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RAPID COMMUNICATION

PD-L1 expression and smoke exposure as biomarkers for optimizing adjuvant therapy for patients with resected limited-stage small-cell lung carcinoma

Small-cell lung cancer (SCLC) is a highly malignant cancer with characteristics of rapid growth, abundant angiogenesis, and early distant metastasis that accounts for about 15% of lung cancers. With the wide application of low-dose computed tomography screening in recent years, the incidence of early limited-stage SCLC has increased dramatically. Clinical trials and real-world data have shown that surgical resection followed by adjuvant chemotherapy with or without radiotherapy is the recommended treatment for selected cases of limited-stage SCLC. However, due to chemotherapy resistance, the high frequency of postoperative recurrence reduces the long-term survival of SCLC patients.[1] Therefore, there is an urgent need for more precise classification strategies to identify patients who can benefit from adjuvant chemotherapy.

A previous study reported that elevated expression of programmed cell death ligand 1 (PD-L1) confers resistance to cisplatin in a cellular model of SCLC.[2] Notably, due to the high tumor mutation burden in SCLC caused by smoke exposure, immunotherapy for SCLC has attracted much attention. The combination of anti-PD-L1 immunotherapy (atezolizumab or durvalumab) and chemotherapy was recently approved by the Food and Drug Administration as a first-line treatment for extensive-stage SCLC. Therefore, our study aimed to determine whether PD-L1 affects the response to adjuvant chemotherapy and to propose a clinically feasible tool for guiding adjuvant therapy to optimize outcomes after surgical resection in patients with limited-stage SCLC.

In the study, we enrolled 191 patients with limited-stage SCLC who underwent surgery and adjuvant therapy at the Cancer Hospital, Chinese Academy of Medical Sciences (CICAMS). The characteristics of the included patients are shown in Table S1. Of these patients, 92 received adjuvant chemotherapy (aCT), 36 received adjuvant chemoradiotherapy (aCRT), and 38 received adjuvant chemoradiotherapy combined with prophylactic brain irradiation (aCRPT). We collected surgical specimens from these patients and immunohistochemically examined PD-L1 expression using an anti-PD-L1 (SP263) assay. The PD-L1 tumor proportion score (TPS) of each specimen was determined by two experienced pathologists who were blinded to the clinical characteristics.[3] If the scores differed, the two pathologists jointly reviewed the specimens to reach a consensus. The human tissue study was approved by the Ethics Committee of CICAMS, and the approval number was CH-L-043.

To evaluate the predictive value of PD-L1 TPS and other clinical parameters on recurrence-free survival (RFS) of limited-stage SCLC, univariate and multivariate Cox proportional hazard regression modeling were conducted. In the univariate analysis, gender, smoking history, primary tumor site, and PD-L1 level correlated with RFS ($P < 0.05$; Fig. S1A). After adjusting for clinicopathological characteristics, the PD-L1 level and smoking history remained independent predictors of RFS ($P < 0.05$; Fig. 1A). A weakly positive relationship between the PD-L1 TPS and the smoking index was observed ($r = 0.167$; Fig. S1B). We then determined the optimal cut-off values for smoking index and PD-L1 TPS to classify patients by a time-dependent receiver operating characteristic (ROC) curve at 5 years (smoking index: cut-off value = 6, AUC = 0.640, Fig. 1B; PD-L1 TPS: cut-off value = 0, AUC = 0.639, Fig. 1D). Regarding smoking history, patients with a smoking index greater than 6 were considered to have a heavy smoking history. Kaplan–Meier survival analysis showed that patients with heavy smoking history had significantly lower

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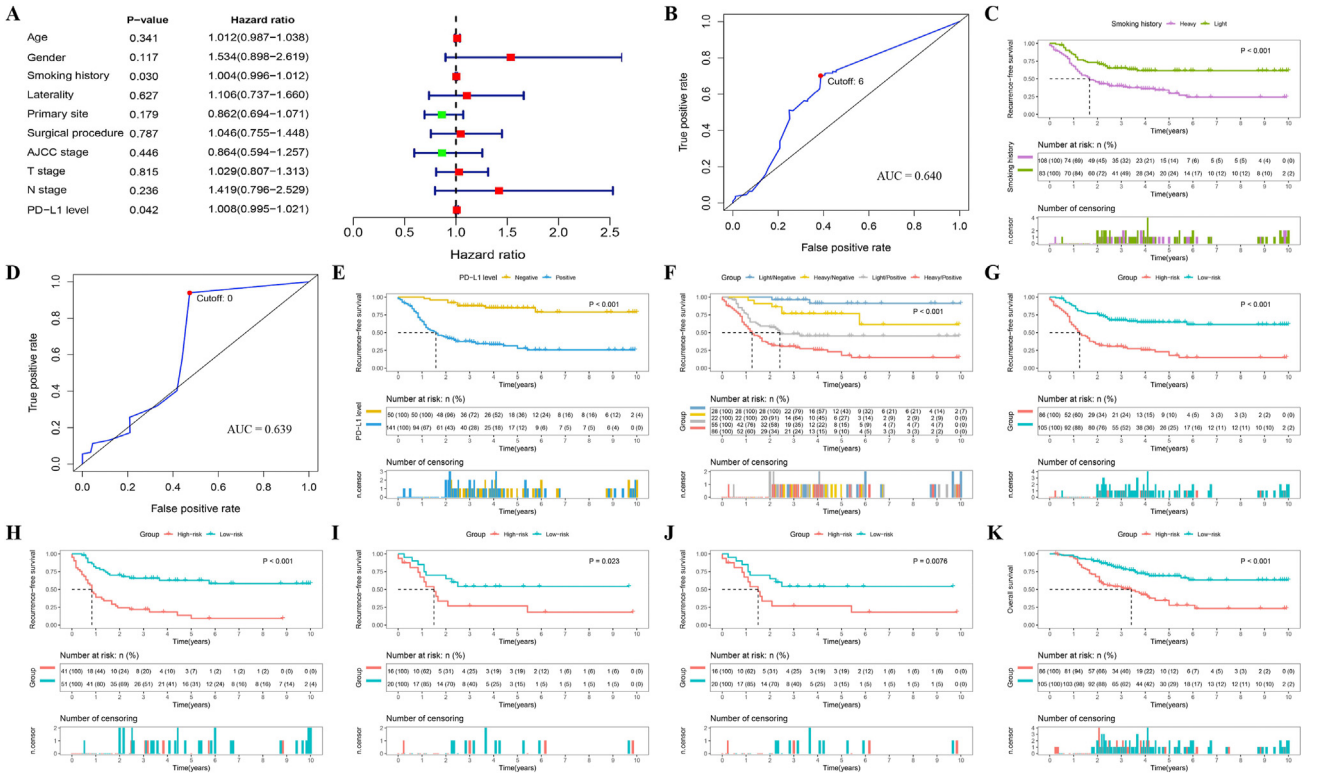

Figure 1 Relationships between clinical parameters and RFS of patients with resected limited-stage SCLC treated with adjuvant therapy. **(A)** Multivariate regression analyses of the associations between clinical parameters and RFS. **(B, D)** ROC curve analysis of smoking index (B) and PD-L1 level (D) on RFS of patients with resected limited-stage SCLC treated with adjuvant therapy. **(C, E)** Kaplan—Meier survival curves of RFS of patients with resected limited-stage SCLC treated with adjuvant therapy based on the smoking index (C) and the PD-L1 level (E). **(F)** Kaplan—Meier survival curves of RFS of patients with resected limited-stage SCLC treated with adjuvant therapy based on smoking index and PD-L1 level. **(G)** Kaplan—Meier survival curves of RFS between high-risk and low-risk SCLC patients with adjuvant therapy. **(H—J)** Kaplan—Meier survival curves of RFS between high-risk and low-risk SCLC patients with adjuvant chemotherapy (H), adjuvant radio-chemotherapy (I), or adjuvant radio-chemotherapy combined with prophylactic brain irradiation (J). **(K)** Kaplan—Meier survival curves of OS between high-risk and low-risk SCLC patients with adjuvant therapy. High-risk: patients with high smoking index and positive PD-L1 expression. Low-risk: patients without high smoking index and positive PD-L1 expression. Heavy/Negative: patients with high smoking index and negative PD-L1 expression. Light/Positive: patients with light smoking index and high PD-L1 expression.

RFS than patients with light smoking history ($P < 0.001$; Fig. 1C). Regardless of the type of adjuvant therapy, aCT, aCRT, or aCRPT, heavy smokers had lower RFS (Fig. S2A—C). On the other hand, survival analysis of the PD-L1 level revealed that patients with positive PD-L1 expression had lower RFS than patients with negative PD-L1 expression ($P < 0.001$; Fig. 1E). Stratified analysis of the aCT, aCRT, and aCRPT subgroups also revealed a marked difference in RFS between patients with and without positive PD-L1 expression (Fig. S3A—C). In addition, we checked the prognostic abilities of smoking index and PD-L1 level on overall survival (OS). Patients with heavy smoking history or positive PD-L1 expression had markedly lower OS in the entire cohort and the aCT subgroup, while significant difference in OS was not observed in the aCRT and aCRPT subgroups (Fig. S2D—G, S3D—G).

To explore the complementary prognostic value of smoking history and PD-L1 level, we performed the Kaplan—Meier survival analysis on the combination of smoking history and PD-L1 level. Patients with heavy smoking history and positive PD-L1 expression had worse RFS and OS than other patients ($P < 0.001$; Fig. 1F; Fig. S4D). Subsequently, we assigned patients with heavy smoking history and positive PD-L1 expression into the high-risk group and the other patients into the low-risk group. As expected, patients in the low-risk group had better RFS and OS compared with patients in the high-risk group ($P < 0.001$; Fig. 1G, K). Analysis of the aCT, aCRT, and aCRPT subgroups also showed that patients in the high-risk group had worse RFS compared to patients in the low-risk group (Fig. 1H—J). The stratified OS analysis revealed that patients in the high-risk group had markedly worse long-term survival in the aCT subgroup, but the difference in OS was not significant in the aCRT and aCRPT subgroups, likely due to relatively small sample size of aCRT and aCRPT subgroups (Fig. S5).

Although, in this study, heavy smoking history and positive PD-L1 expression were found to promote resistance to adjuvant chemotherapy in SCLC, previous studies have shown that these factors activate immunotherapy.[4] Furthermore, anti-PD-1/PD-L1 immunotherapy has been reported to improve the efficacy of standard chemotherapy for SCLC.[5] Therefore, limited-stage SCLC patients with heavy smoking history and positive PD-L1 expression could receive adjuvant chemotherapy combined with immunotherapy to

gain more treatment benefits after surgical resection; yet this finding needs to be validated in a future clinical trial.

In conclusion, our study proposed that smoking history and PD-L1 expression might help to select better adjuvant therapy to optimize outcomes after surgical resection in patients with limited-stage SCLC. Due to their ease of analyses in clinical practice, this biomarker combination may serve as a promising tool to further optimize the personalized medicine treatment paradigm for patients with SCLC.

Author contributions

Chengming Liu, Zhanyu Wang and Qingpeng Zeng: resources, data curation, formal analysis and writing-original draft preparation. Sufei Zheng, Xiaoli Feng and Qi Xue: conceptualization, methodology, visualization and software. Jie He and Nan Sun: project administration, funding acquisition, supervision and writing-reviewing.

Conflict of interests

The authors declare no conflict of interests.

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Consent for publication

The manuscript is approved by all authors for publication.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gendis.2022.02.017.

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