

• 临床研究 •

中性粒细胞/淋巴细胞比值对早期原发乳腺弥漫大 B 细胞淋巴瘤的临床特征及预后的影响*

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[摘要] 目的: 探讨中性粒细胞/淋巴细胞比值(neutrophil to lymphocyte ratio, NLR)对早期原发乳腺弥漫大 B 细胞淋巴瘤(primary breast diffuse large B-cell lymphoma, PB-DLBCL)的临床特征、预后的影响。方法: 回顾性分析 2005 年 9 月至 2015 年 9 月期间四川省肿瘤医院收治的 45 例早期 PB-DLBCL 患者临床资料。统计患者初诊时全血细胞计数中的中性粒细胞数、淋巴细胞数, 计算治疗前 NLR 值。应用 Kaplan-Meier 法进行生存分析, 单因素分析采用 Log-rank 检验, 多因素分析采用 Cox 回归模型。结果: 45 例 PB-DLBCL 患者中, 多为女性(97.8%), 中位发病年龄 45 岁(28 岁~77 岁)。所有患者均以单侧无痛性乳腺包块为首发症状, 其中右侧乳腺包块 29 例, 左侧乳腺包块 16 例; 伴有 B 组症状 5 例。所有患者均接受化疗, 联合利妥昔单抗免疫治疗 31 例, 接受局部放疗 12 例, 接受预防性鞘内化疗 14 例。病理亚型(按 Hans 分型法则)示生化中心 B 细胞型(GCB) 10 例, 非生化中心 B 细胞型(non-GCB) 35 例。中位随访时间 97 个月, 中位无进展生存期未达到, 中位总生存期 38 个月(12~78 个月), 3 年总生存率(OS) 68.9%。通过 ROC 曲线得到 NLR 的截断值(cut off 值) 3.211, 分为低 NLR 组(≤ 3.211)、高 NLR 组(> 3.211)。NLR 与 PB-DLBCL 的 Hans 分型($P=0.020$)、病变部位($P=0.015$)及 IPI 评分($P=0.002$)明显相关。单因素生存分析显示, non-GCB($P=0.011$)、II 期($P=0.038$)、ECOG 评分 ≥ 2 分($P=0.002$)、IPI 评分 ≥ 2 分($P=0.002$)、NLR 值 > 3.211 ($P=0.007$)以及未行预防性鞘内化疗($P=0.002$)是影响 PB-DLBCL 患者预后的因素; 多因素分析中显示, ECOG 评分、IPI 评分、NLR 及预防性鞘内化疗是影响 OS 的独立预后因素($P<0.05$)。结论: NLR 与 PB-DLBCL 的临床特征有相关性, 是影响 PB-DLBCL 患者生存预后的独立危险因素。

[关键词] 早期; 原发乳腺弥漫大 B 细胞淋巴瘤; NLR; 临床特征; 预后 IPI 评分; 预防性鞘内化疗

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Effect of Neutrophil to Lymphocyte Ratio on Clinical Features and Prognosis of Patients with Early Primary Breast Diffuse Large B-cell Lymphoma

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[Abstract] **Objective:** To analyze the effect of neutrophil to lymphocyte ratio (NLR) on clinical features and prognosis of patients with early Primary Breast Diffuse Large B-cell Lymphoma (PB-DLBCL). **Methods:** Clinical data of 45 cases of early PB-

DLBCL in Sichuan Cancer Hospital from September 2005 to September 2015 were retrospectively analyzed. The absolute neutrophils and lymphocytes in the complete blood cell count of the patients before treatment were counted, and the NLR was calculated. The Kaplan-Meier method was used for survival analysis. Univariate analysis was performed with Log-rank test and multivariate analysis was performed with the Cox-regression model. **Results:** Of the 45 patients with PB-DLBCL, most patients were females (97.8%). The median age was 45 years (28 ~ 77 years). The male to female ratio was 1:44. All patients had painless breast mass as the first symptom, it occurred in the right breast in 29 cases and in the left breast in 16 cases. B symptoms occurred in 5 cases. All patients received chemotherapy, 31 patients received Rituximab immunochemotherapy, 12 patients received local radiation therapy, and 14 patients received prophylactic intrathecal chemotherapy. As for the pathological subtype (Hans classification criteria), 10 patients were diagnosed with germinal center B-cell type (GCB type) and 35 patients were diagnosed with non-germinal center B-cell type (non-GCB type). The median follow-up time was 97 months. The median progression-free survival has not been reached. The median overall survival was 38 months (12 ~ 78 months) and 3-year overall survival rate for the 45 PB-DLBCL cases was 68.9%. The optimal cut off value of 3.211 for NLR was obtained by the ROC analysis and the patients were divided into two groups, low NLR group (≤ 3.211) and high NLR group (> 3.211). NLR was significantly associated with Hans typing ($P = 0.02$), site of lesion ($P = 0.015$) and IPI score ($P = 0.002$). The univariate analysis showed that non-GCB ($P = 0.011$), stage II ($P = 0.038$), ECOG score ≥ 2 ($P = 0.002$), IPI score ≥ 2 ($P = 0.002$), NLR value > 3.211 ($P = 0.007$) and no preventive intrathecal chemotherapy ($P = 0.002$) were factors that affect the prognosis in patients with PB-DLBCL; multivariate analysis showed that ECOG score, IPI score, NLR and prophylactic intrathecal chemotherapy were independent risk factors ($P < 0.05$). **Conclusion:** NLR has a correlation with the clinical features of PB-DLBCL, and it may be an important independent prognostic factor of patients with PB-DLBCL.

[**Key words**] Early stage; Primary breast diffuse large B-cell lymphoma; NLR; Clinical features; Prognosis; IPI score; Prophylactic intrathecal chemotherapy

原发乳腺淋巴瘤 (primary breast lymphoma, PBL) 是一种罕见的结外淋巴瘤亚型, 占有结外淋巴瘤的 2%^[1], 约占原发乳腺恶性肿瘤的 0.5%^[2-3]。其中, 最常见的类型为弥漫大 B 细胞淋巴瘤 (diffuse large B-cell lymphoma, DLBCL), 占有病例的 60% ~ 80%^[1]。原发乳腺弥漫大 B 细胞淋巴瘤 (primary breast diffuse large B-cell lymphoma, PB-DLBCL) 病因可能与性激素有关^[2], 但具体机制不明确。由于该病发生的部位特殊, 易被漏诊及误诊为乳腺癌或其他乳腺良性疾病, 目前国内关于 PB-DLBCL 的研究多为小样本回顾性研究, 评估其预后指标多采用 DLBCL 的预后指标。而临床中, PB-DLBCL 患者分期多为早期^[3], 且 IPI 评分低^[4], 这些指标对该类疾病的预后分层不能更好地分析; 且 IPI 评分主要基于临床特征, 并不能全面地反映该疾病的生物学活性。近年来, 越来越多的研究发现炎症指标与恶性肿瘤的临床特征及预后密切相关^[5-11]。目前, 已有较多文献报道了 NLR 高^[6, 12-14]与 DLBCL 的不良预后相关, 但尚没有文献报道 NLR 与 PB-DLBCL 的关系。本研究主要探究 NLR 对 PB-DLBCL 患者的临床特征及预后的影响。

1 材料和方法

1.1 病例资料收集

回顾性收集 2005 年 9 月至 2015 年 9 月期间于

我院就诊, 且病理学确诊为 PB-DLBCL 的患者的完整临床资料。所有患者治疗前均通过 CT、MRI、PET/CT 等 1 项或多项影像学检查及骨髓检查评估淋巴瘤全身受侵范围, 分期均采用 Ann Arbor 系统, 其中 IE 期 23 例, II E 期 22 例。收集完整的临床资料, 包括: Hans 分型、年龄、性别、分期、乳酸脱氢酶水平 (lactate dehydrogenase, LDH)、体力状况 (ECOG 评分)、肿瘤侵犯部位、中性粒细胞、淋巴细胞 (为初诊时自动化全血细胞计数获得) 等。本研究获得我院伦理委员会的批准。

1.2 治疗情况

45 例患者均接受 CHOP 或 CHOP 类方案^[15]化疗 3 ~ 8 周期。其中, 31 例 (68.9%) 患者接受联合利妥昔单抗 (Rituximab) 治疗^[16]; 14 例 (31.1%) 于第 2 周期或所有疗程化疗结束后接受甲氨蝶呤或/和阿糖胞苷预防性鞘内化疗 (intrathecal chemotherapy, IT) 2 ~ 4 个疗程; 12 例化疗结束后行受累侧乳房局部放疗 (radiation therapy, RT) 30 ~ 50 Gy。具体包括: 单纯化疗 7 例 (15.6%)、单纯化疗联合 IT 1 例 (2.2%)、单纯化疗联合 RT 6 例 (13.3%)、单纯联合 Rituximab 12 例 (26.7%)、联合 Rituximab + IT 13 例 (28.9%)、联合 Rituximab + RT 6 例 (13.3%)。

1.3 评价

根据国际淋巴瘤疗效评价标准^[17]疗效评价, 分为完全缓解 (complete response, CR)、部分缓解、疾

病稳定、疾病进展。总生存期(overall survival, OS)及无进展生存期(progression free survival, PFS)评价预后生存情况,OS 定义为从疾病确诊时间到任何原因引起的死亡或末次随访时间间隔。PFS 定义为从疾病确诊时间至疾病复发或(因任何原因)死亡之间的时间。

1.4 随访

所有患者治疗结束后 1 年内每 3 个月随访 1 次,第 2 年每 6 个月 1 次,之后每年 1 次^[18]。发现可疑症状及体征则随时复诊。复查内容包括:浅表淋巴结触诊、CT、MRI、PET/CT 等。随访截止日期为 2018 年 10 月 31 日,45 例患者全部随访,无失访。

1.5 统计学分析

应用 SPSS 22.0 系统软件进行数据分析,采用受试者工作特征曲线(receiver operating characteristic curve, ROC 曲线)获取 NLR 的最佳截断值。采用卡方检验进行组间比较,单因素应用 Kaplan-Meier 法进行生存分析,采用 Log-rank 检验进行比较,多因素分析采用 Cox 回归模型, $P \leq 0.05$ 为差异有统计学意义。

2 结果

2.1 临床特征

45 例 PB-DLBCL 患者中位发病年龄 45 岁(28 岁~77 岁);年龄 >60 岁的患者 9 例(20%);44 例女性,仅 1 例男性。病变部位:右侧乳腺 29 例(64.4%),左侧乳腺 16 例(35.6%)。伴有 B 组症状的患者 5 例(11.1%)。Hans 分型:生化中心 B 细胞型(germinal center B cell type, GCB) 10 例(22.2%),非生化中心 B 细胞型(non-germinal center B cell type, non-GCB)35 例(77.8%)。Ann Arbor 分期系统:IE 期 23 例(51.1%),II E 期 22 例(48.9%)。

2.2 NLR cut-off 值

NLR 的 ROC 曲线如图 1,通过 ROC 曲线获得最具差异性的 NLR cut-off 值 3.21,敏感性是 0.7,特异性 0.72。AUC 值 0.717,95% 置信区间为 0.566~0.868, $P = 0.013$ 。

2.3 NLR 与临床特征之间的关系

低 NLR 组($NLR \leq 3.211$) 24 例,高 NLR 组($NLR > 3.211$)21 例。NLR 值与 Hans 分型、病变部位、IPI 评分有相关性($P < 0.05$),与性别、年龄、B 症状、分期、LDH 值无相关性($P > 0.05$)(表 1)。

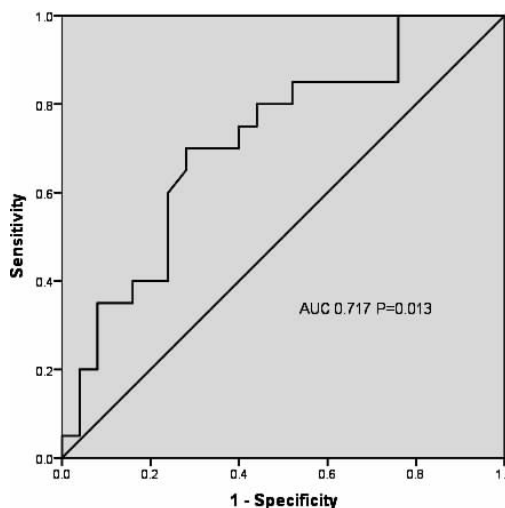


图 1 诊断时 NLR 的受试者工作特征曲线(ROC)和曲线下面积(AUC)

Figure 1. Receiver Operating Characteristic Curve (ROC) and Area Under the Curve (AUC) for NLR at Diagnosis (AUC = 0.717, $P = 0.013$; 70.0% sensitivity and 72.0% specificity)

表 1 NLR 与临床特征的关系

Table 1. Relationship between NLR and Clinical Features

Clinical characteristics	NLR		P	
	NLR > 3.211 (n)	NLR ≤ 3.211 (n)		
Hans typing	GCB	3	7	0.020
	non-GCB	18	17	
Sex	Male	0	1	
	Female	21	23	
Age(y)	≤60	16	20	0.103
	>60	5	4	
B symptoms	No	20	20	0.673
	Yes	1	4	
Stage	IE	6	17	0.221
	IIE	15	7	
LDH (U/L)	≤240	14	17	0.137
	>240	7	7	
Site of lesion	Right	15	14	0.015
	Left	6	10	
IPI score	<2	19	22	0.002
	≥2	2	2	

NLR; neutrophil to lymphocyte ratio; GCB; germinal center B-cell type; Non-GCB; non-germinal center B-cell type; LDH; lactate dehydrogenase.

2.4 生存分析

2.4.1 全组患者 PFS 及 OS 45 例 PB-DLBCL 患者中位随访 97 个月,截止随访日期中位无进展生存期未达到(图 2),中位总生存期 38 个月(12~78 个月),3 年 OS 为 68.9%(图 3);中枢神经系统(central nervous system, CNS)复发 3 例(6.67%)。

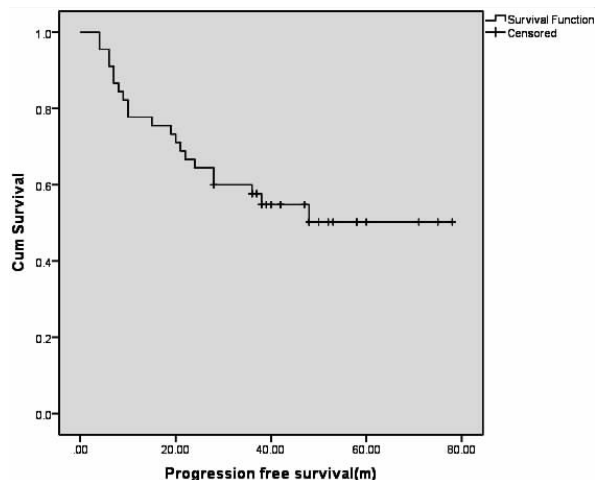


图2 PB-DLBCL 患者的 PFS
Figure 2. PFS of PB-DLBCL Patients

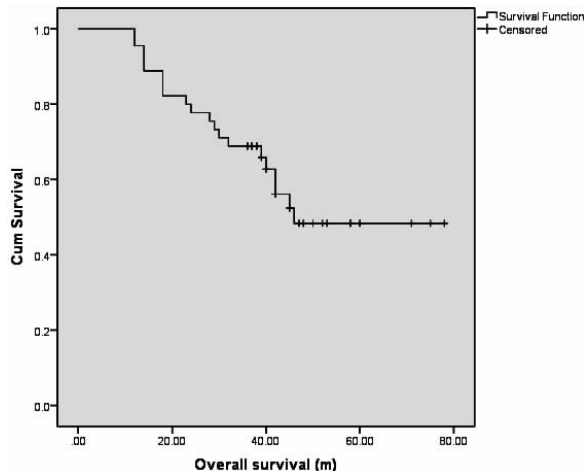


图3 PB-DLBCL 患者的 OS
Figure 3. OS of PB-DLBCL Patients

2.4.2 NLR 对 PFS 及 OS 的影响 NLR > 3.211 组 PB-DLBCL 患者的 3-PFS 率(图 4)及 3-OS 率(图 5)

明显低于 NLR ≤ 3.211 组, 差异有统计学意义 (P < 0.05) (表 2)。

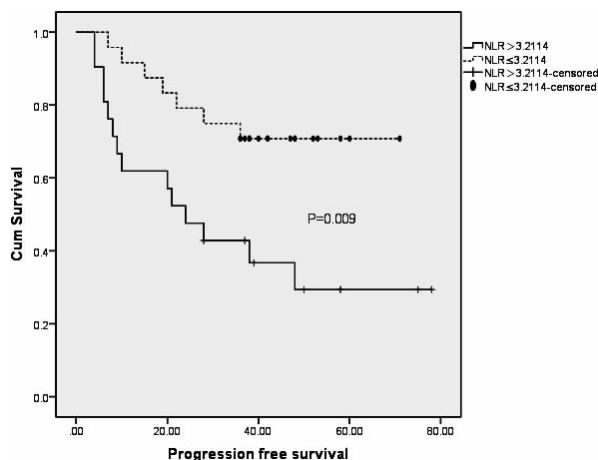


图4 通过 NLR 截断值分层的 PFS Kaplan-Meier 曲线
Figure 4. Kaplan-Meier Curves of PFS Stratified by NLR Cutoff

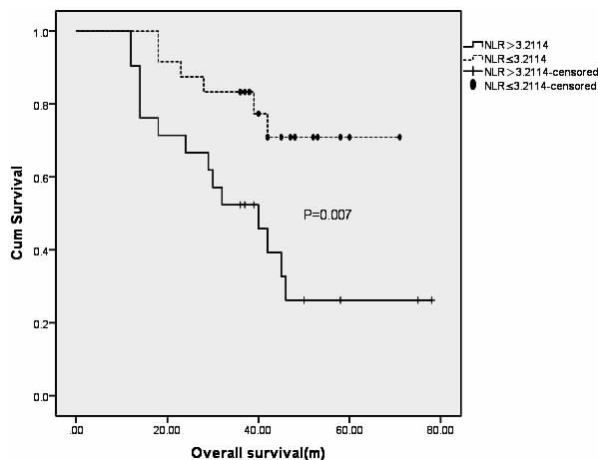


图5 通过 NLR 截断值分层的 OS Kaplan-Meier 曲线
Figure 5. Kaplan-Meier Curves of OS Stratified by NLR Cutoff

表 2 NLR 对 PB-DLBCL 患者预后的影响
Table 2. Effect of NLR on the Prognosis of Patients with PB-DLBCL

Variable	3-PFS (%)	χ^2	P	3-OS (%)	χ^2	P
NLR > 3.211	42.0	6.823	0.009	52.4	7.262	0.007
NLR ≤ 3.211	70.8			83.3		

NLR: neutrophil to lymphocyte ratio; PB-DLBCL: primary breast diffuse large B-cell lymphoma; PFS: progression free survival; OS: overall survival.

表 3 影响 OS 的单因素分析
Table 3. Univariate Analysis of OS

Characteristic	N	3-OS (%)	χ^2	P	Characteristic	N	3-OS (%)	χ^2	P
Hans typing				0.011	Gender				0.387
GCB	10	100	6.43		Male	1	100	0.749	
Non-GCB	35	60			Female	44	68.2		

(Table 3 continues on next page)

2.5 预后分析

在单因素分析中,影响 PB-DLBCL 患者 OS 的预后因素,除了上述所说 NLR 以外,还包括: Hans 分型、分期、ECOG 评分、IPI 评分及预防性鞘内化疗,差异有统计学意义(表 3)。在多因素分析中, ECOG 评分、IPI 评分、NLR 与预防性鞘内化疗是影响 PB-DLBCL 预后的独立因素(表 4)。

(continued from previous page)

Characteristic	N	3-OS(%)	χ^2	P	Characteristic	N	3-OS(%)	χ^2	P
Age(y)				0.057	IPI score				0.002
≤60	36	72.2	3.636		<2	41	73.2	9.932	
>60	9	55.6			≥2	4	25		
B symptoms				0.320	Treatment response				0.362
No	40	67.5	0.988		CR	25	80	0.831	
Yes	5	80			Non-CR	20	55		
Stage				0.038	Rituximab				0.366
I E	23	82.6	4.295		Yes	31	74.2	0.817	
II E	22	54.5			No	14	57.1		
LDH(U/L)				0.109	Prophylactic IT				0.002
≤240	31	77.4	2.573		Yes	14	100	9.848	
>240	14	50			No	31	54.8		
Site of lesion				0.164	Local radiation therapy				0.477
Right	29	75.9	1.934		Yes	12	50	0.505	
Left	16	56.3			No	33	75.8		
ECOG score				0.002	-	-	-	-	-
<2	41	73.2	9.932	-	-	-	-	-	-
≥2	4	25	-	-	-	-	-	-	-

OS:overall survival;GCB:germinal center B-cell type;LDH:lactate dehydrogenase;ECOG:Eastern Cooperative Oncology Group;IPI:International prognostic index;CR:complete response;IT:intrathecal chemotherapy.

表 4 影响 OS 的多因素分析

Table 4. Multivariate Analysis of OS

Variable	β	SE	Wald χ^2	P	OR	95.0% CI for OR	
						Lower	Upper
NLR	1.437	0.663	4.699	0.030	4.210	1.148	15.442
ECOG	-1.971	0.908	4.708	0.030	0.139	0.023	0.826
IPI	-1.971	0.908	4.708	0.030	0.139	0.023	0.826
Hans typing	-12.739	257.375	0.002	0.961	<0.001	<0.001	<0.001
Stage	0.529	0.654	0.654	0.419	1.697	0.471	6.113
Age	0.677	0.652	1.081	0.299	1.969	0.549	7.060
LDH	0.462	0.573	0.650	0.420	1.587	0.516	4.877
Prophylactic IT	2.503	1.090	5.274	0.022	12.222	1.443	103.517

OS:overall survival;NLR: neutrophil to lymphocyte ratio; ECOG:Eastern Cooperative Oncology Group;IPI:International prognostic index;LDH:lactate dehydrogenase; IT:intrathecal chemotherapy.

3 讨论

PB-DLBCL 是一种少见的原发性乳腺肿瘤,仅占乳腺恶性肿瘤的 0.5%^[2-3]。1972 年, Wiseman 等^[19] 提出关于 PBL 的诊断标准,但并没完全阐述淋巴瘤的生物学行为及预后的差异。之后, Yhim 等^[20] 发现按结外受累器官数数目分类可以反映生存差异,又对 PBL 的诊断标准进一步完善。该病多见于中老年女性^[21],男性罕见;临床表现无特异性,常以乳腺包块为首发症状,好发于右侧乳腺^[21-22]、外上象限^[23]。本组资料中,PB-DLBCL 多见于中老年女性,右侧乳腺发病较多见,与文献报道相一致。按 Ann Arbor 临床分期标准,IE 期占 70%~75%^[1,24],II E 期约占 30%^[25],IV E 期双侧乳腺受累少见(目前关于双侧乳腺同时受累分期尚有争议,因其较单侧乳腺受累侵袭性更强,预后更差,考

虑分期为 IV E 期^[2,26])。虽然绝大部分患者分期早^[27],但该病属于侵袭性淋巴瘤,恶性程度高,故预后差于结内 DLBCL^[27-28]。有文献报道^[26],PB-DLBCL 患者的 5 年 OS 为 77.3%,且易出现对侧乳腺、CNS 以及其他结外器官复发^[29],尤其是 CNS^[30],其复发率高达 11.5%^[31]。本组资料中,PB-DLBCL 患者 3 年 OS 为 68.9%,CNS 复发率为 6.67%,低于文献报道,可能与本组资料病例数较少且随访年限短相关。

由于 PB-DLBCL 发病率低,目前与之相关的预后因素报道较少。2013 年,林桐榆等^[27] 提出影响 PBL 的不良预后因素,包括:IPI 中低评分、中高病理分级、肿瘤直径 >5cm、其他结外器官受累、血清可溶性 IL-2 >1 000kU/L 等^[27,32]。随后,国外 Aviv 等^[2] 就提出了关于 PB-DLBCL 不良预后的临床指标,包括:Ann-Arbor 分期 >IE 期,体能状态不佳,LDH 升高,肿瘤大小大于 4~5cm,并可用这些特征

行风险分组。但由于该病发病时分期早^[27],病灶局限,患者机体体能状态评分较低,有学者提出将累及双侧乳腺及分期调整的 IPI 评分 > 2 分作为评价疾病预后指标^[30]。另外,有研究发现, Hans 分型^[33-34]也是影响该类患者预后的指标之一。病理分型中以 non-GCB 多见^[33-34],部分学者认为 non-GCB 型与 PB-DLBCL 不良预后相关^[34]。但也有部分学者^[31]发现, non-GCB 型与患者 OS 无关,而与较差的 PFS 有关。在本组资料中,分期、Hans 分型、ECOG 评分、IPI 评分与 PB-DLBCL 的预后相关,而多因素分析显示只有 ECOG 评分、IPI 评分是临床参数中影响 PB-DLBCL 预后的独立因素,这可能与本组资料病例少相关。

除上述的指标外,在多项临床研究中也发现高 NLR 与肿瘤预后不良相关^[5,9,35-37],也有文献报道治疗过程动态监测 NLR,升高也提示预后不良^[38]。有研究发现,在肿瘤微环境中,肿瘤细胞会分泌多种细胞因子及趋化因子,这些细胞因子吸引更多中性粒细胞等炎症细胞聚集到肿瘤细胞附近^[38],受到刺激的中性粒细胞能分泌细胞因子、趋化因子等,为肿瘤细胞的生长、浸润及转移创造有利条件^[35-36,39]。这可能与中性粒细胞上 N2 表型^[40]表达所致趋化因子受体 CXCR4、VEGF 和明胶酶 B/MMP 9 的高表达有关^[41]。而淋巴细胞是人体免疫系统的重要组成部分,机体有赖于它对肿瘤细胞进行监视及清除^[42]。在相关临床研究发现外周血中淋巴细胞减少是 DLBCL 复发的危险因素^[43],这可能与肿瘤细胞从肿瘤浸润淋巴细胞(TILs)的免疫逃逸有关^[44]。由此可推断高 NLR 与肿瘤预后不良密切相关。近期一项关于 DLBCL 的 Meta 分析报告发现,各个样本所得 NLR 值不同(Cut-off 值在 2.11 ~ 5.54 间),但均与年龄、Ann Arbor 分期、B 组症状、骨髓受累、LDH 水平升高等因素有关^[37]。说明 NLR 值虽然不固定,但与疾病的临床参数却有关联性。本组资料 NLR 值为 3.211,与 Hans 分型、病变部位、IPI 评分有相关性($P \leq 0.05$)。

目前关于原发乳腺淋巴瘤的最佳治疗方案尚无共识,但手术治疗不作为 PBL 的推荐。多研究发现乳房切除术并不能降低该类疾病进展及复发的风险,甚至会导致疾病不良的肿瘤特异性生存率^[27,44]。另外,回顾性研究亦发现腋窝淋巴结清扫术并无长期获益^[27]。除此之外,治疗方案中是否联用利妥昔单抗^[4]、是否加用 RT^[4,45]以及是否预防性鞘内化疗^[26]也与患者预后相关。但大部分研究都是

小样本研究,尚无明确定论。在本组资料的治疗方案相关生存分析中,预防性 IT 是影响 PB-DLBCL 患者预后的独立因素($P < 0.05$),而接受利妥昔单抗靶向治疗及局部 RT 的患者生存并无获益($P > 0.05$)。

总之,NLR 可能成为预测 PB-DLBCL 预后的重要指标,目前国内尚无相关报道。由于本研究是一项回顾性研究,且研究的病例数少且随访年限短,所以研究结果还存在一定的缺陷及偏差,还需要大样本及多中心的前瞻性数据来进一步探讨。

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同行评议:经同行专家双盲外审,达到刊发要求。

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