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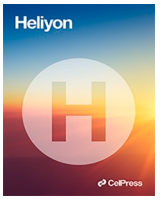

Research article

Exploring the prognostic impact of differences in treatment strategies for SCLC with different histologies and prognostic factors for C-SCLC: A SEER population-based study

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ABSTRACT

Background: Combined small cell lung cancer (C-SCLC) is a rare type of small cell lung cancer (SCLC), and it is controversial whether to choose the same treatment regimen as SCLC due to its multiple histologic components.

Study methods and results: Records of patients with small cell lung cancer diagnosed between 2010 and 2020 were extracted using the SEER database. The OS of patients with different histological types under the same staging and treatment regimen was analyzed. It was found that early-stage (stage IA-IIA) surgical treatment, systemic chemotherapy alone, and chemoradiotherapy were more efficacious than C-SCLC and P-SCLC in patients with limited-stage ($P = 0.054$, $P = 0.001$, $P = 0.019$). In patients with extensive staging, the OS of patients with systemic chemotherapy regimens differed ($P = 0.045$) and was better in C-SCLC than in P-SCLC. We further explored the treatment strategy for patients with C-SCLC, which was shown by a COX regression model based on prognostic factors screened by Random Forest and LASSO regression models. Surgery, radiotherapy, and chemotherapy would be beneficial for survival. In a subgroup analysis based on stage and treatment regimen, it was shown that patients with early staging (stage IA-IIA) had a better prognosis with surgery ($P < 0.001$); in patients with extensive staging, chemoradiotherapy was favorable to the patient's prognosis ($P = 0.022$).

Conclusion: Both limited-stage and extensive-stage C-SCLC patients are more sensitive to chemotherapy than P-SCLC patients. Patients with C-SCLC who have access to surgery should undergo surgery as early as possible, while chemoradiotherapy is recommended for patients with extensive staging. Patient age, gender, tumor size, surgery, chemotherapy, radiotherapy, and metastasis may individually affect patient prognosis.

1. Background

The World Health Organization (WHO) categorizes combined small-cell lung cancer (C-SCLC) as a specific subtype within the broader classification of small-cell lung cancer (SCLC). This subtype is characterized by a histological amalgamation of SCLC with

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components of non-small cell lung cancer (NSCLC), including but not limited to squamous cell carcinoma (SCC), adenocarcinoma (ADC), malignant adenomas, and large-cell neuroendocrine carcinomas (LCNEC). Additionally, although less common, it can encompass spindle cell carcinoma and giant cell carcinoma [1]. The definitive criterion for diagnosing C-SCLC lies in the presence of any amount of SCLC, in conjunction with the NSCLC components, regardless of the proportion of ADC, SCC, or sarcoma cells present. However, for a diagnosis of C-SCLC to be confirmed, there must be at least a 10 % representation of the large cell carcinoma (LCC) or LCNEC component within the tumor. This criterion underscores the importance of thorough histological examination to accurately identify the diverse cellular components, facilitating the correct classification and subsequent treatment planning for patients with this complex form of lung cancer [2].

C-SCLC is distinguished from pure small-cell lung cancer (P-SCLC) by its more complex histological composition. This subtype not only integrates elements of SCLC but also incorporates components of NSCLC, making it a particularly challenging variant to treat. Research indicates several factors influencing the prognosis of patients diagnosed with C-SCLC. Key among these is the degree of tumor differentiation, size, and the presence of distant metastases, all of which have been negatively correlated with survival rates [3]. This underscores the aggressive nature of C-SCLC and its propensity for poorer clinical outcomes compared to P-SCLC.

The role of adjuvant chemotherapy in the management of surgically treated C-SCLC patients has been highlighted in studies demonstrating its beneficial effects on both disease-free survival (DFS) and overall survival (OS) [4]. These findings suggest that systemic chemotherapy post-surgery can substantially impact the disease course, enhancing the likelihood of prolonged survival. Moreover, the utility of postoperative radiotherapy, particularly in C-SCLC patients with pathologic stage pN2, has been shown to improve survival outcomes [5]. This suggests that targeted radiotherapy, when applied judiciously in specific pathologic stages, can contribute significantly to the extension of a patient lifespan.

In the context of surgical intervention, the significance of lobectomy for patients with early-stage C-SCLC has been emphasized. This surgical approach, aimed at removing a lobe of the lung, is advocated based on its potential to offer curative outcomes in the initial stages of this complex disease. Additionally, the practice of prophylactic cranial irradiation (PCI) has been reviewed, with findings suggesting it could enhance the overall survival rates in both P-SCLC and C-SCLC patients [6]. The rationale behind PCI is to preemptively treat microscopic metastases in the brain, a common site for the spread of lung cancer, thereby improving survival prospects.

Collectively, these insights underscore the multifaceted approach required in the treatment of C-SCLC, involving surgical, chemotherapeutic, and radiotherapeutic strategies to optimize patient outcomes. The intricate histology and aggressive behavior of C-SCLC necessitate a tailored treatment plan that addresses the unique characteristics of each patient's disease, thereby enhancing the potential for improved survival rates.

The 2023 edition of the Chinese Society of Clinical Oncology (CSCO) guidelines advocates for a unified treatment regimen for both C-SCLC and P-SCLC, despite the acknowledged complexity in the histological composition of C-SCLC compared to P-SCLC. This approach raises questions about the potential variability in prognosis among lung cancers that, while sharing a common treatment protocol, differ in their histological make-up. Given the intricate nature of C-SCLC, it stands to reason that the prognostic outcomes of cancers with diverse histologic profiles might diverge under identical treatment conditions. However, the specific prognostic differences between small-cell lung cancer patients of the same stage but with different histological types have not been thoroughly investigated, particularly in the context of uniform treatment regimens.

To address this gap in understanding, our research embarked on a two-pronged investigation. Initially, we utilized the Surveillance, Epidemiology, and End Results (SEER) database to compare the OS of P-SCLC and C-SCLC patients who underwent the same treatment regimen. This comparison aimed to elucidate any disparities in survival outcomes attributable to the histological differences between these two subtypes when treated identically. Following the survival analysis, we employed machine learning techniques to dissect the factors influencing the prognosis of C-SCLC patients more deeply. This advanced analytical approach allowed us to sift through complex datasets to identify significant prognostic indicators that might not be readily apparent through traditional statistical methods. Moreover, we conducted a subgroup analysis among C-SCLC patients to pinpoint treatment regimens that may offer prognostic advantages at different stages of the disease. This nuanced examination aimed to uncover tailored therapeutic strategies that could potentially enhance survival outcomes for C-SCLC patients, taking into consideration the specific stage of cancer at diagnosis.

Through these multifaceted investigative efforts, our study seeks to contribute to a more nuanced understanding of how histological differences within small-cell lung cancer subtypes might influence patient prognosis under a standardized treatment protocol. The ultimate goal is to refine and personalize treatment approaches for C-SCLC, thereby improving the clinical outcomes for patients diagnosed with this complex and challenging form of lung cancer.

2. Patients and methods

2.1. Data sources

We screened the corresponding patients in the SEER database (http://seer.cancer.gov/). In this study, we extracted the diagnostic information ICD code 8045/3 for patients with C-SCLC; for patients with P-SCLC, the ICD codes were: 8041/3, 8042/3, 8043/3, and 8044/3. According to the Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) 7th edition TNM staging, Patients with stage IV were defined as extensive and the rest as limited. By accessing the SEER database for "Radiation sequence with surgery", "Chemotherapy recode (yes, no/unk)", and "RX Summ - Surg Prim Site (1998+)" in the SEER database to collect information about the patient's surgery, radiotherapy, and chemotherapy. We 2010 to 2020 screened 1114 patients diagnosed with C-SCLC and 57,776 patients diagnosed with P-SCLC. Included patients should meet the following criteria: pathologically confirmed diagnosis of C-SCLC and SCLC, active follow-up, only one primary tumor, and with or without surgical treatment,

radiotherapy, and chemotherapy. Patients with unknown TNM stage unknown treatment information or unknown diagnosis were excluded. Our study was mainly based on the SEER database. Institutional approval and patient consent were not required for disclosure of the database according to the regulations of Zhejiang Chinese Medical University and Zhejiang Provincial Hospital of Traditional Chinese Medicine.

2.2. Statistical analysis

Our comprehensive analysis encompassed a wide range of demographic and clinical variables for both C-SCLC and P-SCLC patients, such as age, gender, race, tumor size, primary tumor site, and degree of differentiation. To ascertain differences in continuous variables, we employed either the Student's T-test or the Mann-Whitney *U* test, contingent upon the Shapiro-Wilk test's determination of data normality. Categorical variables were analyzed using either the chi-square test or Fisher's exact test, depending on the data's characteristics.

To investigate the disparities in OS between patients with C-SCLC and P-SCLC, we utilized the Kaplan-Meier method for survival curve estimation and employed the log-rank test for comparative analysis.

In examining treatment strategies for C-SCLC patients, our initial approach involved a multifactorial COX regression model to evaluate all potential prognostic factors. Nevertheless, the detection of high correlation among predictor variables raised concerns about multicollinearity and overfitting within the regression model. To circumvent these issues, we applied random forest (RF) and LASSO regression analyses as methodological refinements to curb overfitting and pinpoint prognostic indicators. Following this, the COX regression model was refined to include factors identified by RF and LASSO regression, allowing for the calculation of adjusted odds ratios (OR, 95 % CI). Additionally, we constructed a prognostic nomogram to provide a visual representation of the prognostic factors.

The efficacy of the COX regression model's predictive capacity was evaluated through receiver operating characteristic (ROC) analysis and the construction of prognostic calibration curves. The model's predictive accuracy was further quantified by the area under the curve (AUC) values.

Given the substantial disparity in the sample sizes of patients with different histologic types within the database, we anticipated potential biases in our statistical outcomes. To mitigate this, propensity score matching (PSM) was employed, aiming to equalize the baseline characteristics between the C-SCLC and P-SCLC cohorts. This involved the generation of a propensity score (PS) for each patient based on variables including age, race, gender, tumor size, primary location, and degree of differentiation. A 1:1 matching ratio was implemented without replacement, applying a caliper width of 0.02 to ensure precision in the matching process.

Our analysis was conducted using SPSS 27.0 and R version 4.3.1, accessible at http://www.R-project.org/. This methodological framework was designed to ensure a rigorous and unbiased examination of the prognostic factors influencing overall survival among patients with C-SCLC and P-SCLC, thereby contributing to the refinement of treatment strategies for these distinct patient populations.

Table 1
Clinical characteristics of C-SCLC and P-SCLC patients.

	Crude cohort			PSM model		
Clinical features	C-SCLC (n = 1114)	P-SCLC (n = 57776)	P value (C-SCLC vs. P-SCLC)	C-SCLC (n = 986)	P-SCLC (n = 986)	P value (C-SCLC vs. P-SCLC)
Age,year						
Mean(SD)	68.51(9.461)	67.98(9.597)	0.070	68.54(9.332)	68.58(8.956)	0.903
Tumor size(mm)						
Mean(SD)	43.57(30.274)	51.48(36.245)	<0.001	44.66(30.621)	45.33(32.387)	0.667
Gender,n(%)						
Male	601(53.9 %)	28559(49.4 %)	0.003	536(54.4 %)	552(56.0 %)	0.469
Female	513(46.1 %)	29217(50.6 %)		450(45.6 %)	434(44.0 %)	
Race,n(%)						
White	932(83.7 %)	50214(86.9 %)	0.005	827(83.9 %)	850(86.2 %)	0.131
Black	119 (10.7 %)	4889(8.5 %)		102(10.3 %)	86(8.7 %)	
Other	63(5.7 %)	2586(4.5 %)		57(5.8 %)	47(4.8 %)	
Unknown	/	90(0.16 %)		/	3(0.3 %)	
Primary site,n(%)						
Main bronchus	53(4.8 %)	5964(10.3 %)	<0.001	49(5.0 %)	65(6.6 %)	0.563
Upper lobe	611(54.8 %)	26189(45.3 %)		540(54.8 %)	533(54.1 %)	
Middle lobe lung	37(3.3 %)	2331(4.0 %)		33(3.3 %)	39(4.0 %)	
Lower lobe	294(26.3 %)	11869(20.5 %)		255(25.95 %)	236(23.9 %)	
Overlapping	14(1.3 %)	809(1.4 %)		11(1.1 %)	9(0.9 %)	
Non-specific	105(9.4 %)	10714(18.5 %)		98(9.9 %)	104(10.5 %)	
Differentiation,n(%)						
Well	12(1.0 %)	52(0.1 %)	<0.001	1(0.1 %)	2(0.2 %)	0.210
Moderately	34(3.1 %)	84(0.14 %)		15(1.5 %)	6(0.6 %)	
Poorly	247(22.1 %)	3750(6.5 %)		218(22.1 %)	210(21.3 %)	
Undifferentiated	118(10.6 %)	5399(9.3 %)		98(9.9 %)	116(11.8 %)	
Unknown	703(63.1 %)	48491(84.0 %)		654(66.3 %)	652(66.1 %)	

Abbreviations: C-SCLC, combined small cell lung cancer; * represents P value < 0.05.

3. Results

3.1. Clinical characteristics of patients

We analyzed the differences in clinical characteristics between patients with C-SCLC and P-SCLC from 2010 to 2020. Finally, 57,776 P-SCLC patients and 1114 C-SCLC patients from the SEER database were included in the analysis. In the Crude cohort, males were in the majority among C-SCLC patients (53.9 % vs. 46.1 %) and females were in the majority among P-SCLC patients (50.6 % vs. 49.4 %). The mean age of C-SCLC patients was 68.51 ± 9.46 years and that of P-SCLC patients was 67.98 ± 9.60 years; The mean tumor size was 43.57 ± 30.27 (mm) in C-SCLC patients and 51.48 ± 36.25 (mm) in P-SCLC patients; the largest proportion of C-SCLC patients was white, followed by black and other (83.7 % vs. 10.7 % vs. 5.7 %), and the largest proportion of P-SCLC patients was also white, followed by black, Other and unknown (86.9 % vs. 8.5 % vs. 4.5 % vs. 0.16 %); the probability of tumor location in C-SCLC was from highest to lowest in the Upper lobe (54.8 %), Lower lobe (20.5 %), Non-specific (9.4 %), Main bronchus (4.8 %), Middle lobe (3.3 %), and Overlapping (1.3 %). In contrast, the probability of tumor location in P-SCLC patients from highest to lowest was Upper lobe (45.73 %), Lower lobe (20.5 %), Main bronchus (10.3 %), Non-specific (18.5 %), Middle lobe (4.0 %), and Overlapping (1.4 %). the probability of tumor differentiation in C-SCLC from highest to lowest was Unknown (63.1 %), Poorly (22.1 %), Undifferentiated (10.6 %), Moderately (3.1 %), and Well (1.0 %). the probability of P-SCLC tumor differentiation from high to low was Unknown (84.0 %), Undifferentiated (9.3 %), Poorly (6.5 %), Moderately (0.14 %), and Well (0.1 %). Compared with C-SCLC patients, P-SCLC patients were statistically different in age ($P = 0.070$), gender ($P = 0.003$), tumor size ($P < 0.001$), race ($P = 0.005$), tumor location and tumor differentiation ($P < 0.001$); in the PSM model, there were no statistical differences in all characteristics, and these patients' Baseline characteristics are shown in Table 1.

3.2. Comparing the survival of patients with C-SCLC and P-SCLC

We applied the Kaplan-Meier analysis and log-rank test to compare the survival differences between patients with C-SCLC and P-SCLC. We screened patients before stage IV as limited-stage patients. Patients with early-stage (stage IA-IIA) C-SCLC had a better prognosis after surgery than P-SCLC ($P = 0.054$) (Fig. 1A); patients with limited-stage C-SCLC treated with systemic chemotherapy had longer survival than patients with P-SCLC ($P = 0.001$) (Fig. 1B); and among patients treated with chemoradiotherapy, C-SCLC also had

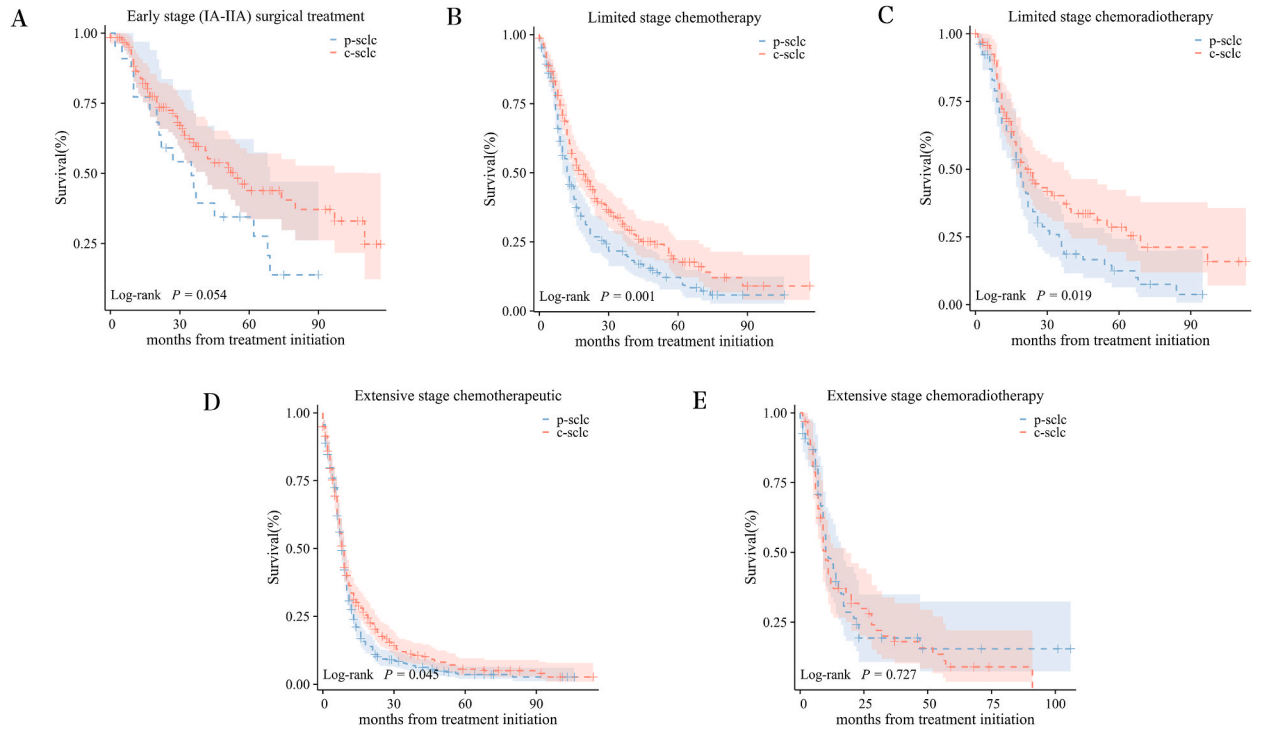

Fig. 1. Comparison of the difference in survival rates between C-SCLC and P-SCLC patients.
Fig. 1A: Difference in survival after surgery between patients with early-stage (stage IA-IIA) C-SCLC and patients with P-SCLC; Fig. 1B: Difference in survival after receiving systemic chemotherapy between patients with limited stage C-SCLC and patients with P-SCLC; Fig. 1C: Difference in survival after receiving chemoradiotherapy between patients with limited stage C-SCLC and patients with P-SCLC; Fig. 1D: Difference in survival rates between extensive-stage C-SCLC patients and P-SCLC patients after receiving systemic chemotherapy; Fig. 1E: Difference in survival rates between extensive-stage C-SCLC patients and P-SCLC patients after receiving chemoradiotherapy.

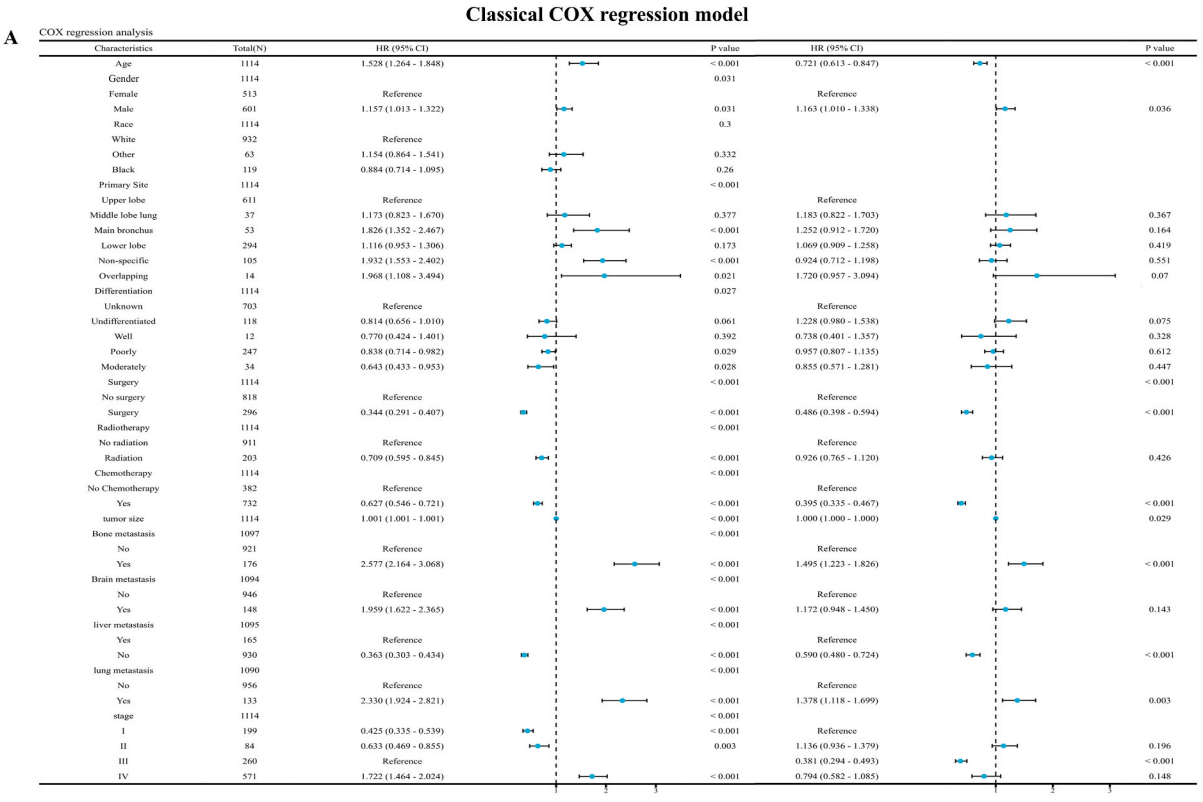

Fig. 2. COX regression model, prognostic nomogram, and validation curves for C-SCLC patients
Fig. 2A: COX regression model for C-SCLC; Fig. 2B: Nomograms predicting 1-, 3-, and 5-year survival probabilities for patients with C-SCLC; Fig. 2C: ROC for the nomogram; Fig. 2D: Prognostic calibration curves for the nomogram at 1-year; Fig. 2E: Prognostic calibration curves for the nomogram at 3-year; Fig. 2F: Prognostic calibration curves for the nomogram at 5-year.

longer survival than P-SCLC patients (P = 0.019) (Fig. 1C). We also screened stage IV patients as an extensive stage. In patients with extensive-stage systemic chemotherapy, C-SCLC had a better prognosis than P-SCLC, and no significant difference in OS was seen in patients treated with chemoradiotherapy (P = 0.045, P = 0.727) (Fig. 1D and E).

Comparison of treatment regimens and survival prediction in patients with C-SCLC To further explore treatment strategies for patients with C-SCLC, patients were divided into two groups based on survival outcomes, and a classical COX regression model was established based on survival status and overall survival time. The relevant risk factors were first included in the univariate COX regression model, and then the risk factors with P < 0.05 were included in the multivariate regression model. We found age (P < 0.001), gender (P = 0.036), surgery (P < 0.001), chemotherapy (P < 0.001), bone metastasis (P < 0.001), liver metastasis (P < 0.001), and lung metastasis (P = 0.003) to be independent predictors (Fig. 2A), and plotted nomograms predicting the probability of 1-, 3-, and 5-year survival .The predictive effect of the nomograms was assessed by plotting nomograms predicting 1-, 3-, and 5-year survival probabilities (Fig. 2B) and ROC. In the ROC curve, the AUC values were also used to assess the prediction performance in training, and the AUC values were 0.814, 0.819, and 0.779, respectively, showing strong prediction performance (Fig. 2C). The 1-, 3-, and 5-year calibration curves showed no significant deviation from the reference line, indicating relatively good agreement between the model predictions and the observed results(Fig. 2D; Fig. 2E; Fig. 2F).

To find out the most effective predictors, we will construct a Random Forest model and a LASSO regression model for prognostic factor screening respectively, and construct a multi-factor COX regression model again based on the screened predictors. A random forest model consisting of 500 decision trees was first constructed. The importance of the variables was thoroughly assessed by summarizing the decision results of all 500 trees. The resulting ranking of the variables is shown in Fig. 3A. The top 50 % of variables, i.e., gender, age, primary site, differentiation status, surgery, chemotherapy, tumor size, and stage were selected, and all selected factors were included in the multifactorial COX model. The relationship between prognostic variables and mortality is shown in Fig. 3B. Nomograms predicting 1-, 3-, and 5-year survival probabilities were constructed based on the COX model (Fig. 3C), and ROC curve and

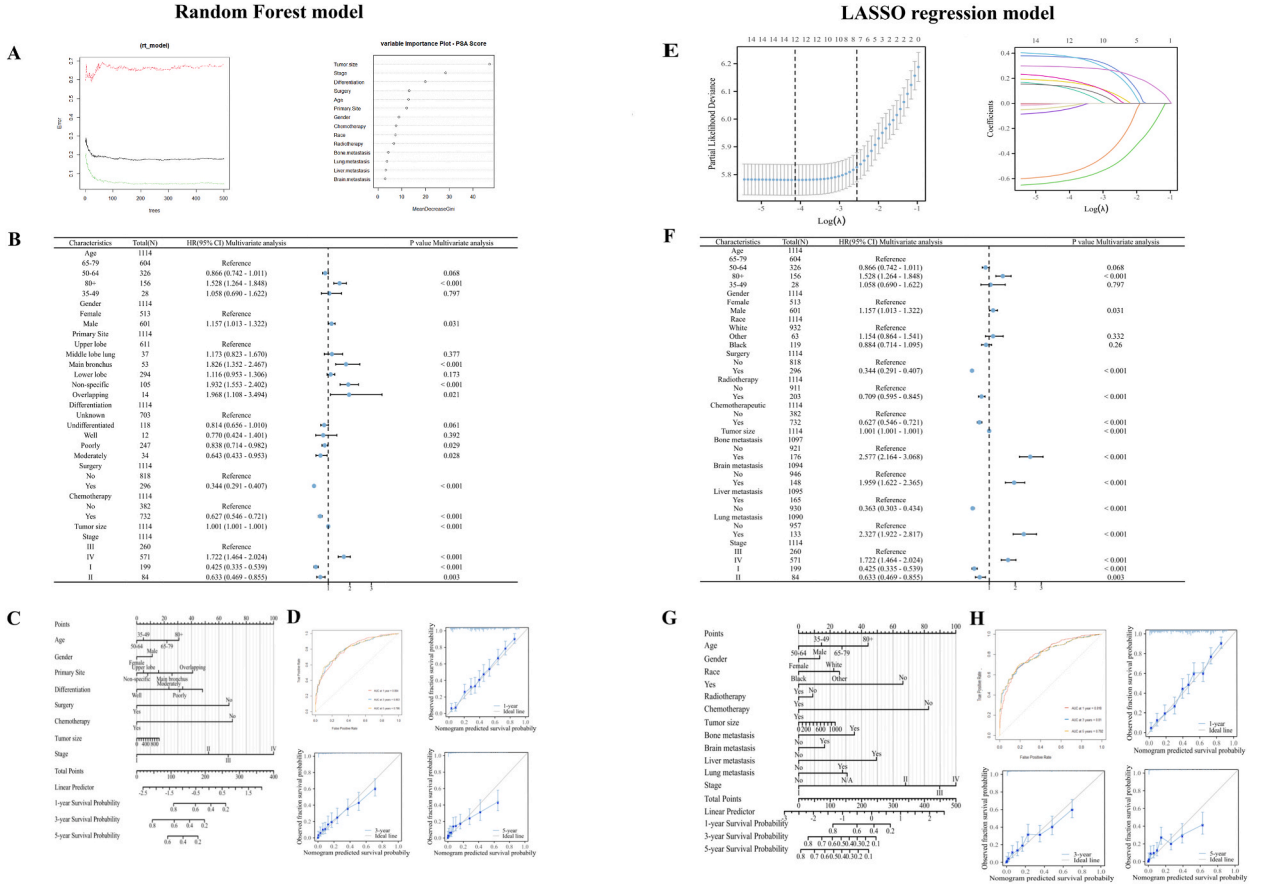

Fig. 3. Comparison of random forest model and LASSO regression model building and prediction
Fig. 3A: Random forest model building and selecting prognostic factors; Fig. 3B: COX regression model building according to the random forest model; Fig. 3C: Nomogram constructed according to the COX model for predicting the probability of survival at 1-, 3-, and 5-years; Fig. 3D: ROC and prognostic calibration curves at 1-, 3-, and 5-years of the nomogram; Fig. 3E: LASSO regression model building and selecting prognostic factors; Fig. 3F: COX regression model based on LASSO regression model; Fig. 3G: Nomogram for predicting 1-, 3-, and 5-year survival probabilities was constructed based on LASSO regression model; Fig. 3H: ROC and 1-, 3-, and 5-year prognostic calibration curves for nomogram.

prognostic calibration curves were created to assess the predictive effect of the nomograms. In the ROC curve, the AUC values were also used to assess the prediction performance in training, and the AUC values were 0.804, 0.803, and 0.786, respectively, which showed strong prediction performance (Fig. 3D). Then, we constructed the LASSO regression model with 14 independent candidate variables (Fig. 3E), and to obtain a simpler and more interpretable model, we used to log(λ) values selected by one standard error of the minimum criterion and chose variables with non-zero coefficients. Finally, we selected 12 predictors (i.e., age, gender, race, surgery, radiotherapy, chemotherapy, tumor size, bone metastasis, liver metastasis, brain metastasis, lung metastasis, and stage) in a multivariate COX regression analysis. The relationship between prognostic variables and mortality is shown in Fig. 3F. These important variables mentioned above were incorporated into the final 1-, 3-, and 5-year OS prognostic models and are shown in the form of nomograms (Fig. 3G). ROC curve and prognostic calibration curves were plotted. In the ROC curve, the AUC values were 0.818, 0.81, and 0.792, respectively, showing strong predictive performance (Fig. 3H).

As shown by Cox regression analysis, we found that surgery, radiotherapy, and chemotherapy were all beneficial to prognosis. In this regard, we performed a subgroup analysis of patients with C-SCLC, first classifying patients into limited and extensive stages (staging principles as before). In patients with limited stage, those who received surgery in the early stage (stage IA-IIA) had better OS than those who did not ($P < 0.001$) (Fig. 4A); there was no difference in the OS of patients who received the chemoradiotherapy and alone ($P = 0.121$) (Fig. 4B). However, in the extensive stage, there was a significant difference in survival between patients treated with chemoradiotherapy and chemotherapy alone, and the prognosis of the combination regimen was better than that of the chemotherapy regimen alone ($P = 0.022$) (Fig. 4C).

4. Discussion

In this research, the study population comprised 57,776 patients diagnosed with P-SCLC and 1114 patients with C-SCLC, as recorded in the SEER database. The cohort of patients with C-SCLC demonstrated an average age of 68.5 years and an average tumor size of 43.57 mm, predominantly consisting of white males with tumors located in the upper lobe and classified as poorly differentiated. Conversely, the cohort of patients with P-SCLC had an average age of 67.98 years and an average tumor size of 51.48 mm, primarily including white females with upper lobe tumors and poor differentiation. This study sought to assess the influence of different histological subtypes on OS through KM analysis. Findings revealed that individuals with C-SCLC experienced a longer OS following systemic chemotherapy, early surgical intervention, and limited-stage chemoradiotherapy compared to those diagnosed with P-SCLC. Moreover, a COX regression model was constructed for patients with C-SCLC after multi-model selection to identify independent prognostic factors, including age, gender, surgical intervention, chemotherapy, and the presence of metastases in bone, liver, and lung. Factors such as age, gender, stage of disease, tumor size, surgical treatment, radiotherapy, and chemotherapy were all significantly correlated with patient outcomes. Subgroup analyses were consequently conducted to further examine the effects of various treatment modalities, highlighting that early surgical intervention and comprehensive phase chemoradiotherapy were linked to improved OS. This led to an investigation into the underlying causes of the pronounced disparities observed between different histological types.

Currently, there is a lack of explicit, universally accepted guidelines for the tailored treatment of C-SCLC. Typically, the therapeutic approach for C-SCLC adheres to the general guidelines for SCLC, encompassing a multimodal strategy that includes surgery, radiotherapy, and chemotherapy. An analysis of treatment modalities for patients with C-SCLC in our research suggests that early surgical intervention is advantageous for prognosis and yields better outcomes compared to treatments for P-SCLC patients. This finding is consistent with the results presented in the clinical study conducted by Babakoohi et al. [7].

Chemotherapy serves as a foundational aspect of SCLC management. However, the effectiveness of systemic chemotherapy varies significantly among patients with different histological subtypes of SCLC. Our research findings indicate that patients with C-SCLC exhibit a higher sensitivity to chemotherapy compared to those with P-SCLC. This observation is contrasted by the hypothesis proposed by Men et al., which suggests that the reduced responsiveness to chemotherapy in C-SCLC patients may be attributed to the presence of

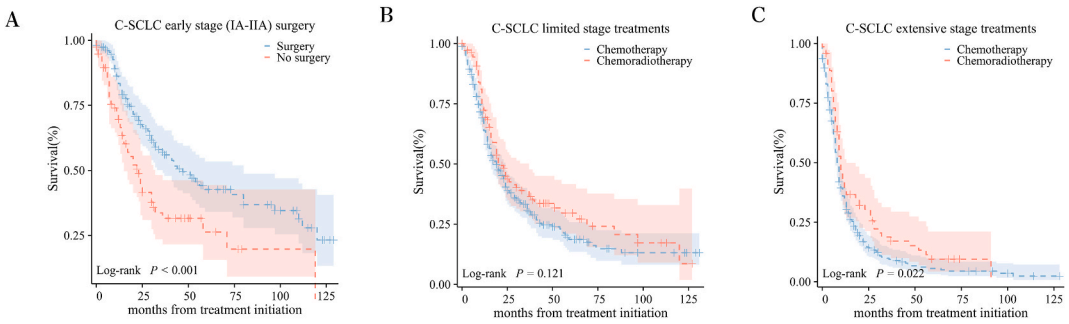

Fig. 4. Comparison of survival rates of C-SCLC patients under different treatment regimens
Fig. 4A: Difference in the survival of early-stage (stage IA-IIA) C-SCLC patients treated with or without surgery; Fig. 4B: Difference in the survival of patients with limited-stage C-SCLC treated with chemoradiotherapy and chemotherapy alone; Fig. 4C: Difference in the survival of patients with extensive-stage C-SCLC treated with chemoradiotherapy and chemotherapy alone.

NSCLC components within the tumor. This highlights the complexity of treating C-SCLC and underscores the necessity for a nuanced understanding of the tumor's histological makeup in devising effective treatment strategies [8]. Consequently, it is imperative to account for both SCLC and NSCLC components when formulating personalized chemotherapy regimens for C-SCLC patients. This approach is substantiated by a previous retrospective study that assessed the effectiveness of two chemotherapy protocols—NIP (navelbine, isocyclophosphamide, and cisplatin) versus EP (etoposide and cisplatin)—as primary treatments for patients with stage III-IV C-SCLC. The findings revealed that the EP regimen offered superior survival advantages compared to the NIP regimen [9]. This suggests that the NIP regimen may be less effective than the EP regimen for treating C-SCLC, highlighting the importance of selecting the most efficacious chemotherapy regimen based on the specific histological characteristics of the tumor [10].

Our analysis extends to additional systemic therapeutic strategies, particularly in the context of C-SCLC cases presenting with positive mutations in driver genes, which are relatively rare. Specifically, mutations in the EGFR serve as a potential biomarker. Prior research has indicated that EGFR mutations occur in less than 5 % of pure SCLC cases and between 15 and 20 % of C-SCLC cases [10–12]. A comprehensive review highlighted 27 patients with de novo SCLC harboring EGFR mutations; of these, 37 % were identified as C-SCLC, including mixed ADC in 9 cases and SCC in 1 case [13]. Additionally, case studies have corroborated the rarity of EGFR mutations in SCLC, while such mutations are more frequently observed in C-SCLC, particularly when associated with ADC [14].

Emerging evidence suggests that TKIs may offer superior efficacy and a more favorable side effect profile compared to conventional chemotherapy in treating EGFR mutation-positive SCLC [15–19]. In a study conducted in Zhejiang Provincial Cancer Hospital, China, 31 C-SCLC patients with driver gene-positive mutations demonstrated that a treatment regimen combining chemotherapy with targeted therapy yielded the longest median progression-free survival (PFS), surpassing the efficacy of first-line chemotherapy alone. Consequently, for patients with driver gene-positive C-SCLC, it is advocated that targeted therapy be considered as an adjunct to the standard treatment protocol, highlighting the significance of genetic profiling in optimizing therapeutic outcomes for this patient subgroup [20].

The histological origin of C-SCLC remains uncertain. Investigative studies employing loss of heterozygosity (LOH) analysis to assess the clonality of the SCLC and non-SCLC components in C-SCLC have provided insights into their possible shared origins. The detection of multiple concordant LOH events across different chromosomal arms suggests a clonal relationship between the two histological components of C-SCLC. Specifically, the observation of identical LOH in two separate chromosomal arms in the majority of C-SCLC cases indicates a close genotypic association between the SCLC and non-SCLC components, implying they may originate from a common clonal precursor. Furthermore, the discovery of deletions in the region 22q13.3, which is frequently lost in SCLC and to a lesser extent in NSCLC (<20 %), adds another layer of complexity. The high frequency of 22q13.3 deletions in C-SCLC cases reinforces the notion that C-SCLC is genetically more akin to SCLC than to NSCLC. This genetic evidence supports the hypothesis that C-SCLC may share a closer relationship with SCLC, suggesting a potential commonality in their origins and providing a rationale for considering targeted therapeutic strategies that address this unique genetic landscape [21].

The variance in prognosis among different histological subtypes of lung cancer may be attributable to distinct molecular mechanisms underlying each subtype. One such pathway involves the Hippo signaling pathway, known for its role in regulating cell proliferation, apoptosis, stem/progenitor cell expansion, and organ size. At the heart of this pathway lies YAP1 (Yes-associated protein 1), a downstream nuclear effector, which traditionally functions as part of a classical tumor suppressor pathway. Its relevance as a tumor marker linked to drug sensitivity has been recognized in various cancers, including both NSCLC and SCLC.

In the context of C-SCLC, YAP1 expression has been observed to be higher in the small cell component compared to P-SCLC, correlating with significantly worse OS in C-SCLC patients who are YAP1-positive. This association suggests that YAP1 overexpression in C-SCLC may lead to disruption of the Hippo pathway, contributing to the poorer prognosis observed in these patients [22]. Interestingly, YAP1 expression does not appear to significantly impact the prognosis of P-SCLC patients, indicating a potential differential role of YAP1 between the histological subtypes.

This differential expression and impact on chemotherapy response and resistance between C-SCLC and P-SCLC underscore the potential of YAP1 as a therapeutic target, particularly in C-SCLC patients exhibiting high YAP1 expression. Furthermore, the involvement of YAP1 in drug metabolism and its effect on chemotherapy sensitivity in SCLC cell lines suggest that targeting YAP1 could offer a novel approach to treating C-SCLC, especially for those patients showing primary resistance to conventional chemotherapy [23,24]. The observation of varying OS between YAP1-positive and YAP1-negative P-SCLC patients receiving adjuvant chemotherapy further supports the exploration of YAP1-targeted therapies, potentially paving the way for more personalized treatment strategies in lung cancer [25].

5. Conclusions

In summary, our study utilized the SEER database to compare the OS of patients with P-SCLC and C-SCLC. Our findings revealed significant differences in OS following early surgery or chemotherapy alone and limited-phase combined chemo-radiotherapy. In addition, we compared the prognosis of different treatment strategies in patients with C-SCLC, and our results suggest that the combination of early surgery and extensive phase radiotherapy chemotherapy may offer potential benefits to patients. However, there is still a lack of high-level clinical trial studies to compare the prognosis of patients with P-SCLC and C-SCLC, especially the prognosis of patients with C-SCLC with different pathologic components should be observed, and whether different pathologies should be treated with different drugs and the related prognosis need to be further studied. We believe that well-planned and personalized multimodal therapy based on pathology will probably improve the prognosis of patients.

6. Limitations

The database study is a type of retrospective study, and although the data sample size is larger, there is still a risk of bias compared to prospective studies. As C-SCLC is a clinically rare type of pathology, we were unable to collect clinical information on real-world patients through hospitals and therefore lacked external validation. This study only applied a single database, which is a risk of bias. It was not possible to collect information on specific pathologies, such as the specific histologic occupancy, and the occupancy of different histologic components may be an important reason to influence the prognosis.

Ethics approval and consent to participate

Review and/or approval by an ethics committee was not needed for this study because article data from publicly available databases are exempt from ethical review.

Consent for publication

Not applicate.

Data availability statement

The datasets generated and/or analyzed in this study are available from the SEER database (http://seer.cancer.gov/).

CRediT authorship contribution statement

Jiaping Liu: Formal analysis, Data curation, Conceptualization. **Yu Cao:** Software, Resources, Project administration. **Tianyu Shao:** Visualization, Validation, Supervision. **Yuguan Wang:** Funding acquisition.

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.

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