

血清铁和铁调素在心衰患者中的表达及其与心功能的相关性分析

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【摘要】目的 探讨血清铁和铁调素在心力衰竭(HF)患者中的表达水平及其与心功能的相关性。**方法** 选取2020年11月—2021年6月于河北省人民医院心内科住院治疗的非贫血HF患者为研究对象。根据患者左室射血分数(LVEF),分为射血分数保留的心力衰竭(HFpEF)组及射血分数降低的心力衰竭(HFrEF)组,另选取同期因其他系统疾病住院治疗的非贫血患者为对照组。收集患者一般临床资料、空腹血液指标、心脏超声指标,检测血清铁和血清铁调素水平,评估三组患者各临床指标和心功能指标的相关性,采用多因素logistic回归分析HF及HF类型的相关因素以及血清铁和铁调素水平与HF的相关性。**结果** 对照组血清铁及铁调素水平最高[血清铁:4.30(2.61,6.79)mg/L;铁调素:(108.96±39.17)pg/mL],HFpEF组次之[血清铁:2.63(1.67,3.85)mg/L;铁调素:(80.84±34.81)pg/mL],HFrEF组最低[血清铁:1.44(0.85,1.99)mg/L;铁调素:(62.75±21.79)pg/mL]($P<0.05$)。三组患者中,血清铁及铁调素与N末端脑钠肽前体(NT-proBNP)负相关(血清铁: $r=-0.525, P<0.001$;铁调素: $r=-0.436, P<0.001$),与LVEF正相关(血清铁: $r=0.563, P<0.001$;铁调素: $r=0.374, P<0.001$)。多因素logistic回归分析结果显示估算的肾小球滤过率(eGFR)($OR=0.902, 95\% CI 0.838\sim0.970, P=0.005$)和血清铁($OR=0.458, 95\% CI 0.279\sim0.754, P=0.002$)是HF的独立负相关因素,eGFR=86.285 mL/(min·1.73 m²)及血清铁3.589 mg/L是有助于诊断HF的临界值。血清铁($OR=0.303, 95\% CI 0.153\sim0.600, P=0.001$)是HF类型的独立负相关因素,血清铁2.083 5 mg/L是有助于诊断HF类型的临界值。**结论** 血清铁及铁调素在HF患者血清中表达水平降低,HFrEF患者更显著。血清铁是HF及HF类型的独立负相关因素。

【关键词】 心力衰竭;血清铁;铁调素;铁缺乏

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The Correlation of Serum Iron and Hepcidin Levels with Cardiac Function in Heart Failure Patients

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【Abstract】 Objective To detect serum iron and hepcidin levels in patients with heart failure (HF) and analyze their correlations with cardiac function. **Methods** The non-anemic patients with HF hospitalized in Department of Cardiology, Hebei General Hospital from November 2020 to June 2021 were selected as research objects, and divided into HF with preserved ejection fraction (HFpEF) and reduced ejection fraction (HFrEF) groups. Non-anemic patients contemporarily hospitalized for other systemic diseases were assigned as control group. We collected the general clinical data, fasting blood indexes, cardiac ultrasound indexes and detected serum iron and hepcidin levels. The correlation between clinical indicators and cardiac function indicators was evaluated. HF and HF type associated factors, the correlation of serum iron and hepcidin with HF were analyzed by multivariate logistic regression. **Results** Serum iron and hepcidin levels were the highest in control group [serum iron 4.30 (2.61, 6.79) mg/L, hepcidin (108.96±39.17) pg/mL], followed by HFpEF group [serum iron 2.63 (1.67, 3.85) mg/L, hepcidin (80.84±34.81) pg/mL], and the lowest in HFrEF group [serum iron 1.44 (0.85, 1.99) mg/L, hepcidin (62.75±21.79) pg/mL] ($P<0.05$). Serum iron and hepcidin levels were negatively correlated with NT-proBNP [serum iron ($r=-0.525, P<0.001$), hepcidin ($r=-0.436, P<0.001$)], and positively correlated with left ventricular ejection fraction [serum iron ($r=0.563, P<0.001$), hepcidin ($r=0.374, P<0.001$)]. Multivariate logistic regression analysis showed estimated glomerular filtration rate (eGFR) ($OR=0.902, 95\% CI 0.838\sim0.970, P=0.005$) and serum iron ($OR=0.458, 95\% CI 0.279\sim0.754, P=0.002$) were the independently negative correlation factors for HF. The eGFR of 86.285 mL/(min·1.73 m²) and serum iron concentration of 3.589 mg/L were considered as critical value for the diagnosis of HF. Serum iron ($OR=0.303, 95\% CI 0.153\sim0.600, P=0.001$) was an independently negative correlation factor for HF types. The serum iron concentration of 2.083 5 mg/L was considered as critical value for the diagnosis of HF types. **Conclusion** The expression levels of serum iron and serum hepcidin were decreased in HF patients, especially in HFrEF patients.

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Serum iron was an independently negative correlation factor for HF and HF types.

【Key words】 Heart failure; Serum iron; Hepcidin; Iron deficiency

心力衰竭(heart failure, HF)是多种类型心血管疾病的终末期阶段,由于通常合并一种或多种合并症而导致其再住院率和死亡率居高不下^[1]。贫血是 HF 常见的合并症之一,使用促红细胞生成素治疗贫血并未改善 HF 的再住院率及死亡率^[2],而单独使用静脉铁剂与静脉铁剂和促红细胞生成素联合使用却可同等程度地改善 HF 的预后^[3],因此,学者们关注的焦点逐渐从促进红细胞生成转移至改善铁缺乏(iron deficiency, ID)。近年来,研究发现 ID 在慢性 HF 患者中很常见^[4],且对 HF 合并 ID 的患者进行静脉铁剂疗法可减轻患者的 HF 表现并提升患者的运动耐力^[5]。铁是有机体、细胞、组织及整个生物体必不可少的微量元素^[6]。铁调素是目前发现的调节铁稳态的主要物质^[7],是由肝脏细胞分泌的肽类物质,主要通过抑制经十二指肠的铁吸收,阻止网状内皮系统的铁释放,最终导致机体缺铁。血清铁调素升高可能是由慢性炎症刺激和/或铁存储过多诱导,血清铁调素降低可反映伴或不伴贫血的机体铁存储过少^[8]。在本研究中,以血清铁及铁调素水平反映机体铁状态,旨在探索血清铁及铁调素在非贫血 HF 患者中的表达水平,进一步分析血清铁及铁调素与心功能的相关性,以期对 HF 的治疗提供新靶点。

1 资料与方法

1.1 研究对象及分组

选取 2020 年 11 月—2021 年 6 月于河北省人民医院心内科住院治疗的非贫血 HF 患者为研究对象。纳入标准:(1)符合《中国心力衰竭诊断和治疗指南 2018》^[9]关于射血分数保留的心力衰竭(heart failure with preserved ejection fraction, HFpEF)诊断标准以及射血分数降低的心力衰竭(heart failure with reduced ejection fraction, HFrEF)诊断标准;(2)非贫血患者:男性血红蛋白 > 120 g/L,女性血红蛋白 > 110 g/L。排除标准:(1)急性冠脉综合征、病毒性心肌炎;(2)严重肝肾功能损害;(3)急慢性感染;(4)甲状腺功能异常、自身免疫性疾病、血液系统以及恶性肿瘤疾病;(5)近 1 个月有 β 受体阻滞剂、血管紧张素转化酶抑制剂/血管紧张素 II 受体阻滞剂(angiotensin converting enzyme inhibitor/angiotensin II receptor blocker, ACEI/ARB)、血管紧张素受体脑啡肽酶抑制剂(angiotensin receptor neprilysin inhibitors, ARNI)、利尿剂等用药调整;(6)应用铁剂、促红细胞生成素、叶酸及维生素类药物。另选取同期因其他系统疾病住院治疗的非贫血患者为对

照组。分为非 HF 对照组、HFpEF 组和 HFrEF 组 3 组,每组 40 例。本研究已通过本院伦理委员会的审查批准,所有患者知情同意。

1.2 一般临床资料收集

收集入组患者的年龄、性别、体重指数(body mass index, BMI)(体重/身高²)、糖尿病史、他汀类药物服用史、 β 受体阻滞剂服用史、ACEI/ARB 类药物服用史、ARNI 类药物服用史、利尿剂服用史及入院时收缩压、舒张压等情况。收集的病例资料,由经过统一培训的临床工作人员录入,且经临床数据收集的监察员进行内容审核。

1.3 血液指标检测

采集所有患者晨起静脉血,应用全自动生化分析仪(COULTER AU5800, BECKMAN 公司,美国)检测患者血清白蛋白、丙氨酸氨基转移酶(alanine transaminase, ALT)、总胆固醇(total cholesterol, TC)、甘油三酯(triglyceride, TG)、高密度脂蛋白胆固醇(high-density lipoprotein cholesterol, HDL-C)、低密度脂蛋白胆固醇(low-density lipoprotein cholesterol, LDL-C)、空腹血糖、钠离子浓度、估算的肾小球滤过率(estimated glomerular filtration rate, eGFR)和 N 末端脑钠肽前体(N-terminal pro-brain natriuretic peptide, NT-proBNP),应用血常规分析仪检测患者血常规,采用血清铁检测试剂盒(南京建成生物工程研究所)检测患者血清铁水平,采用铁调素检测试剂盒(武汉云克隆科技股份有限公司)ELISA 法检测患者血清铁调素水平。

1.4 心脏超声指标检测

由超声科医师应用心脏彩色多普勒超声检测仪(EPIQ7C, 飞利浦公司,日本)采集患者左心室长轴切面,将 M 超取样线置于心室波群,分别测量左心室舒张末期容积和左心室收缩末期容积,并计算左室射血分数(left ventricular ejection fraction, LVEF)。

1.5 统计学分析

正态分布的计量资料用均数 \pm 标准差($\bar{x} \pm s$)表示,多组间比较采用单因素方差分析,事后比较若方差齐采用 Bonferroni's 进行事后检验,若方差不齐采用 Tamhane's 进行事后检验。非正态分布的计量资料以四分位间距 P_{50} (P_{25} , P_{75})表示,多组间比较采用 Kruskal-Wallis H 秩和检验。以频数和百分率表示的计数资料,采用 χ^2 检验法。各临床指标和心功能指标的相关性采用 Spearman 相关分析。采用多因素二元 logistic 回归分析研究 HF 的相关影响因素,并应用

ROC 曲线下面积评估相关因素的诊断价值。数据统计采用 SPSS 25.0 软件处理,以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般临床资料

HFrEF 组患者男性比例高于其他 2 组 ($P < 0.05$)。HFpEF 组与 HFrEF 组收缩压、血清白蛋白、eGFR、TC、HDL-C 和 LDL-C 水平低于对照组 ($P < 0.05$),但他汀类

药物服用比例高于对照组 ($P < 0.05$)。HFrEF 组 NT-proBNP 最高, HFpEF 组次之, 对照组最低 ($P < 0.05$)。对照组血清铁及铁调素最高, HFpEF 组次之, HFrEF 组最低 ($P < 0.05$)。年龄、BMI、舒张压、糖尿病史、 β 受体阻滞剂服用史、ACEI/ARB 类药物服用史、ARNI 类药物服用史、利尿剂服用史、ALT、钠离子浓度、TG、空腹血糖和血红蛋白水平 3 组间无显著差异。见表 1。

表 1 三组患者一般临床资料比较

项目	对照组	HFpEF 组	HFrEF 组	χ^2/F 值	P 值
年龄/岁	65.13±8.30	69.68±11.51	66.68±9.70	2.309	0.137
男性/[n(%)]	16(40.0)	19(47.5)	32(80.0)*	14.666	0.001
BMI/(kg·m ⁻²)	25.51±2.86	24.94±3.33	24.98±3.06	0.427	0.653
收缩压/mm Hg	136.5±15.93	124.00±19.03*	123.±19.70*	6.318	0.002
舒张压/mm Hg	77.90±11.60	74.20±12.55	77.13±11.57	1.073	0.345
糖尿病史/[n(%)]	7(17.5)	10(25.0)	10(25.0)	0.860	0.650
他汀类药物/[n(%)]	13(32.5)	26(65.0)*	26(65.0)*	11.345	0.003
β 受体阻滞剂/[n(%)]	15(37.5)	17(42.5)	23(57.5)	3.491	0.175
ACEI/ARB 类药物/[n(%)]	13(32.5)	19(47.5)	23(57.5)	5.102	0.078
ARNI 类药物/[n(%)]	2(5.0)	7(17.5)	9(22.5)	5.098	0.078
利尿剂/[n(%)]	6(15.0)	13(32.5)	15(37.5)	5.499	0.064
NT-proBNP/(pg·mL ⁻¹)	47.54(26.54,58.78)	781.00(537.78,2 086.25)*	3 463.00(1 346.75,6 594.25)**	89.260	<0.001
LVEF/%	64.00(60.25,68.00)	61.50(56.00,65.75)	32.00*(27.00,35.00)	81.474	<0.001
白蛋白/(g·L ⁻¹)	41.33±3.71	38.66±3.96*	38.07±3.86*	8.169	<0.001
ALT/(U·L ⁻¹)	16.55(11.88,23.68)	16.90(12.98,26.53)	17.50(12.65,24.35)	0.444	0.801
钠离子/(mmol·L ⁻¹)	141.00(140.00,142.00)	140.00(136.00,141.75)	140.00(138.00,141.00)	5.558	0.062
eGFR/(mL·min ⁻¹ ·1.73 m ⁻²)	95.62(89.23,98.01)	84.18(66.57,91.40)*	68.62(59.19,86.71)*	33.640	<0.001
TC/(mmol·L ⁻¹)	4.82±1.01	3.63±0.77*	3.98±0.83*	19.701	<0.001
TG/(mmol·L ⁻¹)	1.16(0.81,1.63)	0.97(0.82,1.34)	1.03(0.87,1.33)	1.172	0.557
HDL-C/(mmol·L ⁻¹)	1.20(1.07,1.47)	1.09(0.89,1.23)*	0.90(0.81,1.11)*	23.583	<0.001
LDL-C/(mmol·L ⁻¹)	3.17(2.49,3.51)	2.11(1.75,2.79)*	2.45(2.11,2.99)*	17.048	<0.001
空腹血糖/(mmol·L ⁻¹)	5.19(4.64,6.01)	5.39(4.38,6.91)	4.94(4.41,6.71)	1.086	0.581
血红蛋白/(g·L ⁻¹)	136.45±11.36	131.18±11.13	135.48±12.62	2.293	0.105
血清铁/(mg·L ⁻¹)	4.30(2.61,6.79)	2.63(1.67,3.85)*	1.44(0.85,1.99)**	51.08	<0.001
血清铁调素/(pg·mL ⁻¹)	108.96±39.17	80.84±34.81*	62.75±21.79**	21.704	<0.001

注:1 mm Hg=0.133 3 kPa; * 表示与对照组相比, $P < 0.05$; # 表示与 HFpEF 组相比, $P < 0.05$ 。

2.2 各临床指标与心功能指标的相关性分析

以 NT-proBNP 和 LVEF 为代表的心功能指标不符合正态分布,故采用 Spearman 相关分析。性别、他汀类药物服用史与 NT-proBNP 正相关,BMI、收缩压、白蛋白、钠离子、eGFR、TC、HDL-C、LDL-C、血清铁及铁调素与 NT-proBNP 负相关。性别、他汀类药物服用史与 LVEF 负相关,eGFR、HDL-C、血清铁及血清铁调素与 LVEF 正相关。见表 2。

2.3 HF 相关因素分析

2.3.1 logistic 回归分析

将是否发生 HF 作为因变量,将单因素筛查组间差异指标作为自变量行多因素二元 logistic 回归分析,结果显示 eGFR ($OR = 0.902, 95\% CI 0.838 \sim 0.970, P < 0.05$)、血清铁 ($OR = 0.458, 95\% CI 0.279 \sim 0.754, P <$

0.05) 是 HF 的负相关因素。见图 1。

表 2 各临床指标与心功能指标的相关性分析

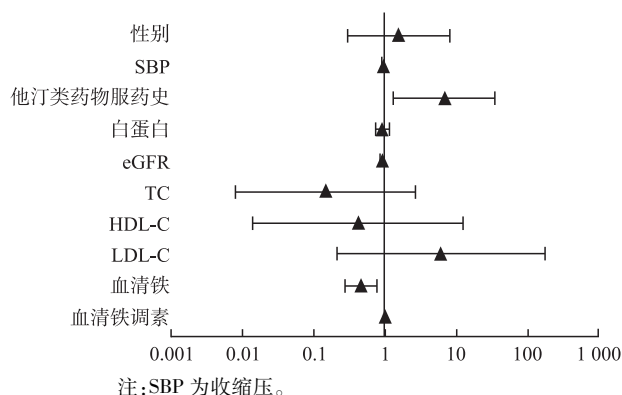
指标	NT-proBNP		LVEF	
	r 值	P 值	r 值	P 值
年龄	0.129	0.161	-0.030	0.744
男性	0.208	0.023	-0.273	0.003
BMI	-0.262	0.004	0.077	0.406
收缩压	-0.346	<0.001	0.135	0.140
舒张压	-0.134	0.146	0.008	0.927
糖尿病史	0.042	0.650	0.001	0.987
他汀类药物服用史	0.204	0.026	-0.256	0.005
白蛋白	-0.374	<0.001	0.169	0.065
ALT	-0.020	0.832	-0.063	0.496
钠离子	-0.205	0.025	0.117	0.204
eGFR	-0.519	<0.001	0.345	<0.001
TC	-0.446	<0.001	0.141	0.125
TG	-0.144	0.117	0.074	0.421

续表

指标	NT-proBNP		LVEF	
	r 值	P 值	r 值	P 值
HDL-C	-0.474	<0.001	0.278	0.002
LDL-C	-0.353	<0.001	0.143	0.121
空腹血糖	-0.124	0.178	0.112	0.225
血红蛋白	-0.161	0.079	0.129	0.161
血清铁	-0.525	<0.001	0.563	<0.001
血清铁调素	-0.436	<0.001	0.374	<0.001

2.3.2 eGFR 和血清铁对 HF 诊断价值的分析

观察 eGFR 及血清铁在诊断 HF 的 ROC 曲线下面积分别为 0.812 (0.737, 0.887) 和 0.838 (0.762, 0.914)。eGFR 约登指数最大值为 0.603, 对应的 eGFR 为 86.285 mL/(min·1.73 m²), 血清铁约登指数最大值为 0.557, 对应的血清铁浓度为 3.589 mg/L, 可认为 eGFR < 86.285 mL/(min·1.73 m²) 及血清铁 < 3.589 mg/L 有助于诊断 HF。见图 2。



OR值	95% CI	P值
1.527	0.291~8.005	0.617
0.941	0.899~0.985	0.009
6.669	1.284~34.641	0.024
0.906	0.729~1.127	0.376
0.902	0.838~0.970	0.005
0.145	0.008~2.641	0.192
0.425	0.014~12.622	0.621
5.995	0.208~172.783	0.296
0.458	0.279~0.754	0.002
0.988	0.965~1.011	0.315

图1 HF 相关因素 logistic 回归分析

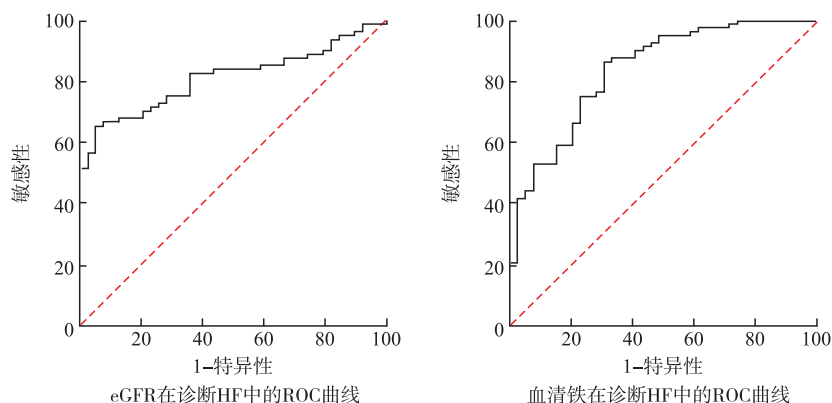


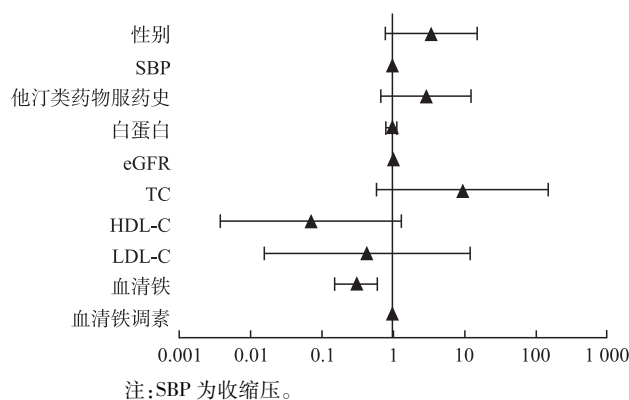
图2 eGFR 与血清铁在诊断 HF 中的 ROC 曲线

2.4 HF 类型相关因素分析

2.4.1 logistic 回归分析

将 HF 类型作为因变量,将单因素筛查组间差异

指标作为自变量行多因素二元 logistic 回归分析,结果显示血清铁 ($OR = 0.303, 95\% CI 0.153 \sim 0.600, P < 0.05$) 是 HF 类型的负相关因素。见图 3。



OR值	95% CI	P值
3.321	0.766~14.397	0.109
0.983	0.951~1.017	0.323
2.815	0.667~11.890	0.159
0.931	0.781~1.109	0.423
0.984	0.950~1.018	0.351
9.040	0.575~142.108	0.117
0.072	0.004~1.271	0.072
0.426	0.016~11.456	0.611
0.303	0.153~0.600	0.001
0.977	0.952~1.002	0.071

图3 HF 类型相关因素 logistic 回归分析

综上,本研究表明,ID 是慢性 HF 的合并症之一,

血清铁作为 HF 及 HF 类型的独立负相关因素,同时具有 HF 的协助诊断价值,为全方面评估 HF 合并症及危险因素提供了新靶点,以期为 HF 的诊疗提供新的生物标志物并延缓 HF 的发生与进展。本研究不足之处在于以血清铁及血清铁调素两项指标来评估 ID 可能不全面,可联合血清铁蛋白、转铁蛋白饱和度、可溶性转铁蛋白受体等指标综合评估;临床样本量较小,且缺少中间范围射血分数心力衰竭相关资料,需扩大临床样本量来进一步证实;且在今后的研究中可深入扩展,如在不同病因(如缺血性心肌病、扩张型心肌病、肺心病等)所致 HF 患者中分类观察,更加深入地探究血清铁及铁调素的基础研究价值与临床价值。

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