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外周血CD8+ TEMRA细胞对胃癌新辅助治疗病理响应的预测价值：一项回顾性研究

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摘 要

目的：探讨胃癌的新辅助治疗(NAT)下外周血免疫图谱的动态演变及其与病理退缩分级(TRG)的关联，并筛选独立预测因子，构建术前疗效评估模型。方法：回顾性纳入2023年12月至2025年3月于重庆医科大学附属第一医院胃肠外科接受新辅助治疗并完成手术切除的48例胃癌患者。按照治疗方式分为新辅助经动脉化疗栓塞联合免疫治疗组(TACE组，33例)与新辅助全身化疗联合免疫治疗组(NACT组，15例)。主要终点为病理退缩分级(TRG)，TRG 0~1级界定为病理响应良好。采用错误发现率(FDR)校正进行横断面差异分析；对18例配对样本(治疗前后)进行纵向动态比较；结合最小绝对收缩和选择算子(LASSO)回归与多因素Logistic回归筛选独立预测变量，绘制受试者工作特征(ROC)曲线，并通过留一法交叉验证(LOOCV)评估模型内部判别效能。结果：全队列中17例(35.4%)实现病理响应良好。横断面多重检验校正提示，术前外周血CD8+ TEMRA细胞比例在响应良好组中显著富集，且为唯一经校正后保持统计学意义的亚群(FDR < 0.05)。纵向配对分析显示，新辅助干预后效应/活化表型细胞(NK、CD8+ HLA-DR+、CD8+ CD38+)比例显著上调，而初始/耗竭表型细胞(CD19+、CD8+ Naive、CD8+ PD-1+)比例显著回落，其中CD8+ PD-1+ T细胞下调幅度最为显著(FDR < 0.001)。组间比较显示，TACE组NK细胞比例显著高于NACT组(FDR = 0.014)，但CD8+ TEMRA分布无方案依赖性差异。LASSO降维及多因素Logistic回归确证，CD8+ TEMRA是预测良好病理响应的独立相关因素(OR = 1.12, 95% CI: 1.040~1.200, P = 0.003)。联合预测模型全队列曲线下面积(AUC)为0.852，经LOOCV内部惩罚后校正AUC为0.824。结论：术前外周血CD8+ TEMRA细胞富集程度与胃癌新辅助治疗后的病理良好响应呈独立正相关。基于该指标构建的联合预测模型在内部验证中展现出稳定的判别效能，可作为无创性外周标志物辅助胃癌围手术期疗效评估，但其临床应用仍需在更大样本中、结合标准化流式细胞术检测流程及明确的临床决策阈值后进一步验证。

关键词

胃癌，新辅助治疗，CD8+ TEMRA，病理退缩，预测模型

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Predictive Value of Peripheral Blood CD8+ TEMRA Cells for Pathological Response to Neoadjuvant Therapy in Gastric Cancer: A Retrospective Study

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Abstract

Objective: To investigate the dynamic evolution of peripheral blood immune profiles during neoadjuvant therapy (NAT) in gastric cancer and its association with tumor regression grade (TRG), and to identify independent predictors for constructing a preoperative efficacy assessment model. Methods: A retrospective cohort of 48 gastric cancer patients who received neoadjuvant therapy and underwent surgical resection at the Department of Gastrointestinal Surgery, The First Affiliated Hospital of Chongqing Medical University between December 2023 and March 2025 was enrolled. Patients were stratified by treatment modality into neoadjuvant transarterial chemoembolization plus immunotherapy group (TACE group, n = 33) and neoadjuvant systemic chemotherapy plus immunotherapy group (NACT group, n = 15). The primary endpoint was tumor regression grade (TRG), with TRG 0~1 defined as favorable pathological response. Cross-sectional differential analysis was performed with false discovery rate (FDR) correction; longitudinal dynamic comparison was conducted in 18 paired samples (pre- and post-treatment). Independent predictive variables were identified through least absolute shrinkage and selection operator (LASSO) regression combined with multivariate logistic regression. Receiver operating characteristic (ROC) curves were generated, and internal discriminative performance was evaluated via leave-one-out cross-validation (LOOCV). Results: Favorable pathological response was achieved in 17 patients (35.4%) in the entire cohort. Cross-sectional analysis with multiple testing correction revealed that preoperative peripheral blood CD8+ TEMRA cell proportion was significantly enriched in the favorable response group and remained the only subset retaining statistical significance after correction (FDR < 0.05). Longitudinal paired analysis demonstrated that effector/activated phenotype cells (NK, CD8+ HLA-DR+, CD8+ CD38+) were significantly upregulated following neoadjuvant intervention, while naive/exhausted phenotype cells (CD19+, CD8+ Naive, CD8+ PD-1+) were significantly downregulated, with CD8+ PD-1+ T cells showing the most pronounced reduction (FDR < 0.001). Inter-group comparison showed that NK cell proportion was significantly higher in the TACE group than in the NACT group (FDR = 0.014), whereas CD8+ TEMRA distribution exhibited no regimen-dependent difference. LASSO dimensionality reduction and multivariate logistic regression confirmed CD8+ TEMRA as an independent correlation of favorable pathological response (OR = 1.12, 95% CI: 1.040~1.200, P = 0.003). The combined predictive model achieved an area under the curve (AUC) of 0.852 in the entire cohort, with a corrected AUC of 0.824 after internal penalization via LOOCV. Conclusion: Preoperative peripheral blood CD8+ TEMRA cell enrichment demonstrates an independent positive correlation with favorable pathological response following neoadjuvant therapy in gastric cancer. The combined predictive model constructed based on this indicator exhibits stable discriminative performance in internal validation and may serve as a non-invasive peripheral biomarker to assist

perioperative efficacy assessment in gastric cancer, but its clinical application requires further validation in larger cohorts using standardized flow cytometry workflows and an explicit clinical decision threshold.

Keywords

Gastric Cancer, Neoadjuvant Therapy, CD8+ TEMRA, Tumor Regression, Predictive Model

1. 引言

胃癌是全球第五大常见癌症及第四大致死性恶性肿瘤，发病率和死亡率均居高不下[1]，尽管根治性手术仍是核心治疗手段，但由于早期症状隐匿，80%以上患者确诊时已进展至局部晚期或伴有淋巴结转移，单纯手术难以实现理想的长期生存[2]-[4]。FLOT4 等多项大型临床研究证实新辅助治疗作为围手术期综合策略的重要组成部分，可显著提高 R0 切除率、降低肿瘤分期并改善病理退缩[3]-[6]。研究显示，新辅助免疫治疗联合化疗(nICT)可将病理完全缓解(pCR)率提升至 20%，主要病理缓解(MPR)率提升至 40%~60%，R0 切除率高达 90%以上[7]-[9]。然而，临床实践中患者对新辅助治疗的病理响应存在显著异质性，仅约 1/4 患者可获得 pCR，且部分患者即使达到 pCR 亦存在远处复发风险[10]-[12]。目前常用的影像学评估方法易受治疗后炎性水肿等影响，难以准确反映真实疗效；而传统临床病理参数在术前对个体疗效预测能力有限[13] [14]。因此，筛选稳定、可靠的术前预测标志物，是当前胃癌围手术期管理的重点方向[15] [16]。

机体抗肿瘤免疫应答具有系统性与动态性，外周血免疫微环境变化可间接映射局部肿瘤微环境的免疫重塑轨迹[17]。相较于有创组织活检，外周血检测具备微创、可重复获取等优势，已成为探索肿瘤免疫应答特征的重要途径[18]-[21]。在介导抗肿瘤效应的免疫细胞中，CD8+ T 细胞占据核心地位，其功能高度依赖于分化阶段与激活状态。多项研究表明，新辅助治疗后 CD8+ T 细胞水平升高与更佳病理响应密切相关，并能作为独立预后因子[22]-[25]。其中，CD8+ TEMRA (终末分化效应记忆 T 细胞)作为经历长期抗原刺激、具备强效细胞毒潜能与快速反应能力的亚群，在外周血中的富集程度可能直接反映机体既往免疫应答强度及当前抗肿瘤免疫储备[26]-[29]。在胰腺癌有关的前瞻性试验中，CD8+ TEMRA 高水平与 PFS 延长显著相关，提示 TEMRA 可能是重要的预测与预后标志物[30]。

本研究回顾性纳入接受新辅助经动脉化疗栓塞联合免疫治疗(TACE 组)或新辅助全身化疗联合免疫治疗(NACT 组)的胃癌患者队列，系统评估术前外周血 18 种免疫细胞亚群分布与术后病理退缩分级的相关性。通过对比治疗前后配对样本，纵向分析新辅助干预诱导的外周免疫图谱重塑轨迹，并采用 LASSO 惩罚回归与多因素 Logistic 回归建模，筛选独立于治疗方案的疗效预测因子。本研究为胃癌新辅助治疗的术前精准分层提供可靠的无创血液学指标。

2. 材料与方法

2.1. 研究设计与对象

本研究为单中心回顾性队列研究。连续纳入 2023 年 12 月至 2025 年 3 月于重庆医科大学附属第一医

院胃肠外科接受新辅助治疗(NAT)并完成根治性手术切除的胃癌患者。

纳入标准：① 经组织病理学确诊为原发性胃癌；② 完成 NAT 周期后接受手术切除；③ 术前临床资料、病理报告及检验记录完整。排除标准：① 新辅助治疗前曾接受其他抗肿瘤干预；② 合并活动性感染、自身免疫性疾病或多发恶性肿瘤；③ 关键临床或检验数据缺失。最终纳入 48 例，按治疗方案分为新辅助经动脉化疗栓塞联合免疫治疗组(TACE 组，33 例)与新辅助全身化疗联合免疫治疗组(NACT 组，15 例)。其中 18 例患者具有完整的治疗前后配对检验记录，用于纵向研究。

2.2. 资料提取与结局定义

所有临床基线特征、治疗等均通过医院电子病历系统(HIS)调取。记录变量包括年龄、性别、肿瘤解剖位置(近端/远端)、术前临床分期(依据 AJCC 第 8 版 TNM 标准)。

主要研究终点为术后病理退缩分级(TRG)。由病理科医师按常规流程出具报告，参照胃癌围手术期治疗常用评价标准，将 TRG 0~1 级定义为病理响应良好组，TRG 2~3 级定义为病理响应不良组。

2.3. 外周血免疫细胞亚群数据提取

本研究外周血 18 种免疫细胞亚群比例数据均直接提取自 HIS 系统。提取内容为患者新辅助治疗前(Pre-NAT)及新辅助治疗后(Post-NAT)阶段的检测报告结果。检测指标涵盖 NK 细胞、B 细胞、CD3+ T 细胞、CD4+ T 细胞、CD8+ T 细胞及其分化状态亚群(如 Naive、TCM、TEM、TEMRA 等)，以及伴随 CD38、HLA-DR、PD-1 等标志物表达的细胞亚群比例。所有数据均以检验报告单记录的百分比结果为准。

2.4. 统计学分析

数据清洗与统计分析采用 R 软件(v 4.4.3)。计量资料经正态性检验后，符合正态分布者以 $\bar{x} \pm s$ 表示，非正态分布者以中位数(四分位间距)表示；计数资料以例数(百分比)表示。组间连续变量比较采用 Mann-Whitney U 检验，配对样本比较采用 Wilcoxon 符号秩检验；分类变量比较采用 Fisher 确切概率法。

针对 18 种免疫亚群的横断面筛选，统一采用 Benjamini-Hochberg 法进行错误发现率(FDR)校正，以 FDR < 0.05 为显著性阈值。采用最小绝对收缩和选择算子(LASSO) Logistic 回归进行变量降维，通过 10 折交叉验证绘制偏差曲线确定最优惩罚参数并保留非零系数变量。将筛选出的特征纳入多因素 Logistic 回归模型，计算优势比(OR)及 95%置信区间(CI)。模型判别效能通过受试者工作特征(ROC)曲线及曲线下面积(AUC)评估，置信区间采用 DeLong 法计算；模型内部稳健性通过留一法交叉验证(LOOCV)进行重抽样评估。所有统计检验均为双侧，P < 0.05 或 FDR < 0.05 为差异有统计学意义。

3. 结果

3.1. 患者基线特征及病理响应情况

本研究共纳入 48 例患者，术后病理评估显示，17 例(35.4%)达到病理响应良好(TRG 0~1)，31 例(64.6%)为病理响应不良(TRG 2~3)。基线特征分析显示(表 1)，病理响应良好组与不良组在年龄、性别、治疗方案及临床分期方面差异均无统计学意义(P > 0.05)；但肿瘤位置分布存在显著差异，近端肿瘤在病理响应良好组中的比例显著高于不良组(P = 0.005)。按治疗方案分层后，TACE 组(n = 33)与 NACT 组(n = 15)在年龄、性别、肿瘤位置及临床分期等基线参数上均无统计学差异(P > 0.05，表 1)，提示两组间基线分布均衡，具备良好的可比性。

Table 1. Baseline clinical characteristics of patients with gastric cancer and comparisons according to pathological tumor regression grade and treatment modality

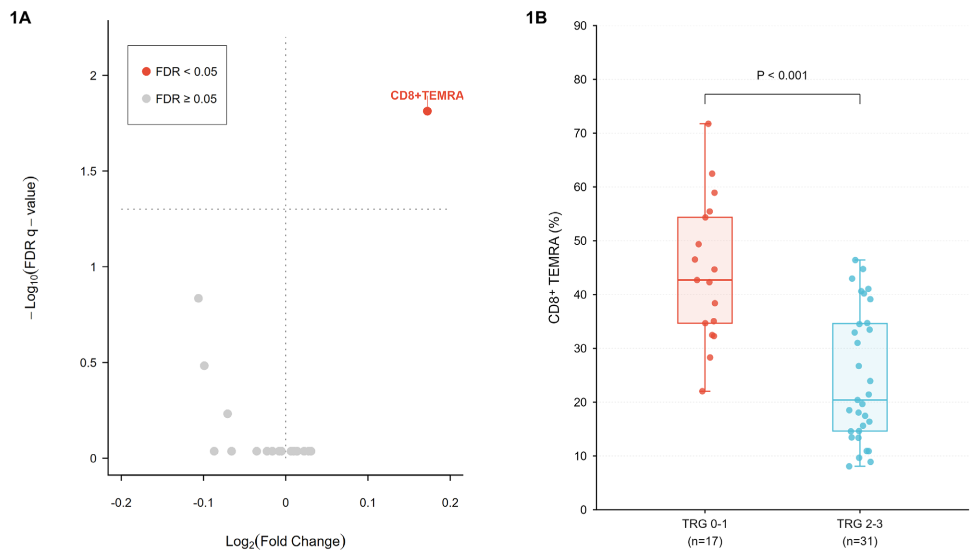
表 1. 胃癌患者基线临床特征及按病理退缩分级与治疗方式分组的比较

临床特征	总计 (n = 48)	TRG 分组			治疗方式分组		
		TRG 0~1 (n = 17)	TRG 2~3 (n = 31)	P 值	TACE (n = 33)	NACT (n = 15)	P 值
年龄(岁)	61.1 ± 12.5	64.8 ± 9.9	59.1 ± 13.5	0.107	61.8 ± 13.1	59.5 ± 11.4	0.540
性别							
女	12 (25.0%)	4 (23.5%)	8 (25.8%)	1.000	10 (30.3%)	2 (13.3%)	0.292
男	36 (75.0%)	13 (76.5%)	23 (74.2%)		23 (69.7%)	13 (86.7%)	
肿瘤位置							
近端	20 (41.7%)	12 (70.6%)	8 (25.8%)	0.005	14 (42.4%)	6 (40.0%)	1.000
远端	28 (58.3%)	5 (29.4%)	23 (74.2%)		19 (57.6%)	9 (60.0%)	
新辅助治疗方案							
TACE	33 (68.8%)	13 (76.5%)	20 (64.5%)	0.521	-	-	
NACT	15 (31.2%)	4 (23.5%)	11 (35.5%)		-	-	
cT 分期							
T3	23 (47.9%)	8 (47.1%)	15 (48.4%)	1.000	14 (42.4%)	9 (60.0%)	0.353
T4	25 (52.1%)	9 (52.9%)	16 (51.6%)		19 (57.6%)	6 (40.0%)	
cN 分期							
N0	6 (12.5%)	2 (11.8%)	4 (12.9%)	0.956	4 (12.1%)	2 (13.3%)	0.812
N1	12 (25.0%)	5 (29.4%)	7 (22.6%)		7 (21.2%)	5 (33.3%)	
N2	27 (56.2%)	9 (52.9%)	18 (58.1%)		20 (60.6%)	7 (46.7%)	
N3	3 (6.2%)	1 (5.9%)	2 (6.5%)		2 (6.1%)	1 (6.7%)	
cTNM 分期							
II 期	6 (12.5%)	2 (11.8%)	4 (12.9%)	1.000	4 (12.1%)	2 (13.3%)	0.420
III 期	41 (85.4%)	15 (88.2%)	26 (83.9%)		29 (87.9%)	12 (80.0%)	
IV 期	1 (2.1%)	0 (0.0%)	1 (3.2%)		0 (0.0%)	1 (6.7%)	

注：TRG 为病理退缩分级，0~1 级定义为病理响应良好，2~3 级定义为病理响应不良；TACE 为新辅助经动脉化疗栓塞联合免疫治疗组，NACT 为新辅助全身化疗联合免疫治疗组；cT、cN 及 cTNM 为基于 AJCC 第 8 版的临床分期。计量资料以均数 ± 标准差表示，组间比较采用独立样本 t 检验；计数资料以例数(百分比)表示，组间比较采用 Fisher 确切概率法。$P < 0.05$ 为差异有统计学意义。

3.2. 术前外周免疫图谱筛选提示 CD8+ TEMRA 与良好病理响应相关

对术前外周血 18 种免疫细胞亚群进行横断面差异分析(图 1(A))，多数亚群在病理响应良好组与不良组间分布重叠，未达到统计学显著性阈值。经 Benjamini-Hochberg 法进行错误发现率(FDR)校正后，仅 CD8+ TEMRA 细胞亚群保持显著性(FDR < 0.05)。定量比较结果显示(图 1(B))，病理响应良好组术前外周血 CD8+ TEMRA 细胞比例显著高于病理响应不良组($P < 0.001$)，结果显示，术前外周血 CD8+ TEMRA 细胞富集程度与病理退缩程度呈正相关。



1A：18 种免疫细胞亚群在病理响应良好组(TRG 0~1)与病理响应不良组(TRG 2~3)间的差异火山图。CD8+ TEMRA (CD8+终末分化效应记忆 T 细胞)为唯一经错误发现率(FDR)校正后保持显著差异的细胞亚群。1B：病理响应良好组与病理响应不良组外周血 CD8+ TEMRA 细胞比例的箱线图比较，采用 Mann-Whitney U 检验。

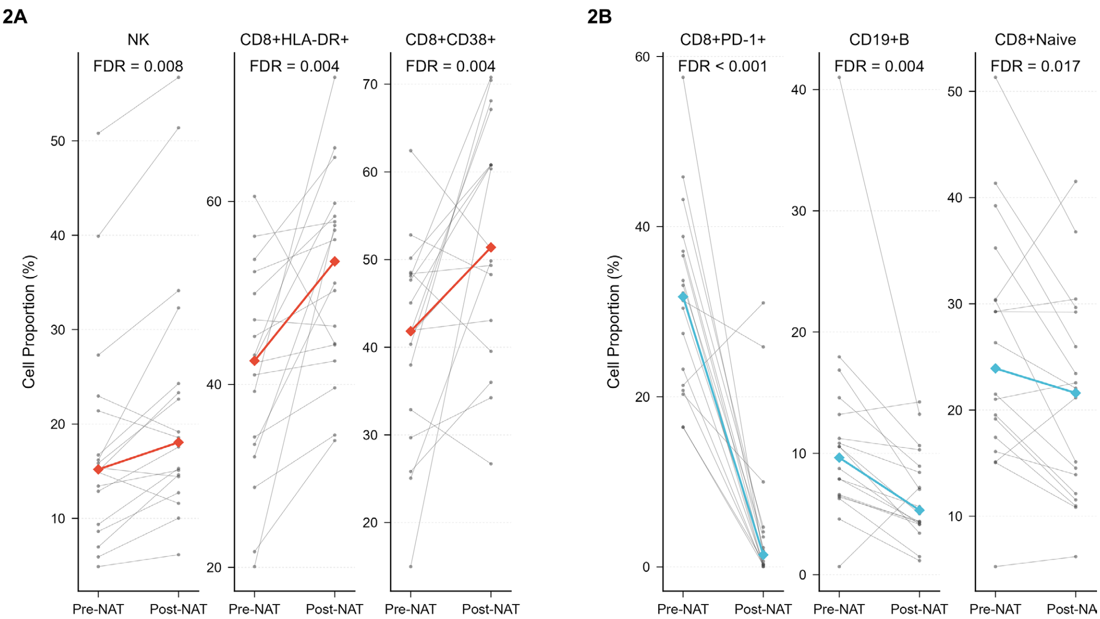
Figure 1. Association between preoperative peripheral blood immune cell subsets and pathological response
图 1. 术前外周血免疫细胞亚群与病理响应的关系

3.3. 新辅助治疗后外周免疫状态发生明显重塑

基于 18 例配对样本(Pre-NAT vs. Post-NAT)的纵向分析显示，新辅助治疗显著改变了外周血免疫细胞亚群的分布格局(图 2(A)、图 2(B))。治疗后，具有效应杀伤及活化表型的细胞亚群比例显著上调，其中 NK 细胞(FDR = 0.008)、CD8+ HLA-DR+ T 细胞(FDR = 0.004)及 CD8+ CD38+ T 细胞(FDR = 0.004)的中位比例均呈一致上升趋势。相反，CD19+ B 细胞与 CD8+ Naive T 细胞比例显著回落。值得注意的是，CD8+ PD-1+ T 细胞亚群在治疗后出现断崖式下降(FDR < 0.001)，其下降幅度及个体一致性均显著高于其他下调亚群。提示新辅助治疗并非引起单一细胞群的孤立波动，而是诱导了外周系统性免疫微环境的重塑。

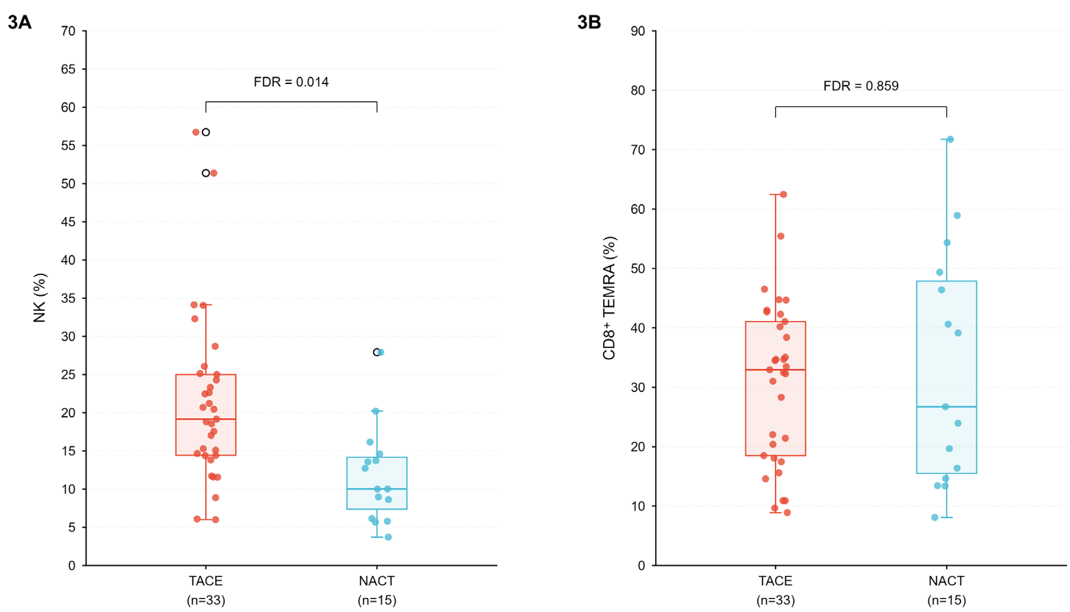
3.4. 不同新辅助方案对外周免疫微环境的影响存在差异

进一步比较不同新辅助干预策略对外周免疫特征的干预效应(图 3(A)、图 3(B))。结果显示，TACE 组外周血 NK 细胞比例显著高于 NACT 组，经多重检验校正后差异仍具统计学意义(FDR = 0.014)。然而，在核心候选标志物 CD8+ TEMRA 细胞方面，两组间分布未见显著差异(FDR = 0.859)。该结果表明，尽管局部介入联合免疫(TACE)与全身化疗联合免疫(NACT)对先天免疫细胞(如 NK 细胞)的激活强度存在方案特异性差异，但 CD8+ TEMRA 细胞的外周富集特征与治疗方式无显著相关性。这一特性进一步支持了 CD8+ TEMRA 作为独立于治疗方式疗效预测指标的可靠性。



2A：新辅助治疗前后(Pre-NAT vs. Post-NAT)效应性及活化表型免疫细胞亚群比例变化。CD8+ CD38+ (CD8+活化 T 细胞)、CD8+ HLA-DR+ (CD8+活化 T 细胞)和 NK 细胞比例显著上升(FDR = 0.004、0.004 和 0.008)。P < 0.05，经 FDR 校正。2B：新辅助治疗前后(Pre-NAT vs. Post-NAT)初始态及耗竭相关免疫细胞亚群比例变化。CD19+ B 细胞、CD8+ Naive T 细胞(CD8+初始 T 细胞)和 CD8+ PD-1+ T 细胞(CD8+耗竭 T 细胞)比例显著下降(FDR = 0.004、0.017 和<0.001)。连线表示同一患者治疗前后的变化趋势。P < 0.05，经 FDR 校正。

Figure 2. Dynamic changes in peripheral immune cell subsets before and after neoadjuvant therapy
图 2. 新辅助治疗前后外周免疫细胞亚群的动态变化

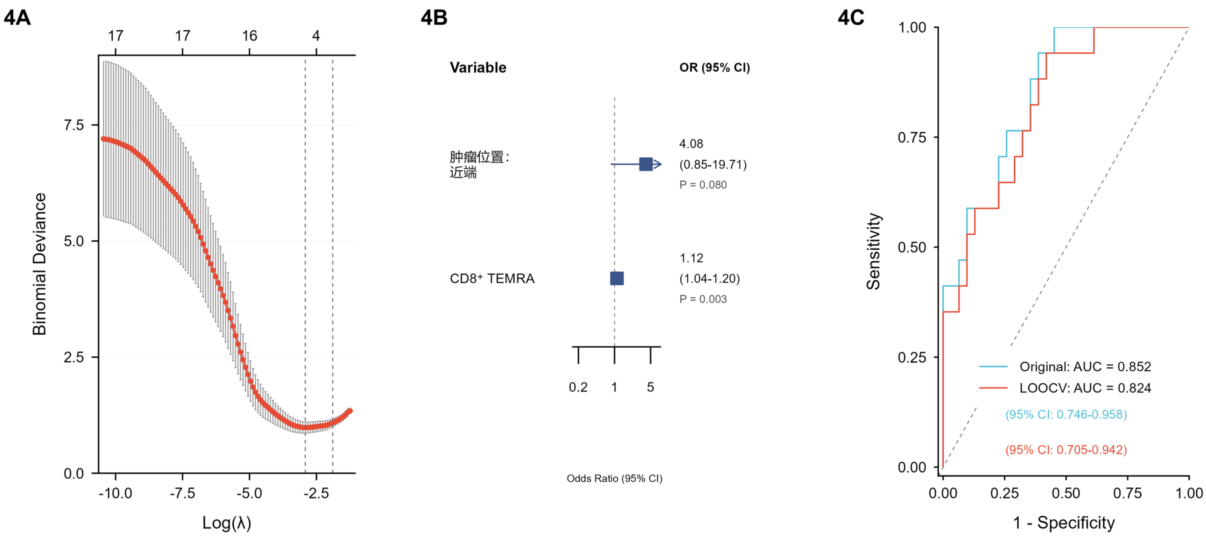


3A：新辅助经动脉化疗栓塞联合免疫治疗组(TACE)与新辅助全身化疗联合免疫治疗组(NACT)外周血 NK 细胞比例比较。TACE 组 NK 细胞比例显著高于 NACT 组(FDR = 0.014)。3B：新辅助经动脉化疗栓塞联合免疫治疗组(TACE)与新辅助全身化疗联合免疫治疗组(NACT)外周血 CD8+ TEMRA 细胞比例比较。两组间 CD8+ TEMRA 细胞比例无显著差异(FDR = 0.859)。采用 Mann-Whitney U 检验。

Figure 3. Effects of different neoadjuvant treatment regimens on the peripheral immune microenvironment
图 3. 不同新辅助治疗方案对外周免疫微环境的影响

3.5. LASSO 筛选与内部验证支持 CD8+ TEMRA 的独立预测价值

为控制高维变量在小样本队列中的过拟合风险，采用 LASSO 回归进行特征降维(图 4(A))。10 折交叉验证的二项式偏差曲线收敛后，模型最终筛选出肿瘤位置与 CD8+ TEMRA 两个非零系数变量。将上述变量纳入多因素 Logistic 回归分析(图 4(B))，结果显示 CD8+ TEMRA 是预测良好病理响应的独立相关因素(OR = 1.12, 95% CI: 1.040~1.200, P = 0.003)；肿瘤位置虽呈现正向关联趋势，但未达到统计学显著性(OR = 4.080, 95% CI: 0.850~19.710, P = 0.080)。基于肿瘤位置和 CD8+ TEMRA 构建的联合预测模型，其全队列受试者工作特征(ROC)曲线下面积(AUC)为 0.852 (95% CI: 0.746~0.958) (图 4(C))。经留一法交叉验证(LOOCV)内部惩罚后，校正 AUC 仍维持在 0.824 (95% CI: 0.705~0.942)。该结果证实，整合 CD8+ TEMRA 与临床解剖位置特征的联合模型在内部验证中具备良好的判别效能。



4A：LASSO 回归的二项式偏差曲线。横坐标表示 Log(λ)，纵坐标表示二项式偏差。红色虚线表示 1 个标准误规则(λ_{1se})确定的最优惩罚参数，对应筛选出的非零系数变量。4B：多因素 Logistic 回归分析结果。显示肿瘤位置(近端)和 CD8+ TEMRA 细胞比例对病理响应良好的预测价值。OR 表示优势比，95% CI 表示 95%置信区间。4C：联合预测模型的受试者工作特征(ROC)曲线。蓝色线表示原始模型 AUC = 0.852，红色线表示留一法交叉验证(LOOCV，Leave-One-Out Cross-Validation)校正后 AUC = 0.824。

Figure 4. Construction and validation of a model for predicting pathological response based on CD8+ TEMRA cells
图 4. CD8+ TEMRA 细胞预测病理响应的模型构建与验证

4. 讨论

本研究发现，新辅助治疗前外周血 CD8+ TEMRA 细胞比例是预测胃癌患者术后病理响应良好的独立指标，且该预测价值在不同治疗方案间保持稳定。胃癌新辅助治疗的临床决策长期面临疗效异质性的挑战，传统影像学评估难以在治疗早期准确区分真实退缩与治疗相关假性进展，而侵入性组织活检又受限于采样偏差与重复可行性等因素[31] [32]。本研究通过分析术前外周免疫图谱，明确了 CD8+ TEMRA 作为无创预测标志物的临床潜力，其治疗后水平与病理退缩分级(TRG 0-1)的正向关联，提示可作为无创性外周标志物评估疗效[33]。

大量前瞻性队列研究证实，治疗前具有效应/记忆表型的 CD8+ T 细胞的丰度与新辅助化疗或免疫检查点抑制剂(ICI)的病理缓解率呈正相关，支持“治疗前免疫储备决定治疗敏感性”的共识[22] [33]-[35]。然而，既往文献多将预测窗口局限于肿瘤组织内部，聚焦于 CD8+ PD-1+、CD103+ CD39+等局部浸润亚

群，其结论主要围绕肿瘤微环境内的耗竭特征或空间分布异质性展开讨论[36]-[39]。组织学标志物虽具有明确的病理指向，但受限于活检创伤性、空间抽样误差及动态监测的方面[40]。本研究将预测载体转向外周循环系统，发现 CD8+ TEMRA 在血液中的预测效能，且其稳定性独立于治疗方式，更契合围手术期临床实践中对无创、可重复监测指标的迫切需求[41]-[43]。

针对新辅助治疗前后的纵向免疫演变，本研究观察到的外周免疫图谱重塑轨迹与多项实体瘤临床队列报道保持一致，并进一步明确了联合免疫干预在系统性激活抗肿瘤应答中的核心作用。新辅助治疗后外周血中 NK 细胞及激活表型 CD8+ HLA-DR+、CD8+ CD38+ T 细胞比例上升，提示全身性抗肿瘤免疫被有效启动，这与多种消化道肿瘤新辅助 PD-1 联合化疗/抗血管治疗中观察到的细胞毒 T 细胞与 NK 细胞扩增高度一致[44]-[46]。在 PD-1/PD-L1 抑制剂参与的方案中，CD8+ T 细胞耗竭相关表型整体下调，IFN-γ 功能特征增强，支持免疫检查点阻断在恢复 CD8+效应功能中的核心作用[47] [48]。同时，治疗后 CD8+ PD-1+ T 细胞比例显著下降，可解释为靶点被抗-PD-1 抗体占用，与多队列中 PD-1 高表达的 CD8+ T 细胞与差预后及化疗获益有限相关[49]-[51]。相比之下，仅接受细胞毒化疗而未联合 ICIs 的队列中，外周 PD-1 表达及 FoxP3+ Treg 在围手术及化疗过程中多表现为仅有限下降甚至再度升高[52]，提示传统治疗难以根本打破 PD-1+ T 细胞-Treg 主导的免疫抑制格局。此外，在方案特异性比较中，尽管 TACE 组 NK 细胞富集程度更高，可能与局部介入引发的肿瘤坏死及抗原暴露有关[53]，但核心预测指标 CD8+ TEMRA 在两组间分布均衡。这表明 CD8+ TEMRA 的基线特征独立于新辅助治疗的具体路径，不受局部介入或全身化疗方案的干预影响，进一步巩固了其作为跨方案通用预测标志物的临床稳定性[54] [55]。

基于多因素回归构建的预测模型在内部验证中展现出良好的区分效能(AUC 0.852，LOOCV 0.824)，其临床转化价值不仅在于统计学指标的优化，更在于为术前决策提供了监测指标[56]。对于胃癌患者而言，若能在治疗前通过常规外周血检测识别潜在的非响应者，临床医生可及时调整治疗策略，从而避免无效治疗带来的肿瘤进展风险与机体损耗[57] [58]。

本研究仍存在若干临床与方法学局限。作为单中心回顾性队列，总体样本量有限，纵向配对样本仅 18 例，可能影响动态演变分析的统计效能与外推性；本研究主要基于临床病理终点进行关联性分析，未同步开展细胞毒性功能或细胞因子分泌的体外验证，CD8+ TEMRA 究竟为直接介导抗肿瘤效应的效应亚群，抑或仅为治疗敏感性的伴随表型，仍需后续研究明确[59]；最后，模型尚未经独立多中心前瞻性队列验证，且缺乏长期生存数据支持，其预后预测价值与最佳临床截断值有待进一步确立。后续研究可进一步将外周血免疫分析与手术切除标本的肿瘤微环境分析相结合，借助空间转录组学、多重免疫荧光等技术，系统考察外周 CD8+ TEMRA 细胞与肿瘤组织内免疫细胞浸润、空间分布及功能状态之间的关联，以阐明其预测价值背后的潜在生物学基础。与此同时，应建立标准化的流式细胞术检测与分析流程，并在更大样本的验证队列中，采用约登指数等方法确定 CD8+ TEMRA 比例的最佳临床决策阈值，进一步明确其在指导治疗决策中的具体应用场景。

5. 结论

综上所述，术前外周血 CD8+ TEMRA 细胞比例与胃癌新辅助治疗后的病理响应密切相关，且具备跨治疗方案的独立预测效能。本研究为胃癌围手术期无创疗效分层提供了具有临床转化潜力的血液学指标，其后续临床应用仍需结合更大规模前瞻性验证、标准化流式检测流程及基于约登指数确定的临床决策阈值进一步确认。

声　明

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《赫尔辛基宣言》的规定。

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