

# IL-2受体水平对晚期非小细胞肺癌患者免疫检查点抑制剂联合化疗疗效和预后的预测价值

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**【摘要】 目的** 探讨血清IL-2受体(IL-2 receptor, IL-2R)水平对晚期非小细胞肺癌(non-small cell lung cancer, NSCLC)患者免疫检查点抑制剂(immune checkpoint inhibitor, ICI)联合化疗疗效及预后的预测价值。**方法** 采用回顾性队列研究设计,纳入2021年12月至2023年5月在复旦大学附属中山医院住院并接受ICI联合化疗的168例晚期NSCLC患者。根据实体瘤疗效评价标准(Response Evaluation Criteria in Solid Tumors, RECIST)将患者分为治疗有效组与无效组,收集临床资料并随访患者疗效及预后。采用 $t$ 检验比较组间差异,通过ROC曲线评估IL-2R的预测效能,并利用Cox比例风险回归模型及Kaplan-Meier法结合Log-rank检验分析IL-2R水平与NSCLC患者无进展生存期(progression-free survival, PFS)的相关性。**结果** IL-2R水平与治疗疗效呈显著负相关( $P<0.001$ ),高水平IL-2R预示治疗反应不佳。ROC分析显示,IL-2R预测疗效的AUC为0.825(95%CI: 0.754~0.895),最佳截断值为568.5 U/mL(约登指数为0.530),敏感度为80.2%,特异度为72.2%。生存分析表明,高IL-2R组中位PFS显著低于低IL-2R组(9个月 vs. 14个月,  $P=0.011$ )。多因素Cox回归分析证实IL-2R升高是疾病进展的独立危险因素( $P=0.003$ )。**结论** 血清IL-2R水平可作为晚期NSCLC患者ICI联合化疗疗效及预后的潜在预测标志物,高水平IL-2R提示治疗反应不佳且PFS较短。

**【关键词】** 非小细胞肺癌(NSCLC); IL-2受体(IL-2R); 免疫检查点抑制剂(ICI); 细胞因子; 化疗; 疗效; 预后

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## Predictive value of IL-2 receptor levels for the efficacy and prognosis of immune checkpoint inhibitors combined with chemotherapy in patients with advanced non-small cell lung cancer

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**【Abstract】 Objective** To investigate the predictive value of serum IL-2 receptor (IL-2R) levels in the efficacy and prognosis of immune checkpoint inhibitors (ICIs) combined with chemotherapy in patients with advanced non-small cell lung cancer (NSCLC). **Methods** A retrospective cohort study was

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conducted, enrolling 168 advanced NSCLC patients who received ICIs combined with chemotherapy at Zhongshan Hospital, Fudan University between Dec 2021 and May 2023. Patients were divided into responders and non-responders based on the Response Evaluation Criteria in Solid Tumors (RECIST). Clinical data were collected, and patient outcomes and prognosis were followed up. The *t*-test was used to compare intergroup differences, the ROC curve was employed to evaluate the predictive performance of IL-2R, and Cox proportional hazards regression models along with Kaplan-Meier analysis and the log-rank test were used to analyze the correlation between IL-2R levels and progression-free survival (PFS). **Results** IL-2R levels were significantly negatively correlated with treatment efficacy ( $P < 0.001$ ), with high IL-2R levels indicating poorer therapeutic response. ROC analysis revealed that the AUC for IL-2R in predicting efficacy was 0.825 (95%CI: 0.754–0.895), with an optimal cutoff value of 568.5 U/mL (Youden index of 0.530), the sensitivity of 80.2%, and the specificity of 72.2%. Survival analysis showed that the median PFS in the high IL-2R group was significantly shorter than that in the low IL-2R group (9 months *vs.* 14 months,  $P = 0.011$ ). Multivariate Cox regression confirmed that elevated IL-2R was an independent risk factor for disease progression ( $P = 0.003$ ). **Conclusion** Serum IL-2R levels may serve as a potential predictive biomarker for the efficacy and prognosis of immune checkpoint inhibitor combined with chemotherapy in advanced NSCLC patients. High IL-2R level indicates poorer treatment response and shorter PFS.

**【Key words】** non-small cell lung cancer (NSCLC); IL-2 receptor (IL-2R); immune checkpoint inhibitor (ICI); cytokine; chemotherapy; efficacy; prognosis

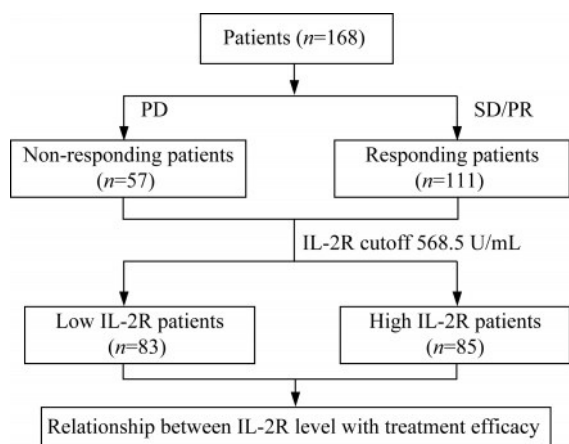
肺癌是全球癌症相关死亡的首要原因,其中约80%为非小细胞肺癌(non-small cell lung cancer, NSCLC),大部分患者在发现时已是晚期<sup>[1-2]</sup>,因此疗效预测及治疗策略直接影响其生存时间。目前CSCO 2025及NCCN 2025指南推荐免疫检查点抑制剂(immune checkpoint inhibitor, ICI)联合化疗作为无基因突变的晚期NSCLC患者的一线治疗<sup>[3-5]</sup>。但临床上缺乏对ICI联合化疗的疗效评估及预后预测的指标。因此,寻找可靠的生物标志物是近年来相关研究的重点和难点。IL-2受体(IL-2 receptor, IL-2R)作为免疫调节的核心分子,通过 $\alpha$ 、 $\beta$ 和 $\gamma$ 亚基调控T细胞功能,其异常表达与肿瘤免疫逃逸密切相关<sup>[6]</sup>。基础研究显示,IL-2R信号通路激活可促进调节性T细胞(regulatory T cell, Treg)增殖,抑制抗肿瘤免疫<sup>[7-8]</sup>,但血清IL-2R水平与肺癌患者ICI联合化疗疗效及预后的临床关联尚缺乏系统性证据。本研究通过回顾性分析晚期NSCLC患者的血浆细胞因子谱、免疫细胞计数、无进展生存期(progression-free survival, PFS)、治疗疗效等资料,探讨IL-2R水平与疗效的相关性及IL-2R对PFS的影响。

## 资料和方法

**试验设计** 回顾性收集2021年12月25日至2023年5月20日在复旦大学附属中山医院住院治疗的NSCLC患者的病历资料。纳入标准:(1)年龄 $\leq 75$ 岁;(2)病理诊断为NSCLC, TNM分期Ⅲ~Ⅳ期;(3)至少接受2个周期的化疗和ICI治疗;(4)签署生物样本获取与知情同意书。排除标准:(1)妊娠;(2)在化疗和免疫治疗期间出现严重不良反应而导致治疗暂停;(3)病理诊断不明。严重不良反应包括与化疗相关的3~4级骨髓抑制、严重感染、因免疫治疗导致的肺炎或其他器官炎症。本研究获复旦大学附属中山医院伦理委员会批准(批准号:B2025-063)。

按照实体瘤疗效评价标准(Response Evaluation Criteria in Solid Tumors, RECIST) 1.1, 定期完善胸腹CT、颅脑MRI与骨扫描检查,最终纳入168例患者,按照治疗疗效分为无效组和有效组。无效组定义为靶病灶最长径总和增加 $\geq 20\%$ 或出现新病灶;有效组定义为靶病灶最长径总和缩小 $\geq 30\%$ 且维持 $\geq 4$ 周;或靶病灶缩小 $> 30\%$ ,或靶病灶

增大20%。构建预测模型探索IL-2R对免疫联合化疗疗效的预测作用,采用多因素Cox回归判断IL-2R对疗效的预测作用,采用Kaplan-Meier法和Log-rank检验等生存分析方法探索IL-2R与患者PFS的关系。研究流程详见图1。



PD: Progressive disease; SD: Stable disease; PR: Partial response.

图1 研究流程图

Fig 1 Study flow chart

**试验方法** 本研究收集性别、年龄、病理类型、肿瘤分期、细胞因子、免疫细胞数量等临床资料。病理类型分为腺癌和鳞癌;肿瘤分期(TNM分期)为Ⅲ期、Ⅳ期;细胞因子包含肿瘤坏死因子- $\alpha$ (tumor necrosis factor- $\alpha$ , TNF- $\alpha$ );IL-1 $\beta$ 、IL-2R、IL-6、IL-10;免疫细胞数量包括淋巴细胞计数、B淋巴细胞计数、T淋巴细胞计数、Th淋巴细胞计数、Treg淋巴细胞计数、自然杀伤细胞计数。临床疗效评估为疾病进展(progressive disease, PD)的患者纳入无效组,临床疗效评估为疾病稳定(stable disease, SD)和部分缓解(partial response, PR)的患者纳入有效组。通过医院电子病历系统、门诊及住院记录获取生存与复发信息,随访截止日期为2023年4月30日。

**统计学方法** 使用SPSS 27.0统计软件对数据进行统计分析。符合正态分布的计量数据以 $\bar{x} \pm s$ 表示,组间比较采用 $t$ 检验;分类变量的相关性分析使用 $\chi^2$ 检验。采用AUC分析IL-2R表达水平对临床疗效的预测价值。采用Cox比例风险回归模型评估IL-2R的预测作用,结合Kaplan-Meier法分析患者生存数据,并绘制生存曲线,再使用Log-rank法进行显著性检验。 $P < 0.05$ 为差异有统计学意义。

## 结 果

**一般情况** 本研究共纳入168例患者,其中男性142人,女性26人;肺腺癌101人,肺鳞癌67人;肿瘤分期Ⅲ期50人,Ⅳ期118人。无效组和有效组分别为57人和111人,平均年龄分别为 $(65.63 \pm 7.61)$ 岁和 $(64.27 \pm 7.79)$ 岁。除性别外,两组在年龄、病理学分类、肿瘤分期等方面的差异均无统计学意义(表1)。

表1 入组患者临床特征

Tab 1 Baseline characteristics of enrolled patients

[ $n(\%)$  or  $\bar{x} \pm s$ ]

| Parameters              | Non-responding group (n=57) | Responding group (n=111) | P     |
|-------------------------|-----------------------------|--------------------------|-------|
| Gender                  |                             |                          | 0.030 |
| Female                  | 4 (7.0)                     | 22 (19.8)                |       |
| Male                    | 53 (93.0)                   | 89 (80.2)                |       |
| Age (y)                 | 65.63 $\pm$ 7.61            | 64.27 $\pm$ 7.79         | 0.281 |
| Pathological type       |                             |                          | 0.673 |
| Adenocarcinoma          | 33 (57.9)                   | 68 (61.3)                |       |
| Squamous cell carcinoma | 24 (42.1)                   | 43 (38.7)                |       |
| Clinical stage          |                             |                          | 0.077 |
| Ⅲ                       | 12 (21.1)                   | 38 (34.2)                |       |
| Ⅳ                       | 45 (78.9)                   | 73 (65.8)                |       |

**高水平IL-2R与疗效不佳相关** 对两组患者细胞因子进行 $t$ 检验发现,无效组IL-2R水平高于有效组 [ $(863.93 \pm 339.03)$  U/mL vs.  $(514.41 \pm 181.83)$  U/mL], 差异有统计学意义( $P < 0.001$ )。TNF- $\alpha$  [ $(11.14 \pm 5.24)$  pg/mL vs.  $(14.97 \pm 24.21)$  pg/mL,  $P = 0.240$ , 1 pg/mL = 1 ng/L, 下同]、IL-1 $\beta$  [ $(15.17 \pm 50.89)$  pg/mL vs.  $(11.39 \pm 20.99)$  pg/mL,  $P = 0.498$ ]、IL-6 [ $(6.58 \pm 4.69)$  pg/mL vs.  $(10.78 \pm 23.30)$  pg/mL,  $P = 0.180$ ]、IL-10 [ $(5.39 \pm 2.22)$  pg/mL vs.  $(5.16 \pm 0.73)$  pg/mL,  $P = 0.331$ ]等细胞因子与治疗疗效无关,免疫细胞计数差异无统计学意义(表2、图2)。因此,高水平IL-2R可能与治疗效果不佳相关。

**IL-2R可预测晚期NSCLC患者ICI联合化疗的疗效** 通过ROC曲线构建IL-2R的预测模型,明确IL-2R在晚期NSCLC患者的免疫联合化疗疗效中的预测作用,AUC为0.825(95%CI:0.754~0.895),ROC曲线的灵敏度为0.802,特异度为0.722。预测模型中IL-2R的最佳预测值为568.5 U/mL(约登指数为0.530),提示IL-2R可用于预测晚期NSCLC患

表2 两组 NSCLC 患者细胞因子的差异  
Tab 2 Differences in cytokine of NSCLC patients

| in the two groups ( $\bar{x} \pm s$ ) |                             |                          |        |        |
|---------------------------------------|-----------------------------|--------------------------|--------|--------|
| Parameters                            | Non-responding group (n=57) | Responding group (n=111) | t      | P      |
| TNF- $\alpha$ (pg/mL)                 | 11.14 $\pm$ 5.24            | 14.97 $\pm$ 24.21        | -1.179 | 0.240  |
| IL-1 $\beta$ (pg/mL)                  | 15.17 $\pm$ 50.89           | 11.39 $\pm$ 20.99        | 0.679  | 0.498  |
| IL-2R (U/mL)                          | 863.93 $\pm$ 339.03         | 514.41 $\pm$ 181.83      | 8.707  | <0.001 |
| IL-6 (pg/mL)                          | 6.58 $\pm$ 4.69             | 10.78 $\pm$ 23.30        | -1.345 | 0.180  |
| IL-8 (pg/mL)                          | 26.44 $\pm$ 30.20           | 24.08 $\pm$ 34.87        | 0.433  | 0.665  |
| IL-10 (pg/mL)                         | 5.39 $\pm$ 2.22             | 5.16 $\pm$ 0.73          | 0.974  | 0.331  |

TNF- $\alpha$ : Tumor necrosis factor- $\alpha$ . 1 pg/mL=1 ng/L.

者免疫联合化疗疗效,高于 568.5 U/mL 提示疗效较差,低于 568.5 U/mL 提示疗效较好(图3)。

**IL-2R 与晚期 NSCLC 患者 PFS 相关** 为明确 IL-2R 是否与 ICI 联合化疗的临床疗效以及预后具有相关性,根据 IL-2R 的阈值将患者分为低表达组与高表达组,分别绘制生存曲线,其中低表达组和高表达组的中位 PFS (median PFS, mPFS) 分别为 14 个月(95%CI: 12.225~15.775)和 9 个月(95%CI: 7.711~10.289),差异有统计学意义( $P=0.011$ , 图4)。因此,IL-2R 较高提示 PFS 较短。

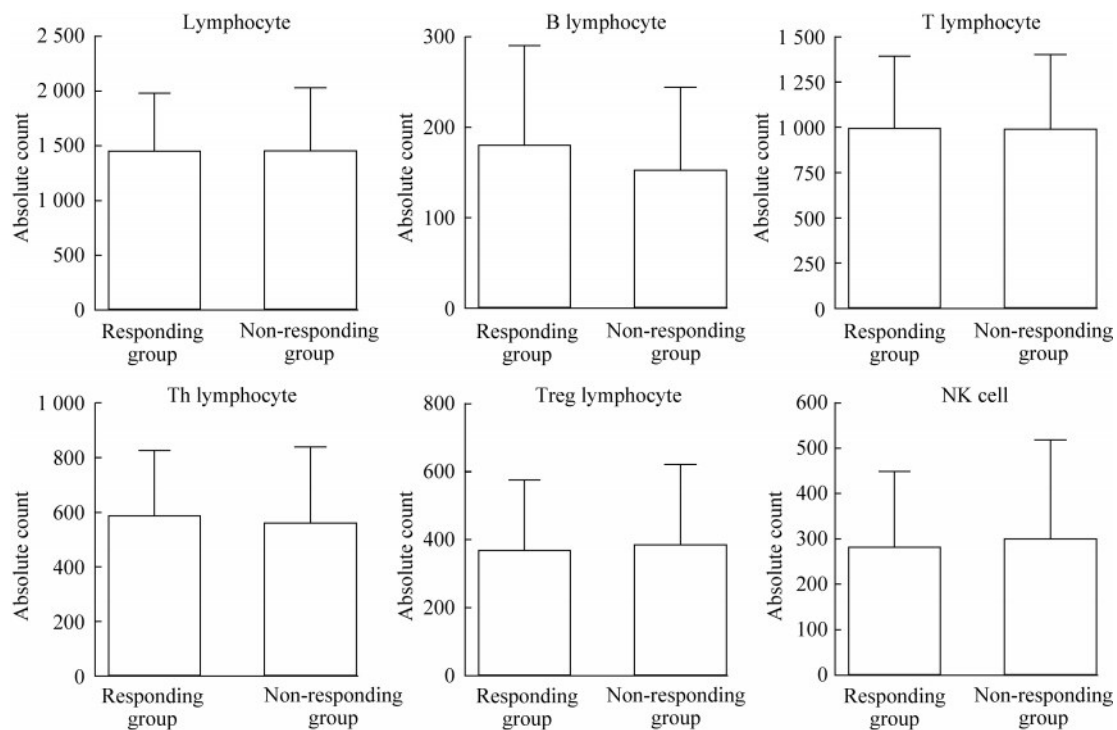


图2 两组 NSCLC 患者免疫细胞计数的差异

Fig 2 Differences in immune cell count of NSCLC patients in the two groups

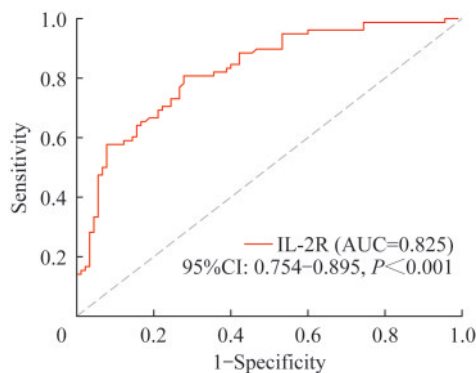


图3 IL-2R 预测 ICI 联合化疗治疗 NSCLC 疗效的 ROC 曲线  
Fig 3 ROC curve of IL-2R for predicting the efficacy of ICIs combined with chemotherapy on NSCLC

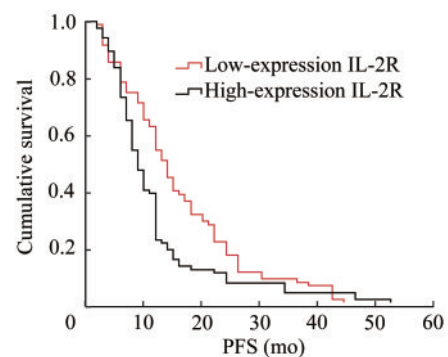


图4 IL-2R 高表达组和低表达组 NSCLC 患者的 PFS 曲线图  
Fig 4 PFS curves of NSCLC patients in high-expression IL-2R group and low-expression IL-2R group

**IL-2R是晚期 NSCLC 患者 ICI联合化疗治疗疗效的独立预测因子** 利用多变量Cox回归模型分析细胞因子与疗效的关系,明确IL-2R的预测作用。

结果发现,IL-2R可作为晚期NSCLC患者免疫-化疗联合治疗疗效的独立预测因子,IL-2R水平与疗效呈负相关(表3)。

表3 ICI联合化疗治疗晚期 NSCLC 患者预后的多因素分析

Tab 3 Multivariate analysis of the prognosis of patients with advance NSCLC treated by ICI combined with chemotherapy

| Factors | B      | SE    | Wald  | df | P            | Exp (B) | 95%CI       |
|---------|--------|-------|-------|----|--------------|---------|-------------|
| Age     | 0.020  | 0.011 | 3.145 | 1  | 0.076        | 1.021   | 0.998–1.044 |
| Gender  | 0.066  | 0.222 | 0.090 | 1  | 0.765        | 1.069   | 0.692–1.651 |
| IL-1β   | 0.000  | 0.003 | 0.005 | 1  | 0.941        | 1.000   | 0.995–1.005 |
| IL-2R   | 0.001  | 0.000 | 8.889 | 1  | <b>0.003</b> | 1.001   | 1.000–1.001 |
| IL-6    | −0.004 | 0.004 | 0.953 | 1  | 0.329        | 0.996   | 0.987–1.004 |
| IL-8    | 0.004  | 0.003 | 2.729 | 1  | 0.099        | 1.004   | 0.999–1.009 |
| IL-10   | 0.089  | 0.050 | 3.153 | 1  | 0.076        | 1.093   | 0.991–1.207 |

讨 论

肺癌是全球范围内发病率和死亡率最高的恶性肿瘤之一,化疗与免疫治疗可延长患者生存期<sup>[9-10]</sup>,但是肿瘤的耐药性、异质性及早诊断不足导致肺癌患者的治疗效果与预后难以预测<sup>[11]</sup>。因此对肺癌患者化疗和/或免疫治疗的疗效进行预测与评估是提升肺癌患者生存质量的重点<sup>[12]</sup>。在胰腺癌中,IL-2R被抗体拮抗后,胰腺癌对放疗的敏感度提高,可能和STAT5通路的激活有关<sup>[13]</sup>。但是IL-2R与肺癌疗效及预后是否相关,是否可以作为肺癌疗效与预后评估的预测生物标志物尚不明确。

本研究分析了168例完成至少2个周期ICI联合化疗的晚期NSCLC患者的细胞因子、免疫细胞与免疫联合化疗疗效及PFS等的相关性,评估了不同疗效患者的IL-2R的差异,结果发现IL-2R水平与联合治疗疗效呈负相关,且IL-2R是肺癌患者预后较差的独立危险因素。

近年来,肿瘤免疫微环境在肺癌发生、发展及治疗中的作用日益受到重视,其中细胞因子网络调控是影响肿瘤免疫应答的关键环节。IL-2R作为免疫调节的核心分子,由α、β和γ等3个亚基组成<sup>[14]</sup>,在T细胞活化、增殖及免疫稳态维持中发挥重要作用<sup>[15]</sup>。在肺癌免疫微环境中,IL-2R信号网络发挥着复杂而关键的双重调控作用。其主要功能高度依赖于表达该受体的细胞类型:肿瘤浸润的Treg细胞通过高亲和力IL-2R竞争性消耗IL-2,可能抑制效应T细胞的抗肿瘤功能,促进免疫逃逸;而若能

有效激活细胞毒性T细胞或自然杀伤细胞上的IL-2R,则可增强免疫清除<sup>[16]</sup>。该信号受到以JAK-STAT5为核心的内在通路、微环境中其他细胞因子(如IL-15)及抑制性受体(如PD-1)构成的交叉调控网络、以及肿瘤驱动的代谢与缺氧压力的共同精细调控<sup>[17]</sup>。理解这一动态网络有助于解释当前免疫疗法的局限性,并为开发选择性靶向IL-2R通路(如偏向性IL-2变体)以重塑肺癌免疫微环境提供理论基础<sup>[18]</sup>。近年来,研究发现IL-2R与免疫功能存在一定联系:IL-2R信号通路的异常激活不仅参与肿瘤免疫逃逸过程,还可能影响依匹木单抗与纳武利尤单抗的治疗效果<sup>[14]</sup>;CD25的特异性抗体可能可以选择性清除Treg细胞,并增强抗肿瘤免疫<sup>[7]</sup>。这两项研究进一步佐证了本研究的结论。

IL-2R靶向治疗用于其他类型肿瘤的研究进展也为肺癌提供了借鉴。在一项黑色素瘤和肾细胞癌的研究中,高剂量IL-2疗法奠定了细胞因子治疗的基础<sup>[19]</sup>;另一项血液肿瘤的基础研究中,靶向CD25的抗体-药物偶联物成功应用验证了该靶点的治疗价值<sup>[20]</sup>;在实体瘤中,CAR-T细胞工程化表达IL-2R信号以增强持久性的策略展示了改造该通路以赋能细胞疗法的前景<sup>[21]</sup>。

综上所述,较高的血清IL-2R水平可能是晚期NSCLC患者疗效及预后较差的生物学标志物,高水平IL-2R可作为独立预测因子预测晚期NSCLC患者的免疫联合化疗疗效。后续可增加病例数,进一步开展前瞻性临床研究。未来研究应聚焦于建立标准化的检测体系,并通过大规模前瞻性队列研究,深入探索IL-2R在NSCLC治疗中的精确截断值及其指导个体化治疗决策中的循证医学价值。

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