

doi: 10.13241/j.cnki.pmb.2021.18.025

先天性心脏病患儿术后急性肾损伤的影响因素 及尿 NGAL、KIM-1 的诊断价值分析 *

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摘要 目的:探讨影响先天性心脏病患儿术后急性肾损伤(AKI)的影响因素及尿中性粒细胞明胶酶相关脂质运载蛋白(NGAL)、肾损伤分子 1(KIM-1)的诊断价值。**方法:**选择 2018 年 1 月至 2019 年 12 月我院心胸外科收治的 60 例先天性心脏病术后并发 AKI 患儿(AKI 组)和同期收治的 172 例先天性心脏病术后未发生 AKI 患儿(NAKI 组)作为研究对象。收集患儿临床基线资料,检测尿 NGAL、KIM-1 水平,采用 Logistic 回归分析先天性心脏病患儿术后发生 AKI 的影响因素,受试者工作特征曲线(ROC)分析尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的价值。**结果:**AKI 组年龄、体重低于 NAKI 组($P<0.05$),手术时间、心肺转流(CPB)时间、主动脉阻断(ACT)时间、机械通气时间、重症监护室(ICU)住院时间长于 NAKI 组($P<0.05$),术后平均动脉压(MAP)、尿素氮(BUN)、血肌酐(Scr)、NGAL、KIM-1 高于 NAKI 组($P<0.05$)。Logistic 回归分析结果显示低龄、低体重、CPB 时间长、高 NGAL、KIM-1 水平是先天性心脏病患儿术后发生 AKI 的危险因素($P<0.05$)。ROC 分析显示尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的灵敏度分别为 81.67%,83.33%,特异度分别为 84.30%,87.79%。**结论:**低龄、低体重、CPB 时间长、高 NGAL、KIM-1 水平是先天性心脏病患儿术后发生 AKI 的危险因素,尿 NGAL、KIM-1 诊断先天性心脏病术后 AKI 具有较高价值。

关键词:先天性心脏病;急性肾损伤;中性粒细胞明胶酶相关脂质运载蛋白;肾损伤分子 1;尿素氮;血肌酐

中图分类号:R541.1;R692 **文献标识码:**A **文章编号:**1673-6273(2021)18-3515-05

The Influencing Factors of Postoperative Acute Kidney Injury in Children with Congenital Heart Disease and the Diagnostic Value of Urinary NGAL and KIM-1 *

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ABSTRACT Objective: To investigate the influencing factors of postoperative acute kidney injury (AKI) in children with congenital heart disease and the diagnostic value of urinary neutrophil gelatinase-associated lipocalin (NGAL) and kidney injury molecule 1 (KIM-1). **Methods:** From January 2018 to December 2019, 60 children with congenital heart disease postoperative with AKI (AKI group) and 172 children with congenital heart disease postoperative without AKI (NAKI group) who were admitted to the cardiac surgery department of our hospital were selected as the research objects. The clinical baseline data of the children were collected, urine NGAL and KIM-1 levels were detected, and the influencing factors of postoperative AKI in children with congenital heart disease were analyzed by Logistic regression. The receiver operating characteristic curve (ROC) was used to analyze the value of urinary NGAL and KIM-1 in diagnosing postoperative AKI in children with congenital heart disease. **Results:** Age, body weight in AKI group were below than those of NAKI group ($P<0.05$), operation time, cardiopulmonary bypass (CPB) time, aortic clamping time (ACT), mechanical ventilation time and intensive care unit (ICU) length of hospital stay time were longer than those of NAKI group ($P<0.05$), postoperative mean arterial pressure (MAP), urea nitrogen (BUN), serum creatinine (Scr), NGAL, KIM-1 were higher than those of NAKI group ($P<0.05$). Logistic regression analysis showed that low age, low body weight, long CPB time, high NGAL and KIM-1 levels were risk factors for postoperative AKI in children with congenital heart disease ($P<0.05$). ROC analysis showed that the sensitivity of urine NGAL, KIM-1 diagnosis of postoperative AKI in children with congenital heart disease were 81.67%, 83.33%, the specificity were 84.30%, 87.79%. **Conclusion:** Low age, low body weight, long CPB time, high NGAL and KIM-1 levels are risk factors for postoperative AKI in children with congenital heart disease. Urine NGAL and KIM-1 have high value in diagnosing AKI after congenital heart disease.

Key words: Congenital heart disease; Acute kidney injury; Neutrophil gelatinase-associated lipocalin; Kidney injury molecule 1; Urea nitrogen; Serum creatinine

Chinese Library Classification(CLC): R541.1; R692 **Document code:** A

Article ID: 1673-6273(2021)18-3515-05

* 基金项目:国家自然科学基金项目(30960445);江苏省卫生厅重点科研课题(H201545)

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(收稿日期:2021-03-06 接受日期:2021-03-28)

前言

急性肾损伤(Acute kidney injury, AKI)是先天性心脏病患儿术后常见并发症之一, AKI的发生显著延长住院时间, 增加患儿死亡率^[1-3]。先天性心脏病术后 AKI 的发生机制尚不清楚, 探讨其发病的危险因素有助于预防 AKI 的发生。中性粒细胞明胶酶相关脂质运载蛋白 (Neutrophil gelatinase-associated lipocalin, NGAL)是载脂蛋白家族成员, 广泛分布于人体各组织器官, 正常情况下, 在肾组织中很少表达, 在肾脏损伤时可快速合成分泌, 是 AKI 诊断的早期敏感生物标记物^[4-6]。肾损伤分子 1(Kidney injury molecule 1, KIM-1)主要分布于肾近曲小管上皮细胞, 在 AKI 发生时可特异性升高, 并维持较高浓度直至细胞损伤完全修复^[7-9]。本研究通过探讨影响先天性心脏病患儿术后 AKI 的影响因素, 分析尿 NGAL、KIM-1 对其的诊断价值, 以期临床防治提供参考。

1 资料与方法

1.1 临床资料

选择 2018 年 1 月至 2019 年 12 月我院心胸外科收治的 60 例先天性心脏病术后并发 AKI 患儿(AKI 组)和同期收治的 172 例先天性心脏病术后未发生 AKI 患儿(NAKI 组)作为研究对象。纳入标准:①经超声心动图、CT、MRI 等诊断为先天性心脏病;②均于气管插管全麻下手术治疗;③术前肾功能正常。排除标准:①先天性肾病, 合并急慢性肾炎、肾病综合征、尿毒症等;②术后发生严重并发症或死亡者;③临床资料不全者。AKI 诊断标准^[10]:术后 48 h 内肌酐清除率降低 25%, 连续 8h 尿量<0.5 mL(kg·h), 并排除系统红斑狼疮、创伤、大手术后等其它因素引起的肾功能损伤。本研究获得我院伦理会批准, 患儿家属均知情同意且签署同意书。

1.2 尿 NGAL、KIM-1 检测

所有患儿术后 12 h 均采集清晨空腹中段尿 10 mL, 酶联免疫吸附试验法测定尿 NGAL、KIM-1 水平, 试剂盒购自厦门仑

昌硕生物有限公司, 仪器为 DNM-9602G 酶标仪(北京普朗新技术有限公司), 所有操作均按说明书严格执行。

1.3 临床资料收集

收集患儿年龄、性别、体重、先天性心脏病类型、先天性心脏病手术风险分级评估(Risk adjustment classification for congenital heart surgery-1, RACHS-1)^[11]、心肺转流(Cardiopulmonary bypass, CPB)时间、主动脉阻断(Aortic clamping time, ACT)时间、手术时间、术后平均动脉压(Mean arterial pressure, MAP)、机械通气时间、重症监护室(Intensive care unit, ICU)住院时间, 采用免疫散射比浊法(日本岛津 CL-7200 全自动生化分析仪)测定术后血肌酐(Serum creatinine, Scr)、尿素氮(Urea nitrogen, BUN)、总蛋白、白蛋白水平, 采用美国贝克曼库尔特 DxH800 全自动血细胞分析仪测定术后中性粒细胞、白细胞、淋巴细胞、血红蛋白、血小板水平。

1.4 统计学分析

SPSS 25.0 进行数据分析, NGAL、KIM-1 等计量资料符合正态分布以($\bar{x} \pm s$)表示, 采用独立样本 t 检验。计数资料以例(%)表示采用 χ^2 检验。二元 Logistic 回归分析先天性心脏病患儿术后发生 AKI 的危险因素。受试者工作特征曲线(Receiver operator characteristics curve, ROC)分析尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的价值。所有统计均采用双侧检验, 检验水准 $\alpha=0.05$ 。

2 结果

2.1 影响先天性心脏病患儿术后发生 AKI 的单因素分析

AKI 组年龄、体重低于 NAKI 组 ($P<0.05$), 手术时间、CPB 时间、ACT 时间、机械通气时间、ICU 住院时间长于 NAKI 组 ($P<0.05$), 术后 MAP、BUN、Scr、NGAL、KIM-1 高于 NAKI 组 ($P<0.05$), 两组性别、先天性心脏病类型、RACHS-1 分级、术后总蛋白、白蛋白、中性粒细胞、白细胞、淋巴细胞、血红蛋白、血小板比较无统计学差异 ($P>0.05$), 见表 1。

表 1 影响先天性心脏病患儿术后发生 AKI 的单因素分析

Table 1 Single factor analysis of postoperative AKI in children with congenital heart disease

Groups	AKI group(n=60)	NAKI group(n=172)	t/ χ^2	P
Age(years)	1.25± 0.36	1.95± 0.73	7.124	0.000
Gender[n(%)]				
Male	39(65.00)	89(51.74)	3.160	0.075
Female	21(35.00)	83(48.26)		
Body weight(kg)	8.12± 2.01	9.46± 3.07	3.151	0.002
Type of congenital heart disease[n(%)]				
Atrial septal defect	15(25.00)	46(26.74)	0.470	0.993
Ventricular septal defect	14(23.33)	40(23.26)		
Tetralogy of Fallot	11(18.33)	34(19.77)		
Patent ductus arteriosus	10(16.67)	28(16.28)		
Double exits to the right ventricle	8(13.33)	19(11.05)		

Others	2(3.33)	5(2.91)		
RACHS-1 grade[n(%)]				
1 grade	13(21.67)	48(27.91)	2.843	0.241
2 grade	29(48.33)	62(36.05)		
3 grade	18(30.00)	62(36.05)		
CPB time(min)	105.24± 23.16	61.24± 19.35	14.389	0.000
ACT time(min)	60.49± 6.79	35.12± 6.43	25.609	0.000
Operation time(min)	211.35± 49.43	142.02± 34.16	11.962	0.000
Postoperative MAP (mmHg)	118.35± 15.42	102.35± 12.05	7.292	0.000
Mechanical ventilation time (h)	3.94± 1.25	2.13± 0.94	50.377	0.000
ICU hospital stay time(d)	4.12± 1.35	1.01± 0.28	11.738	0.000
BUN(mmol/L)	16.05± 3.76	8.82± 1.24	22.079	0.000
Scr(μmol/L)	63.49± 8.12	25.43± 6.53	15.972	0.000
NGAL(pg/mL)	224.51± 52.51	13.26± 3.02	52.725	0.000
KIM-1(pg/mL)	55.65± 12.04	3.05± 0.46	57.409	0.000
Total protein(g/L)	62.35± 4.12	63.12± 6.37	0.875	0.383
Albumin(g/L)	39.42± 3.76	40.55± 4.01	1.909	0.058
Neutrophils(× 10 ⁹ /L)	3.24± 0.97	3.05± 0.73	1.587	0.114
White blood cells(× 10 ⁹ /L)	10.42± 2.35	9.96± 2.18	1.379	0.169
Lymphocyte(× 10 ⁹ /L)	5.32± 1.18	5.43± 1.33	0.567	0.571
Hemoglobin(g/L)	119.24± 12.08	120.43± 13.42	0.606	0.545
Platelet(× 10 ⁹ /L)	342.24± 26.35	343.21± 26.98	0.241	0.810

2.2 影响先天性心脏病患儿术后发生 AKI 的 Logistic 回归分析

以先天性心脏病患儿术后发生 AKI 为因变量,年龄、体重、手术时间、CPB 时间、ACT 时间、机械通气时间、ICU 住院时间、MAP、BUN、Scr、NGAL、KIM-1 为自变量,建立 Logistic

回归方程,结果显示低龄、低体重、CPB 时间长、高 NGAL、KIM-1 水平是先天性心脏病患儿术后发生 AKI 的危险因素($P<0.05$),见表 2。

表 2 影响先天性心脏病患儿术后发生 AKI 的 Logistic 回归分析

Table 2 Logistic regression analysis of postoperative AKI in children with congenital heart disease

Factors	β	SE	Wald χ^2	OR(95%CI)	P
Age	0.432	0.142	9.255	1.540(1.436~1.682)	0.003
Body weight	0.512	0.193	7.038	1.669(1.542~1.730)	0.009
CPB time	0.493	0.162	9.261	1.637(1.542~1.720)	0.002
NGAL	0.621	0.136	20.850	1.861(1.705~1.935)	0.000
KIM-1	0.423	0.126	11.270	1.527(1.423~1.683)	0.000

2.3 尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的价值分析

ROC 分析尿 NGAL、KIM-1、BUN、Scr 诊断先天性心脏病患儿术后发生 AKI 的曲线下面积 (Area under curve, AUC) 分别为 0.836、0.845、0.716、0.754,尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的灵敏度和特异度高于 BUN、Scr 诊断,见表 3。

3 讨论

AKI 是短时间内发生的肾功能急性下降,临床表现为尿量减少、无尿、浮肿,Scr 升高,手术是 AKI 的主要诱因之一,随着体外循环心脏手术的应用,先天性心脏病患儿术后 AKI 的发病率呈增加趋势^[12,13]。目前 AKI 治疗方法有限,合并 AKI 患儿预后差,死亡率高达 80%^[14]。因此探讨先天性心脏病术后 AKI

危险因素,准确预测 AKI 的发生具有重要临床意义。

表 3 尿 NGAL、KIM-1 诊断先天性心脏病患儿术后发生 AKI 的效能

Table 3 Efficacy of urinary NGAL and KIM-1 in diagnosing postoperative AKI in children with congenital heart disease

Indicators	AUC(95%CI)	P	Cut-off	Sensitivity(%)	Specificity (%)
NGAL	0.836(0.772~0.900)	0.000	182.35 pg/ml	81.67	84.30
KIM-1	0.845(0.777~0.913)	0.000	39.64 pg/ml	83.33	87.79
BUN	0.713(0.632~0.794)	0.000	14.35 mmol/L	65.00	78.49
Scr	0.754(0.680~0.828)	0.000	41.29 μ mol/L	70.00	80.81

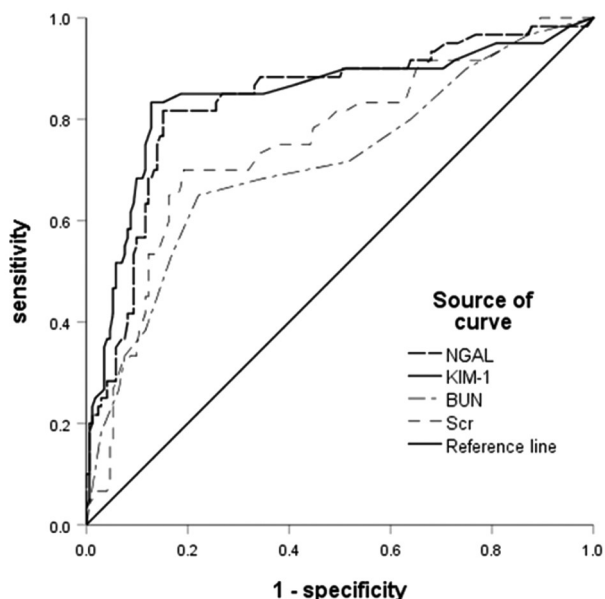


图 1 尿 NGAL、KIM-1、BUN、Scr 诊断先天性心脏病患儿术后发生 AKI 的 ROC 图

Fig.1 ROC figure of NGAL, Kim-1, BUN and Scr in the diagnosis of postoperative AKI in children with congenital heart disease

本研究发现低龄、低体重、CPB 时间长、高 NGAL、KIM-1 水平是先天性心脏病患儿术后 AKI 发生的危险因素。先天性心脏病患儿多生长发育迟缓,且合并其它遗传性疾病,整体机体功能、免疫以及营养状态偏差,因此年龄较小者 AKI 发病风险更高。低体重患儿心脏偏小,手术操作复杂,难度加大,手术时间明显延长,增加肾脏缺血缺氧损伤风险。杨宇齐等人^[13]认为低体重是先天性心脏病患儿术后 AKI 的危险因素, Lee 等人^[16]报道显示低体重与先天性心脏病患儿术后 AKI 发生有关。对于主动脉弓修复术患儿,体重 <3.0 kg 是术后 AKI 风险增加的危险因素(OR=7.569)^[17]。CPB 是心脏直视手术中必不可少的技术手段,但是 CPB 术后肾损伤发生率明显增加,逐渐引起医学界关注^[18]。CPB 过程中血液与 CPB 管道直接接触,导致炎症介质、氧自由基、趋化因子等大量合成,导致肾组织损伤。加之 CPB 期间心输出量降低,肾脏处于低灌注状态,术中使用血管活性药物,导致肾血管收缩,肾小球滤过率下降,继发代谢性酸中毒,导致 AKI 发生^[19,20]。CPB 时间越长,肾组织缺血缺氧时间越长,缺血再灌注损伤越重,氧化应激反应、炎症反应越激烈, AKI 发病风险越大。Newland 等人^[21]指出 CPB 过程中,保持氧传递指数大于 280 mL/min/m²,可降低 AKI 发病机率,提示体

CPB 介导的低氧状态是 AKI 发病的主要因素。

NGAL 是脂质转运蛋白,具有调节细胞凋亡、脂质发泄、免疫应答、炎症反应等作用^[22],NGAL 在活性氧、炎症反应时或上皮细胞损伤时均表达升高^[23],尿液中 NGAL 对 AKI 诊断具有较高敏感性^[24]。KIM-1 是 I 型跨膜糖蛋白,在肾脏缺血、毒性损伤时在近端肾小管迅速表达,并由肾小管上皮脱落进入尿液,尿液 KIM-1 是肾损伤的主要生物学标志物^[25-27]。本研究结果显示高水平 NGAL、KIM-1 是先天性心脏病患儿术后 AKI 的危险因素,ROC 分析结果显示 NGAL、KIM-1 诊断先天性心脏病患儿术后 AKI 的效能高于常规指标 BUN 和 Scr,说明 NGAL、KIM-1 在 AKI 诊断方面具有较高价值。Mosa 等人^[28]认为术后血清 NGAL 是 CPB 胸外科患者术后 AKI 的敏感标志物, Lee 等人^[29]发现术后 6h 尿 NGAL 预测心脏直视手术患者术后 AKI 的 AUC 为 0.732,略低于本研究结果,可能与采集尿液时间差异有关,术后 12 h 尿液中 NGAL 可能更能反映肾损伤程度。温昱鹏^[30]报道指出儿童非紫绀型心脏病体外循环术后 2、4、10h 尿 KIM-1 诊断 AKI 的 AUC 分别为 0.940、0.939、0.959,高于本研究结果,可能与选择的病例差异有关。

综上,本研究回归分析结果显示低龄、低体重、CPB 时间长、高 NGAL、KIM-1 水平是先天性心脏病患儿术后发生 AKI 的危险因素。尿 NGAL、KIM-1 对于诊断先天性心脏病术后 AKI 具有较高价值,可用于评估先天性心脏病患儿术后 AKI 的风险。

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(上接第 3563 页)

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