

维持性血液透析患者血液 Lp(a), Fib 水平检测与自体动静脉内瘘血管钙化及严重程度的关系

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摘要:目的 探讨维持性血液透析 (maintenance hemodialysis, MHD) 患者血液脂蛋白 [lipoprotein(a), Lp(a)]、纤维蛋白原 (fibrinogen Fib) 水平检测与自体动静脉内瘘 (autogenous arteriovenous fistula, AVF) 血管钙化及严重程度的关系。方法 选择2021年11月~2023年11月于遂宁市中心医院就诊的112例MHD患者作为研究对象。根据其AVF血管钙化程度将所有患者分为无钙化组 ($n=45$) 和钙化组 ($n=67$), 其中钙化组分为轻度钙化组 ($n=19$)、中度钙化组 ($n=28$) 和重度钙化组 (20例)。比较无钙化组和钙化组患者的一般资料及Lp(a)和Fib水平。采用多因素Logistic回归模型确定MHD患者AVF血管钙化的独立风险预测因子。比较不同钙化程度患者临床资料。采用广义混合效应模型分析Lp(a)和Fib水平与MHD患者AVF血管钙化程度的关系。采用限制性立方样条模型分析Lp(a)和Fib与AVF血管重度钙化的剂量反应关系。分析Lp(a)和Fib对AVF血管钙化严重程度的交互作用。**结果** 钙化组患者透析时间、血磷(P)、甲状旁腺素(PTH)、血清肌酐(Scr)、血红蛋白(Hb)、骨形态发生蛋白-2(BMP-2)、成纤维细胞生长因子21(FGF-21)、Lp(a)和Fib水平明显升高 ($t=17.420, 9.644, 4.863, 6.646, 2.158, 12.046, 13.290, 2.395, 6.674$, 均 $P<0.05$), Ca水平则明显降低 ($t=2.820, P=0.006$), 差异具有统计学意义。多因素分析结果显示, 透析时间 (OR: 3.130, 95%CI: 1.652~5.931), P (OR: 4.760, 95%CI: 2.103~7.133), PTH (OR: 3.314, 95%CI: 1.062~6.045), Scr (OR: 2.288, 95%CI: 1.168~4.481), Hb (OR: 4.616, 95%CI: 2.384~7.949), BMP-2 (OR: 5.527, 95%CI: 2.598~9.212), FGF-21 (OR: 6.242, 95%CI: 1.201~11.184), Lp(a) (OR: 5.509, 95%CI: 2.787~10.886) 和 Fib (OR: 6.159, 95%CI: 2.125~12.140) 均为影响MHD患者AVF血管钙化的独立危险因素 (均 $P<0.05$)。轻度、中度及重度钙化组在透析时间、Ca, PTH, Scr, Hb, BMP-2, FGF-21, La(a)和Fib水平差异有统计学意义 ($F=2.028\sim6.324$, 均 $P<0.05$), 重度钙化组患者透析时间, PTH, Scr, Hb, BMP-2, FGF-21, Lp(a)和Fib水平高于轻度钙化组 ($t=2.204\sim11.064$) 和中度钙化组 ($t=2.025\sim3.197$), Ca水平则明显降低 ($t=3.121, 2.471$), 差异具有统计学意义 (均 $P<0.05$)。广义混合效应模型结果显示, Lp(a)和Fib水平与MHD患者AVF血管钙化程度有关。限制性立方样条模型结果显示, Lp(a)和Fib水平与AVF血管重度钙化的关联呈非线性的剂量反应关系。血清Lp(a)和Fib水平对AVF血管钙化严重程度的影响存在交互作用 (OR=6.324, 2.534, 均 $P<0.05$)。**结论** Lp(a)和Fib与患者血管钙化程度具有一定相关性, 可能是MHD患者自体AVF血管钙化的影响因素。

关键词: 脂蛋白; 纤维蛋白原; 维持性血液透析; 动静脉内瘘; 血管钙化

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Relationship between Lp (a), Fib Levels and Vascular Calcification and Severity of Autogenous Arteriovenous Fistula in Maintenance Hemodialysis Patients

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Abstract: Objective To explore the relationship between lipoprotein (a) [Lp (a)], fibrinogen (Fib) levels and vascular calcification and severity of autogenous arteriovenous fistula (AVF) in maintenance hemodialysis (MHD) patients. **Methods** A total of 112 MHD patients who visited Suining Central Hospital from November 2021 to November 2023 were selected as the study subjects. According to the degree of AVF vascular calcification, these patients were divided into a non calcified group ($n=45$) and a calcified group ($n=67$), in which the calcified group was divided into a mild calcification group ($n=19$), a moderate calcification group ($n=28$) and a severe calcification group ($n=20$). The general information and Lp (a) and Fib levels between non calcified group and calcified group were compared. Multivariate logistic regression model was used to determine the independent risk predictors of AVF vascular calcification in MHD patients. Clinical data of patients with different degrees of calcification were compared. Generalized mixed effects model was used to analyze the relationship between Lp (a), Fib levels

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and the degree of AVF vascular calcification in MHD patients. Restricted cubic spline model was used to analyze the dose-response relationship between Lp (a) and Fib and severe vascular calcification in AVF. The interaction between Lp (a) and Fib on the severity of vascular calcification in AVF was analyzed. **Results** Dialysis time, P, PTH, Scr, Hb, BMP-2, FGF-21, Lp (a) and Fib levels of patients in the calcification group were increased ($t=17.420, 9.640, 4.863, 6.646, 2.158, 12.046, 13.290, 2.395, 6.674$, all $P<0.05$), while Ca level was decreased ($t=2.820, P=0.006$), the differences were statistically significant, respectively. The results of multivariate analysis showed that dialysis time(OR: 3.130, 95%CI: 1.652~5.931), P(OR: 4.760, 95%CI: 2.103~7.133), PTH(OR: 3.314, 95%CI: 1.062~6.045), Scr(OR: 2.288, 95%CI: 1.168~4.481), Hb(OR: 4.616, 95%CI: 2.384~7.949), BMP-2(OR: 5.527, 95%CI: 2.598~9.212), FGF-21(OR: 6.242, 95%CI: 1.201~11.184), Lp(a)(OR: 5.509, 95%CI: 2.787~10.886) and Fib(OR: 6.159, 95%CI: 2.125~12.140) were all independent risk factors for AVF vascular calcification in MHD patients (all $P<0.05$). There were statistically significant in dialysis time, Ca, PTH, Scr, Hb, BMP-2, FGF-21, Lp(a) and Fib levels among the three groups($F=2.028\sim6.324$, all $P<0.05$). Patients in the severe calcification group had higher dialysis time, PTH, Scr, Hb, BMP-2, FGF-21, Lp (a) and Fib levels than those in the mild calcification group($t=2.204\sim11.064$) and the moderate calcification group($t=2.025\sim3.197$), while Ca level was reduced($t=3.121, 2.471$), with statistically significant differences (all $P<0.05$), respectively. The results of the generalized mixed effects model showed that the levels of Lp (a) and Fib were related to the degree of AVF vascular calcification in MHD patients. The results of the restricted cubic spline model showed a non-linear dose-response relationship between Lp (a) and Fib levels and severe vascular calcification in AVF. There was an interactive effect between serum Lp (a) and Fib levels on the severity vascular calcification in AVF (OR=6.324, 2.534, all $P<0.05$). **Conclusion** Lp (a) and Fib have a certain correlation with the degree of vascular calcification in patients, which may be influencing factors of autogenous AVF vascular calcification in MHD patients.

Keywords: lipoprotein (a); fibrinogen; maintenance hemodialysis; arteriovenous fistula; vascular calcification

维持性血液透析 (maintenance hemodialysis, MHD) 是临床上治疗慢性肾功能衰竭尿毒症患者的常用方法^[1]。近年来全球 MHD 患者逐年增多且呈持续增长趋势^[2]。长期的透析治疗使患者血管弹性降低, 自体动静脉内瘘 (autogenous arteriovenous fistulas, AVF) 血管钙化是 MHD 患者常见的并发症之一。同时 AVF 血管钙化也是引起 MHD 患者发生心血管疾病的重要危险因素之一, 严重者甚至危及患者的生命安全^[3]。因此, 为了进一步提升患者治疗效果, 延长动静脉内瘘的使用周期, 对 MHD 患者 AVF 血管钙化的相关影响因素进行研究具有重要临床价值。之前的研究指出, 脂蛋白 (a)[lipoprotein(a), Lp(a)] 和纤维蛋白原 (fibrinogen, Fib) 作为急性时相反应蛋白, 是导致动脉粥样硬化的独立危险因素, 在血管钙化过程中发挥一定作用^[4-5]。但目前关于 Lp(a) 和 Fib 与 AVF 血管钙化关系的研究仍鲜见报道。基于此, 本研究以 2021 年 1 月~2023 年 1 月于本院就诊的 112 例 MHD 患者作为研究对象, 旨在探讨 Lp(a), Fib 与 MHD 患者 AVF 血管钙化及严重程度的关系, 现报道如下。

1 材料与方法

1.1 研究对象 选择 2021 年 1 月~2023 年 1 月于遂宁市中心医院就诊的 112 例 MHD 患者作为研究对象, 其中男性 63 例, 女性 49 例, 年龄 31~72 (52.14 ± 8.60) 岁。纳入标准: ①符合 MHD 诊断标准^[6]; ②血液透析时间 ≥ 3 个月, 且病情稳定; ③年龄 > 18 岁; ④一般情况及精神状态稳定。排除标准: ①并发恶性肿瘤; ②并发严重肝脏疾病; ③临床资料不全。根据其内瘘血管钙化程度将所有

患者分为无钙化组 ($n=45$) 和钙化组 ($n=67$), 其中钙化组分为轻度钙化组 ($n=19$)、中度钙化组 ($n=28$) 和重度钙化组 ($n=20$)。本研究经我院医学伦理委员会审核批准 (审批编号: SCH517)。

1.2 仪器与试剂 德国西门子 CS5100 全自动血凝分析仪及其配套试剂; 德国西门子 ADVIA 2400 全自动生化分析仪及其配套试剂盒。

1.3 方法

1.3.1 实验室指标检测: 所有研究对象均于清晨抽取空腹静脉血 3ml, 3 000r/min 离心 15min, 收集上层血清, 用于 Lp(a) 和实验室生化指标检测, 另抽取空腹静脉血 2ml, 用于血浆 Fib 测定。所有样本于采集后 2h 内进行检测, 所有检验项目均严格按照试剂盒说明书和实验室 SOP 文件进行。

1.3.2 观察指标: 收集所有研究对象临床资料, 包括年龄、性别、体质指数 (body mass index, BMI)、透析时间、吸烟史、饮酒史、并发高血压、糖尿病等。收集实验室检查结果, 包括血钙 (Ca)、血磷 (P)、甲状旁腺素 (PTH)、25-羟维生素 D[25 (OH) D]、空腹血糖 (FPG)、碱性磷酸酶 (ALP)、尿素氮 (BUN)、血清肌酐 (Scr)、清蛋白 (Alb)、总胆固醇 (TC)、血红蛋白 (Hb)、骨形态发生蛋白-2 (bone morphogenetic protein-2, BMP-2)、成纤维细胞生长因子 21 (fibroblast growth factor 21, FGF-21)。记录患者就诊时血压指标, 包括舒张压 (diastolic blood pressure, DBP)、收缩压 (systolic blood pressure, SBP)、平均动脉压 (mean arterial pressure, MAP)。

1.4 统计学分析 利用 SPSS 23.0 统计软件进行数据统计分析, 以均数 \pm 标准差 ($\bar{x} \pm s$) 表示计量资

料, 两组间比较采用独立样本 t 检验; 使用 n (%) 表示计数资料, 组间比较采用 χ^2 检验。采用多因素 Logistic 回归模型确定 MHD 患者 AVF 血管钙化的独立风险预测因子。采用广义混合效应模型分析 Lp(a) 和 Fib 水平与钙化程度的关系。采用限制性立方样条模型分析 Lp(a) 和 Fib 与 AVF 血管重度钙化的剂量反应关系。分析 Lp(a) 和 Fib 对 AVF 血管钙化严

重程度的交互作用。 $P < 0.05$ 为差异具有统计学意义。

2 结果

2.1 钙化组与无钙化组临床资料比较 见表 1。与无钙化组相比, 钙化组患者透析时间、P, PTH, Scr, Hb, BMP-2, FGF-21, Lp(a) 和 Fib 水平明显升高, Ca 水平则明显降低, 差异具有统计学意义 (均 $P > 0.05$), 其余指标差异无统计学意义 (均 $P > 0.05$)。

表 1 钙化组与无钙化组临床资料比较 [$\bar{x} \pm s, n(\%)$]

| 类别 | 无钙化组 (n=45) | 钙化组 (n=67) | t/χ^2 值 | P 值 |
|--------------------------|-----------------|-----------------|--------------|---------|
| 年龄 (岁) | 51.55 ± 8.25 | 52.60 ± 8.93 | 0.629 | 0.531 |
| BMI (kg/m ²) | 23.64 ± 3.18 | 24.12 ± 3.35 | 0.822 | 0.413 |
| 性别 | | | | |
| 男 | 24 (53.33) | 39 (58.21) | | |
| 女 | 21 (46.67) | 28 (41.79) | 0.260 | 0.610 |
| 透析时间 (月) | 6.10 ± 2.02 | 18.76 ± 4.58 | 17.420 | < 0.001 |
| 吸烟史 | | | | |
| 有 | 22 (48.89) | 40 (59.70) | | |
| 无 | 23 (51.11) | 27 (40.30) | 1.274 | 0.259 |
| 饮酒史 | | | | |
| 有 | 20 (44.44) | 36 (53.73) | | |
| 无 | 25 (55.56) | 31 (46.27) | 0.929 | 0.335 |
| 高血压 [n(%)] | | | | |
| 有 | 24 (53.33) | 40 (59.70) | | |
| 无 | 21 (46.67) | 27 (40.30) | 0.446 | 0.504 |
| 糖尿病 | | | | |
| 有 | 23 (51.11) | 44 (65.67) | | |
| 无 | 22 (48.89) | 23 (34.33) | 2.375 | 0.123 |
| Ca (mmol/L) | 2.14 ± 0.12 | 2.05 ± 0.19 | 2.820 | 0.006 |
| P (mmol/L) | 1.57 ± 0.13 | 2.32 ± 0.51 | 9.644 | < 0.001 |
| PTH (ng/L) | 182.43 ± 95.42 | 316.56 ± 167.50 | 4.863 | < 0.001 |
| 25(OH)D (nmol/L) | 65.26 ± 25.55 | 70.58 ± 20.82 | 1.209 | 0.229 |
| FPG (mmol/L) | 4.92 ± 0.52 | 4.87 ± 0.65 | 0.431 | 0.667 |
| ALP (U/L) | 1.02 ± 0.35 | 0.94 ± 0.25 | 1.411 | 0.161 |
| BUN (mmol/L) | 24.46 ± 6.20 | 25.50 ± 5.61 | 0.851 | 0.397 |
| Scr (μmol/L) | 581.82 ± 189.06 | 796.33 ± 151.35 | 6.646 | < 0.001 |
| Alb (g/L) | 46.20 ± 3.32 | 46.43 ± 3.58 | 0.343 | 0.732 |
| TC (mmol/L) | 4.74 ± 2.00 | 5.27 ± 2.62 | 1.150 | 0.253 |
| Hb (g/L) | 94.10 ± 17.46 | 102.12 ± 20.40 | 2.158 | 0.033 |
| SBP (mmHg) | 132.22 ± 20.54 | 133.64 ± 18.63 | 0.379 | 0.705 |
| DBP (mmHg) | 81.90 ± 10.88 | 82.92 ± 12.75 | 0.440 | 0.661 |
| MAP (mmHg) | 96.84 ± 18.05 | 100.39 ± 13.76 | 1.179 | 0.241 |
| BMP-2 (pg/ml) | 23.12 ± 6.07 | 50.10 ± 14.16 | 12.046 | < 0.001 |
| FGF-21 (pg/ml) | 108.28 ± 42.40 | 347.22 ± 115.34 | 13.290 | < 0.001 |
| Lp(a) (mg/L) | 143.20 ± 79.36 | 203.52 ± 155.74 | 2.395 | 0.018 |
| Fib (g/L) | 3.29 ± 0.33 | 4.15 ± 0.82 | 6.674 | < 0.001 |

2.2 影响 MHD 患者 AVF 血管钙化的多因素 Logistic 回归分析 见表 2。以 MHD 患者 AVF 血管是否发生钙化为因变量, 以表 1 结果筛选出的两组差异显著 ($P < 0.05$) 的指标为自变量进行多因素分析, 结果显示, 透析时间、P, PTH, Scr, Hb, BMP-2, FGF-21, Lp(a) 和 Fib 均为影响 MHD 患者 AVF 血管钙化的独立危险因素 (均 $P < 0.05$)。

2.3 相关性 E 值法的敏感性分析 采用 E 值法对本研究的参数估计进行敏感性分析, 结果显示, 结

局在研究对象中的发生率 $> 20\%$, $RR = \sqrt{OR}$, 得出 E 值 $= RR + \sqrt{RR \times (RR - 1)} = 2.18$, 95%CI 下限为 1.54。当混杂因素的风险值在 E 值区间内, 说明上述因素与 MHD 患者 AVF 血管钙化之间的关联有效。

2.4 不同钙化程度患者临床资料比较 见表 3。轻度钙化组、中度钙化组和重度钙化组在透析时间、Ca, PTH, Scr, Hb, BMP-2, FGF-21, Lp(a) 和 Fib 水平方面差异具有统计学意义 (均 $P < 0.05$); 重度钙化组患者透析时间、PTH, Scr, Hb, BMP-2, FGF-21, Lp(a) 和 Fib 水平高于轻度钙化组

($t=11.064, 2.240, 5.036, 2.204, 3.299, 2.645, 2.317, 2.034$)和轻度钙化组($t=2.842, 2.212, 3.197, 2.266, 2.829, 2.025, 2.044, 2.159$), Ca水平低于轻度钙化组和中度钙化组($t=3.121, 2.471$), 差异具有统计学意义(均 $P<0.05$); 其余指标差异无统计学意义(均 $P>0.05$)。

表2 影响MHD患者AVF血管钙化的多因素Logistic回归分析

| 因素 | β | SE | Wald χ^2 | OR(95%CI) | P |
|--------|---------|-------|---------------|----------------------|---------|
| 透析时间 | 1.141 | 0.326 | 12.251 | 3.130 (1.652~5.931) | < 0.001 |
| Ca | 0.844 | 0.328 | 6.624 | 2.326 (1.224~4.421) | 0.060 |
| P | 1.560 | 0.387 | 16.254 | 4.760 (2.103~7.133) | < 0.001 |
| PTH | 0.839 | 0.398 | 4.444 | 3.314 (1.062~6.045) | 0.035 |
| Scr | 0.828 | 0.343 | 5.823 | 2.288 (1.168~4.481) | 0.016 |
| Hb | 0.962 | 0.325 | 8.755 | 4.616 (2.383~7.949) | 0.003 |
| BMP-2 | 1.510 | 0.396 | 14.541 | 5.527 (2.598~9.212) | 0.004 |
| FGF-21 | 0.807 | 0.318 | 6.446 | 6.242 (1.201~11.184) | 0.011 |
| Lp(a) | 1.706 | 0.348 | 24.043 | 5.509 (2.787~10.886) | < 0.001 |
| Fib | 1.425 | 0.346 | 16.969 | 6.159 (2.125~12.140) | 0.001 |

表3 不同钙化程度患者临床资料比较 [$\bar{x} \pm s, n(\%)$]

| 类别 | 轻度钙化组 (n=19) | 中度钙化组 (n=28) | 重度钙化组 (n=20) | F值 | P值 |
|--------------------------|-----------------|-----------------|-----------------|-------|---------|
| 年龄 (岁) | 51.82 ± 8.63 | 52.96 ± 8.51 | 52.73 ± 8.40 | 1.322 | 0.159 |
| BMI (kg/m ²) | 24.05 ± 3.24 | 24.21 ± 3.18 | 23.91 ± 3.22 | 1.157 | 0.206 |
| 性别 | | | | | |
| 男 | 11 (57.89) | 16 (57.14) | 12 (60.00) | | |
| 女 | 8 (42.11) | 12 (42.86) | 8 (40.00) | 1.714 | 0.424 |
| 透析时间 (月) | 6.10 ± 2.02 | 15.32 ± 3.79 | 18.76 ± 4.58 | 6.324 | < 0.001 |
| 吸烟史 | | | | | |
| 有 | 12 (63.16) | 15 (53.57) | 13 (65.00) | | |
| 无 | 7 (36.84) | 13 (46.43) | 7 (35.00) | 0.765 | 0.682 |
| 饮酒史 | | | | | |
| 有 | 11 (57.89) | 15 (53.57) | 10 (50.00) | | |
| 无 | 8 (42.11) | 13 (46.43) | 10 (50.00) | 0.245 | 0.885 |
| 高血压 | | | | | |
| 有 | 10 (52.63) | 18 (64.29) | 12 (60.00) | | |
| 无 | 9 (47.37) | 10 (35.71) | 8 (40.00) | 0.640 | 0.726 |
| 糖尿病 | | | | | |
| 有 | 13 (68.42) | 17 (60.71) | 14 (70.00) | | |
| 无 | 6 (31.58) | 11 (39.29) | 6 (30.00) | 0.535 | 0.765 |
| Ca (mmol/L) | 2.11 ± 0.14 | 2.08 ± 0.16 | 1.97 ± 0.14 | 3.871 | 0.008 |
| P (mmol/L) | 1.86 ± 0.37 | 2.09 ± 0.44 | 2.13 ± 0.45 | 2.024 | 0.079 |
| PTH (ng/L) | 234.47 ± 130.11 | 251.56 ± 121.55 | 322.90 ± 116.32 | 4.194 | < 0.001 |
| 25(OH)VD (ng/ml) | 68.53 ± 19.54 | 69.20 ± 16.95 | 74.06 ± 18.32 | 1.421 | 0.157 |
| FPG (mmol/L) | 4.97 ± 0.62 | 4.82 ± 0.58 | 4.71 ± 0.55 | 0.532 | 0.596 |
| ALP (U/L) | 0.96 ± 0.24 | 0.86 ± 0.31 | 0.87 ± 0.22 | 1.453 | 0.215 |
| BUN (mmol/L) | 25.03 ± 5.66 | 25.91 ± 5.83 | 26.70 ± 5.86 | 0.397 | 0.874 |
| Scr (μmol/L) | 628.94 ± 167.70 | 751.31 ± 162.35 | 911.26 ± 182.34 | 4.315 | < 0.001 |
| Alb (g/L) | 46.22 ± 3.53 | 46.15 ± 3.64 | 47.07 ± 3.80 | 0.416 | 0.678 |
| TC (mmol/L) | 5.14 ± 2.01 | 5.19 ± 1.62 | 5.96 ± 1.91 | 0.485 | 0.594 |
| Hb (g/L) | 93.71 ± 18.49 | 94.45 ± 19.03 | 106.42 ± 20.26 | 2.028 | 0.031 |
| SBP (mmHg) | 133.50 ± 18.23 | 133.72 ± 17.56 | 132.91 ± 18.08 | 0.452 | 0.650 |
| DBP (mmHg) | 82.89 ± 12.46 | 83.08 ± 11.80 | 82.54 ± 12.10 | 0.537 | 0.591 |
| MAP (mmHg) | 98.32 ± 14.58 | 101.76 ± 14.16 | 103.29 ± 15.09 | 1.394 | 0.171 |
| BMP-2 (pg/ml) | 45.34 ± 15.22 | 49.51 ± 14.87 | 62.89 ± 17.82 | 5.940 | < 0.001 |
| FGF-21 (pg/ml) | 307.65 ± 99.18 | 332.54 ± 114.50 | 402.75 ± 123.75 | 7.211 | < 0.001 |
| Lp(a) (mg/L) | 188.64 ± 121.67 | 206.92 ± 112.63 | 271.74 ± 101.90 | 2.993 | 0.027 |
| Fib (g/L) | 4.05 ± 0.73 | 4.13 ± 0.75 | 4.62 ± 0.81 | 4.165 | < 0.001 |

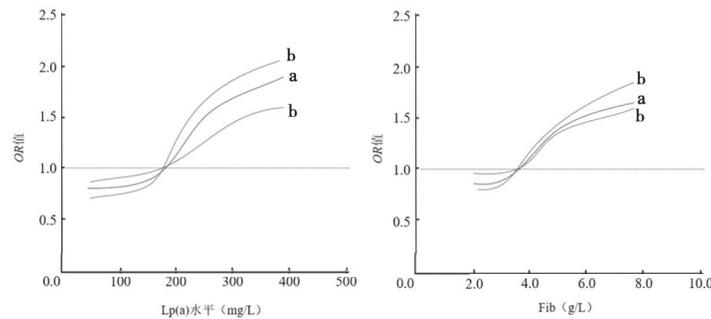
2.5 Lp(a)和Fib水平对钙化程度的回归分析 见表4。以患者AVF血管重度钙化为因变量拟合广义线性混合效应模型,单因素分析结果(模型1)显示,Lp(a)升高患者AVF血管重度钙化风险性更大。同理,Fib升高患者AVF血管重度钙化风险性更大。调整年龄、性别等因素后(模型2)不同Lp(a),Fib水平与患者AVF血管重度钙化仍存在统计学关

联,线性趋势检验差异具有统计学意义($P < 0.05$)。2.6 Lp(a)和Fib与AVF血管重度钙化的剂量反应关系 见图1。结果显示,Lp(a)和Fib水平与AVF血管重度钙化的关联呈非线性的剂量反应关系,当 $Lp(a) \geq 181.56\text{mg/L}$ 和 $Fib \geq 3.75\text{g/L}$ 时,AVF血管重度钙化的风险随Lp(a)和Fib水平升高而升高。

表4 Lp(a)和Fib水平对钙化程度的广义混合效应模型

| 模型 | 因素 | 分级 | β | SE | t | P | OR(95%CI) |
|-----|--------------|---------------|---------|-------|-------|---------|---------------------|
| 模型1 | Lp(a) (mg/L) | <125.33 | 0.152 | 0.046 | 3.969 | 0.021 | 1.159 (1.025~1.240) |
| | | 125.33~190.82 | - | - | - | - | Ref (1.00) |
| | | 190.82~224.71 | 0.103 | 0.034 | 3.162 | 0.009 | 1.325 (1.192~2.575) |
| | | >224.71 | 0.228 | 0.043 | 5.823 | 0.004 | 2.288 (1.968~2.581) |
| | Fib (g/L) | <3.31 | 0.291 | 0.062 | 4.251 | 0.031 | 1.351 (1.182~1.539) |
| | | 3.31~3.98 | - | - | - | - | Ref (1.00) |
| | | 3.98~4.50 | 0.105 | 0.031 | 3.651 | < 0.001 | 1.289 (1.215~1.368) |
| 模型2 | Lp(a) (mg/L) | <125.33 | 0.103 | 0.034 | 3.162 | 0.007 | 1.102 (1.042~1.175) |
| | | 125.33~190.82 | - | - | - | - | Ref (1.00) |
| | | 190.82~224.71 | 0.233 | 0.039 | 2.395 | < 0.001 | 1.154 (1.091~1.220) |
| | | >224.71 | 0.194 | 0.42 | 4.618 | 0.005 | 1.411 (1.236~1.624) |
| | Fib (g/L) | <3.31 | 0.208 | 0.063 | 3.566 | 0.004 | 1.065 (0.993~1.147) |
| | | 3.31~3.98 | - | - | - | - | Ref (1.00) |
| | | 3.98~4.50 | 0.271 | 0.054 | 4.082 | 0.002 | 1.214 (1.118~1.316) |
| | | >4.50 | 0.360 | 0.067 | 5.054 | < 0.001 | 1.406 (1.213~1.602) |

注:模型1为单因素模型;模型2调整年龄、性别、BMI,透析时间、吸烟史、饮酒史、并发高血压、糖尿病;模型1,2的随机效应估计值分别为2.572(2.541~2.611),2.513(2.478~2.546)。



a. 为Lp(a)和Fib水平实际测量值, b. 为其对应的95%CI。

图1 Lp(a)和Fib水平与AVF血管重度钙化的剂量反应关系

2.7 Lp(a)和Fib对AVF血管钙化严重程度的交互作用 见表5。调整潜在混杂因素后,相加模型和相乘

模型中,Lp(a)和Fib水平对AVF血管钙化严重程度的影响均存在交互作用($OR=6.324, 2.534, P < 0.05$)。

表5 Lp(a)和Fib的交互作用分析

| 因素1 | 因素2 | AVF血管钙化程度(轻中度/重度) | OR(95%CI) | OR ^a (95%CI) |
|---------------|-------------|---|----------------------|-------------------------|
| Lp(a) (mg/L) | Fib (g/L) | | | |
| < 181.56 | < 3.75 | | 1 | 1 |
| < 181.56 | ≥ 3.75 | | 1.407 (1.019~1.744) | 1.401 (1.012~1.795) |
| ≥ 181.56 | < 3.75 | | 1.932 (1.561~4.287) | 1.987 (1.595~4.403) |
| ≥ 181.56 | ≥ 3.75 | | 6.215 (2.723~22.590) | 6.324 (2.781~22.604) |
| 交互作用 | 相加模型 | RERI=1.576 (95%CI: -1.012~4.382), $P > 0.05$ AP=0.612 (95%CI: 0.334~1.975), $P < 0.05$ S=1.743 (95%CI: 0.350~7.428), $P > 0.05$ | | |
| | 相乘模型 | OR=2.534 (95%CI: 1.476~5.459), $P < 0.05$ | | |

注: ^a调整年龄、性别、BMI,透析时间、吸烟史、饮酒史、并发高血压、糖尿病、Ca, P, PTH, Scr, Hb, BMP-2, FGF-21等的影响。

3 讨论

MHD是终末期肾病患者主要治疗方式,对改善患者临床症状,延长患者生存周期起到积极作用^[7]。AVF血管钙化是MHD患者发生率较高的相关并发症之一,并且随着钙化程度的增加,其不仅会导致心血管事件的发生,还与患者AVF血栓形成密切相关^[8]。有研究指出Lp(a)和Fib可能在血管病变中具有一定影响作用^[9]。但是目前,临床中关于Lp(a)联合Fib对MHD患者自体AVF血管钙化关系的研究还鲜有报道。因此,为保障MHD患者的身体健康,积极对MHD患者AVF血管钙化的影响因素进行深入分析,就显得十分必要。

本研究结果显示,Lp(a)和Fib是MHD患者AVF血管钙化的影响因素,与患者血管钙化程度具有一定相关性。Fib是由肝脏合成的一种糖蛋白,属于II类急性期蛋白,同时又是一种体内重要的凝血因子,参与凝血过程,同时Fib还具有促进血小板聚集的功能^[10]。Fib浓度增高可引起血管内皮细胞应力损伤,从而导致血管钙化的发生和发展。本研究结果显示血管钙化组患者Fib水平明显高于无钙化组,且不同钙化程度患者间Fib水平差异明显。提示Fib水平升高是MHD患者发生AVF血管钙化的一个独立危险因素,Fib水平和机体微血管病变具有密切相关性,这与已有的报道结果一致^[11]。

Lp(a)是一种特殊的脂蛋白,在人体内不受年龄等因素的影响,主要与遗传因素有关,是公认的导致动脉粥样硬化及血栓形成的危险因素^[12]。由于其与纤溶酶原(plasminogen, PLG)同源性较高,因此可以竞争性地抑制PLG的活化,从而促进动脉粥样硬化和血栓形成,并阻止已存在凝块的溶解^[13]。同时,Lp(a)还可以通过与组织纤溶酶原激活剂-1(t-PA)竞争性结合,干扰纤溶系统平衡。因此,Lp(a)在脂质代谢、凝血等过程中起到重要调节作用,是机体血管钙化的高危因素。本研究结果也显示血管钙化组患者Lp(a)水平明显高于无钙化组,重度钙化组Lp(a)水平更高。说明随着Lp(a)水平升高,患者纤溶系统平衡被破坏,导致血管狭窄闭塞,血管内皮损伤加重,促进血管病变的发生与发展,最终导致血管钙化。

除此之外,本研究结果还显示透析时间、P,PTH,Scr,Hb,BMP-2,FGF-21,Lp(a)和Fib均为影响MHD患者AVF血管钙化的独立危险因素。分析其原因可能为:当患者发生高磷情况时,其容易在血管壁中沉积钙盐,从而引起动静脉内瘘通畅率降低,而引起高磷、高PTH情况也多与患者的饮食方式以及透析方式有着密切的关系,这也使得血管钙化情况在透析时间增加上有着明确的体现^[14]。当患者发生血管钙化情况时,其会造成动脉僵硬,使得充盈减少,此时患者的透析流量不够充分,就会造成血肌酐水平升高^[15]。FGF-21通过降低成骨细胞基因的表达起到抑制血管钙化及其

进展的作用^[16]。BMP-2则主要通过调节Runx2相关转录因子2(Runx2)和ALP的表达来引起血管钙化^[17]。并且已有研究证明,BMP-2的表达情况可反映病人血管的钙化程度^[18]。

本研究存在一定的局限性:由于本研究纳入的样本量相对较小且为单中心研究,可能导致研究结果出现一定偏倚,后续有待多中心、大样本量的研究进行更加全面地分析和验证。

综上所述,Lp(a)和Fib是MHD患者AVF血管钙化的影响因素,与患者血管钙化程度具有一定相关性。因此,定期检测MHD患者Lp(a)和Fib指标,对临床诊治和判断AVF血管钙化及严重程度具有一定的指导作用。

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