (HR: 1.75, 95%CI 1.19–2.59) (Supplementary figure 1C). Third, 2 studies used 62.5 nmol/L (25 ng/mL) as a threshold\(^{31,32}\), and vitamin D level less than 62.5 nmol/L was also associated with poorer OS (HR: 1.77, 95%CI 1.36–2.29) and PFS (HR: 1.32,
95% CI 1.04–1.68) (Supplementary figure 1D and E). Therefore, all subgroup analyses demonstrated that lower vitamin D levels were associated with poorer outcomes.

The impact of geographical distribution on vitamin D level in lymphoid malignancies

Geographical factors such as latitude and sunlight exposure affect the levels of vitamin D in normal population\(^\text{11}\), thus we performed subgroup analysis in lymphoid malignancies for each country: US\(^\text{24,26,31,32,35}\), China\(^\text{22,23,33,34}\), Italy\(^\text{25,29,39,40}\), and Germany\(^\text{27,36}\). Lower vitamin D level was significantly associated with poorer OS (HR: 1.96, 95% CI 1.56–2.46) and PFS (HR: 1.40, 95% CI 1.12–1.75) in the US, poorer OS (HR: 3.26, 95% CI 2.00–5.30) and PFS (HR: 2.99, 95% CI 2.12–4.21) in China, poorer PFS (HR: 3.80, 95% CI 1.90–7.60) in Italy, and poorer OS (HR: 1.85, 95% CI 1.59–2.15) and PFS (HR: 1.92, 95% CI 1.54–2.39) in Germany (Supplementary figure 2A-G).

Vitamin D level at ASCT

We then focused on the significance of vitamin D levels during HSCT. First, we analyzed the data of ASCT in patients with lymphoma and myeloma. The data on 141 lymphoma and 332 myeloma patients from 3 articles were eligible for the analysis of
OS\textsuperscript{41–43}, which showed that lower vitamin D status was associated with significantly poorer OS (HR: 1.65, 95%CI 1.04–2.61 using the fixed effect model) with low heterogeneity ($I^2 = 21\%, p = 0.28$) (Figure 6A).

**Vitamin D level at allo-HSCT**

Next, we extracted allo-HSCT data for hematological malignancies. The data on 1094 patients from 5 cohorts were eligible for the analysis of OS\textsuperscript{44–46}. Bajwa et al. analyzed OS in patients with malignancy and non-malignancy separately, thus we only used the data of patients with malignancy\textsuperscript{44}. The meta-analysis showed that lower vitamin D status was associated with significantly poorer OS (HR: 1.50, 95%CI 1.03–2.18) (Figure 6B). The data of relapse rate and NRM were available from 3 cohorts in only one article\textsuperscript{45}, including 890 patients, and lower vitamin D status was related to a high relapse rate (HR: 2.12, 95%CI 1.41–3.19), but not to NRM (HR: 1.23, 95%CI 0.72–2.10) (Figures 6C and D).

**Discussion**

This meta-analysis comprehensively investigated the impact of circulating vitamin D levels at diagnosis on the prognosis of hematological malignancies and each subset of
lymphoid malignancies. We showed that lower vitamin D level at diagnosis was related to significantly impaired prognosis of myeloid and lymphoid malignancies, as previously reported\textsuperscript{5,10}. Moreover, further subgroup analysis revealed that lower vitamin D level was associated with the poorer prognosis of several lymphoma subtypes: DLBCL, FL, HL, and TCL. Although the survival data in patients with MCL and CLL did not reach statistical significance, lower vitamin D status shortened TTT in CLL.

Vitamin D is associated with not only bone homeostasis, but also tumorigenesis via many different mechanisms\textsuperscript{2,3,11}. Several reports have confirmed the direct anti-tumor effect of vitamin D against both leukemia and lymphoma cells \textit{in vitro}: anti-proliferation effect in non-Hodgkin lymphoma\textsuperscript{69} and myeloma\textsuperscript{70}, and induction of apoptosis in B-cell CLL\textsuperscript{71}. Vitamin D also exerts synergistic effects with other anti-cancer agents, such as azacytidine against myeloid cell lines\textsuperscript{19}, and etoposide and doxorubicin against HL cell lines\textsuperscript{36}. Moreover, vitamin D potentiates anti-tumor immunity by activating NK cells\textsuperscript{27} and macrophages\textsuperscript{72}; thus, vitamin D has a wide variety of protective mechanisms against hematological malignancies and further investigation is warranted to understand the whole aspect\textsuperscript{73}.

Several meta-analyses were performed previously to elucidate the role of vitamin D in hematological malignancies as summarized in Table II. Vitamin D deficiency was
consistently associated with poorer OS and PFS in leukemia and lymphoma patients\textsuperscript{5,10,74}. Also, some meta-analyses focused on the relationship between vitamin D status and risk of lymphoma, and revealed no significant relationship\textsuperscript{75–77}.

We also performed a meta-analysis on the association between pre-transplant vitamin D levels and prognosis for the first time, which showed a significant negative impact of lower vitamin D status on OS in both ASCT and allo-HSCT patients, despite the limited number of reports. Lower vitamin D level at allo-HSCT was not associated with NRM, but with a higher relapse rate, which might have resulted in a worse prognosis. Studies on pediatric transplantation including a substantial proportion of non-malignant diseases were excluded from this meta-analysis. Some of them concluded that vitamin D deficiency was associated with worse outcome\textsuperscript{62,66}; thus, subgroup analysis, differentiating malignant and non-malignant diseases, is needed in the future. Pre-transplant vitamin D deficiency has also been implicated in the pathogenesis of graft-versus-host disease (GVHD) via immunomodulatory effects\textsuperscript{46,78}, but a recent meta-analysis did not show a statistically significant association\textsuperscript{79} (Table II).

Evidence for the impact of vitamin D levels on cancer prognosis has been accumulating gradually, but whether vitamin D supplementation can improve cancer
prognosis is still uncertain. A recent meta-analysis demonstrated the clinically meaningful benefit of vitamin D supplementation on colorectal cancer survival outcomes\textsuperscript{80}. With regard to hematological malignancies, some studies suggested that vitamin D supplementation was associated with improved event-free survival in DLBCL patients\textsuperscript{39} and relapse-free survival after ASCT\textsuperscript{81}. Larger randomized clinical trials are needed to establish further evidence.

This meta-analysis has several limitations. First, the threshold for vitamin D level differed between articles. The threshold is determined based on clinical effects in bone health such as osteoporosis, bone mineral density and hip fractures, or the inverse relationship between serum parathyroid hormone and vitamin D level\textsuperscript{82,83}. Several studies deduced different thresholds from each clinical data, thus a consensus has not been achieved yet\textsuperscript{82}. For example, endocrine society clinical practice guideline defines deficiency as below 20 ng/mL, insufficiency as 21-29 ng/mL, and sufficiency as above 30 ng/mL\textsuperscript{84}. Another report defines severe deficiency as below 5 ng/mL, moderate deficiency as 5-10 ng/mL, mild deficiency as 10-20 ng/mL, and replete as above 20 ng/mL\textsuperscript{83}. Other reviews suggest 10 ng/mL, 12 ng/mL, 20 ng/mL\textsuperscript{11} or 30 ng/mL\textsuperscript{85} as a cut-off. Therefore, the definition is different among guidelines and reviews, and the studies in our meta-analyses referred to them individually, resulting in the discrepancies
as shown in Table I. Vitamin D levels are also influenced by geographic region, diet, environmental factors, and lifestyle, and the optimal target are still unclear. In MM patients, vitamin D deficiency was associated with poor OS only in Caucasian patients, but not in African Americans, suggesting the importance of racial differences. To clarify the significance of these discrepancies, we performed subgroup analysis classified by each cutoff value (25, 50, and 62.5 nmol/L) and each country (US, China, Italy, and Germany) in lymphoid malignancies, which confirmed the significant relationship between lower vitamin D levels and poorer outcomes in all subgroups. Second, the measurement method was also different between articles. Liquid chromatography-tandem mass spectrometry is currently recommended as the most accurate method, but immunoassays are used in some articles; thus, the measurement method should be unified. Third, the number of studies specific to each subtype of leukemia and lymphoma remains insufficient. With regard to myeloid malignancies, we could not analyze AML, MDS, CML/JMML, and PMF patients individually. These subtypes are quite different in disease biology; thus, they should be analyzed separately. Regarding lymphoid malignancies, the data on DLBCL patients were relatively abundant – five articles, including seven cohorts, but other lymphoma subgroups were examined in only one to three articles. In addition, the condition of transplantation is
quite different according to the type of disease, disease status, age, donor source, pre-conditioning regimen, and so on, and thus should be adjusted in further investigation. Fourth, 25(OH)D is commonly used as a reliable indicator of vitamin D status, but some articles recommend bioavailable 25(OH)D level as a precise biomarker\textsuperscript{33}. Moreover, Peter et al. showed that peritransplant $1,25(OH)_{2}D_{3}$ levels but not 25(OH)D predicted survival after stem cell transplantation\textsuperscript{49}. Therefore, the most precise biomarker of vitamin D levels in predicting the outcome of malignancies should be further investigated. Fifth, although our meta-analysis clarified the association of low vitamin D level with poorer PFS and OS, it does not establish causality and cannot exclude the possibility of residual confounding or reverse causality. Sixth, some patients with vitamin D deficiency were prescribed vitamin D supplementation\textsuperscript{39}, but most articles did not mention whether patients received supplementation. Thus, we could not include this factor in this meta-analysis. However, even if patients with vitamin D deficiency received supplementation, our results still suggest that lower vitamin D status at diagnosis has worse prognosis. The significance of vitamin D supplementation needs to be addressed in future prospective trials.

In conclusion, this meta-analysis demonstrated that lower vitamin D status at diagnosis was associated with significantly worse prognosis of both myeloid and
lymphoid malignancies, as well as several lymphoma subtypes, including DLBCL, FL, HL, and TCL. We also showed that pre-transplant vitamin D level was an important factor for prognosis in both autologous and allogeneic HSCT. Further studies focusing on each subtype of hematological malignancies are warranted.

**Authorship contributions**

YI conceptualized and designed the study, performed literature research, analyzed data, performed statistical analysis, and drafted the article. AH performed literature review and critically revised the article. MK contributed to supervision.

**Conflict of Interest Disclosures**

All authors declare no competing conflict of interest.
References

1. 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.

2. Bandera Merchan B, Morcillo S, Martin-Nuñez G, Tinahones FJ, Macías-González M. The role of vitamin D and VDR in carcinogenesis: Through epidemiology and basic sciences. *J. Steroid Biochem. Mol. Biol.* 2017;167:203–218.

3. Holick MF. Vitamin D deficiency. *N Engl J Med.* 2007;357(3):266–281.

4. Hall AC, Juckett MB. The role of vitamin D in hematologic disease and stem cell transplantation. *Nutrients.* 2013;5(6):2206–2221.

5. Li M, Chen P, Li J, et al. Review: The impacts of circulating 25-Hydroxyvitamin D levels on cancer patient outcomes: A systematic review and meta-analysis. *J. Clin. Endocrinol. Metab.* 2014;99(7):2327–2336.

6. Song ZY, Yao Q, Zhuo Z, Ma Z, Chen G. Circulating vitamin d level and mortality in prostate cancer patients: A dose–response meta-analysis. *Endocr. Connect.* 2018;7(12):R294–R303.

7. Tsai TY, Kuo CY, Huang YC. The association between serum vitamin D level...
and risk and prognosis of melanoma: a systematic review and meta-analysis. *J. Eur. Acad. Dermatology Venereol.* 2020;34(8):1722–1729.

8. Miyaura C, Abe E, Kuribayashi T, et al. 1α,25-Dihydroxyvitamin D3 induces differentiation of human myeloid leukemia cells. *Biochem. Biophys. Res. Commun.* 1981;102(3):937–943.

9. Harrison JS, Bershadskiy A. Clinical Experience Using Vitamin D and Analogs in the Treatment of Myelodysplasia and Acute Myeloid Leukemia: A Review of the Literature. *Leuk. Res. Treatment.* 2012;2012:125814.

10. Wang W, Li G, He X, et al. Serum 25-hydroxyvitamin D levels and prognosis in hematological malignancies: A systematic review and meta-analysis. *Cell Physiol. Biochem.* 2015;35(5):1999–2005.

11. Soto JR, Anthias C, Madrigal A, Snowden JA. Insights Into the Role of Vitamin D as a Biomarker in Stem Cell Transplantation. *Front. Immunol.* 2020;11:966.

12. Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. *Ann Intern Med.* 2009;151(4):264–269.

13. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur. J. Epidemiol.*
14. Tierney JF, Stewart LA, Ghersi D, Burdett S, Sydes MR. Practical methods for incorporating summary time-to-event data into meta-analysis. Trials. 2007;8:16.

15. Kanda Y. Investigation of the freely available easy-to-use software “EZR” for medical statistics. Bone Marrow Transplant. 2013;48(3):452–458.

16. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control. Clin. Trials. 1986;7(3):177–188.

17. Hu B, Chen L, Wu X, et al. A retrospective study of the association of low 25(OH) vitamin D3 levels with poor outcomes in elderly patients with de novo acute myeloid leukaemia. Acta Medica Mediterr. 2020;36(6):3573–3578.

18. Jackmann N, Mäkitie O, Harila-Saari A, et al. Vitamin D status in children with leukemia, its predictors, and association with outcome. Pediatr. Blood Cancer. 2020;67(4):e28163.

19. Radujkovic A, Schnitzler P, Ho AD, Dreger P, Luft T. Low serum vitamin D levels are associated with shorter survival after first-line azacitidine treatment in patients with myelodysplastic syndrome and secondary oligoblastic acute myeloid leukemia. Clin. Nutr. 2017;36(2):542–551.

20. Lee HJ, Muindi JR, Tan W, et al. Low 25(OH) vitamin D3 levels are associated
with adverse outcome in newly diagnosed, intensively treated adult acute myeloid leukemia. *Cancer*. 2014;120(4):521–529.

21. Pardanani A, Drake MT, Finke C, et al. Vitamin D insufficiency in myeloproliferative neoplasms and myelodysplastic syndromes: Clinical correlates and prognostic studies. *Am. J. Hematol.* 2011;86(12):1013–1016.

22. Mao J, Yin H, Wang L, et al. Prognostic value of 25-hydroxy vitamin D in extranodal NK/T cell lymphoma. *Ann. Hematol.* 2021;100(2):445–453.

23. Wang WT, Liang J hua, Wang L, et al. The prognostic value of 25-hydroxy vitamin D deficiency and its interaction with c-Myc expression in diffuse large B cell lymphoma. *Ann. Hematol.* 2020;99(10):2377–2384.

24. Tracy SI, Maurer MJ, Witzig TE, et al. Vitamin D insufficiency is associated with an increased risk of early clinical failure in follicular lymphoma. *Blood Cancer J.* 2017;7(8):e595.

25. Cuccaro A, Galli E, Visconti F, et al. 25(OH)Vitamin D serum levels in Hodgkin lymphoma. *Haematologica.* 2017;102:Supplement 2 (462).

26. Kelly JL, Salles G, Goldman B, et al. Low Serum Vitamin D Levels Are Associated With Inferior Survival in Follicular Lymphoma: A Prospective Evaluation in SWOG and LYSA Studies. *J Clin Oncol.* 2015;33(13):1482–1490.
27. Bittenbring JT, Neumann F, Altmann B, et al. Vitamin D deficiency impairs rituximab-mediated cellular cytotoxicity and outcome of patients with diffuse large B-cell lymphoma treated with but not without rituximab. *J. Clin. Oncol.* 2014;32(29):3242–3248.

28. Aref S, Ibrahim L, Azmy E. Prognostic impact of serum 25-hydroxivitamin D [25(OH)D] concentrations in patients with lymphoid malignancies. *Hematology*. 2013;18(1):20–25.

29. Molica S, Digiesi G, Antenucci A, et al. Vitamin D insufficiency predicts time to first treatment (TFT) in early chronic lymphocytic leukemia (CLL). *Leuk. Res.* 2012;36(4):443–447.

30. Tretli S, Schwartz GG, Torjesen PA, Robsahm TE. Serum levels of 25-hydroxyvitamin D and survival in Norwegian patients with cancer of breast, colon, lung, and lymphoma: A population-based study. *Cancer Causes Control*. 2012;23(2):363–370.

31. Shanafelt TD, Drake MT, Maurer MJ, et al. Vitamin D insufficiency and prognosis in chronic lymphocytic leukemia. *Blood*. 2011;117(5):1492–1498.

32. Drake MT, Maurer MJ, Link BK, et al. Vitamin D insufficiency and prognosis in non-Hodgkin’s lymphoma. *J. Clin. Oncol.* 2010;28(27):4191–4198.
33. Chen P, Cao Y, Duan X, et al. Bioavailable 25(OH)D level is associated with clinical outcomes of patients with diffuse large B-cell lymphoma: An exploratory study. *Clin. Nutr.* 2021;40(1):157–165.

34. Xu DM, Liang JH, Wang L, et al. 25-Hydroxy vitamin D deficiency predicts inferior prognosis in mantle cell lymphoma. *J. Cancer Res. Clin. Oncol.* 2020;146(4):1003–1009.

35. Yellapragada SV, Fillmore NR, Frolov A, et al. Vitamin D deficiency predicts for poor overall survival in white but not African American patients with multiple myeloma. *Blood Adv.* 2020;4(8):1643–1646.

36. Borchmann S, Cirillo M, Goergen H, et al. Pretreatment Vitamin D deficiency is associated with impaired progression-free and overall survival in Hodgkin lymphoma. *J. Clin. Oncol.* 2019;37(36):3528–3537.

37. Kim SJ, Shu C, Ryu KJ, et al. Vitamin D deficiency is associated with inferior survival of patients with extranodal natural killer/T-cell lymphoma. *Cancer Sci.* 2018;109(12):3971–3980.

38. Djurasinović VT, Mihaljević BS, Šipetić Grujičić SB, et al. 25(OH) vitamin D deficiency in lymphoid malignancies, its prevalence and significance. Are we fully aware of it? *Support. Care Cancer.* 2018;26(8):2825–2832.
39. Hohaus S, Tisi MC, Bellesi S, et al. Vitamin D deficiency and supplementation in patients with aggressive B-cell lymphomas treated with immunochemotherapy. *Cancer Med.* 2018;7(1):270–281.

40. Ferrari A, Ruffini A, Alvarez I, et al. The role of vitamin D as a prognostic factor in diffuse large B cell lymphoma: A monocentric study from hematology unit of Reggio Emilia. *Haematologica.* 2017;102:Supplement 3 (114).

41. Eicher F, Mansouri Taleghani B, Schild C, Bacher U, Pabst T. Reduced survival after autologous stem cell transplantation in myeloma and lymphoma patients with low vitamin D serum levels. *Hematol. Oncol.* 2020;38(4):523–530.

42. Rakhee V, Ahlers S, Rodriguez C, et al. Low pre-transplant vitamin D levels predict an inferior survival in patients with multiple myeloma undergoing an autologous stem cell transplant. *Blood.* 2016;128(22):5655.

43. Clairmont EB, Schoch G, Gopal AK, McDonnell P. 25-hydroxyvitamin D concentrations and overall survival in autologous hematopoietic stem cell subjects. *Biol. Blood Marrow Transplant.* 2014;20(2):S106-107.

44. Bajwa RP, Taylor K, Hoyt AR, et al. Effects of Vitamin D Levels on Outcomes after Allogeneic Hematopoietic Stem Cell Transplantation in Children. *Biol. Blood Marrow Transplant.* 2019;25(3):S239-240.
45. Radujkovic A, Kordelas L, Krzykalla J, et al. Pretransplant vitamin D deficiency is associated with higher relapse rates in patients allografted for myeloid malignancies. *J. Clin. Oncol.* 2017;35(27):3143–3152.

46. Von Bahr L, Blenow O, Alm J, et al. Increased incidence of chronic GvHD and CMV disease in patients with Vitamin D deficiency before allogeneic stem cell transplantation. *Bone Marrow Transplant.* 2015;50(9):1217–1223.

47. Djurasinovic V, Mihaljevic B, Vukovic V, et al. Pretreatment serum 25(OH) vitamin d as predictor of event-free survival in lymphoid malignancies. *Hemasphere.* 2019;3(S1):1018.

48. Robsahm TE, Tretli S, Torjesen PA, Babigumira R, Schwartz GG. Serum 25-hydroxyvitamin D levels predict cancer survival: A prospective cohort with measurements prior to and at the time of cancer diagnosis. *Clin. Epidemiol.* 2019;11:695–705.

49. Peter K, Siska PJ, Roider T, et al. 1,25-dihydroxyvitamin-D3 but not the clinically applied marker 25-hydroxyvitamin-D3 predicts survival after stem cell transplantation. *Bone Marrow Transplant.* 2021;56(2):419–33.

50. Nair R, Hadidi SA, Steiner RE, et al. Association of Vitamin D Deficiency with Inferior Treatment Outcomes in Patients with Newly Diagnosed Classic Hodgkin
Lymphoma: MD Anderson Cancer Center Experience. *Blood.* 2020;136 (Supplement 1):27–28.

51. Thomas X, Chelghoum Y, Fanari N, Cannas G. Serum 25-hydroxyvitamin D levels are associated with prognosis in hematological malignancies. *Hematology.* 2011;16(5):278–283.

52. Ng AC, Kumar SK, Rajkumar SV, Drake MT. Impact of vitamin D deficiency on the clinical presentation and. *Am J Hematol.* 2009;84(7):397–400.

53. Sanchez-Gonzalez B, Platero J, Ortuño A, et al. Vitamin D insufficiency and prognosis in lymphoma. *Hemasphere.* 2019;3(S1):115–6.

54. Seyedalipour F, Mansouri A, Vaezi M, et al. High prevalence of vitamin D deficiency in newly diagnosed acute myeloid leukemia patients and its adverse outcome. *Int. J. Hematol. Stem Cell Res.* 2017;11(3):209–216.

55. Lad DP, Mourad YA, Barnett MJ, et al. Pre-Transplant Vitamin D Deficiency is Associated with Inferior Overall Survival but not Associated with Relapse Free Survival or Cumulative Incidence of GVHD Post Adult Hematopoietic Cell Transplantation for Hematological Malignancies. *Biol Blood Marrow Transpl.* 2016;22(3):S334.

56. Lauter B, Schmidt-Wolf IGH. Prevalence, supplementation, and impact of
Vitamin D deficiency in multiple myeloma patients. Cancer Invest. 2015;33(10):505–509.

57. Hudzik S, Snoad B, Mousa L, et al. The Majority of Myeloma Patients Are Vitamin D Deficient, Unrelated to Survival or Cytogenetics. Blood. 2015;126(23):5336.

58. Ganetsky A, Richman LP, Frey NV, et al. Vitamin D Deficiency Predicts Acute Cutaneous Graft-Versus-Host Disease in Reduced-Intensity Allogeneic Hematopoietic Stem Cell Transplantation. Biol Blood Marrow Transpl. 2014;20(2):S267-8.

59. Glotzbecker B, Ho VT, Aldridge J, et al. Low levels of 25-hydroxyvitamin D before allogeneic hematopoietic SCT correlate with the development of chronic GVHD. Bone Marrow Transplant. 2013;48(4):593–597.

60. Beri N, Friedman DR, Simms TM, et al. Molecular and Clinical Associations Between Vitamin D and Chronic Lymphocytic Leukemia. Blood. 2013;122(21):5282.

61. Bhandari R, Malvar J, Sacapano A, et al. Association between Vitamin D and Risk for Early and Late Post-Transplant Complications. Biol. Blood Marrow Transplant. 2020;26(2):343–350.
62. Beebe K, Magee K, McNulty A, et al. Vitamin D deficiency and outcomes in pediatric hematopoietic stem cell transplantation. *Pediatr. Blood Cancer*. 2018;65(2).

63. Wallace G, Jodele S, Howell J, et al. Vitamin D Deficiency and Survival in Children after Hematopoietic Stem Cell Transplant. *Biol. Blood Marrow Transplant*. 2015;21(9):1627–1631.

64. Perera T, Lim ABM, Mason K, Szer J, Ritchie DS. The Relationship Between Pre-Transplant 25-Hydroxy-Vitamin D Levels, Survival and Graft-Versus-Host Disease, in Allogeneic Haematopoietic Stem Cell Transplantation. *Biol Blood Marrow Transpl*. 2015;21(2):S303-304.

65. Campos DJ, Biagini GLK, Funke VAM, et al. Vitamin D deficiency in children and adolescents submitted to hematopoietic stem cell transplantation. *Rev. Bras. Hematol. Hemoter*. 2014;36(2):126–131.

66. Hansson MEA, Norlin AC, Omazic B, et al. Vitamin D levels affect outcome in pediatric hematopoietic stem cell transplantation. *Biol. Blood Marrow Transplant*. 2014;20(10):1537–1543.

67. Beebe K, Olsen J, Chang Y, et al. Impact Of Vitamin D Level Pre and Post Allogeneic Hematopoietic Stem Cell Transplant. *Blood*. 2013;122(21):4616.
68. Sproat L, Olsen J, Beebe K, et al. Impact of Vitamin D Level After Allogeneic Hematopoietic Stem Cell Transplant. *Blood*. 2012;120(21):1954.

69. Hickish T, Cunningham D, Colston K, et al. The effect of 1,25-dihydroxyvitamin D3 on lymphoma cell lines and expression of vitamin D receptor in lymphoma. *Br. J. Cancer*. 1993;68(4):668–672.

70. Gascoyne DM, Lyne L, Spearman H, et al. Vitamin D receptor expression in plasmablastic lymphoma and myeloma cells confers susceptibility to Vitamin D. *Endocrinology*. 2017;158(3):503–515.

71. Pepper C, Thomas A, Hoy T, et al. The vitamin D3 analog EB1089 induces apoptosis via a p53-independent mechanism involving p38 MAP kinase activation and suppression of ERK activity in B-cell chronic lymphocytic leukemia cells in vitro. *Blood*. 2003;101(7):2454–2460.

72. Bruns H, Büttner M, Fabri M, et al. Vitamin D-dependent induction of cathelicidin in human macrophages results in cytotoxicity against high-grade B cell lymphoma. *Sci. Transl. Med.* 2015;7(282):282ra47.

73. Kulling PM, Olson KC, Olson TL, Feith DJ, Loughran TP. Vitamin D in hematological disorders and malignancies. *Eur. J. Haematol.* 2017;98(3):187–197.
74. Tao Y, Chen H, Zhou Y, Shi Y. Meta-analysis of the prognostic and clinical value of serum 25-hydroxyvitamin D levels in previously untreated lymphoma. *Futur. Oncol.* 2021;17(14):1825–38.

75. Park HY, Hong YC, Lee K, Koh J. Vitamin D status and risk of non-Hodgkin lymphoma: An updated meta-analysis. *PLoS One.* 2019;14(4):e0216284.

76. Lu D, Chen J, Jin J. Vitamin D status and risk of non-Hodgkin lymphoma: a meta-analysis. *Cancer Causes Control.* 2014;25(11):1553–1563.

77. Purdue MP, Freedman DM, Gapstur SM, et al. Circulating 25-hydroxyvitamin D and risk of non-Hodgkin lymphoma: Cohort Consortium Vitamin D Pooling Project of Rarer Cancers. *Am. J. Epidemiol.* 2010;172(1):58–69.

78. Rosenblatt J, Bissonnette A, Ahmad R, et al. Immunomodulatory effects of vitamin D: Implications for GVHD. *Bone Marrow Transplant.* 2010;45(9):1463–1468.

79. Chiengthong K, Cheungpasitporn W, Thongprayoon C, et al. Vitamin D deficiency is not associated with graft versus host disease after hematopoietic stem cell transplantation: A meta-analysis. *J. Evid. Based. Med.* 2020;13(3):183–191.

80. Vaughan-Shaw PG, Buijs LF, Blackmur JP, et al. The effect of vitamin D
supplementation on survival in patients with colorectal cancer: systematic review and meta-analysis of randomised controlled trials. *Br. J. Cancer*. 2020;123(11):1705–1712.

81. Raoufinejad K, Shamshiri AR, Pezeshki S, et al. Oral calcitriol in hematopoietic recovery and survival after autologous stem cell transplantation: a randomized clinical trial. *Darur*. 2019;27(2):709–720.

82. Braegger C, Campoy C, Colomb V, et al. Vitamin D in the healthy European paediatric population. *J. Pediatr. Gastroenterol. Nutr.* 2013;56(6):692–701.

83. Lips P. Which circulating level of 25-hydroxyvitamin D is appropriate? *J. Steroid Biochem. Mol. Biol.* 2004;89–90(1-5):611–614.

84. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: An endocrine society clinical practice guideline. *J. Clin. Endocrinol. Metab.* 2011;96(7):1911–1930.

85. Bischoff-Ferrari HA. Optimal serum 25-hydroxyvitamin D levels for multiple health outcomes. *Adv Exp Med Biol.* 2008;624:55–71.

86. Zgaga L, Theodoratou E, Farrington SM, et al. Diet, Environmental Factors, and Lifestyle Underlie the High Prevalence of Vitamin D Deficiency in Healthy Adults in Scotland, and Supplementation Reduces the Proportion That Are
Severely Deficient. *J Nutr.* 2011;141(8):1535–1542.

87. Giustina A, Adler RA, Binkley N, et al. Controversies in Vitamin D: Summary Statement from an International Conference. *J. Clin. Endocrinol. Metab.* 2019;104(2):234–240.
Table legends

**Table I** Characteristics of studies included in the meta-analysis.
| Ref | author            | publication year | study year | Country | disease                             | median age (range) | total N | low N | high N | mid N | vitamin D threshold | measuring method | median f/u | outcome | NOS |
|-----|-------------------|------------------|------------|---------|-------------------------------------|-------------------|---------|-------|--------|------|---------------------|----------------|------------|---------|-----|
| 1   | [17] Hu et al     | 2020             | 2014-2016  | China   | AML in the elderly (w/o APL, secondary AML) | 70 (60-89) | 68      | 25    | 43     | 0    | 8.84 ng/mL          | ECL             | 2 yr       | OS      | 9   |
| 2   | [18] Jackmann et al | 2020             | 1990-2016  | Sweden  | ALL in children                       | 7 (0.4-17.8)      | 232     | 71    | 161    | 0    | 50 nmol/L          | CLIA            | n.a.       | OS      | 8   |
|     |                   |                  |            |         | AML in children                       |                   | 52      | 22    | 30     | 0    |                     |                 |            |         |     |
|     |                   |                  |            |         | CML/JMML in children                  |                   | 11      | 5     | 6      | 0    |                     |                 |            |         |     |
| 3   | [19] Radujkovic et al | 2017             | 2006-2014  | Germany | MDS, oligoblastic AML                | 69 (31-83)         | 58      | 29    | 29     | 0    | 32.6 nmol/L         | CLIA            | 29 m      | OS      | 7   |
| 4   | [20] Lee et al    | 2014             | n.a.       | US      | AML (w/o APL)                        | 60 (19-91)         | 97      | 29    | 34     | 34   | < 20 ng/mL, ≥ 32 ng/mL | RIA             | 15.6 m    | OS, RFS  | 8   |
| 5   | [21] Pardanani et al | 2011             | n.a.       | US      | PMF                                 | 63 (14-83)         | 247     | 118   | 129    | 0    | 25 ng/mL           | LC-MS/MS        | 34 m      | OS, LFS  | 8   |
|     |                   |                  |            |         | MDS                                 | 72 (44-89)         | 74      | 21    | 53     | 0    |                     |                 |            |         |     |
| 6   | [22] Mao et al    | 2021             | 2014-2019  | China   | ENKTL                               | 55 (21-92)         | 93      | 55    | 38     | 0    | 50 nmol/L          | ECL             | 23 m      | OS, PFS  | 8   |
| 7   | [23] Wang et al   | 2020             | 2016-2018  | China   | DLBCL                               | 58 (19-85)         | 208     | 142   | 66     | 0    | 52.5 nmol/L        | ECL             | 29 m      | OS, PFS  | 9   |
| 8   | [33] Chen et al   | 2020             | 2011-2018  | China   | DLBCL                               | n.a.               | 332     | 111   | 111    | 110  | < 11.5 ng/mL, ≥ 18.7 ng/mL | LC-MS/MS        | 34.2 m    | OS, PFS  | 9   |
| 9   | [34] Xu et al     | 2020             | 2014-2018  | China   | MCL                                 | 61 (39-77)         | 70      | 40    | 30     | 0    | 50 nmol/L          | ECL             | 25.5 m    | OS, PFS  | 8   |
| 10  | [35] Yellapragada | 2020             | n.a.       | US      | MM                                  | 68.9               | 1889    | 582   | 1307   | 0    | 20 ng/mL           | n.a.            | n.a.      | OS      | 8   |
| Study ID | Authors | Year | Country | Diagnosis | Age Range | Male | Female | Median Age | Cutoff | Assay | Follow-up | Outcomes |
|----------|---------|------|---------|-----------|-----------|------|--------|------------|--------|--------|-----------|----------|
| 11       | et al   | 2019 | Germany | HL        | 32 (16-75) | 351  | 175   | 176        | 0      | ELISA  | 13 yr     | OS, PFS  |
| 12       | et al   | 2018 | Korea   | PTCL, ENKTL | (17-85)  | 251  | 105   | 146        | 0      | LC-MS/MS | 35.8 m   | PFS     |
| 13       | et al   | 2018 | Serbia  | lymphoid malignancy | 58 (18-84) | 133  | n.a.  | n.a.       | 0      | CLIA    | 20 m     | PFS     |
| 14       | et al   | 2018 | Italy   | aggressive BCL | 65      | 154  | 104   | 50         | 0      | CLIA    | n.a.     | EFS     |
| 15       | et al   | 2017 | Italy   | DLBCL     | 70 (24-93) | 50   | n.a.  | n.a.       | 0      | CLIA    | n.a.     | OS, PFS |
| 16       | et al   | 2017 | US      | FL        | 60 (23-93) | 642  | 120   | 522        | 0      | LC-MS/MS | 59 m     | OS      |
| 17       | et al   | 2017 | Italy   | HL        | 33      | 76   | 9     | 67         | 0      | CLIA    | 12 m     | PFS     |
| 18       | et al   | 2015 | US      | FL (SWOG cohort) | n.a.  | 183  | 28    | 155        | 0      | LC-MS/MS | 5.4 yr   | PFS, OS |
|          |         |      |         | FL (LYSA cohort) | n.a.  | 240  | 60    | 180        | 0      |          | 6.6 yr   |         |
| 19       | et al   | 2014 | Germany | DLBCL with R #1 in the elderly | (61-80) | 184  | 81    | 103        | 0      | CLIA    | 34.5 m   | PFS, OS |
|          |         |      |         | DLBCL without R in the elderly | (61-80) | 175  | 70    | 105        | 0      |          |         |         |
| Year | Study | Country | Group | Range | Median | Count | Cut-off | Assay | n.a. | OS | RR |
|------|-------|---------|-------|-------|--------|-------|---------|-------|------|----|----|
| 2005-2007 | DLBCL with R #2 in the elderly | Egypt | B-CLL | 57 (50-60) | 75 | 54 | 21 | 0 | 20 ng/mL | ELISA | n.a. | OS | 8 |
| 2013 | Aref et al | Egypt | NHL | 61 (52-67) | 120 | 64 | 56 | 0 | | n.a. | OS | 5 yr |
| 1998-2008 | CLL | Italy | 68 (43-87) | 130 | n.a. | n.a. | 0 | 13.5 ng/mL | CLIA | 39 m | TTT | 7 |
| 2002-2008 | NHL (DLBCL, TCL, MCL, FL, other) | Norway | lymphoma | 56.3 (37-79) | 145 | 40 | 28 | 77 | < 46 nmol/L | RIA | n.a. | OS | 7 |
| 2008 | CLL | US | n.a. | 543 | 180 | 363 | 0 | 25 ng/mL | LC-MS/MS | n.a. | OS, TTT | 9 |
| 2010 | NHL (DLBCL, TCL, MCL, FL, other) | US | 62 (19-94) | 983 | 436 | 547 | 0 | 25 ng/mL | LC-MS/MS | 34.8 m | EFS, OS | 9 |
| 2012-2018 | ASCT (lymphoma, myeloma) | Switzerland | 60 (24-77) | 183 | 102 | 81 | 0 | 52 nmol/L | CLIA | n.a. | OS | 8 |
| 2016 | ASCT (myeloma) | US | n.a. | 158 | 94 | 64 | 0 | 23 ng/mL | n.a. | n.a. | OS | 6 |
| 2009-2010 | ASCT (lymphoma, myeloma) | US | n.a. | 132 | n.a. | n.a. | 0 | n.a. | n.a. | n.a. | OS | 5 |
| 2012-2017 | allo-HSCT in children | US | n.a. | n.a. | 48 | 78 | n.a. | ≤ 20 ng/mL, > 30 ng/mL | n.a. | n.a. | OS | 7 |
| 2017 | allo-HSCT (myeloid #1) | Germany | (17-75) | 242 | 188 | 54 | 0 | 20 ng/mL | CLIA | 51.2 m | OS, RR | 9 |
| Year | Study | Method | NRM | OS | Age | Males | Females | Complete | Partial | >=50 | <50 | >=50 | <50 |
|------|-------|--------|-----|----|-----|-------|---------|----------|---------|-------|------|------|------|------|
| 2005-2011 | Sweden | allo-HSCT (myeloid) | 250 | 208 | 42 | 0 | | | | 59 | 88 | <25 nmol/L | ≥25 nmol/L |
| 2009-2013 | Sweden | allo-HSCT (lymphoid) | 398 | 166 | 19 | 50 | | | | 348 | 0 | 51.3 m | 71 m |
| 2013 | | | | | | | | | | | | | |

Bahr et al 2015

NRM

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ALL: acute lymphoblastic leukemia; allo-HSCT: allogeneic hematopoietic stem cell transplantation; AML: acute myeloid leukemia; APL: acute promyelocytic leukemia; ASCT: autologous stem cell transplantation; BCL: B cell lymphoma; BL: Burkitt lymphoma; CLIA: chemiluminescence immunoassay; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; DLBCL: diffuse large B cell lymphoma; ECL: electrochemiluminescence; EFS: event-free survival; ELISA: enzyme-linked immunosorbent assay; ENKTL: extranodal NK/T cell lymphoma; FL: follicular lymphoma; f/u: follow-up; HL: Hodgkin lymphoma; JMML: juvenile myelomonocytic leukemia; LC-MS/MS: liquid chromatography-tandem mass spectrometry; LFS: leukemia-free survival; LPL: lymphoplasmacytic lymphoma; m: months; MCL: mantle cell lymphoma; MDS: myelodysplastic syndrome; MM: multiple myeloma; N: number; n.a.: not available; NHL: non-Hodgkin lymphoma; NOS: Newcastle-Ottawa scale; NRM: non-relapse mortality; OS: overall survival; PFS: progression-free survival; PMF: primary myelofibrosis; PTCL: peripheral T cell lymphoma; R: rituximab; Ref: reference; RFS: relapse-free survival; RIA: radioimmunoassay; RR: relapse rate; TCL: T cell lymphoma; TTT: time-to-treatment; w/o: without; yr: years.
Table II Characteristics of previous meta-analyses on the role of vitamin D status in hematological malignancies.
| Ref | Author                  | publication year | disease                      | article number | HRs of OS, PFS/RFS, and GVHD (95%CI) |
|-----|-------------------------|------------------|------------------------------|----------------|--------------------------------------|
| 1   | (this meta-analysis)    | -                | myeloid malignancy           | 5              | OS 1.39 (1.06–1.82), PFS 2.03 (1.23–3.32) |
|     |                         |                  | lymphoid malignancy          | 20             | OS 2.07 (1.79–2.40), PFS 1.91 (1.61–2.25) |
|     |                         |                  | ASCT                         | 3              | OS 1.65 (1.04–2.61)                  |
|     |                         |                  | allo-SCT                     | 3              | OS 1.50 (1.03–2.18)                  |
| 2   | [74] Tao et al.         | 2021             | lymphoma                     | 12             | OS 1.94 (1.71–2.19), PFS 2.06 (1.82–2.32) |
| 3   | [79] Chiengthong et al. | 2020             | HSCT                         | 8              | aGVHD 1.07 (0.74–1.53), cGVHD 1.75 (0.72–4.26) |
| 4   | [10] Wang et al.        | 2015             | hematological cancer         | 7              | OS 1.85 (1.54–2.23), RFS 1.45 (1.25–1.70) |
|     |                         |                  | –leukemia                    | 3              | OS 2.17 (1.54–3.05), RFS 1.74 (1.34–2.27) |
|     |                         |                  | –lymphoma                    | 4              | OS 1.95 (1.47–2.59), RFS 1.25 (1.02–1.54) |
| 5   | [5] Li et al.           | 2014             | lymphoma                     | 2              | OS 2.08 (1.56–2.78)                  |
aGVHD: acute graft-versus-host disease; Allo-SCT: allogeneic stem cell transplantation; ASCT: autologous stem cell transplantation; cGVHD: chronic graft-versus-host disease; CI: confidence interval; GVHD: graft-versus-host disease; HSCT: hematopoietic stem cell transplantation; HR: hazard ratio; OS: overall survival; PFS: progression-free survival; RFS: relapse-free survival
Figure legends

Figure 1. PRISMA flow diagram of study selection.

After the screening of titles and abstracts of 1212 articles, 52 articles were considered to be relevant. Among them, 22 articles were excluded due to several reasons, and 30 articles were included for the analysis.

Figure 2. Outcomes in myeloid malignancies.

(A) Hazard ratio (HR) of overall survival in myeloid malignancies and (B) funnel plot.

(C) HR of progression-free survival in myeloid malignancies.

Figure 3. Outcomes in lymphoid malignancies.

(A) Hazard ratio (HR) of overall survival in lymphoid malignancies and (B) funnel plot.

(C) HR of progression-free survival in lymphoid malignancies and (D) funnel plot.

Figure 4. Outcomes in diffuse large B cell lymphoma.

(A) Hazard ratio (HR) of overall survival in diffuse large B cell lymphoma (DLBCL) and (B) funnel plot. (C) HR of progression-free survival in DLBCL and (D) funnel plot.
Figure 5. Outcomes in each subtype of lymphoid malignancies.

Hazard ratios (HRs) of (A) overall survival (OS) and (B) progression-free survival (PFS) in follicular lymphoma. HRs of (C) OS and (D) PFS in mantle cell lymphoma. (E) HR of PFS in Hodgkin lymphoma. HRs of (F) OS and (G) PFS in T cell lymphoma. HRs of (H) OS and (I) time-to-treatment in chronic lymphocytic leukemia.

Figure 6. Outcomes in hematopoietic stem cell transplantation.

(A) Hazard ratio (HR) of overall survival (OS) in autologous hematopoietic stem cell transplantation (HSCT). HRs of (B) OS, (C) relapse rate, and (D) non-relapse mortality in allogeneic HSCT.
Fig. 1 – PRISMA flow diagram of study selection.

- Records identified through database searching:
  - PubMed (n = 361)
  - EMBASE (n = 978)
  - Cochrane Library (n = 42)
  - ASH (n = 16)
  - ASCO (n = 2)
  - EHA (n = 5)

- Additional records identified through other sources\(^{15,11}\) (n = 11)

- Records after duplicates removed (n = 1212)

- Records screened (n = 1212)
  - Records excluded (n = 1160)

- Full-text articles assessed for eligibility (n = 52)
  - Full-text articles excluded, with reasons:
    - Duplicate publications from overlapping cohort (n = 2)\(^{47,48}\)
    - Insufficient data of primary endpoint (n = 12)\(^{49-60}\)
    - Transplantations including many non-malignancies or uncentified diseases (n = 8)\(^{61-68}\)

- Studies included in qualitative synthesis (n = 30)

- Studies included in quantitative synthesis (meta-analysis) (n = 30)\(^{37,46}\)
Fig. 2 - Outcomes in myeloid malignancies.

A

| Study            | TE   | seTE | Hazard Ratio | HR   | 95% - CI     | Weight (fixed) | Weight (random) |
|------------------|------|------|--------------|------|--------------|----------------|-----------------|
| Hu et al 2020    | 0.06 | 0.0256 | 1.06         | 1.06 | [1.00; 1.10] | 95.4%          | 35.1%           |
| Jackmann et al 2020 (AML) | 0.43 | 0.5605 | 1.54         | 1.54 | [0.51; 4.62] | 0.2%           | 5.2%            |
| Jackmann et al 2020 (CML/JMML) | 1.03 | 1.1730 | 2.81         | 2.81 | [0.28; 28.06] | 0.0%           | 1.3%            |
| Raduikovic et al 2017 | 0.71 | 0.3212 | 2.03         | 2.03 | [1.08; 3.81] | 0.8%           | 12.1%           |
| Lee et al 2014    | 1.07 | 0.3806 | 2.93         | 2.93 | [1.36; 6.17] | 0.4%           | 9.6%            |
| Pardanani et al 2011 (PMF) | 0.18 | 0.1468 | 1.20         | 1.20 | [0.50; 2.69] | 2.8%           | 29.3%           |
| Pardanani et al 2011 (MDS) | 0.34 | 0.3351 | 1.40         | 1.40 | [0.73; 2.67] | 0.5%           | 11.5%           |

Fixed effect model: 1.07 [1.02; 1.12] 100.0%  --  100.0%

Random effects model: 1.39 [1.06; 1.82] 100.0%  --  100.0%

Heterogeneity: I² = 57%, t² = 0.0535, p = 0.03


B


C

| Study            | TE   | seTE | Hazard Ratio | HR   | 95% - CI     | Weight (fixed) | Weight (random) |
|------------------|------|------|--------------|------|--------------|----------------|-----------------|
| Lee et al 2014    | 0.95 | 0.3580 | 2.59         | 2.59 | [1.28; 5.22] | 49.9%          | 49.9%           |
| Pardanani et al 2011 (PMF) | 0.59 | 0.4560 | 1.80         | 1.80 | [0.74; 4.40] | 30.7%          | 30.7%           |
| Pardanani et al 2011 (MDS) | 0.26 | 0.5734 | 1.30         | 1.30 | [0.42; 4.00] | 19.4%          | 19.4%           |

Fixed effect model: 2.03 [1.23; 3.32] 100.0%  --  100.0%

Random effects model: 2.03 [1.23; 3.32] 100.0%  --  100.0%

Heterogeneity: I² = 0%, t² = 0, p = 0.57
Fig. 3 - Outcomes in lymphoid malignancies.

### Table A

| Study                        | TE  | seTE | Hazard Ratio | HR 95%–CI | Weight (fixed) | Weight (random) |
|------------------------------|-----|------|--------------|-----------|----------------|-----------------|
| Aref et al 2013 (NHL)        | 1.06| 0.7702 | 5.25 [1.16; 23.00] | 0.6% | 0.9% |
| Tratli et al 2012 (lymphoma) | 1.11| 0.3684 | 3.03 [1.47; 6.26] | 2.6% | 3.7% |
| Drake et al 2010 (post-FL)   | 1.02| 0.7946 | 2.76 [0.58; 13.10] | 0.6% | 0.9% |
| Drake et al 2010 (other lymphoma) | 0.73| 0.4952 | 2.08 [0.78; 5.49] | 1.5% | 2.1% |
| Wang et al 2020 (DLBCL)      | 1.32| 0.4819 | 3.73 [1.45; 9.58] | 1.5% | 2.3% |
| Chen et al 2020 (DLBCL)      | 0.92| 0.4875 | 2.00 [1.00; 4.29] | 1.6% | 2.4% |
| Ferreri et al 2017 (DLBCL)   | 1.75| 0.7744 | 5.75 [1.20; 26.30] | 2.0% | 3.3% |
| Bittner et al 2014 (DLBCL with R #1) | 0.64| 0.3261 | 1.00 [0.20; 5.00] | 3.4% | 4.7% |
| Bittner et al 2014 (DLBCL without R) | 0.59| 0.2606 | 1.80 [1.08; 3.00] | 5.3% | 7.0% |
| Bittner et al 2014 (DLBCL with R #2) | 1.41| 0.7659 | 4.10 [1.32; 12.70] | 1.1% | 1.6% |
| Drake et al 2010 (DLBCL)     | 0.69| 0.3111 | 1.99 [1.27; 3.13] | 6.7% | 8.6% |
| Tracy et al 2017 (FL)        | 0.85| 0.2739 | 2.35 [1.37; 4.20] | 4.8% | 6.4% |
| Kelly et al 2016 (FL- LYSA cohort) | 1.43| 0.4695 | 4.16 [1.66; 10.44] | 1.4% | 2.4% |
| Kelly et al 2016 (FL- SVOG cohort) | 0.55| 0.5614 | 1.02 [0.72; 1.43] | 1.4% | 2.1% |
| Xu et al 2020 (MCL)          | 2.12| 0.7113 | 8.30 [2.06; 33.48] | 0.7% | 1.1% |
| Drake et al 2010 (MCL)       | 0.30| 0.4698 | 1.35 [0.34; 2.39] | 1.6% | 2.4% |
| Bittner et al 2019 (HL)      | 3.00| 0.0552 | 1.62 [1.54; 2.15] | 49.5% | 30.5% |
| Ma et al 2021 (ENKTL)        | 0.96| 0.4303 | 2.60 [1.12; 3.05] | 1.9% | 2.8% |
| Drake et al 2010 (TCL)       | 0.57| 0.4190 | 2.35 [1.05; 5.41] | 2.0% | 2.9% |
| Aref et al 2013 (CLL)        | 1.42| 0.6423 | 4.14 [1.10; 14.68] | 0.9% | 1.3% |
| Shandaresi et al 2011 (CLL)  | 0.39| 0.2126 | 1.47 [0.97; 2.23] | 7.9% | 9.8% |
| Jackman et al 2020 (ALL)     | 0.12| 0.3969 | 1.13 [0.52; 2.46] | 2.3% | 3.3% |

**Fixed effect model**: 1.98 [1.77; 2.23] 100.0%

**Random effects model**: 2.07 [1.79; 2.40] 100.0%

**Heterogeneity**: $I^2 = 10.0$, $P = 0.0100$, $p = 0.03$

### Table B

![Graph showing hazard ratio vs. standard error]

### Table C

| Study                        | TE  | seTE | Hazard Ratio | HR 95%–CI | Weight (fixed) | Weight (random) |
|------------------------------|-----|------|--------------|-----------|----------------|-----------------|
| Djuric et al 2016 (lymphoid malignancy) | 1.07| 0.4104 | 2.92 [1.31; 6.53] | 1.7% | 3.4% |
| Hohe et al 2018 (aggressive BCL) | 1.06| 0.4458 | 2.68 [1.20; 6.96] | 1.4% | 2.9% |
| Drake et al 2010 (post-FL)    | -0.02| 0.3351 | 0.98 [0.51; 1.90] | 2.5% | 4.5% |
| Drake et al 2010 (other lymphoma) | 0.17| 0.5731 | 1.15 [0.42; 3.52] | 2.5% | 4.5% |
| Vitkin et al 2004 (DLBCL)     | 1.04| 0.3227 | 2.83 [1.50; 5.32] | 2.7% | 4.8% |
| Chen et al 2020 (DLBCL)      | 1.31| 0.3733 | 3.70 [1.70; 7.68] | 2.0% | 3.8% |
| Ferreri et al 2017 (DLBCL)   | 1.66| 0.7055 | 4.34 [1.42; 12.59] | 0.5% | 1.1% |
| Bittner et al 2014 (DLBCL with R #1) | 0.59| 0.2063 | 1.60 [0.97; 2.86] | 3.3% | 5.4% |
| Bittner et al 2014 (DLBCL without R) | 0.34| 0.2069 | 1.40 [0.93; 2.10] | 6.6% | 10.1% |
| Bittner et al 2014 (DLBCL with R #2) | 0.96| 0.3337 | 2.60 [0.91; 7.45] | 1.2% | 2.2% |
| Drake et al 2010 (DLBCL)     | 0.34| 0.1985 | 1.41 [0.97; 2.04] | 7.5% | 9.9% |
| Kelly et al 2015 (FL- SVOG cohort) | 0.58| 0.3075 | 1.97 [1.01; 3.83] | 3.2% | 5.3% |
| Kelly et al 2015 (FL- LYSA cohort) | 0.41| 0.2440 | 1.50 [0.59; 4.22] | 4.7% | 6.8% |
| Xu et al 2020 (MCL)          | 1.31| 0.3631 | 1.61 [0.60; 4.63] | 3.2% | 5.3% |
| Drake et al 2010 (MCL)       | 0.09| 0.3122 | 1.05 [0.55; 2.01] | 2.3% | 3.3% |
| Bittner et al 2019 (HL)      | 1.73| 0.9835 | 2.13 [1.03; 4.39] | 6.7% | 13.9% |
| Coquery et al 2017 (HL)      | 0.37| 0.0776 | 2.12 [1.03; 4.39] | 6.7% | 13.9% |
| Mac et al 2021 (ENKTL)       | 0.76| 0.3522 | 2.14 [1.07; 4.27] | 2.3% | 4.2% |
| Kim et al 2016 (TCL)         | 0.64| 0.2521 | 1.05 [0.46; 2.43] | 3.3% | 5.5% |
| Drake et al 2010 (TCL)       | 0.66| 0.3169 | 1.94 [1.67; 2.25] | 100.0% | -- |

**Fixed effect model**: 1.94 [1.75; 2.15] 100.0%

**Random effects model**: 1.91 [1.61; 2.25] 100.0%

**Heterogeneity**: $I^2 = 52.0$, $P = 0.0453$, $p = 0.04$

### Table D

![Graph showing hazard ratio vs. standard error]
### Fig. 4 – Outcomes in diffuse large B cell lymphoma.

#### A

| Study                     | TE   | seTE | Hazard Ratio | HR   | 95%–CI   | Weight (fixed) | Weight (random) |
|---------------------------|------|------|--------------|------|----------|----------------|-----------------|
| Wang et al 2020           | 1.32 | 0.4819 |             | 3.73 | [1.45; 9.58] | 7.6%           | 7.6%            |
| Chen et al 2020           | 0.92 | 0.4675 |             | 2.50 | [1.00; 6.25] | 8.1%           | 8.1%            |
| Ferrari et al 2017        | 1.75 | 0.7748 |             | 5.76 | [1.26; 20.30] | 3.0%           | 3.0%            |
| Bittenbrin et al 2014 (with R #1) | 0.64 | 0.3261 |             | 1.90 | [1.00; 3.66] | 16.7%          | 16.7%           |
| Bittenbrin et al 2014 (without R) | 0.59 | 0.2606 |             | 1.80 | [1.01; 3.20] | 26.1%          | 26.1%           |
| Bittenbrin et al 2014 (with R #2) | 1.41 | 0.5769 |             | 4.10 | [1.32; 12.70] | 5.3%           | 5.3%            |
| Drake et al 2010          | 0.69 | 0.2311 |             | 1.09 | [1.27; 3.13] | 33.2%          | 33.2%           |

**Fixed effect model**

- 2.20 [1.70; 2.86] 100.0% --

**Random effects model**

- Heterogeneity: $I^2 = 0\%$, $t^2 = 0$, $p = 0.55$
- 2.20 [1.70; 2.86] -- 100.0%

#### B

![Graph A](image)

#### C

| Study                     | TE   | seTE | Hazard Ratio | HR   | 95%–CI   | Weight (fixed) | Weight (random) |
|---------------------------|------|------|--------------|------|----------|----------------|-----------------|
| Wang et al 2020           | 1.04 | 0.3227 |             | 2.83 | [1.50; 5.32] | 11.3%          | 14.8%           |
| Chen et al 2020           | 1.31 | 0.3733 |             | 3.70 | [1.78; 7.69] | 8.4%           | 12.6%           |
| Ferrari et al 2017        | 1.86 | 0.7705 |             | 6.45 | [1.42; 29.20] | 2.0%           | 4.2%            |
| Bittenbrin et al 2014 (with R #1) | 0.59 | 0.2936 |             | 1.80 | [1.01; 3.20] | 13.6%          | 16.3%           |
| Bittenbrin et al 2014 (without R) | 0.34 | 0.2069 |             | 1.40 | [0.93; 2.10] | 27.5%          | 21.6%           |
| Bittenbrin et al 2014 (with R #2) | 0.66 | 0.5337 |             | 2.60 | [0.91; 7.40] | 4.1%           | 7.7%            |
| Drake et al 2010          | 0.34 | 0.1685 |             | 1.41 | [0.97; 2.04] | 33.1%          | 22.8%           |

**Fixed effect model**

- 1.80 [1.46; 2.23] 100.0% --

**Random effects model**

- Heterogeneity: $I^2 = 50\%$, $t^2 = 0.0910$, $p = 0.06$
- 2.05 [1.47; 2.86] -- 100.0%

#### D

![Graph B](image)
Fig. 5 - Outcomes in each subtype of lymphoid malignancies.
Figure 6—Outcomes in hematopoietic stem cell transplantation.