

• 临床研究 •

甘油三酯-葡萄糖指数对局晚期和晚期非小细胞肺癌免疫治疗疗效及预后的影响

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[摘要] 目的: 研究胰岛素抵抗标志物甘油三酯-葡萄糖(triglyceride-glucose, TyG)指数是否可预测替雷利珠单抗联合化疗的局部晚期和晚期非小细胞肺癌(non-small cell lung cancer, NSCLC)患者的临床结局。方法: 回顾性分析243例局晚期和晚期接受替雷利珠单抗联合化疗治疗的NSCLC患者的数据, 根据使用X-tile软件确定的最佳截断值9.3, 将患者分为高TyG指数组和低TyG指数组。Cox比例风险回归分析确定了影响总生存期(overall survival, OS)的独立预后因素, 并基于这些因素建立列线图预测模型。结果: 研究队列包括160例高TyG指数患者和83例低TyG指数患者。低TyG指数组的中位无进展生存期和DS显著长于高TyG指数组。低TyG指数组的客观缓解率为55.42%, 而高TyG指数组为30.63%; 相应的疾病控制率分别为95.18%和56.88%。多因素回归分析确定了治疗前最大肿瘤直径、程序性死亡配体1(programmed death ligand 1, PD-L1)阳性比例评分、体重指数(body mass index, BMI)和TyG指数作为DS的独立预后预测因子。列线图模型表明了TyG指数(HR=2.99, 95%CI: 1.73~5.16, $P < 0.001$)作为主要预后预测因子的重要性, 其次是PD-L1阳性比例评分、治疗前肿瘤最大直径和BMI。结论: TyG指数是局晚期和晚期NSCLC患者联合免疫治疗和化疗疗效的长期预测指标, 低TyG指数预后较好。

[关键词] 非小细胞肺癌; 免疫治疗; 预测模型; 有效性; 安全性

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The impact of triglyceride-glucose index on the efficacy of immunotherapy and prognosis of locally advanced and advanced non-small cell lung cancer

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[Abstract] **Objective:** To investigate whether triglyceride-glucose (TyG) index, a marker of insulin resistance, can predict the clinical outcome of patients with locally advanced and advanced non-small cell lung cancer (NSCLC) treated with tislelizumab combined with chemotherapy. **Methods:** We retrospectively analyzed data from 243 patients who were treated with tislelizumab combined with chemotherapy with locally advanced and advanced NSCLC, dividing them into high and low TyG index groups based on an optimal cut-off value of 9.3, determined using the X-tile software. Cox proportional hazards regression analysis identified independent prognostic factors for overall survival (OS), and a prediction nomogram model was developed based on them. **Results:** The study cohort included 160 patients with a high TyG index and 83 with a low TyG index. The median progression-free survival and OS in the low TyG index group were significantly longer than in the high TyG index group. The objective response rate was 55.42% in the low TyG index group and 30.63% in the high TyG index group, while the respective disease control rates were 95.18% and 56.88%. Multifactorial regression analysis identified pre-treatment maximum tumour diameter, proportion score for programmed death ligand 1 (PD-L1) positivity, body mass index (BMI), and TyG index as independent prognostic predictors of OS. The nomogram model emphasized the importance of the TyG index (hazard ratio: 2.99, 95% CI: 1.73–5.16, $P < 0.001$) as a major prognostic predictor, followed by the PD-L1 tumor proportion score, pre-treatment tumour diameter, and BMI. **Conclusion:** TyG index is a long-term

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predictor of the efficacy of combined immunotherapy and chemotherapy in patients with locally advanced and advanced NSCLC, and low TyG index has a better prognosis.

[Key words] non-small cell lung cancer; immunotherapy; prediction model; efficacy; safety

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原发性肺癌是全球最常见的癌症,也是导致癌症相关死亡的主要原因^[1-2]。在治疗非小细胞肺癌(non-small cell lung cancer, NSCLC)时,非手术治疗方案如免疫疗法对患者预后至关重要^[3]。研究表明,程序性死亡配体1(programmed death ligand 1, PD-L1)与其受体(programmed death 1, PD-1)的结合参与了肿瘤细胞的免疫逃逸^[4]。

在正常情况下,PD-1主要表达在活化的T细胞表面。其配体PD-L1在多种细胞类型中表达,包括肿瘤细胞^[5]。当PD-1与PD-L1结合时,会抑制T细胞的活性,防止免疫系统对正常组织的攻击。然而,肿瘤细胞可以利用这一机制,通过表达PD-L1来逃避免疫系统的监视。PD-1抑制剂通过阻断PD-1与PD-L1的结合,解除对T细胞的抑制,从而恢复其杀伤肿瘤细胞的能力。替雷利珠单抗是一种免疫检查点抑制剂(immune checkpoint inhibitor, ICI),通过免疫抑制和T细胞激活阻断PD-1/PD-L1/PD-L2的相互作用,增强抗肿瘤反应^[6-7]。多项研究表明,程序性细胞死亡配体抑制剂与化疗药物联用,显著改善了不可切除的NSCLC患者的预后^[8-10]。对于晚期NSCLC,使用免疫抑制剂和化疗药物的联合疗法可以抑制肿瘤生长,通过双重机制增强机体的免疫功能,提高生存率和生活质量^[11]。因此,PD-1/PD-L1抑制剂与化疗的联合治疗已被批准作为晚期NSCLC患者的主要治疗方式。

ICI在肺癌治疗中已取得显著进展,但并非所有患者都能从中获益。因此,寻找有效的预测生物标志物对于筛选可能受益的患者至关重要。目前,PD-L1表达和肿瘤突变负荷(tumor mutational burden, TMB)是最常用的预测生物标志物,但其预测能力有限。甘油三酯-葡萄糖(triglyceride-glucose, TyG)指数一般用来评估代谢状态,它是血清甘油三酯和葡萄糖水平的乘积。该指数被认为是胰岛素抵抗的一个可靠的替代生物标志物^[12]。研究发现,TyG指数是2型糖尿病、结直肠癌、乳腺癌和肝癌的潜在标志物^[13-15]。此外,研究表明胰岛素抵抗通过改变炎症水平和免疫反应以及损害效应免疫细胞功能,包括细胞毒性T淋巴细胞和自然杀伤细胞,促进肿瘤

生长和转移,进一步影响肿瘤免疫治疗的效果^[16]。一项关于前列腺癌的研究指出,低TyG指数患者的较高生存率可能与特定致癌基因的下调和/或PD-1表达的上调有关^[17]。然而,很少有研究评估TyG指数作为局晚期和晚期NSCLC患者在接受ICI联合化疗治疗时的预后预测因子。这一知识空白在NSCLC中尤为重要,因为胰岛素抵抗可能与PD-1/PD-L1阻断协同作用,成为一种耐药机制。因此,本研究探索TyG指数在晚期NSCLC患者接受化疗免疫治疗中的预后价值。

1 对象和方法

1.1 对象

本研究回顾性分析2020年12月—2024年12月南京医科大学第二附属医院和南京市高淳人民医院收治的NSCLC患者的临床数据,包括年龄、性别、体重指数(body mass index, BMI)、吸烟和饮酒状况、东部肿瘤协作组(Eastern Cooperative Oncology Group, ECOG)评分、慢性阻塞性肺疾病史、治疗前最大肿瘤直径、肺外侵犯,以及各种实验室参数,如空腹血糖、空腹甘油三酯水平。通过电话随访、搜索电子病历等方式获取患者的疾病无进展生存期(progression-free survival, PFS)和总生存期(overall survival, OS)。纳入标准:①病理和影像学确诊为局晚期和晚期NSCLC;②接受替雷利珠单抗联合化疗,并有治疗前生化和血液指标的数据;③至少接受过3个治疗周期;④可测量的肿瘤病灶 ≥ 1 个;⑤治疗时年龄18~70岁;⑥ECOG评分 ≤ 1 分;⑦有完整的临床随访数据。排除标准:①曾接受过PD-1/PD-L1抑制剂或靶向药物治疗;②同时患有严重感染或全身炎症;③同时有血液系统或免疫系统疾病、肝功能不全或肝炎;④有长期使用类固醇或免疫抑制剂史;⑤有严重的心脏、肝脏、肾脏或其他器质性病变;⑥同时有其他恶性肿瘤或非原发性NSCLC;⑦临床数据不准确或不完整。研究期间接受过调脂药物(如他汀类和贝特类)治疗的患者被排除在分析之外,以减少对TyG指数的潜在混杂影响。根据纳入和排除标准,本研究共纳入243例患者。本研究

获得南京医科大学第二附属医院和南京市高淳人民医院伦理审查委员会批准(批件号:2020-070-01、2024-126-01),研究遵循《赫尔辛基宣言》的原则,由于研究的回顾性质,书面知情同意的要求被豁免。

使用X-tile软件确定连续变量TyG指数的最佳截断值,通过最优分组提高变量对预后的预测能力。选择使 χ^2 值最大的分组方式,其对应的截断值即为最佳截断值。患者根据计算出的临界值被分为高(≥ 9.3)和低(< 9.3)TyG指数组。除X-tile筛选的最优cutoff值外,还补充采用中位数法来避免偏倚。该方法结果显示临界值为9.3,高表达组预后差,不存在偏倚。

1.2 方法

1.2.1 治疗方案

所有入组患者均为局晚期或晚期NSCLC。治疗方案为免疫联合化疗:患者每3周接受1次静脉注射替雷利珠单抗(200 mg)。根据病理类型选择不同的化疗方案:对于鳞状细胞癌患者,给予白蛋白结合型紫杉醇(200 mg/m²)联合顺铂(75 mg/m²);对于非鳞癌患者,给予培美曲塞(500 mg/m²)联合顺铂(75 mg/m²)。顺铂可一次性或分次完成给药,均在同一周期内完成。

1.2.2 疗效评估

患者每2个周期进行1次胸腹部CT或MRI检查。治疗效果通过实体瘤疗效评估标准(RECIST 1.1版)进行评估,并分为完全缓解(complete remission, CR)、部分缓解(partial remission, PR)、疾病稳定(stable disease, SD)和疾病进展(progression of disease, PD)。客观缓解率(objective remission rate, ORR)=(CR+PR)/总例数 $\times 100\%$;疾病控制率(disease control rate, DCR)=(CR+PR+SD)/总例数 $\times 100\%$ 。PFS定义为从首次免疫治疗开始到肿瘤进展或死亡的时间。OS定义为从开始治疗到因任何原因(事件)死亡的时间。生存时间以月计算。长期治疗效果通过OS和PFS进行评估。为确保准确性,所有影像数据均由两位具有超过5年经验的独立放射科医生评估。如有分歧,由另一位具有超过5年经验的放射科医生评估信息,以帮助达成共识并尽量减少观察者间的误差。最终随访时间截至2025年2月。

1.3 统计学方法

数据使用R软件(版本4.4.1)进行分析。采用Kolmogorov-Smirnov正态性检验评估数据分布。正态分布的数据以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较采用独立样本 t 检验;定性资料用例数(百分

比)表示,组间比较采用卡方检验和Fisher精确检验。Kaplan-Meier方法用于计算中位OS和PFS,这些数据用于X-tile程序确定TyG的最佳生存相关截断值。Cox比例风险回归用于单因素和多因素分析。单因素分析中显著的变量($P < 0.05$)被纳入多因素回归以识别OS和PFS的独立预后因素。建立列线图预测患者12、24、36个月的生存情况。变量的选择基于其统计显著性和临床相关性,并根据多变量分析得出的风险比(hazard ratio, HR)进行加权。模型的内部验证及其预测准确性通过Bootstrap方法(1 000次重抽样)进行评估。模型生成的预测结果与实际结果进行比较,以评估其校准情况并减少过拟合。所有统计检验均为双侧检验, $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 患者的基线特征

本研究分析了2020年12月—2024年12月在南京医科大学第二附属医院和南京市高淳人民医院接受替雷利珠单抗联合铂类化疗的243例局晚期和晚期NSCLC患者的数据。其中,83例被归类为低TyG指数组(< 9.3),160例为高TyG指数组(≥ 9.3)。两组患者年龄、性别、BMI、吸烟和饮酒状况、ECOG评分、慢性阻塞性肺疾病史、治疗前最大肿瘤直径、肺外侵犯,以及各种实验室参数,如空腹血糖、空腹甘油三酯水平等均差异无统计学意义(表1)。

2.2 患者疗效

2.2.1 两组患者的近期疗效

结果显示,无患者达到CR,95例患者达到PR,75例患者达到SD,82例患者出现PD。低TyG指数组和高TyG指数组的ORR分别为55.42%和30.63%($P < 0.001$),DCR分别为95.18%和56.88%($P < 0.001$,表2)。

2.2.2 两组患者中位PFS、OS比较

低TyG指数组的中位PFS显著长于高TyG指数组[13.8(9.2, 14.4)个月 *vs.* 8.2(7.3, 8.7)个月, $P < 0.001$; HR=0.385, 95% CI: 0.278~0.534;图1A],低TyG指数组的中位OS显著长于高TyG指数组[26.1(23.4~29.8)个月 *vs.* 17.0(13.9~18.3)个月, $P < 0.001$; HR=0.403, 95% CI: 0.268~0.608;图1B]。

2.2.3 单变量和多变量Cox比例风险回归分析

表3展示了单变量和多变量Cox比例风险回归分析的结果,用于评估PFS。多变量回归分析揭示了NSCLC患者中PFS的几个独立预后预测因子。

表1 高低TyG指数组的基线表资料

Table 1 Baseline table data for the high and low triglyceride-glucose index groups

Variable	Total(n=243)	LowTyG(n=83)	HighTyG(n=160)	P	FDR	<i>t</i> / χ^2
BMI[n(%)]				0.804	0.936	0.006
< 25 kg/m ²	194(79.84)	67(80.72)	127(79.38)			
≥25 kg/m ²	49(20.16)	16(19.28)	33(20.63)			
Fasting blood-glucose(mg/dL, $\bar{x} \pm s$)	93.73 ± 7.65	94.32 ± 7.89	93.43 ± 7.53	0.387	0.520	0.847
Fasting triglycerides(mg/dL, $\bar{x} \pm s$)	235.12 ± 43.15	237.82 ± 43.57	233.73 ± 43.01	0.485	0.566	0.697
TyG index($\bar{x} \pm s$)	9.29 ± 0.21	9.30 ± 0.22	9.28 ± 0.20	0.351	0.505	0.693
Age(years, $\bar{x} \pm s$)	64.82 ± 8.94	63.94 ± 8.87	65.28 ± 8.97	0.268	0.424	-1.113
Sex[n(%)]				0.271	0.424	0.868
Female	49(20.16)	20(24.10)	29(18.12)			
Male	194(79.84)	63(75.90)	131(81.88)			
Alcohol history[n(%)]				0.078	0.208	2.614
No	167(68.72)	51(61.45)	116(72.50)			
Yes	76(31.28)	32(38.55)	44(27.50)			
Smoking[n(%)]				0.550	0.566	0.212
No	103(42.39)	33(39.76)	70(43.75)			
Yes	140(57.61)	50(60.24)	90(56.25)			
ECOG[n(%)]				0.083	0.208	2.547
0	150(61.73)	45(54.22)	105(65.62)			
1	93(38.27)	38(45.78)	55(34.38)			
COPD[n(%)]				0.175	0.355	1.448
No	177(72.84)	56(67.47)	121(75.62)			
Yes	66(27.16)	27(32.53)	39(24.38)			
Histologic type[n(%)]				0.646	0.646	0.105
Adenocarcinoma	125(51.44)	41(49.40)	84(52.50)			
Other	118(48.56)	42(50.60)	76(47.50)			
CA-125[n(%)]				0.312	0.472	0.758
<35 U/mL	89(39.63)	34(40.96)	55(34.38)			
≥35 U/mL	154(63.37)	49(59.04)	105(65.62)			
CEA[n(%)]				0.217	0.396	1.204
<3 ng/mL	142(58.44)	53(63.86)	89(55.62)			
≥3 ng/mL	101(41.56)	30(36.14)	71(44.38)			
PD-L1 expression[n(%)]				0.470	0.566	0.345
TPS < 50%	122(50.21)	39(46.99)	83(51.88)			
TPS ≥ 50%	121(49.79)	44(53.01)	77(48.12)			
Diameter of tumor[n(%)]				0.083	0.208	1.431
<50 mm	145(59.67)	46(55.42)	99(61.88)			
≥50 mm	98(40.33)	37(44.58)	55(34.48)			
Extrapulmonary metastasis[n(%)]				0.331	0.486	0.697
No	132(59.67)	46(55.42)	99(61.88)			
Yes	98(40.33)	37(40.58)	61(38.12)			

TPS: tumor proportion score; COPD: chronic obstructive pulmonary disease; CEA: carcinoembryonic antigen; CA-125: cancer antigen 125. Independent-sample *t* test was used for continuous variables, and χ^2 test was used for categorical variables by default. FDR correction was performed for *P* values by Benjamini-Hochberg method.

ECOG 评分较高的患者 PFS 较短(HR=0.31, 95%CI: 0.19~0.51, *P*=0.043)。表 4 列出了与 OS 相关的项

目。良好的代谢功能与较长的 OS 显著相关, 较低的 TyG 指数表明更好的代谢功能, 特别是在 PFS 的良

表2 两组患者的近期疗效

Table 2 Short-term efficacy of the two groups of patients [n(%)]

Variable	Low TyG (n=83)	High TyG (n=160)	χ^2	P
PR			14.11	<0.001
No	37(44.58)	111(69.38)		
Yes	46(55.42)	49(30.63)		
SD			4.16	0.041
No	50(60.24)	118(73.75)		
Yes	33(39.76)	42(26.25)		
PD			38.16	<0.001
No	79(95.18)	91(56.88)		
Yes	4(4.82)	69(43.13)		
ORR			14.11	<0.001
No	37(44.85)	111(69.38)		
Yes	46(55.42)	49(30.63)		
DCR			38.16	<0.001
No	4(4.82)	69(43.13)		
Yes	79(95.18)	91(56.88)		

性预后因素中(HR=4.38, 95% CI: 3.00~6.38, $P < 0.001$)和OS中(HR=2.99, 95% CI: 1.73~5.16, $P < 0.001$),这表明代谢功能较好的患者对治疗反应更佳。肿瘤细胞中PD-L1表达较高(TPS $\geq 50\%$)预示着较长的PFS(HR=0.56, 95% CI: 0.39~0.80, $P < 0.001$)和OS(HR=0.73, 95% CI: 0.38~0.85, $P=0.036$)。尽管BMI为OS的独立预测因子,但在PFS模型中未达到统计学显著性($P=0.362$)。这意味着较高的BMI与长期生存率的提高有关,但与短期治疗耐受性和PFS无关。可能由于与ECOG评分和PD-L1表达等更有影响力的因素重叠效应,年龄、性别、肺外转移和病理分期在多变量回归分析中作为预测因子的作用不显著。基于多变量回归分析获得的独立预后预测因子,针对12、24、36个月开发的列线图模型,在训练集中的一致性指数为0.772,在验证集中为0.786(图2),被认为具有良好的预测性能。

2.2.4 模型验证

NSCLC患者以7:3的比例,随机分配为训练集

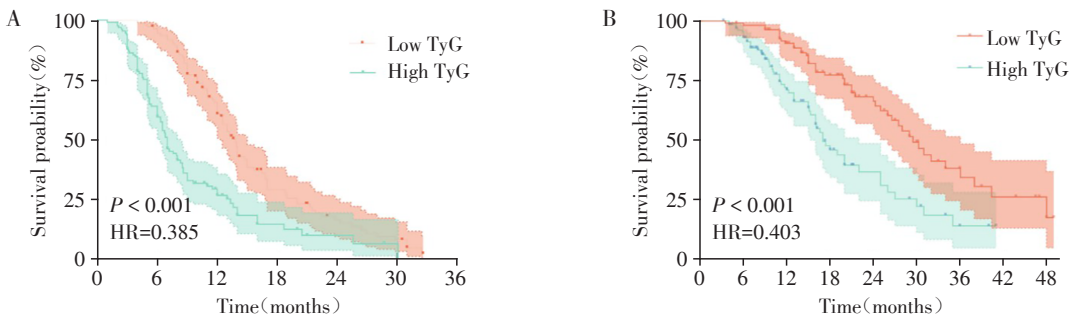


图1 低、高TyG指数与局晚期、晚期NSCLC患者中位PFS(A)和OS(B)的关系

Figure 1 Relationship between the low and high TyG index and median PFS(A) and OS(B) in patients with locally advanced and advanced NSCLC

(170例)、内部验证集(73例)。表5列出了这两个集合的基线特征,训练集($n=170$)与内部验证集($n=73$)在基线特征方面差异均无统计学意义($P > 0.05$),提示两组具有良好的可比性。具体结果如下。年龄:训练集 ≥ 60 岁患者占57.67%,验证集占48.89% ($\chi^2=1.94$, $P=0.164$)。性别:训练集男性77.65%,验证集男性78.08% ($\chi^2=0.01$, $P=0.940$)。吸烟史:训练集吸烟者57.06%,验证集56.16% ($\chi^2=0.02$, $P=0.897$)。饮酒史:训练集饮酒者33.53%,验证集28.77% ($\chi^2=0.53$, $P=0.466$)。ECOG评分:训练集ECOG 0分为55.88%,验证集为65.75% ($\chi^2=2.05$, $P=0.152$)。COPD合并症:训练集28.6%,验证集32.6% ($\chi^2=0.498$, $P=0.311$)。BMI ≥ 25 kg/m²:训练集41.18%,验证集39.73% ($\chi^2=0.04$, $P=0.833$)。病

理学类型(腺癌):训练集44.71%,验证集54.79% ($\chi^2=2.08$, $P=0.149$)。CA-125 ≥ 35 U/mL:训练集52.94%,验证集68.49% ($\chi^2=5.06$, $P=0.403$)。CEA ≥ 3 ng/mL:训练集50.0%,验证集41.10% ($\chi^2=1.62$, $P=0.203$)。PD-L1 TPS $\geq 50\%$:训练集53.53%,验证集54.79% ($\chi^2=0.03$, $P=0.856$)。肿瘤直径 ≥ 50 mm:训练集47.06%,验证集43.84% ($\chi^2=0.21$, $P=0.644$)。肺外转移:训练集39.41%,验证集47.95% ($\chi^2=1.53$, $P=0.217$)。训练集和内部验证集显示在12个月时NSCLC患者的ROC曲线下面积(area under curve, AUC)分别为0.811和0.817(图3A),24个月时AUC分别为0.737和0.720(图3B),36个月时AUC分别为0.755和0.788(图3C)。训练集和内部验证集在12、24、36个月时的OS校准曲线如图4所示。这些曲

表3 NSCLC患者PFS的预后预测因子的单因素和多因素回归分析

Table 3 Univariate and multivariate regression analysis of prognostic predictors for PFS in NSCLC patients

Variable	Univariate		Multivariate	
	HR(95% CI)	P	HR(95% CI)	P
Age(≥ 60 years vs. < 60 years)	0.85(0.59–1.26)	0.410		
TyG index(Low vs. High)	4.81(3.32–6.98)	<0.001	4.38(3.00–6.38)	<0.001
Smoking history(Yes vs. No)	1.08(0.78–1.50)	0.658		
Drinking history(Yes vs. No)	1.20(0.86–1.69)	0.284		
Sex(Male vs. Female)	1.31(0.88–1.96)	0.186		
Tumor diameter(≥ 50 mm vs.< 50 mm)	1.26(0.91–1.75)	0.170		
CEA(< 3 ng/mL vs. ≥ 3 ng/mL)	1.38(1.00–1.91)	0.052		
BMI(< 25 kg/m ² vs. ≥ 25 kg/m ²)	0.71(0.51–0.98)	0.039	0.86(0.62–1.19)	0.362
PD-L1 expression(TPS < 50% vs. TPS ≥ 50%)	0.45(0.31–0.64)	<0.001	0.56(0.39–0.80)	0.001
ECOG (0 vs. 1)	1.39(1.00–1.93)	0.017	0.31(0.19–0.51)	0.043
COPD(Yes vs. No)	1.15(0.69–1.93)	0.593		
Tissue type(Other vs. Adenocarcinoma)	1.38(1.00–1.92)	0.052		
Extrapulmonary metastases(Yes vs. No)	1.29(0.93–1.78)	0.125		
Fasting triglycerides	1.20(0.94–1.53)	0.139		
Fasting blood glucose	0.99(0.90–1.10)	0.916		
CA-125(< 35 U/mL vs. ≥ 35 U/mL)	0.95(0.68–1.32)	0.794		

表4 NSCLC患者OS的预后预测因子的单因素和多因素回归分析

Table 4 Univariate and multivariate regression analysis of prognostic predictors for OS in NSCLC patients

Variable	Univariate		Multivariate	
	HR(95% CI)	P	HR(95% CI)	P
Age(≥ 60 years vs. < 60 years)	1.00(0.98–1.03)	0.770		
TyG index(Low vs. High)	3.19(1.88–5.41)	<0.001	2.99(1.73– 5.16)	<0.001
Smoking history(Yes vs. No)	1.61(0.97–2.68)	0.067		
Drinking history(Yes vs. No)	0.66(0.37–1.17)	0.157		
Sex(Male vs. Female)	1.05(0.59–1.85)	0.871		
Tumor diameter(≥ 50 mm vs. < 50 mm)	2.24(1.36–3.68)	0.001	1.98(1.18–3.33)	0.010
CEA(< 3 ng/mL vs. ≥ 3 ng/mL)	1.09(0.66–1.78)	0.740		
BMI(< 25 kg/m ² vs. ≥ 25 kg/m ²)	0.52(0.31–0.86)	0.010	0.47(0.32–0.98)	0.018
PD-L1 expression(TPS < 50% vs. TPS ≥ 50%)	0.55(0.34–0.71)	0.019	0.73(0.38–0.85)	0.036
ECOG(0 vs. 1)	1.32(0.80–2.18)	0.283		
COPD(Yes vs. No)	0.83(0.49–1.40)	0.480		
Tissue type(Other vs. Adenocarcinoma)	1.31(0.81–2.14)	0.271		
Extrapulmonary metastases(Yes vs. No)	1.16(0.71–1.89)	0.552		
Fasting triglycerides	1.20(0.84–1.73)	0.316		
Fasting blood glucose	1.10(0.98–1.24)	0.112		
CA-125(< 35 U/mL vs. ≥ 35 U/mL)	1.00(1.00–1.00)	0.851		

线表明,模型预测的风险与实际观察到的风险非常吻合。

3 讨 论

本研究分析了TyG指数与NSCLC患者免疫治疗联合化疗疗效之间的关联,并构建了长期预后的

预测模型。结果显示,低TyG指数组的中位OS、PFS、ORR和DCR均优于高TyG指数组。PFS的独立预后预测因子包括ECOG评分、PD-L1表达、治疗前肿瘤最大直径和TyG指数。OS的独立预后预测因子则为PD-L1表达、治疗前肿瘤最大直径、BMI和TyG指数。

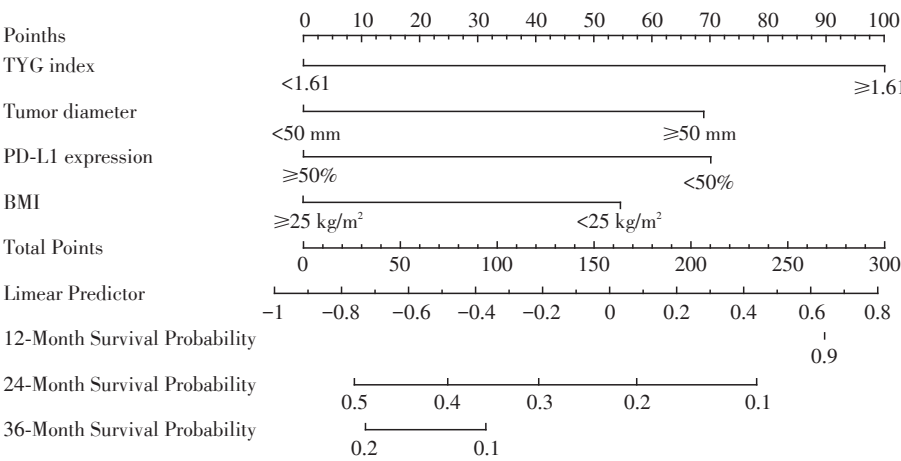


图2 NSCLC患者12、24和36个月OS的列线图预测模型

Figure 2 Nomogram prediction model for 12-, 24-, and 36-month OS in NSCLC patients

表5 训练集和内部验证集之间的特征比较

Table 5 Feature comparison between the training set and the internal validation set [n(%)]

Variable	Internal validation set(n=73)	Training set (n=170)	χ^2	P	Variable	Internal validation set(n=73)	Training set (n=170)	χ^2	P
Age			1.94	0.164	Histology			2.08	0.149
<60 years	37(51.11)	74(42.43)			Adenocarcinoma	40(54.79)	76(44.71)		
≥60 years	36(48.89)	96(57.67)			Other	33(45.21)	94(55.29)		
Sex			0.01	0.940	CA-125			5.06	0.403
Female	16(21.92)	38(22.35)			<35 U/mL	23(31.51)	80(47.06)		
Male	57(78.08)	132(77.65)			≥35 U/mL	50(68.49)	90(52.94)		
Smoking			0.02	0.897	CEA			1.62	0.203
No	32(43.84)	73(42.94)			<3 ng/mL	43(58.90)	85(50.00)		
Yes	41(56.16)	97(57.06)			≥3ng/mL	30(41.10)	85(50.00)		
Drinking			0.53	0.466	PD-L1expression			0.03	0.856
No	52(71.23)	113(66.47)			TPS<50%	33(45.21)	79(46.47)		
Yes	21(28.77)	57(33.53)			TPS≥50%	40(54.79)	91(53.53)		
ECOG			2.05	0.152	Tumor diameter			0.21	0.644
0	48(65.75)	95(55.88)			<50 mm	41(56.16)	90(52.94)		
1	25(34.25)	75(44.12)			≥50 mm	32(43.84)	80(47.06)		
COPD			0.50	0.311	Extrapulmonary metastasis			1.53	0.217
No	49(67.4)	121(71.4)			No	38(52.05)	103(60.59)		
Yes	24(32.6)	49(28.6)			Yes	35(47.95)	67(39.41)		
BMI			0.04	0.833					
<25 kg/m²	44(60.27)	100(58.82)							
≥25 kg/m²	29(39.73)	70(41.18)							

NSCLC是肺癌最常见的病理亚型, 占有病例的80%~85%。免疫检查点抑制剂(immune checkpoint inhibitors, ICI), 如PD-1和PD-L1单抗, 是晚期NSCLC的标准治疗方案^[18]。替雷利珠单抗是一种PD-1抑制剂, 可以缓解PD-1通路介导的免疫抑制, 并激活T淋巴细胞发挥抗肿瘤作用^[19]。随着免疫药

物的广泛应用, 针对NSCLC患者的免疫疗法或联合疗法已进一步优化; 然而, 预测这些患者长期预后的相关研究仍然不足^[20]。近年来, TyG指数受到了越来越多的关注, 但大多数相关研究集中在心血管疾病和代谢异常的患者上^[21-22]。在心血管疾病中, TyG指数与心力衰竭、房颤和高血压的风险显著相

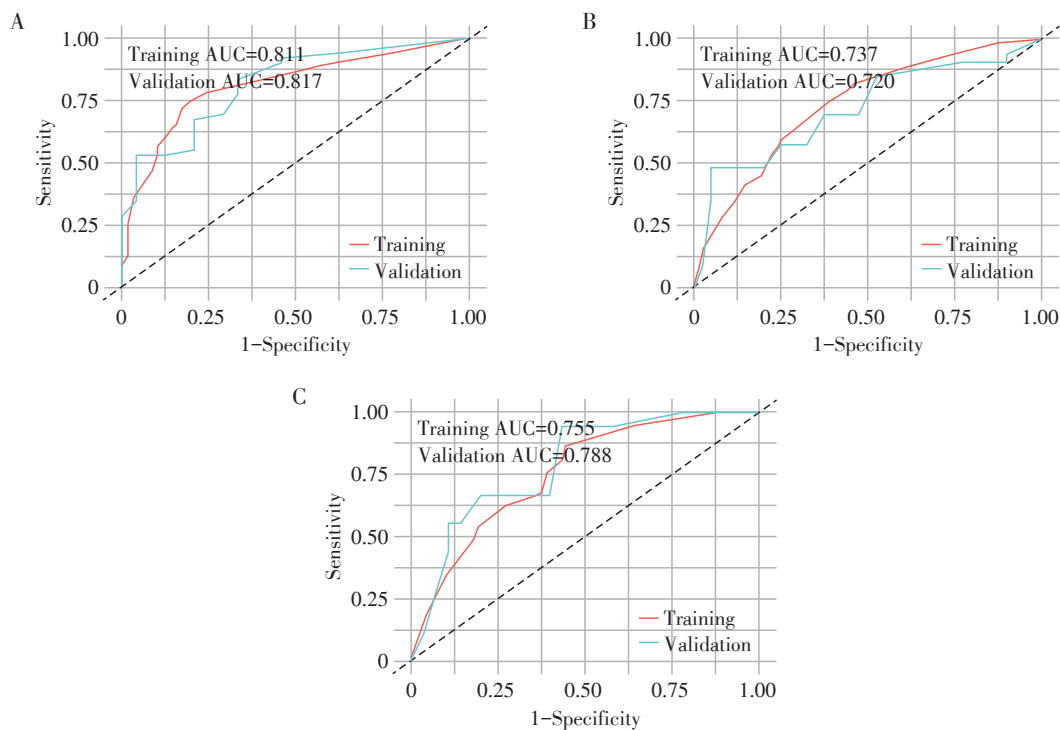
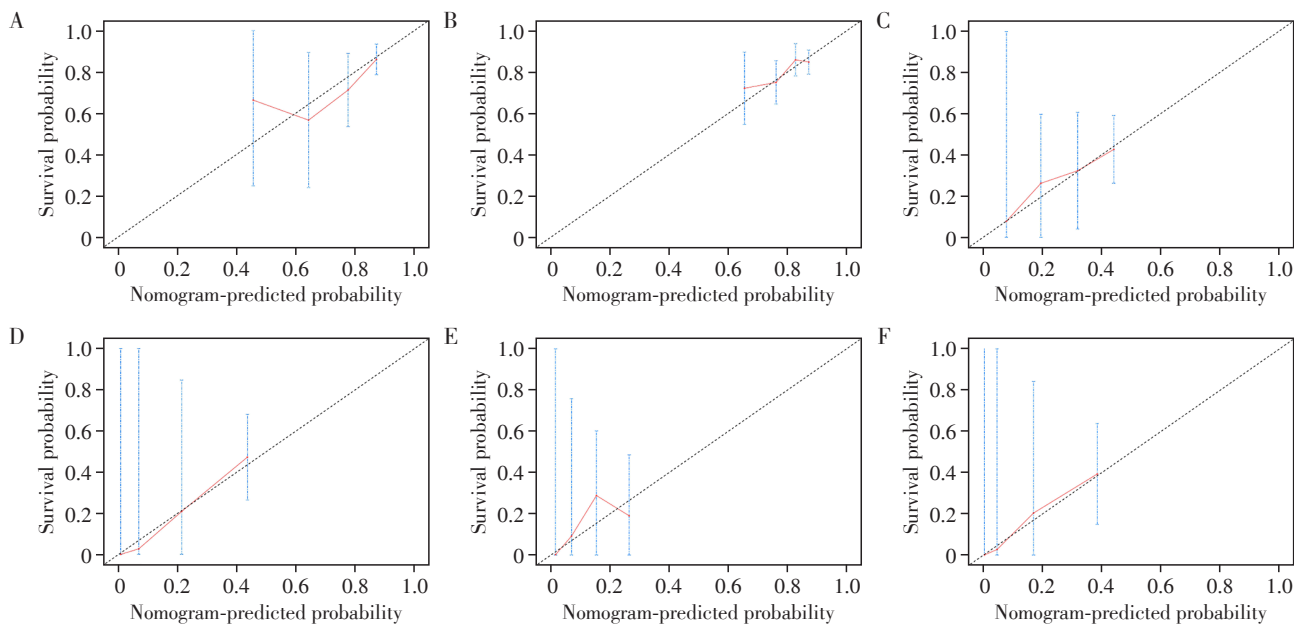


图3 训练集和内部验证集在12(A)、24(B)、36(C)个月时生存预测ROC曲线

Figure 3 ROC curves of survival prediction for the training set and internal validation set at 12(A), 24(B), and 36 months(C)



A: Calibration curve of the OS prediction model at 12 months for the training set. B: Calibration curve of the OS prediction model at 12 months for the validation set. C: Calibration curve of the OS prediction model at 24 months for the training set. D: Calibration curve of the OS prediction model at 24 months for the validation set. E: Calibration curve of the OS prediction model at 36 months for the training set. F: Calibration curve of the OS prediction model at 36 months for the validation set.

图4 训练集和内部验证集在12、24、36个月时OS预测模型的校准曲线

Figure 4 Calibration curves of OS prediction model for training set and internal validation set at 12, 24, and 36 months

关。此外,TyG 指数还被用于预测代谢综合征的发生,显示出优于传统指标的预测能力。本研究将

TyG 指数引入 NSCLC 的联合免疫治疗和化疗中,发现较低的 TyG 指数与接受此类联合治疗的 NSCLC

患者预后更好有关。先前的预后研究表明,在胰腺癌和肾细胞癌患者中也发现了类似的关系^[23-24]。高TyG指数(反映胰岛素抵抗)通过上调固醇调节元件结合蛋白(sterol regulatory element-binding proteins, SREBP)途径,导致CD8⁺ T细胞中的胆固醇酯积累,引发内质网应激和PD-1过表达。同时,这种代谢失调通过mTOR依赖的代谢耗竭损害自然杀伤细胞的细胞毒性^[25]。在胰岛素抵抗状态下,固醇调节元件结合蛋白-1c(sterol regulatory element-binding protein-1c, SREBP-1c)的过度激活可能导致脂质在肿瘤微环境中的积聚,形成免疫抑制性的微环境,抑制T细胞的活性和增殖。此外,脂质代谢的紊乱还可能影响T细胞的代谢重编程,降低其对ICI的响应能力。因此,高TyG指数可能通过SREBP通路的激活,间接影响免疫治疗的效果。值得注意的是,低TyG指数和PD-L1阳性之间的协同效应可能是通过肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)的代谢重编程介导的。临床前证据表明,胰岛素敏感性可减少M2极化的TAM淋巴细胞浸润,从而增强PD-L1抑制剂的反应^[26-27]。不应忽视慢性炎症伴随高TyG指数的情况,因为高TyG指数反映了胰岛素抵抗、血脂异常和葡萄糖代谢障碍,这些通常伴随着系统性炎症水平的升高。先前研究表明,肿瘤状态与慢性炎症有关,而炎症水平的升高通常预示着较差的预后^[28]。高水平的炎症会增加炎症因子,如肿瘤坏死因子- α (tumor necrosis factor- α , TNF- α)、白细胞介素-6(interleukin-6, IL-6)、C反应蛋白(C-reactive protein, CRP)等的产生,进一步限制免疫细胞的恢复和抗血管生成药物的效果^[29-30]。肥胖往往伴随着高TyG指数,然而,在一项针对黑色素瘤和NSCLC患者的回顾性研究中,曾有提示肥胖患者在接受免疫检查点抑制剂治疗时预后优于低BMI患者^[31-32]。这种差异可能是由于患者群体的不同(例如,包括PD-L1阴性亚组)、化疗方案、研究人群和治疗方式的差异。另一项研究中,低TyG指数组的患者在接受免疫治疗联合化疗后,显示出更长的总生存期和无进展生存期,以及更高的客观缓解率和疾病控制率^[33]。这进一步支持了TyG指数作为预测免疫治疗疗效的潜在生物标志物的价值。相比之下,稳态模型胰岛素抵抗指数(homeostasis model assessment of insulin resistance, HOMA-IR)需要测量空腹胰岛素水平。由于胰岛素测定成本较高且在某些临床环境中不易获得,TyG指数在实际应用中更具可行性。此外,BMI存在一些局限性,主要在于它无法解

释代谢综合征和慢性炎症对免疫治疗疗效的影响^[34]。因此,TyG指数是一个有利的生物预测指标。

本研究多变量Cox比例风险回归分析显示,BMI、治疗前肿瘤直径、PD-L1 TPS评分和TyG指数是OS的独立预后预测因子。列线图预测模型显示,TyG指数对OS的解释力最强,其次是PD-L1 TPS评分、治疗前肿瘤直径和BMI。计算了C指数,并生成校准曲线以评估列线图预测模型的有效性。该模型在内部验证集上的C指数为0.776。校准曲线显示模型与实际数据吻合良好,证实了其可靠性和准确性。本研究结果强调了TyG指数在临床实践中的潜在应用价值。作为一种简便、经济的指标,TyG指数可用于早期识别高风险个体,辅助疾病的风险分层和预后评估。未来应致力于建立标准化的参考范围,探索其与其他生物标志物的联合应用,并通过动态监测评估其在疾病管理中的作用,以实现其在临床中的广泛转化和应用。

本研究仍存在局限性。第一,研究样本量有限。第二,本研究选择替雷利珠单抗与化疗的组合,虽然减少了治疗偏差并增强了分级,但仍需验证其他ICI的效果。第三,接受影响脂质代谢药物治疗的患者以及有复杂合并症的患者被排除在研究之外,这限制了本研究结果对更广泛NSCLC患者适用性的范围。第四,本研究采用统计方法确定了TyG指数的最佳临界值;然而,这一标准可能受到样本量和研究人群特征(如种族、年龄和基础代谢状态)等因素的影响,并且可能不适用于其他人群或医疗环境。第五,本研究提出低TyG指数可能通过改善代谢状态,增强PD-L1抑制剂的疗效。尽管当前缺乏直接的肿瘤微环境免疫细胞浸润数据,但已有研究表明,胰岛素抵抗状态与免疫抑制性微环境的形成密切相关^[35]。因此,未来应通过免疫组化分析、多组学整合研究和前瞻性临床研究,进一步验证TyG指数在预测免疫治疗效果中的作用。此外,目前尚缺乏统一的TyG指数参考范围,不同研究中使用的截断值存在差异。未来需要通过大规模、多中心的研究来建立标准化的参考范围,以促进其在临床中的广泛应用。

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所有作者声明无利益冲突。

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All the authors declare no conflicts of interest.

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Author's Contributions:

KONG Ziyue was responsible for literature retrieval and paper writing. MA Xiao was responsible for data analysis; KONG Ziyue, WEI Chenchen, and LU Binbin collected the clinical data; WANG Zhaoxia was responsible for the design and guidance of the project, and financial support.

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