Heliyon 9 (2023) e16483

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Research article

Prophylactic cranial irradiation-related lymphopenia affects survival in patients with limited-stage small cell lung cancer

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ARTICLE INFO

Keywords:
Limited-stage small-cell lung cancer (LS-SCLC)
Overall survival (OS)
Lymphopenia
Prophylactic cranial irradiation (PCI)

ABSTRACT

Background: The study aimed to identify the relations of the absolute lymphocyte count (ALC) nadir during prophylactic cranial irradiation (PCI) and patient outcomes in limited-stage small cell lung cancer (LS-SCLC).

Methods: We analyzed 268 L S-SCLC patients who underwent PCI from 2012 to 2019. ALC values were collected prior, during, and 3 months post PCI. Kaplan–Meier and Cox regression analyses were performed to assess the relation of ALC to patient prognosis. Two nomograms were developed on the basis of clinical variables for survival prediction.

Results: Compared with the ALC before PCI (1.13×10^9 cells/L), the ALC nadir during PCI was significantly reduced by 0.68×10^9 cells/L ($P < 0.001$) and raised to 1.02×10^9 cells/L 3 months post PCI. Patients with a low ALC nadir during PCI ($<0.68 \times 10^9$ cells/L) had inferior progression free survival (PFS) (median PFS: 17.2 *m* vs. 43.7 *m*, $P = 0.019$) and overall survival (OS) (median OS: 29.0 *m* vs 39.1 *m*, $P = 0.012$). Multivariate Cox analysis revealed that age, smoking history, clinical stage, and ALC nadir were independent OS ($P = 0.006$, $P = 0.005$, $P < 0.001$ and $P = 0.027$, respectively), as well as independent PFS predictors ($P = 0.032$, $P = 0.012$, $P = 0.012$ and $P = 0.018$, respectively). After internal cross-validation, the corrected concordance indices of the predictive nomograms for PFS and OS were 0.637 and 0.663, respectively.

Conclusion: LS-SCLC patients with a low ALC nadir during PCI likely have worse survival outcomes. Dynamic evaluation of the ALC during PCI is recommended for LS-SCLC patients.

1. Introduction

Small cell lung cancer (SCLC) is a highly malignant neuroendocrine tumour, and approximately one-third of patients are diagnosed when the disease is at a limited stage [1–3]. Although limited-stage SCLC (LS-SCLC) is sensitive to first line chemoradiotherapy (CRT), its prognosis is still unsatisfactory, with median survival times of 16–30 months and 5-year survival rates of approximately 15–20% [4, 5]. The brain is the most susceptible site for metastasis and relapse in patients with LS-SCLC, and more than half of the patients will develop brain metastasis (BM) within 2 years [6–8]. Therefore, prophylactic cranial irradiation (PCI) has been recommended for some

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https://doi.org/10.1016/j.heliyon.2023.e16483
Received 25 February 2022; Received in revised form 15 May 2023; Accepted 17 May 2023
Available online 21 May 2023

patients with LS-SCLC to improve distant metastasis-free and overall survival (OS) rates.

However, there is currently scant consensus on the utility of PCI in LS-SCLC. Historical studies have suggested that PCI effectively reduces BM and improves survival outcomes of LS-SCLC patients who respond completely to definitive CRT before brain magnetic resonance imaging (MRI) is routinely used for staging [9–13]. In contrast, researchers discovered that PCI did not reduce the risk of BM and did not show a benefit in OS outcomes in patients screened by MRI [14]. In addition, PCI may be related to decreased neurocognitive function, which must be weighed against the reduced incidence of BM [15]. The hippocampus is strongly associated with the consolidation of new memories and has a low incidence of metastasis. Current trials show that there are no differences in brain failure and OS between hippocampus avoidance-PCI and standard PCI [16]. However, it remains controversial whether hippocampus avoidance during PCI protects cognitive function [17]. Further studies with longer follow-up periods are needed to determine the optimal treatment pattern for PCI and who would benefit from it.

Evidence has demonstrated that regulation of the immune microenvironment plays a crucial role in tumour progression and

Table 1
Baseline characteristics of limited-stage small cell lung cancer (LS-SCLC) patients treated with prophylactic cranial irradiation (PCI).

Variables	Patients (N = 268)
	N (%)
Age	
≤60	147 (55)
>60	121 (45)
Gender	
female	79 (29)
male	189 (71)
Smoking history	
yes	125 (47)
no	141 (53)
ECOG PS	
0	126 (47)
≥1	142 (53)
BMI	
< 18.5	3 (1)
18.5–23.9	95 (36)
> 23.9	170 (63)
Alb	
< 35	4 (1)
≥35	264 (99)
Clinical Stage (AJCC 8th)	
stage I-II	83 (31)
stage IIIA	62 (23)
stage IIIB	95 (36)
stage IIIC	28 (10)
PCI technique	
3D-CRT	178 (66)
IMRT	90 (34)
Cycles of total chemotherapy	
≤4	26 (10)
>4	242 (90)
Time interval between last chemotherapy or radiotherapy and PCI (days)	
≤31	134 (50)
> 31	134 (50)
Thoracic radiotherapy	
yes	255 (95)
no	13 (5)
Volume of PTV (per cm3) (Thoracic radiotherapy)	
≤213.9	124 (49)
> 213.9	131 (51)
Brain metastases (Post PCI)	
yes	58 (22)
no	210 (78)
pre-PCI ALC (x 109 cells/L)	
≤1.13	138 (51)
>1.13	130 (49)
ALC nadir (x 109 cells/L)	
≤0.68	158 (59)
>0.68	110 (41)

Abbreviations: ALC: absolute lymphocyte count; Alb: albumin; BMI: body mass index; CRT: conformal radiation therapy; IMRT: intensity-modulated radiation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

metastasis [18,19]. Lymphocytes are an important part of the immune system and play a key role in antitumour immune responses [18]. Lymphopenia is frequent in various cancers, including SCLC, and it strongly affects patient prognosis and survival outcomes [14, 20–22]. In particular, it has been demonstrated that whole brain radiation therapy (WBRT) or stereotactic radiosurgery (SRS)-induced lymphopenia can lead to poor survival rates among brain tumour patients [23–25]. Theoretically, WBRT and SRS have higher biologically effective doses (BEDs) than PCI, but no study has elucidated whether PCI causes lymphopenia and its effect on patient prognosis.

To address these knowledge gaps, the study intended describe the changing absolute lymphocyte count (ALC) trends in patients undergoing PCI. Then, the correlation between the ALC nadir and survival outcome was evaluated. We also constructed nomogram models to predict the survival outcomes.

2. Methods and materials

2.1. Patients

We analyzed 268 patients with LS-SCLC who underwent PCI at Shandong Cancer Hospital between 2012 and 2019. The inclusion criteria were as follows: 1) pathologically or cytologically confirmed SCLC, 2) clinically diagnosed as limited disease, 3) confirmed to have no BM via MRI before PCI, and 4) at least one complete blood count (CBC) test during PCI. Patients were excluded if 1) CBC test data were not available within 1 week before PCI, 2) no detailed information on radiotherapy, 3) active infections or corticoids treatment prior to CBC, and 4) combined with other tumours.

2.2. Treatments and data collection

PCI techniques included either 3-dimensional conformal radiation therapy (3D-CRT) or intensity modulated radiation therapy (IMRT). The total radiation dose was generally 25 Gy, administered in once-daily 2.5-Gy fractions, 5 days per week. The standard first-line chemotherapy regimens were platinum and etoposide. Patient and therapeutic characteristics were collected from electronic medical records as detailed in Table 1.

ALC values were collected before PCI (pre ALC), at the nadir during PCI (ALC nadir) and 3 months after PCI (post ALC). Patient characteristics included age, sex, smoking history, Eastern Cooperative Oncology Group (ECOG) score and nutrition status. Tumour and treatment associated variables included TNM stage, RT technique (3D-CRT vs. IMRT), total cycles of chemotherapy whether to receive chest radiation therapy and radiation volume for the primary tumour.

2.3. Statistical analysis

Progression free survival (PFS) was defined as the period from the date of PCI to the date of disease progression or death. OS was defined as the period from the date of PCI to the date of death due to any cause. Survival rates were calculated using the Kaplan–Meier method and compared using the log-rank test. Logistic regression analyses were used to identify the risk factors associated with the ALC nadir. Cox regression analyses were used to identify potential prognostic factors associated with survival outcomes. Statistical analysis was performed using the SPSS software (for Windows, version 23.0). $P < 0.05$ was considered statistically significant. Based on the variables that remained statistically significant ($P < 0.05$) in the multivariate analysis, two nomogram models were established

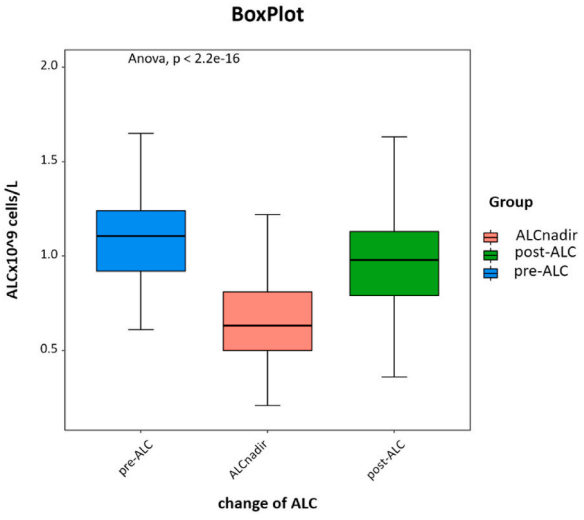

Fig. 1. The absolute lymphocyte count (ALC) trend before prophylactic cranial irradiation (pre-PCI) to 3 months after PCI (post-PCI).

to predict survival. The final OS and PFS prediction models were internally validated by bootstrapping using 100 resamples and cross-validation [26]. Harrell's concordance index (*C*-index) was measured to quantify the discrimination ability of the nomogram models, while the receiver operating characteristic curve (ROC) and area under the curve (AUC) were used to determine the diagnostic efficiency. A calibration curve was generated by plotting the predicted survival probabilities against the observed probabilities. Statistical analyses were performed using R software (http://cran.r-project.org/).

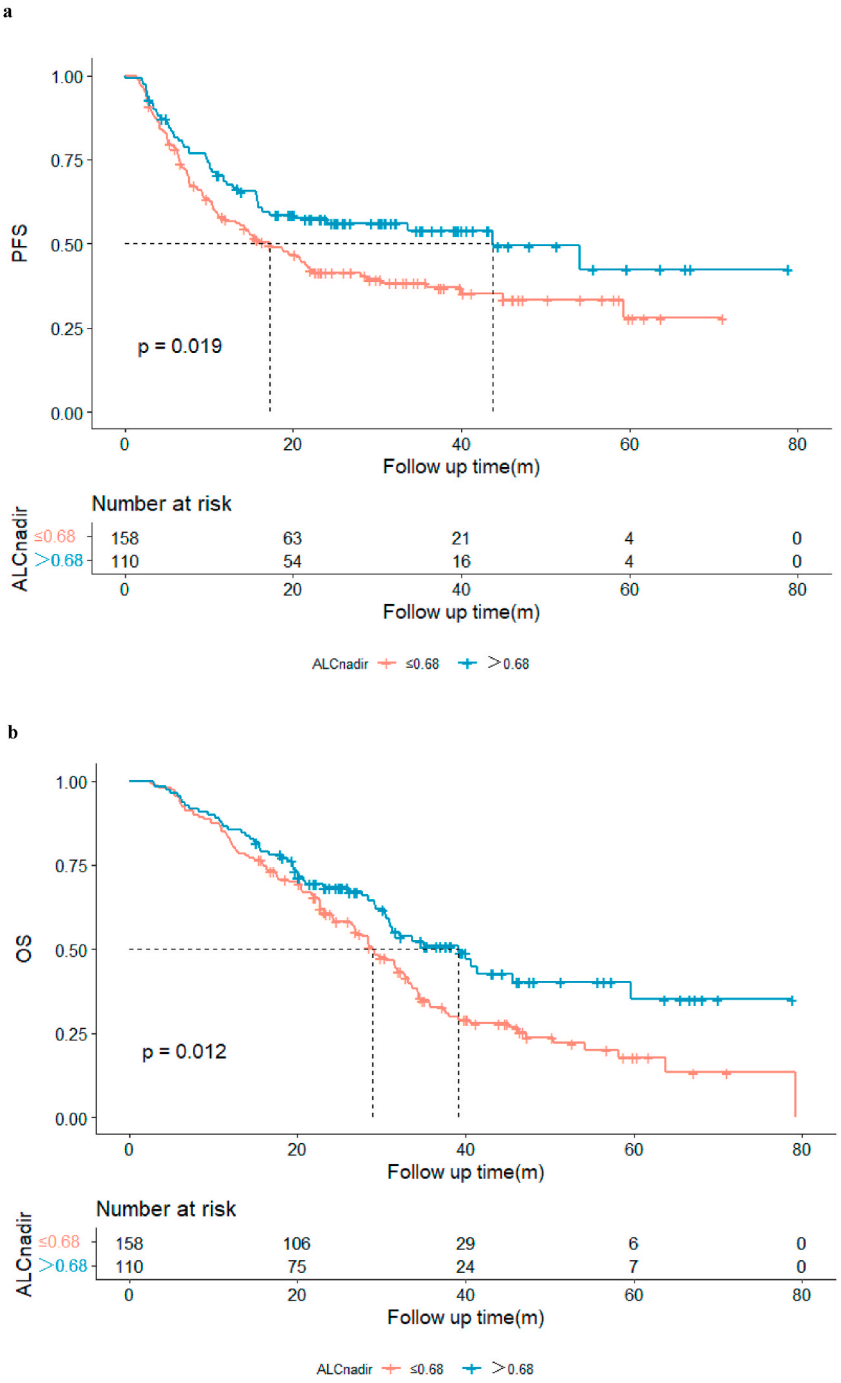

Fig. 2. Kaplan–Meier curves showing clinical outcomes of patients:(a) PFS, (b) OS, and between patients with a high ALC nadir (green line) and with a low ALC nadir (red line) during PCI. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 2
Effects of clinical variables on OS and PFS.

Variables	Overall survival				Progression free survival			
	UVA	P values	MVA	P values	UVA	P values	MVA	P values
Age								
≤60	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
> 60	1.532 (1.119–2.096)	0.008**	1.569 (1.141–2.158)	0.006**	1.473 (1.058–2.049)	0.022*	1.450 (1.033–2.036)	0.032*
Gender								
Female	1 (ref.)				1 (ref.)			
Male	0.960 (0.685–1.344)	0.810			0.973 (0.679–1.394)	0.882		
Smoking history								
no	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
yes	1.662 (1.216–2.271)	0.001**	1.567 (1.146–2.143)	0.005**	1.635 (1.177–2.271)	0.003**	1.529 (1.098–2.129)	0.012*
ECOG PS								
0	1 (ref.)				1 (ref.)			
≥1	1.113 (0.816–1.520)	0.499			1.263 (0.909–1.756)	0.165		
BMI								
< 18.5	1 (ref.)				1 (ref.)			
18.5–23.9	0.611 (0.149–2.513)	0.495			0.604 (0.147–2.483)	0.485		
> 23.9	0.580 (0.142–2.362)	0.447			0.549 (0.135–2.234)	0.403		
Alb								
< 35	1 (ref.)				1 (ref.)			
≥35	0.718 (0.228–2.263)	0.571			0.468 (0.173–1.267)	0.135		
Clinical Stage (AJCC 8th)								
Stage I-II	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
Stage III	2.330 (1.608–3.377)	<0.001***	2.141 (1.474–3.112)	<0.001***	1.655 (1.130–2.424)	0.010*	1.632 (1.112–2.394)	0.012*
PCI technique								
3D-CRT	1 (ref.)				1 (ref.)			
IMRT	1.044 (0.734–1.485)	0.810			0.999 (0.699–1.426)	0.994		
Cycles of total chemotherapy								
≤4	1 (ref.)				1 (ref.)		1 (ref.)	
> 4	0.717 (0.444–1.158)	0.174			0.574 (0.345–0.954)	0.032*	0.652 (0.387–1.100)	0.109
Time interval between last chemotherapy or radiotherapy and PCI (days)								
≤31	1 (ref.)				1 (ref.)			
> 31	1.009 (0.739–1.378)	0.955			1.055 (0.760–1.464)	0.750		
Thoracic radiotherapy								
yes	1 (ref.)				1 (ref.)			
no	1.688 (0.860–3.312)	0.128			1.757 (0.949–3.253)	0.083		
Volume of PTV (per cm3) (Thoracic radiotherapy)								
≤213.9	1 (ref.)		1 (ref.)		1 (ref.)			
> 213.9	1.550 (1.026–2.340)	0.037*	1.482 (0.985–2.231)	0.059	1.124 (0.750–1.685)	0.571		
pre-PCI ALC (x 10^9 cells/L)								
≤1.13	1 (ref.)				1 (ref.)			
> 1.13	1.056 (0.774–1.442)	0.729			0.824 (0.593–1.146)	0.25		
ALC nadir (x 10^9 cells/L)								
≤0.68	1 (ref.)		1 (ref.)		1 (ref.)		1 (ref.)	
> 0.68	0.657 (0.472–0.913)	0.012*	0.684 (0.488–0.958)	0.027*	0.665 (0.471–0.939)	0.020*	0.657 (0.463–0.932)	0.018*

Abbreviations: ALC: absolute lymphocyte count; Alb: albumin; BMI: body mass index; CRT: conformal radiation therapy; IMRT: intensity-modulated radiation therapy; ECOG PS: Eastern Cooperative Oncology Group Performance Status; UVA: Univariate analysis; MVA: Multivariate analysis. Statistically significant p values are highlighted in bold.
*P < 0.05. **P < 0.01.***P < 0.001.

3. Results

3.1. Patient characteristics

A total of 268 patients were enrolled in this retrospective study, and their clinical characteristics are summarized in Table 1. The mean age was 60 years, and 189 patients (71%) were male. Approximately 69% of the patients were initially diagnosed with stage III disease. Most patients had a good nutritional status. All patients received prophylactic cranial irradiation with either 3D-CRT (178 patients, 66%) or IMRT (90 patients, 34%) after completing EP/EC-based first-line chemotherapy. Almost 90% of the patients completed more than 4 cycles of EP/EC-based chemotherapy, and the median time interval between last chemotherapy or radiotherapy and PCI is 31 days. In addition, 255 (95%) patients received chest radiation therapy after 1–2 cycles of chemotherapy.

3.2. Lymphocyte counts

Changes in lymphocyte count are shown in Fig. 1. The mean ALC before PCI for the whole cohort was 1.13×10^9 cells/L. The ALC nadir was 0.68×10^9/L during PCI, which was significantly lower than the pre-ALC value ($P < 0.001$). ALC began to recover slowly after PCI and restored to 1.02×10^9 cells/L 3 months after PCI.

3.3. ALC nadir is associated with patient outcomes

The median follow-up time was 32.2 months. During follow-up, 161 patients (60%) died, and 195 patients (73%) experienced disease progression. In addition, 58 patients (22%) had BM, and the median metastasis time was 14 months. Patients were classified based on the mean ALC nadir into low ALC nadir and high ALC nadir groups. Univariable logistics regression analysis showed the baseline characteristics had no statistically significant impact on ALC nadir (Table S1). PFS (43.7 *m* vs 17.2 *m*, P = 0.019) (Fig. 2a) and OS (39.1 *m* vs 29.0 *m*, P = 0.012) (Fig. 2b) were significantly improved in the high ALC group.

Univariable Cox regression analysis revealed that age, smoking history, clinical stage, cycles of total chemotherapy, and ALC nadir were strong predictors of PFS. Based on the multivariable Cox analysis, age (Hazard Ratio [HR] = 1.450, 95% confidence interval [CI]: 1.033–2.036; P = 0.032), smoking history (HR = 1.529, 95% CI: 1.098–2.129; P = 0.012), clinical stage (HR = 1.632, 95% CI: 1.112–2.394; P = 0.012) and ALC nadir status (HR = 0.657, 95% CI: 0.463–0.932; P = 0.018) were independent prognostic predictors of the PFS rate (Table 2). Multivariate analyses showed that age, smoking history, clinical stage and ALC nadir were also independently associated with the OS rate. The HR for OS was 0.681 (95% CI:0.488–0.958, P = 0.027) when the ALC nadir was $\geq 0.68 \times 10^9$/L (Table 2).

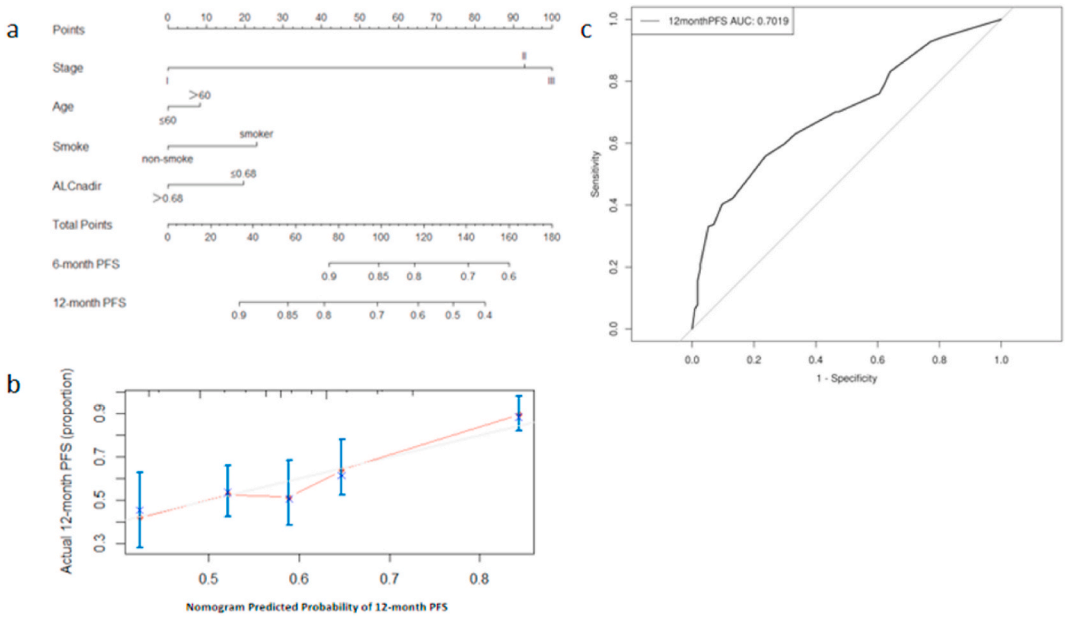

Fig. 3. The development of a nomogram model to predict the progression free survival (PFS) of limited-stage small cell lung cancer (LS-SCLC) patients with prophylactic cranial irradiation (PCI). (a) Nomogram for 6- and 12-month PFS prediction. (b) Calibration plots for predicting 12-month PFS outcomes. On the calibration plot, nomogram-predicted probability of 12-month PFS is plotted on the x-axis while the actual 12-month PFS is plotted on the y-axis. The reference line is 45° and indicates perfect calibration. (c) The area under the curve (AUC) of the prognostic nomogram models for 12-month PFS is 0.7019.

3.4. Construction of a nomogram model to predict PFS and OS

Two prognostic nomogram models were established the aforementioned four clinical variables. We aimed to determine the 6-month and 12-month PFS probabilities (Fig. 3a) and the 1-year and 3-year OS probabilities (Fig. 4a). The uncorrected concordance index (*C*-index) was 0.648 for PFS prediction and 0.674 for OS prediction, and the corrected *C*-indices generated by internal cross-validation were 0.637 and 0.663, respectively. The discrimination of the prognostic models were estimated using the *C*-index. As shown in Figs. 3c and 4c, the ROC curves showed that the AUCs for 12-month PFS and 3-year OS were 0.7019 and 0.6865, respectively. In addition, the prediction falls on the 45-degree diagonal line in a well-calibrated model (Figs. 3b and 4b). It also revealed that calibration of the nomogram for PFS and OS prediction was adequate.

4. Discussion

In our study, we found the following: 1) most LS-SCLC patients experienced significant lymphopenia during PCI, which will slowly recover after PCI; 2) lower ALC nadir during PCI was significantly related to poorer PFS and OS, and multivariable Cox analysis revealed ALC nadir was an independent prognostic factor; and 3) the two nomograms built to predict the 12-month PFS and 3-year OS rates demonstrated good performance.

PCI confers an OS benefit among patients with LS-SCLC and is considered the standard treatment [4]. There is convincing evidence from multiple studies that PCI improves OS outcomes when patients receive brain imaging with computed tomography (CT) or no brain imaging [9–11]. Indeed, MRI has superior sensitivity for detecting BM compared with CT [27]. It could be reasonably argued that a certain proportion of patients with asymptomatic BMs were included in these older trials, and recent studies of patients with LS-SCLC have fuelled a debate regarding the benefits of PCI in the MRI era. More studies suggested that patients staged with MRI received PCI after CRT do not have a decreased risk for developing BM compared with patients without PCI [14,28]. Thus the role of PCI in LS-SCLC remains controversial. Additionally, some retrospective studies did not observe any benefit from PCI in some specific subgroups of LS-SCLC patients, such as early -stage and complete thoracic response patients, and these patients did not obtain additional survival benefit from PCI [29]. Moreover, the benefit of PCI comes at the cost of side effects, particularly cognitive dysfunction. Many eligible patients refuse the treatment, especially elderly patients due to the concerns about neurotoxicity caused by PCI [30]. In our study, PCI-induced lymphopenia was associated with poorer survival outcomes, therefore, the application of PCI in patients with lymphopenia should be carefully evaluated. The accuracy of brain MRI continues to improve, and the survival benefit of PCI in LS-SCLC patients is still uncertain based on current evidence; thus, the characteristics of patients who can benefit most from PCI need further confirmation.

The immune system is closely involved in the development and progression of various solid cancers [31]. Peripheral blood lymphocytes (T cells, B cells and NK cells) are components of the immune system [32,33]. Meanwhile, peripheral blood lymphocytes are known to be highly radiosensitive, and DNA fragmentation can occur at radiation doses as low as 0.5 Gy [34–36]. In particular, B

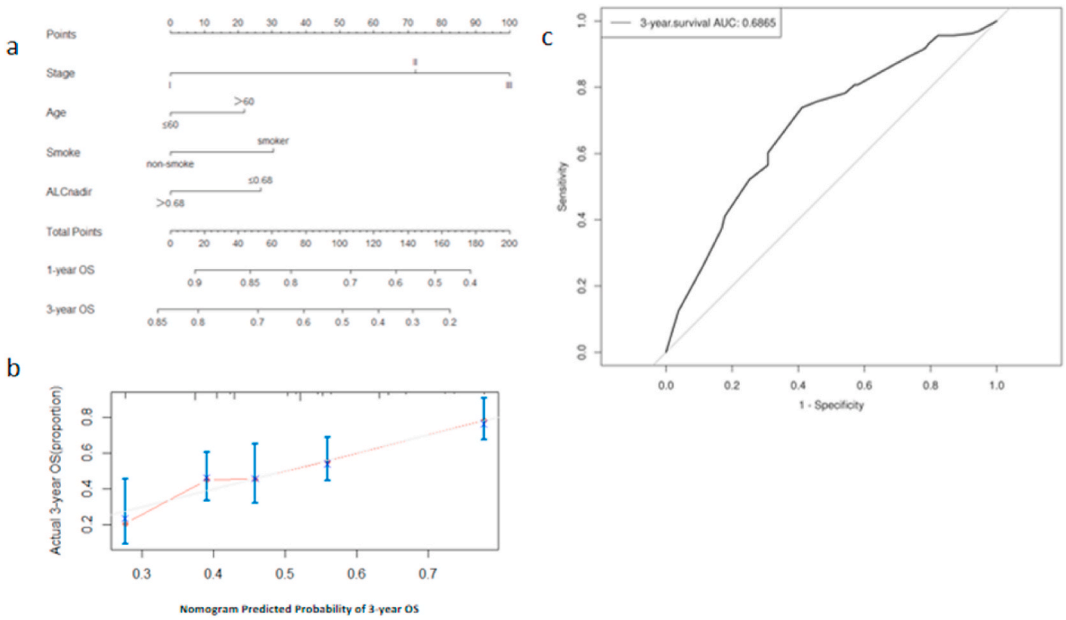

Fig. 4. The development of a nomogram model to predict the overall survival (OS) of LS-SCLC patients with PCI. (a) Nomogram for 1- and 3-year OS prediction. (b) Calibration plots for predicting 3-year OS outcomes. On the calibration plot, nomogram-predicted probability of 3-year OS is plotted on the x-axis while the actual 3-year OS is plotted on the y-axis. The reference line is 45° and indicates perfect calibration. (c) The area under the curve (AUC) of the prognostic nomogram models for 3-year OS is 0.6865.

lymphocytes are slightly more radiosensitive than T lymphocytes [37]. Radiation induced lymphopenia has been extensively studied as an important factor affecting survival. Our previous study confirmed that the effective dose to immune cells (EDIC), the estimated radiation dose to circulating lymphocytes, is an independent predictor of lymphocyte nadir and survival, suggesting the role of immune function in SCLC patients. EDIC is an objective parameter influenced by treatment planning and is estimated using the mean heart, lung and body doses for patients receiving thoracic radiation. It appears to have a better predictive accuracy than the ALC nadir [38]. However, the model itself has inherent limitations, as it is concerned with patients receiving thoracic radiotherapy and is limited by the simple assumptions that lymphocytes only reside in the large organs included in the model. Further efforts should be made to improve the EDIC model, which can be applied to more forms and sites of radiotherapy.

Standard radiation therapy for brain tumours delivers lymphotoxic radiation doses to the circulating blood, resulting in significant lymphopenia; consequently, radiation therapy is associated with adverse clinical outcomes [39]. In our study, ALC decreased from 1.13×10^9 cells/L to 0.68×10^9/L during PCI and then increased 3 months after PCI. Additionally, the ALC nadir was a significant factor associated with OS and PFS outcomes in patients with LS-SCLC who underwent PCI. Thus, biologically effective dose of PCI can lead to lymphopenia and influence the prognosis of patients with LS-SCLC. This finding verified that radiation of the brain, even when lymphatic tissue and bone marrow are not targeted, can cause lymphopenia [39]. This effect may be associated with the entire circulating blood pool receiving a potentially lymphotoxic radiation dose during PCI. To the best of our knowledge, this is the first study to show that PCI-related lymphopenia is correlated with inferior clinical outcomes.

While immunotherapy has been approved for ES-SCLC, the results of studies evaluating the role of immunotherapy in patients with LS-SCLC are awaited. The results of the STIMULI study failed to improve PFS outcomes with nivolumab-ipilimumab consolidation therapy after CRT in LS-SCLC, which could be attributed to short-term active treatment related toxicity and discontinuation of treatment [40]. At present, there are several ongoing clinical trials that employ immunotherapy in patients with LS-SCLC, and this approach may be promising as an initial therapy for LS-SCLC. Lymphocytes are the predominant cytotoxic population involved in the adaptive response to cancer-specific antigens [41]. Emerging evidence suggests that lymphocyte density correlates with non-small cell lung cancer (NSCLC) response to immunotherapy [42]. However, the correlation between PCI-related lymphopenia and immunotherapy efficacy is unknown, and a more comprehensive assessment is needed.

We further established visual nomogram models to quantitatively predict the PFS and OS outcomes of patients with LS-SCLC undergoing PCI. The *C*-indices of the models remained at 0.637 and 0.663 after cross-validation for PFS and OS outcomes, respectively, suggesting the powerful predictive capability of these models. The nomograms could provide patient-specific estimates of OS and PFS outcomes at the individual level based on patient characteristics. Further clinical studies are necessary to verify this hypothesis.

Our research had several limitations. First, selection bias and potential confounding factors were unavoidable owing to the retrospective and single-centre nature of the study. Second, there was heterogeneity in the treatment regimens received before PCI. However, our analysis showed that cycles of total chemotherapy were not related to the ALC nadir and survival. Third, the association between lymphocyte subtypes and patient outcomes could not be analyzed of the lack of determination by flow cytometry during treatment. Moreover, the molecular mechanisms underlying radiation-induced lymphopenia are not yet clear, and further studies are urgently needed.

5. Conclusion

Our study is the first to elaborate the relationship between PCI-related lymphopenia and survival outcomes. We conclude that patients with a lower ALC nadir during PCI are more likely to have inferior survival outcomes. Dynamic evaluation of the ALC during PCI is recommended for patients with LS-SCLC.

Author contribution statement

All authors listed have significantly contributed to the development and the writing of this manuscript.

Data availability

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Additional information

No additional information is available for this paper.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper

Acknowledgements

This work was supported by National Natural Science Foundation of China (Grant number 82172865), Start-up fund of Shandong Cancer Hospital (Grant number 2020-B14), Clinical Research Special Fund of Wu Jieping Medical Foundation (Grant number 320.6750.2021-02-51 and 320.6750.2021-17-13).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e16483.

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