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*Original Article*

# Value of plasma vitamin D level and nomogram model for predicting the prognosis of patients with small cell lung cancer treated with platinum plus etoposide as first-line chemotherapy

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**Abstract:** Background: To assess the value of plasma vitamin D level and nomogram model in predicting the prognosis of patients with small cell lung cancer (SCLC) treated with platinum plus etoposide (PPE) as first-line chemotherapy. Methods: In this retrospective study, we included 178 patients with SCLC. The data of 25(OH)D level, basic clinical information, overall survival (OS) and progression-free survival (PFS) were collected. Moreover, a nomogram was constructed to predict the prognosis of the patients. Results: The median OS value for patients with 25(OH)D < 10 ng/mL was 12.5 months. The median PFS value was 6.6 months. Sex, smoking status, clinical stage, and plasma vitamin D were independent prognostic predictors. Besides, the decision curve analysis and receiver operating characteristic curve indicated that the nomogram prediction models showed positive clinical benefit. Conclusions: The plasma vitamin D level is of great significance in prognosis of patients with SCLC. The construction of nomograms is beneficial in predicting the prognosis of patients with SCLC treated with PPE.

**Keywords:** Vitamin D level, nomogram, small cell lung cancer, survival, prognostic factor

## Introduction

Small cell lung cancer (SCLC) accounts for approximately 13.6% of lung cancer, with a high proliferative index and an incidence associated with smoking [1, 2]. Median survival for SCLC patients is 16-24 months [3]. According to GLOBOCAN, there were about 18.1 million new cancers in 2018 worldwide, including about 2.09 million new cases of lung cancer, accounting for 11.6% [4-8].

Vitamin D, a steroid hormone, comprises vitamin $D_3$ and vitamin $D_2$. A series of preclinical studies have suggested that vitamin D exerts anti-proliferative, anti-metastatic, and anti-angiogenic effects in lung cancer [9, 10]. In addition, vitamin D exhibits numerous immunomodulatory properties [11] and induces the differentiation of lung cancer cells [12-14]. However, no study has focused primarily on the relationship between vitamin D level and the prognosis of SCLC treated with platinum plus etoposide (PPE).

Nomogram model is presented in an intuitive graphical form, which integrates different types of prognostic indicators to provide patients with personalized risk assessment based on evidence, and helps clinicians make treatment decisions and choose appropriate treatment methods [15]. However, there are no relevant prediction models to predict the prognosis of patients with SCLC treated with PPE.

Therefore, this study assessed value of plasma vitamin D level in predicting the prognosis of patients with SCLC treated with PPE and a nomogram model construction.

## Materials and methods

### *Study design and ethics*

The study is a retrospective analysis. Data of 178 SCLC patients treated in Lishui People's Hospital from January 2013 and December 2017 were analyzed in this study. Among them, 105 patients were treated with PPE. This study has been reviewed and approved by the medical ethics committee of Lishui People's Hospital.

### *Inclusion criteria*

(1) Patients who were 18 years or older; (2) Patients who were diagnosed with primary SCLC confirmed by pathology or cytology [16]; Patients with a clinical limited-stage or extensive-stage disease; (3) Patients who were scheduled for 4-6 cycles of PPE based doublet first-line chemotherapy according to the NCCN guidelines [17]; (4) The patients received combined radiotherapy and chemotherapy for small cell lung cancer.

### *Exclusion criteria*

(1) Patients who had a history of mental illness; (2) Patients with metastatic lung cancer; (3) Patients with multiple primary cancers; (4) Patients with incomplete clinical data.

### *Procedures*

In the first-line chemotherapy group, patients were given etoposide (Jiangsu Hengrui Pharmaceutical Co., Ltd) 80-100 mg/m$^2$ (administered on days 1-3 of each 21-day cycle). Meanwhile, patients also received four cycles of platinum (Jiangsu Hengrui Pharmaceutical Co., Ltd) 1500 mg. In the non-first-line chemotherapy group, patients received only etoposide (Jiangsu Hengrui Pharmaceutical Co., Ltd) 80-100 mg/m$^2$ (administered on days 1-3 of each 21-day cycle). Survival was assessed every 2 months following treatment discontinuation.

### *Data collection and measurement*

(1) Plasma vitamin D assay: The vitamin D level was detected by a liquid chromatography-tandem mass spectrometer (Applied Biosystems, Waltham, MA, USA) and an LC-20AD high-performance liquid chromatography system (Shimadzu Corporation, Kanagawa, Japan). (2) Different clinical characteristics (age, clinical stage, progression, PFS, smoking, first-line treatment, ECoG score) of the two groups were analyzed.

### *Statistical analysis*

The SPSS 22.0 statistical software package (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Chi-square test was applied to determine the distributions of categorical variables between the cases and the controls. The risk factors were introduced into R software (R 3.6.3) to construct a nomogram model to predict the prognosis of SCLC patients treated with PPE. Cox proportional risk model was used for single factor and stepwise regression analysis. According to the results of multivariate Cox proportional risk regression analysis, the nomogram model is established with R software.

## Results

### *Clinical characteristics*

The characteristics in terms of age, sex, ECOG status and body mass index were similar in the two groups ($P > 0.05$), but in terms of the smoking status ($P = 0.031$) and clinical stage of SCLC, the two groups showed significant differences ($P = 0.042$) (**Table 1**).

### *Clinicopathologic characteristics of SCLC patients with different plasma vitamin D level*

Using 10 ng/mL as the cut-off value for the baseline plasma 25(OH)D level, patients with 25(OH)D < 10 ng/mL (n = 92) and those with 25(OH)D ≥ 10 ng/mL (n = 86) had similar characteristics in terms of age, sex, smoking status, and body mass index ($P > 0.05$), but they had different ECOG score ($P = 0.020$) and clinical stage of SCLC ($P = 0.042$) (**Table 2**).

### *The relationship between vitamin D level and OS/PFS*

Survival analysis showed that the OS and PFS of patients with vitamin D level < 10 ng/mL were shorter than those of patients with vitamin D ≥ 10 ng/mL (**Figures 1** and **2**). Moreover, the vitamin D level was independently associated with poor OS and PFS (**Figures 1**

**Table 1.** Comparison of clinical data between the two groups

| | First-line chemotherapy group (n = 105) | Non-first-line chemotherapy group (n = 73) | $t/\chi^2$ | *P* |
|---|---|---|---|---|
| Age | 55.44±10.14 | 57.27±10.68 | 1.658 | 0.278 |
| Sex | | | 2.198 | 0.148 |
| Male | 66 (62.9%) | 46 (63%) | | |
| Female | 39 (37.1%) | 27 (37%) | | |
| ECOG status | | | 0.925 | 0.351 |
| 0 stage | 39 (37.6%) | 33 (39.7%) | | |
| I stage | 66 (62.4%) | 44 (60.3%) | | |
| Body mass index | | | 2.39 | 0.108 |
| Underweight | 2 (42.3%) | 2 (2.7%) | | |
| Normal | 66 (62.9%) | 40 (54.8%) | | |
| Overweight/obese | 37 (34.8%) | 31 (42.5%) | | |
| Smoking status | | | 9.52 | 0.031 |
| NO | 37 (35.4%) | 29 (39.7%) | | |
| Prior | 26 (25.3%) | 33 (39.7%) | | |
| Current | 42 (39.3%) | 12 (16.4%) | | |
| Clinical staging | | | 8.21 | 0.042 |
| Limited stage | 67 (64%) | 44 (60.3%) | | |
| Extensive stage | 38 (36%) | 33 (39.7%) | | |

Note: ECOG: Eastern Cooperative Oncology Group.

**Table 2.** Clinicopathologic characteristics of SCLC patients with different plasma vitamin D (VD) levels

| | VD < 10 ng/mL (n = 92) | VD ≥ 10 ng/mL (n = 86) | *P*-value | VD < 20 ng/mL (n = 161) | VD ≥ 20 ng/mL (n = 17) | *P*-value |
|---|---|---|---|---|---|---|
| Sex | | | 0.642 | | | 0.603 |
| Male | 56 | 56 | | 100 | 12 | |
| Female | 36 | 30 | | 61 | 5 | |
| Age | | | 0.212 | | | 0.180 |
| < 60 years | 64 | 52 | | 102 | 14 | |
| ≥ 60 years | 28 | 34 | | 59 | 3 | |
| ECOG status | | | 0.020 | | | 1.000 |
| 0 | 43 | 25 | | 62 | 6 | |
| 1 | 49 | 61 | | 99 | 11 | |
| Body mass index | | | 0.175 | | | 1.000 |
| Underweight | 4 | 0 | | 4 | 0 | |
| Normal | 58 | 54 | | 101 | 11 | |
| Overweight/obese | 30 | 32 | | 56 | 6 | |
| Cigarette smoking status | | | 0.292 | | | 1.000 |
| No | 33 | 30 | | 57 | 6 | |
| Prior | 19 | 26 | | 41 | 4 | |
| Current | 40 | 30 | | 63 | 7 | |
| Clinical staging | | | 0.042 | | | 0.301 |
| Limited | 52 | 62 | | 101 | 13 | |
| Extensive | 40 | 24 | | 60 | 4 | |

Note: SCLC: Small Cell Lung Cancer; VD: Vitamin D.

and **2**). Multivariate analysis showed that vitamin D level < 10 ng/mL was an independent risk factor for poor OS and PFS (**Tables 3** and **4**).

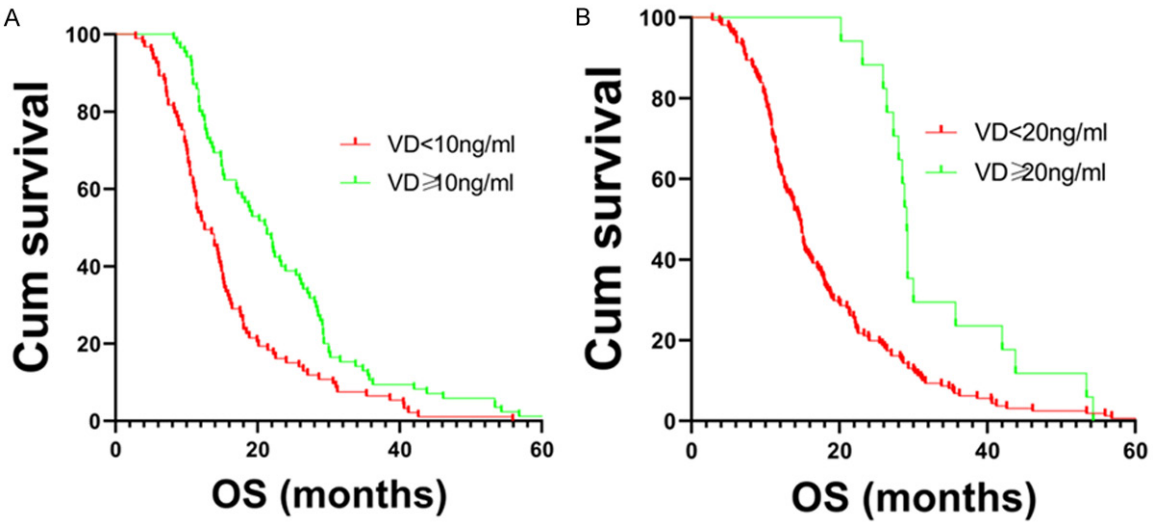


**Figure 1.** Association of plasma VD level with OS. A: Plasma VD level ≥ 10 ng/mL; B: Plasma VD level ≥ 20 ng/mL. VD: Vitamin D; OS: Overall Survival.

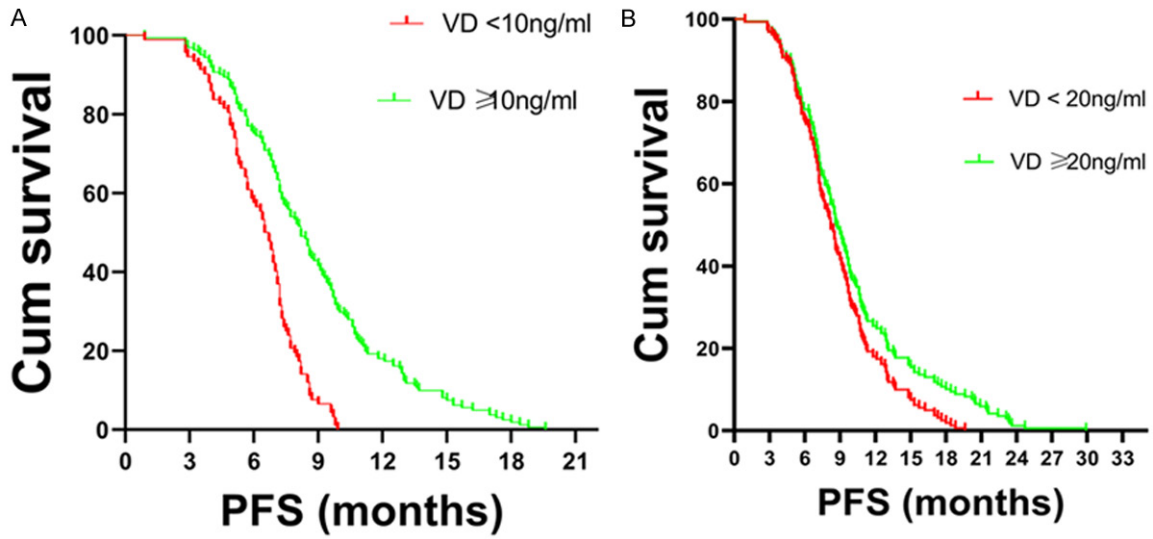


**Figure 2.** Association of plasma VD level with PFS. A: Plasma VD level ≥ 10 ng/mL; B: Plasma VD level ≥ 20 ng/mL. VD: Vitamin D; PFS: Progression-Free Survival.

**Table 3.** Multivariate analysis of plasma VD level with OS

| Plasma VD | HR (95% CI) | *P*-value | HR (95% CI)* | *P*-value |
|---|---|---|---|---|
| < 10 ng/mL | 1.000 | 0.0002 | 1.000 | 0.0001* |
| ≥ 10 ng/mL | 0.475 (0.327, 0.690) | | 0.472 (0.316, 0.706) | |
| < 20 ng/mL | 1.000 | 0.002 | 1.000 | 0.001* |
| ≥ 20 ng/mL | 0.344 (0.173, 0.684) | | 0.294 (0.144, 0.599) | |

Note: Compared with the ≥ 10 ng/mL or ≥ 20 ng/mL, significant difference as *P < 0.05. VD: Vitamin D; HR: Hazard Ratio.

*Univariate and multivariate regression analysis*

As shown in **Table 5**, age, sex, ECOG score, smoking status, clinical staging and plasma vitamin D were correlated with the prognosis of the patients treated with PPE (P < 0.05). Moreover, multivariate regression analysis demonstrated that sex, smoking status, clinical

**Table 4.** Multivariate analysis of plasma VD level with PFS

| Plasma VD | HR (95% CI) | *P*-value | HR (95% CI)* | *P*-value |
|---|---|---|---|---|
| < 10 ng/mL | 1.000 | 0.0003* | 1.000 | 0.0001* |
| ≥ 10 ng/mL | 0.050 (0.028, 0.088) | | 0.034 (0.018, 0.064) | |
| < 20 ng/mL | 1.000 | 0.0002* | 1.000 | 0.863 |
| ≥ 20 ng/mL | 0.017 (0.003, 0.095) | | 0.000 (0.000, 1.884) | |

Note: Compared with the ≥ 10 ng/mL or ≥ 20 ng/mL, significant difference as *P < 0.05. VD: Vitamin D; HR: Hazard Ratio.

**Table 5.** Univariate and multivariate risk analysis

| Indexes | Univariate | | Multivariate | |
|---|---|---|---|---|
| | OR [95% CI] | *P* value | OR [95% CI] | *P* value |
| Age | | | | |
| < 60 | 0.23 [0.131-0.361] | 0.061 | 2.66 [0.99-4.30] | 0.132 |
| ≥ 60 | 5.35 [0.039-0.052] | 0.032 | 4.58 [0.37-0.88] | 0.016 |
| Sex | | | | |
| Male | 2.28 [0.87-1.78] | 0.071 | 2.76 [0.19-2.98] | 0.059 |
| Female | 1.68 [0.5989-0.973] | 0.006 | 2.754 [1.251-2.749] | 0.011 |
| ECOG status | | | | |
| 0 stage | 9.18 [0.67-1.98] | 0.088 | 1.46 [0.99-3.24] | 0.934 |
| I stage | 0.43 [0.133-0.636] | 0.004 | 1.28 [0.77-1.38] | 0.261 |
| Body mass index | | | | |
| Underweight | 1.94 [0.89-1.414] | 0.88 | 1.66 [2.22-4.30] | 0.87 |
| Normal | 1.84 [0.69-1.014] | 0.98 | 5.58 [0.87-0.98] | 0.066 |
| Overweight/obese | 1.44 [0.69-1.114] | 0.54 | 3.98 [0.47-0.58] | 0.051 |
| Smoking status | | | | |
| No | 2.99 [0.57-0.88] | 0.076 | 0.66 [0.27-3.33] | 0.083 |
| Prior | 2.36 [0.414-0.892] | 0.018 | 1.66 [1.29-4.30] | 0.026 |
| Current | 5.95 [0.639-0.652] | 0.012 | 2.58 [0.57-0.88] | 0.006 |
| Clinical staging | | | | |
| Limited stage | 1.46 [0.79-5.30] | 0.08 | 3.86 [0.88-4.44] | 0.055 |
| Extensive stage | 1.44 [0.69-1.114] | 0.04 | 3.98 [0.47-0.58] | 0.021 |
| Plasma VD | | | | |
| < 10 ng/mL | 2.66 [1.09-5.31] | 0.07 | 1.36 [0.69-3.30] | 0.066 |
| ≥ 10 ng/mL | 1.95 [0.6390-0.6522] | 0.022 | 1.58 [0.77-0.38] | 0.006 |
| < 20 ng/ml | 3.24 [0.49-1.114] | 0.08 | 3.18 [0.67-0.98] | 0.003 |
| ≥ 20 ng/mL | 3.67 [0.69-1.114] | 0.152 | 1.18 [1.09-2.23] | 0.004 |

Note: ECOG: Eastern Cooperative Oncology Group; VD: Vitamin D.

staging and plasma vitamin D were independent prognostic predictors for patients with SCLC treated with PPE.

*Development of nomogram model*

The prognostic predictors were included in a prediction model established by R software (R 3.6.3). The prediction probability corresponding to the sum of the integral of each factor was the risk value for patients with SCLC treated with PPE (**Figure 3**). The risk score was computed using the following formula: Riskscore = 0.96 × (Plasma vitamin D) + (-1.33) × (age) + 0.55 × (gender) + (-1.16) × (Smoking status) + 1.25 × (Clinical staging).

*Validation of the nomogram model*

The unadjusted concordance index (C-index) for the nomogram was 0.792 [95% confidence interval (CI), 0.815-0.994]. The calibration pl-

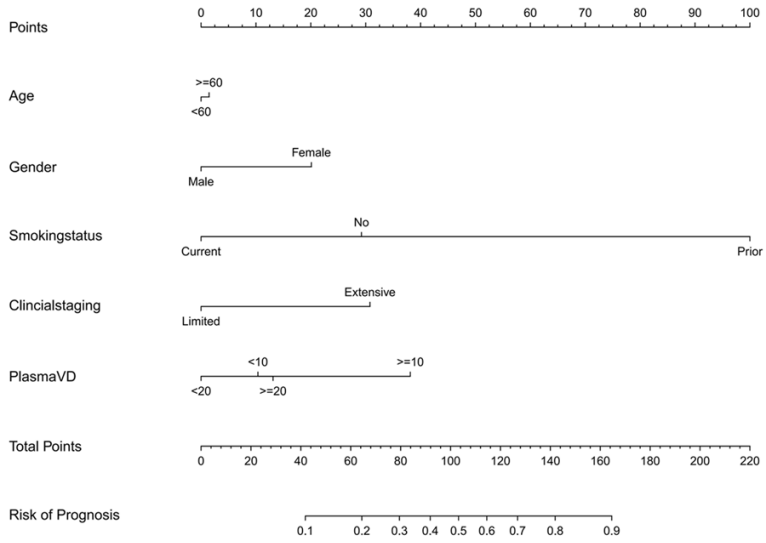


**Figure 3.** The nomogram for predicting the prognosis of patients with small cell lung cancer treated with platinum plus etoposide as first-line chemotherapy. VD: Vitamin D.

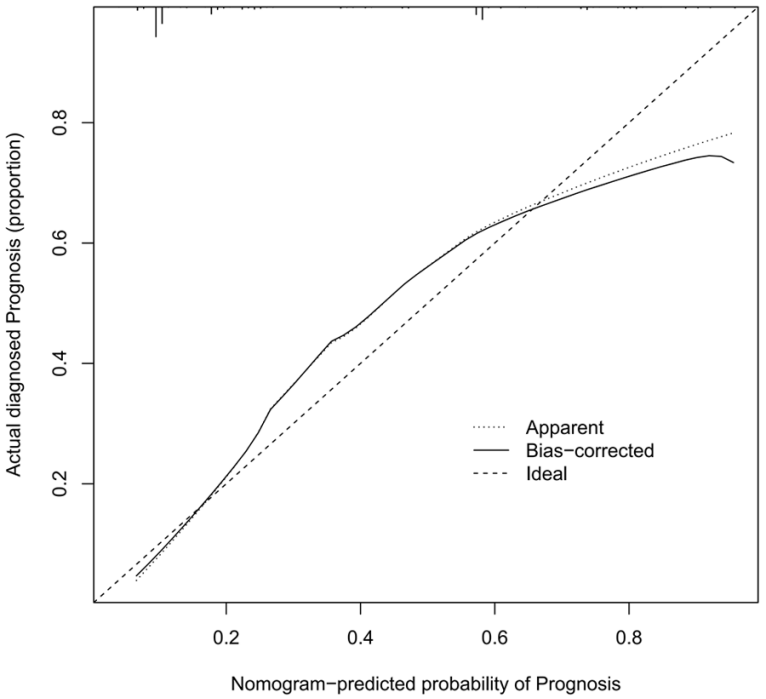


**Figure 4.** The calibration curves for predicting the prognosis of patients with small cell lung cancer treated with platinum plus etoposide as first-line chemotherapy.

ot of the nomogram is shown in **Figure 4**. The area under the curve for the nomogram was 0.8355882 (**Figure 5**). The result of Hosmer-Lemeshow tests are shown in **Table 6**. It is indicated that the nomogram model had a good discrimination and consistency in predicting the prognosis of patients with SCLC treated with PPE.

*The decision curve analysis (DCA)*

DCA demonstrated that if the risk threshold of a patient is between 20% and 70%, there will be more net benefit by using the nomogram to decide whether or not to conduct treatment. The decision curve demonstrated that the nomogram had a favorable clinical utility (**Figure 6**).

## Discussion

Small cell lumng cancer (SCLC) is a serious threat to patients' life [18]. At present, the cause of lung cancer is still considered related to smoking, environmental pollution, chronic lung disease, and genetic factors [19]. Chemotherapy is the first choice for patients with advanced SCLC. The current recommended first-line chemotherapy regimen is PPE [20]. However, due to individual differences, the prognosis after applying the first-line chemotherapy regimen is still unclear [21]. Therefore, it is important to find an index that reflects the prognosis.

This study analyzed the prognostic factors. Univariate and multivariate regression analysis showed that sex, smoking status, clinical staging and plasma vitamin D were independent prognostic predictors. However, there is a strong independence in the prediction of local indicators among various factors, so we established a clinic prediction model to quantify and evaluate their value.

Some experimental studies have demonstrated that vitamin D can suppress tumor progres-

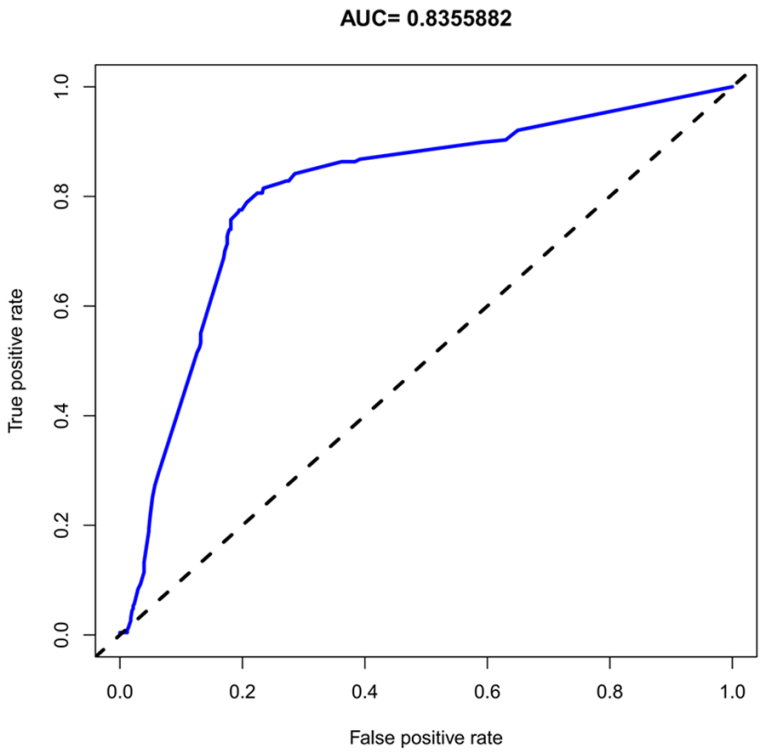


**Figure 5.** ROC curves for predicting the prognosis of patients with small cell lung cancer treated with platinum plus etoposide as first-line chemotherapy. AUC: Area Under the Curve. ROC: Receiver Operating Characteristic.

**Table 6**. Results of the McNemar's test

| Predicted Outcomes | Actual outcomes | | McNemar | *P* value |
|---|---|---|---|---|
| | Good prognosis | Poor prognosis | | |
| Good prognosis | 129 (72.5%) | 49 (27.5%) | $\chi^2$ = 0.003 | 0.883 |
| Poor prognosis | 38 (21.3%) | 20 (11.2%) | | |

sion and metastasis by its effect on cellular proliferation, differentiation, and angiogenesis [22], which are biological properties that might be relevant to mediate its impact on the prognosis of patients with cancer. The antitumor mechanism of vitamin D mainly includes promoting tumor cell cycle arrest, promoting tumor cell differentiation and inducing apoptosis. The details of these findings are as follows. (1) Vitamin D can lead to tumor cell cycle arrest. In vitro experiments showed that vitamin D could induce cell cycle arrest at the G0/G1 phase. Namely, the number of cells in S phase decreased, and the number of cells in G0-G1 phase accumulated, thereby inhibiting the growth of tumor cells [23]. (2) Vitamin D promotes tumor cell differentiation. Akiba et al. showed that vitamin D could inhibit the Hedgehog signaling pathway and induce cell differentiation in embryonic rhabdomyosarcoma and basal cell carcinoma [24]. (3) Vitamin D induces apoptosis in tumor cells. Some studies have used vitamin D and its analogues as treatments in animal tumor models. The number of tumor cells and tumor volumes were significantly reduced by vitamin D treatment, suggesting that vitamin D can be an antitumor agent, in part because of its mediating effect on apoptosis [25]. There are studies showing that vitamin D can also increase the production of TGF-β, change the sensitivity of cells to EGFR, and inhibit tumor cell growth [26, 27].

Our results also showed that age was an independent prognostic predictor for patients with SCLC treated with PPE. In clinical practice, it was found that the physical function of the elderly declines, and their organs age, accompanied by basic diseases such as hypertension, diabetes, and coronary heart disease. Their tolerance to treatment is poor, and the recovery time of side effects from chemotherapy such as bone marrow suppression was relatively long, resulting in poor survival of the elderly [28]. In this study, the effect of age on PFS and OS was analyzed with 65 years as the critical value. We suggest to count the influence of the patient's age on the survival period, and appropriately reduce the dose to ensure the patient's quality of life.

Sex also was an independent prognostic predictor for patients with SCLC treated with PPE. Female sex was shown to be a factor for good prognosis in SCLC [29]. The reason for the better prognosis of women may be related to the different neuroendocrine status between men and women, the lower smoking rate of female patients, and the higher physical strength score

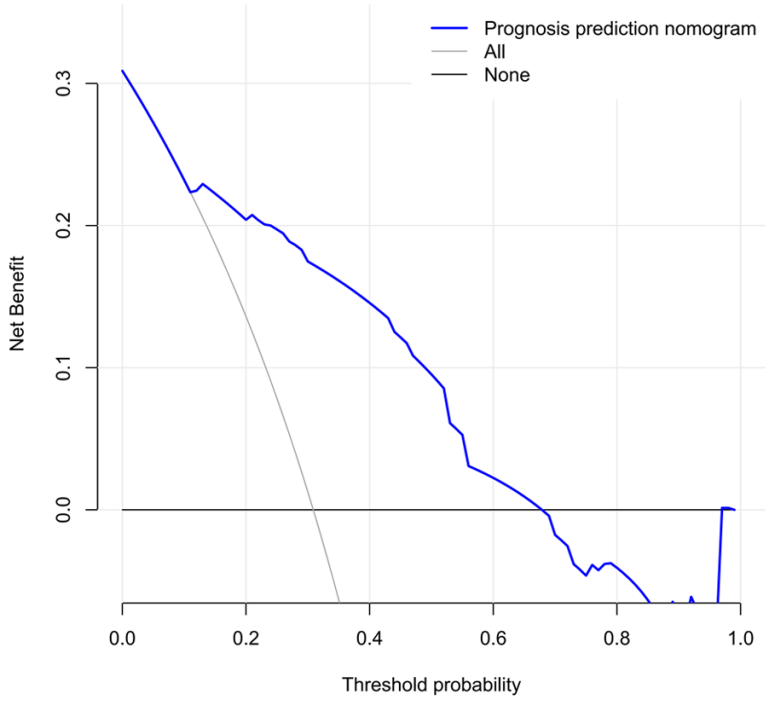


**Figure 6.** Decision curve analysis for the nomogram.

at the initial diagnosis, so that they have a better tolerance to clinical treatment. However, the significance of age in the prognosis of SCLC remains controversial. Geropoulos et al. [30] summarized six studies including 1708 SCLC patients and found that the one-year and three-year survival rates of female patients (42% and 11%) were better than those of male patients (37% and 7%), and their median OS were 10.2 and 9.6 months, respectively, with a significant difference (P = 0.006), but the overall OS advantage was less than one month, without clinical significance.

Smoking history is a high-risk factor for the development of SCLC [31, 32]. Patients' long-term smoking status may cause lung infection, emphysema, pulmonary fibrosis, coronary heart disease and other diseases, leading to the decline of lung function and physical strength, affecting the tolerance of clinical treatment, and prone to rapid progress and distant metastasis of the disease. In this study, the proportion of patients with smoking history was 74%. There was no statistical difference in OS between those with smoking history and those without smoking history. The median PFS was 10.510 months and 9.590 months. Multivariate analysis showed that smoking history was an independent risk factor (HR = 1.586, P = 0.006). Studies have shown a reduced mortality in patients who quit smoking during treatment [33, 34]. Therefore, in clinical work, patients should be actively advocated to quit smoking for disease control.

Compared to the traditional TNM staging system, the nomogram model can provide more accurate survival prediction for lung cancer patients. Chen et al. [35] reported the prognostic nomogram of non-SCLC could only be used for stage IV patients undergoing first-line chemotherapy. The model identified six factors. However, some known prognostic factors, such as age, sex, smoking status, pathologic classification and tumor stage, were not included in the model. The nomogram of this study also included nutritional status, and external validation was conducted through the validation cohort. In addition, the c-index of this study was 0.792, indicating that the prediction of this model is relatively accurate.

This study has some limitations. First, this study is a single center study with small sample size, so selection bias is inevitable. After stratifying the population by tumor types, the sample size in each subgroup was small, which may result in the results of stratification analysis not completely consistent with the model. Besides, stratification results in insufficient sample size of most subgroups makes it difficult to carry out hierarchical analysis on tumor stage and treatment mode. Therefore, a multi-center large-sample study is needed for further verification.

In conclusion, vitamin D is a prognostic factor of patients with SCLC treated with PPE. In addition, we demonstrated that a baseline plasma vitamin D level below either 10 ng/mL or 20 ng/mL was an independent unfavorable prognostic factor. Moreover, this study established a prognostic nomogram. This nomogram

can effectively predict the overall survival of patients with SCLC treated with PPE and provide a reference value.

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## Disclosure of conflict of interest

None.

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