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·专题报道·

程序性死亡受体 1 抑制剂相关内分泌不良反应预测模型构建

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［**摘要**］ **目的**　识别程序性死亡受体 1（programmed death-1, PD-1）抑制剂相关内分泌不良反应的独立预测因素，构建临床可用的风险预测模型。**方法**　回顾性纳入接受 PD-1 抑制剂治疗的 302 例实体瘤患者，根据是否发生内分泌免疫相关不良反应（immune-related adverse events, irAEs）分为病例组与对照组。比较两组患者基线临床、实验室指标。采用多因素 logistic 回归分析评估内分泌 irAEs 的独立预测因子，构建列线图模型，采用受试者工作特征（receiver operating characteristic, ROC）曲线检验模型预测效能。**结果**　内分泌 irAEs 总体发生率为 21.9%（66/302），其中甲状腺功能减退发生率为 19.5%（59/302）。两组患者年龄、PD-1 抑制剂种类、游离甲状腺素、甲状腺过氧化物酶抗体（thyroid peroxidase antibody, TPOAb）、甲状腺球蛋白、淀粉酶、淋巴细胞亚群 CD3 表达水平差异有统计学意义（$P<0.05$）。多因素 logistic 回归分析显示，淋巴细胞亚群 CD3 表达较高是预防内分泌 irAEs 发生的独立保护因素（$P=0.004$），年龄＜60 岁、TPOAb 水平较高及使用帕博利珠单抗是内分泌 irAEs 发生独立危险因素（$P<0.05$）。由此构建的列线图模型阈值概率＞0.1 时，模型的净获益较大；ROC 显示模型预测内分泌 irAEs 的 AUC 为 0.760；模型预测结果与实际结果一致性较高。**结论**　年龄、PD-1 抑制剂类型、基线 TPOAb 水平及基线 CD3 表达与内分泌 irAEs 发生独立相关，基于这些因素构建的列线图模型具有良好预测效能，可为临床早期识别高危患者及其免疫治疗管理提供参考。

［**关键词**］ 免疫检查点抑制剂；免疫相关不良反应；内分泌；预测模型
［**中图分类号**］ R 730.51；R 58　　［**文献标志码**］ A

Construction of predictive model for programmed death-1 inhibitor-related endocrine adverse events

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［**Abstract**］ **Objective**　To identify the independent predictors of programmed death-1 (PD-1) inhibitor-related endocrine adverse events and construct a clinically usable risk prediction model. **Methods**　A total of 302 patients with solid tumors treated with PD-1 inhibitors were retrospectively enrolled. According to the presence or absence of endocrine immune-related adverse events (irAEs), the patients were divided into case group and control group. The clinical and laboratory indexes were compared between the two groups. Multivariable logistic regression was used to confirm independent predictors of endocrine irAEs. The nomogram was constructed, while the receiver operating characteristic (ROC) curve was used to test the prediction performance of the model. **Results**　The overall incidence of endocrine irAEs was 21.9% (66/302), and the incidence of hypothyroidism was 19.5% (59/302). The age, PD-1 inhibitors, free thyroxine, thyroid peroxidase antibody (TPOAb), thyroglobulin, amylase, lymphocyte subset CD3 expression were statistically different between the two groups ($P<0.05$). Multivariable logistic regression showed that higher

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expression of lymphocyte subset CD3 was a protective factor to prevent endocrine irAEs occurrence (P＝0.004), while age＜60 years, higher TPOAb and use of pembrolizumab were independent risk factors of endocrine irAEs (P＜0.05). The nomogram model thus constructed, and when the threshold probability of the model exceeded 0.1, its net benefit was higher. ROC curve showed that the AUC of the model to predict endocrine irAEs was 0.760. The prediction result of the model was highly consistent with the actual result. **Conclusions** The age, type of PD-1 inhibitor, baseline TPOAb level, and baseline CD3 expression can independently predict endocrine irAEs occurrence or not. The nomogram model based on this model has good predictive efficiency, which can provide reference for early identification of high-risk patients and immunotherapy management.

［**Key Words**］ immune checkpoint inhibitor; immune-related adverse event; endocrine; predictive model

免疫检查点抑制剂（immune checkpoint inhibitor, ICI）被广泛用于肿瘤治疗。ICI 通过阻断细胞毒性 T 淋巴细胞相关抗原 4（cytotoxic T lymphocyte-associated antigen-4, CTLA-4）、程序性死亡受体 1（programmed death-1, PD-1）/程序性死亡配体 1（programmed death-ligand 1, PD-L1）等免疫抑制通路，显著增强了抗肿瘤免疫应答，已成为多种恶性肿瘤（如肺癌、黑色素瘤、肝癌）的重要治疗手段[1, 2]。PD-1 抑制剂是常用的 ICI 之一[3]。其中，帕博利珠单抗、信迪利单抗等 PD-1 抑制剂已被广泛用于实体肿瘤的治疗，且临床疗效显著[4]。

然而，ICI 在激活免疫系统的同时，也可能诱发皮肤、心脏及内分泌等多系统免疫相关不良反应（immune-related adverse events, irAEs）[5-6]。irAEs 的发生率为 66.4%～86.8%，涉及直接组织损伤、抗原交叉反应、自身抗体介导的免疫反应等多种机制[7]。而且，irAEs 是免疫治疗中断的重要原因之一。

内分泌 irAEs 发生率为 10%～40%[8]，累及甲状腺、垂体和肾上腺等器官，表现为甲状腺功能异常、垂体炎、肾上腺功能不全等，部分患者可进展为甲状腺危象、糖尿病酮症酸中毒或肾上腺危象等严重并发症[9-11]。因此，明确内分泌 irAEs 相关预测因素，对于提高肿瘤免疫治疗的有效性和安全性至关重要。目前，针对内分泌 irAEs 的研究有限，本研究拟探讨 PD-1 相关内分泌 irAEs 的预测因素，并构建预测模型。

1 资料与方法

1.1 一般资料 纳入 2019 年 5 月至 2025 年 4 月在上海交通大学医学院附属仁济医院（n＝244）和宁波市杭州湾医院（n＝58）接受 PD-1 抑制剂治疗的恶性肿瘤患者。入组标准：（1）经病理学检查确诊为实体恶性肿瘤；（2）接受至少 1 个周期的 PD-1 抑制剂治疗。排除标准：病史资料不完善或缺乏基线数据。

1.2 观察指标 收集患者年龄、性别，肿瘤类型、PD-L1 免疫组化结果，治疗线数等。记录患者 ICI 应用前的血电解质、血常规、肿瘤标志物，肾上腺、垂体、胰腺、甲状腺功能指标，淋巴细胞亚群，白介素及肿瘤坏死因子等水平。内分泌 irAEs 依据美国国家癌症研究所不良事件通用术语标准（Common Terminology Criteria for Adverse Events, CTCAE）评估。分析各类内分泌 irAEs 的发生时间分布。根据发生内分泌 irAEs 与否，将患者分为病例组和对照组。

1.3 统计学处理 采用 SPSS 29.0 和 R 4.4.2 软件处理数据。计数资料以 n(%) 表示，组间比较采用卡方检验或 Fisher 精确概率法。将组间差异有统计学意义的指标（排除存在共线性及缺失值较多者）纳入多因素 logistic 回归分析，并建立列线图模型。通过决策曲线分析（decision curve analysis, DCA）、受试者工作特征（receiver operating characteristic, ROC）和校准曲线评估模型的预测效能。将患者按 7∶3 随机分为训练集和测试集，通过 R 软件 bootstrap 法进行内部验证。检验水准（α）为 0.05。

2 结 果

2.1 研究对象总体特征 302 例患者平均（62.31±11.10）岁，男性占 67.9%，一线治疗者占 60.3%，肿瘤类型中以肺癌最多（32.8%），发生内分泌 irAEs 者 66 例（21.9%，表 1）。

表 1　患者总体临床特征

Table 1　Overall clinical characteristics of patients

n=302

Index	*n*(%)
Age	
＜60 years	93(30.8)
≥60 years	209(69.2)
Sex	
Female	97(32.1)
Male	205(67.9)
Line of treatment	
Neoadjuvant therapy	9(3.0)
First-line treatment	182(60.3)
Second-line treatment	39(12.9)
Third-line treatment	37(12.3)
Fourth-line treatment	9(3.0)
Fifth-line treatment	2(0.7)
Unknown	24(7.9)
Malignant tumor type	
Cancer of the gallbladder or bile duct	8(2.6)
Independent multiple primary tumor	6(2.0)
Lung cancer	99(32.8)
Liver cancer	16(5.3)
Colorectal cancer	34(11.3)
Urinary system neoplasm	24(7.9)
Breast cancer	2(0.7)
Reproductive system neoplasm	8(2.6)
Esophageal cancer	20(6.6)
Cancer of the stomach or duodenum	40(13.2)
Pancreatic cancer	19(6.3)
Other	23(7.6)
PD-1 inhibitor	
Pembrolizumab	127(42.1)
Sintilimab	120(39.7)
Other	55(18.2)
Endocrine irAEs	66(21.9)

irAEs: immune-related adverse events; PD-1: programmed death-1.

2.2　患者内分泌 irAEs 情况及发生时间　结果（图 1）显示：内分泌 irAEs 患者中，甲状腺功能异常最常见（21.2%，64/302），以甲状腺功能减退为主（19.5%，59/302）。甲状腺功能减退发生的中位时间为治疗后 2.57(1.71, 4.12) 个月，甲状腺功能亢进（1.7%，5/302）发生的中位时间为治疗后 3.86(2.19, 6.67) 个月。垂体功能异常 2 例，分别发生于治疗后 4 个月和 19 个月。有 1 例患者出现两个内分泌器官损伤，分别为肾上腺皮质功能减退和甲状腺功能减退。

2.3　两组患者临床、实验室指标比较　结果（表 2）显示：两组患者年龄、PD-1 抑制剂种类，基线游离甲状腺素（free thyroxine, FT4）、甲状腺过氧化物酶抗体（thyroid peroxidase antibody, TPOAb）、甲状腺球蛋白（thyroglobulin, Tg）、淀粉酶、淋巴细胞亚群 CD3 表达水平差异有统计学意义（P＜0.05）。

2.4　内分泌 irAEs 影响因素　将年龄、PD-1 抑制剂种类、TPOAb、淋巴细胞 CD3 表达纳入多因素 logistic 回归分析，结果（表 3）显示：年龄≥60 岁、淋巴细胞 CD3 表达增加患者发生内分泌 irAEs 的风险较小（P＜0.05），TPOAb 升高、应用帕博利珠单抗等患者发生内分泌 irAEs 的风险较大（P＜0.05）。

2.5　内分泌 irAEs 预测模型构建　以年龄、PD-1 抑制剂种类、TPOAb 水平、淋巴细胞亚群 CD3 表达绘制列线图模型，结果（图 2A）显示：模型得分越高，患者越易发生内分泌 irAEs。DCA 曲线（图 2B）显示：当阈值概率＞0.1 时，使用该模型的净获益更显著。ROC 曲线（图 2C）显示：模型预测训练集、测试集和总集患者发生内分泌 irAEs 的曲线下面积（area under the curve, AUC）分别为 0.791、0.675 和 0.760，表明该模型有较高的内分泌 irAEs 预测能力。校准曲线（图 2D）显示预测结果与实际结果相似。

3　讨　论

目前，内分泌 irAEs 的发病机制尚未阐明，临床管理仍面临挑战，部分患者症状隐匿，易被漏诊[12]。由于缺乏相关预测模型，目前临床较难进行个体化风险分层与早期干预。既往研究显示，内分泌 irAEs 的发病率可达 40%，与 ICI 的种类和剂量相关[8]，其中甲状腺功能异常最常见，发生率为 8.0%～30.2%[13]。内分泌 irAEs 发生时间窗多为治疗后 0.3～27.3 个月[14]，大多数在治疗前 20 周发生[15]。本研究中，内分泌 irAEs 发生率为 21.9%，其中甲状腺功能异常发生率为 21.2%，且内分泌 irAEs 多在治疗后 1～5 个月发生，与既往研究相符。

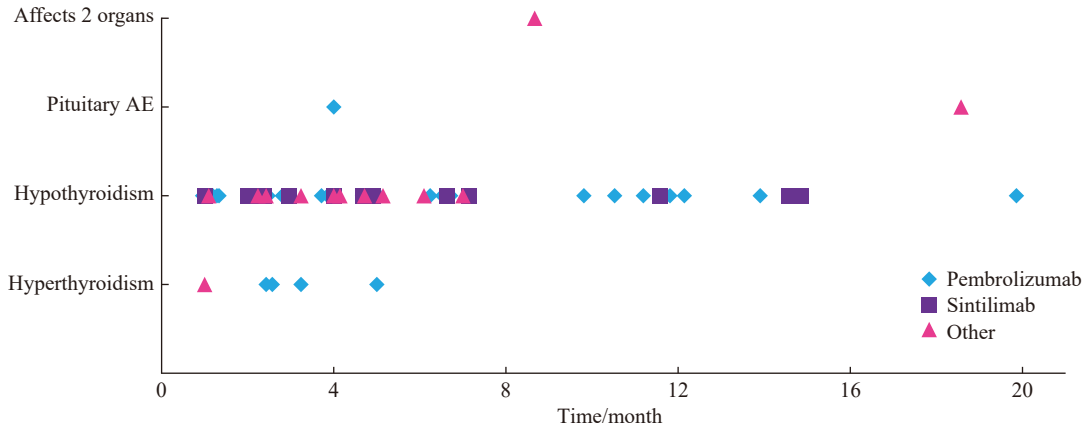

图 1　不同内分泌 irAEs 的诱发药物及发生时间分布

Figure 1　Inducing drugs and temporal distribution of different endocrine irAEs

irAEs: immune-related adverse events.

表 2　内分泌 irAEs 的单因素分析

Table 2　Univariate analysis of endocrine irAEs

n(%)

Index	Control group	Case group	χ^2	*P*
Sex			1.285	0.297
Female	72(23.8)	25(8.3)		
Male	164(54.3)	41(13.6)		
Age			10.368	0.002
＜60 years	62(20.5)	31(10.3)		
⩾60 years	174(57.6)	35(11.6)		
Ki-67			3.309	0.190
＜25%	23(11.9)	13(6.7)		
＞50%	75(38.9)	25(13.0)		
20%-50%	46(23.8)	11(5.7)		
PD-1 inhibitor			11.090	0.004
Pembrolizumab	89(29.5)	38(12.6)		
Sintilimab	105(34.8)	15(5.0)		
Other	42(13.9)	13(4.3)		
PD-L1 negative	40(33.9)	17(14.4)	0.719	0.412
Endocrine function				
Free triiodothyronine			0.954	0.447
Low	14(7.3)	8(4.2)		
Normal	125(65.1)	45(23.4)		
Free thyroxine				0.029
High	3(1.6)	1(0.5)		
Low	28(14.6)	3(1.6)		
Normal	108(56.3)	49(25.5)		
Thyroid stimulating hormone				0.083
High	10(5.2)	9(4.7)		
Low	3(1.6)	0		
Normal	126(65.6)	44(22.9)		
Thyroid peroxidase antibody				0.012
High	6(3.2)	8(4.3)		
Normal	131(70.1)	42(22.5)		

Continued table 2

Index	Control group	Case group	χ^2	P
Thyroglobulin				0.004
High	3(1.6)	7(3.8)		
Normal	133(71.9)	42(22.7)		
Testosterone				0.714
Low	7(7.2)	3(3.1)		
Normal	65(67.0)	22(22.7)		
Progesterone				0.613
Low	1(1.6)	1(1.6)		
Normal	39(60.9)	23(35.9)		
Estradiol				1.000
High	2(2.0)	0		
Low	9(9.2)	3(3.1)		
Normal	62(63.3)	22(22.4)		
Prolactin			1.819	0.238
High	32(32.3)	7(7.1)		
Normal	42(42.4)	18(18.2)		
Follicle stimulating hormone			1.517	0.291
High	21(21.2)	4(4.0)		
Normal	53(53.5)	21(21.2)		
Luteinizing hormone				0.282
High	23(23.2)	4(4.0)		
Low	2(2.0)	0		
Normal	49(49.5)	21(21.2)		
Adrenocorticotropic hormone				0.406
High	20(22.0)	7(7.7)		
Low	0	1(1.1)		
Normal	47(51.6)	16(17.6)		
Cortisol				0.875
High	7(7.4)	2(2.1)		
Low	2(2.1)	1(1.1)		
Normal	57(60.6)	25(26.6)		
Growth hormone			0.009	1.000
High	20(23.3)	8(9.3)		
Normal	42(48.8)	16(18.6)		
Inflammatory and metabolic marker				
C-reactive protein			0.338	0.657
High	81(29.3)	26(9.4)		
Normal	133(48.2)	36(13.0)		
Amylase				0.008
High	6(3.6)	9(5.3)		
Low	3(1.8)	2(1.2)		
Normal	114(67.5)	35(20.7)		
Blood cell				
White cell count			1.608	0.460
High	29(9.8)	12(4.1)		
Low	24(8.1)	5(1.7)		
Normal	176(59.7)	49(16.6)		
Neutrophil count				0.375
High	27(9.2)	12(4.1)		
Low	17(5.8)	5(1.7)		
Normal	185(62.7)	49(16.6)		

Continued table 2

Index	Control group	Case group	χ^2	P
Lymphocyte subset				
$CD19^+$				0.419
High	5(2.6)	1(0.5)		
Low	49(25.1)	11(5.6)		
Normal	94(48.2)	35(17.9)		
$CD3^+$				0.011
High	54(23.8)	7(3.1)		
Low	11(4.8)	8(3.5)		
Normal	111(48.9)	36(15.9)		
$CD4^+$				0.231
High	61(26.9)	12(5.3)		
Low	13(5.7)	6(2.6)		
Normal	102(44.9)	33(14.5)		
$CD8^+$				0.294
High	13(7.3)	1(0.6)		
Low	6(3.4)	2(1.1)		
Normal	113(63.5)	43(24.2)		
$CD4^+/CD8^+$ ratio			5.145	0.073
High	52(22.9)	7(3.1)		
Low	17(7.5)	6(2.6)		
Normal	107(47.1)	38(16.7)		
$CD56^+$				0.406
High	54(23.9)	12(5.3)		
Low	5(2.2)	3(1.3)		
Normal	116(51.3)	36(15.9)		
Regulatory T cell				0.184
High	16(11.3)	2(1.4)		
Low	27(19.1)	9(6.4)		
Normal	59(41.8)	28(19.9)		
Cytokine				
Interferon-α				1.000
High	7(4.7)	2(1.3)		
Normal	107(71.8)	33(22.1)		
Tumor necrosis factor-α				1.000
High	16(7.7)	4(1.9)		
Normal	144(69.2)	44(21.2)		
Interleukin-2				1.000
High	3(1.4)	1(0.5)		
Normal	158(75.6)	47(22.5)		
Interleukin-4			4.225	0.051
High	44(21.2)	6(2.9)		
Normal	117(56.3)	41(19.7)		
Interleukin-6			0.219	0.716
High	117(55.7)	33(15.7)		
Normal	45(21.4)	15(7.1)		
Interleukin-8			0.058	0.845
High	74(48.7)	23(15.1)		
Normal	41(27.0)	14(9.2)		

Continued table 2

Index	Control group	Case group	χ^2	*P*
Interleukin-10			1.151	0.364
High	27(12.9)	5(2.4)		
Normal	134(64.1)	43(20.6)		
Interleukin-17				0.307
High	12(6.0)	1(0.5)		
Normal	142(70.6)	46(22.9)		

irAEs: immune-related adverse events; PD-1: programmed death-1.

表 3　内分泌 irAEs 多因素 logistic 回归分析

Table 3　Multivariate logistic regression analysis of endocrine irAEs

Variable	B	SE	Wald	OR(95% CI)	*P*
Age (≥60 years vs ＜60 years)	−0.939	0.421	4.967	0.391(0.171-0.893)	0.026
TPOAb (high vs normal)	1.864	0.697	7.160	6.448(1.646-25.253)	0.007
CD3 expression (vs normal)					
Low	0.437	0.662	0.436	1.548(0.423-5.669)	0.509
High	−1.945	0.675	8.301	0.143(0.038-0.537)	0.004
PD-1 inhibitor (vs sintilimab)					
Pembrolizumab	1.111	0.519	4.586	3.037(1.099-8.394)	0.032
Other	1.599	0.755	4.482	4.949(1.126-21.752)	0.034

irAEs: immune-related adverse events; TPOAb: thyroid peroxidase antibody, 0-34 IU/mL is as normal, ＞34 IU/mL is as high; CD3 expression 53.3%-81.22% is as normal, ＜ 53.3% is as low, ＞81.22% is as high; PD-1: programmed death-1.

本研究提示，年龄＜60 岁的恶性肿瘤患者更易发生内分泌 irAEs，与 Samani 等[16]的多中心研究结果相似。该研究发现，＜65 岁的患者较≥75 岁的患者更易发生内分泌 irAEs。年龄与内分泌 irAEs 发生的负相关关系可能与免疫衰老有关。irAEs 的发生与机体免疫系统的活性密切相关。衰老的免疫系统中，幼稚 T 细胞产生的记忆细胞增殖减慢，细胞因子水平降低[17]。因此，衰老的免疫系统对抗原刺激的反应能力及有效性降低[18]，使其难以通过直接损伤、交叉抗原等机制损伤正常组织，进而不易导致 irAEs。然而，另有研究[19]发现，年龄较大的肿瘤患者更可能发生致死性 irAEs。这提示尽管老年人群内分泌 irAEs 发生率相对较低，但一旦发生则更可能由于机体功能储备不足而进展为严重不良事件。因此，在临床实践中，对于接受免疫治疗的老年恶性肿瘤患者，仍需及时排查内分泌 irAEs。

本研究中，基线 TPOAb 水平升高的患者更易发生内分泌 irAEs，与多项既往研究[20-21]结果一致，提示甲状腺自身免疫状态可能是甲状腺 irAEs 发生的潜在危险因素。约 11% 的人群携带甲状腺自身抗体，接受 PD-1 抑制剂治疗后，其 T 细胞依赖的 B 细胞体液免疫激活，进一步产生和分泌自身抗体[22-23]，从而加重甲状腺损伤。

CD3 是 T 淋巴细胞的关键表面标志物，表达水平反映 T 细胞的数量和活性[24]。T 细胞通过细胞免疫应答参与抗肿瘤效应，但过度激活可能导致 irAEs，包括内分泌 irAEs（如甲状腺炎、垂体炎）[25]。本研究中，基线淋巴细胞 CD3 表达增加的患者内分泌 irAEs 发生风险降低。CD3 水平较高提示患者有更强的免疫稳态调节能力，从而能抑制自身免疫攻击，降低内分泌 irAEs 风险。

PD-1 抑制剂种类也与内分泌 irAEs 发生有关，不同 PD-1 抑制剂导致的内分泌 irAEs 谱存在差异。CTONG1901 研究[26]显示，尽管信迪利单抗与帕博利珠单抗的总体安全性相似，但信迪利单抗组患者的内分泌 irAEs（如甲状腺功能异常、垂体炎）发生率略低。另有研究[27]发现，在不同 PD-1 抑制剂中，帕博利珠单抗诱导的甲状腺功能减退发生率最高。本研究中，帕博利珠单抗较信迪利单抗更易诱发内分泌 irAEs，内分泌 irAEs 中以甲状腺功能减退为主，与既往研究结果相似。帕博利珠单抗与信迪利单抗的分子结构及结合特性存在差异[28]，后者的抗体依赖性细胞毒性

（antibody-dependent cell-mediated cytotoxicity, ADCC）效应较弱[29]，对内分泌细胞（如甲状腺滤泡细胞）的损伤较小，这可能是两者诱导内分泌 irAEs 发生率不同的原因。

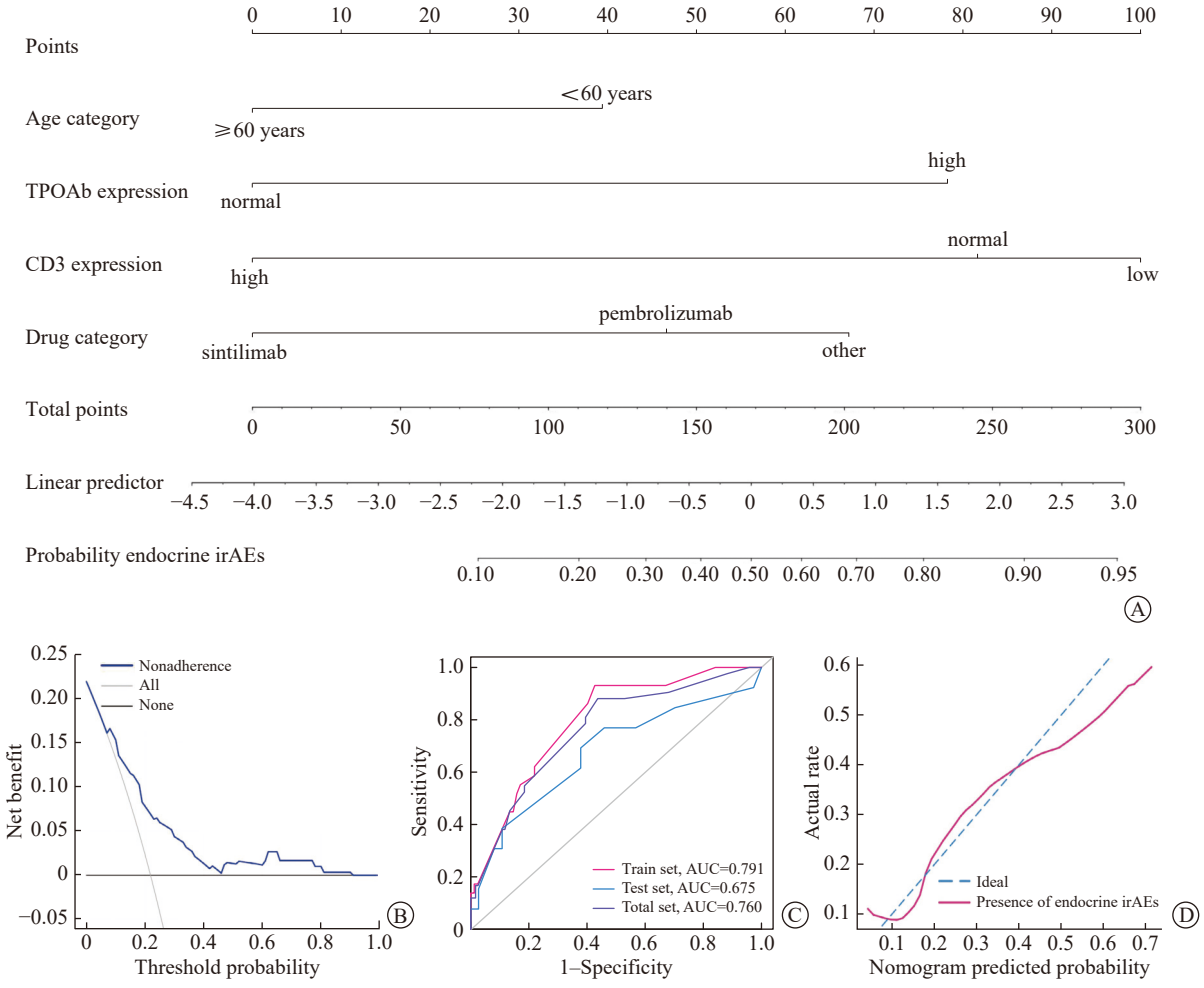

图 2　内分泌 irAEs 列线图预测模型及效能评估

Figure 2　Construction and validation of a nomogram model to predict endocrine irAEs

A: Nomogram model; B: Decision curve analysis; C: Receiver operating characteristic curve; D: Calibration curve. irAEs: immune-related adverse events; TPOAb: thyroid peroxidase antibody, 0-34 IU/mL is as normal, ＞34 IU/mL is as high; CD3 expression 53.3%-81.22% is as normal, ＜ 53.3% is as low, ＞81.22% is as high; AUC: area under the curve.

本研究局限性：（1）样本量较小；（2）为回顾性研究，可能存在信息偏倚；（3）仅以内分泌 irAEs 发生与否分组，而未进行内分泌 irAEs 严重程度的分层分析；（4）未排除合并内分泌疾病患者，可能影响结果的准确性。

综上所述，本研究发现，年龄、PD-1 抑制剂种类、基线 TPOAb 水平、基线淋巴细胞亚群 CD3 表达水平是内分泌 irAEs 的独立预测因素，由此建立的列线图模型有较好的预测效能，有助于临床早期识别高风险患者，从而优化 PD-1 抑制剂的临床应用，提高其使用安全性和有效性。

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