

伴急性肾损伤的 DBD 供肾肾移植的临床结局

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【摘要】 目的 探讨伴急性肾损伤（AKI）的脑死亡器官捐献（DBD）供者供肾肾移植的临床结局。方法 回顾性分析 216 例 DBD 供者的资料，按照改善全球肾脏病预后组织（KDIGO）标准将分为 AKI 组（69 例）与正常组（147 例），AKI 组进一步分为 KDIGO 1 期和 2~3 期两组，AKI 组受者 135 例，正常组受者 288 例。总结受者术后肾功能恢复情况及临床结局。分析移植物功能延迟恢复（DGF）发生的危险因素。结果 AKI 组供者血清肌酐（Scr）最高值、获取前 Scr 值、血钠最高值、获取前血钠值均高于正常组，升压药物应用时间长于正常组，48 h 内液体复苏用量高于正常组，入院 HCO_3^- 值低于正常组，尿崩症、低血压发生率高于对照组；KDIGO 2~3 期供者 Scr 最高值、获取前 Scr 值较 KDIGO 1 期供者高（均为 $P<0.05$ ）。与正常组比较，AKI 组受者 DGF、急性排斥反应发生率较高，行连续性肾脏替代治疗的比例较高，术后 90 d 内 Scr 水平较高，术后 3 d 尿量较少；与 KDIGO 1 期受者比较，KDIGO 2~3 期受者术后 3、4、5、15 d Scr 水平较高，术后 2 d 尿量较少（均为 $P<0.05$ ）。单因素分析结果显示供者年龄、Scr 最高值、血钠最高值、48 h 内液体复苏用量是肾移植术后受者发生 DGF 的危险因素，多因素分析结果显示，供者年龄是肾移植术后受者发生 DGF 的独立危险因素（均为 $P<0.05$ ）。结论 伴 AKI 的 DBD 供者供肾用于肾移植，经过积极的器官维护可纠正 AKI，对术后 6 个月移植物功能和存活率没有影响，可达到与非 AKI 供肾同样的效果，可作为扩大供肾来源。

【关键词】 急性肾损伤；脑死亡；器官捐献；肾移植；边缘供者；器官维护；移植物功能延迟恢复；原发性无功能

【中图分类号】 R617, R692 **【文献标志码】** A **【文章编号】** 1674-7445 (2024) 04-0015-08

Clinical outcome of kidney transplantation from DBD donors complicated with acute kidney injury Wang Hongyu*, Wang Hong, Shen Songying, Zhao He, Qin Xingsong, Qin Wei, Qian Xinling, Dong Huijun, Zhao Yunfeng, Wang Yafang, Li Peiliang.
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【Abstract】 **Objective** To evaluate the clinical outcome of kidney transplantation from donation after brain death (DBD) donors complicated with acute kidney injury (AKI). **Methods** Clinical data of 216 DBD donors were retrospectively analyzed, and they were divided into the AKI group ($n=69$) and control group ($n=147$) according to the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines. Donors in the AKI group were further divided into the KDIGO stage 1 and stage 2-3 subgroups. One hundred and thirty-five recipients were assigned into the AKI group and 288 recipients in the control group. Postoperative recovery of renal function and clinical outcomes of the recipients were recorded. The risk factors of delayed graft function (DGF) were identified. **Results** The highest serum creatinine (Scr) level, Scr level before procurement, the highest blood sodium level and blood sodium level before procurement in the AKI

DOI: 10.3969/j.issn.1674-7445.2024027

基金项目：河南省高等学校重点科研项目（23A320025）

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group were higher than those in the control group. The application duration of vasopressors in the AKI group was longer than that in the control group. In the AKI group, the amount of fluid resuscitation within 48 h was higher, the HCO_3^- level at admission was lower, and the incidence of diabetes insipidus and hypotension was higher than those in the control group. The highest Scr level and the Scr level before procurement in KDIGO stage 2-3 donors were significantly higher than those in KDIGO stage 1 counterparts (all $P < 0.05$). Compared with the control group, the incidence of DGF and acute rejection was higher, the proportion of continuous renal replacement therapy was higher, the Scr level within postoperative 90 d was higher, and the urine amount within postoperative 3 d was less than those of recipients in the AKI group. Compared with KDIGO stage 1 recipients, KDIGO stage 2-3 recipients had higher Scr levels at postoperative 3, 4, 5 and 15 d, and less urine amount at postoperative 2 d (all $P < 0.05$). Univariate analysis showed that donor age, the highest Scr level, the highest blood sodium level and the amount of fluid resuscitation within 48 h were the risk factors for DGF in recipients after kidney transplantation. Multivariate analysis showed that donor age was the independent risk factor for DGF in recipients after kidney transplantation (all $P < 0.05$). **Conclusions** For the application of DBD donors complicated with AKI, active organ maintenance should be performed to alleviate AKI. It exerts no effect upon graft function and survival rate at postoperative 6 months, which may achieve equivalent efficacy as non-AKI donors and may be used as a source of extended criteria donor kidneys.

【Key words】 Acute kidney injury; Brain death; Organ donation; Kidney transplantation; Marginal donor; Organ maintenance; Delayed graft function; Primary nonfunction

脑死亡发生后,会出现一系列的病理生理学改变和血流动力学恶化,造成血容量不足和重要器官灌注障碍^[1],容易出现急性肾损伤(acute kidney injury, AKI)。供肾质量是决定肾移植受者恢复情况的重要因素^[2],而器官捐献供者发生AKI后,移植肾功能恢复结局的临床研究尚少^[3]。本研究拟观察伴AKI的脑死亡器官捐献(donation after brain death, DBD)供者供肾移植的临床结局,旨在了解通过良好的供器官维护,能否使伴发AKI的供肾移植达到与正常供肾同样的移植效果。

1 资料与方法

1.1 研究对象

回顾性分析2017年2月至2022年8月郑州市人民医院器官移植中心216例肾移植供者,根据是否发生AKI分为AKI组69例和正常组147例,对应受者分别135例和288例。其中AKI组根据改善全球肾脏病预后组织(Kidney Disease: Improving Global Outcomes, KDIGO)分期1期43例,2~3期26例。

供者纳入标准:(1)符合脑死亡标准(先决条件+临床判定+确认试验)^[4];(2)年龄18~65岁;(3)符合器官捐献的标准,无血流感染等器官捐献禁忌证。排除标准:(1)供者维护过程中肾功能持续无改善;(2)行肝肾联合移植或胰肾联合移植;(3)二次或多次肾移植;(4)ABO血型不相容肾

移植;(5)随访资料缺失。

所有受者均为首次接受肾移植手术,术前群体反应性抗体均为阴性;所有供受者淋巴细胞毒交叉配合实验均为阴性,人类白细胞抗原配型基因位点(A、B、DR 3个位点)错配数均 < 3 个。本研究得到郑州人民医院伦理委员会批准(编号:KY2022-006-01)。

1.2 诊断标准

AKI诊断标准为肾功能突然减退(48 h内),表现为血清肌酐(serum creatinine, Scr)升高绝对值 $\geq 26.5 \mu\text{mol/L}$ 或Scr较基础值升高 $\geq 50\%$,或尿量减少[尿量 $< 0.5 \text{ mL}/(\text{kg}\cdot\text{h})$,时间超过6 h]^[5]。

AKI的KDIGO分期标准为1期:Scr升高为基线的1.5~1.9倍,或升高超过 $26.5 \mu\text{mol/L}$,尿量 $< 0.5 \text{ mL}/(\text{kg}\cdot\text{h})$ 持续6~12 h;2期:Scr升高为基线的2.0~2.9倍,尿量 $< 0.5 \text{ mL}/(\text{kg}\cdot\text{h}) \geq 12 \text{ h}$;3期:Scr升高为基线的3倍,或绝对值 $\geq 353.6 \mu\text{mol/L}$,或开始使用肾脏替代治疗,或患者年龄 < 18 岁且估算肾小球滤过率(estimated glomerular filtration rate, eGFR) $< 35 \text{ mL}/(\text{min}\cdot 1.73\text{m}^2)$,尿量 $< 0.3 \text{ mL}/(\text{kg}\cdot\text{h}) \geq 24 \text{ h}$,或无尿 $\geq 12 \text{ h}$ ^[6]。

1.3 治疗方法

供者器官维护的集束化治疗方法:(1)维持充足血容量,纠正低血压维持器官灌注,避免使用肾损伤药物,控制尿崩症,纠正电解质紊乱,必要时行连续性肾脏替代治疗(continuous renal replacement therapy,

CRRT)以纠正内环境紊乱;(2)控制感染,常规留取病原学标本行宏基因组二代测序及培养,对供者进行积极抗感染治疗;(3)对于激素水平下降者应用糖皮质激素或者甲状腺素行激素替代。

术后采用他克莫司+吗替麦考酚酯+泼尼松三联免疫抑制方案,其中泼尼松为 0.5 mg/(kg·d)口服,1 个月后改为 10 mg/d 口服。监测他克莫司血药浓度以调整剂量并维持其血药谷浓度在 8~12 ng/mL。根据尿量补液,如出现肾功能未恢复者行床旁透析治疗,预防并监测感染,出现排斥反应时加用抗胸腺细胞球蛋白。

1.4 研究内容

比较两组供者性别、年龄、身高、体质量、体质量指数 (body mass index, BMI)、既往病史、死亡原因、发病至器官获取时间、Scr 最高值、获取前 Scr 值、血钠最高值、获取前血钠值、升压药物应用时间、入院后 48 h 内液体复苏用量、入院时和获取前 HCO_3^- 水平、低血压及尿崩症发生情况。

比较两组受者的一般资料,包括性别、年龄、身高、体质量、BMI、移植前 Scr、移植前尿量、热缺血时间、冷缺血时间等。对比两组受者术后肾功能恢复情况及临床结局,包括术后 6 个月时移植肾存活、12 个月移植肾失功、移植物功能延迟恢复 (delayed graft function, DGF)、急性排斥反应、CRRT、原发性无功能 (primary nonfunction, PNF)、感染、谵妄等的发生情况,以及术后 Scr 水平和尿量。分析 DGF 发生的危险因素。

1.5 统计学方法

采用 SPSS 22.0 软件进行统计学分析。符合正态分布计量资料以均数±标准差表示,比较采用 *t* 检验;非正态分布的计量资料以中位数(下四分位数,上四分位数)表示,比较采用 Mann-Whitney *U* 检验;计数资料以率表示,比较采用 χ^2 检验。采用单因素和多因素分析影响肾功能恢复的因素。 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组供者一般资料比较

两组供者的一般资料比较见表 1。虽然 AKI 组与正常组供者身高、体质量差异有统计学意义,但 BMI 差异无统计学意义 ($P=0.085$)。AKI 组 Scr 最高值、获取前 Scr 值、血钠最高值、获取前血钠值均

高于正常组,升压药物应用时间长于正常组,48 h 内液体复苏用量高于正常组,入院 HCO_3^- 值低于正常组,尿崩症、低血压发生率高于对照组,差异均有统计学意义(均为 $P<0.05$)。

KDIGO 2~3 期 Scr 最高值、获取前 Scr 值较 KDIGO 1 期高(均为 $P<0.05$),其余指标均差异均无统计学意义(均为 $P>0.05$)。

2.2 两组受者一般资料及术后恢复情况比较

与正常组比较,AKI 组受者 DGF、急性排斥反应发生率较高,行 CRRT 的比例较高,差异均有统计学意义(均为 $P<0.05$,表 2)。与正常组比较,AKI 组术后 90 d 内 Scr 水平较高,术后 3 d 内尿量较少(均为 $P<0.05$,图 1A、B)。

与 KDIGO 1 期受者比较,KDIGO 2~3 期受者术后 3、4、5、15 d Scr 水平较高,术后 2 d 尿量较少(均为 $P<0.05$,图 1C、D)。其余资料比较差异均无统计学意义(均为 $P>0.05$,表 2)。

2.3 移植物延迟恢复的危险因素分析

单因素回归分析结果显示供者年龄、Scr 最高值、血钠最高值、48 h 内液体复苏用量是肾移植术后 DGF 发生的危险因素。多因素回归分析结果显示,供者年龄是肾移植术后 DGF 发生的独立危险因素(比值比 1.045, $P<0.001$,表 3)。

3 讨论

随着慢性肾衰竭患者的逐年增多,移植器官短缺一直是制约肾移植发展的瓶颈之一^[7-10],如何利用好每例供器官是我们解决的问题之一^[11],扩大供者来源的途径之一是维护和利用好每例边缘性供者。由于脑死亡后激素水平的变化及血流动力学的变化,加上器官缺血和肾毒性药物损伤,往往合并 AKI^[12-15]。有研究表明合并 AKI 的儿童供者供肾用于肾移植结局良好^[16],但是有关合并 AKI 的成人供者供肾用于肾移植效果的研究尚少^[17]。

本研究中 31.9% (69/216) 的供者出现 AKI,这与之前的报道结果 27.6% 和 31.1% 相似^[18-19],AKI 组供者更容易出现高钠血症,液体复苏用量更多,升压药物应用时间更长,但是经过供者维护后,两组供者发病至获取天数和获取前 HCO_3^- 水平差异无统计学意义,酸中毒纠正的原因考虑为肾脏的组织灌注恢复,因此通过良好的维护迅速恢复组织灌注至关重要^[20]。笔者团队前期按照 Westphal 等提出的器官维护的

表1 两组供者一般资料比较

Table 1 Comparison of general information of donors between two groups

指标	AKI组 (n=69)	正常组 (n=147)	统计值	P值	KDIGO 1期 (n=43)	KDIGO 2~3期 (n=26)	统计值	P值
性别男[n (%)]	63 (91)	125 (85)	1.636	0.201	39 (91)	24 (92)	0.053	1.000
年龄[M (P ₂₅ ,P ₇₅), 岁]	46 (42,54)	50 (43,56)	1.501	0.133	45 (41,45)	49 (41,54)	-0.310	0.757
身高[M (P ₂₅ ,P ₇₅), cm]	172 (170,176)	170 (167,175)	-2.080	0.038	172 (170,178)	172 (170,176)	-0.638	0.523
体质量[M (P ₂₅ ,P ₇₅), kg]	75 (68,80)	70 (65,75)	-3.011	0.003	75 (65,80)	75 (70,80)	-0.559	0.576
BMI[M (P ₂₅ ,P ₇₅), kg/m ²]	25 (23,26)	24 (22,26)	-2.222	0.085	25 (22,26)	25 (23,26)	-0.923	0.356
既往病史[n (%)]								
高血压	28 (41)	57 (39)	0.064	0.800	20 (47)	8 (31)	1.665	0.197
糖尿病	6 (9)	6 (4)		0.205	3 (7)	3 (12)	0.425	0.665
心脏病	2 (3)	1 (1)		0.240	1 (2)	1 (4)	0.133	1.000
死亡原因[n (%)]			1.683	0.794			3.500	0.321
颅脑外伤	23 (33)	54 (37)			14 (33)	9 (35)		
脑出血	37 (54)	75 (51)			23 (53)	14 (54)		
脑梗塞	4 (6)	9 (6)			4 (9)	0		
缺血缺氧性脑病	5 (7)	7 (5)			2 (5)	3 (12)		
其他	0	2 (1)			0	0		
发病至器官获取时间 [M (P ₂₅ ,P ₇₅), d]	5 (3,8)	5 (3,7)	-0.766	0.444	5 (3,8)	5 (4,6)	-0.093	0.926
Scr最高值[M (P ₂₅ ,P ₇₅), μmol/L]	161 (128,212)	67 (53,82)	-11.358	<0.001	137 (117,160)	243 (192,299)	-6.496	<0.001
获取前Scr值 [M (P ₂₅ ,P ₇₅), μmol/L]	98 (73,107)	53 (40,68)	-8.525	<0.001	91 (68,102)	102 (81,117)	-2.348	0.019
血钠最高值 [M (P ₂₅ ,P ₇₅), mmol/L]	158 (151,166)	145 (140,151)	-7.296	<0.001	158 (151,165)	159 (150,168)	-0.217	0.828
获取前血钠值 [M (P ₂₅ ,P ₇₅), mmol/L]	145 (138,151)	139 (135,145)	-3.556	<0.001	145 (138,151)	143 (138,150)	-0.192	0.848
升压药应用时间 [M (P ₂₅ ,P ₇₅), d]	4.0 (0,7.0)	0 (0,3.0)	-4.737	<0.001	3.0 (0,7.0)	4.0 (0.8,7.0)	-0.848	0.397
48 h内液体复苏用量 ($\bar{x} \pm s$, mL)	9 701±2 686	6 961±2 233	-7.869	<0.001	9 369±2 111	10 250±3 410	-1.328	0.189
入院时HCO ₃ ⁻ ($\bar{x} \pm s$, mmol/L)	20±5	22±5	3.577	<0.001	20±4	19±6	-0.746	0.458
获取前HCO ₃ ⁻ ($\bar{x} \pm s$, mmol/L)	22 (18,25)	21 (18,24)	-0.741	0.459	22 (18,25)	21 (17,26)	-0.292	0.770
尿崩症[n (%)]	38 (55)	46 (31)	11.173	<0.001	26 (60)	12 (46)	1.341	0.247
低血压[n (%)]	47 (68)	53 (36)	19.415	<0.001	27 (63)	20 (77)	1.490	0.222

表 2 两组肾移植受者临床资料比较

Table 2 Comparison of clinical data of kidney transplant recipients between two groups

指标	AKI组 (n=135)	正常组 (n=288)	统计值	P值	KDIGO 1期 (n=85)	KDIGO 2~3期 (n=50)	统计值	P值
性别男[n (%)]	104 (77.0)	223 (77.4)	0.008	0.928	68 (80)	36 (72)	1.139	0.286
年龄[M (P ₂₅ , P ₇₅), 岁]	39 (32,47)	40 (32,47)	-0.562	0.574	39 (33,47)	39 (31,47)	-0.716	0.474
身高[M (P ₂₅ , P ₇₅), cm]	170 (165,174)	170 (165,174)	-0.547	0.584	170 (165,173)	170 (162,175)	-0.628	0.530
体质量[M (P ₂₅ , P ₇₅), kg]	62 (56,72)	66 (56,74)	-1.386	0.166	61 (57,70)	68 (55,73)	-0.654	0.513
BMI[M (P ₂₅ , P ₇₅), kg/m ²]	22 (20,24)	22 (20,25)	-1.034	0.301	22 (20,24)	22 (20,24)	-0.868	0.385
移植前Scr值 ($\bar{x} \pm s$, μmol/L)	852±203	830±193	1.075	0.283				
移植前尿量 ($\bar{x} \pm s$, mL/d)	239±95	247±91	-0.890	0.374				
热缺血时间 ($\bar{x} \pm s$, min)	2.8±0.9	2.8±1.1	-0.374	0.708				
冷缺血时间 ($\bar{x} \pm s$, h)	4.0±1.9	3.9±1.8	0.570	0.568				
6个月移植肾存活[n (%)]	130 (96.3)	279 (96.9)	0.901	0.390	80 (94)	50 (100)	1.849	0.291
12个月时失功[n (%)]	14 (10.4)	28 (9.7)	0.055	0.814	10 (12)	4 (8)	0.577	0.448
DGF[n (%)]	55 (40.7)	87 (30.2)	4.471	0.034	30 (35)	25 (50)	2.820	0.093
急性排斥反应[n (%)]	16 (11.9)	12 (4.2)	8.783	0.003	8 (9)	8 (16)	1.308	0.253
感染[n (%)]	7 (5.2)	6 (2.1)	0.127	0.710	4 (5)	3 (6)		
CRRT[n (%)]	29 (21.5)	33 (11.5)	7.382	0.007	15 (18)	14 (28)	2.001	0.157
PNF[n (%)]	4 (3.0)	4 (1.4)	0.274	0.606	4 (5)	0		0.296
谵妄[n (%)]	8 (5.9)	11 (3.8)	0.921	0.337	5 (6)	3 (6)		1.000

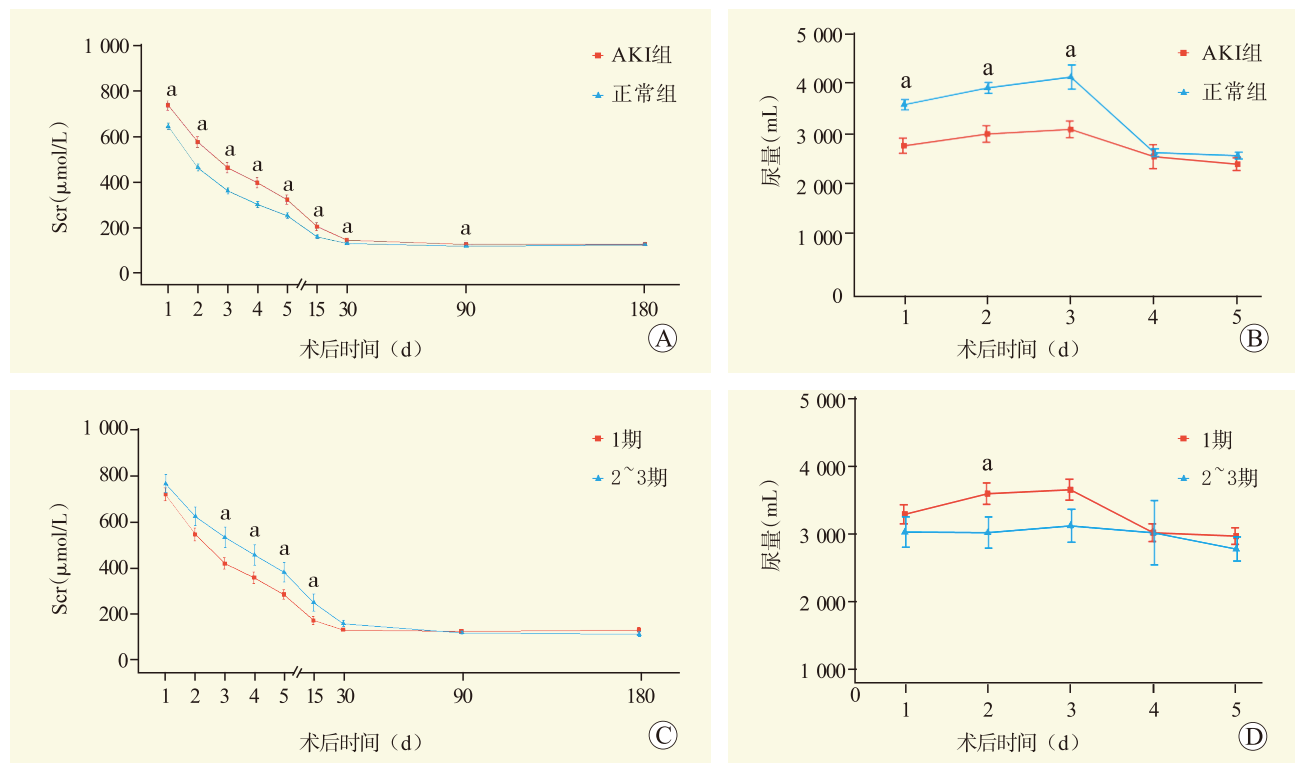
“VIP”方案^[21],制定了供者维护集束化治疗方案^[22],保证了合并AKI的供者可以及时纠正器官功能不全,保证供肾质量,为后续移植后肾功能恢复奠定基础。因此,合并AKI的供者需要经过器官功能维护再行肾移植,会取得相对良好结局,与既往研究结果一致^[16,23]。

在肾移植术后临床效果方面,AKI组术后15 d内Scr水平平均比正常组高,且发生DGF、急性排斥反应、行CRRT例数较多,但术后3个月时两组受者Scr水平差异无统计学意义。术后6个月移植肾存活率、移植肾失功例数、感染、PNF发生率差异均无统计学意义。这些结果提示伴AKI的肾脏会出现更严重的缺血-再灌注损伤,可能会影响早期同种异体移植功能^[24-25],因为肾实质或肾小管的自然修复尚未完成,短期内肾功能恢复较慢,但是术后6个月时两者临床结局无差别。既往研究表明,AKI的修复过程持续并在90 d至6个月间达到高峰,在这段时间之后,肾脏的远期预后不会受到AKI的影响^[26-28]。本研

究提示6个月时的移植肾功能不受AKI的影响,这与既往研究仍基本一致^[29],表明这一规律可能也适用于AKI供者的同种异体移植物的临床结局^[30]。尽管如此,有关AKI供者行肾移植的远期预后仍需要更长时间的随访数据和更大样本的研究来证实。

目前有关AKI定义的标准有危险、损伤、衰竭、丧失、终末期肾病(risk-injury-failure-loss-end stage renal disease, RIFLE)标准, KDIGO标准是结合RIFLE和急性肾脏损伤网络(acute kidney injury network, AKIN)标准提出^[31-33]。有研究表明, KDIGO标准可能比AKIN标准更有助于预测器官移植术后DGF^[34-36]。因此,本研究采用更为准确的KDIGO标准,结果提示KDIGO 1期和2~3期肾移植的临床结果相似,提示基线肾损伤的严重程度对移植肾的影响很小,另一个可能的原因是对供者AKI及时有效的处理,尽早恢复了器官灌注,使得获取前两组肾功能均得到恢复^[37]。

本研究发现仅供者年龄是导致DGF的独立危险



注：A 图为两组受者术后 6 个月 Scr 变化趋势；B 图两组受者术后 5 d 尿量变化；C 图为 KDIGO 1 期、2~3 期受者术后 6 个月 Scr 变化趋势；D 图为 KDIGO 1 期、2~3 期受者术后 5 d 尿量变化。^a*P*<0.05。

图 1 两组受者术后 Scr 及尿量变化趋势图

Figure 1 Trends of postoperative Scr and urine volume changes of recipients in the two groups

表 3 移植物功能延迟恢复的危险因素分析

Table 3 Analysis of risk factors of delayed graft function

项目	单因素分析			多因素分析		
	比值比	95%可信区间	<i>P</i> 值	比值比	95%可信区间	<i>P</i> 值
供者年龄	1.035	1.016~1.054	<0.001	1.045	1.024~1.065	<0.001
供者BMI	1.000	0.942~1.062	0.999			
供者Scr最高值	1.003	1.000~1.006	0.023	1.002	0.999~1.005	0.266
供者血钠最高值	1.023	1.006~1.041	0.010	1.027	1.004~1.050	0.018
供者升压药应用时间	0.986	0.916~1.061	0.707			
供者48 h内液体复苏用量	1.089	1.009~1.175	0.028	1.035	0.945~1.135	0.459
供者入院HCO ₃ ⁻	1.024	0.982~1.068	0.265			
供者尿崩症	1.037	0.686~1.568	0.863			
供者低血压	0.844	0.563~1.267	0.414			

因素，供者 AKI 不是导致 DGF 的危险因素，这可能与 AKI 供者进行了及时的集束化治疗有关^[20]。提示 AKI 供者供肾用于肾移植仍然可行，是扩大供者来源的重要途径^[38]。但如果供者 AKI 没有及时处理，仍

有可能发生 DGF，早期恢复器官灌注治疗对伴 AKI 的供者非常重要。然而，由于本研究 KDIGO 2~3 期受者数量有限，无法得出明确的结论。

综上所述，经过积极的器官维护可纠正供者

AKI, 尽管肾移植术后可能发生 DGF, 但对术后 6 个月移植功能和移植肾存活率没有影响, 可以尝试作为扩大供肾来源的途径之一。但本研究仍存在一些不足之处, 导致 AKI 的因素很多, 本研究并未对引起供者 AKI 的原因做进一步分析, 比如低血容量休克导致 AKI 与合并基础疾病 (糖尿病、高血压等) 导致 AKI 的临床结局可能不同; 本研究随访时间仅为 6 个月, 尚需要更长时间的随访, 才能得出更为严谨的结论。未来仍需要进行多中心、前瞻性队列研究来进一步明确伴 AKI 的 DBD 供肾肾移植的临床结局。

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(收稿日期: 2024-02-18)

(本文编辑: 方引超 吴秋玲)