

· 临床研究 ·

肿瘤相关巨噬细胞在早期胃癌中的表达及其临床病理意义

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[摘要] 目的: 探讨肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)在早期胃癌中的表达及其临床病理意义。方法: 收集2006年1月—2022年12月于常州市第二人民医院行根治性手术治疗的109例早期胃癌患者的临床病理信息。采用免疫组织化学方法检测肿瘤区及癌旁非肿瘤黏膜中CD68和CD163的表达。比较肿瘤区与癌旁非肿瘤黏膜中巨噬细胞的表达差异并分析肿瘤区TAM的表达与临床病理特征的关系。基于受试者工作特征(receiver operating characteristic, ROC)曲线确定的CD163/CD68截断值进行分组, 分析早期胃癌淋巴结转移的危险因素。采用ROC分析评估内镜切除治愈性评价系统(endoscopic curability assessment, eCura)及其联合CD163/CD68比值对早期胃癌淋巴结转移状态的区分能力并通过DeLong检验比较曲线下面积(area under the curve, AUC)差异。采用Kaplan-Meier法进行生存分析。结果: 与癌旁非肿瘤黏膜相比, 肿瘤区CD163和CD68评分显著升高(分别为10% vs. 5%, 35% vs. 10%, $P < 0.001$), 而CD163/CD68比值显著降低(0.33 vs. 0.50, $P < 0.001$)。CD163/CD68比值高与肿瘤低分化、浸润至黏膜下层及淋巴结转移显著相关($P < 0.05$)。多因素分析显示, CD163/CD68比值是早期胃癌淋巴结转移的独立危险因素($P < 0.05$)。在淋巴结转移的判别方面, eCura评价系统联合CD163/CD68比值的区分能力(AUC=0.774)显著优于eCura评价系统(AUC=0.706, $P=0.023$)。TAM(CD163和CD68评分、CD163/CD68比值)与早期胃癌患者5年生存率无显著相关性。结论: TAM可能参与早期胃癌的发生发展, CD163/CD68比值与早期胃癌淋巴结转移密切相关, 可作为反映肿瘤免疫微环境的指标联合eCura评价系统为早期胃癌淋巴结转移风险分层提供补充信息。

[关键词] 早期胃癌; 肿瘤相关巨噬细胞; 淋巴结转移**[中图分类号]** R735.2**[文献标志码]** A**[文章编号]** 1007-4368(2026)05-708-09**doi:** 10.7655/NYDXBNSN260084

Expression patterns and clinicopathological significance of tumor-associated macrophages in early gastric carcinoma

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[Abstract] **Objective:** To investigate the expression of tumor-associated macrophages (TAMs) in early gastric carcinoma (EGC) and their clinicopathological significance. **Methods:** A retrospective analysis was conducted on 109 patients with EGC who underwent radical gastrectomy at the Second People's Hospital of Changzhou between January 2006 and December 2022. Expression of CD68 and CD163 was assessed by immunohistochemistry in tumor regions and paired adjacent non-tumor mucosa. Macrophage expression was compared between tumor and non-tumor regions, and the associations between TAMs and clinicopathological characteristics were further analyzed. The CD163/CD68 ratio was dichotomized using a receiver operating characteristic (ROC) derived cut-off value and included in logistic regression analyses to identify risk factors for lymph node metastasis (LNM) in EGC. ROC analysis was further performed to evaluate the discriminatory ability of the endoscopic curability assessment (eCura) system, both alone and in combination with the CD163/CD68 ratio, for predicting LNM, and the DeLong test was used to compare the area under the curve (AUC). Overall survival was analyzed using the Kaplan-Meier method. **Results:** Compared with paired adjacent non-tumor mucosa, CD163 and CD68 scores were significantly higher in tumor regions (CD163: 10% vs. 5%; CD68: 35% vs. 10%; $P < 0.001$ for both), whereas the CD163/CD68 ratio was significantly lower (0.33 vs. 0.50, $P < 0.001$). A high CD163/CD68 ratio was significantly associated with poor tumor

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differentiation, submucosal invasion, and LNM ($P < 0.05$). Multivariate logistic regression identified the CD163/CD68 ratio as an independent risk factor for LNM in EGC ($P < 0.05$). The discriminatory ability for LNM was significantly improved when the eCura system was combined with the CD163/CD68 ratio (AUC=0.774) compared with the eCura system alone (AUC=0.706, $P=0.023$). No significant association was observed between TAMs (CD163 and CD68 scores, CD163/CD68 ratio) and 5-year overall survival in patients with EGC. **Conclusion:** Tumor-associated macrophages may participate in the tumorigenesis of EGC. The CD163/CD68 ratio is closely associated with LNM in EGC and may serve as an indicator of the tumor immune microenvironment. When combined with the eCura system, the CD163/CD68 ratio provides additional information for risk stratification of LNM in EGC.

[Key words] early gastric carcinoma; tumor-associated macrophage; lymph node metastasis

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近年来,得益于我国内镜技术的快速发展,早期胃癌的检出率显著提高,内镜下治疗已成为重要的早期胃癌治疗方式。淋巴结转移风险的准确评估是判断内镜下治疗能否实现治愈性切除的核心。目前国内外指南对早期胃癌内镜治疗后处理策略的制定,主要基于肿瘤浸润深度、分化类型及脉管侵犯等肿瘤实质的临床病理特征。日本指南提出的内镜切除治愈性评价系统(endoscopic curability assessment, eCura)已在临床广泛应用,其中eCuraC-2被认为淋巴结转移风险较高,应追加根治性手术^[1]。然而有报道显示,该人群中淋巴结转移发生率为5.2%~11.0%^[2-3],提示早期胃癌淋巴结转移风险的评估仍可进一步完善,需引入其他预测指标避免过度手术^[4]。近年来研究表明,肿瘤微环境在肿瘤的发生与发展过程中同样发挥重要作用,肿瘤相关巨噬细胞(tumor-associated macrophage, TAM)是肿瘤微环境的重要组成部分,可分化为经典活化型(M1型)和替代活化型(M2型)两类。已有研究证实TAM与多种实体肿瘤的临床病理特征相关,但尚无关于TAM在早期胃癌中的表达及其与淋巴结转移风险的相关性研究。本研究探讨TAM相关指标在早期胃癌淋巴结转移风险评估中的意义,为早期胃癌的个体化精准治疗提供更为全面的病理学依据。

1 资料和方法

1.1 资料

从病理系统检索常州市第二人民医院病理科2006年1月—2022年12月行胃癌根治术的病例,排除进展期胃癌、残胃癌、多原发灶胃癌、有恶性肿瘤病史、术前接受新辅助治疗、缺乏完整医疗记录的病例,SPSS软件随机选择符合上述条件的109例早期胃癌患者进行研究。本研究经常州市第二人民

医院医学伦理委员会审批(批号:[2024]KY030-01)。

1.2 方法

1.2.1 标本处理及染色

所有手术标本均经4%中性甲醛固定、脱水、包埋、切片并完成HE染色。每个病例选取1个代表性肿瘤蜡块行CD68、CD163免疫组化染色,CD163用于标记M2型TAM,CD68用于标记总TAM。一抗包括CD163抗体(克隆号:10D6,北京中杉金桥生物技术有限公司)、CD68抗体(克隆号:PG-M1,福州迈新生物技术开发有限公司),免疫组化染色采用Roche Benchmark Ultra全自动免疫组化染色系统(CD163)、Dako Link48全自动免疫组化染色系统(CD68)。参照世界卫生组织(2019)标准对早期胃癌病例的组织学类型、分化程度等形态学指标及免疫组化染色结果进行评估。参照日本《胃癌内镜治疗指南(第二版)》对早期胃癌病例进行eCura评价^[5]。

1.2.2 TAM的判读及评分标准

CD68阳性判断标准为细胞质含有清晰的黄褐色或棕黄色颗粒;CD163阳性判断标准为细胞质(膜)含有清晰的黄褐色或棕黄色颗粒。TAM的定量评估参考国际肿瘤浸润淋巴细胞工作组在乳腺癌中建立的面积评估方法。肿瘤区TAM评估,首先在低倍镜下明确肿瘤区的范围,避开以下影响定量评估的区域:坏死、出血、明显溃疡及肉芽组织、组织挤压或折叠伪影、电灼、既往活检或内镜操作形成的瘢痕修复区;然后在中倍镜下对全片包括肿瘤中心区及浸润前沿在内的肿瘤区进行评估,以避免选择偏倚。CD68和CD163评分采用阳性细胞面积占肿瘤区域间质总面积的百分比表示。癌旁非肿瘤黏膜巨噬细胞评估:癌旁非肿瘤黏膜为同一患者、同一次手术切除标本中经常规病理取材获得的肿瘤-非肿瘤移行区蜡块且无肿瘤浸润的区域,癌旁

非肿瘤黏膜 CD68 和 CD163 评分采用阳性细胞面积占癌旁非肿瘤间质面积的百分比表示^[6]。当阳性百分比>5%时,以5%递进间距记录;当阳性百分比≤5%时,以实际的连续变量记录^[7]。所有切片均由两名高年资病理医师独立判读,存在分歧时经共同复核达成一致。

1.2.3 随访

查阅全部患者病历并进行电话随访,总生存期(overall survival, OS)为自手术之日起至患者因任何原因死亡或末次随访时间止。

1.3 统计学方法

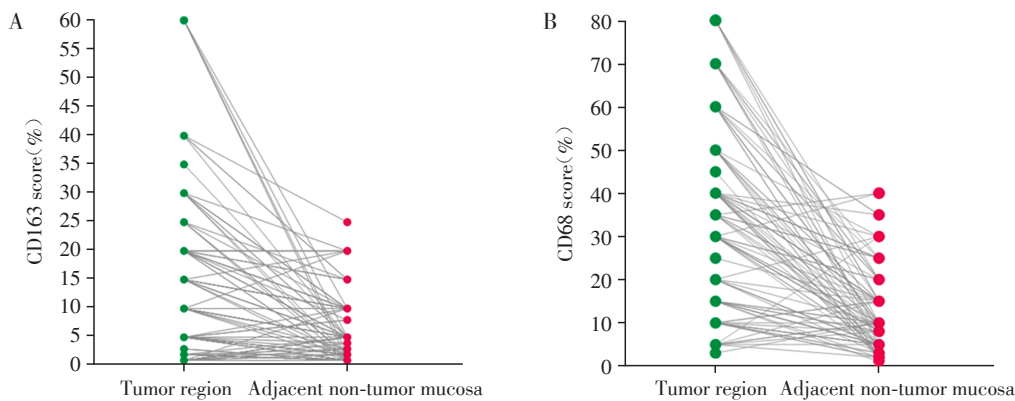
采用 SPSS 27.0 统计软件进行数据分析。分类资料的组间比较采用卡方检验或 Fisher 确切概率率检验,计量资料的组间比较采用 *t* 检验或 Mann-Whitney *U* 检验,配对资料的比较采用 Wilcoxon 符号秩检验。采用二元 Logistic 回归模型对早期胃癌淋巴结转移的危险因素进行单因素及多因素分析。采用受试者工作特征(receiver operating characteristic,

ROC)曲线分析 TAM 指标及其与 eCura 评价系统联合应用对早期胃癌淋巴结转移的判别能力,曲线下面积(area under the curve, AUC)差异采用 ROC 成对样本比较。生存分析采用 Kaplan-Meier 法及 Log-rank 检验,中位随访时间采用逆 Kaplan-Meier 法计算。*P* < 0.05 为差异有统计学意义。

2 结果

2.1 巨噬细胞在早期胃癌肿瘤区域和配对癌旁非肿瘤黏膜的表达

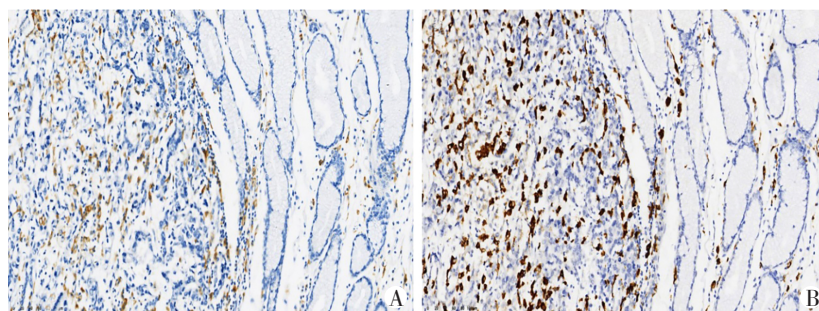
统计 109 例早期胃癌患者 CD163 和 CD68 全部评分结果(图 1),肿瘤区域的 CD163(图 2A 左侧区域)和 CD68(图 2B 左侧区域)评分显著高于癌旁非肿瘤黏膜(CD163:图 2A 右侧区域,CD68:图 2B 右侧区域)(CD163 中位值:10% vs. 5%, CD68 中位值:35% vs. 10%,*P* 均<0.001),肿瘤区域的 CD163/CD68 比值显著低于癌旁非肿瘤黏膜(中位值:0.33 vs. 0.50, *P* < 0.001)。



A: CD163 scores in tumor regions and adjacent non-tumor mucosa from 109 patients. B: CD68 scores in tumor regions and adjacent non-tumor mucosa.

图1 109例患者肿瘤区和癌旁非肿瘤区 TAM 评分结果

Figure 1 TAMs scores in tumor regions and paired adjacent non-tumor mucosa of the 109 patients



A: High CD163 expression in the tumor region (left, score 60%) and low CD163 expression in the adjacent non-tumor mucosa (right, score 2%). B: High CD68 expression in the tumor region (left, score 80%) and low CD68 expression in the adjacent non-tumor mucosa (right, score 4%) from the same patient (×200).

图2 肿瘤区及癌旁 TAM 的表达及对应评分

Figure 2 Expression and scores of TAMs in tumor regions and paired adjacent non-tumor mucosa

2.2 TAM与早期胃癌各临床病理特征的关系

以肿瘤区域CD163、CD68评分及CD163/CD68比值的中位值(10%、35%、0.33)为界,将早期胃癌分为CD163高评分组和CD163低评分组(图3A、B)、CD68高评分组和CD68低评分组(图3C、D)、CD163/CD68高比值组和CD163/CD68低比值组。CD163高评分组与低评分组在患者性别、年龄、溃疡、脉管和神经侵犯方面均无显著差异(P 均 >0.05)。肿瘤区域CD163高评分组发生淋巴结转移、肿瘤浸润至黏膜下层、肿瘤低分化、肿瘤长径 >2 cm的比例均显著高于CD163低评分组(P 均 <0.05);肿瘤区域CD68高评分组肿瘤低分化的比例显著高于CD68低评分组($P < 0.05$),其余临床病理特征差异无统计学意义;肿瘤区域CD163/CD68高比值组发生淋巴结转移、肿瘤浸润至黏膜下层、肿瘤低分化的比例显著高于CD163/CD68低比值组(P 均 <0.05 ,表1),其余临床病理特征差异无统计学意义。

2.3 早期胃癌淋巴结转移的单因素Logistic回归分析

基于ROC分析中鉴别淋巴结转移的最大约登指数所确定的截断值(17.5%, 0.315),将CD163评分及CD163/CD68比值分为高低两组,与早期胃癌的临床病理特征一同纳入早期胃癌淋巴结转移的单因素风险分析。肿瘤分化、浸润深度、脉管侵犯、神经侵犯、肿瘤区CD163高评分及CD163/CD68高比值与淋巴结转移显著相关($P < 0.05$),而患者性别、年龄、肿瘤长径、溃疡与淋巴结转移无显著相关性($P > 0.05$,表2)。

2.4 早期胃癌淋巴结转移的多因素Logistic回归分析

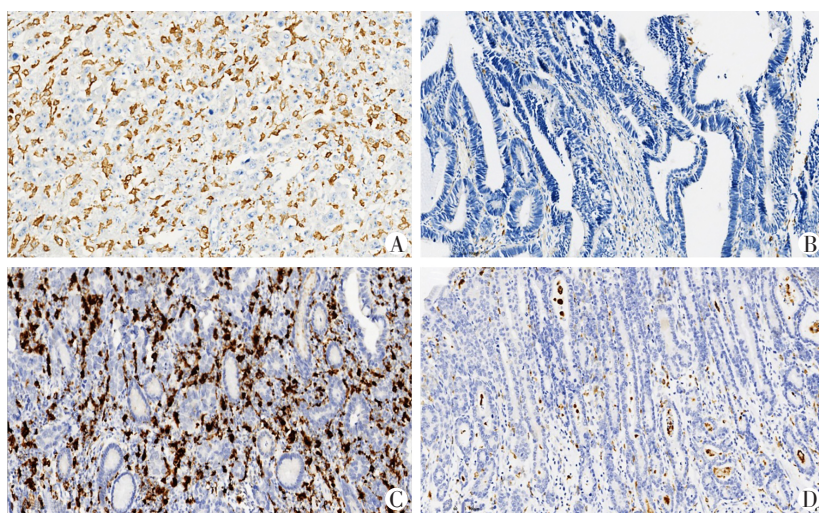
ROC曲线分析显示,CD163/CD68比值对早期胃癌淋巴结转移的判别能力($AUC=0.681$)高于CD163评分($AUC=0.670$, $P=0.390$),由于两指标存在共线性,以CD163/CD68比值作为TAM的代表性指标纳入后续多因素分析。多因素分析结果显示CD163/CD68高比值是早期胃癌患者淋巴结转移的独立危险因素($P < 0.05$,表2)。

2.5 eCura评价系统联合CD163/CD68比值对早期胃癌淋巴结转移风险的ROC分析

ROC曲线分析显示,eCura评价系统联合CD163/CD68比值对早期胃癌淋巴结转移风险的区分能力($AUC=0.774$)显著高于单独eCura评价系统($AUC=0.706$, $P=0.023$,图4)。

2.6 生存分析

截至2024年5月,109例早期胃癌患者中13例失访,85例存活,11例死亡。随访时间5~162个月,中位随访时间为78个月(95%CI: 69.9~86.1个月)。Kaplan-Meier生存分析结果显示,CD163高评分组和低评分组(97.3% vs. 93.2%)、CD68高评分组和低评分组(97.7% vs. 92.5%)、CD163/CD68高比值组和低比值组(94.6% vs. 94.9%)的5年生存率均无显著差异。各组均未达到中位生存时间,CD163高评分组、CD163低评分组、CD68高评分组、CD68低评分组以及CD163/CD68高比值组、CD163/CD68低比值组的平均生存时间分别为151、134、144、138、148、136个月。



A: High CD163 expression (score 85%). B: Low CD163 expression (score 2%). C: High CD68 expression (score 80%). D: Low CD68 expression (score 5%)($\times 200$).

图3 肿瘤区TAM的表达及评分

Figure 3 TAMs expression and scores in the tumor region

表1 CD163、CD68评分和CD163/CD68比值与早期胃癌临床病理特征的关系

Table 1 Association of CD163 and CD68 scores and the CD163/CD68 ratio with clinicopathological characteristics of early gastric carcinoma [n(%)]

Clinicopathological feature	CD163			CD68			CD163/CD68		
	Low	High	P	Low	High	P	Low	High	P
Sex			0.217			0.387			0.280
Female	21(32.8)	20(44.4)		24(41.4)	17(33.3)		21(33.3)	20(43.5)	
Male	43(67.2)	25(55.6)		34(58.6)	34(66.7)		42(66.7)	26(56.5)	
Age			0.631			0.977			0.296
≤66 years	34(53.1)	26(57.8)		32(55.2)	28(54.9)		32(50.8)	28(60.9)	
>66 years	30(46.9)	19(42.2)		26(44.8)	23(45.1)		31(49.2)	18(39.1)	
Diameter			0.031			0.073			0.050
≤2 cm	39(60.9)	18(40.0)		35(60.3)	22(43.1)		38(60.3)	19(41.3)	
>2 cm	25(39.1)	27(60.0)		23(39.7)	29(56.9)		25(39.7)	27(58.7)	
Ulcer	17(26.6)	18(40.0)	0.139	15(25.9)	20(39.2)	0.136	16(25.4)	19(41.3)	0.079
Differentiation			0.005			<0.001			0.023
Moderately/Well	47(73.4)	21(46.7)		45(77.6)	23(45.1)		45(71.4)	23(50.0)	
Poorly	17(26.6)	24(53.3)		13(22.4)	28(54.9)		18(28.6)	23(50.0)	
Depth of invasion			0.005			0.083			<0.001
Mucosa	24(37.5)	6(13.3)		20(34.5)	10(19.6)		26(41.3)	4(8.7)	
Submucosa	40(62.5)	39(86.7)		38(65.5)	41(80.4)		37(58.7)	42(91.3)	
Lymphovascular invasion	14(21.9)	15(33.3)	0.183	12(20.7)	17(33.3)	0.136	15(23.8)	14(30.4)	0.439
Perineural invasion	6(9.4)	5(11.1)	>0.999	6(10.3)	5(9.8)	0.925	5(7.9)	6(13.0)	0.581
Lymph node metastasis	10(15.6)	15(33.3)	0.030	10(17.2)	15(29.4)	0.132	8(12.7)	17(37.0)	0.003

表2 影响早期胃癌淋巴结转移危险因素分析

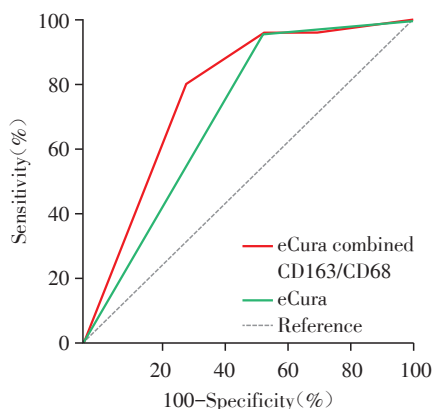
Table 2 Analysis of risk factors for lymph node metastasis in early gastric carcinoma

Clinicopathological feature	Univariate		Multivariate	
	OR(95%CI)	P	OR(95%CI)	P
Sex(Male vs. Female)	0.462(0.186-1.142)	0.095	-	-
Age(>66 years vs. ≤66 years)	0.494(0.192-1.267)	0.142	-	-
Diameter(>2 cm vs. ≤2 cm)	2.370(0.941-5.971)	0.067	-	-
Ulcer	1.573(0.623-3.975)	0.338	-	-
Differentiation(Poorly vs. Moderately/Well)	3.346(1.328-8.432)	0.010	2.035(0.721-5.745)	0.180
Depth of invasion(Submucosa vs. Mucosa)	12.655(1.629-98.331)	0.015	5.588(0.649-48.103)	0.117
Lymphovascular invasion	5.120(1.865-14.059)	0.002	2.435(0.808-7.336)	0.114
Perineural invasion	4.989(1.376-18.092)	0.014	1.872(0.445-7.866)	0.392
CD163(High vs. Low)	2.873(1.146-7.207)	0.024	-	-
CD163/CD68(High vs. Low)	4.615(1.584-13.451)	0.005	3.479(1.084-11.167)	0.036

3 讨论

近年来研究发现肿瘤的发生与发展既受肿瘤细胞自身特性的影响,也受肿瘤微环境的调节。肿瘤微环境由肿瘤细胞、免疫细胞和支持细胞等组成,是一种复杂且动态的生态系统。TAM是肿瘤微环境的重要成分之一^[8-9]。多个研究认为在肿瘤

形成早期,TAM以M1表型为主,通过分泌多种促炎细胞因子激活免疫应答,主要发挥抗肿瘤效应^[10-11];在肿瘤进展期,TAM以M2表型为主,可表达CD163、CD206、血小板衍生生长因子等,通过抑制免疫反应、重塑细胞外基质和刺激血管生成促进组织修复和肿瘤的生长、转移^[12-13]。本研究分析了巨噬细胞在肿瘤区及癌旁非肿瘤黏膜中的分布特征,



The discriminatory ability of the eCura system combined with the CD163/CD68 ratio for distinguishing lymph node metastasis in early gastric carcinoma (AUC=0.774) was significantly higher than that of the eCura system alone (AUC=0.706).

图4 eCura评价系统联合CD163/CD68比值对早期胃癌淋巴结转移风险的ROC分析

Figure 4 ROC analysis of the eCura system combined with the CD163/CD68 ratio for lymph node metastasis risk in early gastric carcinoma

并探讨其与淋巴结转移等临床病理特征及预后的关系。结果显示,早期胃癌中巨噬细胞已呈现明显的空间分布差异,且与肿瘤侵袭性特征尤其是淋巴结转移密切相关。其中CD163/CD68比值是早期胃癌淋巴结转移的独立危险因素,且可在现有eCura评价系统基础上对淋巴结转移的风险进一步分层。

多项包括胃癌在内的泛肿瘤研究中均观察到肿瘤组织中巨噬细胞较非肿瘤组织显著增多^[14-17],但上述研究多未区分肿瘤发展阶段,缺乏TAM在肿瘤发生早期阶段的临床病理意义研究。本研究显示肿瘤区CD163和CD68评分均显著高于癌旁非肿瘤黏膜($P < 0.001$),即在胃癌早期,肿瘤间质中已存在明显的TAM募集现象,TAM的富集可能是肿瘤早期已出现的免疫微环境改变之一。然而CD163/CD68比值却显著低于癌旁非肿瘤黏膜,这一结果似乎与“肿瘤进展伴随TAM向M2表型极化”的传统观点不完全一致^[9,11,18],提示在早期胃癌阶段,TAM的数量变化与表型极化可能并不同步。既往研究认为,癌旁非肿瘤组织中的巨噬细胞多处于相对稳态,主要参与组织修复和免疫调节^[19-20],表现为CD163/CD68比值较高但总体数量有限;而在肿瘤区持续的炎症刺激及趋化信号可大量招募单核细胞进入肿瘤间质^[21],新分化的M2型巨噬细胞尚未完全极化(CD163表达不完全),从而导致CD163和CD68阳性细胞数量增加的同时,其在总TAM中的

比例相对降低。随着肿瘤进展,当CD163阳性细胞在数量积累的基础上,其功能表型进一步向免疫抑制和促侵袭方向重塑,才可能形成稳定的促转移肿瘤微环境。这一过程在其他肿瘤的研究中也得到证实,如肺癌相关的巨噬细胞在肿瘤形成之初更多为M1表型,具备促炎与抑瘤作用;而在肿瘤持续发展过程中,其功能倾向逐步转为M2表型,表现出免疫抑制并促进肿瘤进展^[22]。

既往胃癌研究中,TAM不同指标与临床病理特征之间的关系尚未形成一致结论。Zhu等^[23]、Park等^[24]在不同胃癌队列中观察到CD163高评分与肿瘤大小、T分期、淋巴结转移、低分化显著相关;Su等^[25]发现CD68评分与胃癌淋巴结转移及TNM分期显著相关;然而Yin等^[26]基于Meta分析发现CD68与多数胃癌临床病理特征的关联性有限,仅与TNM分期及分化程度显著相关,此外Pantano等^[27]的研究认为CD163或CD68与胃癌各项临床病理特征均无关。目前胃癌研究中采用CD163/CD68比值作为TAM极化指标的研究十分有限,且现有研究未发现其与胃癌各项临床病理特征存在显著关联^[27]。然而,在结直肠癌^[28-29]、子宫内膜癌^[15]等肿瘤中,M2比例已被报道与多项肿瘤侵袭性临床病理特征显著相关。上述研究结果的不一致可能与TAM缺乏统一评估标准、研究对象未区分早期和进展期病例有关。既往研究中TAM的评估方法多样,有热点视野计数法、随机高倍视野计数法等。本研究参考了国际肿瘤浸润淋巴细胞工作组在乳腺癌中建立的评估方法^[6-7],采用对整张切片中TAM占肿瘤间质面积比例的评估方法,有助于病理医生快速且全面评估TAM。基于上述方法学,本研究针对早期胃癌研究发现,CD163评分与发生淋巴结转移、肿瘤浸润至黏膜下层、肿瘤分化、肿瘤大小显著相关,CD163/CD68比值与淋巴结转移、肿瘤浸润至黏膜下层、肿瘤分化显著相关,而CD68评分仅与肿瘤分化显著相关,这可能是因为CD68作为同时标记M1与M2型TAM的广谱标志物,难以反映TAM的极化状态,其对肿瘤的作用受M1与M2型TAM的比例影响。而M2型TAM的指标如CD163评分及CD163/CD68比值更能反映早期胃癌的生物学行为,也提示M2在早期胃癌的发生发展中起到了重要作用。

对早期胃癌淋巴结转移危险因素的单一因素分析发现,除既往公认的分化程度、浸润深度、脉管侵犯及神经侵犯等传统病理因素外,CD163评分以及CD163/CD68比值也与淋巴结转移显著相关;此外,

采用ROC分析进一步比较不同TAM指标对早期胃癌淋巴结转移的区分能力,结果显示,CD163/CD68比值判断淋巴结转移的AUC高于CD163评分。这一结果与Inagaki等^[29]在结直肠癌的研究具有一致性,该研究发现M1/M2比值对淋巴结转移的判别能力高于总TAM及M1、M2型TAM。鉴于CD163评分与CD163/CD68比值在统计学上存在共线性且ROC分析显示CD163/CD68比值对区分早期胃癌淋巴结转移的区分能力更高,后续多因素分析选取CD163/CD68比值作为TAM代表指标,结果显示CD163/CD68比值为早期胃癌淋巴结转移的独立危险因素。这与既往胃癌研究发现M2型TAM通过多种途径参与肿瘤侵袭和转移,包括诱导肿瘤细胞上皮-间质转化、促进肿瘤相关淋巴管生成以及抑制抗肿瘤免疫反应等的结论一致^[30]。本研究结果从免疫微环境角度补充了传统仅基于肿瘤实质形态学特征的早期胃癌淋巴结转移风险评估模式。临床广泛使用的日本指南eCura评价系统基于肿瘤浸润深度、分化程度、肿瘤大小及脉管侵犯等病理学特征,对早期胃癌内镜切除后的治愈性进行评估,已被广泛应用于临床。这一评估标准基于对肿瘤实质的评估,而本研究进一步比较了eCura评估系统单独应用与联合CD163/CD68比值对早期胃癌淋巴结转移的区分能力,发现二者联合应用较单一使用eCura评分标准对早期胃癌淋巴结转移的评估能力显著提高,提示联合指标的使用有望减少假阳性,有助于进一步对早期胃癌淋巴结转移风险分层,从而为临床决策提供更多参考依据。

本研究中手术患者的5年总生存率为93.6%,未发现不同CD163、CD68表达及CD163/CD68比值患者的OS存在显著统计学差异,这可能与样本量较小有关;此外,本研究受限于无法获得准确的无病生存期数据,也未能进行无病生存期等更特异的预后分析。既往仅1篇文献分析了早期胃癌TAM与预后的关系,发现M2型TAM评分与肿瘤复发相关。但这可能与该研究的样本选择有关,该研究纳入的早期胃癌病例中45.1%出现复发(78/173),明显高于既往文献报道的早期胃癌术后复发水平,可能存在选择偏倚^[31]。相比之下,在肺鳞癌^[32]、多发性骨髓瘤^[33]等研究中,M2型TAM数量或M2比例被证实是OS或无进展生存期的独立预后因素,提示TAM的预后意义可能与肿瘤类型及疾病发展阶段有关。

综上,TAM的增加尤其是M2型TAM可能参与

了早期胃癌的发生发展,CD163高评分、CD163/CD68高比值与不良的临床病理特征如浸润深、分化差、淋巴结转移等显著相关,这提示TAM有望成为潜在治疗靶点,如通过抑制M2巨噬细胞激活,阻止肿瘤中TAM的募集等策略来抑制胃癌的侵袭、生长。另一方面,本研究发现CD163/CD68比值是早期胃癌淋巴结转移的独立危险因素,可联合eCura评价系统提高对淋巴结转移风险的区分能力,为早期胃癌的个体化精准治疗提供更全面的信息。本研究的相关结论尚需在多中心、大样本研究中进一步验证。

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Author's Contributions:

HE Chongfang was responsible for data collection and analysis and drafting the manuscript; LI Ting and SUN Zhentao were responsible for patient follow-up and literature review; WANG Gengfang performed the immunohistochemical staining experiments; ZHOU Xiaoli conducted pathological evaluation; CHENG Yuqing was responsible for study design, pathological evaluation, and manuscript revision and polishing.

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