doi: 10.13241/j.cnki.pmb.2020.08.017

血小板/淋巴细胞比值在老年2型糖尿病患者肾功能损害及病情评估中的应用价值*

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摘要 目的:研究血小板/淋巴细胞比值(PLR)在老年2型糖尿病(T2DM)患者肾功能损害及病情评估中的应用价值。**方法:**测定506例T2DM患者及250例健康体检者(对照组)的血常规、血糖、血脂、肝肾功等生化指标,并收集尿液测定尿白蛋白/肌酐比值(ACR)。根据《糖尿病肾病防治专家共识(2014年版)》,将T2DM患者分为DN组(n=279)和非DN组(n=227),并根据ACR将DN组分为微量白蛋白尿组(n=165,30~300 mg/24 h)、大量白蛋白尿组(n=114,≥ 300 mg/24 h)。比较各组患者临床指标,分析PLR与老年T2DM患者并发DN的相关性。**结果:**与对照组比较,非DN组、DN组HbAlc、FPG、2h PG、Scr、BUN、PLT、PLR明显升高,LYM明显下降(P<0.05);与非DN组比较,微量白蛋白尿组HbAlc、2h PG、Scr、UAER、eGFR明显升高,大量白蛋白尿组HbAlc、FPG、2h PG、Scr、BUN、UAER、eGFR、PLT、PLR明显升高,LYM明显下降(P<0.05);与微量白蛋白尿组,大量白蛋白尿组FPG、Scr、BUN、UAER、eGFR、PLT、PLR明显升高,LYM明显下降(P<0.05)。多因素logistics回归分析显示HbAlc、PLR是T2DM患者进展为DN的独立危险因素,而eGFR则是保护性因素(P<0.05)。HbAlc、eGFR、PLR联合预测T2DM患者并发DN的敏感性、特异性分别为83.1%,特异度为81.9%,均显著高于三个指标单独评估的敏感性、特异性(P<0.05)。**结论:**PLR是老年T2DM患者肾功能损害的独立危险因素,综合HbAlc、eGFR、PLR有助于老年T2DM患者并发DN及病情评估。

关键词:血小板/淋巴细胞比值;老年;2型糖尿病;肾功能损害

中图分类号:R587.2 **文献标识码:**A **文章编号:**1673-6273(2020)08-1481-04

Evaluation Value of Platelet to Lymphocyte Ratio for Renal Impairment and State of Disease in Elderly Patients with Type 2 Diabetes Mellitus*

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ABSTRACT Objective: To explore the evaluation value of platelet to lymphocyte ratio (PLR) for renal impairment and state of disease in elderly patients with type 2 diabetes mellitus (T2DM). **Methods:** Blood routine, blood glucose, blood lipids, liver and kidney function and other biochemical indexes were determined in 506 T2DM patients and 250 healthy subjects (control group), and urine was collected for the determination of urinary albumin/creatinine ratio (ACR). According to expert consensus on prevention and treatment of diabetic nephropathy (2014 edition), T2DM patients were divided into DN group (n=279) and non-DN group (n=227), and DN group was furtherly divided into micro albuminuria group (n=165, 30-300 mg/24 h) and massive albuminuria group (n=114, 300 mg/24 h) according to ACR. Clinical indicators of each group were compared to analyze the influence of PLR on DN in elderly T2DM patients. **Results:** Compared with control group, HbAlc, FPG, 2 h PG, Scr, BUN, PLT and PLR were significantly increased and LYM was significantly decreased in the non-DN group and the DN group (P<0.05). Compared with the non-DN group, HbAlc, 2 h PG, Scr, UAER and eGFR were significantly increased in the microalbuminuria group, while HbAlc, FPG, 2h PG, Scr, BUN, UAER, eGFR, PLT and PLR were significantly increased and LYM was significantly decreased in the massive albuminuria group (P<0.05). Compared with the microalbuminuria group, FPG, Scr, BUN, UAER, eGFR, PLT and PLR were significantly increased and LYM was significantly

* 基金项目:上海市科学技术委员会科研项目(10411956600)

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(收稿日期:2019-07-23 接受日期:2019-08-19)

decreased in the massive albuminuria group (P<0.05). Multiple logistics regression analysis showed that HbAlc and PLR were independent risk factors for DN in T2DM patients, while eGFR was a protective factor (P<0.05). The sensitivity and specificity of combined detection of HbAlc, eGFR and PLR to predict DN in T2DM patients were 83.1% and 81.9%, respectively, which were significantly higher than separate detection (P<0.05). **Conclusions:** PLR is an independent risk factor for renal impairment in elderly T2DM patients, and the combination of HbAlc, eGFR and PLR is helpful for DN and disease evaluation in elderly T2DM patients.

Key words: Platelet to lymphocyte ratio; Elderly; Type 2 diabetes mellitus; Renal impairment

Chinese Library Classification(CLC): R587.2 Document code: A

Article ID: 1673-6273(2020)08-1481-04

前言

糖尿病肾病(DN)是 2 型糖尿病(T2DM)的一种严重微血管并发症，也是导致终末肾脏疾病(ESRD)的首位病因，具有较高的致残率、致死率[1,2]。DN 的发病机制较为复杂，缺乏特殊有效的治疗方法，越来越多的研究显示炎症反应参与了 DN 的发生、进展[3]。由于 DN 早期病情呈可逆性，故早期诊断、准确评估、及时干预，对于改善 DN 患者的预后至关重要。

目前，临床监测肾功能损害的指标多依赖尿微量白蛋白、肾小球滤过率等，但其对于 DN 所致肾功能损害仍缺乏足够的灵敏度和特异性 [4]。近年来研究表明血小板与淋巴细胞比值(PLR)作为一种非特异炎症指标，与多种慢性炎性、自身免疫性疾病等密切相关，可用于糖尿病、恶性肿瘤的诊断及预后评估[5-7]，但其对老年 DN 患者微血管并发症及的预测价值仍鲜有报道。本研究主要探讨了老年 T2DM 患者 PLR 变化，及其对肾功能损害及病情评估的应用价值。

1 资料与方法

1.1 一般资料

回顾性分析 2017 年 1 月 ~2018 年 6 月我院收治的老年 T2DM 患者 506 例，包括男 308 例，女 198 例，年龄 60~82 (69.4± 3.5)岁；病程 3~21(8.1± 2.7)年。入组标准：① 符合 2010 年美国糖尿病协会(ADA)制定的 T2DM 诊断标准[8]；② 年龄≥ 60 岁，临床病历资料完整；③ 排除合并原发性肾小球疾病、心脑血管、凝血功能异常、免疫性疾病或其他病因所致肾功能损害者。另选择本院同期健康体检者(肝肾功能及其他生化指标均在正常范围、无糖尿病病史)250 例作为对照组，包括男 175 例，女 75 例；年龄 60~80 岁(58.9± 5.8)岁。两组研究对象年龄、性别构成比等比较差异均无统计学意义(P>0.05)。本研究均符合《赫尔辛基宣言》，患者或家属均签署知情同意书。

1.2 方法

1.2.1 DN 诊断标准及分组 参照《糖尿病肾病防治专家共识(2014 年版)》[9]的 DN 诊断标准，将 T2DM 患者分为 DN 组(n=279)和非 DN 组(n=227)，并以 ACR 作为 DN 病情程度的评价标准，将 DN 组进一步分为微量白蛋白尿组(n=165，30~300 mg/24h)、大量白蛋白尿组(n=114，≥ 300 mg/24 h)。

1.2.2 生化指标检测 患者入院后采集晨尿标本 2 次并测定尿白蛋白 / 肌酐比值(ACR)，取其平均值作为最终 ACR 值。抽取入院时对照组、DN 组、非 DN 组空腹肘部静脉血 5 mL，置于肝素抗凝管中，3 000 r/min 离心 (离心半径为 10 cm)10-15 min 后，保留上层清液用于检测。采用日立公司生产的 7080 型全自动生化分析仪检测空腹血糖(FPG)、餐后 2 小时血糖(2h PG)、糖化血红蛋白(HbAlc)、血肌酐(Scr)、尿素氮(BUN)、甘油三酯(TG)、低密度脂蛋白 (LDL-C)、总胆固醇 (TC)、谷丙转氨酶(ALT)、谷草转氨酶(AST)，并利用 MDRD 公式计算出肾小球滤过率(eGFR)；采用日本 SYSMEX 公司生产的 KX-21 型血细胞分析仪进行血常规检测，记录血液中血小板、淋巴细胞绝对数，PLR 通过公式计算 =PLT/LYM。

1.3 统计学方法

采用 SPSS 18.0 版统计软件包。计数比较采用 χ^2 检验，计量资料以($\bar{x}\pm s$)表示，组间比较采用单因素方差分析，两两比较采用 LSD-t 检验，采用多因素分析患者并发 DN 的影响因素，并分别计算受试者工作特征曲线(ROC)面积。以 P<0.05 表示差异有统计学意义。

2 结果

2.1 各组生化指标比较

与对照组比较，非 DN 组、DN 组 HbAlc、FPG、2h PG、Scr、BUN、PLT、PLR 明显升高，LYM 明显下降，差异有统计学意义(P<0.05)；与非 DN 组比较，微量白蛋白尿组 HbAlc、2h PG、Scr、UAER、eGFR 明显升高，大量白蛋白尿组 HbAlc、FPG、2h PG、Scr、BUN、UAER、eGFR、PLT、PLR 明显升高，LYM 明显下降，差异有统计学意义(P<0.05)；与微量白蛋白尿组，大量白蛋白尿组 FPG、Scr、BUN、UAER、eGFR、PLT、PLR 明显升高，LYM 明显下降，差异有统计学意义(P<0.05)。见表 1。

2.2 T2DM 患者合并 DN 的多因素回归分析

以 T2DM 患者是否合并 DN 为因变量，将上述单因素分析有意义的 10 个变量纳入多因素 logistics 回归分析，结果显示 HbAlc、PLR 是 T2DM 患者进展为 DN 的独立危险因素，而 eGFR 则是保护性因素(P<0.05)，见表 2。

2.3 各指标对老年 T2DM 患者并发 DN 的预测价值

对 HbAlc、eGFR、PLR 进行 ROC 曲线分析，结果显示 A-PACHE II 评分、Lac、PLR 联合预测老年 T2DM 患者并发 DN 的 AUC 为 0.804[95% CI：0.731~0.853)]，此时 PLR 最佳 cut-off 值为 117.6，灵敏度为 83.1%，特异度为 81.9%，均显著高于三个指标的单独预测结果(P<0.05)，见图 1。

3 讨论

DN 发病早期由于临床症状较为隐匿，易被忽视并进展为不可逆转的 ESRD，故早期诊断尤为重要[10]。研究表明慢性持续性的免疫炎症在 T2DM 整个疾病演变过程中扮演着重要角色，高血糖状态、肾小球血流动力学紊乱、糖基化终产物及肾脏

表 1 各组生化指标比较($\bar{x}\pm s$)

Table 1 Comparison of biochemical indexes of each group($\bar{x}\pm s$)

Index	Control group (n=250)	Non DN group (n=227)	DN group		F	*P*
			Micro albuminuria group(n=165)	Massive albuminuria group(n=114)		
HbAlc(%)	4.25± 0.59	7.65± 1.48[a]	10.55± 1.54[ab]	11.57± 2.55[ab]	19.64	<0.001
FPG(mmol/L)	4.94± 1.57	5.61± 1.37[a]	6.79± 1.24[a]	9.70± 2.56[abc]	71.21	<0.001
2h PG(mmol/L)	6.26± 1.29	11.73± 3.86[a]	15.41± 3.54[ab]	15.77± 3.86[ab]	59.64	<0.001
Scr(μmol/L)	50.84± 10.87	71.87± 13.64[a]	91.27± 18.16[ab]	315.18± 138.54[abc]	95.11	<0.001
BUN(mmol/L)	5.37± 0.50	8.66± 0.86[a]	8.91± 1.17[a]	15.48± 4.05[abc]	61.04	<0.001
UAER(μg/min)	3.12± 1.65	11.75± 4.73[a]	76.18± 43.77[ab]	508.95± 108.93[abc]	1267.2	<0.001
TG(mmol/L)	3.16± 1.57	3.31± 1.45	3.46± 1.48	3.49± 1.55	0.91	0.405
LDL-C(mmol/L)	3.18± 1.29	4.28± 1.49	4.46± 1.56	4.67± 1.85	1.11	0.257
TC(mmol/L)	4.93± 1.30	5.16± 1.57	5.25± 1.74	5.41± 1.64	1.02	0.286
eGFR(ml/min)	101.23± 21.87	103.24± 34.16	87.16± 36.16[ab]	45.13± 13.16[abc]	45.62	<0.001
AST(U/L)	23.28± 4.18	24.08± 4.27	25.76± 4.25	25.97± 5.17	0.93	0.399
ALT(U/L)	21.33± 4.84	23.26± 4.38	22.88± 4.21	25.95± 5.25	1.26	0.306
PLT(10^9/L)	181.43± 43.48	213.66± 54.42[a]	219.26± 50.87[a]	238.47± 47.93[abc]	42.67	<0.001
LYM(10^9/L)	2.23± 0.65	2.09± 0.56[a]	2.02± 0.62[a]	1.82± 0.77[abc]	16.59	0.001
PLR	95.75± 24.72	107.54± 20.84[a]	112.43± 24.48[a]	131.83± 26.81[abc]	62.96	<0.001

注:与对照组比较,[a]*P*<0.05;与非 DN 组比较,[b]*P*<0.05;与微量白蛋白尿组比较,[c]*P*<0.05。

Note: Compared with control group,[a]*P*<0.05. Compared with non-DN group, [b]*P*<0.05. Compared with microalbuminuria group, [c]*P*<0.05.

表 2 T2DM 患者合并 DN 的多因素 logistic 回归分析

Table 2 Multivariate logistic regression analysis of DN in patients with T2DM

Index	β value	SE value	Wald value	ORvalue	OR(95%CI)	*P*
HbAlc	0.180	0.218	9.701	1.97	1.29~2.98	0.003
eGFR	-1.49	0.514	8.146	0.23	0.08~0.61	0.004
PLR	0.142	0.423	7.769	3.25	1.88~4.61	0.000

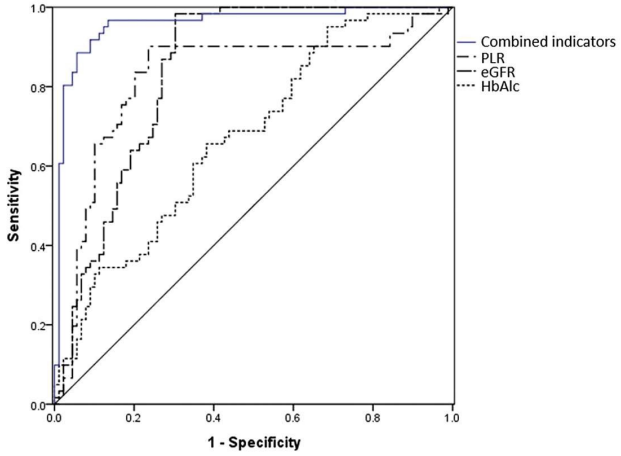

图 1 各指标诊断 T2DM 患者并发 DN 的 ROC 曲线

Fig. 1 ROC curves of all indexes for DN complicated with T2DM patients

局部肾素 - 血管紧张素系统激活等均可诱导激活肾脏固有细胞内多种炎症信号通路,进而产生各种炎症介质,引发或加重间质纤维化、足细胞凋亡、肾小球硬化等病理过程,导致 Scr、BUN 升高,eGFR 降低等肾功能损害表现[11-13],本研究也得到相似结论。血常规检测常用于反映感染与炎症状态,但由于项目较多,单纯凭借个别项目的判断可能造成误判 [14,15]。近年来,PLT、LYM 及中性粒细胞等部分 " 次要 " 指标愈发引起关注,研究发现上述指标变化可一定程度上反映机体感染状态下血细胞有形成分消耗、生成的变化,有助于提高血常规在炎症性疾病中的诊断价值[16,17]。

近年来研究表明 PLR 与 T2DM 患者微血管并发症的发生及预后相关[18-21]。血小板源自成熟巨核细胞的细胞质,通过介导免疫细胞和内皮细胞之间的相互作用,间接调节淋巴细胞功能,释放促炎症介质。机体炎症状态下,血小板细胞增殖增加,而免疫功能抑制,淋巴细胞凋亡增加,PLR 能够更好体现促炎与抗炎反应的平衡,其意义优于单纯的细胞亚型计数[22-24]。既往研究显示 PLR 在早期 T2DM 患者中呈下降趋势,而随着病程的进展,PLR 逐渐升高 [25]。本研究结合 ACR 进行 DN 病情分级,结果显示 T2DM 患者 PLT、LYM 及 PLR 均于正常人群有明显差异,DN 组和微量白蛋白尿组 PLT、LYM 无明显差异,但随着肾功能损害的病情加重,PLR 明显升高,说明 PLR 可较 PLT、LYM 更敏感反映老年 T2DM 患者肾功能损害及病情的

严重程度[26,27]。Hudzik 等[28]研究结果显示 PLR 越高，老年 T2DM 患者的住院期间死亡率、1 年内死亡率亦相应增高，表明 PLR 可作为 T2DM 患者病情及预后的预测指标。

进一步分析结果显示 PLR 是影响老年 T2DM 患者肾功能损害的独立危险因素，ROC 曲线分析显示 HbAlc、eGFR、PLR 联合预测对于老年 T2DM 患者并发 DN 具有更高的灵敏度、特异度，其预测效能高于三个指标的单独预测，可见 PLR 虽能较好反映老年 T2DM 患者的病情进展及 DN 发生，但仍无法完全代替 HbAlc、eGFR 等传统指标，PLR 联合 eGFR、HbAlc 等指标能更加全面综合分析病情变化，有助于早期预测肾功能损害，以便于及时调整治疗策略，更好地改善预后。PLR 是 2 种血常规项目的综合反映，比单一项目更加稳定，可克服标本处理过程多种因素对血液样本的干扰，同时规避应激因素对白细胞各亚型绝对值的影响[29]。此外，多因素回归结果还发现 HbAlc、eGFR 与 DN 存在相关性，其可能原因在于长期低度的慢性炎症反应，导致氧化应激增加、血管损伤及内皮功能紊乱，主要累及肾脏及视网膜等微血管[30]。

综上所述，PLR 是老年 T2DM 患者肾功能损害的独立危险因素，其简单易行、可重复性强，尤其适用于基层医院。综合 HbAlc、eGFR、PLR 有助于老年 T2DM 患者并发 DN 及病情评估，从而指导临床决策。但本研究为回顾性分析，下一步将扩大样本进行前瞻性研究，深入探讨治疗前后 PLR 的变化及其对老年 T2DM 患者预后的评估价值。

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