


Vitamin D deficiency is associated with inferior survival of patients with extranodal natural killer/T-cell lymphoma

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Vitamin D deficiency is a common health issue; however, the effect of vitamin D deficiency on the survival of T-cell lymphoma is still not clear. We evaluated the impact of serum vitamin D level of patients with peripheral T-cell lymphoma (PTCL) and extranodal natural killer/T-cell lymphoma (ENKTL) on survival outcome. Pretreatment levels of 25-hydroxyvitamin D [25(OH)D] and inflammatory cytokines were measured in serum samples that were archived at diagnosis, and we evaluated their association with survival in newly diagnosed patients with PTCL (n = 137) and ENKTL (n = 114) at a university-based hospital in Korea. An independent cohort from Rui Jin Hospital (Shanghai, China) was used for validation. The median 25(OH)D serum level was 12.0 ng/mL (1.3–60.0 ng/mL), and 40% had less than 10 ng/mL, which was defined as vitamin D deficiency. Median serum 25(OH)D levels were similar between PTCL (11.5 ng/mL) and ENKTL (12.9 ng/mL); however, vitamin D deficiency was associated with inferior survival in ENKTL but not with PTCL. The independent validation cohort (n = 115) also showed a significant association of vitamin D deficiency with poor survival in ENKTL. The 25(OH)D level had an inverse relation with inflammatory cytokines; this association had a negative effect only on survival of ENKTL, and not on PTCL. In conclusion, vitamin D deficiency was associated with inferior survival outcome of patients with ENKTL.

KEYWORDS

chemotherapy, NK/T-cell lymphoma, prognosis, survival, vitamin D

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1 | INTRODUCTION

Vitamin D deficiency is highly prevalent in the general population. Low sun exposure and oral intake are the main reasons for vitamin D deficiency.¹ Beside its main effect on bone metabolism, vitamin D deficiency is a risk factor for cancer development as well as poor treatment outcome.² In non-Hodgkin lymphoma (NHL) patients, the prognostic value of vitamin D deficiency has increased interest since a previous cohort study with newly diagnosed NHL patients reported the negative effect of vitamin D deficiency on prognosis.³ Recently, 2 prospective cohort studies demonstrated an association of vitamin D deficiency with survival outcome of patients with diffuse large B-cell lymphoma and follicular lymphoma who received rituximab-containing chemotherapy.^{4,5} Studies have suggested that vitamin D deficiency might impair rituximab-mediated cytotoxicity, leading to an inferior outcome for patients. Yet, there are few data on the association of vitamin D deficiency with the prognosis of T-cell and natural killer (NK)-cell lymphoma. To date, only 1 study has reported the negative effect of vitamin D deficiency on the survival of T-cell lymphoma.³ However, the study analyzed a relatively small number of T-cell lymphomas and information about NK/T-cell lymphoma was lacking. Because the main treatment for T-cell and NK-cell lymphomas does not include monoclonal antibodies unlike B-cell lymphomas, the effect of vitamin D deficiency on the survival outcome of these disease entities and underlying mechanisms might be different from that of B-cell lymphomas.

Thus, the present study aims to investigate the role of vitamin D in patients with peripheral T-cell lymphoma (PTCL) and extranodal NK/T-cell lymphoma, nasal type (ENKTL). We hypothesized that PTCL and ENKTL patients with vitamin D deficiency would have inferior survival outcomes because vitamin D deficiency is associated with the risk of mortality in the general population as well as cancer patients.^{2,6} Therefore, we evaluated the association of survival outcome with vitamin D deficiency in a prospective cohort of consecutively enrolled Korean patients with newly diagnosed PTCL and ENKTL and validated our results in an independent Chinese cohort. Vitamin D deficiency was based on measuring the serum level of 25-hydroxyvitamin D [25(OH)D] because 25(OH)D is currently considered the biomarker that most accurately reflects the storage form of vitamin D.^{1,7} In the present study, we defined a serum level of 25(OH)D < 10 ng/mL as vitamin D deficiency because the global definition of vitamin D deficiency has commonly been serum 25(OH)D < 10 ng/mL.⁸

Peripheral T-cell lymphoma and ENKTL were separately analyzed because the current chemotherapy regimens for ENKTL are nonanthracycline-based and L-asparaginase-containing chemotherapies.⁹ We also analyzed the correlation of serum levels of inflammatory cytokines with 25(OH)D to elucidate the association of vitamin D deficiency with survival outcome in PTCL and ENKTL given the pro-inflammatory effect of vitamin D deficiency.¹⁰

2 | PATIENTS AND METHODS

2.1 | Study design

Patients in the discovery cohort were participants enrolled in 2 prospective cohort studies: Samsung Medical Center-Lymphoma Cohort Studies I (2008-2011, NCT#00822731) and II (2012-2016, NCT#01877109). From May 1 to September 31, 2013, they conducted a multicenter study on 2173 apparently healthy adults who were recruited from 5 Chinese cities: Dalian, Beijing, Hangzhou, Guangzhou, and Urumqi. From these cohort studies, following provision of written informed consent, we gathered clinical and laboratory characteristics, including age, performance status, B symptoms, Ann Arbor stage and serum lactate dehydrogenase (LDH). We also collected pretreatment serum samples at diagnosis and stored them at -80°C until analysis. The Institutional Review Board at the Samsung Medical Center reviewed and approved all aspects of the study. For the establishment of the discovery cohort for this analysis, we selected 251 patients with PTCL or ENKTL according to the following inclusion criteria: (i) newly diagnosed patients with PTCL and ENKTL; (ii) patients receiving treatment with curative intent; and (iii) patients having archived frozen serum samples available for the measurement of vitamin D and cytokine assay (Figure 1A). Cutaneous T-cell lymphomas were excluded from the study cohort because of their indolent nature. A review of pathology data was performed by an expert on lymphoma pathology (K.Y.H) according to the 2008 World Health Organization classification criteria.¹¹ Serum levels of 25(OH)D were measured in the aforementioned archived serum samples, and their association with survival outcomes was analyzed. The last update of survival and disease status for this analysis was done in May 2017. To validate the findings of the study, we used data obtained from the registry of the Shanghai Rui Jin Hospital. In total, 115 patients with PTCL or ENKTL were treated with curative intent between June 2013 and February 2017; their serum level of 25(OH)D was measured at diagnosis during the initial work-up (Figure 1B). The pathologist of the Shanghai Rui Jin Hospital undertook the pathology review and final diagnosis of PTCL and ENKTL.

2.2 | Serum vitamin D measurement

All archived samples of the discovery cohort were sent to the Department of Laboratory Medicine at the Samsung Medical Center, and vitamin D levels were determined from a single baseline serum sample. Serum levels of 25(OH)D₂ and D₃ were determined by high-performance liquid chromatography-tandem mass spectrometry, with an Agilent 6460 Triple Quad mass spectrometer equipped with a 1200 liquid chromatography system (Agilent Technologies, Waldbronn, Germany).¹² The intra-assay and inter-assay imprecisions were <10% of coefficients of variation, and the combination of 25(OH)D₂ and D₃ < 10 ng/mL was defined as vitamin D deficiency. Although various cutoff values for vitamin D deficiency have been used in previous studies, such as 20 ng/mL of 25(OH)D for follicular lymphoma and 8 ng/mL of 25(OH)D₃ for diffuse large B-cell lymphoma,^{4,5} we used a cutoff of 10 ng/mL given the high prevalence of

vitamin deficiency in the Asian population. In the validation cohort, the serum level of 25(OH)D was measured at the Shanghai Rui Jin Hospital laboratory, and the same cutoff value (10 ng/mL) was used.

2.3 | Measurement of serum cytokines

We performed multiplexed assays for the measurement of cytokines using archived serum samples of the discovery cohort to analyze their association with serum vitamin D levels. We used the Procarta cytokine profiling kit (Human ProcartaPlex; Panomics, San Diego, CA, USA) to detect and quantitate the following 34 protein targets simultaneously: eotaxin, GM-CSF, GRO α , IFN α , IFN γ , IL-1 α , IL-1 β , IL-1RA, IL-2, IL-4-10, IL-12p70, IL-13, IL-15, IL-17A, IL-18, IL-21-23, IL-27, IL-31, IP-10, MCP-1, MIP-1 α , MIP-1 β , RANTES, SDF1 α , TNF α and TNF β . All measurements were performed in duplicate according to the manufacturer's instructions.

2.4 | Statistics

The association of serum vitamin D with categorical variables was analyzed using the χ^2 -test. The Kaplan-Meier method and log-rank test

were used to assess the association of vitamin D deficiency and survival. Progression-free survival (PFS) was measured from the date of diagnosis to the date of death from any cause or date of disease progression or relapse, and overall survival (OS) was from the date of diagnosis to the date of death from any cause. Patients without an event or death were censored at the date of the last follow-up visit. THE Cox proportional hazard regression model was used to calculate the hazard ratio of PFS adjusting for prognostic factors, including age, performance status, Ann Arbor stage and serum LDH. All statistical analyses were performed using the software package IBM PASW (version 23.0; SPSS, Chicago, IL, USA) and a 2-sided P-value <.05 was considered significant.

3 | RESULTS

3.1 | Patients

The discovery cohort consisted of patients who were consecutively diagnosed with PTCL (n = 137) and ENKTL (n = 114) between September 2008 and June 2016 at the Samsung Medical Center. The median age of PTCL and ENKTL patients was 57 years (range: 18-85 years) and 53 years (range: 17-78 years),

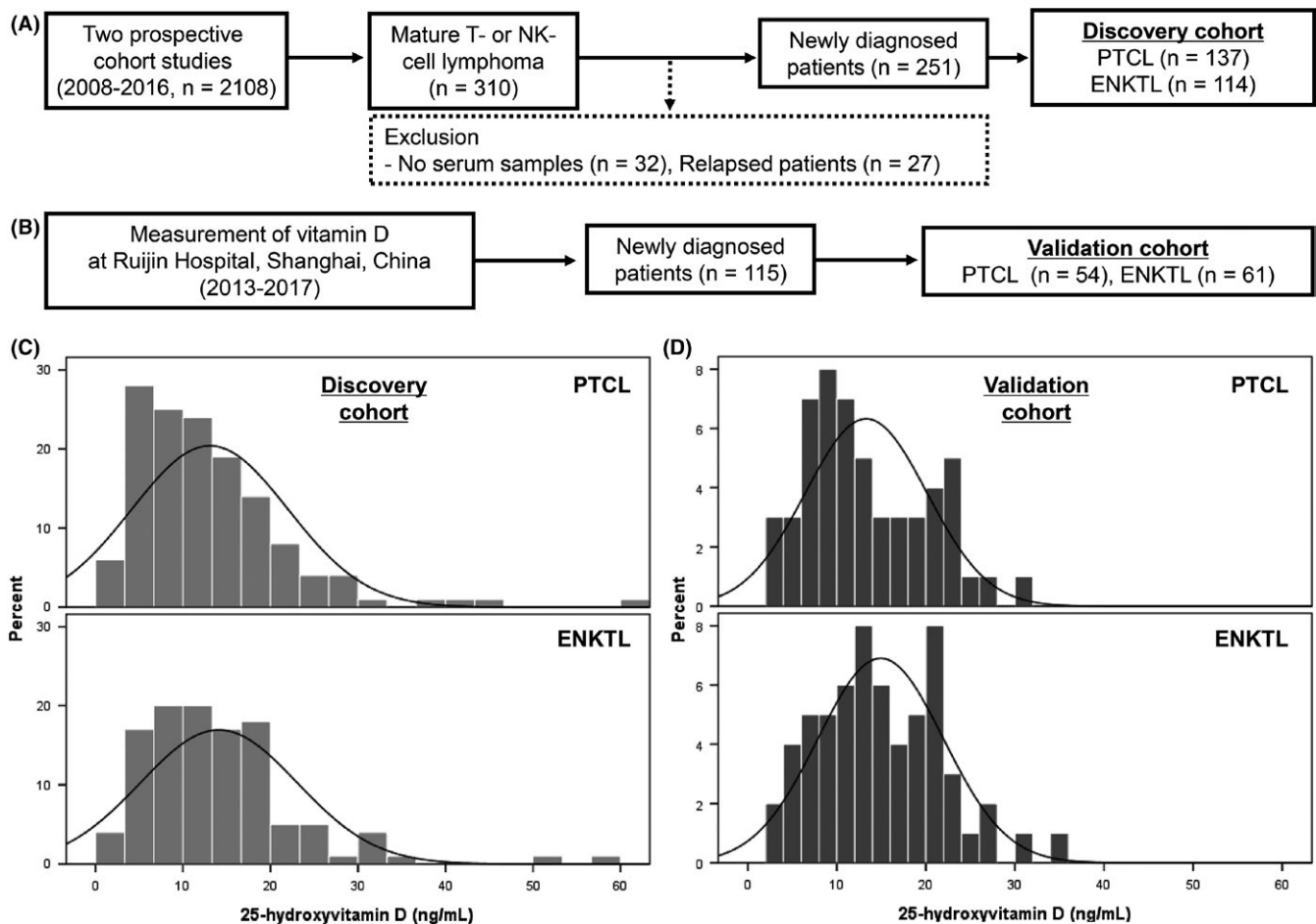


FIGURE 1 A, B, Consort diagram for the establishment of the study and validation cohort. C, D, Serum levels of 25(OH)D in peripheral T-cell lymphoma and extranodal natural killer/T-cell lymphoma of the discovery and validation cohort ENKTL, extranodal natural killer/T-cell lymphoma; PTCL, peripheral T-cell lymphoma

TABLE 1 Patient characteristics of the discovery and validation cohort

	Extranodal NK/T-cell lymphoma		Peripheral T-cell lymphoma	
	Discovery cohort (n = 114)	Validation cohort (n = 61)	Discovery cohort (n = 137)	Validation cohort (n = 54)
Age (y)				
≤60	85 (75%)	48 (79%)	83 (61%)	39 (72%)
>60	29 (25%)	13 (21%)	54 (39%)	15 (28%)
Sex				
Male	80 (70%)	43 (70%)	91 (66%)	37 (69%)
Female	34 (30%)	18 (30%)	46 (34%)	17 (31%)
ECOG performance status				
0/1	99 (87%)	57 (93%)	115 (84%)	48 (89%)
≥2	15 (13%)	4 (7%)	22 (16%)	6 (11%)
Stage				
I/II	72 (63%)	42 (69%)	33 (24%)	4 (7%)
III/IV	42 (37%)	19 (31%)	104 (76%)	50 (93%)
Serum LDH				
Normal	61 (54%)	37 (61%)	59 (43%)	26 (48%)
Increased	53 (46%)	24 (39%)	78 (57%)	28 (52%)
Bone marrow involvement				
Absence	89 (78%)	46 (75%)	97 (71%)	39 (72%)
Presence	25 (22%)	15 (25%)	40 (29%)	15 (28%)
Number of extranodal involvement				
0/1	65 (57%)	50 (82%)	83 (61%)	49 (91%)
≥2	49 (43%)	11 (18%)	54 (39%)	5 (9%)
B symptoms				
Absence	72 (63%)	NA	85 (62%)	NA
Presence	42 (37%)	NA	52 (38%)	NA
International prognostic index				
Low/low-intermediate	78 (68%)	54 (89%)	72 (53%)	33 (61%)
High-intermediate/high	36 (32%)	7 (11%)	65 (47%)	24 (39%)
1st line treatment				
CHOP/CHOP-like			127 (93%)	54 (100%)
CCRT +/- chemotherapy	60 (53%)			
L-asparaginase containing chemotherapy	45 (39%)	60 (98%)		
Other chemotherapy	9 (8%)	1 (2%)	10 (7%)	
Response to 1st line treatment				
Complete response	75 (66%)	40 (66%)	84 (61%)	16 (30%)
Partial response	8 (7%)	8 (13%)	20 (15%)	19 (35%)
Progressive disease	30 (26%)	8 (13%)	27 (20%)	13 (24%)
Not evaluated	1 (1%)	5 (8%)	6 (4%)	6 (11%)
Subtype				
PTCL-NOS/AITL			55/44 (72%)	29/16 (83%)
ALCL-ALK-/-ALK+			25/5 (22%)	3/5 (15%)
Others			8 (6%)	1 (2%)

AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; CCRT, concurrent chemoradiotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; NA, not available; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

respectively. Most PTCL patients ($n = 127$) were treated with CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone) or CHOP-like regimens regardless of stage (Table 1). However, stage I/II ENKTL patients were mainly treated with concurrent chemoradiotherapy followed by systemic chemotherapy ($n = 60$). Remaining stage I/II and III/IV patients received chemotherapy alone ($n = 54$), and most systemic chemotherapies were based on non-anthracycline and L-asparaginase-containing regimens.¹³⁻¹⁵ Other chemotherapy regimens did not include L-asparaginase such as etoposide, ifosfamide, cisplatin and dexamethasone.¹⁶ The validation cohort consisted of patients who were diagnosed with PTCL ($n = 54$) and ENKTL ($n = 61$) between September 2013 and February 2017 at the Shanghai Rui Jin Hospital. The median age of PTCL and ENKTL patients was 57 years (range: 20-75 years) and 44 years (range: 14-72 years), respectively. Like the discovery cohort, most PTCL patients received CHOP or CHOP-like treatment (Table 1). The main treatment for ENKTL patients was based on non-anthracycline and PEGylated L-asparaginase-containing chemotherapy regimens.¹⁷ Vitamin D supplementation was not given to all patients during treatment in the discovery and validation cohort.

3.2 | Vitamin D deficiency

The median 25(OH)D serum level of the discovery cohort ($n = 251$) was 12.0 ng/mL, with a range of 1.3-60.0 ng/mL. One hundred and five patients (42%) of the discovery cohort had below 10 ng/mL of 25(OH)D at diagnosis, whereas 146 patients (58%) had 25(OH)D ≥ 10 ng/mL. The distribution of serum 25(OH)D was similar between PTCL (median: 11.3 ng/mL; range: 1.3-60.0 ng/mL) and ENKTL (median: 12.5 ng/mL; range: 1.6-57.4 ng/mL) patients (Figure 1C). As 25(OH)D was measured from serum samples archived immediately after diagnosis in the discovery cohort, the serum level of 25(OH)D could represent the amount of vitamin D in each patient. Median serum calcium level was also similar between PTCL (median: 8.9 mg/dL, range: 6.5-13.8 mg/dL) and ENKTL (median: 8.9 mg/dL, range: 6.6-10.2 mg/dL) patients. Serum calcium levels were positively correlated with serum levels of 25(OH)D in PTCL ($r = .436$, $P < .001$) and ENKTL ($r = .294$, $P = .002$) patients. The median 25(OH)D serum level of the validation cohort ($n = 115$) was 13.1 ng/mL (range: 3.0-35.0 ng/mL), and it was higher than that of the discovery cohort. Thus, 37 patients (32%) had vitamin D deficiency at diagnosis, whereas 78 patients (68%) had 25(OH)D ≥ 10 ng/mL. However, the distribution of serum 25(OH)D was similar between PTCL (median: 11.5 ng/mL; range: 3.0-30.4 ng/mL) and ENKTL (median: 14.1 ng/mL; range: 3.0-35.0 ng/mL) patients (Figure 1D). Vitamin D deficiency was significantly associated with advanced disease and unfavorable parameters such as serum LDH and poor performance status in the discovery cohort ($P < .05$; Table 2). Accordingly, the response to the first-line treatment was significantly associated with vitamin D deficiency in ENKTL ($P < .05$; Table 2). Although the association between response and vitamin D deficiency was also significant in PTCL, the statistical value was less than that of ENKTL.

3.3 | Association of vitamin D deficiency with survival

The estimated median follow-up time of the discovery and validation cohort was 35.8 months (95% confidence interval [CI]: 29.4-42.2 months) and 15.0 months (95% CI: 12.0-18.0 months), respectively. In the discovery cohort, 102 patients died at the time of analysis, and the cause of death was as follows: disease progression ($n = 72$), treatment-related mortality ($n = 18$) and other causes including accidents ($n = 10$). The PFS and OS were significantly worse in ENKTL patients with vitamin D deficiency, whereas vitamin D deficiency failed to show a significant association with PFS and OS in PTCL patients (Figures 2A,B and S1). The PFS of ENKTL was also different in patients treated with concurrent chemoradiotherapy followed by chemotherapy and patients who received just chemotherapy alone, although it was not statistically significant due to a relatively low number of patients (Figure S2). The survival analysis using the validation cohort showed the same association of vitamin D deficiency with survival outcomes in ENKTL patients but not in PTCL patients (Figures 2C,D and S1). Multivariate analysis with unfavorable parameters, including vitamin D deficiency of the discovery cohort, showed that the vitamin D deficiency was independently associated with poor PFS ($P < .05$; Table 3).

3.4 | Association of vitamin D deficiency with inflammatory cytokines

Sixteen cytokines (IL-6, IL-8, IL-10, IL-18, IL-23, TNF α , MCP-1, MIP-1 α , MIP-1 β , RANTES, Eotaxin, GRO α , IFN α , IFN γ , IP-10 and SDF1 α) were examined because the levels of the other cytokines were too low to be analyzed. The mean value of inflammatory cytokines was significantly higher in patients with vitamin D deficiency than in patients without it (Figure 3A,B). However, the association of inflammatory cytokines with survival was different between ENKTL and PTCL. Thus, when patients were dichotomized into high and low groups according to the median value, high inflammatory cytokines were significantly associated with survival outcome only in ENKTL, and not in PTCL (Figure S3).

4 | DISCUSSION

Vitamin D is one of the most commonly deficient vitamins worldwide and a low level of vitamin D is more common in Asian countries to Western countries.^{18,19} Thus, the National Health and Nutrition Examination Survey (NHNES) in the Korean population that was conducted in 2008 reported 56.9% of Korean people had serum 25(OH)D level below 20 ng/mL, and the multicenter study on 2173 healthy adults in five Chinese cities (Dalian, Beijing, Hangzhou, Guangzhou, and Urumqi) that was conducted in 2013 also showed 55.9% of people had serum 25(OH)D level below 20 ng/mL.^{20,21} These results were higher than 32% of the NHNES in the United States.²² Two Asian studies suggested behavioral changes, including increased

TABLE 2 Comparison of characteristics based on vitamin D deficiency in the discovery cohort

Characteristics	Extranodal NK/T-cell lymphoma			Peripheral T-cell lymphoma		
	Serum 25(OH)D (ng/mL)			Serum 25(OH)D (ng/mL)		
	<10 (n = 44)	≥10 (n = 70)	<i>P</i>	<10 (n = 61)	≥10 (n = 76)	<i>P</i>
Age (y)						
≤60	34	51	.660	41	42	.165
>60	10	19		20	34	
Sex						
M	28	52	.293	39	52	.591
F	16	18		22	24	
ECOG PS						
0/1	33	66	.004	45	70	.005
≥2	11	4		16	6	
Stage						
I/II	19	53	.001	8	25	.009
III/IV	25	17		53	51	
Serum LDH						
Normal	16	45	.004	18	41	.005
Increased	28	25		43	35	
BM						
Not involved	28	61	.005	40	57	.260
Involved	16	9		21	19	
Number of EN						
0/1	19	46	.021	32	51	.113
≥2	25	24		29	25	
B Symptoms						
Absence	21	51	.009	28	57	.001
Presence	23	19		33	19	
IPI						
L/LI	22	56	.002	30	42	.496
HI/H	22	14		31	34	
1st treatment						
L-asparaginase CTx	27	18	<.001			
CCRT + CTx	13	47				
CHOP/CHOP-like				56	72	.511
Others	4	5		5	4	
Response						
CR	18	57	<.001	33	51	.028
PR	4	4		9	11	
PD	22	8		11	14	
NE	0	1		6	0	
Subtype						
PTCL-NOS				19	36	.334
AITL				24	20	
ALCL-ALK -/+				14	16	
Others				4	4	

25(OH)D, 25-hydroxyvitamin D; AITL, angioimmunoblastic T-cell lymphoma; ALCL, anaplastic large cell lymphoma; BM, Bone marrow; BMI, body mass index; CCRT, concurrent chemoradiotherapy; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CR, complete response; CTx, chemotherapy; ECOG, Eastern Cooperative Oncology Group; H, high; HI, high-intermediate; IPI, International Prognostic Index; L, low; LDH, lactate dehydrogenase; LI, low-intermediate; NE, not evaluated; No. of EN, Number of extranodal involvement; PD, progressive disease; PR, partial response; PS, performance status; PTCL-NOS, peripheral T-cell lymphoma, not otherwise specified.

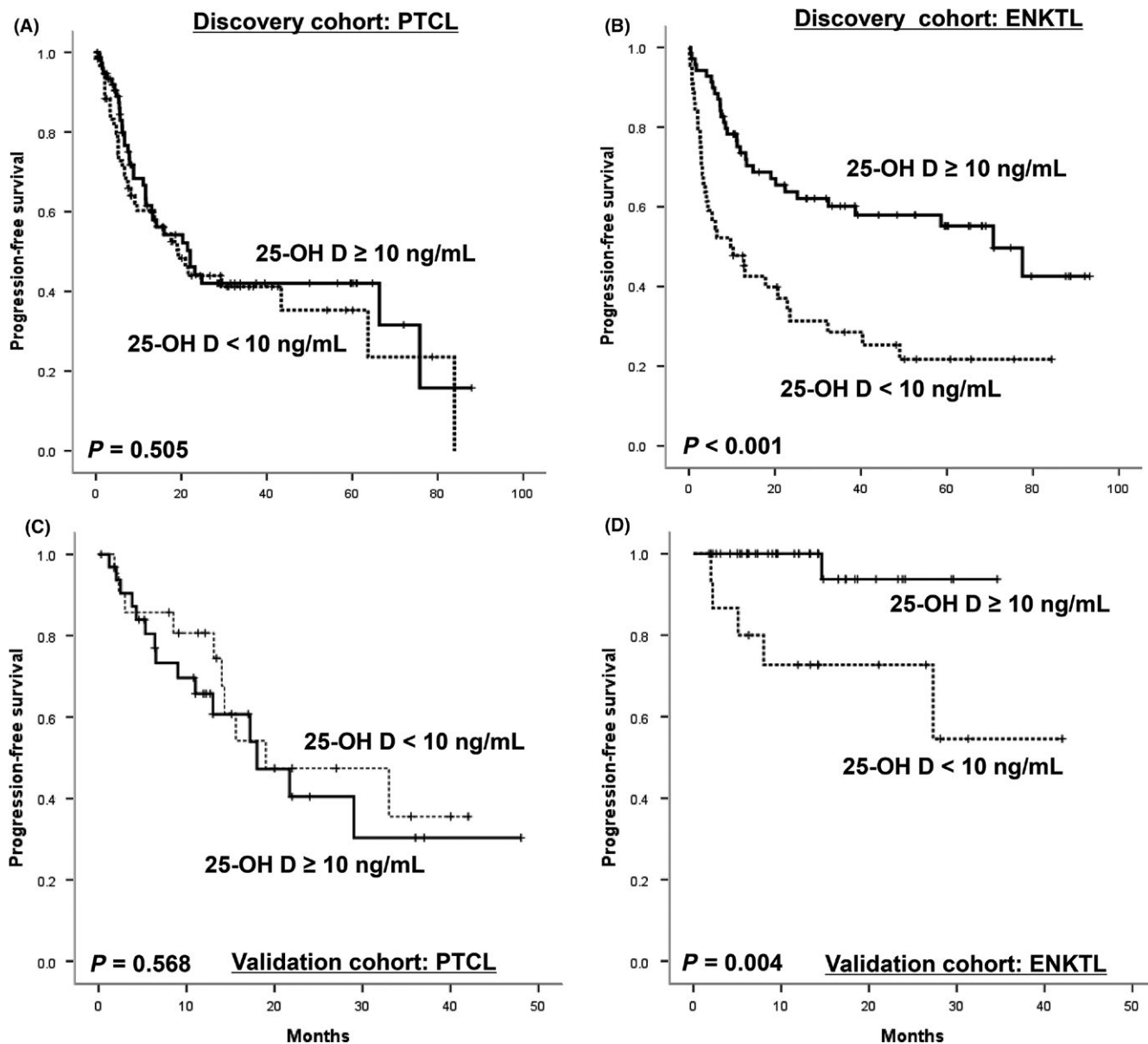


FIGURE 2 A, B, The comparison of progression-free survival according to serum 25(OH)D levels (<10 ng/mL vs ≥ 10 ng/mL) show a significant difference in patients with extranodal natural killer/T-cell lymphoma compared with peripheral T-cell lymphoma of the discovery cohort. C, D, The progression-free survival of the validation cohort shows the same pattern as the study cohort

indoor lifestyle and sunscreen use, as possible factors for their high prevalence. A low level of 25(OH)D was more frequent in cancer patients, and vitamin D deficiency was associated with poor outcome like its proven negative effect in general population.² Our study also showed a high frequency of vitamin D deficiency in Korean and Chinese patients with PTCL and ENKTL at diagnosis, and this might support 2 cohort studies reporting that vitamin D deficiency itself could increase the risk of lymphoma.^{23,24} In other words, patients with PTCL and ENKTL might have vitamin D deficiency at diagnosis because people who have vitamin D deficiency were at a higher risk of developing PTCL and ENKTL. In contrast, the negative effect of lymphoma on general health status leading to impaired outdoor activity and poor oral intake might increase the frequency of vitamin D deficiency in patients with PTCL and ENKTL. Indeed, unfavorable

parameters reflecting tumor burden, such as stage and serum LDH, as well as poor performance status, were significantly related to vitamin D deficiency in the study cohort (Table 2). However, it is also possible that patients with a larger tumor burden might have artificially low serum 25(OH)D levels because they may have increased conversion of 25(OH)D to 1,25(OH)₂D due to increased 1- α -hydroxylase activity from the tumor.

In this study, ENKTL patients with vitamin D deficiency had inferior PFS and OS to patients without it, whereas the PFS and OS were not significantly different in PTCL patients. The analysis of PFS and OS using the validation cohort also showed the same pattern of association even though the median follow-up of the validation cohort (15.0 months) was relatively shorter than that of the discovery cohort (35.8 months, Figure 1). This negative effect

Characteristics	Univariate	Multivariate		P
	P	Hazard ratio event	95% confidence interval	
Age > 60 y	.020	2.008	1.128 - 3.575	.018
ECOG PS \geq 2	<.001	1.631	.776 - 3.428	.197
Stage III/IV	<.001	1.557	.652 - 3.719	.319
Increased serum LDH	<.001	1.204	.626 - 2.313	.578
Extranodal involvement \geq 2	.011	.931	.469 - 1.848	.838
Bone marrow involvement	<.001	2.097	.959 - 4.587	.064
Serum 25(OH)D < 10 ng/mL	<.001	1.888	1.065 - 3.347	.030

TABLE 3 Univariate and multivariate analysis for progression-free survival in the discovery cohort

ECOG, Eastern Cooperative Oncology Group; LDH, lactate dehydrogenase; PS, performance status; Serum 25(OH)D, 25-hydroxyvitamin D.

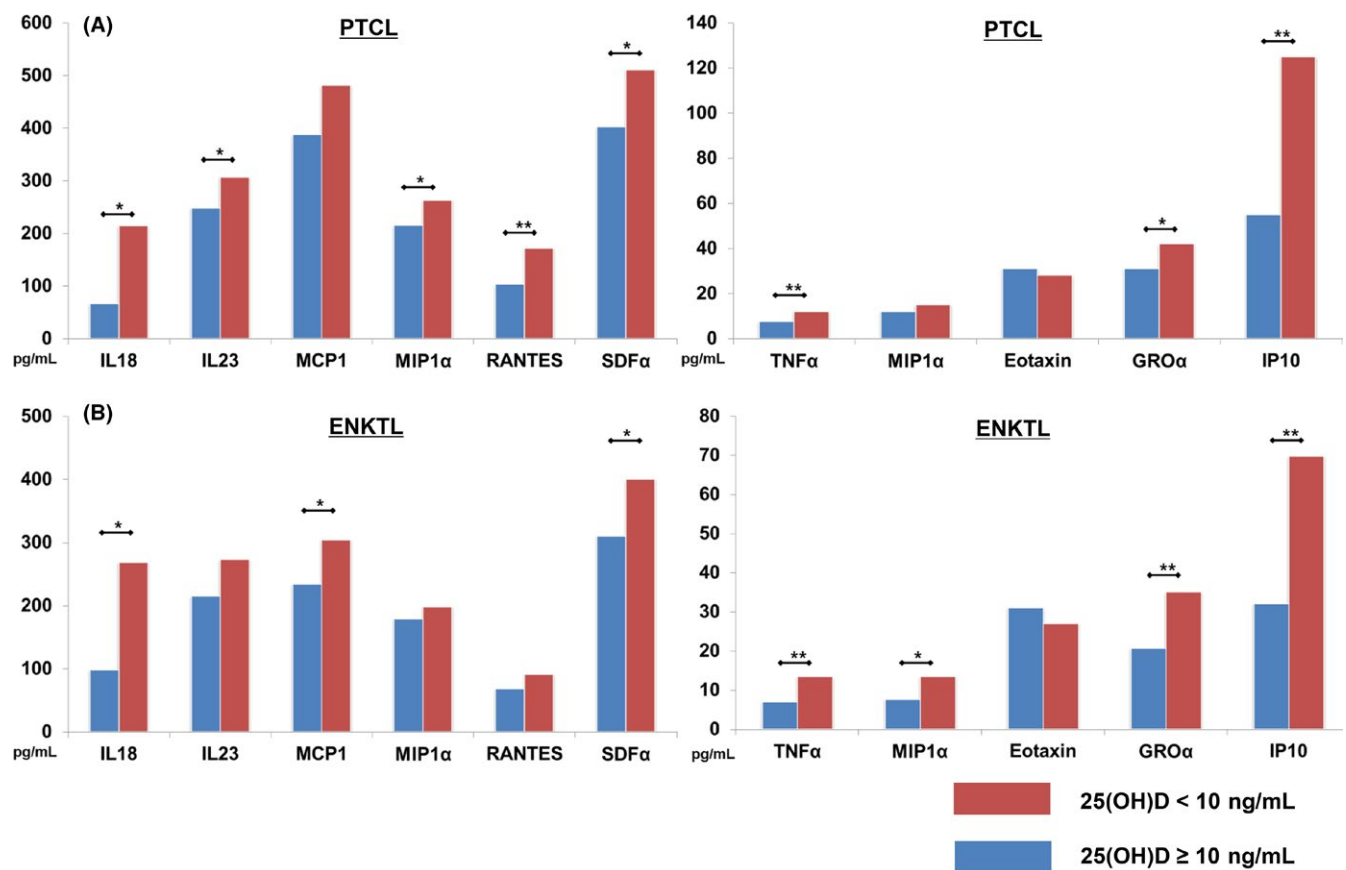


FIGURE 3 A, B, Comparison of mean values of cytokines in peripheral T-cell lymphoma and extranodal natural killer/T-cell lymphoma of the discovery cohort

of vitamin D deficiency on survival of ENKTL patients might be related to the peculiar characteristics of ENKTL. Tumor cells of ENKTL were invariably infected with Epstein-Barr virus and inflammatory milieu surrounding tumor cells might influence the tumor aggressiveness of ENKTL. Indeed, increased inflammatory cytokines in the tumor microenvironment were associated with poor treatment outcome of ENKTL.²⁵ Vitamin D deficiency was

reported to influence the tumor microenvironment, facilitating tumor outgrowth by impairing the immune system.²⁶ Thus, the association of survival with vitamin D deficiency in ENKTL patients could be explained by the contributory effect of vitamin D deficiency on the inflammatory microenvironment. In this study, pretreatment serum inflammatory cytokines were inversely associated with serum levels of 25(OH)D (Figure 3). Therefore, patients

with vitamin D deficiency had increased levels of inflammatory cytokines in accordance with previous reports.^{27,28} The PFS of patients with increased levels of those inflammatory cytokines was worse than that of patients without them in ENKTL. However, this association between inflammatory cytokines and PFS was not evident in PTCL (Figure S3).

Vitamin D is implicated in immune function and inflammation, and vitamin D was found to inhibit the gene expression of proinflammatory cytokines, including interleukins and TNF α .²⁹ Given the prognostic value of these inflammatory cytokines in ENKTL, patients with a vitamin D deficiency might have a poor prognosis due to subsequent elevated levels of cytokines. Although inflammatory cytokines might influence the aggressiveness of PTCL, their contribution to a worse outcome with PTCL might be less than that of ENKTL. Further study with a larger sample is necessary to confirm the results of this finding. The different impact of vitamin D deficiency on PFS in PTCL and ENKTL might be associated with a greater heterogeneity in PTCL than in ENKTL. In our study, PTCL includes several subtypes, such as PTCL-NOS and AITL, whereas ENKTL is a homogeneous disease entity. Indeed, the impact of vitamin D deficiency on PFS was different among PTCL subtypes. The PFS of PTCL-NOS was not associated with vitamin D deficiency, whereas the PFS of AITL showed a modest association, although it failed to show a statistical significance owing to relatively small numbers (data not shown). Considering that various single parameters related with immune function and inflammation, such as ferritin, have been reported to have prognostic value in PTCL, the role of vitamin D deficiency in the prognosis of PTCL needs to be further studied with a larger study population.³⁰

Given the high prevalence of vitamin D deficiency in Asian countries and the negative impact of vitamin D deficiency on the survival of ENKTL patients, vitamin D supplementation might have a positive effect on Asian patients' survival outcome because ENKTL is a more common subtype of NHL in East Asian countries than Western countries.³¹ However, it is still not clear whether vitamin D replacement has an impact on prognosis in lymphoma patients. An ongoing clinical trial with vitamin D replacement for patients with lymphoid malignancies may provide evidence for the role of vitamin D (#NCT01787409). Indeed, a recent interim report from the trial showed that vitamin D replacement therapy could achieve target levels of 25(OH)D of 30 ng/mL at 12 weeks without toxicity.³²

In conclusion, our study demonstrated that vitamin D deficiency might be associated with inferior survival outcome of patients with ENKTL but not with PTCL. Further investigations with larger study populations and longer median follow-up than our study are needed to confirm our findings and to determine the effects of vitamin D supplementation in patients with PTCL and ENKTL on survival.

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CONFLICT OF INTEREST

The authors have no conflict of interests to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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