

糖尿病足患者血清 PIGF, TREM1 水平检测与临床分级和预后的相关性分析

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摘要:目的 探究糖尿病足患者血清胎盘生长因子 (PIGF)、髓系细胞表达触发受体 1 (TREM1) 水平及二者与患者临床分级和预后的相关性。方法 收集 2021 年 1 月~2023 年 1 月桂林医学院附属医院收治的 97 例糖尿病足患者作为研究对象 (糖尿病足组), 另选取同期在该院体检的 102 例健康者作为健康对照组; 糖尿病足患者按照 Wanger 分级标准分为 0~1 级 ($n=33$)、2~3 级 ($n=39$) 和 4~5 级 ($n=25$); 糖尿病足患者进行 6 个月随访, 将其分为预后良好组 ($n=72$) 和预后不良组 ($n=25$); 比较各组血清 PIGF, TREM1 水平; 采用 Spearman 相关分析血清 PIGF, TREM1 水平与患者临床分级的相关性; Logistic 回归分析糖尿病足患者预后的影响因素; 采用受试者工作特征 (ROC) 曲线分析血清 PIGF, TREM1 对糖尿病足患者预后情况的预测效能。结果 糖尿病足组患者血清 PIGF 水平显著低于健康对照组 (53.86 ± 15.13 pg/ml vs 87.57 ± 18.28 pg/ml), TREM1 水平显著高于健康对照组 (279.56 ± 32.25 ng/L vs 195.37 ± 26.28 ng/L), 差异具有统计学意义 ($t=14.133, 20.232$, 均 $P < 0.05$); 临床分级为 4~5 级患者血清 PIGF 表达低于 0~1 级、2~3 级患者 (39.41 ± 13.28 pg/ml vs 66.13 ± 16.30 pg/ml, 52.75 ± 15.32 pg/ml), TREM1 表达高于 0~1 级、2~3 级患者 (326.66 ± 35.75 ng/L vs 248.21 ± 29.83 ng/L, 275.89 ± 32.06 ng/L), 临床分级为 2~3 级患者血清 PIGF 表达低于 0~1 级患者, TREM1 表达高于 0~1 级患者, 差异具有统计学意义 ($q=4.852 \sim 12.945$, 均 $P < 0.05$)。Spearman 相关性分析, 糖尿病足患者血清 PIGF 水平与其临床分级呈现负相关 ($r=-0.696, P < 0.001$), TREM1 水平与其临床分级呈现正相关 ($r=0.657, P < 0.001$)。多因素 Logistic 回归分析, PIGF 是影响糖尿病足患者预后的独立保护因素 [OR (95%CI): 0.725 (0.531 ~ 0.990)], TREM1 是独立危险因素 [OR (95%CI): 2.308 (1.284 ~ 4.147)]; PIGF, TREM1 水平和二者联合预测糖尿病足患者预后情况的 AUC (95%CI) 分别为 0.898 (0.820 ~ 0.950), 0.817 (0.725 ~ 0.888) 和 0.949 (0.885 ~ 0.984), 二者联合预测临床效能优于血清 PIGF, TREM1 单独预测 ($Z=2.150, 2.713, P=0.032, 0.007$)。结论 糖尿病足患者血清 PIGF 表达降低, TREM1 表达升高, 二者与患者临床分级紧密相关, 应用二者预测患者预后情况具有较好的临床效能。

关键词: 糖尿病足病; 胎盘生长因子; 髓系细胞表达触发受体 1

中图分类号: R587.2; R392.11 文献标志码: A 文章编号: 1671-7414 (2025) 01-163-06

doi:10.3969/j.issn.1671-7414.2025.01.031

Correlation Analysis of Serum PIGF, TREM1 Levels with Clinical Grading and Prognosis in Patients with Diabetes Foot

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Abstract: Objective To explore the serum placental growth factor (PIGF) and triggering receptors expressed on myeloid cell-1 (TREM1) levels in patients with diabetes foot, and the correlation between them and clinical grading and prognosis of patients. **Methods** From January 2021 to January 2023, 97 patients with diabetes foot who were admitted to Affiliated Hospital of Guilin Medical University were collected as the study object (diabetes foot group), and 102 healthy people who were examined in the hospital were collected as the healthy control group. The patients with diabetic foot were categorized into 33 cases of grade 0~1, 39 cases of grade 2~3, and 25 cases of grade 4~5 according to Wanger grading criteria. Patients with diabetes foot were followed up for 6 months and divided into good prognosis group ($n=72$) and poor prognosis group ($n=25$). Serum PIGF and TREM1 levels were compared between groups. Spearman correlation analysis was applied to explore the correlation between serum PIGF and TREM1 levels and clinical grading in patients, factors influencing the prognosis of patients with diabetic foot was analyzed by Logistic regression. Receiver operating characteristic (ROC) curve was applied to investigate the predictive effect

基金项目: 玉林市科学研究与技术开发计划 (玉市科 20201606)。

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of serum PIGF and TREM1 on the prognosis of patients with diabetes foot. **Results** The expression level of serum PIGF in the diabetes foot group was lower than that in the healthy control group (53.86 ± 15.13 pg/ml vs 87.57 ± 18.28 pg/ml), and the level of TREM1 was significantly higher than that in the healthy control group (279.56 ± 32.25 ng/L vs 195.37 ± 26.28 ng/L), and the difference was statistically significance ($t=14.133, 20.232$, all $P<0.05$). Serum PIGF expression (39.41 ± 13.28 pg/ml vs 66.13 ± 16.30 pg/ml, 52.75 ± 15.32 pg/ml) was lower in patients with clinical grades 4 ~ 5 than in patients with grades 0 ~ 1 and 2 ~ 3. TREM1 expression (326.66 ± 35.75 ng/L vs 248.21 ± 29.83 ng/L, 275.89 ± 32.06 ng/L) was higher than in patients with grades 0 ~ 1 and 2 ~ 3. Serum PIGF expression was lower in patients with clinical grades 2 ~ 3 than in patients with grades 0 ~ 1. TREM1 expression was higher than in patients with grades 0 ~ 1, and the differences were statistically significant ($q=5.120 \sim 12.945$, all $P<0.05$). Spearman correlation analysis, the serum PIGF expression level in diabetes foot patients was negatively correlated with their clinical grading ($r=-0.696, P<0.001$) and the TREM1 expression level was positively correlated with their clinical grading ($r=0.657, P<0.001$). Multivariate Logistic regression analysis, PIGF was an independent protective factor [OR(95%CI): 0.725(0.531 ~ 0.990)] and TREM1 was an independent risk factor [OR(95%CI): 2.308(1.284 ~ 4.147)] affecting the prognosis of diabetic foot patients. The AUC(95%CI) of PIGF, TREM1 levels and their combination to predict the prognosis of diabetes foot patients was 0.898 (0.820 ~ 0.950), 0.817 (0.725 ~ 0.888) and 0.949 (0.885 ~ 0.984), respectively. The clinical efficacy of the combination of the two in predicting the poor prognosis of patients with diabetes foot was better than that of serum PIGF and TREM1 alone ($Z=2.150, 2.713, P=0.032, 0.007$). **Conclusion** The expression of PIGF in serum of patients with diabetes foot is significantly reduced, and the expression of TREM1 is significantly increased. Both of them are closely related to the clinical grading of patients, and they have good clinical efficacy in predicting prognosis.

Keywords: diabetes foot; placental growth factor; triggering receptors expressed on myeloid cells-1

糖尿病足病是全球非创伤性下肢截肢的主要原因^[1], 糖尿病足病可能会造成患者截肢、生活质量差, 甚至危及生命, 且感染伤口需要很长时间才能愈合, 并且在愈合后可能会复发, 消耗大量的医疗资源^[2]。糖尿病足溃疡通常是由周围神经病变、周围动脉疾病患者足部区域的轻微或重复性创伤引起的, 与感染或缺血有关^[3]。因此, 寻找与糖尿病足病相关指标用于预测患者预后十分重要。胎盘生长因子(placental growth factor, PIGF)是促血管生成的血管内皮生长因子(vascular endothelial growth factor, VEGF)家族成员, 在血管生成、炎症调节、促进内皮细胞生长增殖等方面具有重要意义^[4-5]。髓系细胞表达触发受体1(triggering receptors expressed on myeloid cells 1, TREM1)是一种糖蛋白, 研究证明, 其参与促炎细胞因子和趋化因子的释放, 与机体的炎症反应的发生有紧密联系^[6-7]。但PIGF, TREM1表达在糖尿病足病的发展进程中的表达尚不明确, 因此, 本研究通过检测糖尿病足患者血清PIGF, TREM1水平, 探究二者水平与患者临床分级及预后的相关性。

1 材料与方法

1.1 研究对象 收集2021年1月~2023年1月桂林医学院附属医院收治的97例糖尿病足患者作为研究对象(糖尿病足组), 其中男性52例, 女性45例, 平均年龄 65.21 ± 8.65 岁, 糖尿病病程 7.34 ± 1.65 年。糖尿病足病诊断标准: 参考《中国糖尿病足防治指南(2019版)解读》中的相关诊断

标准^[8]。纳入标准: ①经临床确诊符合上述诊断标准; ②近期未出现过其他急性感染; ③糖尿病病程超过5年; ④同意参与本研究, 签署知情同意书。排除标准: ①并发有先天性的下肢畸形; ②患有视网膜病变、糖尿病肾病; ③并发凝血系统紊乱; ④患有严重的低蛋白血症; ⑤患有下肢广泛坏死, 需截肢; ⑥临床资料不全。另选取同期在本院体检的102例健康者作为健康对照组, 其中男性53例, 女性49例, 平均年龄 65.58 ± 8.98 岁。两组年龄、性别差异无统计学意义($t/\chi^2=0.296, 0.054$, 均 $P>0.05$), 具有可比性。所有受试者均知情同意, 且本研究经过本院伦理委员会批准(批号: 201115904)。

1.2 仪器与试剂 SpectraMax iD5酶标仪[美谷分子仪器(上海)有限公司], PIGF, TREM1酶联免疫吸附(ELISA)测定试剂盒(货号: IB-E10097, IB-E10840, 江西艾博因生物科技有限公司)。

1.3 方法

1.3.1 血清PIGF, TREM1检测方法: 采集所有受试者空腹静脉血3~5ml, 血液静置一段时间后离心以获得血清。采用ELISA法检测血清PIGF, TREM1水平, 具体操作严格按照试剂说明书进行。

1.3.2 临床分级: 参考糖尿病足Wanger分级标准在入院当天对糖尿病足患者进行临床分级: 皮肤完整, 外周血管出现病变, 伴有足部高危体征为0级; 皮肤表面出现溃疡, 但溃疡深度在皮下脂肪层内为1级; 溃疡深入到肌腱、韧带为2级; 并发骨髓炎为

3级；足前端、足趾坏疽为4级；足大部分或整体发生坏疽，需截肢为临床5级^[9]。按照以上分级标准经诊断，纳入的97例糖尿病足患者中有33例为0~1级，39例为2~3级，25例为4~5级。

1.3.3 随访：采用电话或门诊的方式对受试的97例糖尿病足患者进行6个月随访，以获得患者结局。若患者的伤口完全愈合，创口有新生皮肤生长，为预后良好组。若患者随访期间持续存在足部溃疡、截肢、全因死亡，为预后不良组^[10]。本研究中预后良好组为72例，预后不良组为25例。

1.4 统计学分析 采用SPSS 27.0统计学软件对数据进行处理。计量资料以均数±标准差($\bar{x}\pm s$)表示，两组间血清PIGF, TREM1水平比较采用 t 检验；多组间比较采用单因素方差分析，进一步两两比较采用SNK- q 检验；采用Spearman相关分析探究糖尿病足患者血清PIGF, TREM1水平与临床分级的相关性；单因素和多因素Logistic回归分析糖尿病足患者预后的影响因素；血清PIGF, TREM1对糖尿病足患者预后情况的预测效能采用受试者工作特征(ROC)曲线进行分析，利用约登指数分析各指标的敏感度及特异度。 $P < 0.05$ 为差异具有统计学

表1 不同临床分级糖尿病足患者血清PIGF, TREM1水平比较($\bar{x}\pm s$)

项目	0~1级(n=33)	2~3级(n=39)	4~5级(n=25)	F	P
PIGF (pg/ml)	66.13 ± 16.30	52.75 ± 15.32	39.41 ± 13.28	22.219	< 0.001
TREM1 (ng/L)	248.21 ± 29.83	275.89 ± 32.06	326.66 ± 35.75	42.316	< 0.001

2.3 糖尿病足患者血清PIGF, TREM1水平与临床分级的相关性 由Spearman相关分析结果可以看出，糖尿病足患者血清PIGF表达水平与临床分级呈现负相关($r=-0.696$, $P < 0.001$)，TREM1表达水平与临床分级呈现正相关($r=0.657$, $P < 0.001$)。

2.4 不同预后糖尿病足患者血清PIGF, TREM1水平比较 与预后良好组相比，预后不良组血清PIGF水平(33.98 ± 12.07 pg/ml vs 60.76 ± 16.19 pg/ml)降低，TREM1水平(316.21 ± 38.36 ng/L vs 266.83 ± 30.13 ng/L)显著升高，差异具有统计学意义($t=7.562$, 6.564 , 均 $P < 0.001$)。

2.5 Logistic回归分析糖尿病足患者预后的影响因素 见表2。以糖尿病足患者预后情况(预后不良=1, 预后良好=0)为因变量，以年龄、性别、糖尿病病程、空腹血糖、糖化血红蛋白、高血压、白细胞计数、降钙素原、三酰甘油、总胆固醇、低密度脂蛋白-胆固醇、PIGF, TREM1为自变量进行Logistic回归分析。单因素Logistic回归分析结果表明PIGF, TREM1均为糖尿病足患者预后的影响

意义。

2 结果

2.1 糖尿病足组和健康对照组血清PIGF, TREM1水平比较 糖尿病足组患者血清PIGF(53.86 ± 15.13 pg/ml)表达水平低于健康对照组(87.57 ± 18.28 pg/ml)，TREM1(279.56 ± 32.25 ng/L)水平高于健康对照组(195.37 ± 26.28 ng/L)，差异具有统计学意义($t=14.133$, 20.232 , 均 $P < 0.001$)。

2.2 不同临床分级糖尿病足患者血清PIGF, TREM1水平比较 见表1。不同临床分级的糖尿病足患者血清PIGF表达水平从高到低依次降低，TREM1表达水平从高到低依次升高，差异具有统计学意义(均 $P < 0.05$)。临床分级为4~5级的糖尿病足患者血清中PIGF表达水平均显著低于0~1级和2~3级患者($q=9.390$, 4.852)，TREM1表达水平均高于0~1级和2~3级患者($q=12.945$, 8.670)；临床分级为2~3级患者血清PIGF表达水平低于0~1级患者($q=5.271$)，TREM1表达水平高于0~1级患者($q=5.120$)，差异具有统计学意义(均 $P < 0.05$)。

因素(均 $P < 0.05$)。进一步通过多因素Logistic回归分析发现PIGF是影响糖尿病足患者预后的独立保护因素，TREM1是影响糖尿病足患者预后的独立危险因素(均 $P < 0.05$)。

2.6 ROC曲线评估血清PIGF, TREM1对糖尿病足患者预后的预测价值 以糖尿病足患者预后情况作为状态变量(预后不良=1, 预后良好=0)，血清PIGF, TREM1表达水平为检验变量，绘制ROC曲线评价血清PIGF, TREM1表达水平在预测糖尿病足患者预后情况的临床价值，见表3和图1。PIGF, TREM1水平和二者联合预测糖尿病足患者预后情况的AUC(95%CI)分别为0.898(0.820~0.950)，0.817(0.725~0.888)和0.949(0.885~0.984)，血清PIGF, TREM1联合预测糖尿病足患者预后情况的敏感度、特异度分别为96.00%，84.72%，二者联合应用预测糖尿病足患者预后不良的临床效能优于血清PIGF, TREM1单独预测($Z=2.150$, 2.713 , $P=0.032$, 0.007)。

表2 单因素和多因素 Logistic 回归分析糖尿病足患者预后的影响因素

因素	单因素分析			多因素分析		
	OR	95%CI	P	OR	95%CI	P
年龄	1.643	0.859 ~ 3.143	0.134	-	-	-
性别	1.394	0.771 ~ 2.520	0.271	-	-	-
糖尿病病程	1.994	0.964 ~ 4.126	0.063	-	-	-
空腹血糖	1.559	0.989 ~ 2.457	0.056	-	-	-
糖化血红蛋白	2.002	0.889 ~ 4.524	0.095	-	-	-
高血压	1.574	0.856 ~ 2.896	0.145	-	-	-
白细胞计数	2.334	0.927 ~ 5.875	0.072	-	-	-
降钙素原	1.497	0.969 ~ 2.313	0.069	-	-	-
三酰甘油	1.897	0.716 ~ 5.025	0.198	-	-	-
总胆固醇	2.231	0.922 ~ 5.400	0.075	-	-	-
低密度脂蛋白胆固醇	1.787	0.929 ~ 3.439	0.082	-	-	-
PIGF	0.664	0.518 ~ 0.852	0.001	0.601	0.491 ~ 0.735	< 0.001
TREM1	2.557	1.524 ~ 4.290	< 0.001	2.772	1.393 ~ 5.515	0.004

表3 血清 PIGF, TREM1 预测糖尿病足患者预后的临床价值

项目	AUC	95%CI	截断值	敏感度 (%)	特异度 (%)	约登指数
PIGF	0.898	0.820 ~ 0.950	44.02 pg/ml	76.00	87.50	0.635
TREM1	0.817	0.725 ~ 0.888	302.24 ng/L	64.00	91.67	0.557
二者联合	0.949	0.885 ~ 0.984	-	96.00	84.72	0.807

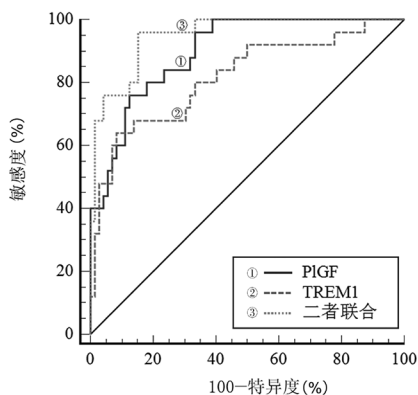


图1 ROC 曲线评估血清 PIGF, TREM1 预测糖尿病足患者预后的临床价值

3 讨论

糖尿病足病是糖尿病常见且严重的并发症。据估计,糖尿病患者一生发生足部溃疡的风险达到25%,全球患病率为6.3%^[11]。糖尿病足病与许多不良后果的高风险相关,包括足部感染和截肢、低活动能力和生活质量,甚至死亡^[2,12]。由于其发病率的增加和相关的沉重负担,糖尿病足病已成为一个

主要的公共卫生问题。伤口愈合受损是糖尿病足病的重要病理特征之一^[13],既往研究表明,血管生成除了帮助肉芽组织形成外,还可以向伤口输送营养和氧气,促进组织再生,在伤口愈合中起着至关重要的作用^[14]。因此,血管生成不足会导致伤口愈合受损。

PIGF 是 VEGF 家族中的关键成员,研究表明,PIGF 对多种功能至关重要,包括血管生成、炎症、伤口愈合和某些癌细胞(如成神经管细胞瘤)的存活^[5,15]。PIGF 通过与 VEGF 受体-1 结合发挥其血管生成作用^[16],其次,它可以促进内皮细胞生长、增殖以及迁移,调控炎症因子的产生及释放,参与肉芽组织的形成和成熟,进而参与伤口愈合过程^[14,17-18]。先前的一项研究发现,糖尿病足患者的 PIGF 浓度低于无足部溃疡的糖尿病患者,说明在糖尿病病例中,PIGF 表达减少会影响伤口愈合^[13]。本研究结果表明,糖尿病足组患者血清 PIGF 表达水平显著降低,提示 PIGF 与糖尿病足的发生有关。且本研究发现 PIGF 表达随着临床分级的加重而逐

渐降低, 其与临床分级呈现负相关。提示 PIGF 表达可能参与糖尿病足病的进展, 推测 PIGF 浓度过低, 可能导致血管生成和血管生成不足, 从而使糖尿病患者的伤口愈合受损, 更容易发生及加重足部溃疡。另外, 本研究发现预后不良组患者血清 PIGF 表达明显低于预后良好组, 且多因素 Logistic 回归分析发现 PIGF 是影响糖尿病足患者预后的独立保护因素, 提示 PIGF 表达与患者预后有关, 其有作为糖尿病足患者预后指标的潜力。另外, 本研究 ROC 曲线分析发现 PIGF 预测糖尿病足患者预后情况的 AUC 为 0.898, 提示血清 PIGF 水平对糖尿病足患者预后预测有一定的临床价值, 其在临床上可以作为一种预测糖尿病足病患者预后情况的有效指标。

TREM1 是一种存在于成熟单核细胞、巨噬细胞和中性粒细胞表面糖蛋白, TREM1 在机体内以细胞膜结合型和可溶性型这两种形式存在, 当机体处于感染时, 这种糖蛋白会参与到炎症免疫反应的信号传递过程中^[19]。有研究显示 2 型糖尿病血浆 TREM1 水平明显升高, 高水平 TREM1 会促进 2 型糖尿病慢性炎症, 并促进糖尿病相关并发症的发生^[20]。SAWAYA 等^[21]研究也发现抑制血浆 TREM1 水平通过调节糖尿病中性粒细胞的募集而促进糖尿病患者体内伤口的愈合。本研究结果与上述结果一致, 糖尿病足组患者血清 TREM1 水平显著高于健康对照组, 且其表达水平与其临床分级呈现正相关, 提示 TREM1 表达水平与糖尿病足病发展过程密切相关, 这可能是当机体发生感染时, TREM1 会促进炎症因子的释放进一步加重炎症反应的发生。本研究进一步通过多因素 Logistic 回归分析发现 TREM1 是影响糖尿病足患者预后的独立危险因素, 且 ROC 曲线分析发现 TREM1 水平预测糖尿病足患者预后情况的 AUC 为 0.817, 提示 TREM1 与糖尿病足患者预后密切相关, 其预测糖尿病足病具有一定的临床应用效能, 但 PIGF, TREM1 二者联合应用预测糖尿病足患者预后不良的临床效能优于其单独预测, 临床中 PIGF 水平低于 44.02pg/ml, TREM1 水平高于 302.24ng/L, 需密切关注糖尿病足患者病情发展, 及时采取治疗, 改善患者预后。

综上所述, 糖尿病足患者血清 PIGF 水平降低, TREM1 水平升高, 二者与患者临床分级紧密相关, 应用二者预测患者预后情况具有较好的临床效能, 临床上要密切关注糖尿病足病患者血清 PIGF, TREM1 表达, 并及时采取有效的干预治疗, 有助于改善患者预后。但本研究样本量较少, 且未能深入分析二者在糖尿病足中的作用机制, 后续本研究将继续扩大样本量, 进一步对本研究结果进行验证,

并通过动物实验深入分析二者作用机制。

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- 收稿日期: 2024-01-29
修回日期: 2024-05-21
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- 收稿日期: 2023-12-26
修回日期: 2024-04-30