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极低出生体重儿急性肾损伤发病的危险因素分析

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摘　要

目的：分析极低出生体重儿急性肾损伤(AKI)发病的临床危险因素，为临床AKI患儿的诊疗方案提供科学根据。方法：收集2019年1月至2021年12月收治的AKI诊断明确且具有完备临床资料的89例极低出生体重儿，设为病例组，并按照1:1配对方法获取未诊断AKI的89例极低出生体重儿，设为对照组，对比两组临床资料，调查分析极低出生体重儿AKI发病的独立危险因素。结果：研究期间共纳入AKI组89例，非AKI组89例。与非AKI组相比，AKI组患儿母孕期合并子痫、肝脏功能损害、妊娠期高血压比例高，病死率高于非AKI组，AKI组患儿发病前患败血症、新生儿坏死性小肠结肠炎发病率高于非AKI组，AKI组患儿需进行有创机械通气、万古霉素治疗比例高于非AKI组($P < 0.05$)。多因素logistic回归分析得出，母孕期子痫(OR = 5.522, 95%CI: 1.814~16.814, $P = 0.003$)、母孕期肝功损害(OR = 5.191, 95%CI: 1.352~19.929, $P = 0.016$)，患儿住院期间合并败血症(OR = 2.935, 95%CI: 1.411~6.103, $P = 0.003$)、需有创机械通气(OR = 2.972, 95%CI: 1.461~6.046, $P = 0.003$)是影响极低出生体重儿AKI发病的独立危险因素。结论：母孕期子痫、母孕期肝功损害、败血症、有创机械通气明显增加极低出生体重儿AKI发病的风险。

关键词

急性肾损伤，极低出生体重儿，危险因素

Risk Factors Analysis of Acute Kidney Injury in Very Low Birth Weight Infants

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Abstract

Objective: To analyze the clinical risk factors of acute kidney injury (AKI) in very low birth weight infants, and to provide scientific basis for the diagnosis and treatment of AKI children. Method: A total of 89 very low birth weight infants with definite diagnosis of AKI and complete clinical data admitted to hospital from January 2019 to December 2021 were selected as the case group, and 89 very low birth weight infants with undiagnosed AKI were selected as the control group according to 1:1 matching method. Clinical data of the two groups were compared. To investigate and analyze the independent risk factors of AKI in very low birth weight infants. Results: A total of 89 cases were included in the AKI group and 89 cases in the non-AKI group during the study. Compared with the non-AKI group, the AKI group had a higher proportion of pregnant mothers complicated with eclampsia, liver function impairment and hypertension during pregnancy, a higher mortality rate than the non-AKI group, and a higher incidence of pre-onset septicemia and neonatal necrotizing enterocolitis than the non-AKI group. The ratio of invasive mechanical ventilation and vancomycin treatment in AKI group was higher than that in non-AKI group ($P < 0.05$). Multivariate logistic regression analysis showed that maternal eclampsia during pregnancy (OR = 5.522, 95%CI: 1.814~16.814, $P = 0.003$), maternal liver work damage during pregnancy (OR = 5.191, 95%CI: 1.352~19.929, $P = 0.016$), the patient was complicated with sepsis during hospitalization (OR = 2.935, 95%CI: 1.411~6.103, $P = 0.003$), and required invasive mechanical ventilation (OR = 2.972, 95%CI: 1.461~6.046, $P = 0.003$) was an independent risk factor for AKI in very low birth weight infants. Conclusions: Maternal eclampsia during pregnancy, maternal liver function impairment during pregnancy, sepsis and invasive mechanical ventilation significantly increase the risk of AKI in very low birth weight infants.

Keywords

Acute Kidney Injury, Very Low Birth Weight Infants, Risk Factor

1. 引言

急性肾损伤(acute kidney injury, AKI)是新生儿期间常见的一种疾病，也是造成危重新生儿死亡的常见原因之一。AKI 在危重新生儿中的发病率为 29.9%，在早产儿中的发病率为 25%，在极低出生体重儿中的发病率为 19%~40% [1] [2] [3] [4]。AKI 在危重新生儿中的病死率为 9.7%，在早产儿中的病死率为 27.5%，在极低出生体重儿中的病死率为 20.1% [2] [5] [6]。AKI 患儿存在后遗症，31%的 AKI 新生儿易发展为慢性肾脏疾病，低白蛋白血症是 AKI 进展为慢性肾脏疾病的独立危险因素[7] [8] [9]。

目前研究发现诸多危险因素与新生儿 AKI 发病有密切的关系，如早产、低出生体重、围产期窒息、败血症、新生儿坏死性小肠结肠炎、先天性心脏病、新生儿呼吸窘迫综合征、机械通气、肾毒性药物的应用[10] [11] [12]。但目前国内关于影响极低出生体重儿 AKI 发病的危险因素研究较少。

本研究通过回顾性分析极低出生体重儿及 AKI 患儿临床资料，分析极低出生体重儿 AKI 发病的危险因素，为我国 AKI 患儿的临床诊疗方案提供科学根据。

2. 对象与方法

2.1. 研究对象及分组

收集2019年1月至2021年12月于重庆医科大学附属儿童医院新生儿病房住院的极低出生体重新生儿的相关临床资料。研究对象纳入标准：1) 入院日龄为0~28天的极低出生体重儿；2) 符合新生儿AKI诊断标准[13]：① 48小时内血清肌酐升高≥0.3 mg/dL (≥26.5 umol/L)；② 过去7天内血清肌酐水平升高至 ≥ 基础值的1.5倍；③ 尿量 < 0.5 mL/(kg·h)持续6小时。排除标准：1) 临床资料不完备；2) 住院时间 ≤48小时及住院期间少于2次有效血清肌酐值；3) 合并先天肾脏畸形和(或)遗传代谢疾病。根据是否诊断AKI分为AKI组及非AKI组。按照①出生体重相差小于150 g；② 胎龄相差小于3天；③ 入院日龄相差小于3天；此三项标准与病例组进行1:1配对，配对成功者纳入对照组。

本研究获医院医学伦理委员会批准[(2022)年伦审(研)第(190)号]。

2.2. 资料收集方法

收集并分析患儿的基本信息(性别、胎龄、分娩方式、出生体重、入院日龄、Apgar评分、AKI分期)；母孕期资料(母亲年龄、子痫、肝脏功能损害、妊娠期高血压、妊娠期糖尿病、产前激素使用、孕期感染、胆汁淤积、甲状腺功能异常、宫内窘迫、胎膜早破、羊水污染)；实验室检查结果(住院期间电解质紊乱、最高肌酐值、最高尿素氮值、24 小时最低尿量)，治疗方式(肺表面活性物质、万古霉素、泰能、阿米卡星、有创机械通气)，临床合并症(败血症、新生儿坏死性小肠结肠炎、新生儿呼吸窘迫综合症、肺出血、颅内出血、呼吸衰竭)、住院天数、病死率等。

2.3. 统计学分析

数据统计分析应用SPSS 22.0统计软件。计量资料呈正态分布且方差齐者采用独立样本 t 检验，非正态分布者以中位数(四分位数范围)表示，组间比较采用Wilcoxon秩和检验。计数资料以率(%)表示，组间比较选用卡方检验或Fisher's精确概率计算法。采用多元logistic回归分析影响极低出生体重儿发生AKI的独立危险因素，如 $P < 0.05$，则差异有统计学意义。

3. 结果

3.1. 一般资料

研究期间，病例组共收集830例极低出生体重儿，其中诊断AKI且符合纳入标准者89例，按照上述配对原则选择89例非AKI患儿为对照组。两组患儿基线信息比较见表1。由表1可见：AKI组患儿入院日龄早于非AKI组，孕母合并子痫、肝脏功能损害、妊娠期高血压病例数高于非AKI组，病死率高于非AKI组，差异有统计学意义($P < 0.05$)。

3.2. 实验室检查结果比较

由表2可见，AKI组高钠血症、低钠血症、低钾血症、低钙血症病例数多于非AKI组，最高肌酐值、最高血尿素氮值高于非AKI组，差异有统计学意义($P < 0.05$)。

3.3. 临床合并症及治疗方式比较

本研究发现AKI患儿发病前存在多种合并症，包括败血症、新生儿坏死性小肠结肠炎、新生儿呼吸窘迫综合症、肺出血等。两组间合并症比较见表3，可见AKI组患儿败血症、新生儿坏死性小肠结肠炎的发生率高于非AKI组，差异有统计学意义($P < 0.05$)；AKI组患儿使用有创机械通气的比例高于非AKI

组，差异有统计学意义($P < 0.05$)。

Table 1. Baseline data for newborns and mothers
表 1. 新生儿及母亲基线资料

变量	AKI 组(n = 89)	非 AKI 组(n = 89)	统计值	*P* 值
新生儿资料				
性别[男(%)]	54 (60.7)	45 (50.6)	1.843	0.175
胎龄[*M* ± 2*SD*]/周	30.5 ± 4.2	30.6 ± 4.0	0.106	0.915
出生体重[*M* (*P*25~*P*75)]/g	1280.0 (1132.5~1385.0)	1280.0 (1175.0~1390.0)	−0.067	0.947
剖宫产[*n* (%)]	56 (62.9)	58 (65.2)	0.098	0.755
入院日龄[*M* (*P*25~*P*75)]/d	0.08 (0.04~0.96)	0.04 (0.04~0.08)	−2.003	0.045
住院天数[*M* (*P*25~*P*75)]/d	48.0 (39.5~63.0)	47.0 (38.0~59.0)	−0.447	0.655
Apgar 5 分钟 ≥8 分	78 (87.6)	78 (87.6)	0.000	1.000
AKI 分期(1~3)	15/18/56	0	−12.412	0.000
母孕期资料				
高龄产妇[*n* (%)]	15 (16.9)	19 (21.3)	0.582	0.446
子痫[*n* (%)]	20 (22.5)	5 (5.6)	10.471	0.001
肝功损害[*n* (%)]	14 (15.7)	3 (3.4)	7.869	0.005
妊娠期高血压[*n* (%)]	29 (32.6)	17 (19.1)	4.221	0.040
妊娠期糖尿病[*n* (%)]	26 (29.2)	23 (25.8)	0.253	0.615
产前激素[*n* (%)]	66 (74.2)	64 (71.9)	0.114	0.736
孕期感染[*n* (%)]	29 (32.6)	37 (41.6)	1.541	0.214
胆汁淤积[*n* (%)]	8 (9.0)	10 (11.2)	0.247	0.619
甲功异常[*n* (%)]	17 (12.4)	14 (15.7)	0.352	0.553
宫内窘迫[*n* (%)]	18 (20.2)	17 (19.1)	0.036	0.850
胎膜早破[*n* (%)]	30 (33.7)	35 (39.3)	0.606	0.436
羊水污染[*n* (%)]	14 (15.7)	9 (10.1)	1.248	0.264
病死率[n (%)]	29 (32.6)	15 (16.9)	5.917	0.015

Table 2. Comparison of laboratory test results between the two groups
表 2. 两组患儿实验室检查结果对比

变量	AKI 组(n = 89)	非 AKI 组(n = 89)	统计值	*P* 值
高钠血症[*n* (%)]	6 (6.7)	0 (0.0)	4.312	0.038
低钠血症[*n* (%)]	29 (32.6)	14 (15.7)	6.899	0.009
高钾血症[*n* (%)]	48 (53.9)	36 (40.4)	3.246	0.072
低钾血症[*n* (%)]	43 (48.3)	29 (32.6)	4.571	0.033
高钙血症[*n* (%)]	5 (5.6)	5 (5.6)	0.000	1.000
低钙血症[*n* (%)]	58 (65.2)	42 (47.2)	5.842	0.016
最高肌酐值[*M* ± 2*SD*]/umol·L^{-1}	107.6 ± 85.6	63.1 ± 25.6	−9.389	0.000
最高尿素氮值[*M* ± 2*SD*]/mmol·L^{-1}	11.4 ± 10.8	6.2 ± 4.2	−8.508	0.000
24 小时最低尿量[*M* ± 2*SD*]/ml	79.3 ± 50.0	85.2 ± 47	−1.507	0.132
尿量值[*M* ± 2*SD*]/ml·(kg·h)$^{-1}$	2.5 ± 1.6	2.7 ± 1.6	−1.456	0.145

Table 3. Analysis of clinical complications and treatment methods in the two groups
表 3. 两组患儿临床合并症及治疗方式分析

变量	AKI 组(n = 89)	非 AKI 组(n = 89)	统计值	*P* 值
临床合并症				
败血症(AKI 之前)	27 (30.3)	0 (0.0)	31.828	0.000
新生儿坏死性小肠结肠炎(AKI 之前)	7 (7.9)	0 (0.0)	5.353	0.021
新生儿呼吸窘迫综合症	58 (65.2)	59 (66.3)	0.025	0.875
肺出血(AKI 之前)	13 (14.6)	11 (12.4)	0.193	0.661
颅内出血(AKI 之前)	22 (24.7)	31 (34.8)	2.176	0.140
呼吸衰竭(AKI 之前)	72 (80.9)	81 (91.0)	3.769	0.052
治疗(AKI 之前)				
肺表面活性物质	61 (68.5)	63 (70.8)	0.106	0.744
有创机械通气	39 (43.8)	0 (0.0)	49.942	0.000
万古霉素	2 (2.2)	2 (2.2)	0.000	1.000
泰能	6 (6.7)	10 (11.2)	1.099	0.295
阿米卡星	0 (0.0)	2 (2.2)	0.506	0.477

Table 4. Logistic regression analysis
表 4. Logistic 回归分析

变量	回归系数	WaldX^2	*P*	OR (95%CI)
子痫	1.709	9.048	0.003	5.522 (1.814~16.814)
孕母肝功损害	1.647	5.759	0.016	5.191 (1.352~19.929)
有创机械通气(AKI 之前)	1.077	8.309	0.004	2.935 (1.411~6.103)
败血症(AKI 之前)	1.089	9.043	0.003	2.972 (1.461~6.046)

3.4. VLBW 儿发生 AKI 危险因素分析

由表 4 可见，将上述研究结果中有统计学意义的指标纳入二元 logistic 回归分析，结果显示母孕期子痫、母孕期肝功损害，患儿住院期间合并败血症、需有创机械通气是影响极低出生体重儿 AKI 发病的独立危险因素。

4. 讨论

明确极低出生体重儿 AKI 发病相关的危险因素有助于临床早期采取针对性防治措施，有助于改善其预后。本研究发现母孕期子痫、母孕期肝功损害，患儿住院期间合并败血症、需要有创机械通气是极低出生体重儿 AKI 发病的独立危险因素。

本研究发现母孕期子痫及母孕期肝功损害是影响极低出生体重儿 AKI 发病的独立危险因素。母孕期发生子痫的患儿 AKI 风险增加，且 AKI 患儿的死亡率更高，可能与子痫发生后导致宫内缺氧，进一步导致胎儿的身体结构、激素水平和代谢发生变化[14] [15] [16]。母亲孕期患有妊娠期肝内胆汁淤积肝功能损害，可导致孕母合并高浓度胆汁酸，促成与浓度依赖性有关的血管收缩，进一步导致脐血流急性减少，胎儿出现急性缺氧甚至窒息，从而导致 AKI 发病风险增加[17] [18] [19]。因此，积极关注孕产妇子痫发

作情况及肝功指标并及时识别及处理，可改善 AKI 的发病率。

本研究发现败血症是影响极低出生体重儿 AKI 发病的独立危险因素。重症败血症患儿发生 AKI 的病因包含多种因素，如继发于感染性休克导致的肾灌注不足、炎症介质作用、肾血管系统微血栓形成、肾实质缺血和坏死、肾毒性药物的应用等[20] [21] [22]。发生败血症时，败血症与急性肾损伤相关的调节因子长链非编码 RNA (lncRNAs)会出现损伤，激活非编码 RNA (NORAD)在血清中高度表达，促进 HK-2 细胞凋亡，诱发炎症，导致肾损伤；同时，尿白细胞介素 6 也可被视为败血症的早期标志物[23] [24]。积极适当地治疗败血症可能有助于降低新生儿 AKI 的发病率。

本研究结果显示，住院期间需有创机械通气是极低出生体重儿 AKI 发病的独立危险因素。在进行有创机械通气时，氧气对肺和大脑等器官有急慢性毒性作用，能影响血液循环、内分泌功能、酶系统和分子结构，高浓度的吸入氧甚至会影响肺表面活性物质的合成，产生的过量氧自由基会攻击全身多器官及免疫系统，导致肾脏等多器官损伤[25] [26] [27]。机械通气可引发急性肺损伤，机体产生的炎症介质以及机械通气导致的肺损伤与 AKI 的发生密切相关；机械通气也可能改变神经体液系统，影响交感神经、肾素－血管紧张素－醛固酮系统、抗利尿激素释放及心房利钠肽产生，导致肾脏灌注不足、肾小球滤过率下降、水钠潴留和尿量减少，从而诱发 AKI [28]。因此，选择适当的呼吸支持治疗方式并严格控制有创机械通气时间可能改善新生儿 AKI 发病率。

本研究的局限性：本研究为回顾性研究，存在回顾性研究的内在局限：① 本研究依赖于常规收集的临床数据的完整性，但部分病例资料可能存在偏差，研究结果可能受到未注意到的偏倚和混杂因素的影响；② 回顾性研究中，研究人员无法控制暴露和干预措施；③ 本研究病例数较少，样本量偏小，临床资料来源单一，今后有待进行大样本、多中心研究进一步证实本研究结果。

综上，母孕期子痫、肝功损害，患儿住院期间合并败血症、需有创机械通气是影响极低出生体重儿急性肾损伤发病的独立危险因素，因而积极治疗母孕期子痫、肝功损害及患儿住院期间败血症，选择适当的呼吸支持治疗方案并严格控制有创机械通气时间，可能对降低极低出生体重儿 AKI 的发病率有帮助。

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