

• 临床研究 •

血清脂联素和瘦素与原发性醛固酮增多症靶器官损害和术后临床转归的相关性

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[摘 要] 目的: 探索基线血清脂联素和瘦素与原发性醛固酮增多症(primary aldosteronism, PA)靶器官损害和术后临床转归的相关性。方法: 纳入68例行单侧肾上腺切除术且有术后至少6个月随访信息的PA患者, 检测患者基线血清脂联素和瘦素浓度, 依据PA手术结局(primary aldosteronism surgical outcome, PASO)标准进行术后临床转归分型, 分析脂联素和瘦素与靶器官损害指标和不同术后分型的相关性。结果: 28例(41.2%)PA患者术后临床治愈, 40例(58.8%)临床未治愈。临床治愈组基线脂联素和估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)水平均高于临床未治愈组(P 均 < 0.05), 体重指数(body mass index, BMI)、高血压药物限定日剂量值、高脂血症占比和糖尿病占比低于临床未治愈组(P 均 < 0.05), 两组间瘦素水平差异无统计学意义。瘦素水平与心脏彩超指标二尖瓣舒张早期E峰峰值速度/舒张晚期A峰峰值速度比值和踝肱指数呈负相关(P 均 < 0.05), 脂联素水平与靶器官损害指标无相关。多因素逐步Logistic回归分析显示, 低BMI($OR=0.422$, 95%CI: 0.272~0.653, $P< 0.001$)和高脂联素($OR=1.359$, 95%CI: 1.004~1.840, $P=0.047$)水平与临床治愈独立相关。进一步按BMI分层, 在非肥胖PA患者中高eGFR($OR=1.074$, 95%CI: 1.023~1.127, $P=0.004$)和高脂联素($OR=1.816$, 95%CI: 1.261~2.616, $P=0.001$)水平与临床治愈有关。结论: 基线血清脂联素和瘦素检测有助于评估PA靶器官损害, 预测术后临床转归, 协助指导PA精准管理。

[关键词] 原发性醛固酮增多症; PA手术结局标准; 靶器官损害; 临床转归; 脂联素; 瘦素

[中图分类号] R586.2

[文献标志码] A

[文章编号] 1007-4368(2024)11-1541-09

doi: 10.7655/NYDXBNSN240586

Correlation of serum adiponectin and leptin levels with target organ damage and postsurgical clinical outcomes of patients with primary aldosteronism

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[Abstract] **Objective:** To investigate the correlation of baseline serum adiponectin and leptin levels with target organ damage and postoperative clinical outcomes of patients with primary aldosteronism (PA). **Methods:** A total of 68 PA patients who underwent unilateral adrenalectomy and had follow-up information for at least 6 months after surgery were included. Serum adiponectin and leptin concentrations were detected at baseline. Postoperative clinical outcomes were evaluated according to primary aldosteronism surgical outcome (PASO) criteria. The correlation of serum adiponectin and leptin levels with target organ damage and postsurgical clinical outcome was analyzed. **Results:** After surgery, 28 patients (41.2%) with PA were clinically cured and 40 patients (58.8%) were not clinically cured. The levels of baseline adiponectin and estimated glomerular filtration rate (eGFR) in the clinically cured group were higher than those in the clinically uncured group (all $P < 0.05$), while body mass index (BMI), the daily defined dose value of hypertension medications, the proportion of hyperlipidemia and diabetes were lower (all $P < 0.05$). No difference in leptin levels was detected between the two groups. Leptin levels were negatively correlated with the E/A ratio and ankle-brachial pressure index (all $P < 0.05$). Adiponectin levels were not correlated with target organ damage indicators. Multivariate stepwise logistic regression analysis showed that lower BMI ($OR=0.422$, 95%CI: 0.272~0.653, $P< 0.001$) and higher adiponectin levels ($OR=1.359$, 95%CI: 1.004~1.840, $P=0.047$) were independently associated with postoperative clinical cure. We further stratified patients based on BMI, and identified

[基金项目] 江苏省科技计划专项资金(基础研究计划自然科学基金)青年基金(BK20220717)

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that higher eGFR (OR=1.074, 95% CI: 1.023–1.127, $P=0.004$) and adiponectin levels (OR=1.816, 95% CI: 1.261–2.616, $P=0.001$) were associated with postoperative clinical cure in non-obese patients with PA. **Conclusion:** Baseline serum adiponectin and leptin detection is helpful to evaluate PA target organ damage, predict postoperative clinical outcomes, and assist in guiding the accurate management of PA.

[Key words] primary aldosteronism; PASO criteria; target organ damage; clinical outcome; adiponectin; leptin

[J Nanjing Med Univ, 2024, 44(11): 1541-1549]

原发性醛固酮增多症(primary aldosteronism, PA)是内分泌性高血压的最常见形式,与原发性高血压相比,PA相关代谢并发症与靶器官损害更严重^[1],因此PA的靶器官损害评估与针对性治疗非常重要。PA主要分为单侧PA和双侧PA^[2],单侧PA,即由单侧肾上腺病变所致,通常采取患侧肾上腺切除治疗,但仅有37%的患者术后可达到临床完全缓解(临床治愈)^[2],即未使用高血压药物情况下血压维持正常,因此需对术后临床未治愈的患者进行早期识别与规律随访。

有研究报道,与非肥胖PA患者相比,肥胖的PA患者心脏和代谢状况更差,需要服用更大剂量的抗高血压药物,肾上腺切除术后高血压治愈率更低^[3]。脂联素和瘦素作为主要由脂肪组织分泌的脂肪因子,研究最为广泛,其水平与代谢综合征和动脉粥样硬化的发生密切相关^[4],研究显示相较于原发性高血压患者,PA患者脂联素水平降低、瘦素水平升高^[5]。然而,脂联素和瘦素是否与PA靶器官损害和术后临床转归相关尚不明确。本研究探索了血清脂联素和瘦素与PA靶器官损害和术后临床转归的相关性,以期PA患者的靶器官损害评估和术后临床转归判别提供帮助。

1 对象和方法

1.1 对象

选取2017年4月—2022年4月南京医科大学第一附属医院内分泌科确诊的PA患者68例。纳入标准:①符合《原发性醛固酮增多症诊断治疗的专家共识(2020版)》的诊断标准^[6],包括I筛查试验阳性,醛固酮肾素活性比值(aldoosterone-to-renin ratio, ARR):血浆醛固酮浓度(plasma aldosterone concentration, PAC, pg/mL)/血浆肾素活性[plasma renin activity, PRA, $\mu\text{g}/(\text{L}\cdot\text{h})$] ≥ 30 ;II以下确诊试验至少一项阳性,生理盐水试验:试验后醛固酮 $>100\text{ pg/mL}$,诊断明确,50~100 pg/mL须根据患者临床表现、实验

室检查及影像学表现综合评价;卡托普利试验:服药2 h后醛固酮下降 $\leq 30\%$;III对于合并自发性低钾血症、血浆肾素活性低于可检测水平且醛固酮 $>200\text{ pg/mL}$ 的患者,直接诊断为PA而无需进行额外的确诊试验;②符合单侧PA诊断标准(满足一项及以上):I同步双侧肾上腺静脉采血提示单侧优势分泌[SI(肾上腺静脉与下腔静脉皮质醇比值) ≥ 2 ,LI(优势侧醛固酮皮质醇比值与非优势侧醛固酮皮质醇比值之比) ≥ 2];II如拒绝行肾上腺静脉采血,影像学符合单侧病变;III符合专家共识不需要行肾上腺静脉采血分型的单侧腺瘤的标准;③单侧PA患者排除手术禁忌症,同意行手术治疗。排除标准:①严重心、肝、肾功能不全;②严重脑血管疾病;③急慢性感染;④自身免疫性疾病;⑤血样无法满足脂联素和瘦素检测要求;⑥缺失术后6个月以上的临床转归随访信息。本研究由南京医科大学第一附属医院伦理委员会批准(伦审号:2021-SR-417.A2),所有纳入研究对象均签署知情同意书。

1.2 方法

1.2.1 观察指标

①一般资料:年龄、性别、体重指数(body mass index, BMI)、高血压病程、高血压用药、收缩压、舒张压、最低血清血钾、PAC、PRA、ARR、血脂(总胆固醇、甘油三酯、高密度脂蛋白胆固醇和低密度脂蛋白胆固醇)以及是否诊断高脂血症、糖尿病。②靶器官损害:心脏彩超指标(根据心脏彩超指标计算并判定是否存在左心室肥厚)、估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)、踝肱指数和臂踝脉搏波传导速度。③术后随访结局:根据术后6个月以上随访结果,参考PA手术结局(primary aldosteronism surgical outcome, PASO)标准进行术后临床和生化转归评估^[2]。临床完全缓解定义为未服用高血压药物情况下血压正常($<140/90\text{ mmHg}$);临床部分缓解定义为高血压药物规定日剂量(defined daily dose, DDD)值减少 $\geq 50\%$ 的情况下血

压较术前不变(收缩压下降<20 mmHg 和舒张压下降<10 mmHg),或高血压药物 DDD 值减少<50%的情况下血压较术前下降(收缩压下降≥20 mmHg 或舒张压下降≥10 mmHg);临床未缓解定义为高血压药物 DDD 值减少<50%或增加的情况下血压较术前不变或上升。生化完全缓解定义为血钾和 ARR 正常;生化部分缓解定义为血钾正常和 ARR 升高,但术后 PAC 较术前下降≥50%;生化未缓解定义为持续性低钾血症和/或 ARR 升高,且卡托普利试验结果阳性。

1.2.2 血清脂联素和瘦素检测方法

所有研究对象于入院后第1天清晨(空腹至少8 h)采集肘静脉血,分别应用放射免疫法(试剂盒购于深圳亚辉龙生物科技公司)和酶联免疫吸附法(试剂盒购于武汉华美生物公司)检测血清脂联素和瘦素浓度。

1.3 统计学方法

采用 SPSS 27.0 和 GraphPad Prism 8.2.1 软件进行统计学分析。采用 Kolmogorov-Smirnov 检验计量资料是否符合正态分布,正态分布资料以均数±标准差($\bar{x} \pm s$)表示,两组间比较采用独立样本 *t* 检验,非正态分布资料以中位数(四分位数)[*M*(*P*₂₅, *P*₇₅)]表示,两组间比较采用 Mann-Whitney 检验。计数资料以百分率(%)表示,两组间比较采用 χ^2 检验或

Fisher 确切概率法检验。采用 Spearman 相关分析非正态分布资料间的相关性。采用多因素逐步 Logistic 回归分析独立影响因素。*P* < 0.05 为差异有统计学意义。

2 结果

2.1 研究对象的临床特征

68 例 PA 患者年龄为 51.0(37.5, 56.0)岁,38.2% 为女性,高血压病程 5.0(1.0, 10.0)年,最低血钾水平为(2.90±0.68)mmol/L。根据 PASO 标准进行术后临床转归评估和分组,41.2%为术后临床治愈(即临床完全缓解),58.8%为术后临床未治愈(即临床部分缓解和临床未缓解)。临床治愈组基线 eGFR(*P*=0.016)和高密度脂蛋白胆固醇水平(*P*=0.005)高于临床未治愈组,BMI(*P* < 0.001)、高血压药物 DDD 值(*P*=0.006)、糖尿病占比(*P*=0.004)、高脂血症占比(*P*=0.012)和甘油三酯水平(*P*=0.001)低于临床未治愈组,其余基线临床参数两组间差异无统计学意义。临床治愈组术后高血压药物 DDD 值(*P* < 0.001)和 Δ DDD[(术后高血压药物 DDD 值-术前高血压药物 DDD 值)/术前高血压药物 DDD 值×100%](*P* < 0.001)低于临床未治愈组,临床治愈组的术后生化治愈率(即生化完全缓解)高于临床未治愈组(*P*=0.008,表 1)。

表 1 不同临床转归患者的临床特征
Table 1 Clinical characteristics of patients with distinct clinical outcomes

Variable	Total(<i>n</i> =68)	Clinically cured (<i>n</i> =28)	Clinically uncured (<i>n</i> =40)	<i>P</i>
Baseline parameter				
Age[years, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	51.0(37.5, 56.0)	49.0(32.5, 57.5)	51.5(45.3, 56.0)	0.292
Female[<i>n</i> (%)]	26(38.2)	14(50.0)	12(30.0)	0.095
BMI[kg/m ² , <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	26.1(23.4, 27.8)	22.9(21.1, 24.9)	27.5(26.1, 28.7)	< 0.001
Duration of hypertension[a, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	5.0(1.0, 10.0)	3.0(0.4, 10.0)	8.0(2.0, 10.0)	0.109
DDD value of anti-hypertensive medications[<i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	1.9(1.0, 2.4)	1.2(1.0, 2.0)	2.0(1.4, 2.7)	0.006
Systolic blood pressure[mmHg, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	143(129, 154)	143(128, 148)	144(130, 158)	0.244
Diastolic blood pressure (mmHg, $\bar{x} \pm s$)	87.74 ± 13.85	87.39 ± 11.50	87.98 ± 15.42	0.866
Lowest serum potassium (mmol/L, $\bar{x} \pm s$)	2.90 ± 0.68	2.71 ± 0.70	3.04 ± 0.65	0.055
PAC[pg/mL, <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	153(119, 215)	149(105, 266)	154(123, 210)	0.893
PRA[μg/(L·h), <i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	0.2(0.1, 0.4)	0.2(0.1, 0.4)	0.2(0.1, 0.4)	0.915
ARR[<i>M</i> (<i>P</i> ₂₅ , <i>P</i> ₇₅)]	79.8(34.6, 145.7)	84.1(32.2, 156.5)	74.1(34.7, 134.5)	0.938
Percentage of diagnosis[<i>n</i> (%)]				
Unilateral aldosterone production confirmed by AVS	18(26.5)	4(14.3)	14(35.0)	0.057
Unilateral lesion confirmed by CT	56(70.6)	25(89.3)	31(77.5)	0.352
Bypass AVS	12(16.2)	8(28.6)	4(10.0)	0.098
Metabolic parameter				

(续表 1)

Variable	Total(<i>n</i> =68)	Clinically cured (<i>n</i> =28)	Clinically uncured (<i>n</i> =40)	<i>P</i>
Diabetes[<i>n</i> (%)]	14(20.6)	1(3.6)	13(32.5)	0.004
Hyperlipidemia[<i>n</i> (%)]	39(57.4)	11(39.3)	28(70.0)	0.012
Use of lipid-lowering medications[<i>n</i> (%)]	9(13.2)	1(3.6)	8(20.0)	0.109
TC(mmol/L, $\bar{x}\pm s$)	4.5±0.9	4.5±1.0	4.5±0.8	0.748
TG[mmol/L, $M(P_{25},P_{75})$]	1.2(0.9,1.7)	1.1(0.7,1.3)	1.4(1.1,1.9)	0.001
HDL-C(mmol/L, $\bar{x}\pm s$)	1.2±0.3	1.3±0.3	1.1±0.2	0.005
LDL-C(mmol/L, $\bar{x}\pm s$)	2.7±0.7	2.6±0.7	2.8±0.6	0.254
Baseline target organ damage				
Left ventricular hypertrophy[<i>n</i> (%)]	25(37.0)	8(28.6)	17(44.0)	0.306
eGFR[mL/(min·1.73 m ²), $\bar{x}\pm s$]	94.29±22.46	102.14±20.38	88.71±22.44	0.016
ABI[$M(P_{25},P_{75})$]	1.2(1.1,1.2)	1.2(1.1,1.2)	1.2(1.1,1.2)	0.760
baPWV[cm/s, $M(P_{25},P_{75})$]	1 531(1 400,1 726)	1 519(1 400,1 754)	1 564(1 391,1 733)	0.853
Postoperative follow-up				
DDD value of anti-hypertensive medications[$M(P_{25},P_{75})$]	1.00(0.00,1.32)	0.00(0.00,0.00)	1.00(1.00,1.93)	<0.001
Systolic blood pressure[(mmHg, $M(P_{25},P_{75})$)]	130(120,140)	130(120,130)	130(125,150)	0.078
Diastolic blood pressure [(mmHg, $M(P_{25},P_{75})$)]	85(80,90)	80(80,90)	80(80,90)	0.186
Δ%DDD[$M(P_{25},P_{75})$]	-50(-100,-23)	-100(-100,-100)	-29(-50,-7)	<0.001
ΔSystolic blood pressure(mmHg, $\bar{x}\pm s$)	-12.53±18.78	-13.35±15.91	-12.10±20.28	0.812
ΔDiastolic blood pressure(mmHg, $\bar{x}\pm s$)	-3.44±15.93	-4.65±14.05	-2.82±16.96	0.680
Biochemically cured[<i>n</i> (%)]	42(61.8)	28(100.0)	14(35.0)	0.008
Serum potassium[mmol/L, $M(P_{25},P_{75})$]	4.29(4.10,4.50)	4.28(4.10,4.38)	4.32(4.13,4.50)	0.386
PAC[pg/mL, $M(P_{25},P_{75})$]	144(94,184)	138(95,160)	161(94,194)	0.316
PRA[μg/(L·h), $M(P_{25},P_{75})$]	1.4(0.7,6.1)	1.4(1.0,4.8)	1.4(0.6,8.1)	0.659
ARR[$M(P_{25},P_{75})$]	5.5(2.4,29.5)	5.5(2.7,22.6)	5.5(2.2,37.7)	0.715
Δ% PAC[$M(P_{25},P_{75})$]	-13.0(-46.8,27.2)	-19.2(-47.7,24.3)	-6.6(-44.0,31.8)	0.776

AVS: adrenal venous sampling; CT: computed tomography; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; ABI: ankle-brachial index; baPWV: brachial-ankle pulse wave velocity; Δ%DDD: (DDD value of postoperative anti-hypertensive medications-DDD value of preoperative anti-hypertensive medications)/DDD value of preoperative anti-hypertensive medications×100%; Δsystolic blood pressure: (postoperative systolic blood pressure-preoperative systolic blood pressure)/preoperative systolic blood pressure×100%; Δdiastolic blood pressure: (postoperative diastolic blood pressure-preoperative diastolic blood pressure)/preoperative diastolic blood pressure×100%; Δ%PAC: (postoperative plasma aldosterone concentration-preoperative plasma aldosterone concentration)/preoperative plasma aldosterone concentration×100%.

2.2 血清脂联素、瘦素与靶器官损害的相关性

基线血清瘦素水平与心脏彩超指标升主动脉内径($r=-0.316, P=0.031$)、二尖瓣舒张早期E峰峰值速度/舒张晚期A峰峰值速度比值($r=-0.473, P=0.001$)和踝肱指数($r=-0.361, P=0.009$)呈负相关(图1),与eGFR和臂踝脉搏波传导速度无相关。基线血清脂联素水平与靶器官损害指标无相关。

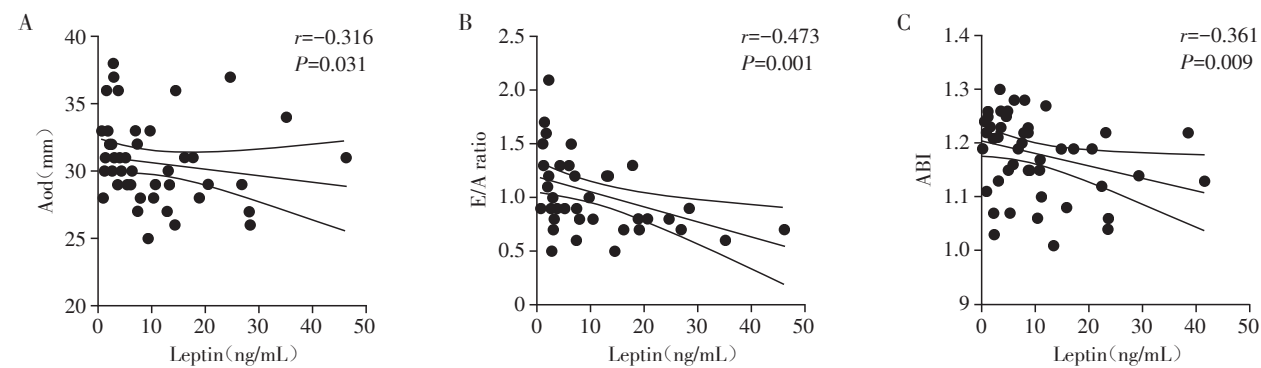
2.3 不同临床转归的血清脂联素和瘦素水平

临床治愈组的基线血清脂联素水平[9.1(7.7,12.5)μg/mL]高于临床未治愈组[6.7(5.9,7.9)μg/mL, $P<0.001$],但两组间瘦素水平无显著差异[临床治愈组 *vs.* 临床未治愈组: 6.8(2.4,12.8)ng/mL *vs.* 7.8

(4.4,16.2)ng/mL, $P=0.323$,图2]。

2.4 多因素逐步 Logistic 回归分析临床转归的影响因素

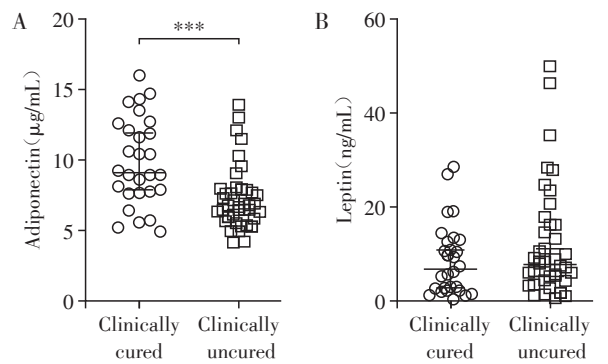
将不同临床转归分组间有统计学意义的因素(BMI、高血压药物 DDD 值、eGFR、糖尿病、高脂血症、甘油三酯、高密度脂蛋白胆固醇和脂联素)作为自变量进行多因素逐步 Logistic 回归分析,以校正上述因素对于因变量临床转归结局的影响,回归分析结果显示更低的 BMI(OR=0.422, 95% CI: 0.272~0.653, $P<0.001$)和更高的脂联素(OR=1.359, 95% CI: 1.004~1.840, $P=0.047$)水平的患者更易获得临床治愈(表2)。



The correlations were assessed by Spearman test. Fit curves and 95% confidential intervals were shown in the figures.

图1 血清瘦素与升主动脉内径(A)、二尖瓣舒张早期E峰峰值速度/舒张晚期A峰峰值速度比值(B)和踝肱指数(C)的相关性

Figure 1 The correlations of serum leptin concentrations with ascending aorta diameter(A), E/A ratio(B) and ankle-brachia index(C)



Comparison of serum adiponectin(A) and leptin(B) levels between the clinically cured group (n=28) and the clinically uncured group (n=40) by Mann-Whitney test. ***P < 0.001.

图2 不同临床转归患者的血清脂联素和瘦素水平比较

Figure 2 Serum adiponectin and leptin concentrations in patients with distinct clinical outcomes

2.5 按BMI分层分析临床转归的影响因素

研究显示,BMI和脂联素两者间存在负相关关系^[4],本研究根据BMI将患者分为非肥胖(BMI<28 kg/m²,n=53)和肥胖(BMI≥28 kg/m²,n=15)两个亚组,进一步分析临床转归的影响因素,非肥胖亚组中,临床治愈组患者的基线eGFR(P=0.009)、高密度脂蛋白胆固醇(P=0.025)和脂联素水平(P=0.002)高于临床未治愈组,甘油三酯(P=0.016)、糖尿病占比(P=0.017)和高脂血症占比(P=0.005)低于临床未治愈组,其余基线临床参数两组间差异无统计学意义。肥胖亚组中,由于临床治愈组仅有1例,临床治愈组与未治愈组间基线临床参数未进行统计学差异分析(表3)。将非肥胖亚组中不同临床转归分组间有统计学意义的因素(eGFR、甘油三酯、高

表2 Logistic回归分析影响PA患者术后临床转归的独立因素

Table 2 Logistic regression analysis to identify the factors associated with postsurgical clinical outcomes in patients with PA

Variable	OR(95%CI)(Clinically cured vs. Clinically uncured)	
	Univariate analysis	Multivariate analysis
BMI	0.407(0.264-0.625)**	0.422(0.272-0.653)**
DDD value of anti-hypertensive medications	0.446(0.242-0.821)**	-
eGFR	1.032(1.005-1.060)*	-
Diabetes	13.000(1.588-106.451)*	-
Hyperlipidemia	3.606(1.305-9.962)*	-
TG	0.185(0.053-0.647)**	-
HDL-C	23.073(2.534-210)**	-
Adiponectin	1.424(1.154-1.758)**	1.359(1.004-1.840)*

CI: confidence interval; OR: odds ratio; *P < 0.05, **P < 0.01.

密度脂蛋白胆固醇、糖尿病、高脂血症和脂联素)作为自变量进行多因素逐步Logistic回归分析,以校正上述因素对于因变量临床转归结局的影响,回归分析结果显示更高的eGFR(OR=1.074, 95% CI: 1.023~1.127, P=0.004)和脂联素(OR=1.816, 95% CI: 1.261~2.616, P=0.001)水平的患者更易获得临床治愈(表4)。

表3 分层分析不同临床转归转归分组的临床特征

Table 3 Stratified analysis of clinical characteristics of patients with distinct clinical outcomes

Variable	Non-obese subgroup (BMI<28 kg/m ² , n=53)		Obese subgroup (BMI≥28 kg/m ² , n=15)	
	Clinically cured	Clinically uncured	Clinically cured	Clinically uncured
Baseline parameter				
Case[n(%)]	27(50.9)	26(49.1)	1(6.7)	14(93.3)
Age[years, M(P ₂₅ , P ₇₅)]	47(32, 58)	52(47, 57)	55	52(39, 56)
Female[n(%)]	13(48.1)	8(30.8)	1(100.0)	4(28.6)
BMI[kg/m ² , M(P ₂₅ , P ₇₅)]	23.9(20.9, 26.8)	25.4(23.1, 27.5)	28.3	29.5(28.1, 31.8)
Duration of hypertension[a, M(P ₂₅ , P ₇₅)]	3.0(0.3, 10.0)	8.0(1.8, 13.5)	3.0	3.5(1.8, 10.0)
DDD value of anti-hypertensive medications[M(P ₂₅ , P ₇₅)]	1.4(1.0, 2.0)	1.8(1.4, 2.5)	1.0	2.1(1.8, 2.9)
Systolic blood pressure(mmHg, $\bar{x} \pm s$)	141 ± 15	147 ± 20	125	146 ± 18
Diastolic blood pressure(mmHg, $\bar{x} \pm s$)	88 ± 12	88 ± 17	78	88 ± 14
Lowest serum potassium(mmol/L, $\bar{x} \pm s$)	2.7 ± 0.7	3.0 ± 0.7	3.4	3.1 ± 0.7
PAC[pg/mL, M(P ₂₅ , P ₇₅)]	144(105, 267)	154(110, 206)	166.7	166(127, 255)
PRA[μg/(L·h), M(P ₂₅ , P ₇₅)]	0.2(0.1, 0.4)	0.3(0.1, 0.5)	0.4	0.2(0.1, 0.3)
ARR[M(P ₂₅ , P ₇₅)]	90.8(30.0, 167.3)	46.7(33.6, 127.8)	40.7	97.8(65.1, 244.9)
Percentage of diagnosis[n(%)]				
Unilateral aldosterone production confirmed by AVS	4(14.8)	11(42.3)	0(0)	3(21.4)
Unilateral lesion confirmed by CT	24(88.9)	19(73.1)	1(100.0)	12(85.7)
Bypass AVS	8(29.6)	3(11.5)	0(0)	1(7.1)
Metabolic parameter				
Diabetes[n(%)]	1(3.7)	9(34.6)*	0(0)	4(28.6)
Hyperlipidemia[n(%)]	10(37.0)	20(76.9)**	1(100.0)	8(57.1)
Use of lipid-lowering medications[n(%)]	3(11.1)	5(19.2)	1(100.0)	13(92.9)
TC[mmol/L, M(P ₂₅ , P ₇₅)]	4.7(3.8, 5.0)	4.4(3.8, 4.9)	5.6	4.7(4.1, 5.1)
TG[mmol/L, M(P ₂₅ , P ₇₅)]	1.0(0.7, 1.3)	1.4(1.1, 2.0)*	1.4	1.4(1.2, 1.6)
HDL-C(mmol/L, $\bar{x} \pm s$)	1.3 ± 0.3	1.1 ± 0.2*	1.2	1.1 ± 0.2
LDL-C(mmol/L, $\bar{x} \pm s$)	2.6 ± 0.7	2.7 ± 0.7	3.8	2.9 ± 0.5
Adiponectin[μg/mL, M(P ₂₅ , P ₇₅)]	9.2(7.7, 12.6)	6.5(5.5, 7.9)**	8.9	7.0(6.4, 7.9)
Leptin[ng/mL, M(P ₂₅ , P ₇₅)]	6.2(2.2, 12.6)	5.8(3.2, 15.0)	19.1	8.2(6.3, 25.6)
Baseline target organ damage				
Left ventricular hypertrophy[n(%)]	8(30.0)	13(50.0)	0(0)	3(21.4)
eGFR[mL/(min·1.73 m ²), $\bar{x} \pm s$]	102 ± 21	83 ± 23**	103	98 ± 19
ABI[M(P ₂₅ , P ₇₅)]	1.2(1.1, 1.2)	1.2(1.2, 1.2)	1.1	1.2(1.1, 1.2)
baPWV[cm/s, M(P ₂₅ , P ₇₅)]	1 531(1 429, 1 802)	1 597(1 461, 1 709)	1 391	1 532(1 342, 1 759)

Compared with the clinically cured group *P < 0.05, **P < 0.01.

3 讨 论

既往多项研究表明PA患者更易合并代谢综合征如糖脂代谢异常等^[1,7-8],而代谢异常可能加重靶器官损害,造成不良预后^[3]。脂肪因子与代谢并发症密切相关,因此,本研究围绕基线血清脂联素和瘦素水平与PA的靶器官损害和术后临床转归的相关性进行了探索。本研究发现高瘦素水平与PA靶器官损害相关,高脂联素水平提示可能更易获得术

后临床治愈。

PA比原发性高血压更易发生代谢并发症和靶器官损害的主要原因被认为是醛固酮分泌失调,出现醛固酮自主合成分泌和水平增高^[1]。研究显示醛固酮介导血管炎症^[9],引起内皮细胞功能失调和间质纤维化^[10],促进动脉粥样硬化^[11],导致心脑血管靶器官损害^[12];同时,醛固酮抑制胰岛素分泌和降低胰岛素敏感性^[13-14],促进代谢综合征和2型糖尿病等代谢并发症发生^[13],进一步加剧靶器官损害。

表4 Logistic回归分析影响非肥胖PA患者术后临床转归的独立因素

Table 4 Logistic regression analysis to identify the factors associated with postsurgical clinical outcomes in non-obese patients with PA

Variable	OR(95%CI)	
	(Clinically cured vs. Clinically uncured)	
	Univariate analysis	Multivariate analysis
eGFR	1.043(1.011-1.076)**	1.074(1.023-1.127)**
TG	0.220(0.064-0.752)*	-
HDL-C	13.760(1.382-136.900)*	-
Diabetes	13.770(1.596-118.700)*	-
Hyperlipidemia	5.667(1.705-18.830)**	-
Adiponectin	1.465(1.146-1.874)**	1.816(1.261-2.616)**

* $P < 0.05$, ** $P < 0.01$.

多项高血压或正常血压人群队列研究也发现,与醛固酮分泌受正常生理调控的人群相比,存在肾素非依赖性的醛固酮自主合成的人群靶器官损害发生率更高^[15-17]。本研究发现瘦素与PA靶器官损害相关,提示瘦素可能是PA代谢异常与靶器官损害的关联因素之一。

瘦素主要由白色脂肪组织分泌,其水平随脂肪组织增多而升高,胰岛素抵抗状态下瘦素水平通常升高^[18]。既往研究发现瘦素可与醛固酮形成瘦素-醛固酮轴,进而影响心血管功能:瘦素直接作用于肾上腺皮质细胞表达的瘦素受体可刺激醛固酮合成^[19];或通过刺激交感神经系统激活肾素-血管紧张素-醛固酮系统间接促进醛固酮合成^[20];Balb/C雌鼠在连续7 d瘦素注射处理后出现内皮功能障碍和心脏促纤维化标志物水平升高,而将瘦素与醛固酮受体拮抗剂合用后,上述作用减弱^[19]。本研究与上述基础研究结果一致,发现瘦素水平越高,由二尖瓣舒张早期E峰峰值速度/舒张晚期A峰峰值速度比值代表的左心室舒张功能越差,由踝肱指数代表的外周动脉血管狭窄可能性越高。然而本研究并未发现瘦素与醛固酮或ARR的相关性,这可能与醛固酮分泌受药物、容量等多种因素影响,导致其检测变异度较大有关^[21]。既往研究已证实PA患者瘦素水平比原发性高血压患者更高^[5],与本研究结果一致,此外,在PA患者中发现与瘦素同样反映胰岛素抵抗状态的脂肪因子抵抗素也与射血分数和左心室舒张功能相关^[5]。

2017年提出的PASO标准统一了单侧PA患者的术后转归评估方法,其中,依据患者术后6个月的血压和高血压用药变化情况,明确了3个不同临床

转归结局,即临床完全缓解(临床治愈)、临床部分缓解和未缓解。该标准在我国单侧PA患者术后管理中尚未广泛应用,然而单侧PA患者术后转归评估非常重要^[2]。PASO研究发现在已进行肾上腺静脉采血标准化分型诊断的前提下,仅有37%的患者可达到术后临床治愈,女性、年轻、术前较少使用高血压药物和无左心室肥厚的患者术后更易获得临床治愈^[2]。另有研究发现,与非肥胖PA患者相比,肥胖的PA患者肾上腺切除术后高血压治愈率更低^[3]。与既往研究类似,本研究发现较低BMI、较高eGFR和脂联素水平的PA患者更易获得临床治愈。

脂联素主要由白色脂肪组织分泌,具有胰岛素增敏、改善动脉粥样硬化和炎症的作用^[4, 22]。研究显示,脂联素在肥胖、胰岛素抵抗和冠心病患者中水平降低,与血压呈负相关^[4, 23];与原发性高血压患者相比,PA患者脂联素水平更低^[5]。动物研究中,低脂联素血症可促进干扰素 γ 、肿瘤坏死因子 α 等炎症蛋白表达,升高利钠肽水平,加剧醛固酮诱导的左心室肥厚和舒张功能障碍,促进舒张性心力衰竭发生^[24-25]。因此,本研究中,高脂联素水平可能反映了更好的代谢和靶器官功能状态,高脂联素水平患者患病期间代谢和靶器官功能损害可能更小,手术解除病变后更易获得临床治愈。然而,本研究并未发现脂联素与靶器官损害指标的相关性,可能与样本例数较少有关。此外,本研究术后临床未治愈组中生化治愈的患者可能因合并原发性高血压,且该占比可能高于临床治愈组,因此与血压呈负相关性的脂联素也表现为与PA术后的临床转归相关。

本研究尚存在以下不足:①横断面研究,未收集术后血样进行脂联素和瘦素检测,无法确定脂联素和瘦素水平与PA靶器官损害及术后临床结局的因果关系;②单中心、小样本研究,可能存在选择偏倚;③本研究醛固酮检测方法为放射免疫法,可能影响醛固酮检测敏感性。然而,本研究仍存在以下优势:①依据国际标准化严格的PASO标准对患者术后至少6个月的临床和生化转归进行评估,术后转归评估方法准确可靠;②首次探索基线血清脂联素和瘦素与PA靶器官损害和术后临床转归的相关性,提示其潜在临床应用价值。

综上所述,本研究发现了血清脂联素和瘦素与PA靶器官损害和术后临床转归的相关性,高瘦素水平的PA患者可能存在更为严重的靶器官损害,高脂联素水平可能提示更易获得术后临床治愈。本

研究结果显示基线脂联素和瘦素检测在PA的精准管理中可能具有筛选和预测价值。未来大样本的队列研究可进一步明确脂联素和瘦素在预测PA靶器官损害和术后临床转归中的价值,以期应用于临床。此外,本研究结果也侧面提示了脂联素和瘦素在PA病理生理机制中的作用,为PA的治疗提供了潜在的靶点信息。

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[收稿日期] 2024-06-07
(本文编辑: 蒋 莉)



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[收稿日期] 2024-05-13
(本文编辑: 唐 震)