SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 DOI: 10.5937/jomb0-63260

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1–10, 2026

Original paper
Originalni naučni rad

A NOVEL PROGNOSTIC SIGNATURE COMBINING SERUM INFLAMMATORY CYTOKINES AND CELL-FREE TELOMERE LENGTH IN SMALL CELL LUNG CANCER

NOVI PROGNOSTIČKI POSTUPAK KOJI KOMBINUJE SERUMSKE INFLAMATORNE CITOKINE I DUŽINU SLOBODNIH TELOMERA U MALOĆELIJSKOM KARCINOMU PLUĆA

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Summary

Background: Small Cell Lung Cancer (SCLC) is a deadly cancer with few reliable prognostic biomarkers. Although systemic inflammation contributes to SCLC progression, no studies have combined cellular senescence biomarkers with inflammatory markers. We proposed that measuring both serum inflammatory cytokines and cell-free telomere length together could improve prognostic accuracy.
Methods: We enrolled 187 patients with extensive-stage SCLC before they started first-line chemo-immunotherapy. At baseline, we measured serum levels of IL-6, IL-8, TNF-α, CRP, and cell-free telomere length (cfTL). We used Cox regression to create an Inflamm-Ageing Index (IAI). The main outcome was overall survival (OS).
Results: High IL-6 (HR 2.14, 95% CI 1.45–3.16, p<0.001) and short cfTL (HR 2.87, 95% CI 1.92-4.29, p<0.001) were each linked to worse overall survival. The IAI grouped patients into low-, intermediate-, and high-risk groups, with median OS of 14.2, 9.1, and 5.3 months, respectively (p<0.001). The IAI stayed an independent predictor after adjusting for other factors (HR 3.42, 95% CI 2.18–5.37, p<0.001) and outperformed individual biomarkers (C-index 0.78).
Conclusion: After a median follow-up of 16.8 months and 148 events (79.1%), the Inflamm-Aging Index, which combines inflammatory cytokines and cellular senescence biomarkers, showed promise for risk stratification in extensive-stage SCLC. However, since the biomarker thresholds were set using this cohort, external validation with pre-set cutoffs is needed before clinical use.

Keywords: small cell lung cancer, inflammation, telomere, senescence, biomarkers, prognosis

Kratak sadržaj

Uvod: Malоćelijski karcinom pluća (SCLC) predstavlja smrtonosni malignitet sa malim brojem pouzdanih prognostičkih biomarkera. Iako sistemska inflamacija doprinosi progresiji SCLC-a, nijedna studija do sada nije kombinovala biomarkere ćelijskog starenja sa inflamatornim markerima. Pretpostavljeno je da bi istovremeno merenje serumskih inflamatornih citokina i dužine slobodnih telomera moglo poboljšati prognostičku preciznost.
Metode: U studiju je uključeno 187 pacijenata sa ekstenzivnim stadijumom SCLC-a pre započinjanja prve linije hemoimunoterapije. Na početku studije određivani su serumski nivoi IL-6, IL-8, TNF-α, CRP-a i dužina slobodnih telomera (cfTL). Za kreiranje Inflam-Ageing indeksa (IAI) korišćena je Cox regresiona analiza. Glavni ishod je bilo ukupno preživljavanje (OS).
Rezultati: Visok nivo IL-6 (HR 2,14; 95% CI 1,45–3,16; p<0,001) i kratka cfTL (HR 2,87; 95% CI 1,92–4,29; p<0,001) su bili pojedinačno povezani sa lošijim ukupnim preživljavanjem. IAI je grupisao pacijente u nisko-, srednje- i visokorizične grupe, sa medijanom OS od 14,2, 9,1 i 5,3 meseca, redom (p<0,001). IAI je ostao nezavisan prediktor nakon prilagođavanja za druge faktore (HR 3,42; 95% CI 2,18–5,37; p<0,001) i pokazao bolje performanse u odnosu na pojedinačne biomarkere (C-indeks 0,78).
Zaključak: Nakon medijane praćenja od 16,8 meseci i 148 događaja (79,1%), Inflamm-Aging indeks, koji kombinuje inflamatorne citokine i biomarkere ćelijskog starenja, pokazao je potencijal za stratifikaciju rizika kod pacijenata sa ekstenzivnim stadijumom SCLC-a. Međutim, pošto su granične vrednosti biomarkera određene na osnovu ove kohorte, neophodna je eksterna validacija sa unapred definisanim pragovima pre kliničke primene.

Ključne reči: malоćelijski karcinom pluća, inflamacija, telomera, starenje, biomarkeri, prognoza

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Introduction

Small Cell Lung Cancer (SCLC) makes up about 15% of lung cancers but causes a much higher share of deaths because it spreads quickly and is very aggressive (1). Even with new treatments like immune checkpoint inhibitors added to platinum-etoposide chemotherapy, median survival for extensive-stage SCLC is still only 12–13 months (2, 3). This highlights the urgent need for improved prognostic biomarkers to guide treatment decisions and identify patients who might benefit from new therapies.

Systemic inflammation is now recognised as an important factor in cancer outcomes across many types of cancer (4, 5). In SCLC, higher levels of inflammatory cytokines, such as IL-6, IL-8, and TNF-α, are associated with a worse prognosis (6, 7). These cytokines help create a tumour-friendly environment by promoting blood vessel growth, facilitating cancer spread, and weakening the immune response (8). C-reactive protein (CRP), which is easy to measure, is also a well-known marker of inflammation and has proven value in predicting outcomes in lung cancer (9).

Alongside inflammation, cellular ageing and senescence also play a big role in how cancer develops and progresses (10, 11). Telomeres, which protect the ends of chromosomes, shorten each time a cell divides and serve as markers of cellular ageing (12). Recently, it has become possible to measure telomere length in cell-free DNA (cfDNA) from blood, which reflects overall cellular ageing (13, 14). In cancer patients, shorter telomeres are associated with greater genetic instability, higher mutation rates, and worse outcomes (15, 16). But the importance of cell-free telomere length (cfTL) in SCLC has not yet been studied.

The overlap between inflammation and cellular ageing, known as »inflamm-ageing,« is a concept gaining attention in chronic diseases and cancer (17, 18). Inflamm-ageing involves both elevated levels of inflammatory markers and reduced cellular repair capacity, features of ageing (19). While this link has not been established in SCLC, it may promote cancer progression by causing DNA damage, disrupting the immune system, and harming tissues (20). It is still unclear whether inflammation causes telomere shortening, telomere shortening leads to more inflammation, or if another factor, such as oxidative stress, drives both.

Despite these findings, no previous study has combined inflammatory cytokines and telomere-related biomarkers to create a single prognostic tool for SCLC. We believe that combining both pathways will provide better prognostic information than using either alone. This study aims to: (1) confirm the individual prognostic value of serum inflammatory markers and cfTL in SCLC, (2) develop a new Inflamm-Ageing Index (IAI), and (3) compare its prognostic performance to existing clinical factors.

Materials and Methods

Study design and population

This prospective observational cohort study was performed at [College of Health Medicine,China Three Gorges University, YiChang, Hubei, China] from January 2022 to December 2023. The study protocol was reviewed and approved by the Institutional Review Board, and all patients gave written informed consent. We identified 187 consecutive patients with previously untreated, newly diagnosed extensive-stage SCLC who were candidates for first-line platinum-etoposide chemotherapy with atezolizumab. The extensive-stage was determined according to the Veterans' Administration Lung Study Group (VALG) guidelines (21).

Inclusion criteria: (1) Histologically confirmed SCLC; (2) Extensive-stage disease; (3) Age ≥18 years; (4) Planned first-line chemo-immunotherapy; (5) ECOG performance status 0–2.

Exclusion criteria: (1) Prior systemic therapy for SCLC; (2) Active autoimmune disease; (3) Acute infection or inflammatory condition; (4) Other active malignancies within 5 years.

Biomarker measurements

Blood samples were collected in serum separator tubes and EDTA tubes before treatment initiation. Serum was separated within 2 hours and stored at -80 °C until analysis.

Inflammatory markers: Levels of IL-6, IL-8, and TNF-α were assessed using a Luminex multiplex assay (R&D Systems, Minneapolis, MN) according to the manufacturer's instructions (22). C-reactive protein (CRP) was measured via immunonephelometry (Siemens, Munich, Germany). Absolute counts of neutrophils and lymphocytes were obtained from routine complete blood counts performed within the 7 days preceding treatment initiation. The neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count. The Glasgow Prognostic Score (GPS) was derived from a combination of serum CRP (>10 mg/L=1 point) and albumin (<3.5 g/dL=1 point), resulting in a three-tiered scale (0, 1, or 2), as originally described by McMillan et al. (32). All measurements were performed in duplicate, with intra- and inter-assay coefficients of variation <10%.

Cell-free telomere length: cfDNA was extracted from 1 mL of plasma using the QIAamp Circu-

lating Nucleic Acid Kit (Qiagen, Hilden, Germany) (23). cfTL was measured by quantitative PCR using established primer sequences and normalisation to a single-copy gene (36B4) (14, 24). The relative cfTL was calculated as the T/S ratio (telomere signal to single-copy gene signal). All samples were analysed in triplicate, with samples re-run if the coefficient of variation exceeded 15%.

Clinical data and follow-up

Baseline clinical characteristics, including age, sex, smoking history, ECOG performance status, laboratory values (LDH, albumin), and metastatic sites, were recorded. Response to therapy was assessed every 2 cycles using RECIST v1.1 criteria (25).

Following completion of first-line therapy, patients were monitored at three-month intervals until death, loss to follow-up, or the study's data cutoff date. Overall survival (OS) was defined as the interval from diagnosis to death from any cause. Patients who were alive at the cutoff date or lost to follow-up were censored at their last known contact. Median follow-up time was estimated using the reverse Kaplan-Meier method, and follow-up adequacy was evaluated by comparing the median follow-up duration with the median OS and by reporting the proportion of censored patients (26).

Statistical analysis

Continuous variables were compared using Student's t-test or Mann-Whitney U test as appropriate. Categorical variables were compared using [or Fisher's exact test. Biomarker cutoffs were determined using maximally selected rank statistics in an exploratory, data-driven manner to identify thresholds associated with overall survival. Since these cutoffs were derived from the same cohort used for model development, they should be regarded as hypothesis-generating rather than as definitive clinical thresholds. No prespecified or externally validated cutoff values exist for cfTL in extensive-stage SCLC, and thus the reliability of these thresholds needs to be confirmed in independent cohorts (27).

The Inflamm-Ageing Index (IAI) was constructed using a weighted scoring system derived from a multivariable Cox regression model. Each variable's rounded regression coefficient (β) was multiplied by a constant factor of 10 and rounded to the nearest integer to enhance clinical usability. This approach produced the following simplified scores: IL-6 high = 2 points, CRP high = 1 point, and cfTL short = 3 points, resulting in the formula:

$$IAI=(2\times IL\text{-}6\ \text{high})+(1\times CRP\ \text{high})+(3\times cfTL\ \text{short})$$

Only biomarkers that remained independent predictors ($p<0.05$) in multivariable analysis were retained in the final model; IL-8 and TNF-α were excluded due to non-significant adjusted associations (28). Prior to model construction, variance inflation factors (VIFs) were calculated to assess collinearity among candidate variables; all were below 2.5, indicating acceptable collinearity that did not prevent their simultaneous inclusion. As a sensitivity analysis, an unweighted IAI that assigns one point to each high-risk biomarker was also tested. The weighted model was ultimately retained owing to its superior discriminative performance, reflected in a higher C-index.

Model discrimination was evaluated using Harrell's C-index and time-dependent receiver operating characteristic (ROC) curves (29). To assess the incremental prognostic value of the IAI over established inflammatory indices, the discriminative performance of the IAI was compared with the Glasgow Prognostic Score (GPS) and the neutrophil-to-lymphocyte ratio (NLR) using Harrell's C-index. For NLR, a threshold of ≥5 was used based on the most commonly reported cutoff in SCLC literature (30, 31).

Differences in C-indices between models were compared using a bootstrap-based method with 1000 resamples to estimate 95% confidence intervals for ΔC-index. As a sensitivity analysis, model-specific optimal NLR cutoffs were also evaluated using maximally selected rank statistics. Additionally, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were calculated to quantify the added prognostic value of the IAI over the GPS (32).

Internal validation was performed using 1000 bootstrap samples (33). No external validation cohort was available for the present analysis; therefore, model validation was limited to internal bootstrap resampling. The bootstrap procedure was used to estimate optimism-corrected model performance. It should not be interpreted as evidence of transportability to other institutions, treatment settings, or laboratory platforms. Statistical analyses were performed using R version 4.2.0 (R Foundation, Vienna, Austria) with packages survival, survminer, and timeROC. Two-sided p-values <0.05 were considered statistically significant.

Although the multivariable Cox models were adjusted for age, sex, ECOG performance status, and LDH, other clinically relevant prognostic factors, such as disease burden (number of metastatic sites), presence of liver or brain metastases, baseline corticosteroid use, and treatment-related variables (e.g., chemoimmunotherapy regimens, radiotherapy), were not consistently included. This limitation was due to a relatively low number of events compared with the number of covariates and to incomplete data availability for all patients. This represents a trade-off be-

tween model complexity and stability when analysing survival in moderately sized cohorts. Future studies with larger patient populations should consider incorporating these additional covariates to address potential residual confounding more comprehensively.

Results

Patient characteristics

Table I presents the baseline characteristics of the 187 SCLC patients. Median age was 67 years (range 45–82), with 62% males. Most patients were current or former smokers (94%). The majority had ECOG performance status 1 (58%), and elevated LDH (>ULN) was present in 64% of patients. Common metastatic sites included liver (52%), brain (28%), and bone (45%).

At the time of data cutoff, 148 of 187 patients (79.1%) had died, while 39 patients (20.9%) remained alive and were censored. No patients were lost to follow-up prior to the cutoff date. Median follow-up, estimated using the reverse Kaplan-Meier method, was 16.8 months (95% CI, 14.5–19.2; range, 0.7–30.2 months). Across the overall cohort and within each IAI risk group, median follow-up exceeded median OS (Low: 18.4 vs 14.2 months; Intermediate: 16.1 vs 9.1 months; High: 14.8 vs 5.3 months), supporting the adequacy of follow-up for reliable survival estimation. The censoring rates reflected the expected gradient in mortality risk: 34.9% (22/63) in the low IAI group, 16.9% (12/71) in the intermediate group, and 9.4% (5/53) in the high-risk group.

Table I Baseline characteristics of SCLC patients (n=187).

Characteristic	Total (n=187)	Low IAI (n=63)	High IAI (n=124)	p-value
Age, years	67 (45–82)	65 (45–78)	68 (47–82)	0.032
Sex, n (%)				0.421
Male	116 (62)	37 (59)	79 (64)	
Female	71 (38)	26 (41)	45 (36)	
Smoking, n (%)				0.215
Current	88 (47)	27 (43)	61 (49)	
Former	88 (47)	32 (51)	56 (45)	
Never	11 (6)	4 (6)	7 (6)	
ECOG PS, n (%)				0.008
0	43 (23)	21 (33)	22 (18)	
1	109 (58)	34 (54)	75 (60)	
2	35 (19)	8 (13)	27 (22)	
LDH >ULN, n (%)	120 (64)	31 (49)	89 (72)	0.002
Albumin, g/dL	3.8±0.6	4.1±0.5	3.6±0.6	<0.001
Metastatic sites				
Liver	97 (52)	25 (40)	72 (58)	0.018
Brain	52 (28)	14 (22)	38 (31)	0.216
Bone	84 (45)	24 (38)	60 (48)	0.184
Biomarker levels				
IL-6 (pg/mL)	12.4 (3.2–85.6)	5.8 (3.2–15.1)	18.9 (8.7–85.6)	<0.001
IL-8 (pg/mL)	24.3 (8.5–156.2)	16.2 (8.5–42.3)	31.7 (12.4–156.2)	<0.001
TNF-α (pg/mL)	8.7 (2.1–34.8)	5.3 (2.1–12.6)	11.4 (4.2–34.8)	<0.001
CRP (mg/L)	18.2 (1.5–124.7)	6.4 (1.5–24.8)	28.9 (8.7–124.7)	<0.001
cfTL (T/S ratio)	0.85 (0.21–2.34)	1.32 (0.86–2.34)	0.61 (0.21–1.08)	<0.001

Biomarker distributions and cutoffs

Exploratory data-derived cutoffs for prognostic stratification were: IL-6 ≥15 pg/mL, IL-8 ≥25 pg/mL, TNF-α ≥10 pg/mL, CRP ≥20 mg/L, and cfTL ≤0.80 T/S ratio. These thresholds were derived within the development cohort. They should therefore be interpreted as provisional cutoffs requiring external validation rather than fixed clinical decision thresholds. Using these cutoffs, 58% had high IL-6, 52% had high IL-8, 49% had high TNF-α, 61% had high CRP, and 59% had short cfTL. Significant correlations were observed between inflammatory markers (IL-6 with CRP: r=0.68, p<0.001; IL-6 with IL-8: r=0.52, p<0.001), but cfTL showed only weak inverse correlations with inflammatory markers (cfTL with IL-6: r=-0.31, p=0.012). Despite moderate correlations among inflammatory markers, formal collinearity diagnostics indicated acceptable variance inflation factors (VIFs: 1.2–2.1) for all covariates in the multivariable model, suggesting that collinearity did not substantially affect coefficient stability or model fit. The lowest tolerance value observed was 0.48, remaining above conventional thresholds for concern (<0.20).

Survival analysis of individual biomarkers

Table II presents the univariate and multivariate analyses of individual biomarkers. In univariate analysis, all biomarkers significantly predicted OS. High IL-6 (HR 2.14, 95% CI 1.45–3.16, p<0.001), high CRP (HR 1.89, 95% CI 1.28–2.79, p=0.001), and short cfTL (HR 2.87, 95% CI 1.92–4.29, p<0.001) were the strongest predictors.

In multivariate analysis including clinical factors, IL-6 (HR 1.76, p=0.006), CRP (HR 1.58, p=0.026), and cfTL (HR 2.41, p<0.001) remained independent prognostic factors alongside ECOG PS (HR 1.61, p=0.022) and LDH (HR 1.74, p=0.005).

Development and validation of the Inflamm-Ageing Index

Based on the multivariable regression coefficients (β values, rounded and multiplied by a constant factor of 10 to generate integer weights, as detailed in Methods), the Inflamm-Ageing Index (IAI) was defined as:

IAI=(2×IL-6 high)+(1×CRP high)+(3×cfTL short)

For the sensitivity analysis, an unweighted additive score was also constructed, assigning 1 point each to IL-6 high, CRP high, and cfTL short (range 0–3). The weighted model showed superior discriminative performance compared with the unweighted model (C-index 0.78 vs 0.74; bootstrap-corrected ΔC-index=0.035, 95% CI 0.01–0.06), supporting the use of differential weighting. In Lasso-penalised Cox regression, the same three biomarkers were consistently selected (λ=1 standard error above the minimum), confirming their dominant prognostic contribution. Patients were stratified into three risk categories: Low (IAI 0–2, n=63), Intermediate (IAI 3–4, n=71), and High (IAI 5–6, n=53). Because the biomarker thresholds were derived from the same dataset, the IAI should be considered an exploratory prognostic index, and its cutoff-dependent performance may be optimistic until validated using pre-specified thresholds in an independent cohort.

The IAI showed remarkable discriminatory power. Median OS was 14.2 months in the low-risk group, 9.1 months in the intermediate-risk group, and 5.3 months in the high-risk group (p<0.0001, log-rank test). In multivariable analysis including all clinical factors, high IAI remained the strongest independent predictor of poor OS (HR 3.42, 95% CI 2.18–5.37, p<0.001).

Table II Univariate and multivariate Cox analysis of individual biomarkers for overall survival.

Biomarker	Cutoff	Univariate HR (95% CI)	p-value	Multivariate* HR (95% CI)	p-value
IL-6	≥15 pg/mL	2.14 (1.45–3.16)	<0.001	1.76 (1.18–2.63)	0.006
IL-8	≥25 pg/mL	1.65 (1.14–2.39)	0.008	1.32 (0.90–1.94)	0.157
TNF-α	≥10 pg/mL	1.54 (1.07–2.22)	0.021	1.24 (0.85–1.81)	0.266
CRP	≥20 mg/L	1.89 (1.28–2.79)	0.001	1.58 (1.06–2.36)	0.026
cfTL	≤0.80 T/S	2.87 (1.92–4.29)	<0.001	2.41 (1.59–3.65)	<0.001
Age	≥70 years	1.35 (0.95–1.92)	0.097	1.22 (0.85–1.75)	0.285
ECOG PS	1–2 vs 0	1.88 (1.26–2.81)	0.002	1.61 (1.07–2.42)	0.022
LDH	>ULN	2.02 (1.38–2.96)	<0.001	1.74 (1.18–2.57)	0.005

* Multivariate model adjusted for age, sex, ECOG PS, and LDH.

Table III Survival outcomes by Inflamm-Ageing Index risk groups.

Risk Group	n (%)	Median OS (months)	6-month OS %	12-month OS %	HR (95% CI)*	p-value
Low	63 (34)	14.2 (11.8–16.6)	92.1	58.7	Reference	-
Intermediate	71 (38)	9.1 (7.8–10.4)	76.1	32.4	2.34 (1.55–3.53)	<0.001
High	53 (28)	5.3 (4.2–6.4)	41.5	13.2	4.87 (3.18–7.45)	<0.001
Total	187 (100)	9.4 (7.9–10.9)	72.2	36.4	–	-

*Adjusted for age, sex, ECOG PS, and LDH.
Median follow-up by reverse Kaplan-Meier method: 16.8 months (95% CI 14.5–19.2)

Table IV Comparison of prognostic performance for 12-month overall survival.

Model	C-index (95% CI)	AUC at 6 months	AUC at 12 months	Integrated Brier Score
Clinical model alone	0.64 (0.58–0.70)	0.67	0.66	0.184
Clinical + NLR	0.68 (0.62–0.74)	0.70	0.69	0.176
Clinical + IL-6	0.69 (0.63–0.75)	0.72	0.71	0.168
Clinical + GPS	0.70 (0.64–0.76)	0.73	0.72	0.164
Clinical + cfTL	0.73 (0.67–0.79)	0.76	0.75	0.152
Clinical + IAI	0.78 (0.72–0.84)	0.81	0.80	0.139

Prognostic performance comparison

The IAI demonstrated superior prognostic performance compared with individual biomarkers, established inflammatory indices (GPS and NLR), and clinical factors alone. The C-index for the IAI was 0.78 (95% CI 0.72–0.84), significantly higher than the clinical model alone (0.64, p<0.001). Time-dependent ROC analysis showed AUCs of 0.81 and 0.80 for 6- and 12-month OS prediction, respectively. Bootstrap internal validation suggested limited optimism in model performance, with an optimism-corrected C-index of 0.75. The maturity of the survival data (79.1% event rate) and adequate follow-up duration (median 16.8 months, exceeding median OS in all risk groups) support the reliability of these estimates. However, because no independent external cohort was available, these results should be interpreted as internally validated performance rather than evidence of external generalizability.

Comparison with established inflammatory indices

To determine whether the IAI offers incremental prognostic value beyond routinely available inflammatory markers, its discriminative performance was compared with the Glasgow Prognostic Score (GPS) and the neutrophil-to-lymphocyte ratio (NLR). Baseline GPS was calculated for all patients using serum CRP and albumin values: 52 patients (28%) had GPS 0, 81 (43%) had GPS 1, and 54 (29%) had GPS 2. Higher GPS was significantly associated with worse overall survival (GPS 1 vs 0: HR 1.72, 95% CI 1.14–2.59, p = 0.009; GPS 2 vs 0: HR 2.91, 95% CI 1.88–4.51, p<0.001; C-index 0.70, 95% CI 0.64–0.76). Baseline NLR was available for all patients (median 4.2, range 0.8–28.5). Using a cutoff of NLR ≥5, patients with high NLR had significantly shorter overall survival (median OS 7.4 vs 11.2 months; HR 1.81, 95% CI 1.28–2.56, p=0.001; C-index 0.68, 95% CI 0.62–0.74).

The IAI demonstrated superior discriminative performance compared with both the GPS and NLR. The C-index for the clinical + IAI model (0.78, 95% CI 0.72–0.84) was significantly higher than that for clinical + GPS (0.70, 95% CI 0.64–0.76; bootstrap ΔC-index=0.08, 95% CI 0.03–0.13, p=0.008) and clinical + NLR (0.68, 95% CI 0.62–0.74; bootstrap ΔC-index=0.10, 95% CI 0.05–0.15, p=0.002). Reclassification metrics further supported the improved performance of the IAI: compared with the GPS-based model, the addition of the IAI resulted in a continuous net reclassification improvement (NRI) of 0.41 (95% CI 0.22–0.59, p<0.001) and an integrated discrimination improvement (IDI) of 0.12 (95% CI 0.07–0.18, p<0.001). These findings suggest that the IAI captures incremental prognostic information beyond that conveyed by established single-timepoint systemic inflammation indices.

Discussion

This study presents the first integration of systemic inflammatory markers with cellular senescence biomarkers to create a novel prognostic index in SCLC. Our findings demonstrate that the Inflamm-Ageing Index (IAI), combining serum IL-6, CRP, and cell-free telomere length, provides superior prognostic stratification compared to established clinical factors or individual biomarkers alone. The three-tiered risk classification identified patients with dramatically different median survival (14.2 vs 5.3 months), offering clinically meaningful discrimination.

The strong prognostic value of individual inflammatory markers aligns with previous studies showing that systemic inflammation promotes SCLC progression through multiple mechanisms (6, 34). IL-6, in particular, has been implicated in SCLC pathogenesis by activating STAT3, promoting tumour cell proliferation, survival, and chemoresistance (35). Our finding that IL-6 was the strongest inflammatory predictor supports its central role in SCLC biology. The independent prognostic value of CRP further emphasises the clinical relevance of measuring systemic inflammation, consistent with its established role in other cancers (36).

The novel aspect of our study is the incorporation of cell-free telomere length as a biomarker of systemic cellular ageing. While tissue telomere length has been studied in various cancers (37, 38), measurement in circulating cfDNA represents a non-invasive approach that reflects systemic rather than local cellular ageing (39). Our finding that short cfTL was the strongest individual predictor (HR 2.87) suggests that biological ageing processes significantly influence SCLC outcomes. This may reflect increased genomic instability, impaired DNA repair capacity, or accelerated cellular senescence in the tumour microenvironment (40).

The synergistic prognostic value of combining inflammatory and senescence biomarkers supports the »inflamm-ageing« hypothesis in cancer (17, 41). Chronic inflammation can accelerate telomere shortening through oxidative stress and reduced telomerase activity (42), while senescent cells secrete pro-inflammatory cytokines, creating a vicious cycle (43). In SCLC, this synergy may create a particularly aggressive tumour phenotype characterised by rapid progression and therapeutic resistance. Although we observed statistically significant associations between cfTL shortening and elevated inflammatory cytokines, these results are purely correlative. This study did not include mechanistic or functional experiments to establish causality between telomere attrition and inflammation in SCLC. Plasma cell-free telomere length likely reflects a mixture of DNA fragments from multiple cell populations, including tumour cells, normal somatic cells undergoing apoptosis or necrosis, and immune cells with high turnover. While cfDNA in cancer patients can contain tumour-derived fragments (circulating tumour DNA), the precise contribution of cfTL from tumour versus non-tumour sources remains unclear without targeted sequencing or tumour-specific mutation analysis. Chronic systemic inflammation and age-related immune changes have been linked to telomere shortening and cellular senescence, reflecting the biological process of inflamm-ageing. Elevated pro-inflammatory cytokines, such as IL-6 and TNF-α, are associated with increased cellular turnover and replicative stress, which can further accelerate telomere attrition in both immune and somatic cells (44, 45).

Clinically, the IAI presents several potential applications. It may identify high-risk patients who could benefit from more aggressive or novel therapeutic approaches, such as senescence-targeting agents (senolytics) or anti-inflammatory therapies (46). Additionally, the IAI could facilitate patient selection for clinical trials based on biological risk rather than clinical staging alone. Serial measurement of IAI components may also enable monitoring of treatment response and the emergence of resistance. The non-invasive nature of blood-based measurement enhances the feasibility of repeated assessments.

The IAI demonstrated incremental prognostic value compared with two widely validated systemic inflammation indices in cancer: the Glasgow Prognostic Score and the neutrophil-to-lymphocyte ratio. Although both GPS and NLR were independently prognostic in this cohort, their discriminative performance was significantly lower than that of the IAI. This observation is biologically plausible, as the IAI captures both the intensity of systemic inflammation (via IL-6 and CRP) and a dimension of host biology, cellular ageing, not reflected in conventional inflammatory indices. The NRI of 0.41 indicates that the IAI meaningfully reclassifies patients into more appropriate risk categories than GPS alone. However, GPS and NLR offer the advantage of immediate calculation from routine laboratory tests available in most clinical settings. The added complexity of the IAI, which requires cfTL measurement via qPCR, should be considered in future cost-effectiveness and implementation studies.

This study has several limitations. First, it was conducted at a single centre, and no independent external validation cohort was available. Although bootstrap resampling was used for internal validation and estimation of optimism-corrected performance, this approach does not substitute for external validation in an independent cohort. Consequently, the transportability and generalizability of the In-

flamm-Ageing Index across different patient populations, treatment settings, ethnic backgrounds, and laboratory platforms remain uncertain. Inter-laboratory variability in cytokine assays and cfTL measurement may also affect the reproducibility of the proposed cutoffs. Multicentre studies employing standardised pre-analytical and analytical protocols are necessary to externally validate the IAI, assess calibration and discrimination in independent cohorts, and determine whether recalibration is required before clinical implementation.

Second, biomarker cutoffs were derived using maximally selected rank statistics within the same dataset used for model development. While this method is useful for exploratory threshold identification, outcome-driven cutoff selection can increase the risk of overfitting and optimistic estimates of prognostic performance. The absence of pre-specified or biologically validated cutoff values, particularly for cfTL in extensive-stage SCLC, limits the robustness and reproducibility of the proposed index. Therefore, the reported thresholds should be considered provisional and hypothesis-generating. Future studies should validate the IAI using pre-specified cutoffs in independent cohorts and evaluate biomarker effects as continuous variables to minimise information loss from dichotomisation. Third, the point-based scoring system relied on rounding of regression coefficients derived from a single dataset, which may affect the precision and generalizability of the assigned weights. Although sensitivity analyses supported differential weighting, the optimal weighting scheme should be re-evaluated in external cohorts. Fourth, this study was not designed to evaluate the mechanistic relationship between cfTL shortening and elevated inflammatory cytokines; the reported associations are purely correlational. Causal inferences regarding 'inflamm-ageing' in SCLC cannot be drawn from these observational data alone. Future mechanistic studies incorporating paired tissue and circulating biomarkers, cellular senescence markers, and functional assays are required to establish the biological basis of the IAI. Fifth, the models did not incorporate some established prognostic factors in extensive-stage SCLC, such as total disease burden (e.g., number of metastatic sites), site-specific metastases (brain and liver involvement), baseline corticosteroid use, and detailed treatment variables, including chemotherapy type and radiotherapy. Prior studies have reported that liver and brain metastases are independent adverse prognostic factors in SCLC (46, 47). Because these variables were not uniformly available in the dataset, residual confounding cannot be excluded and may have influenced some reported associations. Sixth, although the overall event rate (79.1%) and median follow-up duration (16.8 months, exceeding median OS across all risk strata) indicate adequate follow-up for the primary survival analysis, the relatively small number of long-term survivors limits the precision of 12-month and later OS estimates, particularly in the high-risk IAI group with few patients at risk at later time points (48).

Future studies should explore associations with specific genomic alterations, treatment responses, and the therapeutic potential of targeting inflamm-ageing pathways. Also, investigations should include mechanistic studies and tumour-specific cfDNA analyses (e.g., ctDNA mutational profiling) to distinguish the relative contributions of tumour-derived versus immune cell-derived cfTL and to clarify whether inflammatory cytokines drive telomere attrition or vice versa.

Conclusion

In conclusion, the Inflamm-Ageing Index represents a novel, biologically grounded prognostic approach that showed promising internally validated performance for risk stratification in extensive-stage SCLC. By integrating systemic inflammation and cellular ageing biomarkers, it captures two key host-derived pathways that influence cancer outcomes. This approach may pave the way for more personalised management strategies in this aggressive malignancy. Nevertheless, external validation in independent, multicentre cohorts with standardised biomarker measurement is essential before the IAI can be recommended for routine clinical use. Direct comparison with established prognostic scores in these future validation studies will be critical to define the incremental clinical utility of incorporating cfTL measurement into routine prognostic assessment.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Received: April 14, 2026
Accepted: May 08, 2026