·临床研究·

非小细胞肺癌免疫检查点抑制剂相关肺炎发生的危险因素

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【摘 要】 **目的** 探讨免疫检查点抑制剂相关肺炎(ICI-P)发生的危险因素及预后,为有效防治提供策略。**方法** 回顾性分析2018年1月至2023年9月在中国人民解放军总医院接受免疫治疗的753例非小细胞肺癌患者的临床资料,根据是否发生ICI-P,将患者分为ICI-P组(102例)与非ICI-P组(651例),比较两组患者的临床特征;根据ICI-P的严重程度,将ICI-P患者分为轻度组(69例)和重度组(33例),对两组进行生存分析。采用SPSS 27.0统计软件进行数据分析。根据数据类型,分别采用t检验,Mann-Whitney U检验或χ^2检验进行组间比较。采用logistic回归模型分析ICI-P发生的危险因素。采用Kaplan-Meier法评估轻度组和重度组的总生存期(OS),并采用Log-rank检验对两组患者的生存期进行比较。**结果** ICI-P发生率为13.5%(102/753)。间质性肺病(ILD)(OR=3.85,95%CI 1.99~7.46;P<0.001)、胸部放疗史(OR=2.65,95%CI 1.56~4.48;P<0.001)、同期胸部放疗(OR=3.56,95%CI 1.69~7.47;P<0.001)及使用程序性死亡受体-1(PD-1)抑制剂(OR=3.54,95%CI 1.05~11.98;P=0.04)为ICI-P的独立危险因素。轻度组预期OS为927 d,重度组为573 d,差异有统计学意义(P=0.033)。**结论** ILD、既往或同期胸部放疗及使用PD-1抑制剂是ICI-P发生的危险因素,治疗前对ILD及有胸部放疗史的患者进行重点评估、避免同步放疗是预防ICI-P的可行策略。

【关键词】 非小细胞肺癌;免疫检查点抑制剂;免疫检查点抑制剂相关肺炎
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Risk factors of immune checkpoint inhibitor-related pneumonitis in non-small cell lung cancer

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【**Abstract**】 **Objective** To study the risk factors and prognosis of immune checkpoint inhibitor-related pneumonitis (ICI-P) and provide effective strategies for its prevention and treatment. **Methods** A retrospective investigation was conducted of the medical record of 753 non-small cell lung cancer cases treated with immune checkpoint inhibitors (ICIs) at Chinese PLA General Hospital from January 2018 to September 2023. According to whether or not ICI-P occurred, the patients were divided into ICI-P group (102 cases) and non-ICI-P group (651 cases), and the clinical characteristics of the two groups were compared. According to severity of ICI-P, the patients with ICI-P were divided into a mild group (69 cases) and severe group (33 cases), and survival analysis was performed for the two groups. t test, Mann-Whitney U test or χ^2 test was used for comparison between groups. Logistic regression analyses were employed to determine the risk factors of ICI-P. Kaplan-Meier method was used to calculate the overall survival (OS) for the mild and severe groups, and Log-rank test was used to compare the survival of the two groups. **Results** The incidence of ICI-P was 13.5% (102/753). Its independent risk factors included interstitial lung disease (ILD) (OR=3.85, 95%CI 1.99-7.46; P<0.001), history of chest radiotherapy (OR=2.65, 95%CI 1.56-4.48; P<0.001), concurrent chest radiotherapy (OR=3.56, 95%CI 1.69-7.47; P<0.001) and the use of programmed cell death 1 (PD-1) inhibitors (OR=3.54, 95%CI 1.05-11.98; P=0.04). The expected OS of the mild group was 927 d against 573 d in the severe group, and the difference was statistically significant (P=0.033). **Conclusion** ILD, prior or concurrent chest radiotherapy and the use of PD-1 inhibitors are risk factors of ICI-P. Focusing on the assessment of patients with ILD and a history of chest radiotherapy before treatment and avoiding concurrent radiotherapy are feasible strategies for preventing ICI-P.

【**Key words**】 non-small cell lung cancer; immune checkpoint inhibitors; immune checkpoint inhibitor-related pneumonia
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免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)可改善晚期非小细胞肺癌(non-small cell lung cancer, NSCLC)患者的预后。研究显示,与传统化疗相比,接受 ICIs 治疗的患者总生存期增加了 5 倍[1]。但是,ICIs 可能导致机体免疫稳态失衡,从而对正常组织器官造成损害[2]。免疫检查点抑制剂相关肺炎(immune checkpoint inhibitor-related pneumonitis, ICI-P)为一种免疫系统介导的肺炎,可引发广泛的呼吸系统症状并伴有肺实质异常[3]。NSCLC 队列中 ICI-P 的发生率为 7% ~ 19%[4]。一项关于免疫相关不良事件的荟萃分析显示,ICI-P 的死亡率为 14%[5]。ICI-P 常导致肿瘤治疗延期,患者住院时间延长,死亡风险显著增加[6],阻碍了临床应用。研究 ICI-P 发生的危险因素是对其进行有效防治的重要手段。

既往研究报道,ICI-P 发生的危险因素主要包括:年龄≥70 岁[7]、吸烟史[8]、间质性肺病[7,9](interstitial lung disease, ILD)、慢性阻塞性肺疾病[6]、既往放疗[10,11]以及使用抗程序性死亡因子 1(programmed cell death 1, PD-1)药物[12,13]。但是,上述研究的样本量普遍较小,中国学者开展的较大 ICI-P 样本量研究也仅为 75 例[14],吸烟史对 ICI-P 的影响也存在不一致的研究结果。因此,本研究开展此项大样本回顾性调查,将上述潜在危险因素全部纳入研究,以期阐明 ICI-P 发生的危险因素。

1 对象与方法

1.1 研究对象

经中国人民解放军总医院医学伦理委员会批准(批准号:S2024-619-02),检索 2018 年 1 月至 2023 年 9 月集成病例系统(patient record integrated digital enterprise, PRIDE)数据,以“肿瘤免疫治疗”为关键词检索 ICIs 治疗的患者,去重并排除非 NSCLC 患者,经数据核查员核查后确定总病例数。

本研究纳入标准与排除标准参照文献[6]。纳入标准:(1)病理学确诊 NSCLC;(2)病历记录 ICIs 治疗并有医嘱,符合 ICI-P 诊断标准;(3)有完善的影像学资料。排除标准:(1)不符合 ICI-P 诊断标准;(2)临床资料缺失。

本研究成立由肿瘤科、呼吸科和放射诊断科专家组成的诊断小组,对初筛病历进行审核,内容包括:病史及治疗数据、检验及影像资料等;在排除确诊的感染、肿瘤进展等因素后做出诊断。ICI-P 诊断标准参照《2019 年免疫检查点抑制剂相关肺炎诊治专家共识》[15]。根据不良事件通用术语标准第 5 版对肺炎进行严重程度分级。共纳入 753 例 NSCLC 患者,将总人群按是否发生 ICI-P 分为 ICI-P 组(102 例)与非 ICI-P 组(651 例),比较其临床特征;将 ICI-P 患者按严重程度分为轻度组(69 例)和重度组(33 例),并进行生存分析。

1.2 数据采集

采集 ICIs 治疗前的基线指标,包括:(1)基本人口学资料;(2)吸烟史、既往肺部疾病史等;(3)病理及临床分期,程序性死亡因子配体 1(programmed cell death-ligand 1, PD-L1)表达、既往治疗史(手术史、化疗、靶向治疗、放疗),ICIs 用药方案(抗 PD-1/PD-L1 单药或 ICIs 联合治疗)等;(4)ICI-P 患者的生存数据,随访截止日期为 2024 年 6 月 30 日。

1.3 统计学处理

采用 SPSS 27.0 统计软件进行数据分析。符合正态分布的计量资料使用均数±标准差($\bar{x}\pm s$)表示,组间比较采用 t 检验;不符合正态分布的计量资料使用中位数(四分位数间距)[$M(Q_1, Q_3)$]表示,组间比较采用 Mann-Whitney U 检验。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。采用单因素和多因素 logistic 回归模型分析 ICI-P 发生的危险因素。采用 Kaplan-Meier 方法评估两组的总生存期(overall survival, OS),并采用 Log-rank 检验对两组生存期进行比较。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 ICI-P 组与非 ICI-P 组的整体特征

753 例患者中,ICI-P 发生率为 13.5%(102/753)。在基线资料方面,两组患者高龄、男性占比、吸烟史、ILD、既往胸部放疗及手术治疗等比较,差异有统计学意义($P<0.05$);PD-L1 表达、COPD、病理分型、临床分期、联合化疗及靶向治疗情况比较,差异无统计学意义($P>0.05$;表 1)。在肿瘤治疗方案上,两组在同步放疗、ICIs 应用种类及应用 PD-1 抑制剂方面比较,差异有统计学意义($P<0.05$;表 2)。部分患者入院前在外院进行了外周血生物标志物检验,数据在本院无法检索。因此,两组患者外周血生物标志物情况纳入统计的病例数分别为 ICI-P 组(95 例)和非 ICI-P 组(589 例)。外周血生物标志物情况比较,ICI-P 组的基线白细胞计数、中性粒细胞计数和淋巴细胞与单核细胞比例显著高于非 ICI-P 组,差异有统计学意义($P<0.05$);两组患者血红蛋白、血小板计数、嗜酸性粒细胞计数、单核细胞计数、淋巴细胞计数情况比较,差异无统计学意义($P>0.05$;表 3)。

表1 两组患者基线资料比较

Table 1 Comparison of baseline data between two groups

Item	All Patients(n=753)	ICI-P group(n=102)	Non-ICI-P group(n=651)	P value
Age[years, $M(Q_1, Q_3)$]	64(57,69)	66(60,71)	64(57,69)	0.024
Gender[n(%)]				0.019
Male	615(81.7)	92(90.2)	523(80.3)	
Female	138(18.3)	10(9.8)	128(19.7)	
History of smoking[n(%)]				0.003
No	207(27.5)	16(15.7)	191(29.3)	
Current/ former	519(68.9)	83(81.4)	436(67.0)	
Unknown	27(3.6)	3(2.9)	24(3.7)	
Smoking pack year≥30[n(%)]	408(54.2)	65(63.7)	343(52.7)	0.035
ILD[n(%)]	57(7.6)	20(19.6)	37(5.7)	<0.001
COPD/emphysema[n(%)]	190(25.2)	30(29.4)	160(24.6)	0.327
Obstructive pneumonia[n(%)]	198(26.3)	31(30.4)	167(25.7)	0.334
Tumor histologic type[n(%)]				0.764
Squamous	354(47.0)	48(47.1)	306(47.0)	
Adenocarcinoma	356(47.3)	50(49.0)	306(47.0)	
Other	43(5.7)	4(3.9)	39(6.0)	
PD-L1 expression[n(%)]				0.548
Positive	341(45.3)	46(45.1)	295(45.3)	
Negative	95(12.6)	16(15.7)	79(12.1)	
Not assessed	317(42.1)	40(39.2)	277(42.5)	
PD-L1 expression≥50%[n(%)]	137(18.2)	22(21.6)	115(17.7)	0.592
Stage[n(%)]				0.222
Ⅰ/Ⅱ	40(5.3)	4(3.9)	36(5.5)	
Ⅲ	302(40.1)	49(48.0)	253(38.9)	
Ⅳ	411(54.6)	49(48.0)	362(55.6)	
Prior cancer treatment[n(%)]				
Thoracic surgery	156(20.7)	13(12.7)	143(22.0)	0.035
Chemotherapy	433(57.5)	58(56.9)	375(57.6)	0.914
Targeted therapy	189(25.1)	26(25.5)	163(25.0)	0.903
Thoracic radiotherapy	127(16.9)	28(27.5)	99(15.2)	0.004

ICI-P: immune checkpoint inhibitor-related pneumonitis; ILD: interstitial lung disease; COPD: chronic obstructive pulmonary disease; PD-L1: programmed cell death-ligand 1.

表2 两组患者治疗方案比较

Table 2 Comparison of ICIs strategy between two groups [n(%)]

Item	ICI-P group(n=102)	Non-ICI-P group(n=651)	P value
Line of therapy			0.450
First line	57(55.9)	390(59.9)	
At least second line	45(44.1)	261(40.1)	
ICIs monotherapy	24(23.6)	151(23.2)	1.000
Concurrent treatment with ICIs			0.355
Chemotherapy	51(50.0)	290(44.5)	
Targeted therapy	13(12.7)	72(11.1)	
Chemotherapy and targeted therapy	14(13.7)	138(21.2)	
Concurrent radiation	89(87.3)	619(95.1)	0.005
ICIs			0.004
Pembrolizumab	41(40.2)	238(36.6)	
Sintilimab	17(16.7)	153(23.5)	
Nivolumab	13(12.7)	73(11.2)	
PD-L1 inhibitor	3(2.9)	56(8.6)	
Tislelizumab	16(15.7)	40(6.1)	
Toripalimab	4(3.9)	44(6.8)	
Camrelizumab	5(4.9)	36(5.5)	
Ipilimumab	2(2.0)	2(0.3)	
Other	1(1.0)	9(1.4)	
PD-1/PD-L1 inhibitor			0.048
PD-1 inhibitor	99(97.1)	595(91.4)	
PD-L1 inhibitor	3(2.9)	56(8.6)	

ICIs: immune checkpoint inhibitors; ICI-P: immune checkpoint inhibitor-related pneumonitis; PD-L1: programmed cell death-ligand 1; PD-1: programmed cell death 1.

表 3 两组患者外周血生物标志物情况比较

Table 3 Comparison of peripheral blood biomarkers between two groups

Item	ICI-P group(n=95)	Non-ICI-P group(n=589)	P value
WBC($\times10^9$/L, $\bar{x}\pm s$)	7.51±3.12	6.85±2.55	0.023
ANC($\times10^9$/L, $\bar{x}\pm s$)	5.32±2.82	4.69±2.19	0.012
Hb(g/L, $\bar{x}\pm s$)	126.38±18.80	126.96±18.38	0.775
PLT[$\times10^9$/L, $M(Q_1, Q_3)$]	229(185,290)	229(181,289)	0.536
AEC[$\times10^9$/L, $M(Q_1, Q_3)$]	0.16(0.06,0.28)	0.12(0.06,0.22)	0.242
AMC[$\times10^9$/L, $M(Q_1, Q_3)$]	0.50(0.35,0.67)	0.46(0.34,0.60)	0.159
ALC[$\times10^9$/L, $M(Q_1, Q_3)$]	1.39(0.91,1.78)	1.38(1.01,1.79)	0.742
LDH[U/L, $M(Q_1, Q_3)$]	167(147,205)	174(149,205)	0.668
LMR[$M(Q_1, Q_3)$]	2.70(1.99,3.65)	3.06(2.08,4.34)	0.024
PLR[$M(Q_1, Q_3)$]	176(140,238)	166(126,238)	0.128
ENR[$M(Q_1, Q_3)$]	0.03(0.01,0.06)	0.03(0.02,0.06)	0.613
NLR[$M(Q_1, Q_3)$]	3.36(2.47,5.51)	3.12(2.13,4.56)	0.052

ICI-P: immune checkpoint inhibitor-related pneumonitis; WBC: white blood cell; ANC: absolute neutrophil count; Hb: hemoglobin; PLT: platelet; AEC: absolute eosinophil count; AMC: absolute monocyte count; ALC: absolute lymphocyte count; LDH: lactic dehydrogenase; LMR: lymphocyte to monocyte ratio; PLR: platelet to lymphocyte ratio; ENR: eosinophil to neutrophil ratio; NLR: neutrophil to lymphocyte ratio.

2.2 ICI-P 发生的危险因素的 logistic 回归分析

Logistic 回归模型中,变量赋值情况见表 4。单因素 logistic 回归分析发现,男性、年龄≥65 岁、吸烟史、ILD 病史、既往胸部放疗、同期胸部放疗与 ICI-P 发病风险增加相关(P<0.05);手术史与 ICI-P 风险降低相关(P<0.05)。将单因素分析中 P<0.1 的变量纳入多因素 logistic 回归分析,结果显示,既往 ILD 病史、胸部放疗史、同期胸部放疗和 PD-1 抑制剂是 ICI-P 发生的独立危险因素(表 5)。

2.3 ICI-P 对生存期的影响

102 例 ICI-P 病例中,轻度 69 例(67.6%);重度 33 例(32.4%)。中位诊断时间 141(73,329)d。ICI-P 按等级的累积发病率见图 1。重度组的预期 OS 为 573 d,轻度组为 927 d,两组差异有统计学意义(P=0.033;图 2)。

表 4 变量赋值

Table 4 Variable assignment

Variable	Assignment condition
Gender	Male=1, Female=0
Age	≥65 years= 1, <65 years=0
History of smoking	Yes=1, No=0
History of ILD	Yes=1, No=0
COPD/ emphysema	Yes=1, No=0
Postobstructive pneumonia	Yes=1, No=0
Thoracic surgery	Yes=1, No=0
Prior chest radiotherapy	Yes=1, No=0
Priorchemotherapy	Yes=1, No=0
Priortargeted therapy	Yes=1, No=0
Concurrentchest radiotherapy	Yes=1, No=0
Type of ICIs	PD-1=1, PD-L1=0
Line of therapy	1=1, >1=0

ILD: interstitial lung disease; COPD: chronic obstructive pulmonary disease; ICIs: immune checkpoint inhibitors.

表 5 ICI-P 发生的危险因素的 logistic 回归分析

Table 5 Logistic regression analysis of risk factors of ICI-P occurrence

Factor	Univariate Analysis		Multivariate analysis	
	OR(95%CI)	P value	OR(95%CI)	P value
Gender	2.25(1.14-4.45)	0.019	1.31(0.55-3.15)	0.550
Age	1.69(1.10-2.58)	0.016	1.47(0.94-2.31)	0.090
History of smoking	2.27(1.30-3.96)	0.004	1.71(0.83-3.51)	0.150
History of ILD	4.05(2.24-7.31)	<0.001	3.85(1.99-7.46)	<0.001
COPD/ emphysema	0.78(0.49-1.24)	0.297		
Postobstructive pneumonia	0.79(0.50-1.25)	0.313		
Thoracic surgery	0.52(0.28-0.96)	0.035	0.59(0.31-1.11)	0.100
Prior chest radiotherapy	2.11(1.30-3.43)	0.003	2.65(1.56-4.48)	<0.001
Priorchemotherapy	1.03(0.68-1.57)	0.888		
Priortargeted therapy	1.02(0.63-1.65)	0.922		
Concurrent chest radiotherapy	2.83(1.43-5.59)	0.003	3.56(1.69-7.47)	<0.001
Type of ICIs	3.11(0.95-10.12)	0.060	3.54(1.05-11.98)	0.040
Line of therapy	1.18(0.77-1.80)	0.442		

ICI-P: immune checkpoint inhibitors-related pneumonitis; ILD: interstitial lung disease; COPD: chronic obstructive pulmonary disease; ICIs: immune checkpoint inhibitors.

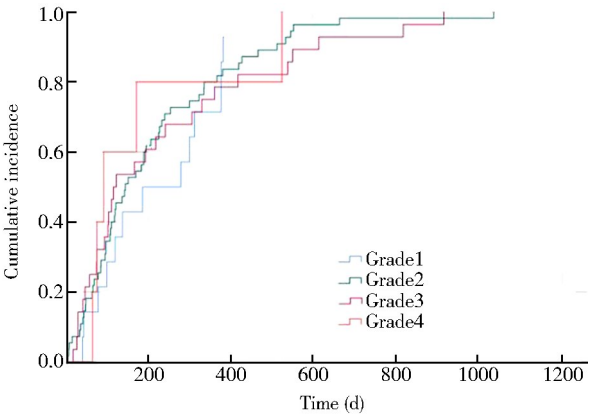
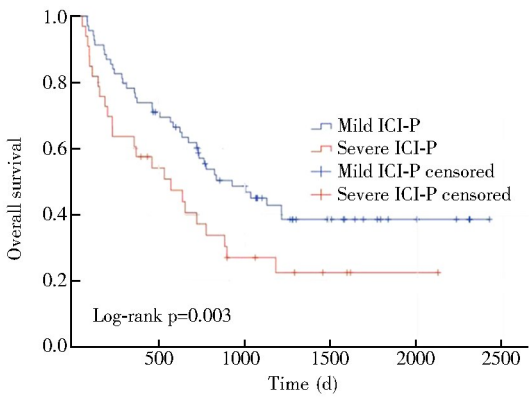


图1 免疫检查点抑制剂相关肺炎累积发病率曲线

Figure 1 Cumulative incidence curve of ICI-P

ICI-P: immune checkpoint inhibitors-related pneumonitis.



Patients at risk (*n*)

Mild ICI-P	69	47	28	13	4	0
Severe ICI-P	33	16	7	3	1	0

图2 轻度组与重度组免疫检查点抑制剂相关肺炎的生存期比较

Figure 2 Expected overall survival of mild and severe ICI-P groups

ICI-P: immune checkpoint inhibitors-related pneumonitis.

3 讨 论

本研究纳入753例接受ICIs治疗的NSCLC病例，对确诊的102例ICI-P患者进行危险因素及生存研究，为迄今为止国内该领域样本量较大的回顾性研究。在本研究中，ICI-P发病率为13.5%，与真实世界的研究结果一致[4]，但明显高于前瞻性研究结果[16,17]。原因可能有两个方面：(1)随着时间推移，ICI-P诊断水平不断提升；(2)研究队列的特征对结果可能有一定影响，本队列中男性占81.7%，吸烟率为68.9%，吸烟是ICI-P发生及致死的高危因素[18]，不能排除男性吸烟者比例较高对ICI-P发生率的影响。

NSCLC中ICI-P的发生率高于其他恶性肿瘤，如黑色素瘤和胃肠道肿瘤[16,19]，这可能与NSCLC肺部基础病、肺部原发病灶及治疗有关[2]。因此，本研究将基础性肺病史纳入研究，发现ILD病史与ICI-P发生显著有关，这与针对实体肿瘤ICI-P的研究结果一致[9,20]。有研究发现COPD是ICI-P发病的危险因素[6]，肺功能检测异常也可能是发生ICI-P的危险因素[20]。本研究中，大多数患者没有进行肺功能评估，COPD主要通过影像学检查被动发现，没有得出与之一致的结果。

本研究结果显示，无论是既往还是同步胸部放疗，都是ICI-P发生的独立危险因素。近年研究证实，放疗与肺癌患者的肺部炎症和纤维化密切相关[21]，但其对ICI-P的具体影响尚不清楚，且放射治疗与ICI-P相关联的机制还没有完全阐明，可能是局部放疗暴露了肿瘤抗原，后者成为免疫细胞的靶点[22]，而ICIs激活了免疫系统的活性，从而增加了肺炎的发生率。

有研究结果显示，与PD-L1抑制剂相比，PD-1抑制剂的毒性更高[12,13]，研究者认为PD-L1抑制剂对负抑制信号的阻断作用不那么明显，减少了自身免疫反应[23,24]。目前，缺乏这两种抑制剂在现实环境中的比较研究，本研究结果显示，PD-1抑制剂的ICI-P发生率显著高于PD-L1抑制剂，这对改进防治策略具有重要参考意义。

多项研究分别或共同研究了外周血淋巴细胞、嗜酸性粒细胞和单核细胞计数对免疫相关毒性的影响，发现细胞数量增加与免疫相关不良事件风险相关[25-27]。Pavan等[28]发现中性粒细胞与淋巴细胞比值可能与免疫毒性的发生、严重程度和预后相关。本研究结果显示，基线白细胞计数、中性粒细胞计数和淋巴细胞与单核细胞比值越高，更有可能发生ICI-P。在ICIs治疗开始前进行血常规检测可能对预测ICI-P的发生有一定的提示作用。受回顾性研究限制，治疗前的血常规结果并未全部记录，因此本研究并未将这些有显著差异的变量纳入多因素分析。

综上所述，本研究通过大样本回顾性分析发现ICI-P的发生率较高，间质性肺病、既往或同步胸部放疗以及使用PD-1抑制剂为ICI-P发生的危险因素。轻度ICI-P预后较好，预期总生存期显著高于重度组。治疗前对ILD及有胸部放疗史的患者进行重点评估、避免同步放疗是可行的防治策略。

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