卓越医见：肿瘤和免疫治疗 DOI：10.13406/j.cnki.cyxb.003844



免疫检查点抑制剂相关性肺炎的风险因素和预后

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【摘 要】免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）被广泛应用于晚期实体瘤治疗，并获得了良好的临床获益。然而，ICIs 在激活机体免疫反应发挥抗肿瘤效果的同时，也会导致全身多个器官系统的炎症反应，称为免疫相关不良事件（immune-related adverse events，irAEs）。免疫检查点抑制剂肺炎（checkpoint inhibitor pneumonitis，CIP）是严重的 irAE 之一，可影响免疫治疗疗效，甚至危及生命。因此，识别 CIP 的危险因素和寻找预测标志物对于实体瘤患者接受 ICIs 治疗的前期评估和全程监测和治疗至关重要。本文总结了 CIP 的研究进展，包括发生率、危险因素、治疗及预后，并讨论了 CIP 的管理和预测生物标志物，为临床诊断和机制研究提供参考。

【关键词】免疫治疗；免疫检查点抑制剂；免疫相关不良事件；免疫检查点抑制剂肺炎；危险因素；生物标志物；预后
【中图分类号】R392.1；R730.51 【文献标志码】A 【收稿日期】2025-01-06

Risk factors and prognosis of checkpoint inhibitor pneumonitis

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【**Abstract**】Immune checkpoint inhibitors（ICIs）have been widely used in the treatment of advanced solid tumors and have brought good clinical benefits. However，while ICIs can activate immune response in the body to exert an antitumor effect，they can also cause inflammatory response in multiple organ systems throughout the body，known as immune-related adverse events（irAEs）. Checkpoint inhibitor pneumonitis（CIP）is one of severe irAEs，which can affect the efficacy of immunotherapy and even be life-threatening. Therefore，identifying the risk factors for CIP and exploring related predictive markers are of great importance for the pre-treatment assessment and whole-course monitoring and treatment of patients with solid tumors receiving ICIs. This article summarizes the research advances in CIP，including incidence rate，risk factors，treatment，and prognosis，and discusses the biomarkers for the clinical management and prediction of CIP，in order to provide a reference for clinical diagnosis and mechanism studies.

【**Key words**】immunotherapy；immune checkpoint inhibitors；immune-related adverse events；checkpoint inhibitor pneumonitis；risk factors；biomarkers；diagnosis

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基金项目：国家自然科学基金面上资助项目（编号：81572875）；山东省自然科学基金面上资助项目（编号：ZR202102190539）；CSCO 领航肿瘤研究基金资助项目（编号：Y-2019AZMS-0440）；CSCO 默沙东肿瘤研究基金资助项目（编号：Y-MSD2020-0350）。
优先出版：https://link.cnki.net/urlid/50.1046.R.20250418.1630.014（2025-04-21）

免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）通过阻断免疫细胞上的抑制性受体来增强机体对肿瘤的免疫反应[1]，包括程序性死亡受体 1（programmed death protein 1，PD-1）抗体、程序性死亡配体 1（programmed death ligand-1，PD-L1）抗体和细胞毒性 T 淋巴细胞抗原 4（cytotoxic T lymphocyte-associated protein-4，CTLA-4）抗体等。ICIs 目前已广泛应用于晚期实体瘤的治疗，提高了患者临床获益，延长了总生存期（overall survival，OS），且安全性良好[2]。尽管 ICIs 的疗效获得了肯定，但其在激活机体免疫反应的同时，也会使正常组织产生炎症反应，临床上称为免疫相关不良事件（immune-related adverse events，irAEs）[3]。这种 irAEs 可累及全身各个器官及系统，如皮肤、内分泌器官、结肠、肝脏和肺等[4-5]。确诊 irAEs 的患者需酌情停用 ICIs，并联合糖皮质激素和免疫抑制剂治疗。然而，针对严重 irAEs 的治疗可能延误抗肿瘤治疗的时机，降低抗肿瘤疗效[6-7]。

免疫检查点抑制剂肺炎（checkpoint inhibitor pneumoni-

tis，CIP）是严重的irAE之一，可能危及生命，有研究显示其占ICIs相关死亡率的35.0%[8]。识别CIP的危险因素和预测标志物对于实体瘤患者接受ICIs治疗的前期评估和全程监测和治疗至关重要。本文总结了CIP的研究进展，包括发生率、危险因素、治疗及预后，并讨论了CIP的管理和预测生物标志物，旨在为临床诊断和机制研究提供参考。

1 发生率

肺部肿瘤[小细胞肺癌（small cell lung cancer，SCLC）[9]、非小细胞肺癌（non-small cell lung cancer，NSCLC）[10]]患者CIP发生率较结直肠癌[11]、食管癌[12]及黑色素瘤[13-14]等肺外肿瘤更高。此外，接受ICIs治疗的肾癌患者CIP发生率也较高，即使其中高级别CIP发生率较NSCLC患者明显降低[15]。虽然实体瘤患者接受ICIs治疗的临床试验中，CIP发生率通常在1.3%~10.1%[15-16]，但某些特定情况下，如舒格利单抗联合同步/序贯放化疗的临床试验中CIP的发生率达18.8%[17]，但是在真实世界的研究中，CIP发生率较前瞻性临床试验更高[18-19]。

2 预测因子

研究显示，在接受PD-1/PD-L1抑制剂治疗基线时患者特征、外周血循环生物标志物、基础疾病、肿瘤相关特征及抗肿瘤治疗等因素均有可能是CIP的危险因素（表1）。

2.1 临床风险因子

2.1.1 患者基线特征 研究显示，患者性别[34,42]、既往吸烟史及吸烟量[20-21,36]、年龄（或≥65岁）[20]、基线ECOG PS≥2[22]、抗血小板药物使用史[25]、高血压病史[26]及肥胖[43]等与CIP发病风险相关，此外，使用PD-1/PD-L1抑制剂的男性及使用CTLA-4抑制剂的女性发生CIP的风险较高[44-45]。

2.1.2 肺部基础疾病 研究显示肺组织耐受外部损伤能力差的患者CIP发病率高[46-47]。合并肺部疾病，如肺部纤维化[22]、胸腔积液[23]、COPD[24]、间质性肺炎[35]及肺气肿[23]等是CIP发生的风险因素，并且肺气肿与高级别CIP独立相关[37]。但也有研究显示，合并COPD并不能预测CIP的发生[48]。除基线肺组织受损之外，哮喘也与高级别CIP发生有关，这种风险在吸烟患者中相对显著吸烟[49]。此外，Sumi T等[39]发现免疫基线时低%DLCO与高级别CIP发生相关。但是，Frost

表1 CIP发生危险因素及生物标志物

文献	危险因素（OR）
［20］	年龄≥65岁（1.86），吸烟史（2.04）
［21］	吸烟量（20.33），肺部转移（10.08）
［22］	ECOG PS≥2（6.53），肺部纤维化（20.13）
［23］	肺气肿（2.87）、ILD（4.76）、胸腔积液（3.00）、ICI期间放疗史（4.30）
［24］	COPD（7.194）、PD-L1表达≥50%（7.184）、基线IL-8水平（<9.0 pg/mL，*OR*=0.758）
［25］	抗血小板药物使用史（3.46）
［26］	ILD（15.580），肺气肿（15.179），高血压（6.796），高PLR水平（8.765）
［27］	高剂量胸部放疗（≥6 000 cGy）（2.642）
［28］	ILD（6.03），胸腔外转移（0.34）
［29］	间质性肺异常（6.42）、间质异常中磨玻璃病变（4.05）
［30］	既往胸部放疗（3.33）、既往肺病（2.82）和联合治疗（3.42）
［31］	高WBC（6.04），低RLC（5.01）
［32］	吸烟史（168.56）、IL-6（25.28）、CRP（12.85）、$CD8^+$T淋巴细胞计数（74.68）、SP-A（46.92）和KL-6（123.44）
［33］	年老（1.056）、ECOG PS较差（6.170）、既往放疗史（4.005）、WBC（>7.1×10^9/L）（1.604）和ALC（<1.0×10^9/L）（0.288）
［34］	年龄增长（1.04/年），基线呼吸短促（2.51），女性（0.33），血小板计数增加（0.52/对数单位）
［35］	间质性肺炎（14.7）
［36］	全级别CIP：吸烟量≥50包年（3.01），ECOG PS≥2（3.44）；高级别CIP：吸烟量≥50包年（3.65），ECOG PS≥2（4.36）
［37］	基线纤维化（aOR=6.61），阻塞性肺病（aOR=2.79）
［38］	肺间质异常（9.77）、既往胸部放疗（2.15）
［39］	高级别CIP：高SP-D水平（≥103）（13.57），低%DLCO（≤71.1）（6.71），鳞状细胞癌（5.03）
［40］	FVC，% pred（0.734）
［41］	TICA，早发性CIP（8.2）

注：比值比，odds ratio，OR；ECOG体力状态评分，Eastern Cooperative Oncology Group Performance Status，ECOG PS；间质性肺疾病，interstitial lung disease，ILD；慢性阻塞性肺疾病，chronic obstructive pulmonary disease，COPD；血小板/淋巴细胞比值，platelet-lymphocyte ratio，PLR；中性粒细胞/淋巴细胞比值，neutrophil-lymphocyte ratio，NLR；表面活性剂蛋白A，surfactant pulmonary-associated protein A，SP-A；表面活性剂蛋白D，surfactant protein，SP-D；涎液化糖链抗原，Krebs Von den Lungen-6，KL-6；一氧化碳弥散量，diffusing capacity for carbon monoxide，%DLCO；用力肺活量，forced vital capacity，FVC；中央气道肿瘤浸润，tumor invasion in the central airway，TICA

N等[50]的研究得到了相反的结果。除了%DLCO之外，Suzuki Y等[40]还发现基线时降低的1s用力肺活量（forced expiratory volume in one second，FEV1）和用力肺活量（forced vital capacity，FVC）是ir-ILD的危险因素。Osaki M等[51]发现较其他ILD患者而言，ICIs治疗肺癌时孤立的胸膜肺实质弹性纤维增生症（pleuroparenchymal fibroelastosis，PPFE）患者中CIP发生率明显降低，且中位OS更长（575 vs. 326 d）。

2.1.3 肿瘤相关特征 肺癌患者较其他肿瘤患者更易发生CIP[52]，且鳞状细胞癌患者发生CIP的风险更高，但是肺腺癌患者发生CIP时死亡率更高（2.7倍）[53]，这或许与肺部肿瘤浸润导致肺部免疫微环境改变有关。除肺原发肿瘤之外，肺部转移[23]、针对肺部的胸部放疗[50]尤其是高剂量胸部放疗[27]、ICIs一线治疗[54]、ICIs基线前30 d内使用皮质醇激素[55]及CMV病毒感染[56]等同样会改变肺部免疫微环境改变，增加CIP的易感性。此外，肿瘤免疫微环境（包括PD-L1表达水平）的差异及正常间质中T细胞数量差异也是CIP的风险因素，研究显示PD-L1表达水平不仅提示CIP高风险[24]，且与CIP影像分型及发生时间相关。Watanabe S等[57]发现在PD-L1表达高水平的亚组中，影像表现为隐源性机化性肺炎（ground glass opacities，GGO）的CIP患者中位发病时间较影像表现为磨玻璃影型（cryptogenic organizing pneumonia，COP）明显提前。此外，有研究发现肿瘤分期较低的患者接受ICIs联合治疗时，CIP发生率较高[19]，或许与早期肿瘤对肺部炎症环境的影响不同有关。

2.1.4 抗肿瘤治疗 研究表明，放疗相关因素，如放疗剂量（≥6 000 cGy）[27]、放疗方式（根治性放疗vs.姑息性放疗）[47]等与CIP风险增加相关联。在放疗时机上，基线前存在放疗史与CIP风险增加相关[58]，Anscher MS等[59]还发现放疗后90 d内接受ICIs治疗也与CIP高风险有关，虽然放疗后超过90 d后接受ICIs治疗也会导致低级别CIP的发生，其潜在原因可能是放疗后细胞死亡及免疫原性分子暴露，二者与ICIs引发的炎症反应相互叠加，最终导致过度的炎症反应[60]。在ICIs方面，单药治疗时PD-L1抑制剂安全性较PD-1抑制剂更高（3.8% vs. 8.4%），但在高级别CIP发生率上，二者并无明显差异[61-62]。CTLA4抑制剂单用不会增加CIP风险，但联合PD-1/PD-L1抑制剂则与更高的CIP发生风险相关[63]。虽然ICIs与CIP风险增加有关，但增加剂量并不会影响CIP发生[64]。另外，多种免疫联合治疗模式同样是CIP发生的危险因素，如化疗[65]、靶向VEGF[66]、免疫[67]及放疗或同步/序贯放化疗[17]等，这可能与联合治疗导致的肺毒性重叠效应相关[68]。但是也有研究显示，与单药治疗相比，联合治疗不会明显增加CIP的发病率[69]。值得注意的是，ICIs序贯靶向治疗不仅与早发性肺炎相关（发病时间分别为35 d和62 d），还会大幅增加高级别CIP的风险（≥3级的发生率分别为100%和0%）[27]。

2.2 预测标志物

2.2.1 外周血细胞计数 Sheshadri A等[34]在AML队列中发现较高的基线血小板计数与CIP低风险相关，也有研究发现WBC和绝对淋巴细胞计数是NSCLC[61]和黑色素瘤[31]患者发生CIP的独立危险因素。此外，基线时较高的嗜酸性粒细胞计数（$\geq 0.125 \times 10^9$个/L）[70]、嗜酸性粒细胞百分比[71]、$CD8^+$ T淋巴细胞计数[72]及高CD4T淋巴细胞比例[73]等与CIP高风险相关，且预示着更好的疗效和预后。

2.2.2 血细胞相关比值 研究显示，NLR和PLR升高与肺癌患者发生CIP有关[39]，Matsukane R等[74]发现患者发生CIP前约4周开始出现NLR升高，且NLR升高与CIP严重程度密切相关。除CIP开始前升高的NLR以外，Chu XL等[70]还发现基线时较高PLR和SII水平也与CIP严重程度相关。

2.2.3 血清蛋白 Li XQ等[32]发现急性期蛋白（IL-6和CRP）和血清肺泡上皮蛋白（如SP-A和KL-6）是CIP的危险因素。也有研究发现基线时较低的HB和ALB水平与CIP发生相关[18,75]。Tan P等[76]发现CIP发生时外周血中较高的LDH水平与难治性CIP独立相关。此外，研究显示CIP发生时外周血中也存在潜在预测CIP发展的标志物，如自身抗体CD74水平升高有助于识别CIP的发生[77]，CIP患者血清中高迁移率族蛋白B1（HMGB1）水平升高[78]及高级别CIP患者平均KL-6水平升高[79]。但是Matsukane R等[74]发现CIP发生时KL-6升高与CIP严重程度无关。

2.2.4 细胞因子 IL-6、IL-10和LDH水平升高和ALB水平降低与肺癌患者CIP发生相关[21]。基线IL-8水平较高与较低的CIP发生率相关[24]，而基线IL-10高水平患者CIP风险更高（*HR*=9.969）[80]。治疗前CXCL9、MMP-1、IL-6和IL-19水平与ICI-ILD相关[81]。

3 CIP患者的疗效与预后

3.1 CIP与疗效、预后的总体关系

研究显示，NSCLC[82]，SCLC[83]患者发生CIP可提示更好的客观缓解率（objective response rate，ORR）、无进展生存期（progression free survival，PFS）及OS。不过，不同研究存在差异，如Redelman-Sidi G等[84]发现CIP虽提示更好的ORR但不影响OS，还有研究基于永生时间偏倚后的生存分析显示，CIP与较短的PFS和OS明显相关[85]。

3.2 CIP等级与疗效、预后的关系

Huang Y等[86]的meta分析表明，CIP与更好的ORR相关，且高级别CIP提示更短的OS，但CIP发生并不会改善PFS。Murata D等[81]发现CIP发生似乎并不影响PFS及OS，但是低级别CIP则提示更好的PFS和OS，他们还发现高水平IL-19与更差的PFS和OS相关。Tone M等[87]也发现高级别CIP（11/22）与更低的ORR、更短的PFS和OS相关。但是Yang J等[73]却发现高级别CIP提示更好的ORR（高级别 vs. 低级别 vs. 无CIP：44.4% vs. 35.3% vs. 28.4%）。

3.3 CIP其他因素与疗效、预后的关系

①影像类型：Zhang J等[83]发现1~2级CIP和影像表现为COP、过敏性肺炎（hypersensitivity pneumonitis，HP）型的CIP与ICIs疗效增强相关。Watanabe S等[57]发现ICI-ILD与良好预后相关（mPFS：未达到 vs. 8.6个月，mOS：14.8 vs. 24.5个月），且GGO型CIP患者OS劣于COP型患者（7.8 vs. 13.2

月），这可能与GGO亚型患者的CIP发病时间、抗PD-1治疗周期、类固醇治疗频率等因素有关。②CIP发生时机：Huang A等[88]发现早发型CIP中高级别CIP发病率和死亡率都比晚发型CIP更高。

3.4 CIP对激素治疗的敏感性与疗效及预后相关

研究发现类固醇难治性CIP会增加患者死亡率[19,89]。此外，Shimomura K等[90]指出早发型高级别irAEs（包括CIP）和大剂量激素治疗irAEs是实体瘤患者的不良预后因素，他们还发现ICIs治疗60 d内不同糖皮质激素剂量与中位OS相关，但60 d后使用的糖皮质激素剂量与预后无明显相关性。但是Albarrán V等[55]得到了不同的结果，他们发现ICIs治疗后短期内使用类固醇导致ORR和是疾病控制率（disease control rate，DCR）下降，不影响PFS，且6个月后使用类固醇的患者累积剂量越高，PFS越长。

4 CIP的治疗和转归

4.1 CIP的诊断与分级治疗

ASCO指南推荐，应用ICIs治疗的患者出现呼吸道症状或影像表现时，确诊CIP后需分级治疗，且需根据CIP等级考虑停用ICIs，并酌情给予免疫抑制剂[7]，如糖皮质激素或二线免疫抑制剂治疗[91-92]（图1）。此外，激素治疗期间需注意预防激素相关副作用，如胃肠道刺激、高血压、高血糖，尤其特殊病原菌感染性，如念珠菌、卡氏孢子虫等真菌感染的发生，若4~6周内未能按计划将激素减量完毕，需长期使用糖皮质激素的患者（≥12周），可使用PPI和Bactrim用于胃肠道和肺孢子菌预防，并且同时补充钙和维生素D[93-97]。

4.2 CIP的转归

一般情况下，无症状CIP或者1级CIP可自行缓解，Valente M等[98]发现肺嗜酸性粒细胞增多亚型的CIP可短期内自发消退。有研究显示肺癌患者发生CIP并接受糖皮质激素治疗后，多数（67/74）可完全康复，但有14例在重启ICIs治疗后发生其他系统irAEs（43%）[50]。另外，2项不同研究发现CIP患者重启ICIs治疗后CIP复发率为33.3%[99]及34.0%[100]，且重启免疫治疗后相同irAEs的复发率为28.8%[100]。此外，糖皮质激素不敏感的难治性CIP给予二线免疫治疗后全因死亡率更高，且免疫抑制剂相关感染的风险也很高[19,101]。因此，准确识别CIP的临床特征，提早预防CIP发生及CIP的早期诊断，及时且精准处理及长程管理对于降低CIP相关死亡率，尤其是致死性CIP，提高患者生活质量至关重要。

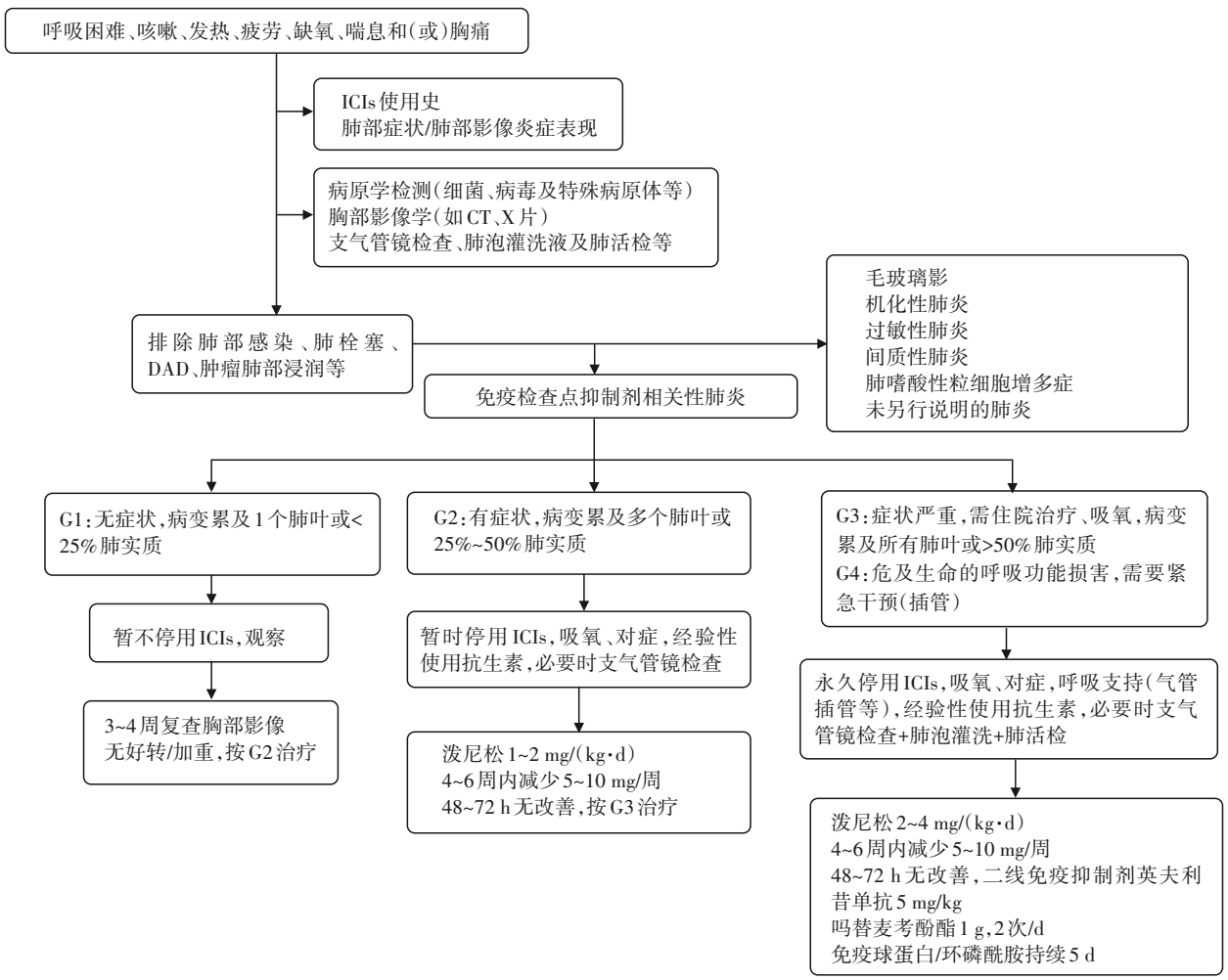


图1 CIP诊疗流程

5 结 论

CIP是与ICIs治疗相关的常见不良事件，临床试验报道的CIP发生率为1.3%~18.8%，但真实世界数据高达35%。尽管CIP的发生可能预示着良好的疗效，但需要停用ICIs的高级别CIP预示着更差的预后，如降低的PFS和OS，严重CIP可能导致患者死亡、治疗期间肺炎恶化、免疫抑制剂相关感染等。

CIP的风险因素包括性别、吸烟史、高龄、高基线ECOG评分、肺部基础疾病、肺部高肿瘤负荷、既往胸部放疗史及免疫联合治疗等。外周血中的细胞计数、血清蛋白、细胞因子等标志物与CIP发生密切相关。

CIP的诊断为排除性诊断，确诊的CIP需要分级诊疗，高级别CIP需停用ICIs及激素治疗。虽然目前的研究证明激素治疗CIP有效，但是长期使用激素的并发症仍需要密切关注。此外，难治性CIP的治疗是临床难点，如Beattie J等[101]发现接受英夫利昔单抗、吗替麦考酚酯或两药联合治疗后，CIP临床改善率仅38.5%，还有研究显示类固醇难治性CIP患者在接受二线治疗后，死亡率仍高达75%[102]。

目前在irAEs的发病机制包括：T细胞和B细胞反应性激活；抗原交叉反应；脱靶效应；Treg存活受损；细胞因子；肠道菌群；HLA等位基因异常（遗传因素）[101]，并且也发现了很多预测irAEs的生物标志物，如microRNA、肺部及全身的免疫微环境、肠道菌群等，但是这些标志物在CIP的预测、诊断中的敏感度及特异度有限，在CIP的发病机制及临床转化治疗方面也远远不足。因此，CIP的预测标志物、诊断指标及通过阻断CIP作用通道治疗CIP方面的研究仍有待探索。

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（责任编辑：李青颖）

本文引用格式：

谢 虹，王 俊. 免疫检查点抑制剂相关性肺炎的风险因素和预后[J]. 重庆医科大学学报，2025，50(6)：734-741.