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Research Article

Keywords: Small-cell lung cancer, Brain metastasis, Nomogram, Risk prediction, Prophylactic cranial irradiation, Neutrophil-to-lymphocyte ratio

Posted Date: November 20th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-11207250/v1

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Additional Declarations: No competing interests reported.

Development and Validation of a Comprehensive Nomogram for Predicting Brain Metastasis Risk in Extensive-Stage Small-Cell Lung Cancer: A Multicentre Retrospective Cohort Study

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Abstract

Background. Brain metastasis (BM) is a frequent and devastating complication of extensive-stage small-cell lung cancer (ES-SCLC) that impairs neurological function and survival. Although prophylactic cranial irradiation (PCI) reduces the incidence of BM, its routine use remains controversial because of neurocognitive toxicity and the absence of tools that estimate the risk of BM in an individual patient. An accurate, individualised prediction model is therefore needed to support PCI decision-making.

Methods. In this multicentre retrospective cohort study, 1408 patients with histologically confirmed ES-SCLC treated at three cancer centres between 2018 and 2023 were assessed, and 1212 patients without BM on baseline brain MRI were included in the analysis. Patients were randomly divided into a training cohort (n = 849) and a validation cohort (n = 363) at a ratio of 7:3. Candidate predictors comprised clinical characteristics, metastatic patterns and inflammatory biomarkers. Least absolute shrinkage and selection operator (LASSO) regression followed by stepwise multivariable Cox proportional hazards regression was used to identify independent predictors of BM, and a nomogram was constructed to estimate the probability of BM at 6 months, 1 year and 2 years. Performance was assessed by time-dependent area under the receiver operating characteristic curve

(AUC), calibration curves with bootstrap resampling, decision curve analysis (DCA) and risk stratification.

Results. During follow-up, 371 patients (30.6%) developed BM. Eight independent predictors of BM were identified: ECOG performance status ≥3, AJCC stage IV, adrenal metastasis, hepatic metastasis, synchronous chemoradiotherapy, Ki-67 index >20%, an elevated neutrophil-to-lymphocyte ratio (NLR) and receipt of PCI, which was protective. The nomogram showed good discrimination, with AUCs of 0.722, 0.744 and 0.772 at 6 months, 1 year and 2 years in the training cohort and 0.723, 0.744 and 0.784 in the validation cohort. Calibration curves showed close agreement between predicted and observed probabilities, and DCA indicated a higher net benefit than the treat-all and treat-none strategies across threshold probabilities of 11%–83% in the training cohort and 13%–73% in the validation cohort.

Conclusions. This nomogram integrates clinical, metastatic and inflammatory variables to estimate the risk of BM in patients with ES-SCLC, and it enabled effective risk stratification in both cohorts. Internal validation was used, so external validation is required before the model is applied to guide PCI. This tool may support individualised discussion of PCI and of imaging surveillance.

Keywords

Small-cell lung cancer; Brain metastasis; Nomogram; Risk prediction; Prophylactic cranial irradiation; Neutrophil-to-lymphocyte ratio

1. Introduction

Small-cell lung cancer (SCLC) is an aggressive neuroendocrine tumour, and most patients present with extensive-stage disease (ES-SCLC) [1]. Brain metastasis (BM) is a common and devastating complication of ES-SCLC, and it develops in a substantial proportion of patients during follow-up, with the highest incidence within the first two years after diagnosis [2-3]. The development of BM causes severe neurological morbidity and shortens survival, with a median overall survival of 6.6 months after the diagnosis of BM in extensive-stage disease reported in a national database analysis [4]. Prognostic indices are used to stratify these patients for treatment, and treatment options for established BM include whole-brain radiotherapy and stereotactic radiosurgery [5-6]. The central nervous system is a sanctuary site because the blood-brain barrier restricts the penetration of systemically administered agents, and neurotropic features of SCLC may further favour intracranial dissemination [7-8]. Baseline brain magnetic resonance imaging (MRI) is recommended during staging and identifies the patients who already harbour intracranial disease [9].

Prophylactic cranial irradiation (PCI) is the principal strategy for reducing the incidence of BM. In patients with limited-stage SCLC who achieved complete remission, an individual patient data meta-analysis showed that PCI reduced the incidence of BM and improved overall survival [10]. In ES-SCLC, the EORTC 08993 trial found that PCI reduced symptomatic BM and prolonged survival among patients who responded to chemotherapy [11], whereas a later Japanese randomised trial that incorporated protocol-specified MRI surveillance reported no overall survival benefit [12]. PCI carries a risk of neurocognitive decline, and hippocampal avoidance has been investigated as a means of reducing memory impairment [13]. As chemoimmunotherapy has become the standard first-line treatment [14], the magnitude of the benefit of PCI in the immunotherapy era has become uncertain [15]. Active MRI surveillance has been proposed as an alternative for selected patients [16], randomised comparisons of PCI with surveillance are ongoing [17], and guidelines present PCI as an option for patients who respond to initial therapy while recommending regular brain imaging during follow-up [9]. Applying either strategy to all responding patients, without an estimate of the individual probability of BM, exposes some patients to irradiation that may never be needed.

Several nomograms have been developed to estimate the risk of BM in SCLC, each within a defined population. One model was restricted to men with stage III disease treated with chemoradiotherapy [18], two models were developed for limited-stage disease [19-20], another covered SCLC more broadly [21], and one was constructed in ES-SCLC specifically to guide PCI [22]. These tools were built largely from clinical, staging and treatment variables, and adherence to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) standard remains incomplete among published prognostic models, as shown for radiological prediction models in oncology [23], and calibration is frequently incompletely reported [24]. The contribution of routinely available proliferation and inflammation markers to the prediction of BM in SCLC has received little direct evaluation. Ki-67, an immunohistochemical index of proliferation, has been related to prognosis in SCLC [25], and the pretreatment neutrophil-to-lymphocyte ratio (NLR) has been associated with survival in SCLC, including in extensive-stage disease [26]. Metastatic patterns differ in organ distribution and in the timing with which individual sites become involved, so the pattern of distant disease may also carry information about the risk of intracranial progression [27-28].

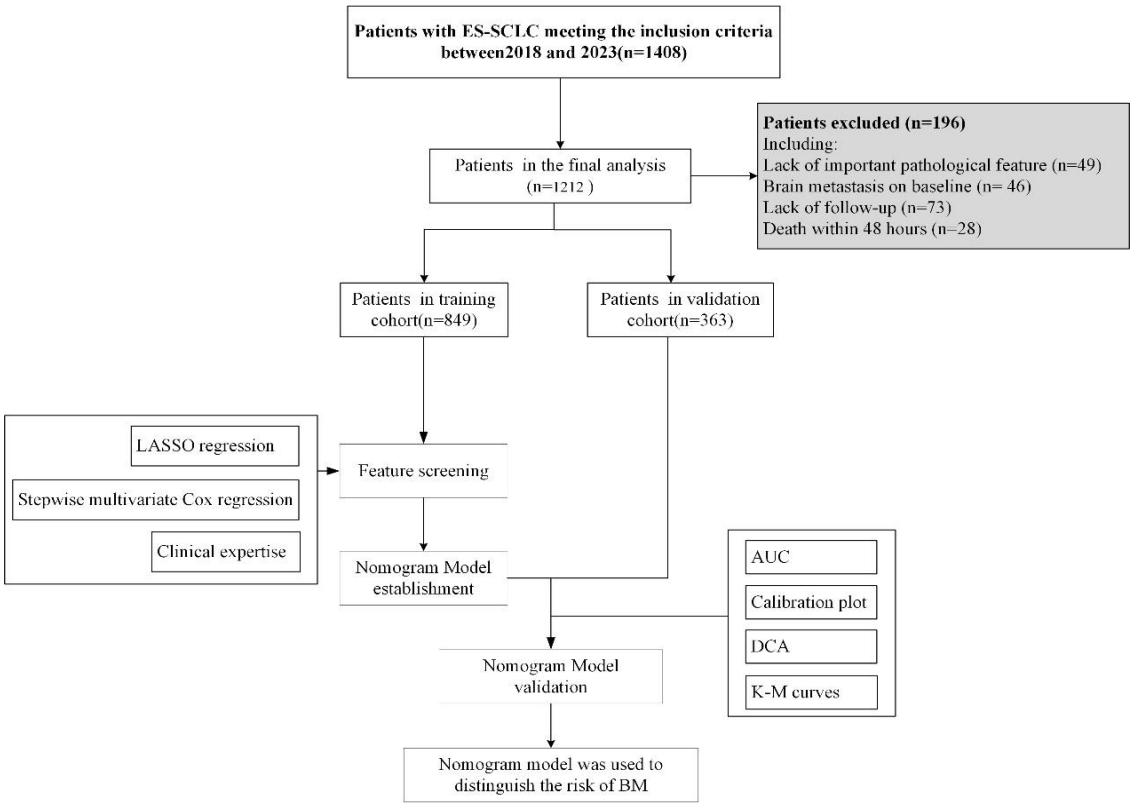
We therefore developed and internally validated a comprehensive nomogram for patients with ES-SCLC who had no BM on baseline MRI, integrating clinical characteristics, metastatic patterns and inflammatory and proliferation markers. The model estimates the probability of BM at 6 months, 1 year and 2 years, and it is intended to support the individualised discussion of PCI and of imaging surveillance.

2. Materials and Methods

2.1 Study design and participants

This multicentre retrospective cohort study included patients with histologically confirmed ES-SCLC who were treated at three cancer centres between 2018 and 2023. For the present analysis, ES-SCLC was operationalised as AJCC 8th edition stage IV disease, or inoperable stage III disease that did not receive definitive chemoradiotherapy; patients with inoperable stage III disease were therefore eligible, and AJCC stage (III versus IV) was retained as a candidate predictor rather than restricting the cohort to stage IV disease. Patients were eligible if they met all of the following criteria: histological confirmation of SCLC, no BM on baseline brain MRI, and complete data for all candidate predictors. Patients were excluded if they had previously received cranial radiotherapy, had a concurrent malignancy, or had a follow-up duration shorter than 6 months. Of 1408 patients assessed for eligibility, 196 were excluded: 49 because important pathological features were unavailable, 46 because BM was present on baseline imaging, 73 because of insufficient follow-up, and 28 because of death within 48 hours of admission. The remaining 1212 patients formed the analysis cohort (Figure 1). Data were collected retrospectively from clinical records, and the study is reported in accordance with the TRIPOD statement [29] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement [30].

Figure 1. Flow chart of the study.



Patients with ES-SCLC treated at three cancer centres between 2018 and 2023 were assessed for eligibility (n = 1408); 196 patients were excluded and 1212 were included in the analysis, which was randomly divided at a ratio of 7:3 into a training cohort (n = 849) and a validation cohort (n = 363). ES-SCLC, extensive-stage small-cell lung cancer; BM, brain metastasis; LASSO, least absolute shrinkage and selection operator; AUC, area under the receiver operating characteristic curve; DCA, decision curve analysis; K-M, Kaplan-Meier.

2.2 Candidate predictors

Candidate predictors were selected from variables that are recorded in routine clinical and laboratory data in ES-SCLC, so that the model could be applied without additional testing. Clinical characteristics comprised age, sex, smoking and drinking history, body mass index, Eastern Cooperative Oncology Group (ECOG) performance status, primary tumour category (T1–T2 versus T3–T4), nodal category (N0–N1 versus N2–N3) and AJCC stage (III versus IV). Performance status was included because it is an established prognostic factor in SCLC, including in extensive-stage disease [31]. Metastatic patterns comprised the presence or absence of adrenal, hepatic, bone, pleural and abdominal lymph node metastases, documented by computed tomography (CT) or MRI; organ-specific involvement was considered because metastatic patterns in SCLC differ in organ distribution and in the timing with which individual sites become involved [27]. Treatment variables comprised whether PCI and synchronous chemoradiotherapy had been administered, and tumour markers comprised chromogranin A (CgA), CD56, lactate dehydrogenase (LDH), pro-gastrin-releasing peptide (PROGRP) and neuron-specific enolase (NSE). PCI was included as a candidate predictor because randomised evidence in SCLC shows that it alters the subsequent occurrence of BM [11], and synchronous chemoradiotherapy was included because thoracic radiotherapy has been reported to affect the timing of BM in ES-SCLC [32]. Ki-67 expression was determined by immunohistochemistry and categorised as ≤20% versus >20% [25], and the systemic inflammatory response was represented by the pretreatment NLR, calculated as the ratio of the absolute neutrophil count to the absolute lymphocyte count and analysed per unit increase together with the platelet-to-lymphocyte ratio [33].

2.3 Outcome ascertainment

The primary outcome was BM confirmed by imaging during follow-up. Patients were required to have no BM on baseline brain MRI, and the occurrence of BM was ascertained from imaging performed as part of routine care. The event time was defined as the date of the imaging study that first documented BM, and time to BM was calculated from the date of histological diagnosis; patients without documented BM were censored at the last available clinical contact or death. BM was analysed as a time-to-event outcome, so that the probability of BM could be estimated at several horizons from a single model rather than from fixed follow-up windows. Death is a competing event for BM, and estimates of the cumulative probability of BM can be biased when the competing risk is not accounted for [34].

2.4 Model construction and evaluation

Patients were randomly divided into a training cohort (n = 849) and a validation cohort (n = 363) at a ratio of 7:3 with a fixed random seed to ensure reproducibility. Candidate predictors were screened by least absolute shrinkage and selection operator (LASSO) regression, and the penalty parameter λ was chosen by cross-validation using the minimum criterion [35-36]. The variables retained were entered into a stepwise multivariable Cox proportional hazards regression model, and the model with the minimum Akaike information criterion was selected; the proportional hazards assumption was examined with a test based on Schoenfeld residuals. Associations were expressed as hazard ratios (HRs) with 95% confidence intervals (CIs). A nomogram was constructed by assigning points according to the regression coefficients of the final model using the rms package, and the construction and interpretation of the tool follow established guidance for oncology nomograms [37]. The total score is translated into the probability of BM at each horizon.

Discrimination was quantified by the time-dependent area under the receiver operating characteristic curve (AUC) at 6 months, 1 year and 2 years [38], and time-dependent AUC and concordance index (C-index) curves were generated for 1–24 months. Calibration was assessed by comparing predicted with observed probabilities of BM, and bootstrap resampling with 1,000 iterations was used to obtain bootstrap-corrected curves [39]. Decision curve analysis (DCA) was used to estimate net benefit across a range of threshold probabilities, with the treat-all and treat-none strategies as comparators, because discrimination measures alone do not indicate whether a model is useful at a given threshold probability [40-41]. Patients were also stratified into high-risk and low-risk groups according to the optimal cut-off of the nomogram score, and the cumulative incidence of BM in the two groups was compared by Kaplan-Meier analysis. The performance of the model was described in the training cohort and in the held-out validation cohort.

2.5 Statistical analysis

Continuous variables with a normal distribution were described as means and standard deviations and compared with t-tests, whereas variables with a non-normal distribution were described as medians and interquartile ranges and compared with non-parametric tests. Categorical variables were expressed as frequencies and proportions and compared with chi-square tests. Missing data were handled by multiple imputation using the mice package. Two-sided P values < 0.05 were considered statistically significant. Analyses were performed with R version 4.1.2 (caret, glmnet, rms, tableone and mice packages).

3. Results

3.1 Patient characteristics

The analysis cohort comprised 1212 patients with ES-SCLC treated at three cancer centres between 2018 and 2023, of whom 371 (30.6%) developed BM during follow-up. The mean age was 62.72 ± 9.32 years and 1040 patients (85.8%) were male. Most patients had stage IV disease (888, 73.3%), hepatic metastases (362, 29.9%) and an ECOG performance status of 1 (796, 65.7%), and a Ki-67 index greater than 20% was recorded in 58.6% of patients. The baseline characteristics of the cohort, and their comparison between patients who did and did not develop BM, are summarised in Table 1.

The incidence of BM was higher in male than in female patients and in smokers than in non-smokers (P = 0.030 and P = 0.010, respectively). Patients with adrenal, hepatic or bone metastases had a significantly higher incidence of BM than those without (P < 0.001, P < 0.001 and P = 0.001, respectively), as did patients with a higher T category, a higher N category or stage IV disease (P < 0.001 for all). Among the laboratory variables, the Ki-67 index and the NLR differed significantly between patients who developed BM and those who did not (P < 0.001 and P = 0.002), as did CgA and CD56 expression (P = 0.001 for both), whereas LDH, PROGRP, NSE and the platelet-to-lymphocyte ratio did not.

Table 1. Baseline characteristics of the study cohort

Variable	Overall cohort (n = 1212)	Without BM (n = 841)	With BM (n = 371)	P
Age, years (mean ± SD)	62.72 ± 9.32	63.24 ± 9.51	61.54 ± 8.78	0.003
Sex, male	1040 (85.81)	709 (84.30)	331 (89.22)	0.030
Sex, female	172 (14.19)	132 (15.70)	40 (10.78)	
Smoking, yes	882 (72.77)	593 (70.51)	289 (77.90)	0.010
Smoking, no	330 (27.23)	248 (29.49)	82 (22.10)	
Drinking, yes	618 (50.99)	413 (49.11)	205 (55.26)	0.056
Drinking, no	594 (49.01)	428 (50.89)	166 (44.74)	
BMI 18.5–24	672 (55.45)	467 (55.53)	205 (55.26)	0.392
BMI ≥24	465 (38.37)	317 (37.69)	148 (39.89)	
BMI <18.5	75 (6.19)	57 (6.78)	18 (4.85)	
ECOG PS 1	796 (65.68)	575 (68.37)	221 (59.57)	< 0.001
ECOG PS 2	336 (27.72)	235 (27.94)	101 (27.22)	
ECOG PS ≥3	80 (6.60)	31 (3.69)	49 (13.21)	
Tumour T1–T2	300 (24.75)	236 (28.06)	64 (17.25)	< 0.001

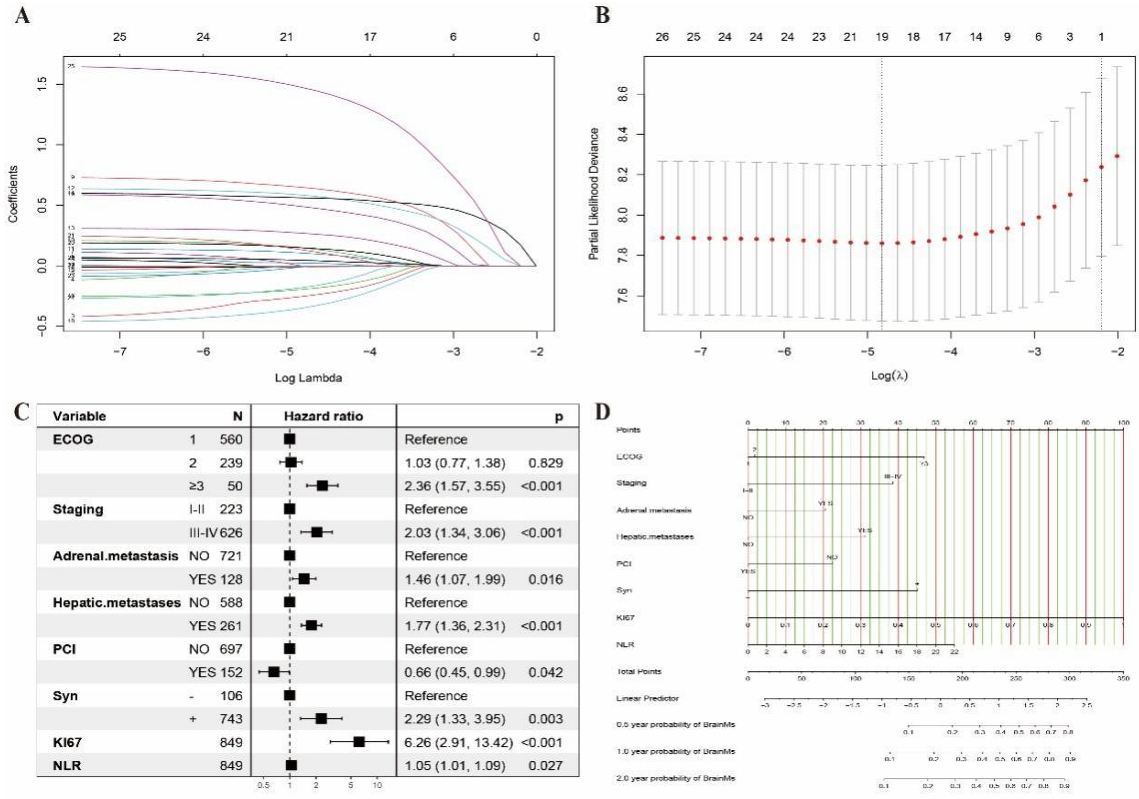
Variable	Overall cohort (n = 1212)	Without BM (n = 841)	With BM (n = 371)	P
Tumour T3–T4	912 (75.25)	605 (71.94)	307 (82.75)	
Node N0–N1	520 (42.90)	402 (47.80)	118 (31.81)	< 0.001
Node N2–N3	692 (57.10)	439 (52.20)	253 (68.19)	
AJCC stage III	324 (26.73)	282 (33.53)	42 (11.32)	< 0.001
AJCC stage IV	888 (73.27)	559 (66.47)	329 (88.68)	
Adrenal metastasis	190 (15.68)	98 (11.65)	92 (24.80)	< 0.001
Hepatic metastasis	362 (29.87)	187 (22.24)	175 (47.17)	< 0.001
Bone metastasis	403 (33.25)	254 (30.20)	149 (40.16)	0.001
Pleural metastasis	186 (15.35)	134 (15.93)	52 (14.02)	0.443
Abdominal lymph node metastasis	79 (6.52)	54 (6.42)	25 (6.74)	0.936
PCI	215 (17.74)	172 (20.45)	43 (11.59)	< 0.001
Synchronous chemoradiotherapy	1062 (87.62)	717 (85.26)	345 (92.99)	< 0.001
CgA positive	761 (62.79)	501 (59.57)	260 (70.08)	0.001
CD56 positive	1118 (92.24)	761 (90.49)	357 (96.23)	0.001
LDH >200 U/L	825 (68.07)	569 (67.66)	256 (69.00)	0.692
PROGRP ≥100 pg/mL	866 (71.45)	593 (70.51)	273 (73.58)	0.306
NSE ≥15.4 ng/mL	657 (54.21)	452 (53.75)	205 (55.26)	0.672
Ki-67 index (mean ± SD)	0.67 ± 0.21	0.64 ± 0.22	0.73 ± 0.15	< 0.001
NLR (mean ± SD)	4.06 ± 2.71	3.90 ± 2.53	4.43 ± 3.04	0.002
PLR (mean ± SD)	205.23 ± 114.28	205.13 ± 114.72	205.44 ± 113.45	0.966

Note. BM, brain metastasis; SD, standard deviation; BMI, body mass index; ECOG PS, Eastern Cooperative Oncology Group performance status; AJCC, American Joint Committee on Cancer; PCI, prophylactic cranial irradiation; CgA, chromogranin A; LDH, lactate dehydrogenase; PROGRP, pro-gastrin-releasing peptide; NSE, neuron-

specific enolase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio. Values are n (%) unless otherwise indicated; percentages are calculated with the number of patients in each column as the denominator.

3.2 Independent predictors and nomogram construction

A test based on Schoenfeld residuals confirmed that the proportional hazards assumption of the Cox model was satisfied. In the training cohort, LASSO regression followed by stepwise Cox regression identified eight variables that were independently associated with BM (Figure 2A–2C): ECOG PS ≥3 (HR 2.36, 95% CI 1.57–3.55, P < 0.001), stage IV disease (HR 2.03, 95% CI 1.34–3.06, P < 0.001), adrenal metastasis (HR 1.46, 95% CI 1.07–1.99, P = 0.016), hepatic metastasis (HR 1.77, 95% CI 1.36–2.31, P < 0.001), synchronous chemoradiotherapy (HR 2.29, 95% CI 1.33–3.95, P = 0.003), a Ki-67 index >20% (HR 6.26, 95% CI 2.91–13.42, P < 0.001), an elevated NLR (HR 1.05 per unit, 95% CI 1.01–1.09, P = 0.027) and PCI (HR 0.66, 95% CI 0.45–0.99, P = 0.042), which was associated with a lower hazard of BM. ECOG PS 2 did not differ significantly from ECOG PS 1 (HR 1.03, 95% CI 0.77–1.38, P = 0.829). **Figure 2. Results of LASSO regression analysis and the nomogram for predicting BM.**



A: each curve represents the trajectory of the coefficient of one candidate variable; B: the partial likelihood deviance of the LASSO regression according to the penalty parameter λ, selected by cross-validation; C: forest plot of the multivariable Cox regression analysis; D: nomogram for predicting the 0.5-year, 1-year and 2-year

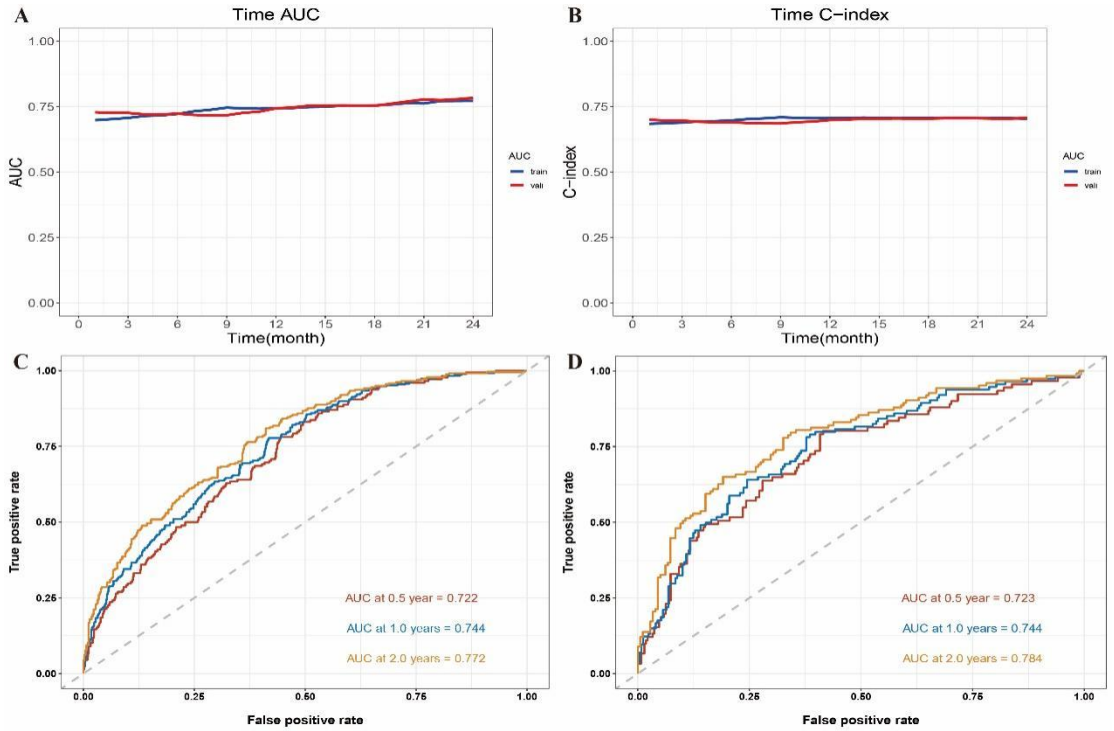
probability of BM in the training cohort. HR, hazard ratio; CI, confidence interval; LASSO, least absolute shrinkage and selection operator; ECOG PS, Eastern Cooperative Oncology Group performance status; AJCC, American Joint Committee on Cancer; PCI, prophylactic cranial irradiation; Ki-67, proliferation index determined by immunohistochemistry; NLR, neutrophil-to-lymphocyte ratio; BM, brain metastasis.

A nomogram was constructed to estimate the probability of BM at 6 months, 1 year and 2 years (Figure 2D). Points were assigned to each predictor according to its regression coefficient, so that the variables contributing the largest number of points were a Ki-67 index >20% (100 points), hepatic metastasis (40 points) and stage IV disease (35 points), whereas PCI received a negative score because of its inverse association with BM. The three probability axes of the nomogram are labelled as the 0.5-year, 1.0-year and 2.0-year probability of BM.

3.3 Model validation

Time-dependent AUC and C-index curves generated over 1–24 months of follow-up showed that discrimination was stable across the whole follow-up period in both cohorts (Figure 3A and 3B). The nomogram showed good discrimination at the three prediction horizons, with AUCs of 0.722 at 6 months, 0.744 at 1 year and 0.772 at 2 years in the training cohort, and corresponding values of 0.723, 0.744 and 0.784 in the validation cohort (Figure 3C and 3D).

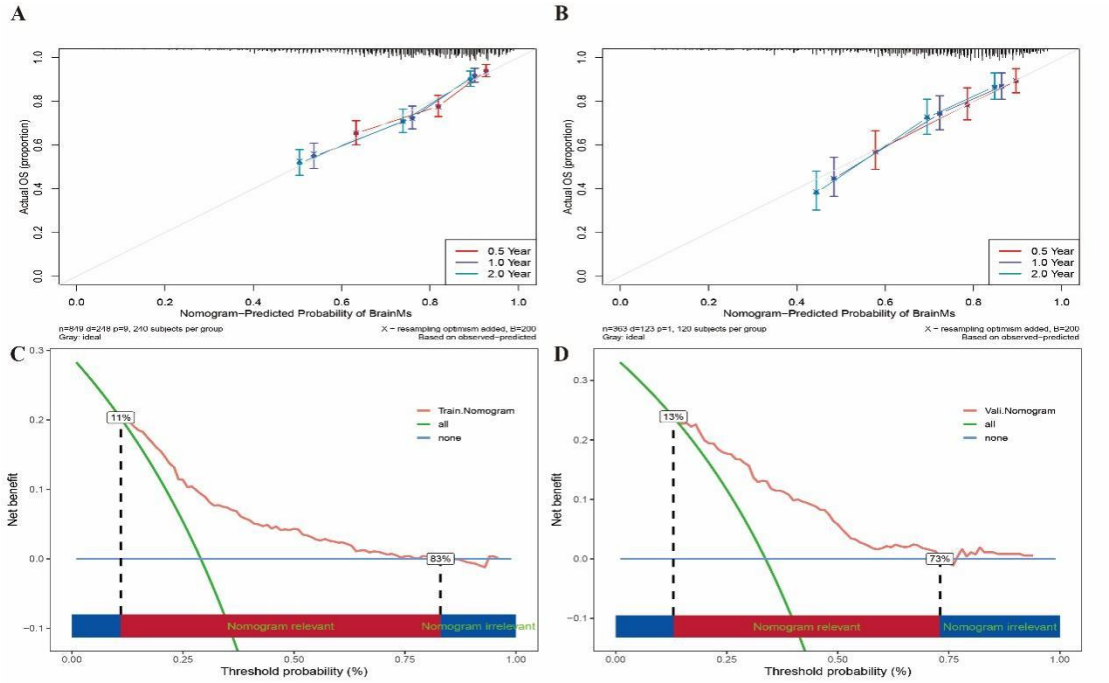
Figure 3. Time-dependent discrimination of the nomogram.



A: time-dependent AUC at different time points; B: time-dependent C-index at different time points; C: time-dependent ROC curves at 0.5, 1 and 2 years in the training cohort; D: time-dependent ROC curves at 0.5, 1 and 2 years in the validation cohort. AUC, area under the receiver operating characteristic curve; C-index, concordance index; ROC, receiver operating characteristic.

Calibration curves for the three prediction horizons showed minimal deviation from the ideal line in both the training and the validation cohorts, indicating close agreement between the predicted and observed probabilities of BM (Figure 4A and 4B). In the decision curve analysis, the nomogram provided a higher net benefit than both the treat-all and the treat-none strategies across a threshold probability range of 11%–83% in the training cohort (Figure 4C) and of 13%–73% in the validation cohort (Figure 4D).

Figure 4. Calibration and decision curve analysis of the nomogram.

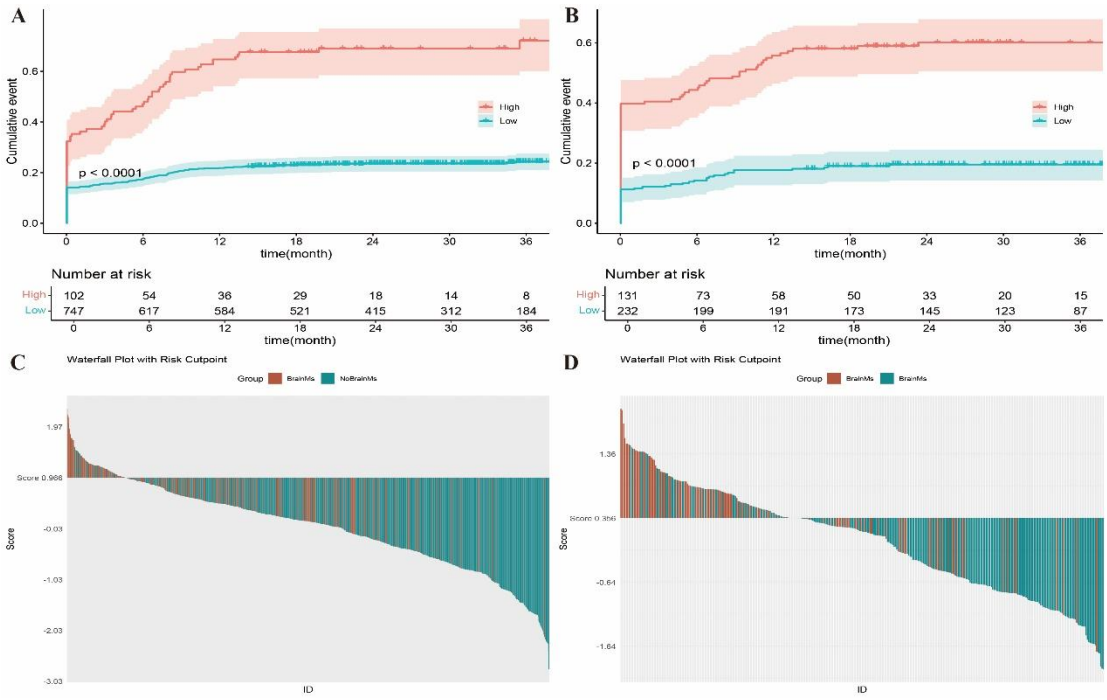


A: calibration curves for 0.5, 1 and 2 years in the training cohort; B: calibration curves for 0.5, 1 and 2 years in the validation cohort; C: decision curve analysis in the training cohort; D: decision curve analysis in the validation cohort. The dashed line in A and B represents perfect agreement between predicted and observed probabilities; the horizontal lines in C and D represent the treat-none strategy and the ascending line represents the treat-all strategy. BM, brain metastasis.

After stratification by the nomogram score, the high-risk group had a substantially higher cumulative incidence of BM than the low-risk group in both the training cohort and the validation cohort ($P < 0.0001$ for both; Figure 5A and 5B). The distribution of predicted scores across individual patients is shown in the waterfall

plots, in which patients who developed BM were concentrated at the higher scores (Figure 5C and 5D).

Figure 5. Risk stratification and individual prediction of BM.



A: Kaplan-Meier curves of the high-risk and low-risk groups in the training cohort; B: Kaplan-Meier curves of the high-risk and low-risk groups in the validation cohort; C: waterfall plot of predicted scores in the training cohort; D: waterfall plot of predicted scores in the validation cohort. BM, brain metastasis; K-M, Kaplan-Meier.

4. Discussion

4.1 Proliferation and the dominance of Ki-67 in risk prediction

The strongest predictor of BM in this cohort was a Ki-67 index greater than 20%, which carried an HR of 6.26. Ki-67 is a nuclear protein associated with cell proliferation and is widely used as an index of tumour aggressiveness, and higher expression has been associated with poorer survival in SCLC series in which cut-offs of 75% and 79.77% were applied, whereas a cut-off of 20% was used here [42-43]. Findings in SCLC have not been uniform, and one series of 159 patients with extensive-stage disease reported no significant association between Ki-67 expression and survival [44]. An association of this magnitude with a proliferation marker is compatible with a contribution of proliferative activity to intracranial dissemination, and SCLC shows neurotropic behaviour that favours seeding in the brain [8]; the present result identifies a group at higher risk of BM rather than the route by which dissemination occurs. The inclusion of a routinely reported

proliferation marker is one of the features that distinguishes this model from nomograms built from clinical and staging variables alone.

4.2 Metastatic pattern and haematogenous dissemination

Hepatic metastasis was independently associated with BM (HR 1.77), and adrenal metastasis was associated with a smaller increase in risk (HR 1.46). Organ-specific metastatic patterns in SCLC differ in their distribution and in the timing with which individual sites become involved [27], and prognosis in extensive-stage disease differs according to the organ involved [28]. These findings are consistent with a larger overall metastatic burden being accompanied by a higher probability of intracranial involvement, which is the reason why the metastatic variables were retained in a model intended for routine use.

4.3 PCI as a protective factor

PCI was associated with a lower hazard of BM in this cohort (HR 0.66), which is smaller than the effect reported in the randomised evidence for extensive-stage disease. In the EORTC 08993 trial of patients who responded to chemotherapy, PCI reduced the 1-year cumulative incidence of symptomatic BM to 14.6% from 40.4% (HR 0.27, 95% CI 0.16–0.44) [11]. That trial ascertained symptomatic BM without protocol-specified MRI and enrolled only patients who had responded to chemotherapy, so its estimate and the hazard derived here describe different endpoints and different populations. In limited-stage disease, an individual patient data meta-analysis of patients in complete remission reported a relative risk of 0.46 (95% CI 0.38–0.57) for BM [10], whereas a randomised trial in extensive-stage disease that used protocol-specified MRI surveillance found no overall survival benefit from PCI (median 11.6 versus 13.7 months, HR 1.27, 95% CI 0.96–1.68, P = 0.094) [12]. In a recent observational cohort of patients with ES-SCLC and no baseline BM, PCI was independently associated with a lower risk of BM after adjustment for confounders (subdistribution HR 0.431, 95% CI 0.195–0.955, P = 0.038) [45]. The direction of the association observed here is therefore consistent with the randomised and observational evidence that PCI lowers the occurrence of intracranial disease, while the magnitude of any survival effect remains uncertain, and the cognitive consequences of cranial irradiation and the option of active MRI surveillance are the considerations against which a predicted probability would be weighed [13, 16].

4.4 Systemic inflammation and the NLR

An elevated NLR was retained with a small per-unit hazard (HR 1.05). Pretreatment NLR has been associated with poorer outcome in SCLC, including in extensive-stage disease [26], and a meta-analysis of 20 studies in SCLC reported a pooled HR of 1.40 (95% CI 1.26–1.55) for overall survival in patients with a high pretreatment NLR [33]. Evidence that pretreatment NLR predicts the occurrence of BM is more limited: in a cohort of 293 patients with SCLC and no BM at diagnosis, pretreatment platelet count, radiotherapy dose and the absence of PCI were independently associated

with brain metastasis-free survival, and no independent association with NLR was reported [46]. The NLR term is therefore interpreted as information about the systemic inflammatory response that may contribute to risk rather than as an established predictor of BM.

4.5 Comparison with existing prediction models

Several nomograms for BM in SCLC have been published, each developed in a defined population. In men with stage III disease treated with chemoradiotherapy, the reported AUC was 0.764 [18]. In patients with limited-stage disease who did not receive PCI, the reported AUCs were 0.72 at 3 years and 0.67 at 5 years for intracranial progression-free survival [19]. A model developed in 631 patients with SCLC reported a C-index of 0.830 and 0.788 in bootstrap-corrected internal validation and 0.818 in an external cohort [21]. A model for limited-stage disease developed to optimise PCI selection reported AUCs of 0.763 and 0.782 at 1 year and 0.759 and 0.732 at 2 years in the training and validation sets [20], and the model closest to the population studied here, developed in ES-SCLC to guide PCI, reported AUCs of 0.77 at 9 months, 0.74 at 12 months and 0.75 at 18 months for intracranial progression-free survival in the training set [22].

These values cannot be compared directly with the results reported here, because the populations, outcome definitions, prediction horizons and validation designs differ, and several estimates were obtained in split samples rather than in independent cohorts. The discrimination observed in the present cohort lies within the range reported for SCLC models of BM, and the relative performance of these models has not been established in a common dataset. The predictors retained here include Ki-67 and the NLR, which are not components of the models described above, and whether these variables add predictive information beyond clinical and treatment variables would require a head-to-head comparison on shared data.

4.6 Clinical utility and decision curve analysis

In the decision curve analysis, the nomogram provided a higher net benefit than both default strategies across a wide range of threshold probabilities in the training and validation cohorts, which indicates that decisions based on the model would improve on decisions made without it within the threshold range examined. DCA is a useful complement to discrimination measures because it considers the benefits and harms associated with treatment at a given threshold rather than the ranking of patients alone [40-41]. In the present setting, the relevant decision is whether to offer PCI, and a threshold probability range that extends to around 80% corresponds to the range of risks in which patients and clinicians might reasonably differ in their preferences. Stratification into high-risk and low-risk groups also separated patients with clearly different cumulative incidences of BM, which supports the use of the tool for the identification of the patients in whom the greatest benefit from PCI would be expected [5].

4.7 Limitations and future directions

Several features of this study affect the interpretation of the results. Data were collected retrospectively from routine records at three centres in one region, and follow-up imaging was performed as part of routine care rather than according to a protocol, so the timing of detection of BM may differ from that in trials with scheduled surveillance, and selection and information bias cannot be excluded. The cohort includes patients with stage III disease who did not receive definitive chemoradiotherapy; these patients were eligible by design, but their inclusion makes the cohort heterogeneous and reduces comparability with series that define extensive-stage disease by stage IV alone. Validation relied on splitting the cohort, so the performance estimated here provides no information about transportability to other settings, and external evaluation would be required before the model is applied elsewhere, as has been reported for at least one model in this field [21]. Eligibility required complete data for all candidate predictors and missing values were handled by multiple imputation, which may have selected for patients with a more complete diagnostic work-up. The model contains no molecular or genomic markers, and Ki-67 was dichotomised at 20%, a cut-off that differs from those used in published SCLC series [42]; the dynamic nature of cancer progression suggests that serial measurement of biomarkers may be needed to capture changes in risk over time. Finally, death is a competing event for BM, and accounting for competing risks in the analysis of the cumulative probability of BM would be a useful extension.

5. Conclusions

In this multicentre cohort of 1212 patients with ES-SCLC and no BM on baseline MRI, eight routinely available clinical, metastatic, treatment and laboratory variables were independently associated with subsequent BM, and a nomogram based on them estimated the probability of BM at 6 months, 1 year and 2 years with time-dependent AUCs of 0.722 to 0.772 in the training cohort and 0.723 to 0.784 in the validation cohort. Calibration curves showed close agreement between predicted and observed probabilities, decision curve analysis indicated a higher net benefit than the default strategies across a wide range of threshold probabilities, and the model separated patients into groups with clearly different cumulative incidences of BM. Because validation was internal, external evaluation is required before the model is used to select patients for PCI; within this cohort it provides an individual estimate of the probability of BM on which the discussion of PCI and of imaging surveillance can be based.

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki. The study protocol was approved by the ethics committees of the participating centres (Ethics

Committee of Chongqing University Cancer Hospital, Ethics Committee of Chongqing University Three Gorges Hospital and Ethics Committee of Chongqing University Fuling Hospital; approval number CZLS2026089-A), and approval covered the retrospective use of clinical records, including imaging and laboratory results. The requirement for informed consent was waived by the ethics committees because of the retrospective design of the study and the use of anonymised clinical records.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions

Study concept: Hai-Ke Lei and Wei Zhou. Data acquisition: Dan Tao, Ding-Yi Yang and Yong Jiang. Analysis: Hai-Ke Lei and Qianjie Xu. Manuscript drafting: Lu-Lu Wang, Mao Sun and Qian-Jie Xu. Critical revision: Wei Zhou and Hai-Ke Lei. All authors read and approved the final manuscript. Wei Zhou and Hai-Ke Lei are co-corresponding authors.

Acknowledgements

The authors thank all the patients and their families for their participation in this study, and the medical staff at the participating institutions for their assistance with data collection and patient care.

Reporting checklist

The study is reported in accordance with the TRIPOD statement and the STROBE statement.

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