·临床研究·

# 基于老年综合评估构建老年弥漫大B细胞淋巴瘤患者预后不良的预测模型

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【摘 要】 **目的** 分析老年弥漫大B细胞淋巴瘤(CGA)情况,并构建预后不良的预测模型。**方法** 选取2020年3月至2023年2月南京医科大学第一附属医院收治的初诊老年弥漫大B细胞淋巴瘤(DLBCL)患者183例行回顾性研究,以2∶1比例分为训练集(122例)及验证集(61例),以1年生存情况评估预后,生存为预后良好,死亡为预后不良,比较其简化CGA分层、工具性日常生活活动能力及年龄-Charlson合并症指数-白蛋白(IACA)指数等CGA情况及临床分期等基线资料。在训练集中,采用单因素及多因素logistic回归分析筛选老年DLBCL患者预后不良的影响因素,构建老年DLBCL患者预后不良的预测模型;在验证集中,采用Hosmer-Lemeshow检验评估预测模型的拟合度,采用受试者工作特征(ROC)曲线评估预测模型的预测效能。采用SPSS 25.0软件进行数据分析。根据数据类型,组间比较分别采用$t$检验、$\chi^2$检验及Fisher精确概率检验。**结果** 训练集中有21例(17.21%)发生预后不良,验证集中有11例(18.03%),差异无统计学意义($P=0.891$)。训练集单因素分析发现,简化CGA分层、IACA指数、临床分期、化疗疗效共4个变量在老年DLBCL患者发生预后不良上存在显著不同($P<0.05$)。多因素logistic回归分析显示,IACA指数≥3分、Ann Arbor Ⅲ~Ⅳ期均为老年DLBCL患者预后不良的独立危险因素($P<0.05$),简化CGA分层为适合化疗、化疗疗效为完全缓解则为独立保护因素($P<0.05$),构建预测模型为Y=-4.221+(-1.212)×简化CGA分层+1.451×IACA指数+1.269×临床分期+(-1.036)×化疗疗效。Hosmer-Lemeshow检验显示,预测模型的拟合度$\chi^2=12.580$,$P=0.125$,校准度良好。在验证集中,ROC曲线分析显示,预测模型ROC曲线下面积为0.886,95%*CI* 0.832~0.940,灵敏度为72.73%,特异度为88.00%。**结论** 初诊老年DLBCL患者近期预后与简化CGA分层、IACA指数、临床分期、化疗疗效有关,以此建立的预测模型对筛选1年死亡高危患者有积极作用。

【关键词】 老年人;弥漫大B细胞淋巴瘤;初诊;预后;生存;老年综合评估
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# Prediction model of poor prognosis in elderly patients with diffuse large B-cell lymphoma based on comprehensive geriatric assessment

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【**Abstract**】 **Objective** To analyze the comprehensive geriatric assessment (CGA) status of elderly patients with diffuse large B-cell lymphoma (DLBCL) and construct a prediction model of poor prognosis. **Methods** A retrospective study was conducted on 183 elderly patients with newly-diagnosed DLBCL in our hospital from March 2020 to February 2023. They were divided into a training set (122 cases) and a validation set (61 cases) at a ratio of 2∶1. The prognosis was evaluated by 1-year survival status, and survival was taken as good prognosis and death was considered as poor prognosis. Simplified CGA stratification, instrumental activities of daily living, and age, Charlson comorbidity index, albumin (IACA) index and baseline data such as clinical staging were compared. In the training set, univariate and multivariate logistic regression analyses were used to screen the influencing factors of poor prognosis in elderly DLBCL patients, and a prediction model for poor prognosis was then constructed. In the validation set, Hosmer-Lemeshow test was adopted to evaluate the fitting degree of the prediction model, and receiver operating characteristic (ROC) curve was adopted to evaluate the predictive efficiency of the model. SPSS statistics 25.0 was used for statistical analysis. Data comparison between two groups was performed using $t$ test, *Chi-*

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square test or Fisher exact probability test depending on data type. **Results** There were 21 cases (17.21%) with poor prognosis in the training set and 11 cases (18.03%) with poor prognosis in the validation set, without statistical difference between two sets ($P$=0.891). Univariate analysis of the training set found that four variables, including simplified CGA stratification, IACA index, clinical staging, and chemotherapy efficacy, were significantly different in the poor prognosis of elderly patients with DLBCL ($P$<0.05). Multivariate logistic regression analysis showed that IACA index ≥3 and Ann Arbor stage Ⅲ-Ⅳ were independent risk factors for poor prognosis in elderly DLBCL patients ($P$<0.05), and simplified CGA stratified as suitable chemotherapy and chemotherapy efficacy obtaining complete remission were independent protective factors ($P$<0.05). The prediction model was constructed as Y=-4.221+(-1.212)×simplified CGA stratification+1.451×IACA index+1.269×clinical staging+(-1.036)×chemotherapy efficacy. Hosmer-Lemeshow test revealed that the fitting degree of the prediction model was shown as *Chi*-square=12.580, $P$=0.125, with good calibration. In the validation set, ROC curve analysis showed that the area under curve (AUC), 95%*CI*, sensitivity and specificity of the prediction model were 0.886, 0.832-0.940, 72.73% and 88.00%, respectively. **Conclusion** In elderly patients with newly-diagnosed DLBCL, short-term prognosis is related to simplified CGA stratification, IACA index, clinical staging and chemotherapy efficacy. The prediction model established based on these variables has a positive effect on screening patients with high-risk of one-year death.

【**Key words**】 aged; diffuse large B-cell lymphoma; newly-diagnosed; prognosis; survival; comprehensive geriatric assessment

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弥漫大 B 细胞淋巴瘤(diffuse large B-cell lymphoma, DLBCL)作为成人恶性淋巴瘤最常见的类型,标准化疗方案疗效较好,患者整体 5 年总生存率 75%[1]。然而,老年 DLBCL 患者标准化疗方案效果不理想,可能与体能状态、合并症等多因素有关,预后较差,其 5 年总生存率仅为 45.8%,故老年 DLBCL 患者预后状况受到广泛关注[2]。老年 DLBCL 患者预后因素虽然为近年研究热点,但由于 DLBCL 疾病本身在治疗反应上异质性显著,并未在国内外达成共识,仍在探索阶段[3]。《老年弥漫大 B 细胞淋巴瘤诊断与治疗中国专家共识(2024 年版)》[4]中指出,由老年学角度出发,通过年龄、合并症、营养等全面评估的老年综合评估(comprehensive geriatric assessment, CGA)是宿主因素评估的重要工具,对判断老年 DLBCL 患者预后有积极意义。基于此,本研究分析老年 DLBCL 患者近期预后不同者 CGA 体系、化疗方案等的差异,评估其预后不良的影响因素,并构建预测模型,为老年 DLBCL 疾病管理提供新思路。

## 1 对象与方法

### 1.1 研究对象

选取 2020 年 3 月至 2023 年 2 月南京医科大学第一附属医院收治的初诊老年 DLBCL 患者 183 例行回顾性研究。纳入标准:DLBCL 诊断符合《中国弥漫大 B 细胞淋巴瘤诊断与治疗指南(2013 年版)》(以下简称 2013 年指南)[5],经组织活检病理学结合免疫组化确诊;初诊初治;年龄≥60 岁;确诊后接受标准或减量化疗方案;实验室检查及随访数据完整。排除标准:原发结外 DLBCL;合并严重心脑血管疾病;合并其他恶性肿瘤、慢性肺部或肾脏疾病;合并严重感染;既往放疗、化疗及免疫治疗史。

### 1.2 方法

1.2.1 化疗方案 所有老年 DLBCL 患者化疗及疗效标准均参考 2013 年指南[5],标准化疗方案为利妥昔单抗、环磷酰胺、多柔比星、长春新碱、泼尼松 21 d (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone 21-day, R-CHOP21),即利妥昔单抗 375 mg/m$^2$,环磷酰胺 750 mg/m$^2$,第 1 天;多柔比星 50 mg/m$^2$,或表柔比星 70 mg/m$^2$,或脂质体多柔比星 40 mg,第 1 天;长春新碱 1.4 mg/m$^2$(当日最高剂量≤2 mg),第 1 天;泼尼松 100 mg/d,第 1~5天;3 周为 1 个疗程。减量化疗方案为利妥昔单抗及减量 CHOP21 (rituximab and reduced dose CHOP21, R-miniCHOP21),即利妥昔单抗 375 mg/m$^2$,环磷酰胺 400 mg/m$^2$,第 1 天;多柔比星 25 mg/m$^2$,或表柔比星 35 mg/m$^2$,或脂质体多柔比星 20 mg,第 1天;长春新碱 0.7 mg/m$^2$(当日最高剂量≤1 mg),第 1 天;泼尼松 60 mg/d,第 1~5 天;3 周为 1 个疗程。完成 2 个疗程后评估疗效。

1.2.2 CGA 评估 (1)简化 CGA 分层[6]:由意大利淋巴瘤基金会(lymphoma Italian foundation, FIL)提出,根据日常生活活动能力(activities of daily living, ADL)、工具性日常生活活动能力(instrumental activities of daily living, IADL)、改良老年疾病累计评分表(modified cumulative illness rating scale-geriatric, MCIRS-G)分层,分为适合化疗(年龄<80 岁,ADL≥5 分,IADL≥6 分,MCIRS-G 无 3~4 级合并症)、

不适合化疗1(年龄<80岁,ADL<5分,IADL<6分,MCIRS-G有1个及3~4级以上合并症)、不适合化疗2(年龄≥80岁,ADL=6分,IADL=8分,MCIRS-G无3~4级合并症)及脆弱(年龄≥80岁,ADL<6分,IADL<8分,MCIRS-G有1个及3~4级以上合并症)。(2)工具性日常生活活动能力及年龄-Charlson合并症指数-白蛋白(instrumental activities of daily living and age, Charlson comorbidity index, albumin, IACA)指数[7],该量表由北京医院提出,将IADL与ACA量表结合,分为0分(年龄≤75分,IADL为8分,血清白蛋白≥34 g/L,CCI<3)、1分(年龄>75分,IADL为6~7分,血清白蛋白<34 g/L,CCI≥3)、2分(IADL≤5分),计算4项参数总得分,得分越高,老年患者综合状况越差。

1.2.3 资料收集方法 老年DLBCL患者人口学资料、病理免疫分型、体能状态、临床分期、危险分层、随访观察等资料均由电子病历系统获得,其中病理免疫分型通过病理免疫组化检查得到,包含肿瘤增殖抗原Ki67、髓细胞增生原癌基因(myelocytomatosis oncogene, MYC)、B淋巴细胞瘤2基因(B-cell lymphoma 2, BCL2);体能状态采用美国东部肿瘤协作组(eastern cooperative oncology group, ECOG)评分[8]评估,根据活动能力分为0(活动能力与起病前无差异)~5分(死亡);临床分期采用Ann Arbor分期标准[9],分为Ⅰ期(侵犯单个淋巴结或结外部位)、Ⅱ期(侵犯隔肌同侧两个或更多区域淋巴结)、Ⅲ期(隔肌两侧淋巴结区域均有侵犯)、Ⅳ期(多处淋巴结或结外肝、肺等部位受侵犯);危险分层采用淋巴瘤国际预后指数(international prognostic index, IPI)[10]。

1.2.4 预后情况 以1年生存情况评估预后,生存为预后良好,死亡为预后不良。

### 1.3 统计学处理

采用SPSS 25.0统计软件进行数据分析。符合正态分布的计量资料用均数±标准差($\bar{x}\pm s$)表示,采用$t$检验;计数资料用例数(百分率)表示,采用$\chi^2$检验或Fisher精确概率检验,等级资料采用秩和检验。训练集采用logistic回归分析筛选老年DLBCL患者预后不良的影响因素,构建老年DLBCL患者预后不良的预测模型;在验证集中,采用Hosmer-Lemeshow检验评估拟合度,采用受试者工作特征(receiver operating characteristic, ROC)曲线评估老年DLBCL患者预后不良模型的预测效能。$P<0.05$为差异有统计学意义。

## 2 结 果

### 2.1 纳入患者的一般资料

以随机数生成器生成的随机数作为病例编号,将符合纳入排除标准的183例老年DLBCL患者按照病例编号排序(升序),以2∶1比例分为训练集及验证集,即前三分之二为训练集(122例),后三分之一为验证集(61例)。训练集中有21例(17.21%)发生预后不良,验证集中有11例(18.03%)发生预后不良,两组患者差异无统计学意义($\chi^2=0.019$, $P=0.891$)。

### 2.2 老年DLBCL患者预后不良的单因素分析

对训练集的数据行单因素分析发现,简化CGA分层、IACA指数、临床分期、化疗疗效共4个变量在老年DLBCL患者发生预后不良上存在显著不同,差异均有统计学意义(均$P<0.05$;表1)。

### 2.3 老年DLBCL患者预后不良的多因素回归分析及预测模型构建

以预后不良为因变量,将上述单因素分析结果中的4个有统计学意义的变量作为自变量,行多因素logistic回归分析,结果显示,IACA指数≥3分、临床分期为Ⅲ~Ⅳ期均为老年DLBCL患者预后不良的独立危险因素($P<0.05$);简化CGA分层为适合化疗、化疗疗效为完全缓解则为独立保护因素($P<0.05$;表2)。以多因素logistic回归分析结果构建预测模型:Y=-4.221+(-1.212)×简化CGA分层+1.451×IACA指数+1.269×临床分期+(-1.036)×化疗疗效。

### 2.4 预测模型的拟合度分析及预测效能分析

Hosmer-Lemeshow检验显示,预测模型的拟合度$\chi^2=12.580$, $P=0.125$,校准度良好。在验证集中,ROC曲线分析显示,预测模型曲线下面积(area under curve, AUC)值为0.886($P<0.05$),95%$CI$ 0.832~0.940,灵敏度为72.73%,特异度为88.00%(图1)。

## 3 讨 论

我国目前约有30%的DLBCL患者确诊时年龄已超过70岁,随着老龄化现象的加剧,老年DLBCL患者数量逐年增多。研究发现,相较于中青年患者,老年DLBCL患者不良预后基因改变增多,效应免疫细胞功能减弱,预后更差[11]。本研究调查初诊老年DLBCL患者1年预后情况发现,1年死亡(预后不良)率为17.21%、18.03%,与目前报道的8%~25%相近[12]。

**表 1 老年 DLBCL 患者预后不良的单因素分析**

Table 1 Univariate analysis of poor prognosis in elderly DLBCL patients

| Item | Poor prognosis group ($n$=21) | Good prognosis group ($n$=101) | $\chi^2/t/Z$ | $P$ value |
|---|---|---|---|---|
| Gender[$n$(%)] | | | 0.051 | 0.822 |
| Male | 12(57.14) | 55(54.46) | | |
| Female | 9(42.86) | 46(45.54) | | |
| Age[$n$(%)] | | | 2.900 | 0.089 |
| 60-75 years | 8(38.10) | 59(58.42) | | |
| >75 years | 13(61.90) | 42(41.58) | | |
| Body mass index(kg/m$^2$, $\bar{x}\pm s$) | 22.16±2.06 | 22.45±1.95 | 0.614 | 0.540 |
| Hypertension[$n$(%)] | 4(19.05) | 16(15.84) | 0.001 | 0.970# |
| Diabetes mellitus[$n$(%)] | 2(9.52) | 9(8.91) | 0.109 | 0.742# |
| Smoking history[$n$(%)] | 7(33.33) | 29(28.71) | 0.178 | 0.673 |
| Tumor proliferation antigen Ki67 expression[$n$(%)] | | | 1.247 | 0.264 |
| <80% | 8(38.10) | 52(51.49) | | |
| ≥80% | 13(61.90) | 49(48.51) | | |
| MYC expression[$n$(%)] | | | 1.091 | 0.296 |
| ≥40% | 16(76.19) | 65(64.36) | | |
| <40% | 5(23.81) | 36(35.64) | | |
| BCL2[$n$(%)] | | | 3.090 | 0.079 |
| ≥50% | 18(85.71) | 67(66.34) | | |
| <50% | 3(14.29) | 34(33.66) | | |
| Lactate dehydrogenase(U/L, $\bar{x}\pm s$) | 265.12±34.25 | 255.86±29.11 | 1.286 | 0.201 |
| Albumin(g/L, $\bar{x}\pm s$) | 33.45±4.28 | 35.19±5.06 | 1.469 | 0.144 |
| β2 microglobulin(mg/L, $\bar{x}\pm s$) | 2.76±0.59 | 2.59±0.55 | 1.273 | 0.206 |
| B symptom[$n$(%)] | 12(57.14) | 45(44.55) | 1.107 | 0.293 |
| Simplified CGA stratification[$n$(%)] | | | 9.766 | 0.008 |
| Suitable chemotherapy | 15(71.43) | 93(92.08) | 5.407 | 0.020 |
| Unsuitable chemotherapy 1 | 5(23.81) | 8(7.92) | 3.092 | 0.079# |
| Unsuitable chemotherapy 2 + Fragility | 1(4.76) | 0(0.00) | - | 1.000* |
| IACA index[$n$(%)] | | | 18.222 | <0.001 |
| 0 point | 2(9.52) | 30(29.70) | 3.659 | 0.056 |
| 1-2 points | 13(61.90) | 68(67.33) | 0.229 | 0.632 |
| ≥3 points | 6(28.57) | 3(2.97) | 13.140 | <0.001# |
| Physical status ECOG score[$n$(%)] | | | 3.721 | 0.054 |
| 0-1 point | 7(33.33) | 57(56.44) | | |
| ≥2 points | 14(66.67) | 44(43.56) | | |
| Clinical staging[$n$(%)] | | | 6.221 | 0.013 |
| Ⅰ-Ⅱ | 6(28.57) | 59(58.42) | | |
| Ⅲ-Ⅳ | 15(71.43) | 42(41.58) | | |
| Pathological typing[$n$(%)] | | | 0.753 | 0.385 |
| Germinal center B cell type | 6(28.57) | 39(38.61) | | |
| Non-germinal center B cell type | 15(71.43) | 62(61.39) | | |
| Risk stratification[$n$(%)] | | | 3.093 | 0.079 |
| Low risk to low-middle risk | 5(23.81) | 45(44.55) | | |
| Middle-high risk to high risk | 16(76.19) | 56(55.45) | | |
| Chemotherapy regimen[$n$(%)] | | | 1.406 | 0.236# |
| R-CHOP21 | 14(66.67) | 82(81.19) | | |
| R-miniCHOP21 | 7(33.33) | 19(18.81) | | |
| Chemotherapy efficacy[$n$(%)] | | | 2.786 | 0.005 |
| Complete remission | 4(19.05) | 43(42.57) | | |
| Partial remission | 7(33.33) | 39(38.61) | | |
| Stable disease | 7(33.33) | 15(14.85) | | |
| Progression | 3(14.29) | 4(3.96) | | |

DLBCL: diffuse large B-cell lymphoma; MYC: myelocytomatosis oncogene; BCL2: B-cell lymphoma 2; CGA: comprehensive geriatric assessment; IACA: instrumental activities of daily living and age, Charlson comorbidity index, albumin; ECOG: Eastern Cooperative Oncology Group; R-CHOP21: rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone 21-day; R-miniCHOP21: rituximab and reduced dose CHOP21. -: no datum. * Fisher′s exact probability method; # continuous correction *Chi*-square test.

**表2 老年DLBCL患者预后不良的多因素logistic回归分析**

Table 2 Multivariate logistic regression analysis of poor prognosis in elderly DLBCL patients

| Factor | $\beta$ | *SE* | *Wald* $\chi^2$ | *P* value | *OR* | 95%*CI* |
|---|---|---|---|---|---|---|
| Simplified CGA stratification(suitable chemotherapy) | −1.212 | 0.365 | 11.026 | 0.001 | 0.298 | 0.009−0.627 |
| IACA index≥3 points | 1.451 | 0.413 | 12.360 | <0.001 | 4.272 | 2.482−7.351 |
| Clinical stage Ⅲ−Ⅳ | 1.269 | 0.389 | 10.642 | 0.001 | 3.557 | 1.969−6.426 |
| Chemotherapy efficacy(complete remission) | −1.036 | 0.344 | 9.070 | 0.003 | 0.355 | 0.011−0.793 |
| Constant | −4.221 | 1.288 | 10.740 | 0.001 | 0.015 | − |

DLBCL: diffuse large B-cell lymphoma; CGA: comprehensive geriatric assessment; IACA: instrumental activities of daily living and age, Charlson comorbidity index, albumin.

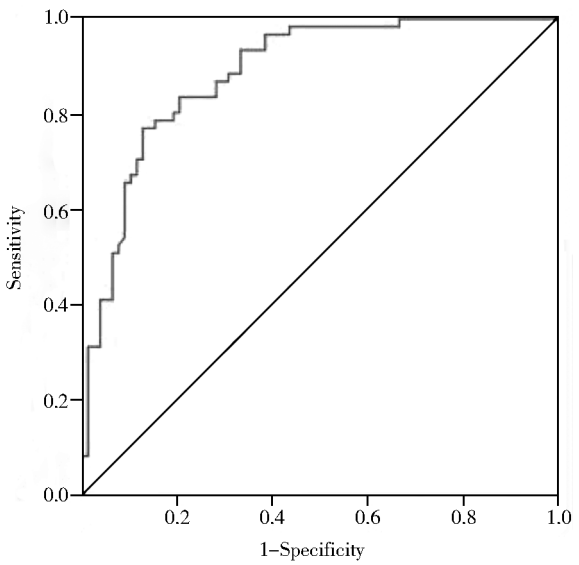



**图1 老年DLBCL患者预后不良预测模型的预测效能分析曲线**

Figure 1 Predictive efficiency curve of prediction model of poor prognosis in elderly DLBCL patients

DLBCL: diffuse large B-cell lymphoma.

据文献报道,Ki67及MYC、BCL2蛋白与淋巴瘤细胞增殖、凋亡等生物学行为相关,故其表达情况是影响DLBCL预后状况的重要因素[13]。然而,本研究中,1年预后不同的老年DLBCL患者肿瘤增殖抗原Ki67与MYC及BCL2表达情况并无显著差异,提示免疫组化分型可能对老年DLBCL近期预后影响较小,考虑与上述不良预后基因在老年DLBCL患者中阳性表达率均较高,且所有患者化疗方案均包含利妥昔单抗,削减了BCL2等蛋白异常表达对预后的不利影响有关[14];另一方面,本研究为单中心小样本量研究,结果可能存在偏倚,故病理免疫分型对老年DLBCL患者预后的影响还需后续多中心大样本量研究的验证。另外,预后不良者Ann Arbor临床分期为Ⅲ~Ⅳ期占比明显高于预后良好者,且其也是预后不良的独立危险因素,提示侵犯范围更广的老年DLBCL患者预后更差,与近年报道一致[15]。分析其原因为Ⅲ~Ⅳ期DLBCL侵袭能力强,短期进展快,预后死亡风险高。本研究初诊老年DLBCL患者均给予R-CHOP21或R-miniCHOP21化疗,预后良好者化疗疗效为完全缓解率更高,完全缓解也是预后不良的独立保护因素,提示初期化疗效果理想者预后死亡风险更低,可能与初期良好的化疗敏感性能避免DLBCL恶性进展、降低死亡率有关[16]。另外,初期化疗效果理想也能减少一线化疗疗程,或避免更换为二线化疗方案,减轻化疗相关毒副反应,有利于改善预后。

CGA是定量分析老年患者合并症、身体状态、营养等的综合评估体系,针对老年DLBCL,国内外机构及学者也提出多个CGA评估工具,简化CGA分层由FIL提出,被建议用于老年DLBCL患者治疗前的综合评估,对指导临床化疗具有重要意义[17]。本研究也发现,经简化CGA分层评估为适合化疗,是老年DLBCL患者预后不良的独立保护因素,提示该CGA工具对老年DLBCL近期预后评估价值高,适合在临床推广应用。IACA指数是将IADL量表与ACA量表结合,综合活动能力、年龄、营养及合并症评估,在预测老年患者是否适合标准化疗中具有积极意义,IACA指数≥3分提示患者身体脆弱,预后较差[18]。本研究结果显示,IACA指数≥3分是老年DLBCL患者预后不良的独立危险因素,提示IACA指数在预测患者近期死亡风险具有良好应用价值,≥3分者即便使用R-CHOP21或R-miniCHOP21化疗也可能难以带来生存获益。本研究基于多因素logistic回归分析结果构建预测模型 Y=−4.221+(−1.212)×简化CGA分层+1.451×IACA指数+1.269×临床分期+(−1.036)×化疗疗效,结合CGA评估、临床分期及疗效综合预测老年DLBCL患者近期预后,在验证集中具有良好预测价值,预测预后不良的灵敏度为72.73%,特异度为88.00%,可为临床诊疗提供指导意见。然而,本研究作为单中心回顾性研究,未对上述预测模型实施外部验证,代表性有所欠缺。且随访时间及收集的资料均有限,在研究结果的可靠

性上可能存在缺陷。未来还需延长随访时间，并联合其他医疗机构开展多中心大样本量研究，对本研究结果加以验证。

综上，简化 CGA 分层及 IACA 指数、临床分期、化疗疗效可能是影响初诊老年 DLBCL 患者近期预后的关键因素，结合 4 项指标的预测模型对预测患者 1 年死亡有积极意义，可指导临床诊疗。

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