临床研究 ·论 著·

联合检测血清正五聚蛋白、高迁移率族蛋白 1 及微小 RNA-21 对急性肾损伤有预测价值*

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摘要 目的:探讨血清正五聚蛋白(PTX3)、高迁移率族蛋白 1(HMGB-1)及微小 RNA(miR)-21 在急性肾损伤(AKI)中的表达及意义。方法:随机选取 87 例 AKI 患者为研究组,并选择同期体检的健康人 50 例为对照组,参照改善全球肾脏病预后组织分期标准,其中Ⅰ期 23 例,Ⅱ期 33 例,Ⅲ期 31 例,根据预后(住院后 28 d 内)情况分为死亡组 19 例和存活组 68 例。监测患者血清 PTX3、HMGB-1 及 miR-21 水平并绘制受试者工作特征(ROC)曲线,计算最佳诊断截断值和曲线下面积(AUC),分析其对 AKI 的预测价值。结果:研究组患者血清 PTX3、HMGB-1 水平高于对照组,miR-21 水平低于对照组(P 均 <0.05);Ⅰ期患者血清 PTX3、HMGB-1 水平低于Ⅱ期、Ⅲ期患者,且Ⅱ期低于Ⅲ期;Ⅰ期患者 miR-21 水平高于Ⅱ期、Ⅲ期患者,且Ⅱ期高于Ⅲ期(P 均 <0.05);死亡组患者血清 PTX3、HMGB-1 水平高于存活组,miR-21 水平低于存活组(P 均 <0.05);PTX3 诊断 AKI 的截断值为13.28 ng/L,*AUC* 为 0.833(95% *CI*:0.771 ~ 0.895);HMGB-1 诊断 AKI 的的截断值为 11.40pg/mL,*AUC* 为 0.916(95% *CI*:0.901 ~ 0.935);miR-21 诊断 AKI 的的截断值为 0.89,*AUC* 为 0.895(95% *CI*:0.842 ~ 0.947);3 项联合检测诊断 AKI 的 *AUC* 为 0.989(95% *CI*:0.981 ~ 0.999),优于各指标单独预测($Z=4.873$、8.062、3.479,P 均 <0.05)。结论:AKI 患者血清 PTX3、HMGB-1 及 miR-21 水平表达明显异常,联合检测有预测价值。

关键词 正五聚蛋白;高迁移率族蛋白 1;微小 RNA-21;急性肾损伤;预测价值

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Predictive value of serum PTX3, HMGB-1 and miR-21 in acute kidney injury

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Abstract Objective: To study the predictive value of serum pentameric protein (PTX3), high mobility group protein 1 (HMGB-1) and miR-21 in acute kidney injury. Methods: Totally, 87 patients with acute kidney injury were selected as the study group, and 50 healthy patients who received physical examination in our hospital during the same period were selected as the control group. The changes of serum PTX3, HMGB-1 and miR-21 levels and their predictive value were analyzed. Results: The serum levels of PTX3 and HMGB-1 in the study group were significantly higher than those in the control group, and the levels of Mir-21 were significantly lower than those in the control group ($P<0.05$). The serum levels of PTX3 and HMGB-1 in stage I acute kidney injury patients were significantly lower than those in acute kidney injury stage Ⅱ and Ⅲ patients, and the level of Mir-21 was significantly higher in stage I acute kidney injury patients than that in stage Ⅱ and Ⅲ patients. The serum levels of PTX3 and HMGB-1 in acute kidney injury stage Ⅱ patients were significantly lower than those in stage Ⅲ patients, and the level of Mir-21 was significantly higher in stage Ⅱ acute kidney injury patients than that in stage Ⅲ patients. The difference was significant ($P<0.05$). The levels of serum PTX3 and HMGB-1 in death group were significantly higher than those in survival group, and the levels of Mir-21 in death group were significantly lower than those in survival group with the differences being significant ($P<0.05$). The AUC of PTX3 in the diagnosis of acute kidney injury was 0.833 and 95% *CI* was 0.771-0.895. The AUC of HMGB-1 in the diagnosis of acute kidney injury was 0.916 and 95% *CI* was 0.901-0.935. The AUC of Mir-21 in the diagnosis of acute kidney injury was 0.895 and 95% *CI* was 0.842-0.947. The

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AUC of combined detection for acute kidney injury was 0.989, 95% *CI* was 0.981-0.999, and there was significant difference in *AUC* area ($Z=4.873$, 8.062, 3.479, $P<0.05$). Conclusion: Serum PTX3, HMGB-1 and miR-21 were significantly abnormal in patients with acute kidney injury, which could be used as an important indicator for the diagnosis of acute kidney injury.

Key words N-pentameric protein; High mobility group protein 1; MiR - 21; Acute kidney injury; Predictive value

急性肾损伤(acute kidney injury,AKI)是由多种病因导致的一种临床综合征,可在短时间内导致肾功能下降[1]。正五聚蛋白(pentraxin3,PTX3)是穿透素家族成员之一,由白介素(IL)-1 刺激内皮细胞和成纤维细胞而产生,在炎症调节中起重要作用,参与多种危重疾病的发生。高迁移率族蛋白 1(high mobility group box 1 protein,HMGB-1)是一种可分泌于细胞外的非组蛋白核蛋白,可通过炎症细胞的分泌和坏死细胞的被动释放介导炎症反应,被发现在脓毒症合并 AKI 中表达异常,可能参与疾病的发展[2]。微小 RNA(microRNA,miR)-21 参与细胞增生、凋亡等多种生物学过程的调控[3,4]。本研究监测 AKI 患者血清 PTX3、HMGB-1 及 miR-21 的表达并评估其对 AKI 的预测价值。

资料与方法

一般资料 随机选择 2018 年 6 月-2020 年 1 月在海口市人民医院住院治疗的 AKI 患者 87 例(男 62,女 25),年龄 48 ~ 72 岁,平均(59.6 ± 3.6)岁,为研究组,参照改善全球肾脏病预后组织(Kidney Disease: Improving Global Outcomes, KDIGO)分期标准[4]进行临床分期,Ⅰ期 23 例,Ⅱ期 33 例,Ⅲ期 31 例;选择同期体检的健康人 50 例(男 28,女 22),年龄 45 ~ 70 岁,平均(59.2 ± 3.6)岁,为对照组。2 组一般资料,差异无统计学意义。

纳入标准:①血肌酐 > 26.5 μmol/L,尿量 < 0.5 mL/(kg · h);②病史、临床症状、实验室指标及影像学检查均符合《KDIGO 急性肾损伤临床实践指南》[5]中 AKI 诊断;③心脑等器官无明显障碍。排除标准:①长期透析治疗者;②沟通障碍者;③有肝脏血管畸形、血管瘤等疾病者;④凝血功能障碍及血液系统疾病者。本研究经医院伦理委员会批准,患者或家属均知情并签署同意书。

方法与评价标准 采集患者入院第 2 天清晨空腹静脉血,以 3 000 转/min、半径 10 cm 离心 10 min,提取上层血清后,置于 -20℃的冷冻箱内存储,采用酶联免疫吸附法测定血清PTX3、HMGB-1及miR-21水平,试剂盒购自深圳晶美生物技术有限公司,操作严格按试剂盒说明进行。根据住院后 28 d 内的存活情况,将 AKI 患者分为死亡组 19 例和存活组 68 例。

统计学分析 采用 SPSS 22.0 统计软件包。计量资料用($\bar{x} \pm s$)表示,采用 t 检验,多组比较采用方差分析,使用受试者工作特征(receiver operating characteristic,ROC)曲线分析血清 PTX3、HMGB-1 及 miR-21 对诊断 AKI 的预测价值。以 $P<0.05$ 为差异有统计学意义。

结 果

2 组血清 PTX3、HMGB-1 及 miR-21 水平 研究组血清 PTX3、HMGB-1 水平高于对照组,miR-21 低于对照组(P 均 <0.05),见表 1。

表 1 2 组血清 PTX3、HMGB-1 及 miR-21 水平比较($\bar{x} \pm s$)

组别	例	PTX3 (ng/L)	HMGB-1 (pg/mL)	miR-21
研究组	87	15.62 ± 5.02	13.41 ± 2.34	0.74 ± 0.21
对照组	50	8.74 ± 3.83	3.34 ± 0.61	1.45 ± 0.41
t 值		6.449	32.195	7.265
P 值		0.000	0.000	0.000

不同分期患者血清 PTX3、HMGB-1 及 miR-21 水平 Ⅰ期患者血清 PTX3、HMGB-1 低于Ⅱ期、Ⅲ期患者,且Ⅱ期低于Ⅲ期患者;Ⅰ期 miR-21 高于Ⅱ期、Ⅲ期患者,且Ⅱ期高于Ⅲ期患者(P 均 <0.05),见表 2。

表 2 不同分期血清 PTX3、HMGB-1 及 miR-21 水平比较($\bar{x} \pm s$)

分期	例	PTX3 (ng/L)	HMGB-1 (pg/mL)	miR-21
Ⅰ期	23	12.65 ± 4.97	9.45 ± 2.15	0.97 ± 0.19
Ⅱ期	33	15.37 ± 5.02	13.19 ± 2.34	0.75 ± 0.23
Ⅲ期	31	18.09 ± 5.11	16.58 ± 2.41	0.56 ± 0.21
F 值		7.759	62.726	24.521
P 值		0.001	0.000	0.000

不同预后血清 PTX3、HMGB-1 及 miR-21 水平 死亡组血清 PTX3、HMGB-1 水平高于存活组,miR-21 低于存活组(P 均 <0.05),见表 3。

表 3 不同预后血清 PTX3、HMGB-1 及 miR-21 水平比较($\bar{x} \pm s$)

预后	例	PTX3 (ng/L)	HMGB-1 (pg/mL)	miR-21
死亡组	19	19.41 ± 5.69	21.39 ± 3.17	0.42 ± 0.12
存活组	68	14.56 ± 5.14	11.18 ± 2.35	0.83 ± 0.19
t 值		3.552	15.455	8.902
P 值		0.001	0.000	0.000

血清 PTX3、HMGB-1 及 miR-21 对 AKI 的预测价值 血清 PTX3、HMGB-1 及 miR-21 联合检测优于各指标单独检测(Z = 4.873、8.062、3.479,P 均 < 0.05),见表 4、5。

表 4 血清 PTX3、HMGB-1 及 miR-21 对 AKI 的 ROC 曲线参数

检测变量	*AUC*	标准误[a]	*P* 值	95% *CI*
PTX3	0.833	0.032	0.000	0.771 ~ 0.895
HMGB-1	0.916	0.009	0.000	0.901 ~ 0.935
miR-21	0.895	0.027	0.000	0.842 ~ 0.947
联合检测	0.989	0.001	0.000	0.981 ~ 0.999

表 5 血清 PTX3、HMGB-1 及 miR-21 对 AKI 的诊断效能

检测变量	灵敏度(%)	特异性(%)	约登指数
PTX3	81.35	79.81	0.51
HMGB-1	83.46	77.95	0.49
miR-21	83.19	76.18	0.54
联合检测	87.78	92.19	0.65

讨 论

PTX3 是近年来发现的新型炎性标记物,是参与免疫应答的保守蛋白家族成员之一,与感染性疾病的发生密切相关,可与 P-选择素结合,调节局部全身炎症反应。PTX3 在正常人体中含量较低,当发生感染时可迅速上升,并在 6 ~ 8 h 内达到高峰。研究显示,PTX3 在脓毒症患者中表达升高,其水平与疾病的严重程度呈正相关[6,7]。本研究中血清 PTX3 在 AKI 中呈高表达,且与疾病预后关系密切,与文献一致[8]。

HMGB-1 是一种促炎因子,具有启动和维持炎症反应的作用,当细胞坏死时可释放大量 HMGB-1[9]。研究显示,约 40% 失血性休克患者可并发 AKI 的发生,血流灌注不足导致的缺血和随之发生的炎症反应可造成 AKI[10]。研究显示,HMGB-1 在失血性休克所致的肾组织过度炎症中起重要作用[11]。本研究中 AKI 患者血清 HMGB-1 水平显著高于健康人群,且可随着疾病的严重程度而升高,可作为预测疾病的标志物。miR-21 参与多种重要的生物学过程,miR-21 对肾脏具有保护作用,在多种肾脏疾病中表达异常[12]。邱玉霞等[13]研究显示,HMGB-1 联合其他指标在预测脓毒症合并 AKI 中具有较高的灵敏度和特异性,本研究结果与之相似。

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