Clin. Lab. 2024;70:XXX-XXX

ORIGINAL ARTICLE

Aspartate Transaminase-to-Albumin Ratio (ATAR), a Novel Prognostic Index, Predicts Outcomes in Patients with Small-Cell Lung Cancer

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SUMMARY

Background: **Small cell lung cancer (SCLC) is characterized by high invasion rates, rapid progression, and poor prognoses. Thus, identifying SCLC patients at high risk of progression and death is critical to improve long-term survival. In this study, the aspartate transaminase-to-albumin ratio (ATAR) was examined as a prognostic factor for SCLC patients.**

Methods: **We screened 196 SCLC patients from December 2013 to September 2022 at the Sichuan Cancer Hospital. The data was collected from patients' medical information as well as from their blood results during diagnosis. Using the Youden index as a cutoff value, patients were divided into high-risk (> 0.54) and low-risk (≤ 0.54) ATAR groups. We analyzed the prognostic factors for overall survival (OS) using the Kaplan-Meier method, univariate and multivariate analyses, Cox regression, and the C-index.**

Results: **There were 109 (55.6%) smokers among the patients, and the median OS was 17.55 months. The Kaplan-Meier analysis indicated that patients with high-risk ATAR had significantly lower OS ($p < 0.0001$). A multivariate analysis demonstrated that elevated ATAR is an independent adverse predictor of OS ($p < 0.001$, HR = 1.907). Our study found that ATAR is an independent predictor of survival outcomes in SCLC, which was superior to ALB, PNI, and SII in predicting outcomes in low-risk and high-risk groups (all $p < 0.05$). Models combining ATAR with ALB, PNI, and SII showed more powerful prognostic value than their corresponding original models. Moreover, the prognostic indicator ATAR can significantly stratify stage I - II and III - IV SCLC patients ($p < 0.05$).**

Conclusions: **Peripheral blood ATAR prognostic index can be used as an independent predictor of SCLC patients before treatment.**

(Clin. Lab. 2024;70:xx-xx. DOI: 10.7754/Clin.Lab.2023.230943)

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Manuscript accepted December 22, 2023

KEYWORDS

aspartate transaminase-to-albumin ratio (ATAR), small cell lung cancer (SCLC), predictor, survival

LIST OF ABBREVIATIONS

SCLC - small cell lung cancer
NSCLC - non-small-cell lung cancer
ATAR - Aspartate transaminase-to-albumin ratio
ALB - Albumin
PNI - prognostic nutritional index
SII - systemic immune-inflammation index
TNM - tumor node
CT - chemotherapy
RT - radiotherapy
CRT - concurrent chemoradiotherapy
IT - immunotherapy

INTRODUCTION

Globally, lung cancer accounts for approximately 11.6% of all cancer types and is one of the leading causes of death from solid tumors [1,2]. As a subtype of lung cancer, small cell lung cancer (SCLC) accounts for 15% [3]. SCLC is an aggressive tumor characterized by rapid doubling time, high proliferation fraction, and early progression of widespread metastases [4]. Based on the extent of progression, SCLC can be classified into limited disease (LD) and extensive disease (ED) [5], the latter being associated with poor outcomes [6]. Approximately 70% of SCLC patients reach ED at diagnosis. Initially, chemotherapeutic and radiotherapeutic treatments are effective in treating SCLC [7,8]. Most SCLC patients suffer a poor prognosis, with a 5-year survival rate of only 7% for patients who relapse within one year after initial treatment [9]. Thus, making an early, accurate prediction of patients' prognoses is imperative to determining the most suitable risk stratification and treatment plan for each individual.

Several clinical indicators are associated with prognosis in SCLC patients. Among them, the TNM Classification of Malignant Tumors is a vital predictor of overall survival (OS) in SCLC patients [10]. Despite this, the issue of adding other non-TNM indicators to risk stratification remains controversial. Numerous tumors with malignancy are correlated with inflammation that contributes to carcinogenesis and prognosis [11]. In recent studies, factors associated with immunity, inflammation, nutritional status, and liver function have been demonstrated to play a significant role in tumor prognosis. Some of these factors include the systemic immune-inflammation index (SII) [12], and the prognostic nutritional index (PNI) [13]. The poor prognosis of SCLC, however, has not improved significantly over the past few decades [14], and the optimal prognostic factors remain controversial [15]. Additionally, multi-center research is currently needed to confirm the association between PNI, SII, and SCLC survival, and to investigate more convenient, practical, and efficient clinical indicators to resolve clinical problems related to SCLC prognosis.

The liver is the most common site of metastasis in small cell lung cancer [16], and a significant number of patients have liver metastases at the time of diagnosis. If extensive liver metastasis occurs, the disease progresses rapidly and survival is short [17,18]. In addition, as a high-grade neuroendocrine carcinoma, most of the abnormal hormones secreted by SCLC are metabolized by the liver, and will enter the systemic circulation when liver metastasis occurs, resulting in poor prognosis of patients [19]. Injuries to liver function can result from liver metastases. The liver function test, which is a common routine blood test that assesses the liver's function, is one of the routine examinations that are completed prior to surgery. Aspartate aminotransaminase (AST) is mainly distributed in hepatocyte mitochondria, and a few are distributed in cytoplasm. If the concentration of AST is found to increase in the liver function test, it may indicate that hepatocyte damage is relatively serious, or that the mitochondria of hepatocytes are mainly damaged and invaded, such as by the use of alcohol [20]. Albumin (ALB) is a protein that makes up about half of the serum proteins. It is synthesized in the liver. Several research studies have suggested that ALB is involved in scavenging free radicals, maintaining colloid osmotic pressure, and protecting neuronal cells, and that it is closely related to nutritional status and systemic inflammation [21]. Continually undernourished cancer patients suffer from poor quality of life, leading to treatment delays or even treatment discontinuity, which has a detrimental effect on their chances of survival. Numerous studies have confirmed the association between ALB alone or based markers and survival in various types of cancer [21-24]. Therefore, we propose the hypothesis that aspartate transaminase-to-albumin ratio (ATAR) can be used as a fast and effective indicator for SCLC prognosis stratification to solve the problem of prognosis stratification.

In our study, we retrospectively analyzed the clinical data of 196 SCLC patients before operation or treatment and explored the clinical significance of ATAR as a predictor of prognosis in small cell lung cancer and its relationship with OS. For further validation, we conducted another test on whether PNI and SII can predict the prognosis of SCLC patients, hoping to provide a reasonable reference for decision-making in clinical practice and aid further research on SCLC.

MATERIALS AND METHODS

Study population

An informed consent exemption statement was completed for this retrospective study. The inclusion criteria were the following: 1) confirmed diagnosis of SCLC

with histopathological methods; 2) blood analysis performed before surgery or treatment; 3) available follow-up data and clinical information. Exclusion criteria include: 1) a severe cardio-cerebrovascular disease or other disease with a potential impact on the prognosis, and 2) failure to follow up on the patient or incomplete patient medical records.

We retrieved all lung cancer cases from 2013 to September 2022 through the follow-up system at Sichuan Cancer Hospital to avoid omitting cases. A total of 2,832 cases of lung cancer were confirmed by pathology with complete follow-up information. Among these, 210 cases were confirmed as SCLC by histopathology. The first measurement is chosen from the patient's clinical laboratory information system if there are multiple measurements. We excluded 14 instances of repeated measurements. The study flow chart is shown in Figure 1. Ultimately, 196 SCLC patients were enrolled in the study.

Clinical data collection

Following treatment protocol, patients were monitored every 3 months for the first 2 years, every 6 months for the next 2 to 5 years, and every 1 year afterward. To obtain survival information, medical records were examined or telephone interviews were conducted. In this study, the primary endpoint was OS, which is defined as the period of time from the time of diagnosis until the date of death or the last follow-up. Information on demographics and clinical characteristics was extracted from the electronic medical records of the Sichuan Cancer Hospital. This includes gender, age, smoking history, tumor location, TNM stage, treatment method, chemotherapy cycle, and OS. TNM staging was based on the 8th edition of the classification system. In this study, laboratory data related to AST, ALB, platelet count (PLT), neutrophil count (NEUT), and lymphocyte count (LY) were retrieved from medical records. Preoperative laboratory data were obtained from the clinical laboratory. Complete blood count was measured with Mindray BC-6800 (Shenzhen, China) using the manufacturer's kit. Blood biochemical examination was performed using the Beckman Coulter AU5800 analyzer (Brea, CA, USA) and manufacturer's kits. PNI and SII were calculated as followed:

PNI = 10 × ALB (g/L) + 0.005 × NEUT (10^9/L) [25,26]

SII = PLT (10^9/L) × NEUT (10^9/L)/LY (10^9/L) [27].

This study was approved by the Medical Committee of Sichuan Cancer Hospital (No. KY-2021-076). We confirm the confidentiality of the data maintained, and compliance with the "Declaration of Helsinki".

Treatment

As recommended by the NCCN (National Comprehensive Cancer Network) Clinical Practice Guidelines in Oncology (NCCN guidelines), patients with stage T1-2N0M0 LS-SCLC are suitable for radical surgery and platinum-based chemotherapy as adjuvant therapy. A platinum-based chemotherapy regimen should be used concurrently with radiation for SCLC that has progressed beyond T1-2N0. In cases of extensive-stage SCLC, chemotherapy or combined immunotherapy is recommended [28]. Chemotherapy regimens include EP, EC, irinotecan combined with cisplatin (IP), irinotecan combined with carboplatin (IC), and etoposide combined with lobaplatin (EL). For patients with recurrence or progression within 6 months after first-line chemotherapy, second-line treatments (irinotecan, gemcitabine, vinorelbine, or paclitaxel, etc.) are available.

Statistical analysis

Variables in the categorical category are represented as numbers and percentages, and groups are compared using the χ^2 test or Fisher's exact test. In accordance with the normal distribution, continuous variables are presented as the means ± the SDs. The variables that did not follow a normal distribution were expressed as median and interquartile ranges (IQR), and Mann-Whitney U tests were used to identify differences. Statistics were performed using the SPSS 26.0 software (IBM SPSS Statistics for Windows; IBM Corp., Armonk, NY, USA). The Kaplan-Meier method was used to draw the survival rate curves, and the log-rank test was used to compare the differences between the curves. Prognostic variables were evaluated using univariate and multivariate Cox proportional hazards models. The C statistic with concordance index (C-index) was utilized to investigate discrimination in survival data [29]. By estimating the probability of concordance between predicted and observed outcomes, the C-index can be used to evaluate a model's ability to classify individual patients into risk groups with different prognoses. Previous studies believe that a C-index between 0.50 and 0.70 is of low accuracy, and between 0.71 - 0.90 is of medium accuracy. Higher than 0.90 indicates high accuracy [30]. We calculated the C-index using the Hmisc R package in R software version 3.2.3. The survival and prognostic data were plotted using Hiplot Pro [31]. A two tailed p-value < 0.05 was considered statistically significant.

RESULTS

Clinical characteristics of selected patients

Table 1 shows the baseline characteristics of 196 SCLC patients, and the relationship between the high-risk and low-risk ATAR groups. In the study population, there were 141 (71.9%) males and 55 (28.1%) females, with a median age of 60.5 years (range: 28 - 79 years). Smokers accounted for the majority of the patients (n = 109, 55.6%). Right-sided tumors account for 52.6% of SCLC cases. Similarly, the staging was conducted in accordance with the staging criteria established by TNM. In total, 78 lesions (39.8%) were graded I - II and 105 (53.6%) were graded III - IV. There were 58 (29.6%) patients without node metastases, and there were 123 (61.8%) patients with node metastases. 131 patients (66.8%) had no distant metastases, while 53 patients

Table 1. Basic characteristics of patients with SCLC by ATAR level.

Characteristics	Overall	ATAR ≤ 0.54	ATAR > 0.54	p-value
	(n = 196)	(n = 86)	(n = 110)	
Age median (IQR), year	60.50 (53.00 - 68.00)	62.00 (52.00 - 66.25)	60.00 (54.00 - 68.00)	0.245
Gender				
Male	141 (71.9)	48 (55.8)	93 (84.5)	< 0.001
Female	55 (28.1)	38 (44.2)	17 (15.5)	
Smoking history				
Never	87 (44.4)	52 (60.5)	35 (31.8)	< 0.001
Ever	109 (55.6)	34 (39.5)	75 (68.2)	
Tumor location				
Left	93 (47.4)	42 (48.8)	51 (46.4)	0.732
Right	103 (52.6)	44 (51.2)	59 (53.6)	
T stage				
I - II	78 (39.8)	35 (40.7)	43 (39.1)	0.551
III - IV	105 (53.6)	47 (54.7)	58 (52.7)	
Uncertain	13 (6.6)	4 (4.7)	9 (8.2)	
Node metastasis				
No	58 (29.6)	30 (34.9)	28 (25.5)	0.040
Yes	123 (62.8)	53 (61.6)	70 (63.6)	
Uncertain	15 (7.7)	3 (3.5)	12 (10.9)	
Distant metastasis				
No	131 (66.8)	71 (82.6)	60 (54.5)	< 0.001
Yes	53 (27.0)	12 (14.0)	41 (37.3)	
Uncertain	12 (6.1)	3 (3.5)	9 (8.2)	
TNM stage				
I	25 (12.8)	13 (15.1)	12 (10.9)	0.001
II	23 (11.7)	15 (17.4)	8 (7.3)	
III	77 (39.3)	41 (47.7)	36 (32.7)	
IV	54 (27.6)	12 (14.0)	42 (38.2)	
Uncertain	17 (8.7)	5 (5.8)	12 (10.9)	
Staging				
Limited stage	125 (63.8)	69 (80.2)	56 (50.9)	< 0.001
Extensive stage	54 (27.6)	12 (14.0)	42 (38.2)	
Uncertain	17 (8.7)	5 (5.8)	12 (10.9)	
Treatment				
Surgery/CT/RT	43 (21.9)	25 (29.1)	18 (16.4)	0.611
CT/RT/CRT/IT	97 (49.5)	41 (47.7)	56 (50.9)	
Uncertain	56 (28.6)	20 (23.3)	36 (32.7)	
Event				
Alive	65 (33.2)	42 (48.8)	23 (20.9)	< 0.001
Dead	131 (66.8)	44 (51.2)	87 (79.1)	
Time median (IQR), month	17.55 (8.27 - 39.64)	36.70 (11.89 - 49.73)	13.59 (6.50 - 33.00)	0.003
Chemo-cycle median (IQR), week	4.00 (2.00 - 6.00)	4.00 (2.00 - 8.00)	5.00 (2.00 - 6.00)	0.218
PNI median (IQR)	401.01 (378.26 - 435.76)	408.01 (385.01 - 443.01)	392.51 (372.01 - 431.01)	0.023
SII median (IQR)	593.62 (390.65 - 846.05)	579.97 (389.66 -7 97.27)	610.32 (391.80 - 943.82)	0.209

The underlined p-value less than 0.05 was considered statistically significant. IQR - interquartile range.

Table 2. Univariate and multivariate analysis of overall survival.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Age (≤ 60 vs. > 60)	1.625 (1.149 - 2.298)	0.006		
Gender (male vs. female)	0.695 (0.464 - 1.041)	0.077		
Smoking history (never vs. ever)	1.636 (1.147 - 2.333)	0.007	1.650 (1.142 - 2.385)	0.008
Tumor location (left vs. right)	1.043 (0.740 - 1.470)	0.811		
T stage (I - II vs. III - IV, uncertain)	1.601 (1.111 - 2.306)	0.012		
Node metastasis (no vs. yes, uncertain)	1.824 (1.212 - 2.744)	0.004		
Distant metastasis (no vs. yes, uncertain)	1.660 (1.166 - 2.363)	0.005		
TNM stage (I/II vs. III/IV/uncertain)	2.696 (1.671 - 4.350)	< 0.001	2.073 (1.058 - 4.063)	0.034
Staging (limited stage vs. extensive stage/uncertain)	1.342 (1.054 - 1.709)	0.017		
Treatment (surgery/CT/RTI vs. CT/RT/CRT/IT, uncertain)	0.516 (0.323 - 0.824)	0.006		
Chemo-cycle (continuous)	0.892 (0.824 - 0.965)	0.005		
ATAR (continuous)	2.341 (1.712 - 3.203)	< 0.001	1.907 (1.383 - 2.631)	< 0.001
PNI (continuous)	0.990 (0.986 - 0.994)	< 0.001	0.994 (0.990 - 0.998)	0.002
SII (continuous)	1.000 (1.000 - 1.001)	0.005		

The underlined p-value less than 0.05 was considered statistically significant. HR - hazard ratio, CI - confidence interval.

Table 3. C-index for discriminatory values on survival.

	C-index for OS	C-index for OS (stage I-II SCLC)	C-index for OS (stage III - IV SCLC)
ALB	0.320	0.249	0.378
ALB + ATAR	0.747	0.821	0.686
PNI	0.319	0.249	0.377
PNI + ATAR	0.747	0.821	0.686
SII	0.602	0.786	0.503
SII + ATAR	0.707	0.871	0.627
TNM	0.661	0.518	0.532
TNM + ATAR	0.705	0.736	0.624

(27.0%) had distant metastases. There were 25 (12.8%) tumors classified as stage I, 23 (11.7%) as stage II, 77 (39.5%) as stage III, and 54 (27.5%) as stage IV. Based on clinical and pathological findings, 125 tumors (63.8%) were classified as limited stage, and 54 tumors (27.6%) were classified as extensive stage. All patients were followed up for an average of 17.55 months. 131 patients (66.8%) died during this period. In terms of chemotherapy cycles, the median number of cycles was four (range: 1 - 16 cycles).

Male patients are significantly more likely to have high-risk ATAR compared with low-risk patients (84.5% vs. 55.8%, respectively, $p < 0.001$). Smoking cases among the high-risk group are significantly higher than those among the low-risk group (68.2% and 39.5%, respectively, $p < 0.001$). ATAR prognostic factors are related to node metastases, distant metastases, and TNM stage and staging. Significantly more node metastases occurred in the high-risk group than in the low-risk group (63.6% and 61.6%, respectively, $p = 0.040$). There are significantly more distant metastasis cases among the high-risk group than among the low-risk group (37.3% vs. 14.0%, respectively, $p < 0.001$), as well as significantly more cases of extensive stages in the high-risk group (38.2% vs. 14.0%, respectively, $p < 0.001$). High-risk groups have significantly more IV cases than low-

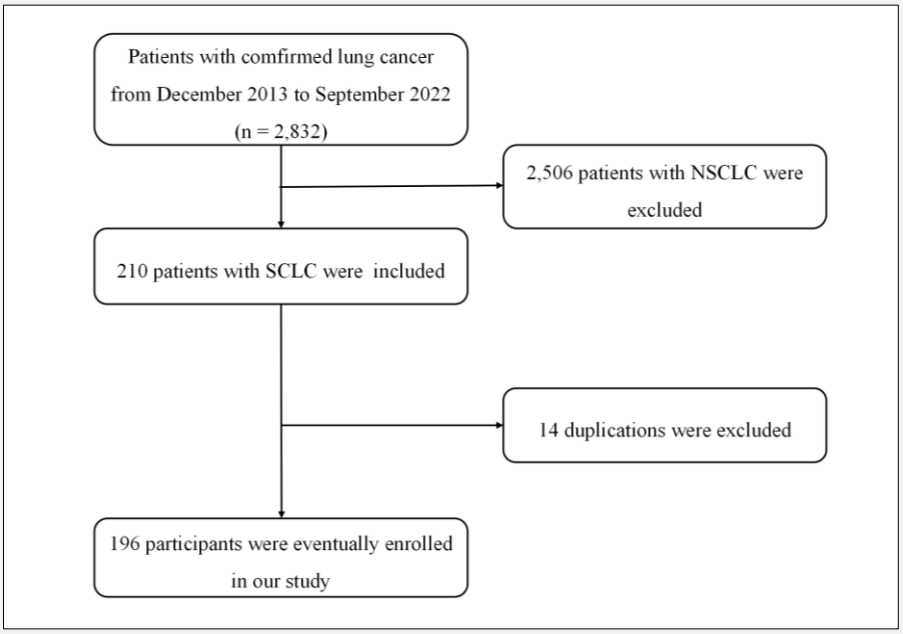

Figure 1. Flow chart of patients' enrollment.

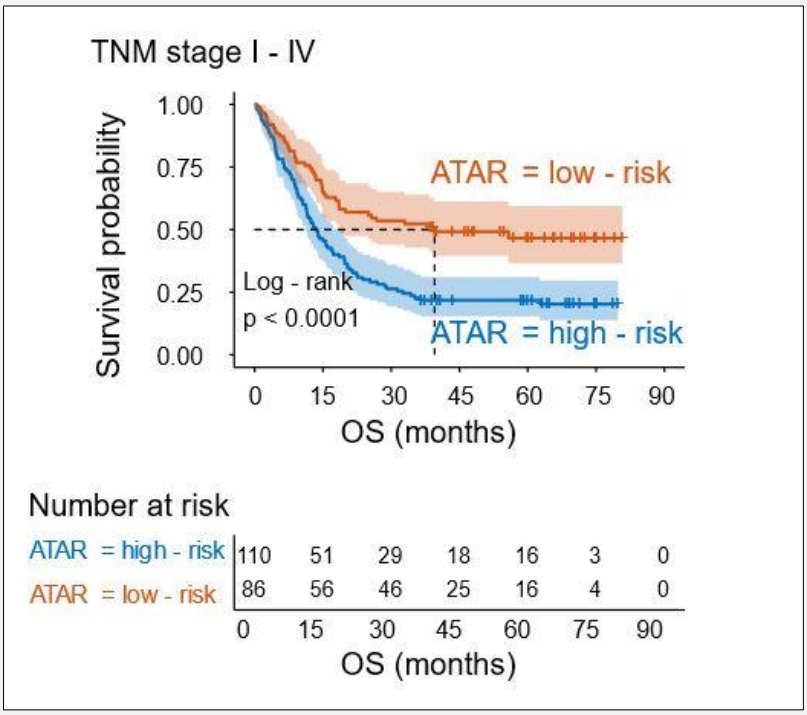

Figure 2. Kaplan-Meier curves for OS in SCLC patients by ATAR.

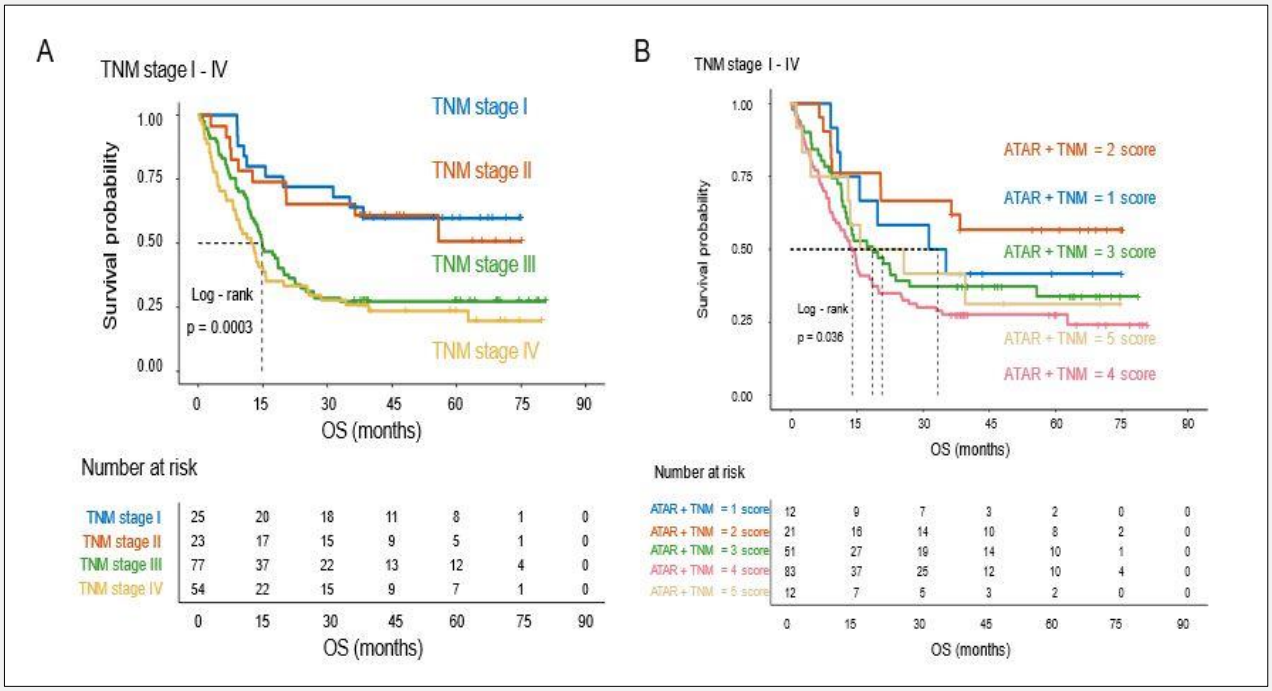

Figure 3. Kaplan-Meier plots of OS for stage I - IV SCLC patients.

Kaplan-Meier plots of overall OS by TNM stage I - IV (A), Kaplan-Meier plots of OS by the new model combining ATAR and TNM stage I - IV (B).

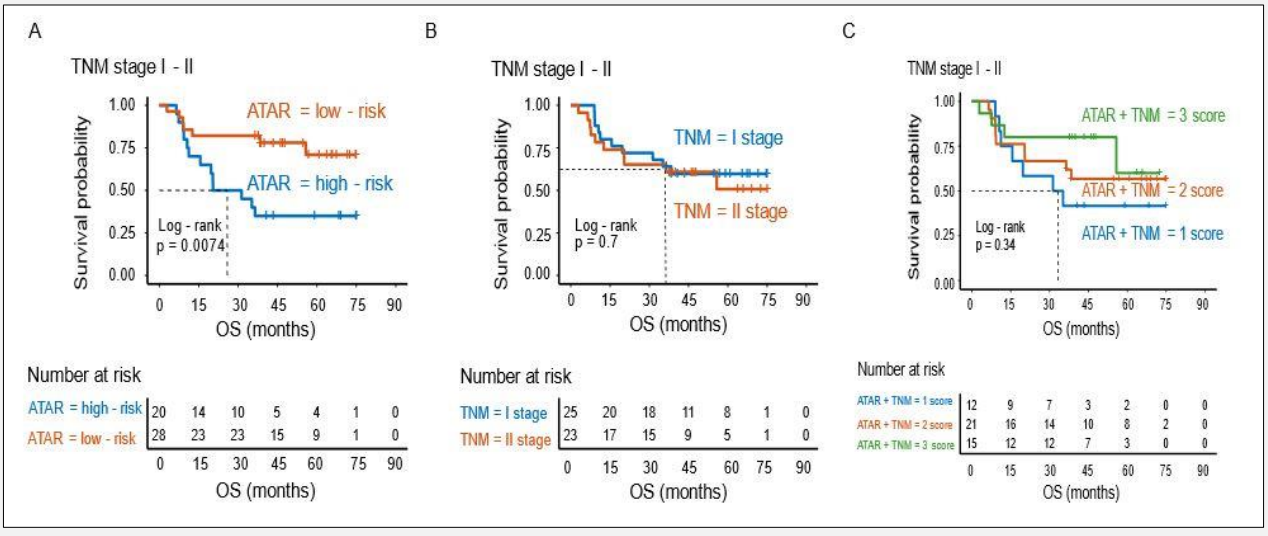

Figure 4. Kaplan-Meier plots of OS for stage I - II SCLC patients.

Kaplan-Meier plots of OS by ATAR (A), TNM stage I - II (B), Kaplan-Meier plots of OS by the new model combining ATAR and TNM stage I - II (C).

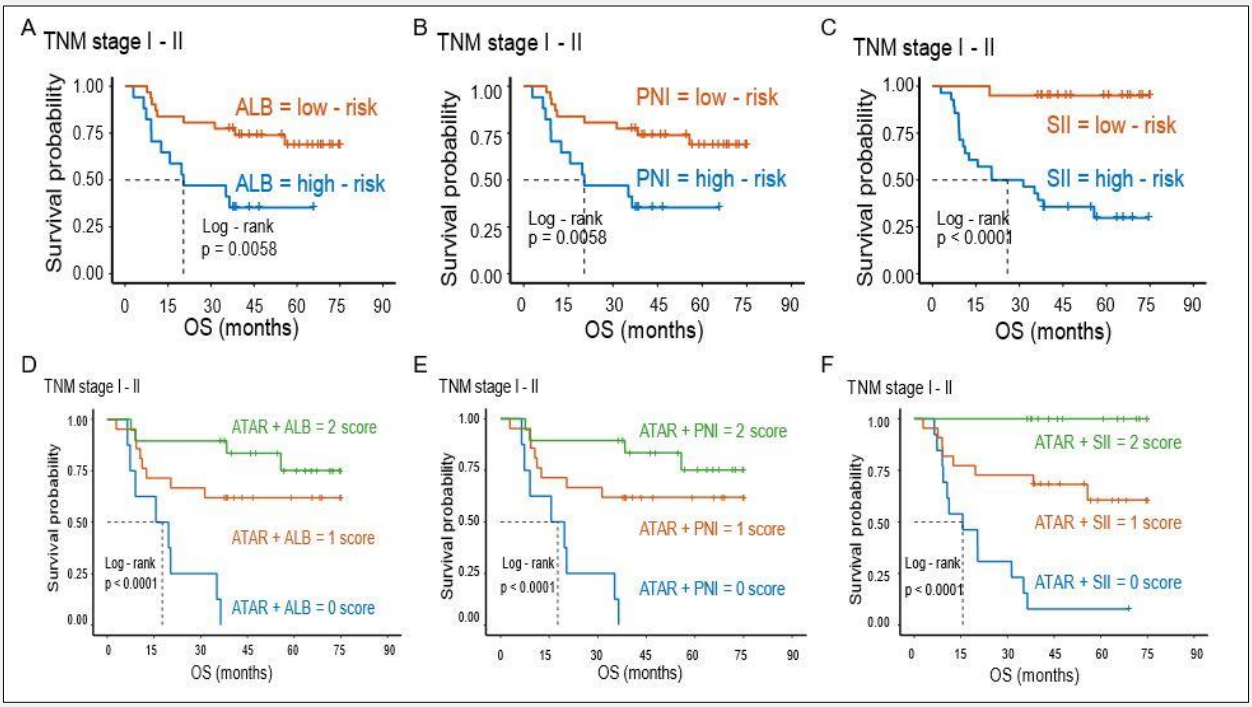

Figure 5. Kaplan-Meier plots of OS for stage I - II SCLC patients.

Kaplan-Meier plots of OS by ALB (A), PNI (B), SII (C), Kaplan-Meier plots of OS by the new model combining ATAR and ALB (D), and PNI (E), and SII (F).

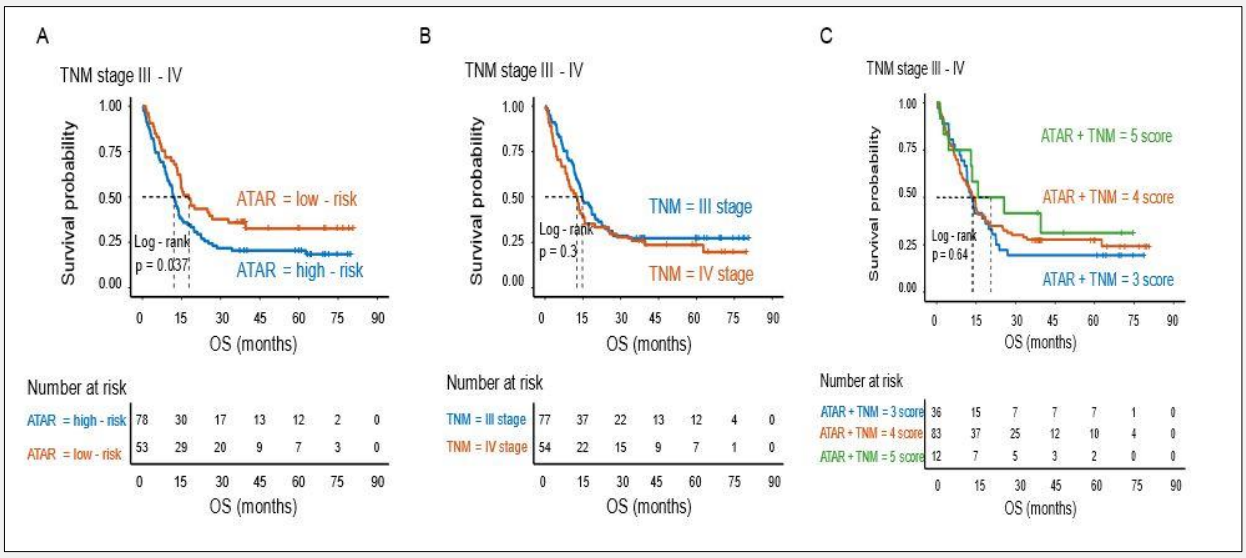

Figure 6. Kaplan-Meier plots of OS for stage III - IV SCLC patients.

Kaplan-Meier plots of OS by ATAR (A), TNM stage III - IV (B), Kaplan-Meier plots of OS by the new model combining ATAR and TNM stage III - IV (C).

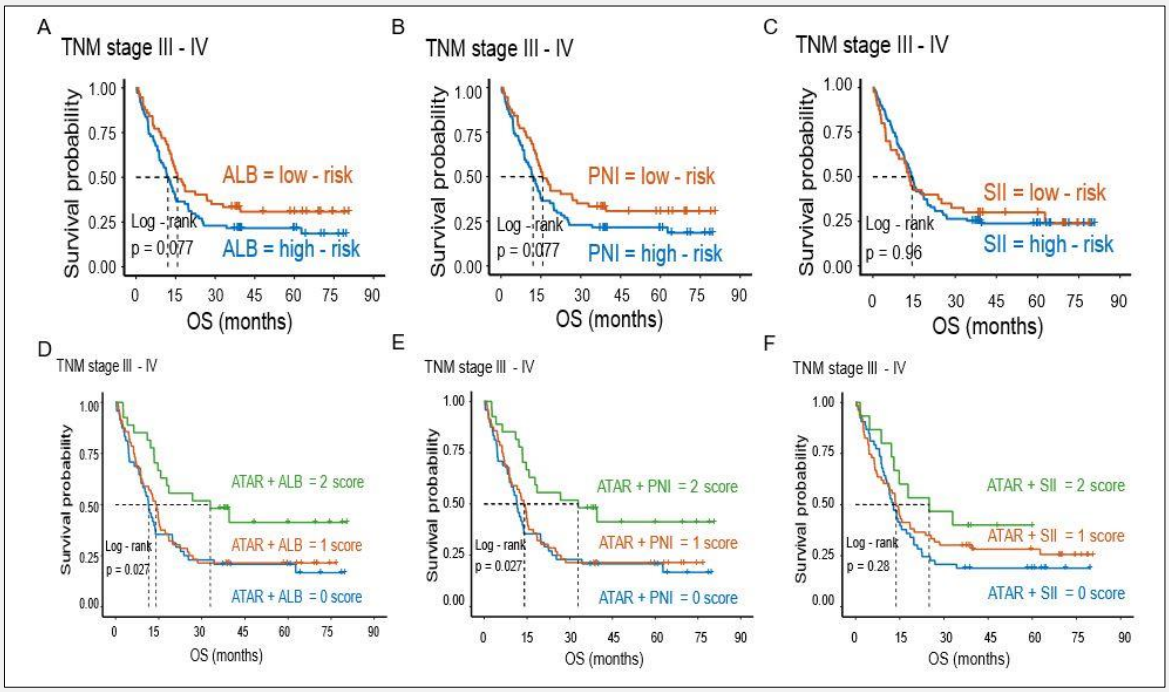

Figure 7. Kaplan-Meier plots of OS for stage III - IV SCLC patients.

Kaplan-Meier plots of OS by ALB (A), PNI (B), SII (C), Kaplan-Meier plots of OS by the new model combining ATAR and ALB (D), and PNI (E), and SII (F).

risk groups (38.2% vs. 14.0%, respectively, p = 0.001). The death ratio of the high-risk group was higher than that of the low-risk group (79.1% and 51.2%, respectively, p < 0.001). Among the high-risk group, the median survival time was shorter than that of the low-risk group (13.59 months vs. 36.70 months, respectively, p = 0.003). There is, however, no statistically significant difference in age, tumor location, T stage, treatment, and chemo-cycle between the high-risk and low-risk groups with different levels of ATAR (p > 0.05).

Univariate and multivariate cox analyses

Table 2 shows the association between clinical characteristics variables and OS of 196 SCLC patients. In univariate analyses, poor survival was significantly associated with age (p = 0.006), smoking history (p = 0.007), T stage (I - II vs. III - IV, uncertain) (p = 0.012), node metastasis (p = 0.004), distant metastasis (p = 0.005), TNM stage (p < 0.001), staging (Limited stage vs. Extensive stage/uncertain) (p = 0.017), treatment (p = 0.006), chemotherapy (p = 0.005), ATAR (p < 0.001), PNI (p < 0.001), and SII (p = 0.005). The factors included in the final multivariate Cox regression analysis were closely related to survival and progress in univariate analyses (p < 0.05). In multivariate analysis, independent risk factors of poor patient survival consisted of smoking history (HR: 1.650 95% CI: 1.142 - 2.385, p = 0.008), TNM stage (HR: 2.073 95% CI: 1.058 - 4.063, p = 0.034), ATAR (HR:1.907 95% CI: 1.383 - 2.631, p < 0.001), and PNI (HR: 0.994 95% CI: 0.990 - 0.998, p = 0.002). Thus, our study suggests that ATAR is a more reliable independent prognostic indicator for SCLC.

Overall survival analysis according to prognostic index (ALB, ATAR, PNI, and SII)

Using the Youden index as a cutoff, the optimal cutoff points for ALB, ATAR, PNI, and SII were 40.10 g/L, 0.54, 401.01, and 447.00, respectively. Kaplan-Meier survival analysis was performed on patients with SCLC to examine the association between ALB, ATAR, PNI, SII, and TNM staging. Compared with patients with low-risk ATAR, those with high-risk ATAR had significantly lower survival rates (p < 0.0001, Figure 2). Additionally, the ALB, PNI, and SII prognostic index showed significant differences in OS between the two groups (p < 0.001, p < 0.001, p = 0.0052, Supplemental Figure 1 A, B, and C, respectively).

In SCLC patients, TNM stage was a significant predictor of OS (p < 0.001, Figure 3A). Our study's findings are consistent with previous data, indicating that our prognosis data and staging are accurate. Despite

this, we found no significant differences between stage I - II SCLC and stage III - IV SCLC based on TNM stage ($p = 0.7$ and $p = 0.3$, Figures 4B and 6B, respectively). In SCLC patients with stage I - II and stage III - IV, we analyzed Kaplan-Meier survival data to determine the relationships between ATAR and OS. It is amazing that ATAR successfully show significant prognostic value in patients with stage I - II and III - IV SCLC ($p = 0.0074$, $p = 0.037$, Figure 4A and Figure 6A, respectively).

Combining ATAR with ALB, PNI, SII, and TNM stage improves survival prediction and risk stratification

We conducted a model for combining ATAR with ALB, PNI, SII, and TNM stage to analyze the survival and prognosis of SCLC. In brief, patients with ATAR or SII above the cutoff value were scored 0 and those below the cutoff value were scored 1. ALB and PNI values above and below the cutoff value were scored as 1 and 0 respectively. After excluding patients with an indeterminate stage, I - IV stages were scored 1, 2, 3, and 4, respectively. Afterward, the ATAR score was added to the ALB, PNI, SII scores, and the TNM stage to construct the new prognostic model. The discriminatory impact of ATAR on OS was evaluated by performing a C-index analysis. As indicated by the C-index analysis in OS, the ALB score, PNI score, SII score, and TNM stage system score were significant (0.320, 0.319, 0.602, 0.661, respectively) (Supplementary Figures A, B, and C; Figure 3A. Table 3). The new prognostic model demonstrated a significant relationship with OS after combining ATAR with the ALB, PNI, SII, and TNM stage system scores, and the C-index indicated a significant improvement in survival prediction and risk stratification (0.747, 0.747, 0.707, and 0.705, respectively) (Supplemental Figures D, E, and F; Figure 3B. Table 3).

New index improves survival prediction and risk stratification in patients with type I - II SCLC and type III - IV SCLC

We further investigated how the ATAR affected ALB, PNI, SII, and TNM staging scores in patients with stage I - II SCLC and stage III - IV SCLC. It was found that the ALB score, the PNI score, and the SII score were significant in stage I - II (0.249, 0.249, and 0.786, respectively) (Figure 5A, B, and C. Table 3). TNM staging and OS were not significantly correlated with a C-index of 0.518 (Figure 4B; Table 3). After combining ATAR with the ALB, PNI and SII scores, the new prognostic model showed significant association with OS, and survival prediction and risk stratification were improved as indicated by the C-index (0.821, 0.821, and 0.871, respectively) (Figure 5D, E, and F. Table 3). Despite this, the combined ATAR and TNM stage system scores did not show any significant association with OS as evidenced by the C-index of 0.736 (Figure 4C; Table 3). Moreover, nutritional status is correlated with the stage of cancer patients, and the later the stage, the more nutritional therapy is necessary [9]. During stage III - IV, the ALB score, PNI score, SII score, and TNM stage system scores showed nonsignificant findings in the C-index analysis in OS (Figure 7A, B and C; Figure 4B, respectively, Table 3). With the combination of ATAR with ALB and PNI scores, the new prognostic model demonstrated significant associations with OS, and survival prediction and risk stratification improved as indicated by the C-index (0.686 and 0.686, respectively) (Figure 7D and E. Table 3). Nevertheless, when ATAR was combined with SII score and TNM stage system scores, no significant association was observed between SII and TNM staging and OS by the C-index (0.627 and 0.624, respectively) (Figure 7F and Figure 6C. Table 3).

DISCUSSION

Over the decades, SCLC patients' survival times have not been significantly prolonged with or without treatment. In this study, we retrospectively analyzed the prognostic power of ATAR in 196 eligible patients with SCLC at our cancer center. To our knowledge, this is the first study to analyze the correlation between ATAR and OS in patients with SCLC. The results of this demonstrated that ATAR is an independent prognostic indicator for patients with SCLC.

The SCLC is a very aggressive form of cancer that is highly responsive to cytotoxic agents and radiotherapy. Unfortunately, the rapid growth of the cancer and the acquired drug resistance associated with treatment lead to the death of most patients [32]. The overall survival rate is an important metric for evaluating the efficacy of different types of therapy. Inadequate predictors of OS could lead to an underestimation of therapeutic benefits [33]. Thus, an accurate prognostic indicator is necessary to identify the patients who are likely to benefit from anti-tumor treatment.

Researchers have found that TNM stage, disease extent, PNI, and SII are significantly correlated with overall survival in patients with SCLC [34]. The findings of our studies are consistent with these findings, showing that patients who did not smoke, had limited staging, had high PNIs, and had low SIIs were significantly more likely to survive than those with a smoking history, extensive staging, declined PNIs, and elevated SII levels (Table 2).

Several recent studies have demonstrated a connection between chronic inflammation and cancer. Inflammatory cells can alter the microenvironment of tumors, which can enhance tumor proliferation, migration, and immune escape [35]. According to these observations, chronic inflammation in cancer patients is associated with poor overall survival. Studies have demonstrated a link between chronic inflammation and tumorigenesis [36,37]. The proinflammatory cytokine IL-6 plays a major role in the development of cancer and closely corre-

lates with AST levels [38]. Further, the level of serum albumin was also found to be a prognostic factor in patients with SCLC. Low albumin levels are associated with malnutrition, weight loss, and increased cancer mortality [39].

In this study, we hypothesized that combining AST and ALB into the new index ATAR could be a better predictor of overall survival in cancer patients. To predict overall survival in SCLC, a 0.54 cutoff value was used. In our study, a univariate analysis showed that the ATAR is associated with poor prognosis ($p < 0.001$) (Table 2). Compared with patients who had ATAR $\leq$ 0.54, those with ATAR > 0.54 had higher chance of death (Table 2). By multivariate analysis, when adjusted for other variables, including cancer stage, ATAR independently predicted the overall survival of patients with SCLC ($p < 0.001$) (Table 2). Subgroup analysis suggested that OS in ATAR $\leq$ 0.54 group was significantly longer than those with ATAR > 0.54 in I - IV stage, I - II stage, and III - IV stage ($p < 0.001$, $p = 0.007$, $p = 0.037$, respectively). To our knowledge, this is the first study to evaluate the prognostic value of ATAR in patients with lung cancer. Furthermore, it is the first study to indicate that ATAR can predict the overall survival in SCLC. Other than PNI and SII, the ATAR is more objectively determined, and would be a simple, optimal, and inexpensive prognostic indicator in patients with SCLC. Despite the clinical benefits of first-line chemotherapy and radiotherapy for patients with SCLC, they are associated with severe adverse reactions. Patients may suffer from myelosuppression, anorexia, and radiation pneumonitis, which suppress the immune system and can negatively impact their nutritional status. Thus, therapeutic decisions must balance the curative effects and the toxic effects of the treatment. In this study, we demonstrate that ATAR can be used as a screening tool for determining which treatment is most appropriate for patients with SCLC.

However, there were some limitations. Firstly, our study is a single-center retrospective study, which implies a selection bias. The results of our study need to be confirmed by more multicenter, prospective studies. Secondly, it was a retrospective study, so ATAR regarding this analysis was determined at a single time point. Therefore, further investigation into the relationship between ATAR level and other factors may contribute to establishing the clinical implications of ATAR as a long-term prognostic indicator for patients with SCLC.

Acknowledgment:
The authors acknowledge the support and interest of Sichuan Cancer Hospital, and thank all the people who participated in this study.

Source of Funds:
This study was supported by grants from Natural Science Foundation of Sichuan Province (Grant No. 22NSFSC0850).

Availability of Data and Materials:
All data of this study are included in this manuscript.

Ethics Approval and Consent to Participate:
This study was approved by the Medical Committee of Sichuan Cancer Hospital (No. KY-2021-076).

Due to the retrospective nature of this study, some survival data were only obtained through telephone follow-ups, because patients could not afford long journeys to reach the hospital. Only verbal informed consent was obtained from these patients or their legal guardians (for those who had passed away).

Declaration of Interest:
The authors declare that they have no competing interests.

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