Prognostic Value of 25-Hydroxy Vitamin D in Extranodal NK/T Cell Lymphoma

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Research article

Keywords: Extranodal NK/T cell lymphoma, 25-Hydroxy vitamin D, Prognosis

Posted Date: July 10th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-40790/v1

Version of Record: A version of this preprint was published at Annals of Hematology on November 2nd, 2020. See the published version at https://doi.org/10.1007/s00277-020-04320-y.

Abstract

Background

25-hydroxy vitamin D [25-(OH)D] is widely used to determine vitamin D status in clinic. The aim of our study was to evaluate the prognostic value of 25-(OH)D in extranodal NK/T cell lymphoma (ENKTL).

Materials and Methods

Ninety-three ENKTL patients with available serum 25-(OH)D values were enrolled in our study. Vitamin D deficiency is defined as a 25-(OH)D below 50 nmol/L. Univariate and multivariate regression analyses were performed to determine independent risk factors for progression-free survival (PFS) and overall survival (OS). Subgroup analyses were performed to determine the applicable subgroups. Receiver operator characteristic (ROC) curves were plotted to estimate the accuracy of PINK-E (prognostic index of natural killer lymphoma added with Epstein-Barr virus-DNA status) and 25-(OH)D deficiency in ENKTL risk-stratification.

Results

Our results suggested that vitamin D deficiency was an independent inferior prognostic factor for both PFS [hazard ratio (HR), 2.869; 95% confidence interval (CI), 1.540 to 5.346; $P = 0.003$] and OS (HR, 3.204; 95%CI, 1.559 to 6.583; $P = 0.006$) in ENKTL patients with age ≤ 60, ECOG PS ≤ 1, stage III—IV and PINK-E score ≥ 3. Additionally, we demonstrated that adding 25-(OH)D deficiency to PINK-E score system indeed has a superior prognostic significance than PINK-E alone for PFS [AUC: 0.796 (95% CI: 0.699 to 0.872) vs. 0.759 (95% CI: 0.659 to 0.841), $P = 0.020$] and OS [AUC: 0.755 (95% CI: 0.655 to 0.838) vs. 0.721 (95% CI: 0.618 to 0.809), $P = 0.040$].

Conclusion

In conclusion, our study proved that 25-(OH)D deficiency was associated with inferior survival outcomes of ENKTL patients.

Introduction

Extranodal natural killer/T-cell lymphoma (ENKTL) is a well-characterized subtype of mature T/NK-cell lymphoma. Asparaginase-based or pegaspargase-based chemotherapy regimens or chemoradiation have been evaluated to improve response rates comparing with anthracycline-based regimens [1]. The latest prognostic index of natural killer lymphoma (PINK) added with Epstein-Barr virus (EBV)-DNA status (PINK-E) is a prognostic model based on non-anthracycline-based chemotherapy and it consists of five risk factors (age, stage, non-nasal type, distant lymph-node involvement, and EBV-DNA status) [2].

As the active metabolite of vitamin D, 1, 25-dihydroxy vitamin D [1,25$(OH)_2$D] is produced from primary circulating form of vitamin D, 25-hydroxy vitamin D [25-(OH)D] and the latter one is used to determine vitamin D status [3]. One study has suggested that 25-(OH)D is associated with cancer mortality [4], and there may be a negative correlation with the risk of tumorigenesis [5]. In terms of lymphoma, although studies have suggested that ultraviolet radiation has a protective effect on the development of lymphoma [6, 7], but 25-(OH)D has no significant effect on the risk of lymphoma [6–10]. Nonetheless, several studies have shown that 25-(OH)D is significant in the prognostic evaluation of lymphoma [11–15]. Therefore, 25-(OH)D may be a good prognostic factor in lymphoma.

A previous report on the prognostic role of 25-(OH)D in T-cell lymphoma found that 25-(OH)D had prognostic significance in ENKTL [16]. However, this report did not further explore whether 25-(OH)D could improve the prognostic effect of the recognized prognostic model - PINK-E, which is based on non-anthracycline-based chemotherapy [2]. Our report further analyzed the specific prognostic significance of 25-(OH)D in ENKTL, identified applicable subgroups, and evaluated whether it could improve the prognostic effect of the existing prognostic scoring system.

Methods

Ethics

The study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University. The measurement for serum 25-(OH)D level and other clinical and laboratorial checkups were performed according to the principles of the Declaration of Helsinki. All subjects involved in this study provided Informed consent and permissions.

Patients

A total of 93 patients diagnosed with ENKTL between January 2014 and January 2019 in the First Affiliated Hospital of Nanjing Medical University were enrolled. Patients were all pathologically confirmed according to the WHO 2016 classification of the tumors and hematopoietic and lymphoid tissues. Patients with metabolic diseases such as rickets, postmenopausal osteoporosis, diabetes mellitus and thyroid dysfunction were excluded. Among the eligible 93 patients, 88 (94.6%) received treatment. Among them, 80 (90.9%) treated with asparaginase or pegaspargase - containing chemotherapy or chemoradiation, including 28 (35.0%) patients with PMED regimen (pegaspargase, methotrexate, etoposide and dexamethasone); 41 (51.3%) with P-GOD regimen (pegaspargase, gemcitabine, oxalipla and dexamethasone); 5 (6.2%) with LMED regimen (L-asparaginase, methotrexate, etoposide and dexamethasone) and 6 (7.5%) with P-GemOx regimen (pegaspargase, gemcitabine and oxalipla). Additionally, 3 (3.4%) with radiotherapy alone and 5 (5.7%) with other non-anthracycline-based chemotherapy regimens.

Data Collection

Basic characteristics such as age, gender, B-symptoms, Ann Arbor stage, Eastern Cooperative Oncology Group performance status (ECOG PS), EBV-DNA levels (EBV-DNA copy number in whole blood with the cut-off value of 5000 copies/ ml), primary lesion, PINK-E and treatment regimens were collected from medical records. Additionally, laboratorial data such as lactate dehydrogenase (LDH) and 25-(OH)D were available within 24 h of first admission from the hospital-based laboratory. The serum 25-(OH)D was measured via electrochemiluminescence immunoassay (Rochee 170, Roche Co., Ltd., Shanghai, China). Vitamin D deficiency is defined as a 25-(OH)D below 50 nmol/L (20 ng/ml) [17].

Statistical analysis

Progression-free survival (PFS) was defined as the period from the date of diagnosis to the date of first line treatment. Overall survival (OS) was measured from the date of diagnosis to the date of death or the date of final follow-up. Data were analyzed by IBM SPSS statistical software (version 21.0, IBM Inc, NY, USA). The figures of the Kaplan-Meier survival curves were modified using GraphPad Prism (version 6.0, GraphPad Software Inc, CA, USA). Clinicopathologic characteristics of enrolled patients were analyzed using descriptive analysis. Survival time was estimated using Kaplan-Meier survival curves and compared with log-rank tests. Univariate and multivariate regression analyses were performed to determine independent risk factors for PFS and OS. Receiver operator characteristic (ROC) curves were plotted and corresponding areas under the curve (AUC) were calculated to estimate the accuracy of PINK-E and 25-(OH)D deficiency in ENKTL risk-stratification. P value < 0.05 was considered statistically significant.

Results

Baseline clinical characteristics

Ninety-three newly diagnosed ENKTL patients were enrolled in the study, including 64 (68.8%) male and 29 (31.2%) female with a median age of 55 (range 21—92) years. The average 25-(OH)D level was 44.3 (range 7.0—136.8) nmol/L. The median follow-up time was 23 (range 3–62) months. Patients with advanced stage (III—IV) (P = 0.034) and inferior ECOG PS (> 1) (P = 0.033) were more likely developed into 25-(OH)D deficiency in Table 1.

Table 1
Baseline characteristics of 93 untreated ENKTL patients

Parameters	No. of cases (%)	25-(OH)D > 50 nmol/L (%) n = 38	25-(OH)D ≤ 50 nmol/L (%) n = 55	*P*-value[1]
Gender				
Male	64 (68.8%)	27 (29.0%)	37 (39.8%)	0.821
Female	29 (31.2%)	11 (11.8%)	18 (19.4%)	
Age				
≤ 60 years	70 (75.3%)	28 (30.1%)	42 (45.2%)	0.810
> 60 years	23 (24.7%)	10 (10.7%)	13 (14.0%)	
B Symptoms				
Absent	48 (51.6%)	22 (23.6%)	26 (28.0%)	0.399
Present	45 (48.4%)	16 (17.2%)	29 (31.2%)	
ECOG PS				
0–1	56 (60.2%)	28 (30.1%)	28 (30.1%)	**0.033**
2–4	37 (39.8%)	10 (10.8%)	27 (29.0%)	
LDH				
≤ULN	58 (62.4%)	26 (28.0%)	32 (34.4%)	0.386
>ULN	35(37.6%)	12 (12.9%)	23 (24.7%)	
EBV-DNA				
≤ 5000 copies/ml	43 (46.2%)	18 (19.4%)	25 (26.9%)	0.856
> 5000 copies/ml	50 (53.8%)	20 (21.5%)	30 (32.3%)	
Stage				
I–II	41 (44.1%)	22 (23.7%)	19 (20.4%)	**0.034**

The tests used in Table 1 were all Chi-Square test or Fisher's exact test.

Abbreviations: 25-(OH)D, 25-hydroxy vitamin D; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA; ULN, upper limit of normal.

[1] P values is according to t-test or Kruskal-Wallis test.

Parameters	No. of cases (%)	25-(OH)D > 50 nmol/L (%) n = 38	25-(OH)D ≤ 50 nmol/L (%) n = 55	*P*-value[1]
III–IV	52 (55.9%)	16 (17.2%)	36 (38.7%)	
Lesion				
Nasal	60 (64.5%)	26 (28.0%)	34 (36.4%)	0.660
Extranasal	33 (35.5%)	12 (12.9%)	21 (22.6%)	
PINK-E				
0–2	58 (62.4%)	27 (29.0%)	31 (33.3%)	0.193
≥ 3	35 (37.6%)	11 (11.8%)	23 (24.8%)	
The tests used in Table 1 were all Chi-Square test or Fisher's exact test.				
Abbreviations: 25-(OH)D, 25-hydroxy vitamin D; EBV, Epstein-Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA; ULN, upper limit of normal.				
[1] P values is according to t-test or Kruskal-Wallis test.				

Prognostic Value Of 25-(oh)d Deficiency In Enktl

We exhibited Kaplan–Meier survival curves according to stratification by 25-(OH)D and we found that 25-(OH)D < 50 nmol/L significantly predicted shorter (HR, 2.869; 95% CI, 1.540 to 5.346; $P = 0.003$) and shorter OS (HR, 3.204; 95%CI, 1.559 to 6.583; $P = 0.006$) (Fig. 1). The 1-year PFS were 76.3 ± 6.9% and 54.5 ± 6.7% in 25-(OH)D normal and 25-(OH)D deficiency groups respectively. The 3-year PFS were respectively 69.0 ± 8.0% and 35.1 ± 6.8% in 25-(OH)D normal and 25-(OH)D deficiency groups which significantly indicated that 25-(OH)D deficiency was related to shorter PFS. Similarly, the 1-year OS were 86.8 ± 5.5% *vs.* 80.0 ± 5.4% and the 3-year OS were 73.4 ± 9.9% *vs.* 46.3 ± 8.0% respectively in 25-(OH)D normal and 25-(OH)D deficiency groups.

The results of univariate and multivariate Cox proportional hazards regression analyses were summarized in Table 2 and Table 3. In the univariate analysis, B symptoms, inferior ECOG PS (> 1), elevated LDH, advanced stage (III–IV), extranasal primary lesion, PINK-E score ≥ 3, and 25-(OH)D deficiency were significantly associated with both inferior PFS and OS in the univariate analysis. EBV-DNA positive was only associated with inferior PFS and age > 60 was only associated with inferior OS (Table 2). PINK-E score and 25-(OH)D deficiency were transferred into multivariate Cox regression analysis which showed that PINK-E score ≥ 3 and 25-(OH)D deficiency were both independent risk factors for both PFS and OS (Table 3).

Table 2
Univariate Cox regression analyses of PFS and OS

Characteristics	Univariate analyses (PFS)		Univariate analyses (OS)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Male	0.927 (0.499–1.724)	0.811	0.814 (0.400–1.656)	0.569
Age > 60 years	1.589 (0.855–2.955)	0.143	3.131 (1.569–6.251)	**0.001**
B symptoms	2.425 (1.314–4.474)	**0.005**	2.485 (1.204–5.132)	**0.014**
ECOG PS 2–4	2.875 (1.585–5.213)	**0.001**	3.578 (1.756–7.291)	**< 0.001**
LDH > ULN	3.151 (1.737–5.715)	**< 0.001**	4.803 (2.316–9.963)	**< 0.001**
EBV-DNA-positive	2.095 (1.126–3.897)	**0.020**	1.751 (0.859–3.572)	0.123
Stage III–IV	3.701 (1.828–7.491)	**< 0.001**	2.537 (1.178–5.465)	**0.017**
Extranasal	2.123 (1.182–3.815)	**0.012**	2.067(1.043–4.097)	**0.038**
PINK-E score: ≥3	3.09 (1.660–5.452)	**< 0.001**	2.529 (1.272–5.028)	**0.008**
25-(OH)D ≤ 50 nmol/L	2.533 (1.282–5.007)	**0.007**	2.943 (1.277–6.787)	**0.011**
Bold indicates $P < 0.05$				
Abbreviations: 25-(OH)D, 25-hydroxy vitamin D; 95% CI, 95% confidence interval; EBV, Epstein–Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; LDH, lactate dehydrogenase; OS, overall survival; PFS, progression free survival; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA; ULN, upper limit of normal.				

Table 3
Multivariate Cox regression analyses of PFS and OS

Characteristics	Multivariate analyses (PFS)		Multivariate analyses (OS)	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
PINK-E score: ≥3	2.667 (1.461–4.868)	**0.001**	2.217 (1.108–4.437)	**0.024**
25-(OH)D ≤ 50 nmol/L	2.143 (1.075–4.274)	**0.030**	2.602 (1.119–6.048)	**0.026**
Bold indicates $P < 0.05$				
Abbreviations: 25-(OH)D, 25-hydroxy vitamin D; 95% CI, 95% confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression free survival; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA.				

Subgroup Analysis Of 25-(oh)d Deficiency In Enktl

In the subgroup analysis, we separated the patients into two groups according to age, ECOG PS, Ann Arbor stage and PINK-E score. We found that patients with 25-(OH)D deficiency showed inferior PFS and OS in subgroups of age ≤ 60 (PFS, $P = 0.002$; OS, $P = 0.003$), ECOG PS ≤ 1 (PFS, $P = 0.008$; OS, $P = 0.043$), EBV-DNA positive (PFS: $P = 0.018$; OS: $P = 0.044$), stage III–IV (PFS: $P = 0.029$; OS: $P = 0.040$) and PINK-E score ≤ 2 (PFS: $P = 0.008$; OS: $P = 0.033$) (Figs. 2 and 3).

Analysis of predictive accuracy through the evaluation of the AUCs

Since 25-(OH)D deficiency is an independent predictor for both PFS and OS in patients with ENKTL, we combined PINK-E and 25-(OH)D deficiency (PINK-ED) together to build a novel prognostic index which might provide more predictive accuracy than the PINK-E alone. ROC curves were generated to evaluate the discrimination ability of PINK-E alone and PINK-ED. 25-(OH)D deficiency was allocated as a risk factor with one point. The AUCs for PINK-E were 0.759 (95% CI: 0.659–0.841) for PFS and 0.721 (95% CI: 0.618–0.809) for OS. The AUCs for the PINK-ED were 0.796 (95% CI: 0.699–0.872) for PFS and 0.755 (95% CI: 0.655–0.838) for PFS. And the combination of PINK-E and 25-(OH)D deficiency was demonstrated to have a superior prognostic significance than PINK-E alone ($P = 0.020$ for PFS, $P = 0.040$ for OS) (Fig. 4).

Discussion

Vitamin D deficiency is an extremely universal phenomenon whether in low, lower-middle and high-income countries, which is a public health priority [18, 19]. The prevalence of serum 25(OH)D < 50 nmol/L is between 24.0–40.4% [20, 21, 22]. There is no single cause for this condition, low ultraviolet B (UVB) availability and/or exposure, low dietary vitamin D supply, and personal characteristics, such as skin pigmentation, age and working environment are all of responsibility [18]. Vitamin D deficiency is also common in lymphoma patients. Previous studies have shown that when the threshold was set at 50 nmol/L, the vitamin D deficiency rate ranged from 67%–88% [11, 23], which mainly among B-cell lymphoma. And the prognostic ability of 25-(OH)D in these B-cell tumors such as mantle cell lymphoma, chronic lymphocytic leukemia (CLL), follicular lymphoma (FL), and diffuse large B-cell lymphoma (DLBCL) has also been demonstrated [11–15, 24]. Until now, few studies have reported the relationship between vitamin D deficiency and the prognosis of T-cell lymphoma [14, 16], and only one study included ENKTL patients, in which 38.6% of the ENKTL patients had below 10 ng/mL (25 nmol/L) of 25-(OH)D at diagnosis [16]. The study demonstrated that 25-(OH)D did have prognostic significance in ENKTL, however, this report did not further explore whether 25-(OH)D could improve the prognostic effect of PINK-E and figure out the applicable subgroups, our report further analyzed the specific prognostic significance of 25-(OH)D in ENKTL.

25-(OH)D is converted to its active form in several body tissues, $1,25(OH)_2D$, which functions as the ligand for vitamin D receptor (VDR). VDR is an essential mediator for the cellular effects of vitamin D, it has been shown to be present in not only intestine, bone and kidney, but also skin, brain, reproductive organs and certain cells of the immune system. As a nuclear transcription factor, it regulates the

expression of multiple genes, including some responsible for cell cycle regulation, proliferation, differentiation, and apoptosis in cancer cell [3, 25, 26]. When it comes to lymphoma, different studies have proposed different mechanisms by which vitamin D affects the prognosis of lymphoma patients. For example, vitamin D deficiency leads to inferior outcomes by impairing rituximab-mediated cellular cytotoxicity in patients with DLBCL [27], 1α,25-dihydroxyvitamin enhances the sensitivity of mantle cell lymphoma cells to lenalidomide by pro-apoptotic protein BCL2-interacting killer in mantle cell lymphoma patients [28] and emerging evidence suggests that calcitriol might up-regulate the expression of programmed tissue death-ligand 1 [29]. Nevertheless, a recent report suggested that when treated with non-rituximab-containing regimens in FL, vitamin D deficiency is also a significant prognostic indicator [15] and vitamin D deficiency has also been shown to be broadly predictive of inferior outcomes in T-cell lymphoma, CLL, or even solid malignancies [3, 4, 13, 16, 25]. So vitamin D may affects the prognosis of lymphoma in multiple mechanisms and further investigation is needed to explore the specific mechanism of how vitamin D affects prognosis in different types of lymphoma.

Considering the realistic effect of vitamin D, several prospective studies have explored whether vitamin D supplementation could improve therapeutic effect and prognosis, and the results show that it does affect tumor cell growth in both Hodgkin's lymphoma (HL) and non-hodgkin’s lymphoma (NHL) [30, 31, 32]. No similar studies have been reported in T-cell lymphoma. The best schedule for vitamin D replacement in deficient patients remains unclear. One study suggested that vitamin D supplementation should be divided into loading phase (50,000 International Units weekly) and maintenance phase (50,000 International Units monthly), in which 97% of patients met the target value during loading phase [33].

Our results suggested that the vitamin D deficiency was an independent inferior prognostic factor for both PFS and OS in patients with ENKTL. In subgroup analyses, we concluded that the vitamin D deficiency was a significant risk predictor especially in patients with age $\leq$ 60, ECOG PS $\leq$ 1, stage III–IV and PINK-E score $\geq$ 3. Additionally, we demonstrated that adding 25-(OH)D deficiency to PINK-E score system indeed has a superior prognostic significance than PINK-E alone. As a retrospective cohort study, our research has limited number of subjects and many confounding variables that might affect the study indicators are beyond our complete control. In the future, larger scale and multicenter prospective studies are required to clarify the prognostic value of vitamin D deficiency in ENKTL.

In conclusion, our study indicated that 25-(OH)D deficiency was associated with inferior survival outcome of ENKTL patients. PINK-E plus 25-(OH)D deficiency could indeed improve the prognostic effect of the existing prognostic scoring system. Since supplementing vitamin D is a relatively easy task with minimal side effects, we hope that more research will emerge to support this approach in the future.

Abbreviations:

25-(OH)D, 25-hydroxy vitamin D; AUC, areas under the curve; CLL, chronic lymphocytic leukemia; DLBCL, diffuse large B-cell lymphoma; ECOG PS, eastern cooperative oncology group performance status; ENKTL, Extranodal natural killer/T-cell lymphoma; FL, follicular lymphoma; HL, Hodgkin's lymphoma;

LDH, lactate dehydrogenase; LMED, L-asparaginase, methotrexate, etoposide and dexamethasone; NHL, non-hodgkin's lymphoma; OS, overall survival; PFS, progression-free survival; P-GemOx, pegaspargase, gemcitabine and oxalipla; P-GOD, pegaspargase, gemcitabine, oxalipla and dexamethasone; PINK-E, prognostic index of natural killer cel lymphoma with Epstein-Barr virus DNA status; PMED, pegaspargase, methotrexate, etoposide and dexamethasone; ROC, receiver operator characteristic; UVB, ultraviolet B; VDR, vitamin D receptor.

Declarations

Ethics approval and consent to participate

The ethics approval of this study was obtained from the Independent Ethics Committee of Nanjing Medical University. The subjects are given written informed consent complying the requirements of the Declaration of Helsinki.

Consent for publication

Informed consent and permissions which containing publishing information on disease, clinical course, etc… were obtained from the subject involved in this study at the time of first admission.

Availability of data and material

The dataset used and analyzed during this study is available from the corresponding author upon reasonable request.

Competing interests

None.

Funding

This study was supported by National Natural Science Foundation of China (81770166, 81720108002), Jiangsu Province's Medical Elite Programme (ZDRCA2016022), Project of National Key Clinical Specialty, Jiangsu Provincial Special Program of Medical Science (BE2017751) and National Science and Technology Major Project (2018ZX09734007).

Authors' Contributions

JM and WX designed the experiment. MJ, LW, HYZ, JHL, YX, JZW and LF organized the clinical materials. JM, WX and JYL performed the data analysis and wrote the paper. All authors contributed to the

interpretation of the data, critically revised the article throughout development for intellectual content, approved the final version and are accountable for the accuracy and integrity of the work.

Acknowledgments

The authors thank the participating patients, their families, and staff at the study site.

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Figures

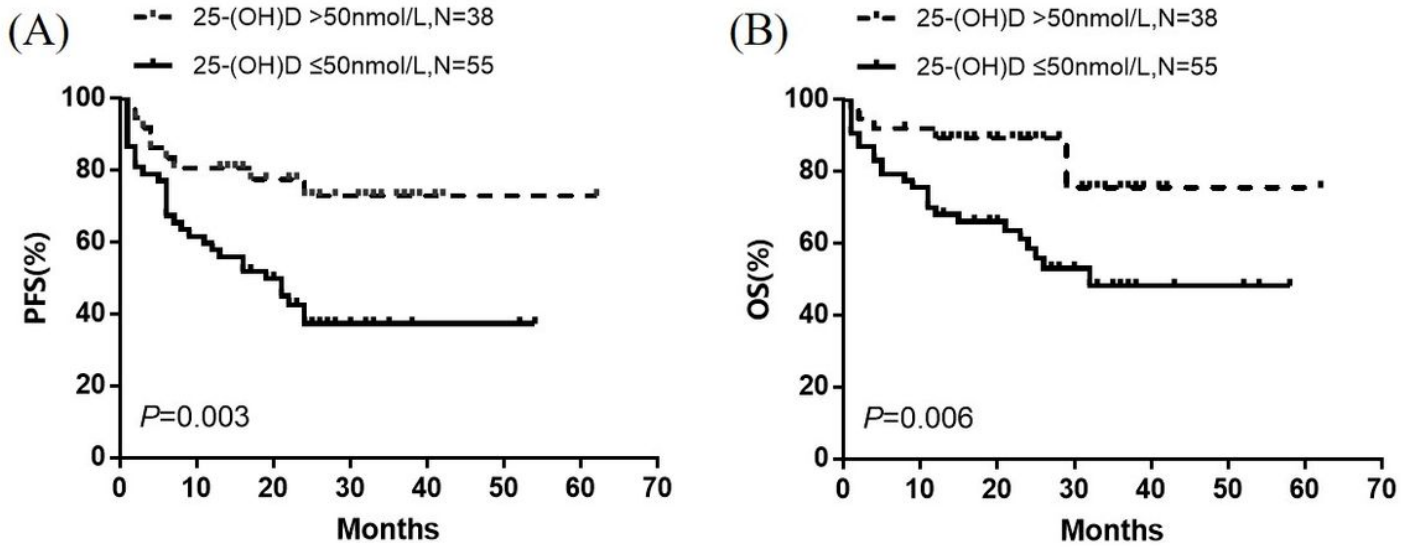

Figure 1

PFS(A) and OS (B) associated with 25-(OH)D deficiency. 25-(OH)D, 25-hydroxy vitamin D; PFS, progression-free survival; OS, overall survival

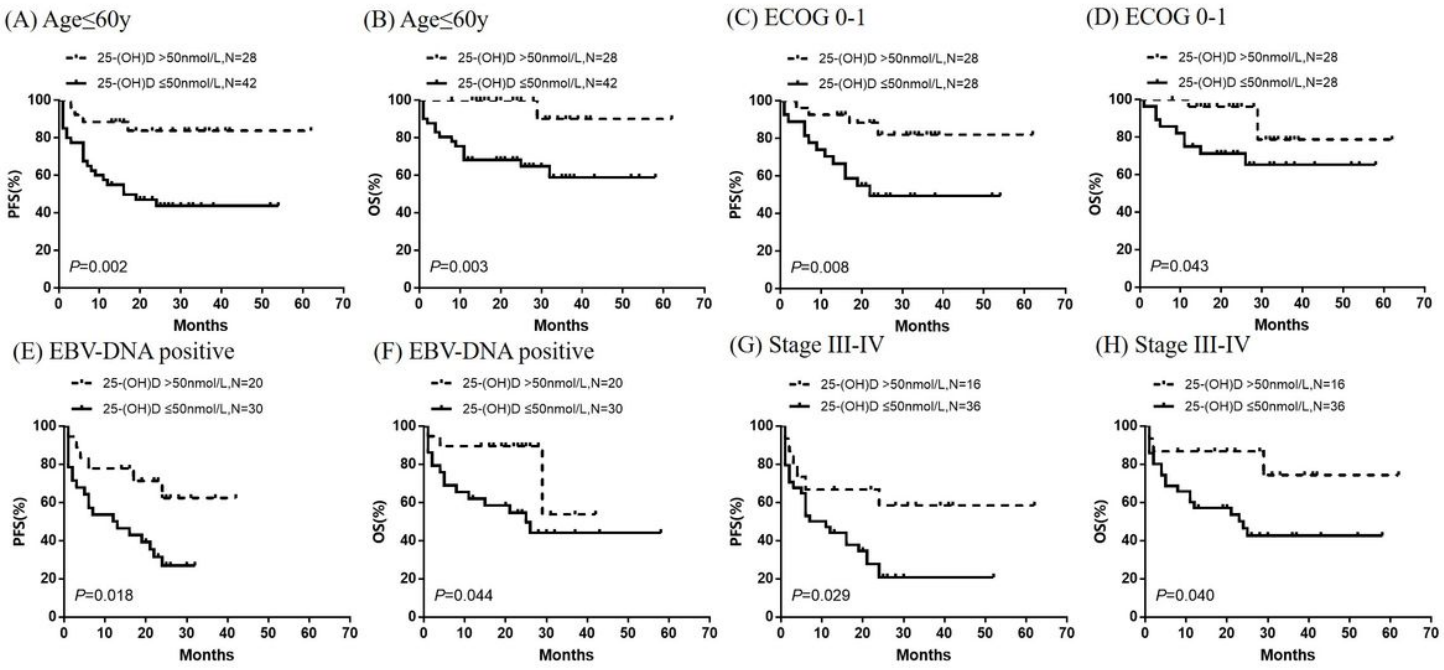

Figure 2

PFS and OS analyses of subgroups of different age, ECOG, EBV-DNA and stage. 25-(OH)D, 25-hydroxy vitamin D; EBV, Epstein–Barr virus; ECOG PS, Eastern Cooperative Oncology Group performance status; PFS, progression-free survival; OS, overall survival.

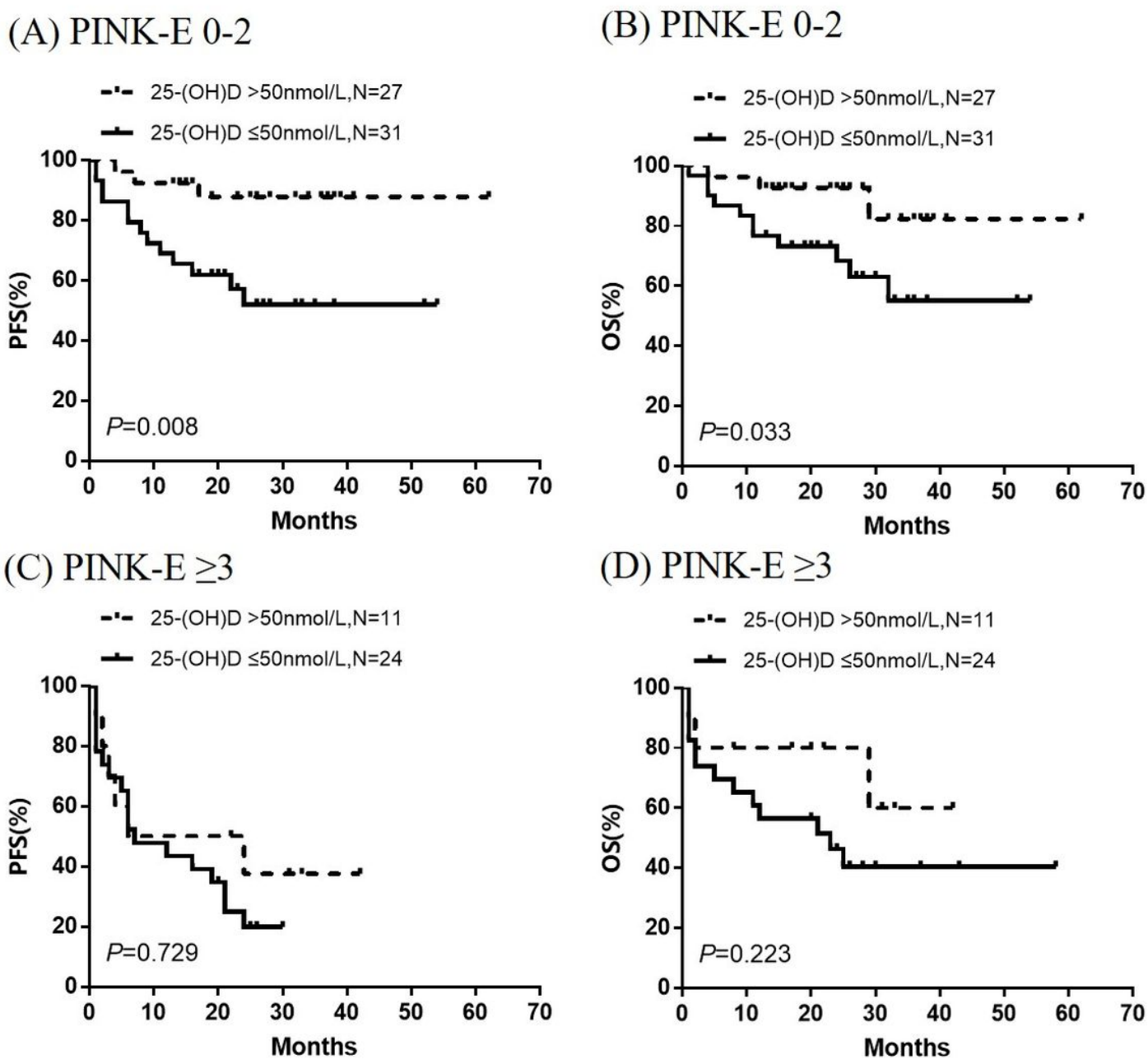

Figure 3

PFS and OS analyses of subgroups of PINK-E. 25-(OH)D, 25-hydroxy vitamin D; PFS, progression-free survival; OS, overall survival; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA.

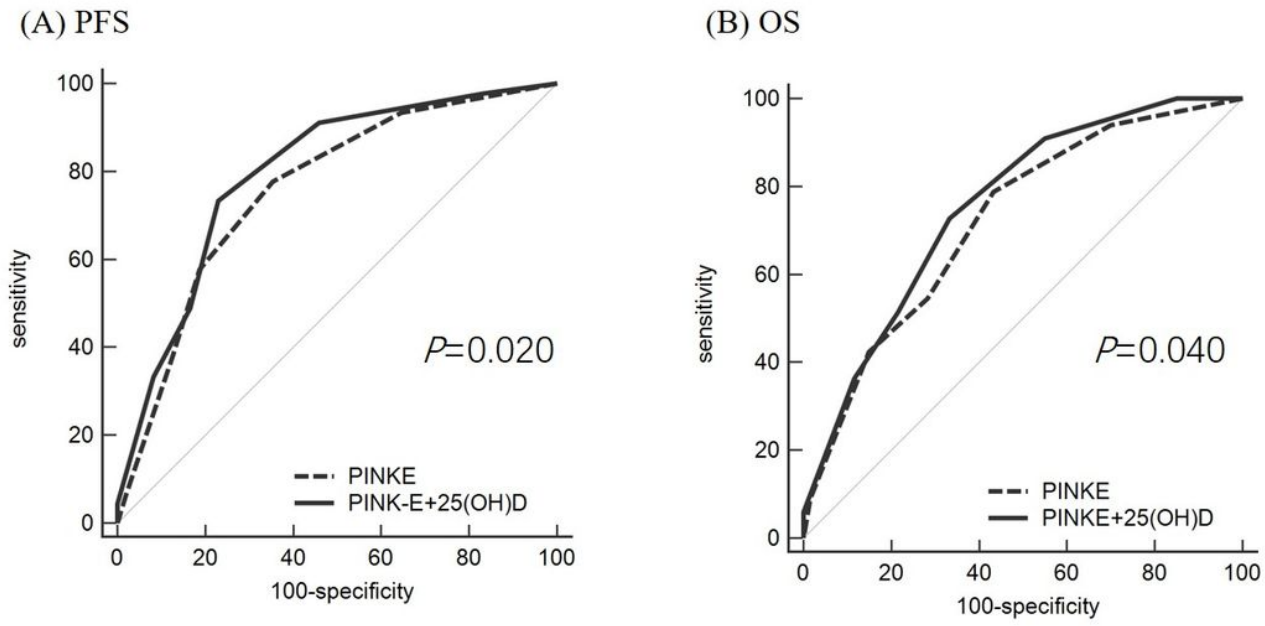

Figure 4

PINK-E combined with 25-(OH)D deficiency is a better prognostic model for PFS (A) and OS (B) in ENKTL. 25-(OH)D, 25-hydroxy vitamin D; OS, overall survival; PFS, progression free survival; PINK-E, prognostic index of natural killer lymphoma with Epstein-Barr virus DNA.