·论　著·

# 不同严重程度的晚期非小细胞肺癌患者免疫检查点抑制剂相关性肺炎的临床特征分析

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［摘要］ **背景和目的：**目前对于免疫检查点抑制剂相关性肺炎（checkpoint inhibitor-associated pneumonia，CIP）的研究多集中于其临床特征、危险因素、患者预后及与临床疗效的关系，但这些研究多数未区分低、高级别CIP。本研究旨在探讨非小细胞肺癌患者低、高级别CIP的临床特征差异及发生高级别CIP的危险因素。**方法：**回顾性收集2018年1月—2023年12月河北北方学院附属第一医院收治的接受免疫检查点抑制剂（immune checkpoint inhibitor，ICI）治疗的92例晚期非小细胞肺癌（non-small cell lung cancer，NSCLC）患者的病历资料，根据不良事件通用术语标准（Common Terminology Criteria for Adverse Events，CTCAE）5.0对CIP进行分级：无症状/轻度（1级）、中度（2级）、重度（3级）、危及生命（4级）和死亡（5级）。将1~2级定义为低级别CIP，3~5级定义为高级别CIP。对比两组患者的临床特征、实验室指标、影像学特征、治疗和预后，采用单因素和多因素logistic回归分析筛选NSCLC患者发生高级别CIP的影响因素，采用Spearman相关系数对中性粒细胞与淋巴细胞比值（neutrophil-lymphocyte ratio，NLR）、血小板与淋巴细胞比值（platelet-lymphocyte ratio，PLR）、全身免疫炎症指数（systemic immune-inflammation index，SII）、涎液化糖链抗原-6（Krebs von den Lungen-6，KL-6）与CIP分级进行相关性分析，采用受试者工作特征曲线分析外周血KL-6水平对高级别CIP的预测价值，采用Kaplan-Meier生存曲线进行生存分析，本研究经河北北方学院附属第一医院伦理委员会批准（编号：L2026025）。**结果：**本研究最终纳入92例CIP患者，其中低级别CIP 56例，高级别CIP 36例。低、高级别CIP在年龄、发热、功能状态（performance status，PS）评分、CIP期间合并感染方面差异有统计学意义（$P<0.05$），高级别CIP的NLR、PLR、SII、KL-6水平均高于低级别CIP（$P<0.05$），低、高级别CIP在非特异性间质性肺炎、合并肺气肿、合并胸腔积液、胸膜增厚方面差异有统计学意义（$P<0.05$）。单因素logistic回归分析显示，发热、PS评分3~4分、合并肺气肿、外周血KL-6高水平为晚期NSCLC患者发生高级别CIP的危险因素（$P<0.05$）。多因素logistic回归分析显示，合并肺气肿、外周血KL-6高水平是晚期NSCLC患者发生高级别CIP的独立危险因素（$P<0.05$）。基线NLR、PLR、SII、KL-6与CIP分级均呈正相关性（$P<0.05$）。KL-6预测高级别CIP的曲线下面积为0.895，灵敏度为83.9%，特异度为86.1%。低、高级别CIP在甲泼尼龙≥80 mg/d的疗程、起始口服激素＞1 mg/kg/d、对激素的反应、使用免疫抑制剂、使用免疫球蛋白、抗生素治疗、抗真菌治疗方面差异有统计学意义（$P<0.05$）。高级别CIP的主要死亡原因为CIP疾病本身，低级别CIP主要死亡原因为肿瘤进展，差异有统计学意义（$P<0.05$）。通过Kaplan-Meier生存曲线分析结果显示，低级别CIP的中位总生存期（overall survival，OS）为19.20个月，高级别CIP为16.60个月，差异有统计学意义（$P<0.05$）。**结论：**与低级别CIP患者相比，高级别CIP患者年龄大、PS评分高、发热及肺部感染性疾病多，NLR、PLR、SII、KL-6水平高且与CIP分级呈正相关性，影像学类型以非特异性间质性肺炎为主，合并肺气肿、胸腔积液、胸膜增厚比例高，使用激素

**基金项目：**河北省自然科学基金（H2025405013）。
**利益冲突：**作者声明无利益冲突。
**伦理批件：**L2026025。
**知情同意：**豁免。
**引用本文：**袁胜芳, 姬泽萱, 任　婕, 等. 不同严重程度的晚期非小细胞肺癌患者免疫检查点抑制剂相关性肺炎的临床特征分析[J]. 中国癌症杂志, 2026, 36(3): 268-277.


**Funding:** Hebei Provincial Natural Science Foundation (H2025405013).
**Conflicts of interest:** authors declare no conflicts of interest.
**Ethical approval:** L2026025.
**Informed consent:** exemption.
**Cite this article:** YUAN S F, JI Z X, REN J, et al. Clinical analysis of immune checkpoint inhibitor-associated pneumonia of varying severity in patients with advanced non-small cell lung cancer[J]. Chin Oncol, 2026, 36(3): 268-277.

剂量高，疗程长，预后差，高水平KL-6和肺气肿是高级别CIP的独立危险因素。

［关键词］ 免疫检查点抑制剂；非小细胞肺癌；肺炎；临床分析；危险因素
**中图分类号**：R734.2 **文献标志码**：A
DOI: 10.19401/j.cnki.1007-3639.2026.03.007

**Clinical analysis of immune checkpoint inhibitor-associated pneumonia of varying severity in patients with advanced non-small cell lung cancer** YUAN Shengfang, JI Zexuan, REN Jie, LI Shaohua, ZHANG Xiulong, WANG Bu (Respiratory and Critical Care Medicine Department, First Affiliated Hospital of Hebei North University, Zhangjiakou 075000)

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［**Abstract**］**Background and purpose**：Currently, research on checkpoint inhibitor-associated pneumonia (CIP) primarily focuses on its clinical characteristics, risk factors, prognosis, and relationship to clinical efficacy. However, these studies fail to distinguish between low-grade and high-grade CIP. This study aims to explore the differences of clinical characteristics between low-grade and high-grade CIP in patients with advanced non-small cell lung cancer (NSCLC), as well as the risk factors for the development of high-grade CIP. **Methods**：We retrospectively collected the case records of 92 patients with advanced NSCLC who received treatment with immune checkpoint inhibitor (ICI) at the First Affiliated Hospital of Hebei North University from January 2018 to December 2023. CIP was graded according to the Common Terminology Criteria for Adverse Events (CTCAE) 5.0: asymptomatic/mild (grade 1), moderate (grade 2), severe (grade 3), life-threatening (grade 4) and death (grade 5). Grades 1-2 were defined as low-grade CIP, and grades 3-5 were defined as high-grade CIP. The clinical characteristics, laboratory indicators, imaging features, treatment and prognosis of the two groups of patients were compared. Univariate and multivariate logistic regression analyses were used to screen the influencing factors of high-grade CIP in NSCLC patients. Spearman's correlation coefficient was used to analyze the correlation between neutrophil-lymphocyte ratio (NLR), platelet-lymphocyte ratio (PLR), systemic immune-inflammation index (SII), Krebs von den Lungen-6 (KL-6), and CIP grading. Receiver operating characteristic curve analysis was used to evaluate the predictive value of peripheral blood KL-6 levels for high-grade CIP, and Kaplan-Meier survival curve analysis was used for survival analysis. This study was approved by the Ethics Committee of the First Affiliated Hospital of Hebei North University (L2026025). **Results**：This study ultimately included 92 CIP patients, with 56 cases of low-grade CIP and 36 cases of high-grade CIP. Low- and high-grade CIP showed statistically significant differences in age, fever, performance status (PS) score and concurrent infections during CIP ($P$<0.05). The levels of NLR, PLR, SII and KL-6 were higher in high-grade CIP than in low-grade CIP ($P$<0.05). There were significant differences in nonspecific interstitial pneumonia, concurrent emphysema, concurrent pleural effusion and pleural thickening between low- and high-grade CIP ($P$<0.05). Univariate logistic regression analysis revealed that fever, PS score of 3-4, concurrent emphysema and high peripheral blood KL-6 levels were risk factors for the development of high-grade CIP in patients with advanced NSCLC ($P$<0.05). Multivariate logistic regression analysis indicated that concurrent emphysema and high peripheral blood KL-6 levels were independent risk factors for the development of high-grade CIP in patients with advanced NSCLC ($P$<0.05). Baseline NLR, PLR, SII and KL-6 levels were positively correlated with CIP grade ($P$<0.05). The area under the curve for KL-6 in predicting high-grade CIP was 0.895, with a sensitivity of 83.9% and a specificity of 86.1%. There were significant differences in the duration of methylprednisolone treatment ≥80 mg/d, initial oral steroid dose >1 mg/kg/d, steroid response, use of immunosuppressants, immunoglobulin, antibiotics and antifungal treatment between low- and high-grade CIP ($P$<0.05). The main cause of death in high-grade CIP was the CIP disease itself, while the main cause of death in low-grade CIP was tumor progression, with a statistically significant difference ($P$<0.05). Kaplan-Meier survival curve analysis showed that the median overall survival (OS) for low-grade CIP was 19.20 months, while for high-grade CIP it was 16.60 months, with a statistically significant difference ($P$<0.05). **Conclusion**：Compared with patients with low-grade CIP, those with high-grade CIP were older, had higher PS scores, more frequently presented with fever and pulmonary infectious diseases, and had higher levels of NLR, PLR, SII and KL-6, which were positively correlated with CIP grade. Imaging findings were predominantly nonspecific interstitial pneumonia, with a high proportion of concurrent emphysema, pleural effusion and pleural thickening. Patients with high-grade CIP had higher steroid doses, longer treatment durations and poorer prognoses. High levels of KL-6 and emphysema were independent risk factors for high-grade CIP.

［**Key words**］Immune checkpoint inhibitors; Non-small cell lung cancer; Pneumonia; Clinical analysis; Risk factor

免疫检查点抑制剂（immune checkpoint inhibitor，ICI）的应用为恶性肿瘤的治疗带来了革命性突破，显著改善了晚期非小细胞肺癌（non-small cell lung cancer，NSCLC）患者的预后[1]。ICI是针对机体免疫检查点的单克隆抗体，可以阻断T细胞负性共刺激信号通路，恢复机体的抗肿瘤应答，促进T细胞对肿瘤细胞的清除[2]。常见的ICI有程序性死亡受体1

（programmed cell death protein1，PD-1）抑制剂、程序性死亡配体1（programmed death-ligand 1，PD-L1）抑制剂及细胞毒性T淋巴细胞相关抗原4（cytotoxic T lymphocyte-associated antigen-4，CTLA-4）抑制剂。然而，ICI在促进自身免疫系统激活的同时，持续活化的T细胞也可导致包括肺在内的多个器官的不良反应，即免疫相关不良反应（immune-related adverse event，irAE）[2]。其中，免疫检查点抑制剂相关性肺炎（checkpoint inhibitor-associated pneumonia，CIP）作为ICI治疗最主要的肺部不良反应，发生率介于2.7%~20.0%，且近半数患者可能出现严重症状，甚至进展为呼吸衰竭等危及生命的并发症[3]。随着CIP治疗水平的提高，大部分1~2级CIP患者和许多3~4级CIP患者在停用ICI和（或）糖皮质激素治疗后均可恢复。然而，既往存在肺部疾病、激素耐药的CIP、继发性肺部感染性疾病等是CIP患者常见的预后不良因素，尤其是高级别CIP患者[4-5]。目前对于CIP的研究多集中于其临床特征、危险因素、预后及与临床疗效的关系，但这些研究多数并未区分低、高级别CIP。因此，本研究重点在于识别低、高级别的CIP患者不同的临床特征及发生高级别CIP的危险因素，以期能够改善重症CIP患者的预后。

## 1 材料和方法

### 1.1 研究对象

本研究为回顾性研究。回顾性收集2018年1月—2023年12月于河北北方学院附属第一医院接受ICI治疗的826例晚期NSCLC患者的临床资料、实验室指标及影像学资料，并通过门诊复查、住院、电话等方式获得患者的随访信息，中位随访时间为18.2个月，随访截至2024年6月30日，总生存期（overall survival，OS）定义为自接受免疫治疗起至死亡的时间，研究日期截止时未达到终点的事件按截尾数据处理。

纳入标准：① 18岁以上；② 临床资料完整；③ 经病理学检查及电子发射计算机体层成像（positron emission tomography and computed tomography，PET/CT）检查确诊的ⅢB或Ⅳ期[6] NSCLC患者；④ 结合患者的临床特征及影像学特征确诊为CIP。排除标准：① 临床资料不完整；② 在ICI治疗前经历过结核病、细菌或真菌感染的患者（排除这些疾病对细胞因子的影响）；③ 临床症状或心脏疾病未得到很好控制的患者。

本研究经河北北方学院附属第一医院伦理委员会批准（编号：L2026025），由于本研究为回顾性研究，因此豁免了患者的知情同意。

### 1.2 诊断标准

CIP的诊断仍为排除性诊断：在免疫治疗期间每3周或每次用药前进行评估，若患者出现新发呼吸系统症状或原有症状加重、发热、乏力等表现，和（或）胸部CT检查发现新发肺部阴影，并排除肺部感染、肺癌进展和（或）肺水肿[7]。

根据国家癌症研究所首次入院时常用的不良事件通用术语标准（Common Terminology Criteria for Adverse Events，CTCAE）5.0对CIP进行分级：无症状/轻度（1级）、中度（2级）、重度（3级）、危及生命（4级）和死亡（5级）[8]。本研究中将1~2级定义为低级别CIP，3~5级定义为高级别CIP。

激素无效性CIP[9]包括激素难治和激素抵抗。其中激素难治性CIP定义为糖皮质激素治疗3 d后临床症状及影像学表现均无改善的CIP；激素抵抗性CIP定义为糖皮质激素治疗3 d后临床症状获得部分缓解但未完全改善的CIP。

本研究中CIP患者的预后包括治愈、改善、稳定、恶化和死亡5种：治愈的标准为CIP相关临床症状完全消失，活动耐力恢复正常，胸部CT检查显示肺部磨玻璃影、实变影等异常表现消失；改善的标准为CIP相关临床症状程度减轻，活动耐力有所提高，胸部CT检查显示肺部病变范围较前缩小，磨玻璃影、实变影等异常表现部分吸收；稳定的标准为CIP相关的临床症状较前改善不显著或轻度改善，胸部CT显示肺部病变范围较前无扩大，磨玻璃影、实变影等异常表现较前无明显进展或吸收；恶化的标准为CIP相关的临床症状较前加重，胸部CT检查显示肺部病变范围较前明显扩大，磨玻璃影、实变影等异常表现较前增多、融合或出现新的肺部病变区域。

### 1.3 方法

对CIP患者的基本临床资料、实验室检查、影像学特征、治疗情况及预后进行总结分析。基本临床资料包括患者的年龄、性别、吸烟史、体质量指数（body mass index，BMI）、是否发热、有无基础疾病（包括肺部基础疾病）、功能状态（performance status，PS）评分、肺癌的病理学类型、分期、免疫治疗时机、免疫药物类型、是否联合其他治疗及CIP期间是否合并肺部感染。首次出现CIP相关症状或影像学改变时ICI治疗前

的血清学指标包括基线白细胞介素（interleukin，IL）-2、IL-4、IL-6、IL-10、肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）、乳酸脱氢酶（lactate dehydrogenase，LDH）、白蛋白（albumin，ALB）、血浆D-二聚体（plasma d-dimer，D-Dimer）、C-反应蛋白（C-reactive protein，CRP）、涎液化糖链抗原-6（Krebs von den Lungen-6，KL-6）、中性粒细胞与淋巴细胞比值（neutrophil-lymphocyte ratio，NLR）、血小板与淋巴细胞比值（platelet-lymphocyte ratio，PLR）、全身免疫炎症指数（systemic immune-inflammation index，SII），SII=中性粒细胞计数×血小板计数/淋巴细胞计数。影像学分型由长期从事肺癌和间质性肺病临床工作的3名胸部放射科医师根据美国胸科协会/欧洲呼吸学会间质性肺炎的分类并结合Naidoo等[10]报道的CIP的影像学模式进行归纳、诊断、分类，同时统计是否合并肺气肿、胸腔积液、胸膜增厚等影像学特征，当意见存在分歧时经讨论达成一致。

### 1.4 统计学处理

采用IBM SPSS 27.0软件进行统计学分析，连续变量若服从正态分布，用$\bar{x}\pm s$表示，组间比较采用独立样本$t$检验，连续变量若不服从正态分布，用M（P25，P75）表示，组间比较采用Mann-Whitney $U$检验；分类变量表示为$n$（%），组间比较采用$\chi^2$检验。采用单因素和多因素logistic回归分析筛选NSCLC患者发生高级别CIP的影响因素，采用Spearman相关系数对NLR、PLR、SII、KL-6与CIP分级进行相关性分析，采用受试者工作曲线分析KL-6预测高级别CIP的价值，采用Kaplan-Meier生存曲线log-rank检验进行生存分析。采用双侧显著性检验，$P$<0.05为差异有统计学意义。

## 2 结　果

### 2.1 晚期NSCLC低、高级别CIP患者的一般临床资料

根据纳入和排除标准，共纳入94例CIP患者，建立数据库的过程中发现高、低级别CIP组各有1例患者治疗信息存在逻辑错误，因此去除2例病例，最终纳入92例CIP患者，CIP患者筛选及分级流程图见图1。CIP 1级18例，CIP 2级38例，CIP 3级28例，CIP 4级8例，CIP 5级0例，低级别CIP 56例，高级别CIP 36例。高级别CIP在年龄≥65岁、出现发热、PS评分3~4分及CIP期间合并感染的比例方面更高，差异有统计学意义（$P$<0.05），在性别、吸烟史、BMI、基础疾病（包括糖尿病、冠心病、心律失常、高血压、脑梗死、陈旧性脑出血、慢性阻塞性肺疾病、类风湿关节炎、干燥综合征、间质性肺病）、病理学类型、肿瘤分期、PD-L1表达（将TPS≥1%定义为PD-L1阳性表达）、免疫治疗时机、免疫治疗药物、联合其他方案治疗及是否有前驱放疗方面差异无统计学意义（$P$>0.05，表1）。

### 2.2 晚期NSCLC低、高级别CIP患者的实验室指标

高级别CIP中的NLR、PLR、SII、KL-6水平高于低级别CIP，其影像学类型以非特异性间质性肺炎（nonspecific interstitial pneumonia，NSIP）为主，合并肺气肿及胸腔积液的比例较高，差异均有统计学意义（$P$<0.05），高级别CIP外周血中的IL-2、IL-4、IL-6、IL-10、TNF-α、LDH、ALB、D-Dimer、CRP水平与低级别CIP相比，差异均无统计学意义（$P$>0.05，表2）。

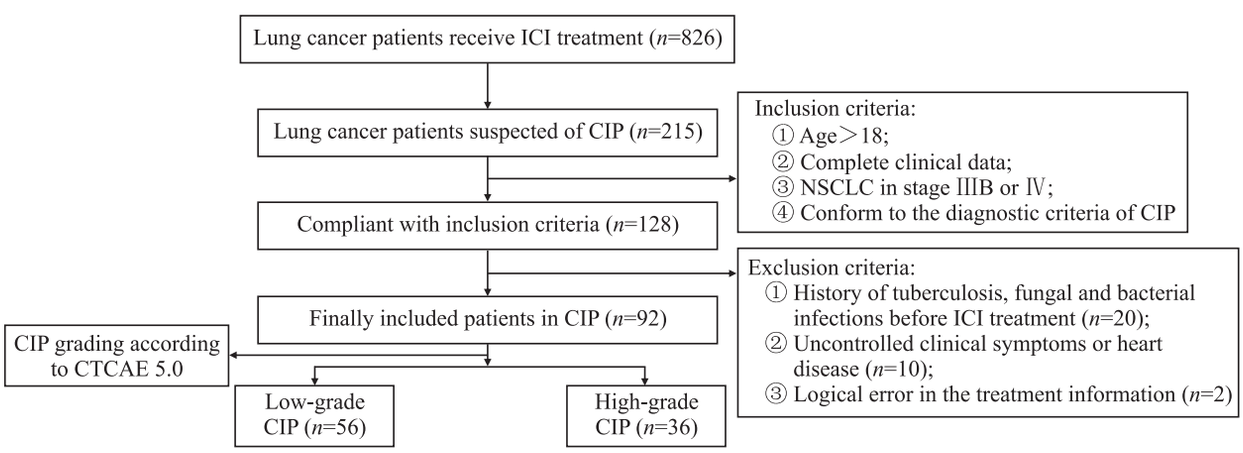


图1 CIP患者筛选及分级流程图

**Fig. 1 Flowchart for screening and grading of CIP patients**

表1 晚期NSCLC低、高级别CIP患者的一般临床资料

**Tab. 1 General clinical data of low- and high-grade CIP patients**

［*n*（%）］

| Variable | Low-grade CIP (*n*=56) | High-grade CIP (*n*=36) | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Age | | | 11.683 | ＜0.001 |
| ≥65 | 20 (35.71) | 26 (72.22) | | |
| ＜65 | 36 (64.29) | 10 (27.78) | | |
| Gender | | | 0.014 | 0.905 |
| Man | 38 (67.86) | 24 (66.67) | | |
| Women | 18 (32.14) | 12 (33.33) | | |
| Smoking history | | | 0.093 | 0.760 |
| Yes | 42 (75) | 28 (77.78) | | |
| No | 14 (25) | 8 (22.22) | | |
| BMI/(kg·m$^{-2}$) | | | 0.692 | 0.405 |
| ≤24 | 44 (78.57) | 27 (75.00) | | |
| ＞24 | 12 (21.43) | 9 (25.00) | | |
| Fever | | | 10.337 | 0.001 |
| Yes | 8 (14.29) | 16 (44.44) | | |
| No | 48 (85.71) | 20 (55.56) | | |
| Underlying disease | | | 0.052 | 0.820 |
| No | 22 (39.29) | 15 (41.67) | | |
| Yes | 34 (60.71) | 21 (58.33) | | |
| Basic pulmonary conditions | | | 0.577 | 0.447 |
| COPD | 16 (28.57) | 13 (36.11) | 0.141 | 0.708 |
| ILD | 6 (10.71) | 3 (8.33) | | |
| Pathological type | | | 0.001 | 0.970 |
| Squamous carcinoma | 34 (60.71) | 22 (61.11) | | |
| Non-squamous carcinoma | 22 (39.29) | 14 (38.89) | | |
| Tumor staging | | | 0.043 | 0.835 |
| ⅢB | 23 (41.07) | 14 (38.89) | | |
| Ⅳ | 33 (58.93) | 22 (61.11) | | |
| Expression of PD-L1 | | | | |
| Not detected | 20 (35.71) | 12 (33.33) | 0.067 | 0.967 |
| Positive | 22 (39.29) | 15 (41.67) | | |
| Negative | 14 (25) | 9 (25) | | |
| PS score | | | 4.955 | 0.026 |
| 1-2 | 38 (67.86) | 16 (44.44) | | |
| 3-4 | 18 (32.14) | 20 (55.56) | | |
| Timing of immunotherapy | | | 0.089 | 0.765 |
| First-line | 45 (80.36) | 28 (77.78) | | |
| Second-line and above | 11 (19.64) | 8 (22.22) | | |
| Immunotherapy drug types | | | 0.139 | 0.933 |
| Tislelizumab | 20 (35.71) | 13 (36.11) | | |
| Camrelizumab | 19 (33.93) | 11 (30.56) | | |
| Sintilimab | 17 (30.36) | 12 (33.33) | | |
| Combination therapy | | | 0.067 | 0.996 |
| No | 6 (10.71) | 3 (8.33) | | |
| Chemotherapy | 32 (57.14) | 19 (52.78) | | |
| Targeted therapy | 8 (14.29) | 5 (13.89) | | |
| Chemotherapy+anti-angiogenic drugs | 10 (17.86) | 6 (16.67) | | |
| Preceding radiotherapy | | | 2.006 | 0.157 |
| No | 12 (21.43) | 11 (30.56) | | |
| Yes | 44 (78.57) | 25 (69.44) | | |
| Complicated with pulmonary infection during CIP | | | 9.113 | 0.003 |
| Yes | 10 (17.86) | 17 (47.22) | | |
| No | 46 (82.14) | 19 (52.78) | | |

COPD: Chronic obstructive pulmonary disease; ILD: Interstitial lung disease.

表2 晚期NSCLC患者低、高级别CIP实验室资料对比

**Tab. 2 Comparison of laboratory data from low- and high-grade CIP**

| Variable | Low-grade CIP (*n*=56) | High-grade CIP (*n*=36) | $Z/t/\chi^2$ value | *P* value |
|---|---|---|---|---|
| Baseline peripheral blood indicator | | | | |
| IL-2/(pg·mL$^{-1}$) M (P25, P75) | 12.34 (11.09, 13.59) | 13.21 (11.62, 14.82) | -0.820 | 0.412 |
| IL-4/(pg·mL$^{-1}$) M (P25, P75) | 13.53 (12.57, 14.54) | 13.64 (12.69, 14.68) | -0.844 | 0.399 |
| IL-6/(pg·mL$^{-1}$) M (P25, P75) | 8.28 (7.20, 9.33) | 8.42 (7.90, 9.58) | -0.896 | 0.370 |
| IL-10/(pg·mL$^{-1}$) M (P25, P75) | 14.75 (12.47, 15.93) | 15.08 (12.60, 16.23) | -0.908 | 0.364 |
| TNF-α/(pg·mL$^{-1}$) M (P25, P75) | 17.95 (16.23, 19.88) | 19.07 (17.11, 20.32) | -1.520 | 0.128 |
| LDH/(U·L$^{-1}$) $\bar{x}\pm s$ | 325.41±85.05 | 330.55±86.64 | -0.281 | 0.780 |
| ALB/(g·L$^{-1}$) $\bar{x}\pm s$ | 32.60±4.78 | 32.72±4.42 | -0.121 | 0.904 |
| NLR M (P25, P75) | 3.09 (2.26, 3.25) | 5.38 (4.42, 6.41) | -7.269 | ＜0.001 |
| PLR M (P25, P75) | 225.72 (155.65, 269.00) | 291.79 (239.25,322.44) | -4.672 | ＜0.001 |
| SII M (P25, P75) | 705.79 (692.37, 712.29) | 848.72 (838.47,860.12) | -8.064 | ＜0.001 |
| D-Dimer/(mg·L$^{-1}$) $\bar{x}\pm s$ | 2.10±0.731 | 2.13±0.57 | -0.213 | 0.832 |
| KL-6/(U·mL$^{-1}$) M (P25, P75) | 634 (599, 862) | 928 (843, 951) | -8.065 | ＜0.001 |
| CRP/(mg·L$^{-1}$) $\bar{x}\pm s$ | 45.74±9.68 | 48.24±9.40 | -1.221 | 0.225 |
| CIP imaging feature | | | | |
| OP *n* (%) | 34 (60.72) | 10 (27.78) | 14.745 | 0.002 |
| NSIP *n* (%) | 20 (35.71) | 18 (50) | | |
| Overlap between OP and NSIP *n* (%) | 0 (0.00) | 5 (13.89) | | |
| Other types *n* (%) | 2 (3.57) | 3 (8.33) | | |
| Other radiological feature | | | | |
| Emphysema *n* (%) | 16 (28.57) | 22 (61.11) | 9.570 | 0.002 |
| Pleural condition | | | | |
| Normal *n* (%) | 34 (60.71) | 13 (36.11) | 12.013 | 0.003 |
| Pleural effusion *n* (%) | 10 (17.86) | 16 (44.44) | | |
| Pleural thickening *n* (%) | 12 (21.43) | 7 (19.44) | | |

OP: Organizing pneumonia.

### 2.3 接受ICI治疗的晚期NSCLC患者发生高级别CIP危险因素的logistic回归分析

以发生高级别CIP为因变量，将两组患者的临床资料、实验室结果中差异有统计学意义的指标（年龄、是否发热、PS评分、是否合并肺气肿、CIP影像学特征、胸膜情况、NLR、PLR、SII、KL-6水平）作为协变量进行单因素logistic回归，结果显示，发热、PS评分3~4分、合并肺气肿、外周血KL-6水平为晚期NSCLC发生高级别CIP的危险因素（*P*＜0.05，表3）。再将差异有统计学意义的指标进行多因素分析，结果显示，合并肺气肿及外周血KL-6水平是晚期NSCLC患者发生高级别CIP的独立影响因素（*P*＜0.05，表3、4）。

表3 晚期NSCLC患者发生高级别CIP的单因素logistic回归分析

**Tab. 3 Univariate logistic regression analysis of high-grade CIP in patients with advanced NSCLC**

| Variable | *B* | *SE* | Wald $\chi^2$ | *P* value | OR | 95% CI |
|---|---|---|---|---|---|---|
| Age (＜65, ≥65) | 0.154 | 0.506 | 0.093 | 0.761 | 1.167 | 0.433-3.145 |
| Fever (yes, no) | -1.569 | 0.508 | 9.525 | 0.002 | 4.800 | 1.773-12.998 |
| PS score (1-2, 3-4) | 0.970 | 0.441 | 4.844 | 0.028 | 2.639 | 1.112-6.262 |
| Emphysema (yes, no) | 0.890 | 0.438 | 4.119 | 0.042 | 2.434 | 1.031-5.748 |
| CIP imaging features (OP, other) | 0.099 | 0.435 | 0.052 | 0.820 | 1.104 | 0.471-2.589 |
| Pleural condition (normal, abnormality) | 0.260 | 0.453 | 0.329 | 0.566 | 1.297 | 0.534-3.148 |
| NLR | 0.001 | 0.003 | 0.080 | 0.777 | 1.001 | 0.996-1.006 |
| PLR | 0.006 | 0.046 | 0.015 | 0.903 | 1.006 | 0.918-1.101 |
| SII | 0.028 | 0.023 | 1.475 | 0.225 | 1.029 | 0.983-1.076 |
| KL-6 | 1.981 | 0.405 | 23.966 | ＜0.001 | 7.429 | 3.280-16.020 |

OR: Odds ratio.

表4　晚期NSCLC患者发生高级别CIP的多因素logistic回归分析

**Tab. 4　Multivariate logistic regression analysis of high-grade CIP in patients with advanced NSCLC**

| Variable | *B* | *SE* | Wald $\chi^2$ | *P* | OR | 95% CI |
|---|---|---|---|---|---|---|
| Fever (yes, no) | 0.472 | 0.995 | 0.225 | 0.635 | 1.603 | 0.228-11.259 |
| PS score (1-2,3-4) | -0.188 | 0.758 | 0.061 | 0.804 | 2.972 | 0.506-17.467 |
| Emphysema (yes, no) | 1.085 | 0.522 | 4.320 | 0.038 | 2.959 | 1.064-8.230 |
| KL-6 | 0.020 | 0.006 | 12.303 | ＜0.001 | 1.021 | 1.009-1.032 |

### 2.4　基线NLR、PLR、SII、KL-6与CIP分级的相关性分析

采用Spearman相关性分析对基线NLR、PLR、SII、KL-6与CIP分级的相关性进行分析，结果显示，基线NLR、PLR、SII、KL-6与CIP分级均呈正相关性（$r$=0.896、0.755、0.727、0.919，$P$=0.001）。

### 2.5　外周血KL-6预测高级别CIP的价值

外周血KL-6预测高级别CIP的曲线下面积为0.895（95% CI：0.831~0.959），约登指数为0.70，最佳截断值为786 U/mL，预测的灵敏度为83.9%，特异度为86.1%（图2）。

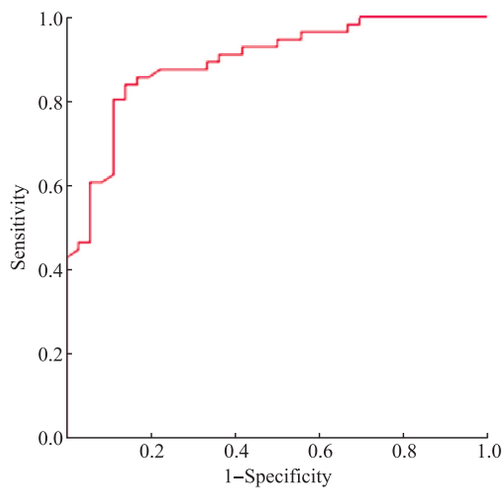


图2　外周血KL-6预测高级别CIP的价值

**Fig. 2　The value of peripheral blood KL-6 in predicting high-grade CIP**

### 2.6　晚期NSCLC低、高级别CIP的治疗

与低级别CIP相比，高级别CIP甲泼尼龙剂量≥80 mg/d、起始口服激素＞1 mg/kg/d、激素无效性CIP、使用免疫抑制剂、免疫球蛋白、抗生素、抗真菌治疗的比例更高，使用甲泼尼龙≥80 mg/d的疗程更长，差异均有统计学意义（$P$＜0.05，表5）。

### 2.7　晚期NSCLC低、高级别CIP的预后

与低级别CIP相比，高级别CIP的死亡率更高（$P$＜0.05），在死亡原因中，低级别CIP归因于肿瘤进展的比例更高，高级别CIP归因于CIP疾病本身的比例更高，差异均有统计学意义（$P$＜0.05，表6）。采用Kaplan-Meier生存曲线分析结果显示，低级别CIP的中位OS为19.20个月，高级别CIP为16.60个月，log-rank检验提示差异有统计学意义（$\chi^2$=63.40，$P$＜0.001，图3）。

表5　晚期NSCLC患者低、高级别CIP的药物管理

**Tab. 5　Drug management for low- and high-grade CIP in patients with advanced NSCLC**

［*n*（%）］

| Item | Low-grade CIP (*n*=56) | High-grade CIP (*n*=36) | $Z/\chi^2$ value | *P* value |
|---|---|---|---|---|
| Methylprednisolone ≥80 mg/d | 18 (32.14) | 30 (83.33) | 23.01 | ＜0.001 |
| Methylprednisolone ≥80 mg/d course of treatment (d) | 4 (3,5) | 10 (9,12) | -8.188 | ＜0.001 |
| Initial oral administration of steroids＞1 mg/kg/d | 8 (14.29) | 24 (66.67) | 26.505 | ＜0.001 |
| Hormone-resistant CIP | | | | |
| Yes | 6 (10.71) | 14 (38.89) | 92.00 | ＜0.001 |
| No | 50 (89.29) | 22 (61.11) | | |
| Immunosuppressant | 3 (5.36) | 10 (27.78) | 9.078 | 0.001 |
| Immunoglobulin | 0 (0.00) | 8 (22.22) | 10.974 | ＜0.001 |
| Antibiotic treatment (excluding sulfanilamide) | 8 (14.29) | 12 (33.33) | 123.156 | ＜0.001 |
| Antifungal treatment | 2 (3.57) | 7 (19.44) | 4.586 | 0.032 |

表6 晚期NSCLC患者低、高级别CIP的预后

**Tab. 6 Prognosis of low-grade and high-grade CIP in patients with advanced NSCLC**

［*n*（%）］

| Item | Low-grade CIP (*n*=56) | High-grade CIP (*n*=36) | $\chi^2$ value | *P* value |
|---|---|---|---|---|
| Cure | 20 (35.71) | 2 (5.56) | | |
| Improve | 10 (17.86) | 3 (8.33) | | |
| Stable | 6 (10.71) | 5 (13.89) | 17.627 | 0.001 |
| Deteriorate | 4 (7.14) | 6 (16.67) | | |
| Death | 16 (28.57) | 20 (55.56) | | |
| Cause of death | | | | |
| CIP | 4 (25.00) | 13 (65.00) | | |
| Tumor progression | 10 (62.50) | 5 (25.00) | 6.062 | 0.048 |
| Other (heart disease or other underlying diseases) | 2 (12.50) | 2 (10.00) | | |

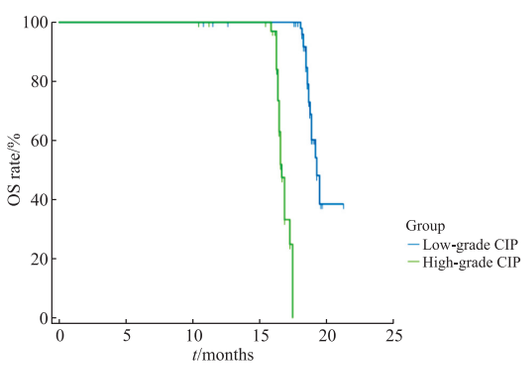


图3 晚期NSCLC患者低、高级别CIP的生存曲线

**Fig. 3 Survival curves for low- and high-grade CIP in patients with advanced NSCLC**

## 3 讨 论

ICI在晚期NSCLC患者的治疗中是一把双刃剑，它可以显著延长患者的OS，但在抗癌免疫治疗过程中，ICI激活宿主免疫会引起irAE，从而导致ICI暂时或永久中断。irAE可能危及生命，通常需要长期服用免疫抑制剂，这可能与患者预后不良有关。CIP，尤其是高级别的CIP，是一种相对罕见但严重的、潜在威胁生命的irAE。本研究旨在识别低、高级别CIP在临床特征、实验室指标、影像学特征、治疗及预后方面的差异，以及发生高级别CIP的危险因素。

研究显示，男性[11]、既往吸烟史[11]、年龄≥65岁[12]、PS评分≥2分[13]、肥胖[14]、PD-L1高表达[15]、合并慢性阻塞性肺炎（chronic obstructive pulmonary disease，COPD）[15]、间质性肺疾病（interstitial lung disease，ILD）[16]、鳞癌[17]、前驱放疗[18]、ICI一线治疗[19]及免疫联合治疗[20]均为发生CIP的危险因素。Huang等[21]研究发现，高级别CIP患者的年龄更大、发热更多、美国东部肿瘤协作组（Eastern Cooperative Oncology Group，ECOG）评分更高。同样，Sun等[22]研究发现，高级别CIP患者的ECOG评分更高。本研究显示，高级别CIP患者的年龄更大、PS评分更高、合并发热更多，而在性别、吸烟史、BMI、PD-L1表达、合并肺部基础疾病、病理学类型、分期、是否前驱放疗、ICI治疗时机、免疫联合治疗方面，低、高级别CIP无显著差异，提示发生CIP的危险因素并非发生高级别CIP的危险因素，在ICI治疗过程中，需要多关注高龄、PS评分3~4分的患者，他们可能是预防高级别CIP发生的重点关注对象。

血清学指标中，基线IL-6、IL-10、CRP、LDH水平的升高和ALB水平的降低与肺癌CIP的发生相关[23]，有研究[4]显示，CIP发生时外周血中较高的LDH水平与难治性CIP独立相关。Sumi等[24]研究发现，NLR和PLR升高与肺癌患者发生CIP有关。Matsukane等[25]研究发现，NLR升高与CIP严重程度相关。陈慧娟等[26]研究发现，基线高水平PLR和SII与CIP严重程度相关。Saito等[27]研究发现，高级别CIP患者外周血KL-6水平升高。Matsukane等[28]研究发现，KL-6预测CIP的受试者工作特征曲线的曲线下面积为0.903，灵敏度为81.8%，特异度为91.6%。目前，KL-6对于高级别CIP的预测价值尚无相关研究。本研究中，低、高级别CIP患者血清中基线IL-2、IL-6、IL-10、TNF-α、LDH、CRP、D-Dimer水平未见显著差异，这可能与上述指标均为COPD的评估指标有关，而两组患者中合并COPD比例差别不大，因此可能导致上述指标差异无统计学意义。高级别CIP的基线NLR、PLR、SII、KL-6水平均高于低级别CIP，并且相关性分析提示基线NLR、PLR、SII、KL-6与CIP分级呈正相关性，提示其基线水平可能与CIP的严重程度相关。KL-6预测高级别CIP的曲线下面积为0.895，预测的灵敏度为83.9%，特异度为86.1%，表明在接受ICI的晚期NSCLC患者中，KL-6可能是高级别CIP的有效筛查标志物。

CIP的影像学分型主要包括机化性肺炎型

（organizing pneumonia，OP）、NSIP、过敏性肺炎型（hypersensitivity pneumonitis，HP）、弥漫性肺泡损伤/急性间质性肺炎型（diffuse alveolar damage/ acute interstitial pneumonitis，DAD/AIP）、支气管肺炎型[29]。赵博峰等[30]研究发现，中、重度CIP的影像模式以弥漫性DAD/AIP为主，而Huang等[21]研究发现，中、高级别CIP中NSIP型所占比例更高，此外还发现高级别CIP CT影像合并肺气肿、胸腔积液、胸膜增厚的比例更高。Atchley等[5]研究发现，肺气肿是高级别CIP的独立影响因素。肺气肿是肺部疾病的病理学表现，是COPD的重要组成部分，当存在肺气肿的患者出现持续气流受限后可发展为COPD，ILD是一组以肺泡为单位的炎症和间质纤维化为基本病变的肺部疾病总称，部分吸烟的患者可出现ILD和肺气肿共存的表现。本研究中，相较于低级别CIP，两者在COPD、ILD中的比例无显著差别，但高级别CIP中NSIP所占比例更高，同时合并肺气肿、胸腔积液、胸膜增厚的比例也更高，通过logistic回归分析结果显示，肺气肿是高级别CIP的独立危险因素，与Saito等[27]和Atchley等[5]的研究结果一致。

治疗CIP的主要药物为糖皮质激素，国内指南[7]对于高、低级别CIP激素治疗的推荐剂量及疗程也有所不同。值得注意的是，有研究[2]表明，3~4级CIP及中性粒细胞绝对计数>7.16×$10^9$/L与激素无效性CIP相关。对于激素无效性CIP，建议使用英夫利昔单抗、霉酚酸酯、他克莫司、环磷酰胺和其他免疫抑制剂[31]。本研究中，相较于低级别CIP，高级别CIP中激素无效性CIP所占比例更高，使用免疫抑制剂、免疫球蛋白的比例更高，这与Schneider等[32]的研究结果一致。另外，尽管国内指南[7]不推荐CIP患者早期使用抗生素治疗，但本研究显示，高级别CIP在CIP治疗期间更容易出现感染，使用抗生素及抗真菌治疗的比例更高，这可能是因为高级别CIP糖皮质激素使用的剂量及疗程均高于低级别CIP，同时部分患者联合应用免疫抑制剂，从而导致机会性感染的发生率更高。所以对于高级别CIP，可以探索采用更短的疗程和（或）更小剂量的糖皮质激素进行优化治疗，包括JAK抑制剂、阿巴西普和托珠单抗，以减少机会性感染的风险。

尽管有研究[28]显示，在接受ICI单一治疗的晚期NSCLC患者中，任何级别的irAE的发展都与更好的临床结果相关。然而本研究显示，高级别CIP的预后要比低级别CIP更差。Sun等[22]研究显示，所有死于CIP的患者PS评分均为2分以上，其中75%合并肺部感染，而本研究中高级别CIP PS评分3~4分及合并肺部感染的所占比例更高，这些因素均可能造成高级别CIP预后不良。此外高级别CIP中激素无效性CIP比例更高也可能是高级别CIP预后不良的危险因素。因此在ICI治疗过程中，预防高级别CIP的发生及积极治疗高级别CIP有助于延长患者的生存期。

本研究仍存在一定的局限性。首先，这是一项单中心回顾性研究，样本量有限，可能存在选择性偏倚；其次，既往病历信息记录存在不一致的情况，造成信息偏倚；最后，收集数据过程中未考虑到患者合并用药、并发症处理差异等情况，未能控制混杂因素，可能影响数据的外推性，未来仍需要大样本量、多中心的前瞻性研究进行验证。

综上所述，与低级别CIP患者相比，高级别CIP患者年龄大、PS评分高、发热及肺部感染性疾病多，NLR、PLR、SII、KL-6水平高且与CIP分级呈正相关性，影像学类型以NSIP为主，合并肺气肿、胸腔积液、胸膜增厚比例高，使用激素剂量高，疗程长，患者预后差，基线高水平KL-6与肺气肿是高级别CIP的独立危险因素。

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（收稿日期：2025-11-21 修回日期：2026-01-05）
（责任编辑：李广涛）