

射血分数保留心力衰竭患者血清 WWP1 和 NLRP3 的表达水平及其临床价值研究

李 强, 邢慧敏, 范海超, 李 玲 (华北医疗健康集团峰峰总医院心内一科, 河北邯郸 056200)

摘要: **目的** 探讨 WW 结构域 E3 泛素蛋白连接酶 1 (WW domain-containing E3 ubiquitin protein ligase 1, WWP1) 和核苷酸结合寡聚化结构域样受体蛋白 3 (nucleotide-binding oligomerization domain-like receptor protein 3, NLRP3) 在射血分数保留心力衰竭 (heart failure with preserved ejection fraction, HFpEF) 患者血清中的表达水平及临床意义。**方法** 选取华北医疗健康集团峰峰总医院 2021 年 1 月 ~ 2022 年 9 月收治的 153 例 HFpEF 患者为观察组, 并根据患者纽约心脏病协会 (New York Heart Association, NYHA) 心功能分级分为心功能分级 I ~ II 级组 ($n=64$) 和心功能分级 III ~ IV 级组 ($n=89$), 另选取同期体检健康的 148 例志愿者为对照组。血清 WWP1, NLRP3 水平与患者心功能指标的相关性采用 Pearson 分析; 受试者工作特征 (receiver operating characteristic, ROC) 曲线分析血清 WWP1 和 NLRP3 水平对 HFpEF 患者心衰严重程度的诊断价值。**结果** 与对照组比较, 观察组血清 WWP1 (1.68 ± 0.35 vs 1.04 ± 0.19) 和 NLRP3 (6.72 ± 1.26 ng/ml vs 4.57 ± 0.84 ng/ml) 表达水平明显升高, 差异具有统计学意义 ($t=19.623, 17.359$, 均 $P < 0.05$); 与心功能分级 I ~ II 级组比较, 心功能分级 III ~ IV 级组血清 WWP1 (1.87 ± 0.39 vs 1.42 ± 0.32) 和 NLRP3 (7.53 ± 1.40 ng/ml vs 5.59 ± 1.18 ng/ml) 表达水平明显升高, 差异具有统计学意义 ($t=7.744, 9.017$, 均 $P < 0.05$); 心功能分级 I ~ II 级组与心功能分级 III ~ IV 级组心率、左心房内径 (left atrial diameter, LAD)、左室舒张末期内径 (left ventricular end-diastolic diameter, LVEDD)、左室舒张末期后壁厚度 (left ventricular end-diastolic posterior wall thickness, LVPWT)、左室射血分数 (left ventricular ejection fraction, LVEF)、二尖瓣舒张早期流速峰值 (peak mitral early diastolic velocity, E) / 舒张晚期流速峰值 (peak late diastolic velocity, A) 以及心房颤动发生率比较差异均具有统计学意义 ($t/\chi^2=2.757 \sim 7.069$, 均 $P < 0.05$); HFpEF 患者血清 WWP1 水平与 LAD, LVEDD, LVPWT 呈正相关 ($r=0.547, 0.471, 0.536$, 均 $P < 0.05$), 与 LVEF 和 E/A 呈负相关 ($r=-0.485, -0.417$, 均 $P < 0.05$); 血清 NLRP3 水平与 LAD, LVEDD, LVPWT 呈正相关 ($r=0.534, 0.494, 0.520$, 均 $P < 0.05$), 与 LVEF 和 E/A 呈负相关 ($r=-0.462, -0.523$, 均 $P < 0.05$)。ROC 结果显示, 血清 WWP1 和 NLRP3 水平单独诊断 HFpEF 患者心衰严重程度的曲线下面积 (area under the curve, AUC) 分别为 0.825 和 0.855, 两者联合诊断的 AUC (0.924) 显著大于血清 WWP1 和 NLRP3 水平单独诊断的 AUC ($Z=3.600, P<0.001; Z=3.053, P=0.002$)。**结论** 血清 WWP1 和 NLRP3 水平在 HFpEF 患者中明显升高, 且与患者心功能密切相关, 血清 WWP1 和 NLRP3 对 HFpEF 患者心衰严重程度具有一定的诊断价值。

关键词: 射血分数保留心力衰竭; WW 结构域 E3 泛素蛋白连接酶 1; 核苷酸结合寡聚化结构域样受体蛋白 3

中图分类号: R541.6; R446.11 文献标识码: A 文章编号: 1671-7414 (2024) 02-151-06

doi:10.3969/j.issn.1671-7414.2024.02.028

Study on Serum WWP1 and NLRP3 Expression Levels and Their Clinical Value in Patients with Heart Failure with Preserved Ejection Fraction

LI Qiang, XING Huimin, FAN Haichao, LI Ling (Department 1 of Cardiology, Fengfeng General Hospital of North China Medical and Health Group, Hebei Handan 056200, China)

Abstract: **Objective** To investigate the expression level and clinical significance of WW domain-containing E3 ubiquitin protein ligase 1 (WWP1) and nucleotide-binding oligomerization domain-like receptor protein 3 (NLRP3) in patients with heart failure with preserved ejection fraction (HFpEF). **Methods** A total of 153 patients with HFpEF admitted to Fengfeng General Hospital of North China Medical and Health Group from January 2021 to September 2022 were collected as the observation group. According to the New York Heart Association (NYHA) cardiac function grading of patients, they were grouped into

基金项目: 邯郸市科学技术研究与发展计划项目 (编号: 19422083012-13): 血清高敏肌钙蛋白 T, sST-2 水平变化在射血分数保留心力衰竭患者预后评估中的价值。

作者简介: 李强 (1975-), 男, 本科, 主治医师, 研究方向: 冠心病与心力衰竭, E-mail: glfj3fa@163.com。

通讯作者: 付静静 (1989-), 女, 研究生, 主治医师, 研究方向: 心力衰竭与心脏电生理, E-mail: irbing412798@163.com。

cardiac function grading I ~ II group ($n=64$) and cardiac function grading III ~ IV group ($n=89$), while 148 healthy volunteers were collected as the control group. The correlation between serum WWP1 and NLRP3 levels and cardiac function indexes of patients was explored by Pearson analysis. The diagnostic value of serum WWP1 and NLRP3 levels on the severity of heart failure in HFpEF patients was analyzed by the receiver operating characteristic (ROC) curve. **Results** Compared with the control group, the expression levels of WWP1 (1.68 ± 0.35 vs 1.04 ± 0.19) and NLRP3 (6.72 ± 1.26 ng/ml vs 4.57 ± 0.84 ng/ml) in the observation group were significantly increased, and the differences were statistically significant ($t=19.623, 17.359$, all $P < 0.05$). Compared with grade I to II groups, WWP1 (1.87 ± 0.39 vs 1.42 ± 0.32) and NLRP3 (7.53 ± 1.40 ng/ml vs 5.59 ± 1.18 ng/ml) expression levels in grade III to IV groups were significantly increased and the differences were statistically significant ($t=7.744, 9.017$, all $P < 0.05$). The differences of heart rate, left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic diameter (LVEDD), left atrial diameter (LAD), left ventricular end-diastolic diameter (LVEDD), left ventricular end-diastolic posterior wall thickness (LVPWT), left ventricular ejection fraction (LVEF), left ventricular ejection fraction (LVEF), peak mitral early diastolic velocity (E) / peak late diastolic velocity (A) and the incidence of atrial fibrillation between the cardiac function grade I to II groups and the grade III to IV groups were significant ($t/\chi^2=2.757 \sim 7.069$, all $P < 0.05$). Serum WWP1 level in HFpEF patients was positively correlated with LAD, LVEDD and LVPWT ($r=0.547, 0.471, 0.536$, all $P < 0.05$), and negatively correlated with LVEF and E/A ($r=-0.485, -0.417$, all $P < 0.05$). Serum NLRP3 level was positively correlated with LAD, LVEDD and LVPWT ($r=0.534, 0.494, 0.520$, all $P < 0.05$), and negatively correlated with LVEF and E/A ($r=-0.462, -0.523$, all $P < 0.05$). ROC results showed that the area under the curve (AUC) of serum WWP1 and NLRP3 levels alone for diagnosing the severity of heart failure in HFpEF patients was 0.825 and 0.855, respectively, and the AUC (0.924) diagnosed by the combination of the two was significantly greater than that diagnosed by the serum WWP1 alone and the AUC diagnosed by the NLRP3 alone ($Z=3.600, P<0.001; Z=3.053, P=0.002$). **Conclusion** The levels of serum WWP1 and NLRP3 were increased in patients with HFpEF, which were closely related to the cardiac function of patients. Serum WWP1 and NLRP3 have certain diagnostic value for the severity of heart failure in patients with HFpEF.

Keywords: heart failure with preserved ejection fraction; WW domain-containing E3 ubiquitin protein ligase 1; nucleotide-binding oligomerization domain-like receptor protein 3

射血分数保留的心力衰竭 (heart failure with preserved ejection fraction, HFpEF) 通常射血分数降低不明显, 而心脏舒张功能存在障碍^[1]。HFpEF易出现肺淤血以及体循环淤血, 心脏泵到主动血的血液减少, 身体脏器供血不足, 表现出胸闷气短、咳嗽、乏力、少尿、下肢水肿等症状^[2-3]。与射血分数减低性心衰相比, 人们对HFpEF的认知有所欠缺, 因此容易错失治疗良机, 寻找与HFpEF心衰程度相关的指标对HFpEF治疗具有积极意义^[4-5]。据相关研究报道, WW结构域E3泛素蛋白连接酶1 (WW domain-containing E3 ubiquitin protein ligase 1, WWP1) 与心脏肥厚的发生发展存在一定关联^[6]。此外, 核苷酸结合寡聚化结构域样受体蛋白3 (nucleotide binding oligomerization domain-like receptor protein 3, NLRP3) 作为一种炎症小体, 能够调节多种细胞因子的表达, 参与炎症性疾病、免疫性疾病、心血管疾病等多种疾病的进展过程^[7]。另有研究表明, WWP1和NLRP3共同调节着脓毒症的发展, 即WWP1和NLRP3可能存在一定靶向关系^[8]。因此, 本研究通过检测HFpEF患者血清WWP1和NLRP3表达水平, 探讨二者对HFpEF患者心衰严重程度的诊断价值, 为HFpEF的临床治

疗提供帮助。

1 材料与方法

1.1 研究对象 选取华北医疗健康集团峰峰总医院2021年1月~2022年9月收诊的153例HFpEF患者为观察组, 男性56例, 女性97例, 平均年龄 61.24 ± 6.53 岁, 平均体质量指数 23.28 ± 2.09 kg/m², 并根据美国纽约心脏病协会 (New York Heart Association, NYHA) 心功能分级将患者分为心功能分级I~II级组 ($n=64$) 和心功能分级III~IV级组 ($n=89$)。纳入标准: ①符合《中国心力衰竭诊断和治疗指南2018版》中HFpEF的诊断标准^[9]; ②年龄>18周岁; ③左心室射血分数 (left ventricular ejection fraction, LVEF) $\geq 50\%$; ④患者依从性良好; ⑤患者及家属同意并签署知情同意书。排除标准: ①患有先天性心脏病者; ②并发恶性肿瘤者; ③伴有严重肝、肾功能异常者; ④传染性 & 自身免疫性疾病者; ⑤伴有心脑血管疾病者; ⑥拒不配合或中途放弃者。另选取同期体检健康的148例志愿者为对照组, 男性58例、女性90例, 平均年龄 61.58 ± 6.71 岁, 平均体质量指数 23.64 ± 2.14 kg/m², 与观察组比较差异无统计学意义 ($t/\chi^2=0.446, 0.214, 1.477$, 均 $P > 0.05$)。本研究

经过医学伦理委员会审核通过。

1.2 仪器与试剂 QuantStudio 3 实时荧光定量 PCR 仪（南京康维达生物科技有限公司）；UReader Eyes 型全波长酶联免疫分析仪（杭州优米仪器有限公司）；逆转录试剂盒 [货号：4366596，赛默飞世尔科技（中国）有限公司]；NLRP3 ELISA 试剂盒（货号：EH4202，武汉菲恩生物科技有限公司）。

1.3 方法

1.3.1 标本采集及处理：观察组入院次日、对照组于体检当日清晨，采集空腹静脉血 10 ml 分置于两个离心管中，4℃ 5 000 r/min 离心 10 min 后将上清液冷冻保存于 -80℃。

1.3.2 WWP1 表达水平检测：TRIzol 试剂提取总 RNA 后采用逆转录试剂盒逆转录为 cDNA，实时荧光定量 PCR 仪进行 RT-qPCR 反应，反应体系 20 μl，95℃预变性 5 min，94.5℃变性 30s，60℃退火 30 s，72℃延伸 30 s，共 40 个循环。WWP1 上游引物 5'-TGCTTCACCAAGGTCTGATACT-3'，下游引物 5'-GCTGTTCCGAACCAAGTTCTTTT-3'，U6 上游引物 5'-CTCGCTTCGGCAGCAGA-3'，下游引物 5'-AACGCTTCACGAATTTGCGT-3'。采用 $2^{-\Delta\Delta Ct}$ 法，U6 为内参，计算 WWP1 mRNA 相对表达水平。

1.3.3 NLRP3 表达水平检测：酶联免疫吸附试验（enzyme-linked immunosorbent assay，ELISA）检测血清 NLRP3 水平，严格按照 NLRP3 ELISA 试剂盒说明书进行操作。

1.3.4 心脏超声检查：彩色多普勒超声仪检测患者左心房内径（left atrial diameter，LAD）、左心室舒张末期内径（left ventricular end diastolic diameter，LVEDD）、左室舒张末期后壁厚度（left ventricular

posterior wall end-diastolic thickness，LVPWT）、左心室射血分数（left ventricular ejection fraction，LVEF）、二尖瓣舒张早期流速峰值（peak mitral early diastolic velocity，E）和舒张晚期流速峰值（peak late diastolic velocity，A），并计算 E/A。

1.4 统计学分析 采用 SPSS 23.0 软件分析数据。计数资料以 n 表示，行 χ^2 检验；计量资料以均数 \pm 标准差 ($\bar{x} \pm s$) 表示，行独立样本 t 检验。血清 WWP1 和 NLRP3 水平与患者心功能指标的相关性采用 Pearson 分析；受试者工作特征（receiver operating characteristic，ROC）曲线分析血清 WWP1 和 NLRP3 水平对 HFpEF 患者心衰严重程度的诊断价值，Z 检验对曲线下面积（area under the curve，AUC）进行比较。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 各组别血清 WWP1 和 NLRP3 表达水平比较 与对照组比较，观察组血清 WWP1 (1.68 ± 0.35 vs 1.04 ± 0.19) 和 NLRP3 (6.72 ± 1.26 ng/ml vs 4.57 ± 0.84 ng/ml) 表达水平均明显升高，差异具有统计学意义 ($t=19.623, 17.359$ ，均 $P < 0.05$)。与心功能分级 I ~ II 级组比较，心功能分级 III ~ IV 级组血清 WWP1 (1.87 ± 0.39 vs 1.42 ± 0.32) 和 NLRP3 (7.53 ± 1.40 ng/ml vs 5.59 ± 1.18 ng/ml) 表达水平均明显升高，差异具有统计学意义 ($t=7.744, 9.017$ ，均 $P < 0.05$)。

2.2 不同心功能分级组临床资料比较 见表 1。心功能分级 I ~ II 级组与心功能分级 III ~ IV 级组心率，LAD，LVEDD，LVPWT，LVEF，E/A 以及心房颤动发生率比较，差异具有统计学意义（均 $P < 0.05$ ）。

表 1 不同心功能分级组临床资料比较 [n (%), ($\bar{x} \pm s$)]					
类别		心功能分级 I~II 级组 ($n=64$)	心功能分级 III~IV 级组 ($n=89$)	t/χ^2	P
年龄 (岁)		60.07 \pm 6.27	62.08 \pm 6.93	1.841	0.068
体质量指数 (kg/m ²)		23.02 \pm 2.02	23.46 \pm 2.13	1.288	0.200
心率 (次/min)		74.59 \pm 7.06	77.83 \pm 7.25	2.757	0.007
LAD (mm)		39.35 \pm 3.98	42.61 \pm 4.37	4.723	< 0.001
LVEDD (mm)		45.67 \pm 3.18	48.52 \pm 3.50	5.160	< 0.001
LVPWT (mm)		10.28 \pm 1.27	11.36 \pm 1.44	4.804	< 0.001
LVEF (%)		57.34 \pm 4.51	54.29 \pm 4.13	4.335	< 0.001
E/A		1.12 \pm 0.16	0.96 \pm 0.12	7.069	< 0.001
性别	男	22 (34.38)	34 (38.20)	0.235	0.628
	女	42 (65.63)	55 (61.80)		
脑血管病	有	12 (18.75)	23 (25.84)	1.062	0.303
	无	52 (81.25)	66 (74.16)		
心房颤动	有	11 (17.19)	29 (32.58)	4.571	0.033
	无	53 (82.81)	60 (67.42)		
冠心病	有	15 (23.44)	27 (30.34)	0.890	0.346
	无	49 (76.56)	62 (69.66)		

2.3 HFpEF 患者血清 WWP1 和 NLRP3 水平与心功能指标的相关性 见表2。Pearson 分析结果显示, HFpEF 患者血清 WWP1 和 NLRP3 水平与 LAD, LVEDD, LVPWT 呈正相关(均 $P < 0.05$), 与 LVEF 和 E/A 呈负相关(均 $P < 0.05$)。

表2 HFpEF 患者血清 WWP1 和 NLRP3 水平与心功能指标的相关性

项目	WWP1		NLRP3	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
LAD	0.547	< 0.01	0.534	< 0.01
LVEDD	0.471	< 0.01	0.494	< 0.01
LVPWT	0.536	< 0.01	0.520	< 0.01
LVEF	-0.485	< 0.01	-0.462	< 0.01
E/A	-0.417	< 0.01	-0.523	< 0.01

2.4 血清 WWP1 和 NLRP3 水平对 HFpEF 患者心衰严重程度的诊断价值 ROC 结果显示, 血清

表3 血清 WWP1 和 NLRP3 水平对 HFpEF 患者心衰严重程度的诊断价值

项目	AUC	截断值	95%CI	敏感度(%)	特异度(%)	Youden 指数
WWP1	0.825	1.61	0.755~0.881	70.79	87.50	0.583
NLRP3	0.855	6.83 ng/ml	0.789~0.906	73.03	85.94	0.590
联合诊断	0.924	-	0.870~0.960	86.52	84.37	0.709

3 讨论

据统计, 心力衰竭在我国 35 岁以上人群中的发病率约为 1%, 预后较差^[10]。HFpEF 通常由高血压、房颤、心肌病等引起, 易发于老年人, 且女性居多^[11]。NYHA 心功能分级具有一定主观性, 为防止 HFpEF 患者心功能分级进展至 IV 级, 应及时应用血清学指标对患者心功能进行辅助性评价, 提高患者预后^[12]。因此, 探讨血清 WWP1 和 NLRP3 表达水平在 HFpEF 患者中的变化及其临床价值具有重要意义。

以往关于 WWP1 的研究多集中在癌症上, 例如, WWP1 参与肺癌、前列腺癌等肿瘤的发生发展^[13]。近两年的研究发现 WWP1 与心脏相关疾病也存在一定关联, 例如, SNYDER 等^[14]研究表明, WWP1 消融后可在一定程度上抑制左心室肥厚的发展、缓解 HFpEF 患者的左室舒张功能障碍。LU 等^[15]通过实验发现, 靶向调节 WWP1 表达可减轻心肌细胞炎症及心肌缺血损伤。本研究结果显示, 观察组血清 WWP1 表达水平明显高于对照组, 推测 WWP1 与 HFpEF 的发生有关; 心功能分级 III ~ IV 级组患者血清 WWP1 表达水平高于心功能分级 I ~ II 级组患者, 推测 WWP1 与 HFpEF 患者的心功能密切相关, 血清 WWP1 高表达的患者心衰程度更为严重。此外, HFpEF 患者血清 WWP1 水平与 LAD, LVEDD, LVPWT, LVEF 和 E/A 存在显著相关性, 提示血清 WWP1 水平与 HFpEF 患者左

室舒张功能关系密切, 血清 WWP1 水平可在一定程度上反映左室舒张功能。

WWP1 和 NLRP3 水平单独诊断 HFpEF 患者心衰严重程度的 AUC 分别为 0.825 和 0.855, 最佳截断值分别为 1.61 和 6.83 ng/ml; 两者联合诊断的 AUC 为 0.924, 显著大于血清 WWP1 和 NLRP3 水平单独诊断的 AUC ($Z=3.600, 3.053, P=0.001, 0.002$)。见图 1 和表 3。

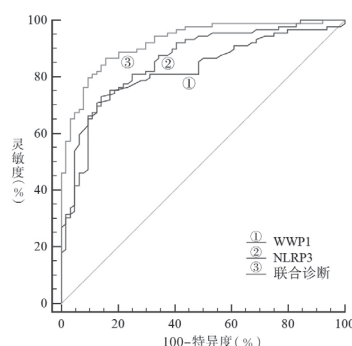


图1 血清 WWP1 和 NLRP3 水平诊断 HFpEF 患者心衰严重程度的 ROC 曲线

室舒张功能关系密切, 血清 WWP1 水平可在一定程度上反映左室舒张功能。

NLRP3 在机体免疫和炎症反应中发挥重要作用, 已成为 2 型糖尿病、帕金森病、自身免疫性疾病的潜在治疗靶点^[16]。刘艳等^[17]研究发现, NLRP3 在慢性心力衰竭患者中表达较高, 且随着心功能分级的升高而升高。田丽^[18]进行的大鼠研究表明, 激活后的 NLRP3 炎症小体促进了 HFpEF 的发生和发展, 推测可能是 NLRP3 激活后刺激其下游炎症因子释放, 从而加剧炎症反应, 参与心脏功能的改变。本研究中观察组血清 NLRP3 表达水平明显高于对照组, 且心功能分级 III ~ IV 级组患者血清 NLRP3 表达水平高于心功能分级 I ~ II 级组患者, 与前人研究结果相一致, 推测 NLRP3 也与 HFpEF 的发生相关, 且与 HFpEF 患者心功能存在关联。相关性分析结果显示, HFpEF 患者血清 NLRP3 水平与 LAD, LVEDD, LVPWT 呈正相关, 与 LVEF 和 E/A 呈负相关, 提示血清 NLRP3 水平与 HFpEF 患者左室舒张功能密切相关, 其水平也可在一定程度上反映 HFpEF 患者左室舒张功能。GUO 等^[19]的研究表明, NLRP3 介导肺动脉高压大鼠心室免疫微环境紊乱并促进右心衰竭, NLRP3 抑制剂可改善其免疫微环境和心功能障碍。结合前及本研究结果推测 NLRP3 通过促进炎症因子和细胞凋亡相关因子的分泌加剧炎症反应、促使心肌

细胞焦亡,进而影响心脏结构和功能。

本研究进一步对血清 WWP1 和 NLRP3 水平对 HFpEF 患者心衰严重程度的诊断价值进行了分析,结果显示,血清 WWP1 水平单独诊断 HFpEF 患者心衰严重程度的 AUC 为 0.825,敏感度、特异度较高,提示血清 WWP1 水平对 HFpEF 患者心衰严重程度具有一定的诊断价值;血清 NLRP3 水平单独诊断 HFpEF 患者心衰严重程度的 AUC 为 0.855,其敏感度、特异度也较高,提示血清 NLRP3 水平也能够一定程度上诊断 HFpEF 患者心衰严重程度;血清 WWP1 和 NLRP3 联合诊断的 AUC 为 0.924,显著优于血清 WWP1 和 NLRP3 水平分别单独诊断的 AUC,提示二者联合的诊断价值更高,当患者血清 WWP1 水平高于 1.61 且 NLRP3 水平高于 6.83 ng/ml 时,患者心衰程度可能较严重,心功能分级为 III 级及以上的概率较高,临床上可根据患者血清 WWP1 和 NLRP3 水平对心衰程度进行辅助性判断,并于患者 WWP1 和 NLRP3 水平接近截断值前,积极采取干预措施,提高患者生存质量。

综上所述, HFpEF 患者血清 WWP1 和 NLRP3 水平明显较高,二者水平与患者心功能密切相关,联合检测对 HFpEF 患者心衰严重程度具有较高的诊断价值。然而本研究为小样本研究,研究结果的准确度尚需大样本研究进行验证,且 WWP1 和 NLRP3 影响 HFpEF 发生发展的具体作用机制也仍需进一步探讨。

参考文献:

- [1] ELTELBANY M, SHAH P, DE FILIPPI C. Biomarkers in HFpEF for diagnosis, prognosis, and biological phenotyping[J]. *Current Heart Failure Reports*, 2022, 19(6): 412-424.
- [2] BORLAUG B A. Evaluation and management of heart failure with preserved ejection fraction[J]. *Nature Reviews Cardiology*, 2020, 17(9): 559-573.
- [3] 张丽伟, 李晓丹, 赵赫, 等. 射血分数正常心力衰竭患者 Fibrosis-4 指数与右心室功能及预后的相关性研究[J]. *现代检验医学杂志*, 2022, 37(2): 167-172. ZHANG Liwei, LI Xiaodan, ZHAO He, et al. Correlation between Fibrosis 4 index and right ventricular function and prognosis in patients with heart failure with preserved ejection fraction[J]. *Journal of Modern Laboratory Medicine*, 2022, 37(2): 167-172.
- [4] JIN Xuanyi, NAUTA J F, HUNG C L, et al. Left atrial structure and function in heart failure with reduced (HFrEF) versus preserved ejection fraction (HFpEF): systematic review and meta-analysis[J]. *Heart Failure Reviews*, 2022, 27(5): 1933-1955.
- [5] PAGEL P S, TAWIL J N, BOETTCHER B T, et al. Heart failure with preserved ejection fraction: a comprehensive review and update of diagnosis, pathophysiology, treatment, and perioperative implications[J]. *Journal of Cardiothoracic and Vascular Anesthesia*, 2021, 35(6): 1839-1859.
- [6] ZHAO Dingsheng, ZHONG Guohui, LI Jianwei, et al. Targeting E3 ubiquitin ligase WWP1 prevents cardiac hypertrophy through destabilizing DVL2 via inhibition of K27-linked ubiquitination[J]. *Circulation*, 2021, 144(9): 694-711.
- [7] ZHANG Jie, LIU Xinqiang, WAN Chunyan, et al. NLRP3 inflammasome mediates M1 macrophage polarization and IL-1 β production in inflammatory root resorption[J]. *Journal of Clinical Periodontology*, 2020, 47(4): 451-460.
- [8] ZHANG Shuyao, GUAN Xinmin, LIU Wei, et al. YTHDF1 alleviates sepsis by upregulating WWP1 to induce NLRP3 ubiquitination and inhibit caspase-1-dependent pyroptosis[J]. *Cell Death Discovery*, 2022, 8(1): 244.
- [9] 中华医学会心血管病学分会心力衰竭学组, 中国医师协会心力衰竭专业委员会, 中华心血管病杂志编辑委员会. 中国心力衰竭诊断和治疗指南 2018[J]. *中华心血管病杂志*, 2018, 46(10): 760-789. Heart Failure Group of Chinese Society of Cardiology of Chinese Medical Association, Chinese Heart Failure Association of Chinese Medical Doctor Association, Editorial Board of Chinese Journal of Cardiology. Chinese guidelines for the diagnosis and treatment of heart failure 2018[J]. *Chinese Journal of Cardiology*, 2018, 46(10): 760-789.
- [10] 屈慧, 李娅, 黄瑶楠, 等. 心力衰竭患者外周血 RDW 和 NT-pro-BNP 联合检测对临床诊断及分级的相关性研究[J]. *现代检验医学杂志*, 2020, 35(5): 65-67, 72. QU Hui, LI Ya, HUANG Yaonan, et al. Correlation study on the combined detection of RDW and NT-Pro-BNP in patients with heart failure to clinical diagnosis and grading[J]. *Journal of Modern Laboratory Medicine*, 2020, 35(5): 65-67, 72.
- [11] WITHAAR C, MEEMS L M G, MARKOUSIS-MAVROGENIS G, et al. The effects of liraglutide and dapagliflozin on cardiac function and structure in a multi-hit mouse model of heart failure with preserved ejection fraction[J]. *Cardiovascular Research*, 2021, 117(9): 2108-2124.
- [12] HEATH R, JOHNSEN H, STRAIN W D, et al. Emerging horizons in heart failure with preserved ejection fraction: the role of SGLT2 inhibitors[J]. *Diabetes Therapy*, 2022, 13(2): 241-250.
- [13] 张成伟, 毕昕, 闫睿, 等. 敲低 WWP1 对肺癌 SPC-A1 细胞增殖和侵袭能力影响及其机制[J]. *中华肿瘤防治杂志*, 2021, 28(16): 1203-1208. ZHANG Chengwei, BI Xin, YAN Rui, et al. Effect of knockdown of WWP1 on the proliferation and invasion of lung cancer SPC-A1 cells and its mechanism[J]. *Chinese Journal of Cancer Prevention and Treatment*, 2021, 28(16): 1203-1208.
- [14] SNYDER L B, LAI Yimu, DOVIAK H, et al. Ubiquitin ligase Wwp1 gene deletion attenuates diastolic dysfunction in pressure-overload hypertrophy[J]. *American Journal of Physiology. Heart and Circulatory Physiology*, 2021, 321(5): H976-H984.
- [15] LU Xia, YANG Boshen, QI Ruiqiang, et al. Targeting WWP1 ameliorates cardiac ischemic injury by suppressing KLF15-ubiquitination mediated myocardial inflammation[J]. *Theranostics*, 2023, 13(1): 417-437.

- [16] 焦雪, 黄树宣. 基于 NLRP3 炎症小体复合物为靶点的帕金森病治疗研究新进展 [J]. 中国临床新医学, 2022, 15(12): 1123-1129.
JIAO Xue, HUANG Shuxuan. New advances in therapy of Parkinson's disease based on NLRP3 inflammasome[J]. Chinese Clinical of New Clinical Medicine, 2022, 15(12): 1123-1129.
- [17] 刘艳, 史伟东. 老年慢性心力衰竭患者血清 miR-223, NLRP3 水平与心肌重构及心功能的相关性 [J]. 海南医学, 2022, 33(19): 2471-2475.
LIU Yan, SHI Weidong. Correlation of serum microRNA-223 and NOD-like receptor protein 3 levels with myocardial remodeling and cardiac function in elderly patients with chronic heart failure[J]. Hainan Medical Journal, 2022, 33(19): 2471-2475.
- [18] 田丽. 钙调控蛋白参与的 NLRP3 炎症小体激活在高血压所致射血分数保留的心力衰竭中的作用机制研究 [D]. 兰州: 兰州大学, 2022.
TIAN Li. Study on the mechanism of calcium regulatory protein involving in NLRP3 inflammasome activation in heart failure with preserved ejection fraction induced by hypertension[D]. LAN Zhou: Lanzhou University, 2022.
- [19] GUO Lizhe, QIN Gang, CAO Yanan, et al. Regulation of the immune microenvironment by an NLRP3 inhibitor contributes to attenuation of acute right ventricular failure in rats with pulmonary arterial hypertension[J]. Journal of Inflammation Research, 2021, 14: 5699-5711.

收稿日期: 2023-03-13

修回日期: 2023-11-09

(上接第 27 页)

- [4] HUANG Bo, LI Yiliang, DENG Zhuoxia, et al. Regulatory mechanism of LncRNA CTBP1-AS2 in nasopharyngeal carcinoma cell proliferation and apoptosis via the miR-140-5p/BMP2 axis[J]. Protein and Peptide Letters, 2022, 29(7): 621-630.
- [5] YOU Rui, ZOU Xiong, WANG Shunlan, et al. New surgical staging system for patients with recurrent nasopharyngeal carcinoma based on the AJCC/UICC rTNM classification system[J]. European Journal of Cancer, 2015, 51(13): 1771-1779.
- [6] EISENHAUER E A, THERASSE P, BOGAERTS J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)[J]. European Journal of Cancer, 2009, 45(2): 228-247.
- [7] ZHONG Guihua, WEI Wei, LIAO Wei, et al. Tumor microbiome in nasopharyngeal carcinoma and its association with prognosis[J]. Frontiers in Oncology, 2022, 12: 859721.
- [8] 薛玉峰, 张会平, 王芳, 等. 鼻咽癌患者血清 miR-144-3p 及 miR-151-3p 的表达水平及临床价值 [J]. 现代检验医学杂志, 2021, 36(5): 65-68.
XUE Yufeng, ZHANG Huiping, WANG Fang, et al. Expression and clinical value of serum miR-144-3p and miR-151-3p levels in patients with nasopharyngeal carcinoma[J]. Journal of Modern Laboratory Medicine, 2021, 36(5): 65-68.
- [9] AI Q H, HUNG K F, SO T Y, et al. Prognostic value of cervical nodal necrosis on staging imaging of nasopharyngeal carcinoma in era of intensity-modulated radiotherapy: a systematic review and meta-analysis[J]. Cancer Imaging, 2022, 22(1): 24.
- [10] NG W T, CHOW J C H, BEITLER J J, et al. Current radiotherapy considerations for nasopharyngeal carcinoma[J]. Cancers, 2022, 14(23): 5773.
- [11] WANG Haihua, WANG Weiyuan, FAN Songqing. Emerging roles of LncRNA in nasopharyngeal carcinoma and therapeutic opportunities[J]. International Journal of Biological Sciences, 2022, 18(7): 2714-2728.
- [12] GUO Zhen, WANG Youhong, XU Heng, et al. LncRNA linc00312 suppresses radiotherapy resistance by targeting DNA-PKcs and impairing DNA damage repair in nasopharyngeal carcinoma[J]. Cell Death & Disease, 2021, 12(1): 69.
- [13] WANG Weifeng, ZHANG Zhuo, LI Yundong, et al. Down-regulated long non-coding RNA LHFPL3 antisense RNA 1 inhibits the radiotherapy resistance of nasopharyngeal carcinoma via modulating microRNA-143-5p/homeobox A6 axis[J]. Bioengineered, 2022, 13(3): 5421-5433.
- [14] LI Yongfeng, ZONG Jin, ZHAO Cong. LncRNA CTBP1-AS2 promotes proliferation and migration of glioma by modulating miR-370-3p-Wnt7a-mediated epithelial-mesenchymal transition[J]. Biochemistry and Cell Biology, 2020, 98(6): 661-668.
- [15] LIU Lixia, LIU Bin, YU Jie, et al. SP1-induced upregulation of LncRNA CTBP1-AS2 accelerates the hepatocellular carcinoma tumorigenesis through targeting CEP55 via sponging miR-195-5p[J]. Biochemical and Biophysical Research Communications, 2020, 533(4): 779-785.
- [16] LE T A H, LAO T D. Circulating microRNAs as the potential diagnostic and prognostic biomarkers for nasopharyngeal carcinoma[J]. Genes, 2022, 13(7): 1160.
- [17] TIAN Yutong, TANG Lu, YI Pin, et al. MiRNAs in radiotherapy resistance of nasopharyngeal carcinoma[J]. Journal of Cancer, 2020, 11(13): 3976-3985.
- [18] SONG Qingxu, CHEN Pengxiang, CHEN Xin, et al. Dynamic change of amide proton transfer imaging in irradiated nasopharyngeal carcinoma and related histopathological mechanism[J]. Molecular Imaging and Biology, 2021, 23(6): 846-853.
- [19] 叶裕丰, 许宗为, 曾伟华, 等. 酰胺质子转移成像技术在鼻咽癌放疗后疗效预测的价值 [J]. 磁共振成像, 2020, 11(8): 635-640.
YE Yufeng, XU Zongwei, ZENG Weihua, et al. The value of amide proton transfer imaging in predicting the effect of nasopharyngeal carcinoma after chemoradiotherapy[J]. Chinese Journal of Magnetic Resonance Imaging, 2020, 11(8): 635-640.

收稿日期: 2023-08-15

修回日期: 2023-10-16