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· 专题研究 ·

胃癌患者术前中性粒细胞与淋巴细胞比与临床病理特征及 预后关系

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摘要

目的:探讨胃癌患者术前中性粒细胞与淋巴细胞比(NLR)与临床病理特征及预后的关系。

方法:回顾性分析 2010 年 1 月—2011 年 1 月安徽医科大学第一附属医院收治的 269 例胃癌患者的临床病理及随访资料。根据受试者工作特征曲线,确定 NLR 的截断值为 2.4(敏感性:53.3%,特异性:71.4%),将患者分为低 NLR 组(NLR<2.4,153 例)和高 NLR 组(NLR≥2.4,116 例),比较两组患者临床病理特征及生存率的差异,并分析胃癌患者的预后因素。

结果: 比较结果显示,两组年龄、性别、淋巴结转移无明显差异(均 P>0.05),但高 NLR 组较低 NLR 组肿瘤直径大、肿瘤浸润深度深、TNM 分期高(均 P<0.05);全组患者 5 年总生存率为 44.3%,生存分析显示,高 NLR 组患者总生存率明显低于低 NLR 组($\chi^2=17.511$,P<0.01);单因素分析结果表明,术前 NLR、肿瘤大小、肿瘤浸润深度和 TNM 分期与胃癌患者总生存率有关(均 P<0.05),多因素分析显示,NLR 和肿瘤大小为影响胃癌患者预后的独立因素(均 P<0.05)。

结论:术前 NLR 是影响胃癌患者预后的独立预测因素,高术前 NLR 值提示胃癌患者有较差的临床病理情况及生存预后。

关键词

胃肿瘤;中性白细胞;淋巴细胞比;炎症;预后

中图分类号: R735.2

Relations of preoperative neutrophil to lymphocyte ratio with clinicopathologic features and prognosis in gastric cancer

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Abstract

Objective: To investigate the relations of preoperative neutrophil to lymphocyte ratio (NLR) with clinicopathologic characteristics and prognosis of patients with gastric cancer.

Methods: The clinicopathologic and follow-up data of 269 patients with gastric cancer treated in the First Affiliated Hospital of Anhui Medical University between January 2010 and January 2011 were retrospectively analyzed. The cutoff value of NLR was 2.4 (susceptibility: 53.3%, specificity: 71.4%) that was determined by receiver operating characteristic curve, and then, according to that, the patients were divided into low NLR group (NLR<2.4, 153 cases) and high NLR group (NLR≥2.4, 116 cases). The differences in clinicopathologic

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characteristics and survival rates between the two groups of patients were compared, and the prognostic factors for gastric cancer patients were also analyzed.

Results: The results of comparison showed that there was no significant difference in age, gender and lymph node metastasis between the two groups (all P>0.05), but the tumor diameter was larger, depth of tumor invasion was deeper, and TNM stage was higher in high NLR group than those in low NLR group (all P<0.05). The overall 5-year survival rate was 44.3% for the entire group, and the results of survival analysis showed that the overall survival rate in high NLR group was significantly lower than that in low NLR group ($\chi^2=17.511$, P<0.01). Univariate analysis indicated that the overall survival of the gastric cancer patients was significantly associated with preoperative NLR, tumor size, the depth of tumor invasion and TNM stage (all P<0.05), and multivariate analysis identified that preoperative NLR and tumor size were independent risk factors for the prognosis of gastric cancer patients (both P<0.05).

Conclusion: Preoperative NLR is an independent prognostic factor for gastric cancer patients, and high preoperative NLR may associated with unfavorable clinicopathologic conditions and poor prognosis.

Key words

Stomach Neoplasms; Neutrophils; Lymphocytes; Inflammation; Prognosis

CLC number: R735.2

胃癌是世界上最常见的肿瘤之一,其致死率在肿瘤中高居第二,在东亚国家发病率较高,尤其是中国、日本及韩国等^[1]。早期胃癌患者临床症状不典型,且缺乏有效的胃镜普查,故在诊断时已处于局部进展期^[2]。根治性胃癌切除术+D₂淋巴结清扫仍是治疗胃癌的唯一有效治疗措施,但进展期胃癌患者即使通过根治性手术治疗,其5年生存率也只有30%~50%^[3]。

术前临床分期及术后病理分期、分化类型和 切除范围已被众多研究证实为独立的预后因素, 由于我国胃癌的高发病率,关于其他简单有效可 靠的预测因子成为近几年研究热点。最近关于肿 瘤与炎症的关系研究越来越多,肿瘤产生的炎症 反应通过调节炎症因子介导炎症免疫反应, 从而 导致了DNA损伤,细胞周期失调控以及病灶的微 转移^[4]。全身炎症反应(systemic inflammatory response, SIR)可以加剧癌症患者营养水平及 机体功能降低,促进肿瘤进展[5]。研究[6]表明, 中性粒细胞和淋巴细胞在肿瘤进展引起的炎症 中起到重要作用,中性粒细胞与淋巴细胞比值 (neutrophil to lymphocyte ratio, NLR) 被认为是 有前景的诊断预测。多项研究[7-11]表明NLR在泌尿 癌、结肠癌、食管癌、肺癌和乳腺癌中与临床病 理特征及预后相关, 且NLR具有经济、快速、方 便获取、易于推广等优点。然而, 关于NLR与胃 癌患者的临床病理及预后的相关研究鲜有报道。 本研究回顾性收集了269例胃癌患者临床病例资料, 以探讨胃癌患者术前NLR与临床病理特征间关系

及预测生存预后的价值。

1 材料与方法

1.1 一般资料

回顾性收集2010年1月—2011年1月安徽医科大学第一附属医院收住的269例胃癌患者的完整临床病理资料,其中男212例,女57例;年龄<60岁者96例,≥60岁者173例;按肿瘤最长径5 cm为临界值进行分组,<5 cm 124例,≥5 cm 145例;术后病理分期以2010年国际抗癌联盟和美国癌症联合会共同发布的胃癌TNM指南为依据,其中肿瘤侵犯深度局限于黏膜及黏膜下层32例,固有肌层19例,侵及黏膜下组织14例,侵犯浆膜或邻近组织204例。

1.2 纳入及排除标准

患者术前均经胃镜活检,病理证实为胃恶性肿瘤并行根治性切除手术;血液标本是在手术前1周内获得的。排除标准:(1)患者术前已行新辅助放化疗;(2)有同时或异时的多原发性肿瘤;(3)伴随其他较严重的疾病可能影响外周血细胞的数值,例如自身免疫性疾病、感染等;(4)围手术期出现穿孔、大出血等严重并发症;(5)随访过程中患者因感染、意外事故等其他非胃癌相关因素而死亡。

1.3 随访方式及确定分组

共收集胃癌患者完整临床病理资料302例, 术后对所有纳入患者进行随访,随访方式为门 诊复查或电话随访等,患者死亡即停止随访。根据纳入及排除标准,剔除非胃癌相关死亡22例(7.3%)和失访11例(3.6%),最终269例患者入选本研究。根据约登系数兼顾敏感性和特异性,利用受试者工作特征(ROC)曲线,最终确定NLR的截点值为2.4(敏感性:53.3%,特异性:71.4%),故将患者分为低NLR组(NLR<2.4,153例)和高NLR组(NLR≥2.4,116例)。

1.4 统计学处理

采用SPSS 16.0统计软件进行数据分析,计数资料比较采用 χ^2 检验或者 Fisher确切概率法;采用 Kaplan-Meier法绘制生存曲线,生存的曲线比较采用 Log-rank 检验,采用 Cox 回归模型分析各临床病理指标对预后的影响,P<0.05 为差异有统计学意义。

2 结 果

2.1 不同患者的临床病理特征与 NLR 的关系

NLR与胃癌患者临床病理资料关系的 χ^2 检验结果显示,低NLR组与高NLR组比较,性别、年龄、淋巴结转移方面差异无统计学意义(均 P>0.05),但肿瘤大小、肿瘤浸润深度、TNM分期差异有统计学意义(均P<0.05)(表1)。

表 1 胃癌患者术前 NLR 与临床病理因素的关系 [n (%)]

Table 1 Relaions of preoperative NLR with clinicopathologic factors of gastric cancer patients [n (%)]

factors of gastric cancer patients [n (70)]							
因素	低 NLR 组	高 NLR 组	P				
	(n=153)	(n=116)	I				
性别							
男	120 (78.4)	92 (79.3)	0.492				
女	33 (21.6)	24 (20.7)	0.492				
年龄(岁)							
< 60	58 (37.9)	38 (32.8)	0.220				
≥ 60	95 (62.1)	78 (67.2)	0.229				
肿瘤大小 (cm)							
< 5	87 (56.9)	37 (31.9)	< 0.01				
≥ 5	66 (43.1)	79 (68.1)	<0.01				
浸润深度							
$T_1 \sim T_2$	38 (24.8)	13 (11.2)	۰۵.01				
$T_3 \sim T_4$	115 (75.2)	103 (88.8)	< 0.01				
淋巴结转移							
N_0	59 (38.6)	38 (32.8)	0.197				
$N_1 \sim N_3$	94 (61.4)	78 (67.2)	0.197				
TNM 分期							
I~II	68 (44.4)	39 (33.6)	0.047				
III~IV	85 (55.6)	77 (66.4)	0.047				

2.2 低 NLR 组与高 NLR 组患者生存率比较

269例胃癌患者的5年总生存率为44.3%。通过Kaplan-Meier分析比较低NLR组与高NLR组患者,结果显示: 低NLR组的胃癌患者生存时间比高NLR的胃癌患者生存时间长,两者差异有统计学意义(χ^2 =17.511,P<0.01),低NLR组生存状况好于高NLR组(图1)。

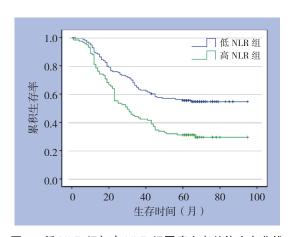


图 1 低 NLR 组与高 NLR 组胃癌患者总体生存曲线
Figure 1 Survival curves of gastric cancer patients in low NLR
group and high NLR group

2.3 影响胃癌患者预后的因素分析

单因素分析显示:胃癌患者的预后与NLR、肿瘤大小、肿瘤侵犯深度、TNM分期有关(均P<0.05)(表2);多因素分析显示:肿瘤大小和NLR为影响胃癌患者预后的独立因素(均P<0.05)(表3)。

表 2 269 例胃癌患者总体生存的单因素分析

Table 2 Univariate analysis of factors affecting overall survival of the 269 gastric cancer patients

因素						
年齢(<60 岁 \upsigna ≥ 60 岁) 0.213 1.082(0.773~1.515) 0.644 NLR(<2.4 \upsigna ≥ 2.4) 17.170 1.952(1.414~2.694) <0.01 肿瘤大小(<5 cm \upsigna ≥ 5 cm) 18.891 2.093(1.489~2.942) <0.01 浸润深度(\upsigna \upsigna \upsigna \upsigna 12.876 2.504(1.490~4.207) <0.01	因素	χ^2	HR (95% CI)	P		
NLR(<2.4 \bowtie ≥ 2.4)	性别 (男 vs. 女)	3.255	1.408 (0.971~2.042)	0.071		
肿瘤大小(<5 cm $^{\text{vs.}} \ge 5$ cm) 18.891 2.093(1.489~2.942) <0.01 浸润深度($T_1 \sim T_2 \sim T_3 \sim T_4$) 12.876 2.504(1.490~4.207) <0.01	年龄(<60岁 vs.≥60岁)	0.213	1.082 (0.773~1.515)	0.644		
浸润深度(T ₁ ~T ₂ vs. T ₃ ~T ₄) 12.876 2.504(1.490~4.207) <0.01	NLR ($<2.4 \text{ vs.} \ge 2.4$)	17.170	1.952 (1.414~2.694)	< 0.01		
	肿瘤大小 (<5 cm vs. ≥ 5 cm)	18.891	2.093 (1.489~2.942)	< 0.01		
淋巴结转移(无 vs. 有) 2.674 1.334(0.944~1.884) 0.102	浸润深度($T_1 \sim T_2 \nu s. T_3 \sim T_4$)	12.876	2.504 (1.490~4.207)	< 0.01		
	淋巴结转移(无 vs. 有)	2.674	1.334 (0.944~1.884)	0.102		
TNM 分期(I~II vs. III~IV) 7.612 1.622(1.150~2.288) <0.01	TNM 分期(I~II vs. III~IV)	7.612	1.622 (1.150~2.288)	<0.01		

表 3 269 例胃癌患者总体生存的多因素分析 Table 3 Multivariate analysis of factors affecting overall

survival of the 269 gastric cancer patients

survivar of the 20% gastric cancer patients						
因素	χ^2	HR (95% CI)	P			
NLR ($<2.4 \text{ vs.} \ge 2.4$)	8.074	1.624 (1.162~2.269)	< 0.01			
肿瘤大小 (<5 cm vs. ≥ 5 cm)	4.743	1.530 (1.043~2.242)	0.029			
浸润深度(T ₁ ~T ₂ vs. T ₃ ~T ₄)	2.188	1.625 (0.854~3.094)	0.139			
TNM 分期(I~II vs. III~IV)	0.264	1.110 (0.746~1.652)	0.607			

3 讨论

炎症可以促进肿瘤的增殖、血管生成、转移以及对激素和化疗的抵抗,许多炎症因子是众多癌症的诊断及预后标志物^[12-13]。研究^[14]表明,NLR的水平的升高会增加肿瘤所导致的全身炎症反应,加快恶性肿瘤的发生发展,其反应机制可能与中性粒细胞的增加或淋巴细胞数量的减少限制机体免疫系统杀伤肿瘤细胞,从而增加其增殖和转移的能力。多项研究发现,中性粒细胞通过释放肿瘤坏死因子、白介素1、白介素和血管内皮生长因子促进肿瘤的发生发展^[6, 15-16]。代辉等^[17]研究发现,胃癌患者外周血中调节性T细胞表达水平明显高于正常人,调节性T细胞可通过抑制效应T细胞功能下调机体对肿瘤的免疫监视^[18]。临床和流行病学的研究表明慢性炎症与胃癌发生发展密切相关,提示胃癌病理进展是由炎症所介导的^[19]。

研究[20-24]表明, NLR作为全身炎症反应的特 征因子之一,与乳腺癌、肾癌、前列腺癌、胆管 癌、肝癌、肺癌等多种肿瘤病理特征及生存预后 有密切关系。本研究发现,在胃癌中NLR与肿瘤 大小、浸润深度及TNM分期有关,与性别、年龄 及淋巴转移无关,这与前期研究[25-26]的多中心研 究结果类似。多因素分析结果表明NLR是胃癌患 者生存预后的一项独立危险因素,且低NLR组的 胃癌患者总生存率明显高于高NLR组,这提示NLR 对于评估胃癌预后可能是一个简便可靠的预测因 子。对于大多数胃癌患者,复发和转移是主要的 致死原因,并且影响患者的生存率,即使是进行 了根治性手术切除,术前高NLR组患者与低NLR组 相比其总生存时间较短[27]。利用NLR与预后的关系 可以协助对患者进行综合术前评估从而采取不同 的治疗手段,例如可对手术前NLR评分高的患者 进行新辅助放化疗,改善患者的预后,以达到更 好的治疗效果。与此同时,对于术前高NLR值的 患者,其术后生存时间较短与肿瘤的复发和转移 可能存在一定的关系, 故术后严格规律的随访和 定期体检就显得尤其重要。

根据国内外发表研究中,不同肿瘤中NLR分界值不尽相同,即便是同种肿瘤中不同研究中心报道的NLR也无统一分界值。目前确定NLR分界值方法主要有3种:依据约登系数通过ROC曲线确定NLR分界值^[28];以NLR中位数或平均值作为分界值^[29];参考其他已发表研究中的NLR分界值进行分析。相比其他两种方法,根据约登系数最大原则

确定分界值,可兼顾敏感性和特异性,然而采用 此法在不同研究样本中得到的NLR分界值也有细 微差别^[30-31]。由于本研究属于单中心回顾性研究, 统计结果可能会出现选择偏倚,故还需多中心的 前瞻性随机对照研究进一步证实NLR在预测胃癌 患者生存预后中的重要价值;另外,对于患者因 放化疗引起NLR值变化,是否可以作为新的预测 生存预后的重要手段,值得进一步探讨。

另外,肿瘤最长径作为影响胃癌患者生存预后的另一独立危险因素,与肿瘤浸润深度及淋巴转移明显相关,这与Pang等^[32]研究结果相似。通过对962例早期胃癌患者临床资料分析发现,肿瘤大小是影响早期胃癌淋巴结转移危险因素之一,肿瘤直径越大,发生早期淋巴结转移风险越大(研究结果待发表)。因此,结合肿瘤大小和术后TNM病理分期能否更准确评估胃癌患者预后尚需大样本多中心研究证实。

总的来说,NLR与患者的性别、年龄无关,与肿瘤大小、TNM分期和侵犯深度相关,低NLR组胃癌患者的生存时间较高NLR组长,NLR和肿瘤大小是影响胃癌患者预后的独立因素,NLR可作为评估胃癌患者预后的重要指标,从而制定一个更精准有效的治疗方案。

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