

• 临床研究 •

## GDF-15: 冠状动脉慢血流现象的无创预警新靶标

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**[摘要]** 目的: 冠状动脉慢血流(coronary slow flow phenomenon, CSFP)是冠脉造影无狭窄但血流延迟的病理状态, 易引发心绞痛和心血管事件; 当前诊断高度依赖有创检查, 尚缺乏简便、有效的无创预测手段。本研究旨在探讨血清生长分化因子-15(growth differentiation factor 15, GDF-15)在CSFP中的表达水平及其预测价值, 以期为当前依赖有创冠状动脉造影(金标准)的诊断模式提供替代方案。方法: 纳入2023年12月—2024年6月于青岛大学附属医院接受冠状动脉造影的患者, 术中血管无明显异常者纳入正常组( $n=42$ ), 血流延迟但无狭窄者纳入CSFP组( $n=69$ )。收集患者临床资料及术前1 d血清, 采用酶联免疫吸附法(enzyme-linked immunosorbent assay, ELISA)统一检测术前血清GDF-15水平, 进行Logistic回归并检验共线性; 采用受试者工作特征(receiver operating characteristic, ROC)曲线评估诊断效能并进行交叉验证与Bootstrap内部验证。结果: CSFP组GDF-15水平显著高于正常组[957.01(716.27, 1 373.16)ng/L vs. 745.14(585.43, 812.41)ng/L,  $z=-4.14$ ,  $P < 0.001$ ]。单因素和多因素Logistic回归分析显示在调整体重指数(body mass index, BMI)等混杂因素后, GDF-15浓度每增加1个自然对数单位(即浓度升高约2.718倍), CSFP风险增加14.06倍(95%CI: 1.82~68.76,  $P < 0.05$ ); 高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)每增加1 mmol/L, CSFP风险降低16%(OR=0.16, 95%CI: 0.07~0.34,  $P < 0.05$ )。ROC分析显示, GDF-15诊断CSFP的AUC为0.791, 联合HDL-C后AUC提升至0.953, 且灵敏度由57.97%提高至91.30%, 交叉验证和Bootstrap提示cut-off总体稳定。结论: GDF-15在CSFP患者中显著升高, 具有良好的无创预警能力。其与HDL-C联合建立的模型大幅提升了诊断准确性, 有望为CSFP提供便捷、高效的筛查工具, 减少对有创冠脉造影的依赖。

**[关键词]** 生长分化因子-15; 冠状动脉; 微循环; 冠状动脉造影; 高密度脂蛋白胆固醇

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## GDF-15: a novel non-invasive early warning target for coronary slow flow phenomenon

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**[Abstract]** **Objective:** Coronary slow flow phenomenon (CSFP) is a pathological condition characterized by delayed coronary blood flow in the absence of significant stenosis on coronary angiography, which predisposes patients to angina pectoris and cardiovascular events. Current diagnosis relies heavily on invasive investigations, and simple, effective non-invasive predictive tools are lacking. This study aimed to investigate the expression levels of serum growth differentiation factor-15 (GDF-15) in CSFP and evaluate its predictive value, with the goal of providing an alternative to the current diagnostic paradigm dependent on invasive coronary angiography (the gold standard). **Methods:** Patients undergoing coronary angiography at the Affiliated Hospital of Qingdao University were enrolled between December 2023 to June 2024. Those with angiographically normal coronary arteries were assigned to the normal group ( $n=42$ ), while patients exhibiting delayed coronary flow without significant stenosis comprised the CSFP group ( $n=69$ ). The serum GDF-15 levels from the day before the surgery were measured using enzyme-linked immunosorbent assay (ELISA). Logistic regression was performed and collinearity was examined; diagnostic efficacy was assessed by using receiver operating characteristic (ROC) curves and cross-

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validated with Bootstrap internal validation. **Results:** GDF-15 levels were significantly higher in the CSFP group versus controls [957.01 (716.27, 1 373.16) ng/L vs. 745.14 (585.43, 812.41) ng/L;  $z=-4.14$ ,  $P < 0.001$ ]. Both univariate and multivariate logistic regression adjusted for body mass index (BMI) and other confounders showed that each 1-unit increase in  $\ln(\text{GDF-15})$  (corresponding to a 2.718-fold increase in raw concentration) was associated with a 14.06-fold higher CSFP risk (95% CI: 1.82-68.76,  $P < 0.05$ ). Conversely, for each 1 mmol/L increase in high-density lipoprotein cholesterol (HDL-C), the risk was reduced by 16% (OR=0.16, 95% CI: 0.07-0.34,  $P < 0.05$ ). ROC analysis indicated that GDF-15 alone had an AUC of 0.791 for diagnosing CSFP. Combining GDF-15 with HDL-C increased the AUC to 0.953, improving sensitivity from 57.97% to 91.30%; furthermore, cross-validation and Bootstrap indicated cut-off generally stable. **Conclusion:** Elevated serum GDF-15 level in CSFP patients establishes its potential as a non-invasive early warning biomarker. The combined GDF-15/HDL-C diagnostic model demonstrates substantially improved accuracy, suggesting its utility as a practical clinical screening tool. This approach could reduce dependence on invasive coronary angiography for CSFP detection.

[Key words] growth differentiation factor 15; coronary; microcirculation; coronary angiography; high-density lipoprotein cholesterol  
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冠状动脉慢血流 (coronary slow flow phenomenon, CSFP) 是一种介于正常冠状动脉和阻塞性冠状动脉粥样硬化性心脏病之间的微血管功能障碍, 患者常表现为心绞痛样的胸痛或不适, 伴心电图异常, 尽管侵入性冠状动脉造影 (invasive coronary angiography, ICA) 并未见大血管有明显的狭窄或阻塞, 但出现远端血流灌注延迟。流行病学研究显示, CSFP 在 ICA 人群中的患病率达 5.5%, 约 10% 的患者因反复胸痛需重复接受 ICA。长期存在的微循环障碍不仅影响心肌供血、降低患者生活质量, 更增加了心血管事件风险<sup>[1-3]</sup>。然而, 当前 CSFP 的诊断仍高度依赖 ICA, 缺乏有效的早期、无创生物标志物预警体系。既往研究虽关注其与内皮功能障碍和微血管炎症的关联, 却未能确立可在临床症状前期或首次造影前实现风险分层的实用指标, 导致高危人群识别滞后以及对 ICA 的过度依赖。

生长分化因子-15 (growth differentiation factor 15, GDF-15) 主要由巨噬细胞产生, 属于转化生长因子  $\beta$  (transforming growth factor beta, TGF- $\beta$ ) 超家族中的激活素/肌肉生长抑制素亚家族, 是一种在诱导和促进动脉粥样硬化的发生中发挥着关键作用的炎症指标, 单独或联合其他指标用于识别早期急性冠脉综合征 (acute coronary syndrome, ACS) 风险及预测不良心血管结局的价值已得到充分验证<sup>[4-5]</sup>。然而, GDF-15 与 CSFP 之间的相关性尚未阐明。鉴于 CSFP 缺乏有效的无创预警手段, 本研究旨在探究 GDF-15 与 CSFP 的潜在关联, 评估其作为 CSFP 无创诊断标志物的价值。通过提供早期、无创的风险识别工具, 本研究有望规避不必要的 ICA, 将治疗干

预窗口前移, 从而改善患者预后、缓解医疗负担, 并推动 CSFP 诊断模式从“造影依赖”向“血清生物标志物精准分层”转型。

## 1 对象和方法

### 1.1 对象

本研究连续纳入 2023 年 12 月—2024 年 6 月在青岛大学附属医院心血管内科接受 ICA 且显示无明显狭窄的患者, 对所有符合纳入与排除标准的患者实行连续入组。CSFP 组入选标准<sup>[6]</sup>: ICA 排除  $\geq 40\%$  的冠状动脉狭窄; 冠状动脉校正 TIMI 帧计数 (corrected thrombolysis in myocardial infarction frame count, CTFC) 超过正常均值的 2 个标准差 (大约  $> 27$  帧)。同时需排除患者存在以下继发性因素<sup>[7-9]</sup>: 大冠脉痉挛, 在诱发试验或自发发作中, 出现典型胸痛及缺血性心电图改变, 并且造影示目标主冠状动脉一过性狭窄  $\geq 90\%$ ; 非 CSFP 型冠状动脉微循环障碍 (coronary microvascular disease, CMD), 包括但不限于侵入性血流储备受损, 冠脉血流储备 (coronary flow reserve, CFR) 低于常用阈值或微循环阻力指数 (index of microcirculatory resistance, IMR) 升高; 微血管痉挛, 乙酰胆碱试验中出现胸痛/心电变化而无显著大血管痉挛; 影像学灌注受限, 心肌灌注储备 (如正电子发射断层扫描/心脏磁共振成像相关指标) 显著降低, 且造影未呈慢流表型; 血液学异常 (高血黏度、高同型半胱氨酸等); 系统性疾病 (系统性红斑狼疮、甲状腺功能异常等); 药物因素 (可卡因、 $\beta$ 受体阻滞剂等)。共纳入患者 69 例, 同时, 随机选取冠状动脉血流正常患者 42 例作为对照组。所有患者均

签署知情同意书,本研究经医院伦理委员会批准(伦理批件号:QYFYWZLL30417)。

## 1.2 方法

使用西门子大型数字减影血管造影机(Artis zee III ceiling, 106577),经桡动脉或股动脉路径,以碘克沙醇为造影剂,行多体位血管造影,评估患者冠脉情况。正常冠状动脉血流速度参考值,左前降支(left anterior descending artery, LAD)≤21.1 帧;左回旋支(left circumflex artery, LCX)≤22.2 帧;右冠状动脉(right coronary artery, RCA)≤20.4 帧。通过将患者的TIMI帧数除以正常参考值来获得CTFC,CTFC>2个标准差(大约>27 帧)表明该患者存在显著的CSFP。按照既定的纳入排除标准,由两名资深心内科介入医师在盲法下独立判读造影结果,实施入组病例筛选,若有分歧则由第3名专家裁决,排除即时影响因素如造影药量/注射速率、严重心动过速/过缓、显著低血压、造影技术瑕疵等,均记录与控制。

患者术前1 d的血清于-80℃低温冰箱储存,置于室温(10℃~30℃)平衡30 min并小心混匀,选用成都迈克生物公司GDF-15测定试剂盒(maccura-221230-01),经校准、质控后,使用迈克i 3000化学发光分析仪与厂家提供的校准/质控品按照双抗体夹心法原理进行免疫检测。校准在首次上机、校准有效期届满、设备维护/参数调整后或质控失控时进行,以厂家溯源校准品建立多点校准曲线,曲线拟合、残差、回收率及校准因子均需达标。质控于每个检测日/批次及每次校准后进行至少两水平(低/高)判定;任一水平超出可接受范围则触发失控规则,立即暂停样本检测,按说明书排查,必要时重影校准,复测质控至合格后再继续检测。仅在“校准合格+质控合格”时报告受试者结果;失控期间产生的样本一律重测。

同步获取入组对象的全面基线数据,包含人口学特征[年龄、性别、体重指数(body mass index, BMI)]、既往健康记录(疾病史、吸烟史、饮酒史、用药史)及医学检测数据(体格检查:心率、血压;实验室检查:血常规、血脂四项、空腹血糖、肝肾功能全套等生化指标),统计分析前对分组信息进行盲法编号处理。

## 1.3 统计学方法

在正式研究入组前,本研究基于预实验数据估算样本量。结果显示,在 $\alpha=0.05$ (双侧)、Power=0.80的条件下,等比例分组时每组需约32例。本研究最终实际纳入CSFP组69例、正常组42例,超过上述最低

样本量的需求,从而保证了主要结论的统计学效能。

采用SPSS 21.0统计学软件进行统计分析,符合正态分布的计量资料以均数±标准差( $\bar{x} \pm s$ )表示,两样本均数比较采用独立样本 $t$ 检验;不符合正态分布的计量资料用中位数(四分位数)[ $M(P_{25}, P_{75})$ ]表示,两组间数据比较采用Mann-Whitney  $U$ 检验;计数资料以例数(百分比)[ $n(\%)$ ]表示,两组间比较采用 $\chi^2$ 检验或Fisher精确检验;3组间数据比较采用ANOVA或Kruskal-Wallis检验;计算标准化均数差(standardized mean difference, SMD)评估基线特征平衡性;采用单因素Logistic回归分析确定CSFP的预测因素,强关联与混杂因素及单因素筛选阈值 $P < 0.20$ 的因素纳入多因素Logistic回归分析,多因素分析中 $P < 0.05$ 的变量即予保留,以EPV(事件数/参数数量)≥10预先限定模型复杂度;对连续自变量与logit关系进行Box-Tidwell检验,以评估其是否满足Logistic回归线性假设;多重共线性以方差膨胀因子(variance inflation factor, VIF)评估;采用Spearman  $\rho$ 评估主要指标的相关性;利用受试者工作特征(receiver operating characteristic, ROC)曲线分析GDF-15对CSFP的预测价值,阈值以训练集Youden指数确定,以重复5折×10次交叉验证与Bootstrap( $B=1\ 000$ )对曲线下面积(area under curve, AUC)与阈值进行内部验证与校正; $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 两组一般情况比较

本研究共纳入69例CSFP患者(男33例,女36例),年龄为(60.22±10.09)岁;同时纳入42例正常对照者(男15例,女27例),年龄为(62.60±8.69)岁。两组除BMI外( $z=-2.06, P=0.039$ ),性别、年龄、吸烟史、饮酒史、糖尿病史、高血压病史、心脑血管疾病史及降脂药物用药史等一般特征的差异无统计学意义( $P$ 均>0.05)。此外,入院时两组患者的心率、血压及左心室射血分数(left ventricular ejection fraction, LVEF)差异亦无统计学意义( $P$ 均>0.05,表1)。

### 2.2 两组血液学检查比较

CSFP组患者GDF-15较正常对照组显著升高( $z=-4.14, P < 0.001$ ),高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)及D-二聚体(D-dimer)指标明显下降( $P$ 均<0.05),而肌钙蛋白I(troponin I, Tn-I)、N末端B型利钠肽原(N-terminal pro B-type natriuretic peptide, NT-proBNP)及血常规、肝肾功能等生化标志在两组间的差异无统计学意

表1 CSFP组与正常组一般临床资料比较

Table 1 Comparison of baseline clinical characteristics between the CSFP group and the control group

Characteristic	Normal group (n=42)	CSFP group (n=69)	<i>z</i> / <i>t</i> / $\chi^2$	SMD	<i>P</i>
Female[n(%)]	27(64.29)	36(52.17)	0.72	0.247	0.396
Age(years, $\bar{x} \pm s$ )	62.60 $\pm$ 8.69	60.22 $\pm$ 10.09	1.27	-0.252	0.208
BMI[kg/m <sup>2</sup> , <i>M</i> ( <i>P</i> <sub>25</sub> , <i>P</i> <sub>75</sub> )]	25.53(23.84, 27.47)	26.44(24.97, 28.41)	-2.06	0.425	0.039
Smoking history[n(%)]			0.78	0.237	0.676
Never smoked	34(80.95)	51(73.91)			
Former smoker	4(9.52)	8(11.59)			
Current smoker	4(9.52)	10(14.50)			
Drinking history[n(%)]			1.96	0.293	0.376
Never drank	31(73.81)	53(76.81)			
Former drinker	4(9.52)	10(14.49)			
Current drinker	7(16.67)	6(8.70)			
Diabetes[n(%)]	5(11.90)	8(11.59)	0.00	-0.010	1.000
Hypertension[n(%)]	18(42.86)	28(40.58)	0.06	-0.046	0.813
Cardiovascular and cerebrovascular disease history[n(%)]	3(7.14)	6(8.70)	0.00	0.058	1.000
History of lipid-lowering drug use[n(%)]			0.24	0.140	0.626
No	31(73.81)	55(79.71)			
Yes	11(26.19)	14(20.29)			
Heart rate(beats/min, $\bar{x} \pm s$ )	76.81 $\pm$ 10.89	74.45 $\pm$ 9.61	1.19	-0.230	0.236
Systolic blood pressure(mmHg, $\bar{x} \pm s$ )	132.36 $\pm$ 17.78	138.29 $\pm$ 20.02	-1.58	0.313	0.117
Diastolic blood pressure(mmHg, $\bar{x} \pm s$ )	80.21 $\pm$ 12.37	83.16 $\pm$ 11.15	-1.29	0.250	0.198
LVEF[% , <i>M</i> ( <i>P</i> <sub>25</sub> , <i>P</i> <sub>75</sub> )]	60.00(60.00, 61.00)	60.00(60.00, 62.00)	-0.88	0.132	0.379

义(*P*均> 0.05, 表2)。

鉴于HDL-C在CSFP与正常组之间存在显著差异,且既往降脂药物用药史可能影响HDL-C,为评估潜在混杂,本研究按用药情况将受试者分为未用药组(*n*=86)和用药组(*n*=25)两组,首先使用Mann-Whitney *U*检验比较了用药组和未用药组之间的HDL-C水平,结果显示两组之间差异无统计学意义(*P*=0.924)。随后,进行了多因素线性回归分析,控制了年龄、性别、BMI、吸烟、饮酒等潜在混杂因素,结果表明降脂药物使用对HDL-C水平的影响并不显著(*P*=0.950)。该结果提示,降脂药物暴露不足以解释CSFP组与正常组之间观察到的HDL-C差异。

### 2.3 CSFP患者发病的危险因素分析

单因素Logistic回归分析结果显示,BMI、HDL-C及GDF-15水平与CSFP的发生显著相关(表3)。基于目的性变量选择策略,将GDF-15、HDL-C、BMI、年龄、性别、葡萄糖及降脂药物用药史纳入多因素Logistic回归。为保证模型的合理性和稳健性,对连续自变量GDF-15、HDL-C、BMI和年龄进行了Box-Tidwell检验,结果各交互项*P*值均>0.05,表明这些连续变量与logit之间近似线性。各变量VIF为

1.01~1.12(容忍度>0.80),未见多重共线性(表4)。多因素分析结果提示,关键生物标志物的效应量保持稳定且方向一致:血清GDF-15浓度(经自然对数变换,单位ng/L)每增加1个自然对数单位(即浓度升高约2.718倍),CSFP发病风险增加14.06倍(95%CI: 1.82~68.76, *P*< 0.05),为CSFP的独立危险因素,而HDL-C水平升高与CSFP风险显著降低相关,为CSFP的保护因素(OR=0.16, 95%CI: 0.07~0.34, *P*< 0.001, 表5)。对两变量间的相关与共线性进行检验,考虑到数据呈偏态分布,采用Spearman相关性评估GDF-15与HDL-C的相关性,结果 $\rho=-0.155$ , *P*=0.202,提示相关较弱(图1)。进一步在联合GDF-15与HDL-C的联合模型中计算所得的VIF为1.010(容忍度0.990),显著低于常用阈值,未见多重共线性。据此,两指标联合纳入不会引起预计结果不稳定,且与前述结果一致,支持GDF-15为独立危险因素,HDL-C为保护因素。

### 2.4 GDF-15和HDL-C在CSFP中的预测效能

采用ROC曲线评估GDF-15对CSFP的诊断价值,结果显示其AUC为0.791(95% CI: 0.708~0.863),提示较好区分度。以Youden指数确定最佳截断值

表2 CSFP组与正常组血液学指标比较

**Table 2 Comparison of routine laboratory parameters between the CSFP group and the control group**

Characteristic	Normal group(n=42)	CSFP group(n=69)	$z/t/\chi^2$	SMD	P
GDF-15[ng/L, $M(P_{25}, P_{75})$ ]	745.14(585.43, 812.41)	957.01(716.27, 1 373.16)	-4.14	0.979	<0.001
Tn- I [ $\mu$ g/L, $M(P_{25}, P_{75})$ ]	0.01(0.01, 0.01)	0.01(0.01, 0.01)	-0.01	0.014	0.989
NT-proBNP[pg/L, $M(P_{25}, P_{75})$ ]	51.85(20.00, 84.50)	48.10(20.00, 95.90)	0.00	-0.037	1.000
Hb(g/L, $\bar{x} \pm s$ )	140.43 $\pm$ 14.56	143.19 $\pm$ 15.37	-0.94	0.184	0.352
WBC[ $\times 10^9$ /L, $M(P_{25}, P_{75})$ ]	5.88(4.91, 6.96)	6.40(4.76, 7.80)	-0.52	0.108	0.605
PLT[ $\times 10^9$ /L, $M(P_{25}, P_{75})$ ]	217.50(182.50, 272.50)	226.00(190.00, 252.00)	-0.23	0.007	0.820
Glu[mmol/L, $M(P_{25}, P_{75})$ ]	5.42(5.03, 5.80)	5.70(4.92, 7.04)	-1.06	0.547	0.290
Hba1c[% , $M(P_{25}, P_{75})$ ]	5.70(5.55, 6.08)	5.85(5.40, 6.50)	-0.74	0.427	0.457
LDL-C[mmol/L, $M(P_{25}, P_{75})$ ]	2.48(1.90, 3.25)	2.64(2.03, 3.34)	-0.48	0.064	0.631
HDL-C[mmol/L, $M(P_{25}, P_{75})$ ]	3.62(2.57, 4.54)	1.27(1.05, 1.64)	-7.15	-1.891	<0.001
TC(mmol/L, $\bar{x} \pm s$ )	4.47 $\pm$ 0.93	4.34 $\pm$ 1.06	0.65	-0.128	0.520
TG[mmol/L, $M(P_{25}, P_{75})$ ]	1.23(0.75, 1.60)	1.41(1.11, 1.76)	-1.33	0.019	0.182
ApoA1(g/L, $\bar{x} \pm s$ )	1.56 $\pm$ 0.20	1.55 $\pm$ 0.24	0.05	-0.010	0.956
AST[U/L, $M(P_{25}, P_{75})$ ]	20.45(16.33, 26.75)	19.00(14.30, 27.00)	-1.45	0.144	0.147
ALT[U/L, $M(P_{25}, P_{75})$ ]	19.70(15.30, 29.87)	20.10(14.70, 26.60)	-0.54	-0.176	0.590
SCr[ $\mu$ mol/L, $M(P_{25}, P_{75})$ ]	56.60(45.37, 67.85)	57.00(49.40, 68.00)	-0.74	0.214	0.460
UA[mmol/L, $M(P_{25}, P_{75})$ ]	287.00(245.00, 338.00)	306.00(267.00, 356.00)	-1.46	0.225	0.145
D-dimer[ng/mL, $M(P_{25}, P_{75})$ ]	340.00(290.00, 370.00)	300.00(270.00, 350.00)	-2.10	0.077	0.036

Tn-I: troponin I; NT-proBNP; N-terminal pro B-type natriuretic peptide; Hb: hemoglobin; WBC: white blood cell; PLT: platelet; Glu: glucose; Hba1c: glycated hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; HDL-C: high-density lipoprotein cholesterol; TC: total cholesterol; TG: tri-glyceride; ApoA1: apolipoprotein A1; AST: aspartate aminotransferase; ALT: alanine aminotransferase; SCr: serum creatinine; UA: uric acid.

表3 CSFP危险因素的单因素 Logistic 回归分析

**Table 3 Univariate logistic regression analysis of risk factors for CSFP**

Characteristic	OR(95%CI)	P
GDF-15 <sup>a</sup>	10.27(3.09-34.11)	<0.001
HDL-C	0.19(0.11-0.34)	<0.001
BMI	1.16(1.01-1.34)	0.043

Univariate logistic regression analysis was used to assess the risk factors, with results presented as odds ratio (OR) and their 95% confidence interval (95% CI). a: GDF-15 was included in the analysis after logarithmic transformation.

(cut-off)为 908 ng/L, 对应的灵敏度 57.97%、特异度 90.48%。为降低过拟合风险, 对该阈值进行内部验证: 重复 5 折交叉验证(10次)显示, 各训练折中重新选定的阈值中位数为 946.8 ng/L, 且有 78.0% 的阈值落在 908 ng/L 的 $\pm 10\%$ 区间(即 817~999 ng/L); Bootstrap(B=1 000)给出阈值 95%分位区间为 839.3~1 138.3 ng/L。上述结果支持 908 ng/L 在内部重采样下的相对稳定性, 但仍需在外部分立队列进一步验证并视情况再校准。

ROC 曲线分析进一步评估了 GDF-15 联合 HDL-C

表4 多重共线性诊断: 全模型逐项 VIF 与容忍度

**Table 4 Multicollinearity diagnostics: full model-by-model VIF and tolerance**

Characteristic	VIF	Tolerance(1/VIF)
HDL-C	1.11	0.902
GDF-15 <sup>a</sup>	1.12	0.895
Age	1.01	0.994
Use of lipid-lowering drugs	1.01	0.993
BMI	1.02	0.977

VIF=1/(1-R<sup>2</sup>), calculated item by item based on the design matrix including the intercept. A VIF < 5 (tolerance > 0.2) suggests no significant collinearity. a: GDF-15 was included in the analysis after logarithmic transformation.

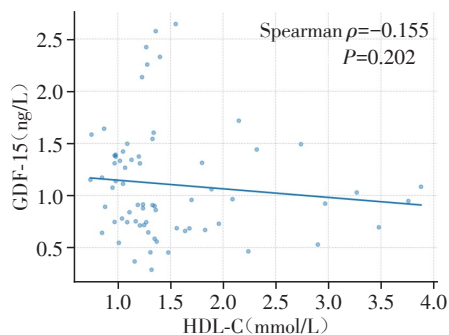
模型的诊断效能。结果显示联合模型的 AUC 为 0.953(95% CI: 0.913~0.984), 高于单一 GDF-15 指标(图 2), 表明联合策略极大提升了 CSFP 的识别能力。在最佳截断值(预测概率=0.73)下, 联合模型的灵敏度为 91.30%(95% CI: 86.06%~96.54%), 特异度为 88.10%(95% CI: 82.08%~94.12%)。为检验稳健性并降低过拟合风险, 本研究实施重复 5 折交叉验证(10次)与 Bootstrap 校正: 测试 AUC(0.927 $\pm$ 0.053), 校正 AUC 0.925, 显示 AUC 存在轻度乐观偏倚, 但联

表5 CSFP危险因素的多因素 Logistic 回归分析

Table 5 Multivariable logistic regression analysis of risk factors for CSFP

Characteristic	OR(95%CI)	P
GDF-15 <sup>a</sup>	14.06(1.82-68.76)	0.011
HDL-C	0.16(0.07-0.34)	<0.001
BMI	1.21(0.97-1.51)	0.087

Multivariate logistic regression analysis was used to assess the risk factors, with results presented as odds ratio (OR) and their 95% confidence interval (95% CI). a: GDF-15 was included in the analysis after logarithmic transformation.



The x-axis represents HDL-C (mmol/L) levels, and the y-axis represents GDF-15 (ng/L) levels; each point corresponds to one subject, and the blue line represents the least squares fitted line. The correlation was assessed using Spearman's rank correlation ( $\rho = -0.155, P = 0.202$ ).

图1 CSFP组GDF-15与HDL-C的相关散点图

Figure 1 Scatter plot of correlation between GDF-15 and HDL-C in CSFP group

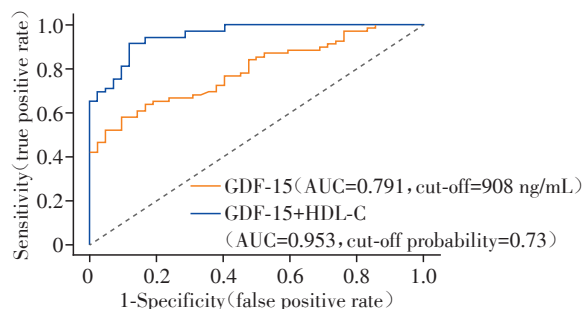
合模型在内部验证后仍保持较高的区分度。综合判断, GDF-15联合HDL-C在CSFP诊断中展现出较高的诊断准确性、灵敏度与特异度。

### 3 讨论

CSFP患者常表现为胸痛或ACS症状,但因冠脉造影未见显著狭窄,易被误诊为非心源性胸痛,导致诊断延迟及治疗不足<sup>[10]</sup>。研究证实,CSFP与心肌缺血、心律失常及不良心血管预后显著相关<sup>[11-12]</sup>。因此,探索能够早期识别CSFP并进行风险分层的特异性生物标志物至关重要,这有助于减少对ICA的过度依赖,具有重大的临床价值。

#### 3.1 CSFP患者的临床特征

本研究共纳入69例CSFP患者与42例冠状动脉血流正常的对照者,结果发现两组在年龄、性别、吸烟史、糖尿病史、高血压病史及心脑血管疾病史等基本特征上差异无统计学意义,提示CSFP的发生可能与传统冠心病的危险因素无显著关联。这一结果与Kopetz等<sup>[13]</sup>的研究结果基本一致,其研究



The ROC curve demonstrated the predictive performance of the single GDF-15 model and its combined model with HDL-C for CSFP. The area under the curve (AUC) for the single GDF-15 model was 0.791 (optimal cut-off value=908 ng/mL), while the AUC for the combined model increased to 0.953 (optimal cut-off probability=0.73). Based on the reference standards (low predictive value: AUC 0.5-0.7; moderate predictive value: AUC 0.7-0.9; and high predictive value: AUC >0.9), the combined model indicated extremely high diagnostic efficacy.

图2 GDF-15和HDL-C对CSFP的预测效能

Figure 2 Predictive performance of GDF-15 and HDL-C for CSFP

指出CSFP更可能是一种独立于大血管狭窄的微血管病变状态,有别于传统动脉粥样硬化<sup>[14]</sup>。

已有研究表明,肥胖尤其是内脏脂肪堆积所导致的胰岛素抵抗、慢性低度炎症及脂肪因子分泌异常,会损害血管内皮功能,从而可能促进CSFP的形成<sup>[15-17]</sup>。本研究结果提示CSFP组患者的BMI高于正常组,但是在多因素Logistic回归中未达到统计学显著水平( $P = 0.087$ ),此结果与既往研究存在差异<sup>[18]</sup>。此差异可能与样本量偏小、BMI分布范围有限或潜在混杂因素(如代谢状态及脂肪分布类型)未被充分评估有关,这些因素可能削弱了BMI的独立影响。但BMI升高的趋势仍提示其对CSFP发生可能具有影响,需大样本研究进一步验证。

在血压、心率及左室射血分数方面,两组患者未见显著差异,这与Wang等<sup>[19]</sup>的研究一致,该研究在CSFP患者中亦未观察到显著的射血分数下降,但提示CSFP患者存在左室收缩及舒张功能受损,同时还可能影响右室的舒张功能,而右室收缩功能则基本保留。另有研究指出,CSFP患者的左心房储备功能与收缩功能下降,提示其心功能异常可能早期波及多腔室,仍处于功能代偿阶段<sup>[20-21]</sup>。

#### 3.2 血清GDF-15及HDL-C在CSFP中的诊断价值及潜在机制

GDF-15是TGF- $\beta$ 超家族中的一种应激诱导因子,在多种病理生理状态下表达升高,尤其在炎症、组织缺血、氧化应激及细胞凋亡等过程中起重要调

控作用<sup>[22-23]</sup>。近年来,GDF-15在心血管疾病领域的研究迅速增加,已被证实与心力衰竭、心律失常及ACS等多种心血管疾病的发生、发展及预后密切相关<sup>[24-26]</sup>。

在本研究中,GDF-15在CSFP组中显著升高,单因素和多变量Logistic回归分析进一步证实其为独立危险因素。这一结果提示GDF-15可能在CSFP的病理生理机制中发挥重要作用。综合既往证据,GDF-15在CSFP中可能呈时间依赖性的双向调控:在急性应激或缺血早期,GDF-15通过激活GFRAL/Smad与PI3K/Akt通路提高一氧化氮(nitric oxide, NO)的生物利用度,并抑制炎症和氧化应激,体现出一定的内皮保护作用<sup>[27-29]</sup>。然而在慢性炎症或持续氧化应激状态下,GDF-15的持续高表达可能诱导内皮细胞凋亡、抑制修复,促进平滑肌增殖与血管重塑,从而使微循环阻力升高、血流减慢,提示病变持续进展<sup>[30]</sup>。此外,其通过作用于炎症通路、促进巨噬细胞募集及激活氧化应激等过程,也可能加剧微血管内皮功能紊乱,造成冠状动脉流速减慢<sup>[31]</sup>。需强调的是,本研究为横断面设计且未严格区分急、慢性病程,上述“阶段差异”仅为基于文献的探索性推断,有待在分期明确、动态随访的人群中通过多时点测定以及交互/分层分析进一步验证。

虽然目前关于GDF-15与CSFP的直接关联研究有限,但现有文献支持其在CMD中的潜在作用<sup>[32]</sup>。如Tian等<sup>[33]</sup>的研究证实,在接受经皮冠状动脉介入治疗的ST段抬高型心肌梗死(ST-elevation myocardial infarction, STEMI)患者中,GDF-15水平升高与CMD显著相关,提示其可能作为一种“微血管应激响应因子”参与冠状动脉血流调节。基于此理论基础,不同于多数研究关注GDF-15在ACS、慢性心衰等大血管病变中的预测价值,本研究提示其在无明显血管狭窄情况下,仍可作为有效的微血管病变指征,进一步揭示了GDF-15在CSFP这一特定CMD亚型中的表达特征及诊断效能,为拓展其在非阻塞性冠状动脉疾病(ischemia with no obstructive coronary arteries, INOCA)领域的临床应用提供了新的证据。

值得注意的是,CSFP患者的HDL-C水平显著低于正常组( $P < 0.001$ )。多因素回归分析显示,HDL-C是独立的保护因素,符合既往研究结果<sup>[34]</sup>。为评估药物的混杂效应,本研究比较了不同降脂用药分组的HDL-C水平。使用Mann-Whitney  $U$ 检验和多因素线性回归分析后,结果均未显示降脂药物使用对HDL-C水平存在显著影响( $P$ 均 $>0.05$ )。这

一结果提示,降脂药物使用对本研究中的HDL-C差异影响有限,主结论的稳健性得到支持。HDL-C除在胆固醇逆转运中发挥关键作用外,还通过其介导的抗氧化、抗炎反应,有效清除循环中氧化低密度脂蛋白(oxidized low-density lipoprotein, ox-LDL),抑制血管内皮炎症激活<sup>[35-36]</sup>。同时,HDL-C可上调内皮一氧化氮合酶(endothelial nitric oxide synthase, eNOS)表达,促进NO合成,维持血管舒张功能和内皮稳态<sup>[37]</sup>。HDL-C水平下降时,这些保护性机制受损,导致氧化应激增强、NO生物利用度降低和内皮功能障碍,最终促进微血管收缩、血流阻力升高,加剧CMD,为CSFP的发生提供病理基础<sup>[38]</sup>。

HDL-C降低常是多种病理过程共同作用的结果,在CSFP等伴有慢性微血管功能障碍的心血管疾病中尤为显著。一方面,持续低度炎症状态抑制脂蛋白A及卵磷脂胆固醇酰基转移酶(lecithin-cholesterol acyltransferase, LCAT)等的合成,影响HDL的生成与功能;另一方面,氧化应激增强破坏HDL的结构与稳定性,形成功能障碍型HDL,削弱其清除ox-LDL、抗炎抗氧化及促进胆固醇外排的能力<sup>[38]</sup>。此外,代谢紊乱可干扰HDL介导的逆转运途径,而炎症或应激状态加速肝脏对HDL的摄取清除,进一步降低其循环水平<sup>[39]</sup>。上述机制协同作用,共同解释了本研究中CSFP患者HDL-C显著降低的现象。

ROC曲线分析结果亦支持GDF-15在CSFP诊断中的价值,其AUC达0.791,显示其具有中等的判别能力。值得注意的是,整合炎症标志物GDF-15与代谢标志物HDL-C构建的联合诊断模型,其诊断效能得到显著提升(AUC=0.953, 95% CI: 0.913~0.984),该值显著高于任一单一指标。这一结果明确表明,融合炎症与代谢信息的联合诊断策略在识别CSFP方面效能卓越(AUC $>0.90$ ),显著优于单一指标。

同时,本研究发现CSFP患者D-二聚体水平下降,但在多因素回归分析中并未成为独立预测因素,提示其更可能为内皮功能障碍伴随的纤溶抑制现象,而非病因驱动因素。既往有研究报道D-二聚体与CMD存在关联,有学者还提出纤维蛋白原/D-二聚体比值对CSFP具有预测价值,说明凝血-纤溶平衡与微循环功能密切相关<sup>[40-42]</sup>。在机制层面,D-二聚体作为纤维蛋白降解产物,其水平主要取决于纤溶活性的强弱。内皮功能障碍和慢性炎症背景下,纤溶酶原激活物抑制剂-1(plasminogen activator inhibitor-1, PAI-1)水平常常上调,它通过抑制组织

型纤溶酶原激活物(tissue plasminogen activator, t-PA)的活性来减少纤溶反应, 导致纤维蛋白降解受限, 从而表现为D-二聚体水平降低<sup>[43]</sup>。已有多项研究在冠心病、糖尿病及代谢综合征等人群中证实PAI-1升高与D-二聚体变化存在联系, 提示两者在凝血-纤溶系统中的交互作用具有普遍性<sup>[44]</sup>。结合上述证据, 本研究推测CSFP中D-二聚体的下降, 可能是PAI-1介导的纤溶抑制在内皮损伤和炎症环境下的下游反应, 而并非独立致病环节。未来研究应结合PAI-1、t-PA等纤溶因子的动态测定, 以及微血栓/微循环功能指标, 系统验证这一调控机制。

上述结果与既往关于GDF-15在ACS、心力衰竭、高血压等疾病中的研究结论基本一致, 如其他研究指出GDF-15可预测心血管事件风险<sup>[45-47]</sup>。然而, 针对CSFP这一独特的微血管功能障碍, GDF-15在其诊断与风险评估中的应用证据仍显匮乏。当前, CSFP诊断高度依赖ICA, 亟需建立有效的早期无创预警体系。尽管既往研究关注了GDF-15与内皮功能障碍和微血管炎症的关联, 但尚未确立可在临床症状前期或首次ICA前实现有效风险分层的实用生物标志物, 导致高危人群识别滞后及ICA的过度应用。本研究不仅验证了GDF-15作为CSFP独立危险因素及诊断标志物的价值, 更重要的是, 通过整合炎症标志物(GDF-15)与代谢标志物(HDL-C)构建的联合诊断模型, 显著提升了识别效能(AUC>0.90), 为建立基于血清生物标志物的CSFP早期筛查与风险分层路径提供了关键性证据, 在一定程度上填补了该领域无创预警工具的重要空白。

### 3.3 研究局限性

本研究为单中心横断面设计, 样本量有限, 代表性不足; 即便采用严格纳排标准, 仍可能存在选择偏倚与不可控混杂, 限制因果推断, 且未严格区分急/慢性病程, 无法检验“阶段差异机制”, 外推性受限。为减轻上述影响, 本研究在设计期完成效能评估, 实际入组高于最低需求; 针对基线不均衡(如年龄)开展多种敏感性分析, 结果方向一致、主要结论稳健, 但仍存在残余混杂。联合模型可能存在乐观偏倚, 后续将于独立外部队列验证并视情况再校准, 并在更大样本的多中心前瞻性研究中加强年龄匹配/分层随机与纵向随访, 以检验普适性并完善因果链条。

生物标志物时序方面, 仅于术前检测1次GDF-15, 未行围术期序列监测。CSFP人群目前缺乏序列化动态证据; 而在非CSFP急性应激情境中, GDF-15可于术后数小时内短暂升高<sup>[48]</sup>。鉴于本研

究对象多为慢性/亚急性且未实施介入治疗, 谨慎推测短期重复测量(术前后数小时至数天)的变动可能有限, 单次术前测值也许更能代表稳定状态, 但该判断属推测, 缺乏直接证据。后续研究将开展动态随访, 重点监测中长期及治疗后GDF-15水平, 并记录肾功能、炎症指标等共变量, 评估其对模型辨别度与校准度的增益。

检测学方面, 本研究严格依照说明书实施“校准-质控放行”流程, 仅在两者均合格时报告结果。受样本体积与通量限制, 并未开展样本级平行重复测量, 未系统报告重复测量的变异系数(coefficient of variation, CV)。在校准合格与质控受控的前提下, 残余测量误差更可能为非差异性随机误差, 其统计效应倾向将效应量向零偏倚(保守), 而非夸大真实关联。

资料收集方面, 虽然血液学指标均在空腹 $\geq 8$  h后采血, 但近期的饮食与酒精摄入及入院前急性疾病的发生未作细化记录, 可能遗留少量保守性混杂。同时, 本研究未能同步检测高敏C反应蛋白(high-sensitivity C-reactive protein, hs-CRP)、白介素-6(interleukin-6, IL-6)等经典炎症指标, 无法直接比较它们与GDF-15的相对预测力, 这在一定程度上限制了对GDF-15独特性的判断。未来研究将完善病例报告表, 细化记录近期饮食、酒精、急性事件、炎症指标、肝肾功能、用药种类及起始/剂量变动; 在统计模型中纳入批号与板别因素并开展分层、交互与敏感性分析; 对代表性样本实施重复测定并报告CV及其置信区间; 一旦发生批号更替, 及时通过桥接样本评估批间一致性并进行必要的校正。同时, 在多中心前瞻性队列中补充检测hs-CRP等炎症指标、标准12导联心电图、心超参数等, 并与GDF-15进行系统比较与联合建模, 从而提升研究结论的可重复性与外推性。

### 3.4 结论与展望

本研究证实, CSFP患者血清GDF-15显著高表达且为其独立危险因素, 整合炎症标志物GDF-15与代谢标志物HDL-C构建的联合诊断模型, 实现CSFP的精准血清学分型, 诊断效能显著提升, 灵敏度达91.30%、特异度达88.10%。然而, 既往关于GDF-15与内皮功能障碍、微血管炎症关联的研究尚未转化出适用于临床症状前期或首次ICA前风险分层的实用工具, 导致高危人群识别滞后。本研究不仅验证了GDF-15作为高效无创生物标志物的价值, 更通过跨病理机制联合策略, 为CSFP的早期筛

查提供了可避免ICA的关键循证工具,填补了该领域无创预警体系的空白。未来研究需在多中心前瞻性队列中,通过动态随访并整合炎症、症状、心电图及超声等多模态信息,验证并优化本模型,以建立真正可用于临床早期预警和风险分层的无创工具。

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所有作者声明无利益冲突。

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#### Author's Contributions:

YIN Yankui contributed to study design and manuscript drafting; LUN Limin, XU Longqiang, and HOU Baoyu conducted experiments and revised the manuscript; JIA Fenghao and LIU Zhen designed statistical methodologies; ZHANG Xuezhi supervised the project and critically reviewed the manuscript.

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