

骨 科 学

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膝关节骨关节炎外周血标志物变化的临床研究

王 猛, 陈敬东, 王佳蔚

(华中科技大学同济医学院附属武汉市中心医院新洲院区骨科, 武汉 431400)

【摘要】目的:探讨外周血清学指标在膝骨关节炎中的变化及诊断价值。**方法:**收集 2013 年 1 月至 2018 年 1 月就诊华中科技大学同济医学院附属武汉市中心医院新洲院区骨科的 228 例行全膝关节置换术(total knee arthroplasty, TKA)的膝骨关节炎患者(knee osteoarthritis, KOA)及 120 例健康体检志愿者的血清学指标检查资料。记录所有参与者的年龄、性别、血中性粒细胞百分比(neutrophil percentage, NEU%)、中性粒细胞计数、单核细胞计数、淋巴细胞计数、红细胞分布宽度(red blood cell distribution width, RDW-CV)、血清碱性磷酸酶(alkaline phosphatase, ALP)和血尿酸(uric acid, UA)等指标,计算中性粒细胞-淋巴细胞比率(neutrophil-lymphocyte ratio, NLR)、单核细胞-淋巴细胞比率(monocyte-lymphocyte ratio, MLR),并比较 2 组差异,绘制受试者操作工作曲线(receiver operating curve, ROC)确定诊断阈值。随访 TKA 术后 1 d、3 个月、6 个月及 1 年的膝关节 HSS 评分并与血 NLR、MLR 作相关性分析。**结果:**膝骨关节炎患者外周血 NLR、MLR 和 RDW-CV 明显高于健康体检志愿者($P<0.001$),且 ROC 曲线示 $NLR \geq 2.005$ 、 $MLR \geq 0.165$ 及 $RDW-CV \geq 12.45$ 为骨关节炎诊断阈值。术后仅有 26 例骨关节炎患者完成整个随访过程并发现随膝关节 HSS 评分的升高,外周血 NLR、MLR 逐渐降低,二者具有显著相关性。**结论:**膝骨关节炎患者外周血 NLR、MLR 及 RDW-CV 能够反映骨关节炎进程且 NLR、MLR 对预估 TKA 术后膝关节功能有参考价值。

【关键词】骨关节炎;血标志物;中性粒细胞淋巴细胞比率;单核细胞淋巴细胞比率;红细胞分布宽度

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Clinical study on changes of peripheral blood markers of knee osteoarthritis

Wang Meng, Chen Jingdong, Wang Jiawei

(Department of Orthopedics, Xinzhou Division, Wuhan Central Hospital, Tongji Medical College, Huazhong University of Science and Technology)

【Abstract】Objective: To study the changes and diagnostic value of peripheral serological indexes in knee osteoarthritis. **Methods:** A total of 228 patients with knee osteoarthritis (KOA) admitted to our hospital undergoing total knee arthroplasty (TKA) from January 2013 to January 2018 and 120 healthy volunteers were enrolled in this study. They were divided into KOA group and healthy control group. Demographic parameters, blood neutrophil percentage (NEU%), monocyte count, lymphocyte count, red blood cell distribution width (RDW-CV), serum alkaline phosphatase (ALP), and serum uric acid (UA) of all participants were recorded, and the neutrophil-lymphocyte ratio (NLR) and monocyte-lymphocyte ratio (MLR) were calculated and compared between the two groups. Then the receiver operating curve (ROC) was drawn to determine the diagnostic threshold. The HSS scores of knee joint at 1 day, 3 months, 6 months and 1 year after TKA were followed up, and the correlation between HSS scores and NLR and MLR was analyzed. **Results:** Elevated blood NLR, MLR and RDW-CV were apparent features in KOA patients compared with healthy individuals ($P<0.001$) and $NLR \geq 2.005$, $MLR \geq 0.165$ and $RDW-CV \geq 12.45$ were the diagnostic thresholds for KOA based on the ROC characteristics. These blood indicators of only 26 patients with KOA were followed up for one year after TKA, and the results indicated that NLR and MLR were gradually reduced with the improvement of knee joint HSS scores, with significant correlation. **Conclusion:** Our present results show that both NLR, MLR and RDW-CV are promising peripheral blood markers of KOA, and the NLR and MLR may be served as the serum markers to predict the prognosis of TKA.

【Key words】osteoarthritis; blood marker; neutrophil-lymphocyte ratio; monocyte-lymphocyte ratio; red blood cell distribution width

作者介绍: 王 猛, Email: wangmenghuake1975@163.com,

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骨关节炎是影响全球老年人健康最常见的慢性骨骼肌肉疾病,常出现关节软骨损伤、滑膜炎、软骨下骨硬及骨赘形成等典型病理变化^[1]。在过去几十年里,疼痛管理及外科手术干预一直是治疗骨关节炎的主要临床策略。尽管骨关节炎的病因并未完全阐释清楚,但肥胖、过量运动、关节损伤、基因遗传及代谢综合征已成为其高危因素^[2]。骨关节炎的本质是炎性反应,大量炎性因子如肿瘤坏死因子(tumor necrosis factor, TNF)- α 、白介素(interleukin, IL)-1 β , -8, -6, -10, -17, -18 和转化生长因子(transforming growth factor, TGF)- β 等在软骨中高表达^[4-5]。一些研究也证实了外周血中的中性粒细胞、单核细胞及淋巴细胞浸润等在关节局部机械损伤中发挥重要作用^[6-7]。

正因为骨关节炎与炎症的关系密切且目前已有证据表明外周血指标的变化在其发生发展中的作用越来越重要^[8-10]。因此,本研究系统全面地分析了外周血中性粒细胞百分比(neutrophil percentage, NEU%)、中性粒细胞计数、单核细胞计数、淋巴细胞计数、红细胞分布宽度(red blood cell distribution width, RDW-CV)、血清碱性磷酸酶(alkaline phosphatase, ALP)和血尿酸(uric acid, UA)在膝骨关节炎患者中的变化,并评估全膝关节置换术(total knee arthroplasty, TKA)后中性粒细胞-淋巴细胞比率(neutrophil-lymphocyte ratio, NLR)、单核细胞-淋巴细胞比率(monocyte-lymphocyte ratio, MLR)与膝关节功能恢复程度的相关性。

1 资料与方法

1.1 一般资料

收集华中科技大学同济医学院附属武汉市中心医院新

洲区骨科 2013 年 1 月至 2018 年 1 月就诊于关节外科行单侧 TKA 的骨关节炎患者 228 例,男性 51 例,女性 177 例,平均年龄(64.16 ± 8.19)岁;120 例健康体检志愿者,男性 23 例,女性 97 例,平均年龄(64.87 ± 7.03)岁;膝骨关节炎的诊断依据美国风湿病学会诊断标准^[11]。该研究经本院临床伦理部门批准后实施,所有参与者均自愿配合并已签署知情同意书(伦理批号:XZYY2019068)。

纳入标准:临床及影像学确诊膝骨关节炎;单侧 Kellgren-Lawrence(K-L)分级^[12]3~4 级的膝骨关节炎患者;初次行全膝关节置换术。

排除标准:合并强直性脊柱炎、类风湿关节炎或其他关节骨关节炎的患者;存在影响血细胞计数的炎症疾病,如肺炎、肾炎等;长期服用激素及肿瘤患者。

1.2 观察指标

记录 2 组参与者性别、年龄及膝骨关节炎患者术前外周血 NEU%、中性粒细胞计数、单核细胞计数、淋巴细胞计数、RDW-CV、ALP、UA 等指标,随访膝骨关节炎患者 TKA 术后 1 d、1 个月、3 个月、6 个月及 1 年血 NLR、MLR 与膝关节功能 HSS 评分^[13]。

1.3 统计学处理

应用 SPSS 17.0 软件进行统计学分析。计量资料用均数 $\pm$ 标准差($\bar{x} \pm s$)表示,服从正态分布的各类血细胞计数等计量资料的比较采用 t 检验。性别等计数资料比较采用卡方检验。统计学分析并绘制 NLR、MLR 及 RDW-CV 的 ROC 曲线,利用约登指数找出最佳的诊断阈值、敏感度、特异度、95% 可信区间及曲线下面积(area under the curve, AUC),并作随访期间血 NLR、MLR 与 HSS 评分的 Pearson 相关性分析。检验水准 $\alpha=0.05$ 。

2 结果

2.1 2 组参与者临床资料及外周血指标对比

膝骨关节炎患者与健康体检志愿者的性别、年龄、NEU%、ALP、UA 及淋巴细胞计数均服从正态分布,2 组间独立样本 t

表 1 膝骨关节炎患者与健康体检志愿者临床资料与外周血指标对比($\bar{x} \pm s; n$)

指标	骨关节炎($n=228$)	健康人($n=120$)	t/χ^2 值	P 值
年龄	64.16 ± 8.19	64.87 ± 7.03	-0.844	0.400
性别(男:女)	51:177	23:97	0.481	0.582
NEU%	57.85 ± 9.21	56.87 ± 8.95	0.956	0.340
NLR	2.08 ± 1.40	1.75 ± 0.61	3.093	0.002
MLR	0.20 ± 0.11	0.17 ± 0.60	4.182	<0.000 1
ALP	85.26 ± 25.37	83.28 ± 24.74	0.706	0.480
RDW-CV	13.17 ± 1.11	12.63 ± 0.87	4.606	<0.000 1
UA	311.25 ± 90.91	318.24 ± 81.86	-0.705	0.481
中性粒细胞计数/(10^9 个 $\cdot$ L $^{-1}$)	3.61 ± 1.86	3.12 ± 1.09	3.050	0.002
单核细胞计数/(10^9 个 $\cdot$ L $^{-1}$)	0.37 ± 0.18	0.30 ± 0.12	3.780	<0.0001
淋巴细胞计数/(10^9 个 $\cdot$ L $^{-1}$)	1.89 ± 0.56	1.84 ± 0.62	0.664	0.507

检验比较差异无统计学意义($P>0.05$),而膝骨关节炎患者的血中性粒细胞计数、单核细胞计数、NLR、MLR 和 RDW-CV 显著高于健康体检志愿者($P=0.02, <0.000 1, <0.000 1$)(表1)。

2.2 膝骨关节炎患者外周血指标 ROC 曲线绘制

通过统计分析绘制 NLR、MLR 及 RDW-CV 的 ROC 曲线,3 项指标的曲线下面积依次为 0.61、0.61 和 0.63,且 $NLR \geq 2.005$ 、 $MLR \geq 0.165$ 、 $RDW-CV \geq 12.45$ 诊断膝骨关节炎的灵敏度为 41.7%、63.6%和 80.7%,95%CI 为 0.55~0.67、0.55~0.67 和 0.57~0.70(图1、表2)。

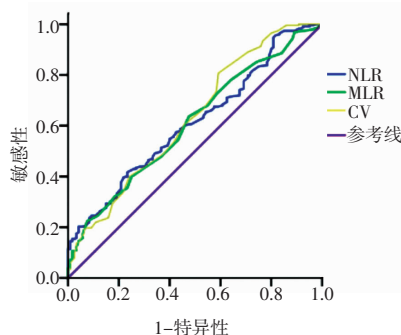


图1 NLR、MLR 及 RDW-CV 指标绘制 ROC 曲线

表2 ROC 曲线中 NLR、MLR 和 RDW-CV 的诊断阈值

指标	AUC	95%CI	诊断阈值	P值
NLR	0.612	0.551~0.672	2.005	0.001
MLR	0.608	0.547~0.669	0.165	0.001
RDW-CV	0.629	0.567~0.692	12.45	<0.000

2.3 TKA 术后血 NLR、MLR、RDW-CV 与膝关节功能 HSS 评分的关系

THA 术后仅有 26 例患者完成整个随访过程及采取血样,随访术后 1 d、1 个月、3 个月、6 个月及 1 年的 HSS 评分显示随膝关节功能的改善,外周血 NLR、MLR 随之下降,且 HSS 评分与膝骨关节炎血 NLR、MLR 的 Pearson 相关性分析具有统计学差异($P<0.05$)(图2、表3)。

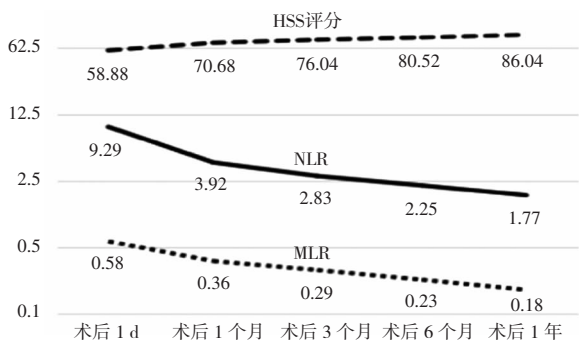


图2 26 例膝骨关节炎患者术后随访不同时间点 HSS 评分与血 NLR、MLR 的关系

表3 HSS 评分与 NLR、MLR 的 Pearson 相关性分析

指标	HSS评分与 NLR	HSS评分与 MLR
P 值	0.014	0.003

3 讨论

尽管膝骨关节炎的病理机制仍不清楚,但无论是在分子生物学还是细胞生物学方面其病理变化都在不断被揭示。目前,关于风湿免疫疾病的多项研究中已经报道血中性粒细胞-淋巴细胞比率升高能有效反映疾病活动性^[14-17],但此项指标的变化在膝骨关节炎中的水平尚不可知。一般认为血中性粒细胞计数与慢性炎症反应产生的促炎细胞因子、趋化因子和蛋白水解酶密切相关^[18-20]。且用胶原酶诱导的膝骨关节炎模型也显示嗜中性粒细胞浸润滑膜并释放 IL-1、IL-8 和金属基质蛋白酶破坏软骨^[21-22]。本研究也发现膝骨关节炎患者中血 NLR 水平明显高于健康人,这与 Tasoğlu Ö 等^[23]对 179 例膝骨关节炎患者血清学检测后发现 NLR 升高的结论一致。在某种程度上,这些结果也反映了膝骨关节炎与慢性炎症密不可分,同时骨免疫学的不断发展也逐渐证实了这一点^[24]。

单核细胞通过血液循环进入组织器官可进一步分化为巨噬细胞参与机体免疫应答反应,其数量变化通常作为某些肿瘤和炎症性疾病发展过程中的血液学指标^[25-27]。骨关节炎中关节软骨损伤后释放的促炎性细胞因子会激活巨噬细胞释放 IL、TNF 及血管内皮生长因子(vascular endothelial growth factor, VEGF)等在循环中被募集^[28]。最近的一项研究证实,单核细胞增多可提高 TNF- α 和 IL-8 的分泌水平,而单核细胞的衰老与年龄相关疾病的关系密切^[29]。Loukov D 等^[30]研究发现,单核细胞的募集有可能成为骨关节炎新的治疗靶点。本研究发现,膝骨关节炎患者外周血中性粒细胞及单核细胞计数的增加是 NLR、MLR 升高的根本原因,且 ROC 分析表明, $NLR \geq 2.005$ 、 $MLR \geq 0.165$ 被认为是膝骨关节炎可能的诊断阈值。因此,笔者测定膝骨关节炎中血 NLR 和 MLR 水平并将二者水平纳入术后对 TKA 后关节功能的评估,发现随着膝关节功能的改善,膝骨关节炎患者血 NLR 和 MLR 的下降趋势表明炎症活动的降低和抑炎因子的释放。这很有可能证明了随术后炎症的减轻,膝关节功能逐渐恢复,但其具体机制可能需要进一步探讨及更大的样本量佐证。

有报道称,红细胞分布宽度在一些炎症性疾病

中出现增高的趋势^[31]。并且,抗炎治疗后红细胞分布宽度会与反应炎性活动的血细胞沉降率、C 反应蛋白同时降低^[32]。Rong R 等^[33]发现细胞因子(如 IL-1、TNF- α 等)在炎症反应中可能会通过影响铁代谢并抑制促红细胞生成素的产生而导致红细胞大小不均,阻碍红细胞成熟。但目前膝关节炎与血细胞分布宽度之间的关系研究甚少,本研究数据显示膝关节炎患者血细胞分布宽度明显升高,与正常人相比有显著差异,这与类风湿性关节炎的表现相似^[34],提示它可能作为诊断膝关节炎潜在的外周血指标。本研究同样发现,当血细胞分布宽度 ≥ 12.45 时诊断膝关节炎的敏感度达 80.7%。然而,对于血碱性磷酸酶的测定,Fazelipour S 等^[35]研究表明局部炎性环境中碱性磷酸酶的活性与关节软骨厚度相关,碱性磷酸酶的升高可降低软骨细胞的炎性反应。但 Kim H 等^[36]在对 64 例强直性脊柱炎患者的 3 年随访中并未发现外周血碱性磷酸酶的临床意义。同样,本研究也未发现膝关节炎患者与正常人外周血碱性磷酸酶的差异。最后,骨关节炎中尿酸水平的升高在一些研究中被认为是由于 NLRP3 炎性小体的激活产生级联反应释放多种炎性因子来加速骨关节炎的进展^[37]。在一项调查中对 69 例膝关节炎患者血清与滑液尿酸水平比较发现前者升高更明显^[38]。尿酸水平还关系到关节间隙的狭窄程度和炎性小体活性的判断^[39]。但在本研究中,膝关节炎患者外周血尿酸水平与正常人并无统计学差异,这可能需要在下一步研究中采集更大样本的血样并联合关节滑液尿酸水平进行联合评估。

本研究存在一定的局限性。首先,本研究为单中心研究,横断面样本较少,结果相对保守。同时,很少有患者对 TKA 后进行常规血液检查以致数据较少代表性不强。其次,结合 NLR、MLR 和 RDW-CV 三项指标可能对膝关节炎的预测和诊断更有帮助。再次,对膝关节炎患者外周血指标变化的研究相对较少,本研究的数据仅代表目前采集的血液样本的特征,详细的机制仍然需要进一步探索。

综上所述,外周血 NLR、MLR 和 RDW-CV 的升高可作为膝关节炎的辅助诊断指标。尽管随访的样本量较少,但从本研究结果来看血 NLR、MLR 水平与 TKA 术后膝关节功能恢复紧密相关。

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