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中性粒细胞 - 淋巴细胞比率与老年 NSCLC 患者临床病理及预后的相关性分析

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摘要 目的:研究中性粒细胞 - 淋巴细胞比率(NLR)与老年非小细胞肺癌(NSCLC)患者临床病理及预后的相关性分析。**方法:**回顾性分析我院收治的 68 例老年 NSCLC 患者的临床病理资料。根据化疗前 NLR 分为低 NLR 组(<2.95)、高 NLR 组(≥ 2.95)。比较两组患者临床病理特点及无病生存期(DFS),并分析预后的影响因素。**结果:**与低 NLR 组比较,高 NLR 组临床分期Ⅳ期、吸烟及淋巴转移的比例更大(P<0.05),而两组间年龄、性别、病理类型及合并症比较差异均无统计学意义(P>0.05)。低 NLR 组中位 DFS 为 7.2 个月(95%CI: 5.9~8.4),显著高于高 NLR 组中位 DFS 6.7 个月(95%CI: 5.4~7.9)(P<0.05)。淋巴转移、NLR 是老年 NSCLC 患者 DFS 的独立危险因素,而年龄、化疗次数则是独立保护因素(P<0.05)。**结论:**NLR 与老年 NSCLC 患者的临床分期和淋巴结转移有明显相关性,并可作为预后评估参考指标之一。

关键词:中性粒细胞 - 淋巴细胞比率;非小细胞肺癌;老年;临床病理;预后

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Correlative Analysis of Neutrophil/lymphocyte Ratio with the Clinicopathology and Prognosis of Elderly Patients with Non-small Cell Lung Cancer

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ABSTRACT Objective: To explore the correlation of neutrophil/lymphocyte ratio (NLR) with the clinicopathology and prognosis of elderly patients with non-small cell lung cancer (ARDS). **Methods:** The clinical data of 68 cases of elderly patients with NSCLC in our hospital were retrospectively analyzed. According to the NLR before chemotherapy, patients were divided into the low NLR(<2.95)group and the high NLR (≥ 2.95)group. The clinicopathological characteristics and disease-free survival (DFS) were compared between two groups, and the influencing factors of prognosis were analyzed. **Results:** Compared with low NLR group, higher proportion of clinical stage Ⅳ, smoking and lymph node metastases were observed in high NLR group (P<0.05), while no statistically significant difference was found in the age, sex, pathological types and complications between two groups (P>0.05). The median DFS in low NLR group was 7.2 months (95% CI: 5.9~8.4), which was significantly longer than 6.7 months (95% CI: 5.4~7.9) in high NLR group (P<0.05). Lymph node metastases and NLR were the independent risk factors of DFS in elderly patients with NSCLC, while age, number of chemotherapy were independent protection factors (P<0.05). **Conclusions:** NLR was obviously correlated with the clinical stage and lymph node metastases of elderly patients with NSCLC, it could also be used as evaluation index of prognosis.

Key words: Neutrophil/lymphocyte ratio; Non-small cell lung cancer; Elderly; Clinicopathology; Prognosis

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非小细胞肺癌(non-small cell lung cancer,NSCLC)是一种发病率、死亡率均较高的恶性肿瘤,约占全部肺癌的 75~80%,由于其解剖特殊性以及缺乏有效的早期筛查手段,绝大多数在中晚期或远处转移时才被确诊,往往错过最佳根治性手术切除的时机,术后 5 年生存率仍低于 15%[1]。目前对于 NSCLC 患者的生存期评估多集中于病理分期,敏感性与特异性均不十分理想。近年来,慢性炎症、免疫功能与恶性肿瘤发生、发展之间的关系一直是研究的热点[2-4]。中性粒细胞 - 淋巴细胞比率(neutrophil/lymphocyte ratio,NLR)是外周血中性粒细胞与淋巴细胞的比值,可有效反映系统性炎性反应,现已广泛应用于胃癌、乳腺癌、直肠癌等实体肿瘤的疗效及预后评估[5-7],但其与老年 NSCLC 的相关研究仍较少。本研究通过检测老年 NSCLC 患者化疗前 NLR,探讨其与临床病理及预后的相关性,现报道如下。

1 资料与方法

1.1 一般资料

收集 2011 年 1 月 ~2013 年 6 月在我院肿瘤内科住院的老

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年 NSCLC 患者 68 例作为研究对象。入组标准：① 经影像学、临床病理或细胞学检查确诊，且临床病理及随访资料完整；② 年龄 60 岁及以上，未接受过化疗、放疗等肿瘤相关治疗；③ 排除合并严重感染、严重心肝肾等器质性功能障碍者。其中，男 41 例，女 27 例，年龄 60~79(69.1± 4.5)岁；病理类型：腺癌 52 例，鳞癌 16 例；TNM 分期：ⅢA 期 26 例，ⅢB 期 21 例，Ⅳ期 21 例。

1.2 资料收集

收集所有患者的临床病理资料，包括年龄、性别、吸烟史、病理类型、TNM 临床分期、合并症、淋巴结转移及化疗次数等，同时于化疗前采集静脉血患者检查相关实验室指标，包括如中性粒细胞、淋巴细胞、白细胞、血浆白蛋白、C 反应蛋白(C-reactive protein，CRP)等。NLR= 外周血中性粒细胞计数 / 淋巴细胞计数。由于 NLR 呈偏态分布，以其中位数的临界值分为低 NLR 组(<2.95)、高 NLR 组(≥ 2.95)。

1.3 随访

化疗期间及化疗后通过电话、门诊复查等方式进行随访，了解患者的复发、转移、死亡等预后情况，记录无病生存期(Disease free survival，DFS)。DFS 定义为患者从确诊时间至疾病复发或因疾病复发导致死亡的时间。随访时间从确诊之日起计算，截至 2015 年 6 月。

1.4 统计学分析

采用 SPSS 18.0 版软件包进行数据整理和统计分析，计数比较采用 X^2 检验，采用 Kaplan-Meier 生存分析法分析 NLR 值与 DFS 的相关性，采用 Log-rank 进行差异性检验，采用 Cox 单因素和多因素分析 DFS 的影响因素，P<0.05 表示差异有统计学意义。

2 结果

2.1 高 NLR 组和低 NLR 组临床病理特征的比较

与低 NLR 组比较，高 NLR 组临床分期Ⅳ期、吸烟及淋巴转移的比例更高 P<0.05)，而两组间年龄、性别、病理类型及合并症比较，差异均无统计学意义(P>0.05)。见表 1。

表 1 高 NLR 组和低 NLR 组临床病理特征比较

Table 1 Comparison of the clinicopathological features between high NLR group and low NLR group

Clinical parameter		n	High NLR group (n=35)	Low NLR group (n=33)	X^2	P
Age(year)	60~69	44	20	24	1.81	>0.05
	≥ 70	24	15	9		
Gender	Male	41	20	21	0.30	>0.05
	Female	27	15	12		
Pathological type	Adenocarcinoma	52	24	28	2.50	>0.05
	Squamous carcinoma	16	11	5		
Smoking	Yes	32	10	22	9.89	<0.05
	No	36	25	11		
Clinical stage	Ⅲ	47	29	18	6.38	<0.05
	Ⅳ	21	6	15		
Complications	Yes	25	11	14	0.88	>0.05
	No	43	24	19		
Lymph node metastases	Yes	38	15	23	4.96	<0.05
	No	30	20	10		

2.2 高 NLR 组和低 NLR 组的预后比较

通过 Kaplan-Meier 法对老年 NSCLC 患者进行生存分析。68 例老年 NSCLC 患者的中位 DFS 为 6.9 个月 (95% CI: 5.3~8.6)，其中低 NLR 组中位 DFS 为 7.2 个月 (95% CI: 5.9~8.4)，高 NLR 组中位 DFS 为 6.7 个月(95%CI: 5.4~7.9)。经 log-rank 检验，低 NLR 组中位 DFS 显著高于高 NLR 组，差异有统计学意义(X^2=3.54，P<0.05)。

2.3 老年 NSCLC 患者预后的单因素、多因素分析

以 DFS 作为预后分析的因变量，单因素分析显示年龄、临床分期、白蛋白、淋巴转移、化疗次数、NLR 与 DFS 相关(P<0.05)。将上述变量纳入多因素分析中，结果显示淋巴转移、NLR 是老年 NSCLC 患者 DFS 的独立危险因素，而年龄、化疗次数则是独立保护因素(P<0.05)。见表 3。

3 讨论

越来越多的研究表明肿瘤的发生发展与机体慢性炎症密切相关。局部长期的慢性炎症状态削弱了体内的免疫状态，可使肿瘤的生长获益，促进其恶性生物学行为[8,9]。因此，减轻或抑制局部炎症状态可能有助于减缓甚至阻断影响肿瘤进展的关键通路。炎性反应通过一系列炎性介质、炎性细胞及炎性蛋白

表 2 老年 NSCLC 患者 DFS 的单因素、多因素分析

Table 2 The DFS of elderly patients with NSCLC by univariate and multivariate analysis

Variate	Univariate analysis			Multivariate analysis		
	HR	95%CI	P value	HR	95%CI	P value
Gender	0.912	0.516~1.401	0.715			
Age	0.558	0.405~0.718	0.006	0.417	0.286~0.651	<0.001
Smoking	0.948	0.639~1.406	0.792			
Pathological type	1.117	0.755~1.651	0.581			
Clinical stage	2.076	1.400~3.078	<0.001	1.714	0.993~2.896	0.061
Complications	1.187	0.808~1.746	0.438			
Albumin	0.611	0.402~0.895	0.011	0.771	0.587~1.083	0.066
Lymph node metastases	1.436	1.330~1.551	0.007	1.889	1.665~2.158	0.004
Number of chemotherapy	0.407	0.269~0.628	0.004	0.334	0.167~0.51	<0.001
NLR	1.675	1.467~1.914	0.007	1.587	1.430~1.762	0.008
CRP	1.229	0.781~1.746	0.971			

得以反映,CRP 是临床上较为常用的评估指标，但一般不作为常规检测指标。NLR 作为系统性炎症反应的高敏感性、高特异性的标志物之一,可准确反映机体的免疫功能状态,同时因其易于获取、可比性强等特点现已在临床广泛应用[10-12]。

NLR 水平升高表明中性粒细胞的升高和(或)淋巴细胞的相对减少,前者反映炎性反应增加,后者反应免疫功能下降,机体抗肿瘤免疫的平衡状态被打破，由抗肿瘤向促肿瘤方向发展,形成适宜肿瘤生长的微环境[13,14]。研究表明肿瘤细胞可释放髓样生长因子,诱导中性粒细胞释放多种细胞因子,如血管内皮生长因子、白介素、肿瘤坏死因子 -α 等,从而促进肿瘤细胞的增殖和存活以及肿瘤新生血管的形成和转移[15-17]。本研究结果显示与低 NLR 组比较,高 NLR 组临床分期偏晚,吸烟及淋巴转移的比例更高,说明 NLR 的升高与老年 NSCLC 恶性生物学行为密切相关,预示着不良的预后。

目前，国内外对于 NLR 与肿瘤总体预后的关系仍未达成一致 [18-20]。从预后方面来看，低 NLR 组中位 DFS 为 7.2 个月(95%CI: 5.9~8.4)，显著高于高 NLR 组中位 DFS 6.7 个月(95% CI: 5.4~7.9)(P<0.05)，提示 NLR 的升高可作为老年 NSCLC 患者预后不良的有效生物学标志物。在控制相关影响因素的干扰后,NLR 是老年 NSCLC 患者 DFS 的独立危险因素(P<0.05),进一步证实 NLR 升高在老年 NSCLC 患者中可作为预后不良的独立危险因素。Lee 等 [21] 研究发现化疗前高 NLR 经治疗后 NLR 下降者的预后优于经过治疗 NLR 仍居高不降者。

综上所述,NLR 与老年 NSCLC 患者的病理特征及生物学行为有明显相关性,可作为患者的预后评估指标之一。但由于本研究为回顾性分析,样本量较少,NLR 临界值的选择可能存在一定局限性,故确切的结论有待积累更多样本、前瞻性研究设计进一步证实 NLR 与预后的相关性。

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