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有核红细胞数在白血病患者危险度分层评估中的意义 *

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摘要 目的：探讨有核红细胞数(nucleated red blood cell count，NRBCs)在白血病患者危险度分层评估中的意义。**方法：**选择 2016 年 2 月到 2019 年 7 月在厦门大学附属成功医院(本院)诊治的急性髓系白血病(Acute myeloid leukemia，AML)患者 120 例，检测其 NRBCs 并进行危险度分层，回顾分析患者的临床资料并与其 NRBCs 进行相关性分析。**结果：**120 例患者中，危险度分层为低危 40 例，中危 60 例，高危 20 例。低危组和中高危组的患者年龄、性别、核仁磷酸蛋白(nucleophosmin，NPM1)突变、骨髓原始细胞等对比差异无统计学意义(P>0.05)，其外周血原始细胞、FMS 样酪氨酸激酶 -3(FMS-like tyrosinekinase 3，FLT3)突变、急性生理和慢性健康状况Ⅱ (acute physiology andchron ic health evaluationⅡ，APACHEⅡ) 评分、白细胞 (white blood cell，WBC)、血红蛋白(hemoglobin，Hb)、血小板(platelet，PLT)、白蛋白(albumin，ALB)与丙氨酸氨基转移酶(alanine aminotransferase，ALT)值等对比差异有统计学意义(P<0.05)。低危组的 NRBCs 为 3.94± 0.29 个，显著低于中高危组(11.87± 2.11 个，P=0.000)。Pearson 相关分析显示危险度分层与 NRBCs、外周血原始细胞、APACHEⅡ评分、FLT3 突变、PLT 有显著相关性(r=0.823、0.566、0.494、0.578、0.781，P<0.05)。logistic 回归分析显示 NRBCs、外周血原始细胞、APACHEⅡ评分、FLT3 突变、PLT 为影响急性髓系白血病患者危险度分层的主要因素(P<0.05)。**结论：**不同危险度分层的白血病患者的 NRBCs 具有显著差异，其与患者的病理特征显著相关，也是影响患者危险度分层的主要因素。

关键词：有核红细胞数；急性髓系白血病；危险度分层；外周血原始细胞
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Significance of Nucleated Red Blood Cell Count of in the Risk Stratified Assessment of Leukemia Patients*

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ABSTRACT Objective: To investigate the significance of stratified assessment of risk of nucleated red blood cell count (NRBCs) in leukemia patients. **Methods:** 120 patients with acute myeloid leukemia (AML) were enrolled in our hospital from February 2016 to July 2019, their NRBCs were detected and risk stratification were performed, and patients were retrospectively analyzed clinical data and correlation analysis with its NRBCs. **Results:** Among the 120 patients, the risk stratification were 40 patients at low-risk, 60 patients at intermediate-risk, and 20 patients at high-risk. There were no significant differences in age, gender, NPM1 mutation and bone marrow blasts compared between in the low-risk group and middle-high-risk group(P>0.05). Peripheral blood blasts, FLT3 mutation, APACHE II score, WBC, Hb, PLT, ALB and ALT values in the low-risk group and middle-high-risk group compared difference were statistically significant (P<0.05). The NRBCs in the low-risk group were 3.94± 0.29, which was significantly lower than that in the medium-high-risk group (11.87± 2.11, P=0.000). Pearson correlation analysis showed that risk stratification were significantly correlated with NRBCs, peripheral blood blasts, APACHE II score, FLT3 mutation, and PLT (r=0.823, 0.566, 0.494, 0.578, 0.781, P<0.05). Logistic regression analysis showed that NRBCs, peripheral blood blasts, APACHE II score, FLT3 mutation and PLT were the main factors affecting the risk stratification of patients with acute myeloid leukemia (P<0.05). **Conclusion:** There are significant differences in NRBCs between leukemia patients with different risk stratification, which are significantly related to the pathological characteristics of patients, and is also the main factor affecting the risk stratification of patients.

Key words: Nucleated red blood cell count; Acute myeloid leukemia; Risk stratification; Peripheral blood blast
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前言

急性髓系白血病(Acute myeloid leukemia，AML)是一类高度异质的恶性血液系统克隆性肿瘤，也是白血病的主要类型[1,2]。流行病学调查显示 65-70 岁为急性髓系白血病的高发年龄，且随年龄增长发病率逐渐上升[3]。采用客观指标准确地判断急性髓系白血病的危险度与预测患者死亡风险对临床上判断预后、指导治疗都具有重要意义[4,5]。

有核红细胞数(Nucleated red blood cell count，NRBCs)即未成熟的红细胞，是网织红细胞和成熟红细胞的前体细胞，很少出现在健康机体的外周血中[6]；外周血中出现 NRBCs 提示机体处于病理状态[7]。既往研究显示当人体患有溶血性贫血、白血病、骨髓纤维化、骨髓增生异常综合征等血液疾病时，外周血中 NRBCs 上升，而且这些患者的预后相对较差[8,9]。且红细胞在人体中以有核形式存在，NRBCs 可直接参与免疫复合物反应，对机体免疫发挥重要的作用[10,11]。本研究主要探讨了 NRBCs 在白血病患者中危险度分层评估中的意义，以期为急性髓系白血病的早期辅助诊断提供参考指标。

1 资料与方法

1.1 一般资料

本研究得到所有入选者的知情同意与本院伦理委员会的批准。选择 2016 年 2 月到 2019 年 7 月在本院诊治的急性髓系白血病患者 120 例，纳入标准：符合《成人急性髓系白血病(非急性早幼粒细胞白血病)中国诊疗指南》诊断标准；年龄 20-70 岁；临床调查资料完整。排除标准：急性全髓增殖症伴骨髓纤维化、急性早幼粒细胞白血病、髓系肉瘤；1 月内有化疗史；入院后未满 24 h 死亡者；临床资料不完整者；既往有慢性肾衰或血液病病史者。

1.2 NRBCs 检测

采集所有患者的外周静脉血 3 mL，置于含 10 %乙二胺四乙酸二钠 30 μL 的试管中，混匀后采用迈瑞 6800 全自动血细胞分析仪检测 NRBCs，计数时间均在血液采集后 1 h 内完成。同时记录所有患者的常规血液生化指标，包括 WBC、Hb、PLT、ALB 与 ALT 等值。

1.3 调查资料

调查所有患者的年龄、性别、骨髓原始细胞、外周血原始细胞、FLT3 基因突变、NPM1 突变、急性生理和慢性健康状况Ⅱ(APACHEⅡ)评分等基本资料，同时进行预后危险分层，包括低危与中高危。

1.4 统计学分析

采用 SPSS 21.0 软件进行数据分析，计数资料以(%)的形式表示，计量资料以($\bar{x}\pm s$)表示，组间对比分别采用卡方 x^2 分析与 t 检验，相关性分析采用 Pearson 相关分析与回归分析，以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 AML 患者的危险度分层情况

在 120 例 AML 患者中，危险度分层为低危 40 例 (低危组)，中危 60 例，高危 20 例，后两者归为中高危组。

2.2 低危组与中高危组的一般资料对比

低危组与中高危组的患者的年龄、性别、NPM1 突变、骨髓原始细胞等对比差异无统计学意义($P>0.05$)，而外周血原始细胞、FLT3 突变与 APACHEⅡ评分等对比差异有统计学意义($P<0.05$)。见表 1。

表 1 低危组与中高危组的一般资料对比

Table 1 Comparison of the general data between the low-risk group and the middle-high-risk group

Groups	n	Age (years)	Sex (Male / female)	NPM1 mutation (n)	Bone marrow primordial cells (%)	Peripheral blood (%)	FLT3 mutation (n)	APACHEⅡ score (score)
Low-risk group	40	45.56± 1.55	22/18	26 (65.0%)	52.22± 2.19	67.92± 3.11*	13 (32.5%)*	14.98± 1.34*
Middle and high risk group	80	45.01± 2.11	44/36	50(62.5%)	50.09± 1.42	22.19± 1.85	56 (70.0%)	25.92± 1.44

Note: Compared with middle and high risk group, *$P<0.05$.

2.3 低危组与中高危组的常规血液学指标对比

低危组的 WBC、Hb、PLT、ALB 与 ALT 值与中高危组对比差异有统计学意义($P<0.05$)，见表 2。

表 2 低危组与中高危组常规血液学指标对比(均数± 标准差)

Table 2 Comparison of the routine hematological indicators betweenthe low-risk group and the middle-high-risk group ($\bar{x}\pm s$)

Groups	n	WBC (× 10^9/L)	Hb (g/L)	PLT (× 10^9/L)	ALB (g/L)	ALT (U/L)
Low-risk group	40	10.93± 1.77*	8.42± 1.22*	124.09± 25.20*	30.44± 1.24*	48.76± 2.44*
Middle and high risk group	80	14.55± 2.14	9.89± 1.32	98.02± 15.92	27.09± 2.14	10.28± 16.03

2.4 低危组与中高危组的 NRBCs 对比

低危组的 NRBCs 为 3.94± 0.29 个，显著低于中高危组(11.87± 2.11 个，$P=0.000$)。

2.5 AML 患者危险度分层与临床指标的相关性分析

Pearson 相关分析显示 AML 患者的危险度分层与 NRBCs、外周血原始细胞、APACHEⅡ评分、FLT3 突变、PLT 显著相关(r=0.823、0.566、0.494、0.578、0.781，P<0.05)。logistic 回归分析显示 NRBCs、外周血原始细胞、APACHEⅡ评分、FLT3 突变、PLT 为影响急性髓系白血病患者危险度分层的主要因素(P<0.05)。见表 3 与表 4。

表 3 急性髓系白血病患者危险度分层与其他指标的相关性(n=120)

Table 3 Correlation between risk stratification and other indicators in patients with AML(n=120)

Index	NRBCs	Peripheral blood	APACHEⅡscore	FLT3 mutation	PLT
r	0.823	0.566	0.494	0.578	0.781
P	0.000	0.007	0.016	0.008	0.000

表 4 影响急性髓系白血病患者危险度分层的因素分析(n=120)

Table 4 AffectingFactors of risk stratification in patients with AML(n=120)

Index	β	SE	Wald x^2	OR	95%CI	P
NRBCs	3.023	0.654	11.321	2.212	1.654-8.123	0.000
Peripheral blood	2.234	0.643	17.721	1.875	1.323-10.345	0.000
APACHEⅡ score	2.134	0.555	11.123	2.116	1.214-12.565	0.000
FLT3 mutation	2.076	0.621	10.123	1.986	1.054-9.543	0.000
PLT	2.131	0.565	11.965	2.656	1.754-9.545	0.000

3 讨论

急性髓系白血病在临床上比较常见，多发于中老年人[12]，目前尚无统一的治疗标准，导致患者预后较差[13,14]。老年患者多存在脏器功能衰退、合并症增多及不良细胞遗传等原因，使得其生存期仅有 5-10 个月，2 年生存率不到 20 %[15,16]。因此，早期进行危险度分层对预测患者的预后具有重要价值。

外周血原始细胞、FLT3 突变与 APACHE Ⅱ评分都是客观、实用的评估病情严重程度并对预后作出预测的评分方法，都与白血病患者预计及实际病死率呈显著正相关 [17,18]。其中 APACHE Ⅱ评分分值越高，患者预后越差[19,20]。本研究显示低危组外周血原始细胞高于中高危组，FLT3 突变与 APACHEⅡ评分低于中高危组，说明外周血原始细胞、FLT3 突变与 APACHEⅡ评分能够评价白血病患者的不同危险度分层，有一定的临床指导意义。血常规参数的变化特征对白细胞的诊断鉴别有重要参考价值，尤其是高的 WBC 计数往往意味着白血病[21]，本研究结果显示低危组的 WBC、Hb、PLT、ALB 与 ALT 值与中高危组对比差异也都有统计学意义。说明 WBC、Hb、PLT、ALB 与 ALT 值可以评价白血病患者的不同危险度分层，其原因为白血病的病例机制是血液中未分化白细胞异常增多，分化异常的细胞类型或分化方向出现转变，可能为红细胞或 PLT，造成 PLT 数目下降，WBC 数目增多[22]。

NRBCs 作为未成熟红细胞，是机体造血系统一个特征性标记，健康儿童和成年人的血液中的数量很少，但常见于新生儿脐血及外周血中 [23]。而当成人的血液系统受损时，可导致 NRBCs 增加[24,25]。特别是在缺氧缺血的条件下，机体需要更多的血红蛋白参与携氧，为了满足红细胞的需求，反馈刺激造血系统加速红细胞的生成与释放，可导致 NRBCs 被大量释放到血液中[26]。本研究显示低危组的 NRBCs 显著低于中高危组，表明中高危急性髓系白血病患者伴随有外周血 NRBCs 增加。外周血中出现 NRBCs 与各种严重疾病密切相关，且随着 NRBCs 水平的增高，各种危重疾病患者的病死率也越高[26]。从机制上分析，组织缺氧时促使骨髓幼红细胞增生旺盛，由于炎症细胞激活使炎症介质异常大量释放、肠道屏障功能破坏，导致器官组织细胞广泛损伤，加速释放 NRBCs 进入血液循环[27,28]。当机体出现氧供和氧耗的失衡及氧利用障碍，可使 NRBCs 进一步加速释放[29,30]。Pearson 相关分析显示急性髓系白血病的危险度分层与 NRBCs、外周血原始细胞、APACHE Ⅱ评分、FLT3 突变、PLT 有显著相关性；logistic 回归分析显示 NRBCs、外周血原始细胞、APACHE Ⅱ评分、FLT3 突变、PLT 为影响急性髓系白血病患者危险度分层的主要因素。APACHE Ⅱ评分、FLT3 突变、PLT 异常可提示机体可能发生感染等，伴随着不同程度的电解质失衡、血液生化的改变，更易诱发患者脑出血或心肺功能不全，从而影响危险度分层[31,32]。FLT3 是潜在的白血病的原癌基因，FLT3 突变对正常血细胞增殖、分化产生破坏，影响 AML 进展[33,34]。

总之，不同危险度分层的白血病患者的 NRBCs 具有显著差异，其与患者的病理特征显著相关，也是影响患者危险度分层的主要因素。本研究也存在一定的不足，危险度分层还不够细化，没有对预后进行调查分析，将在后续研究中深入分析。

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