枸橼酸抗凝

在人工肝治疗肝衰竭中的应用

四川大学华西医院感染性疾病中心

白　　浪

内　容

- 肝衰竭与人工肝概述
- 局部枸橼酸抗凝（RCA）概述
- 肝衰竭患者代谢枸橼酸的能力
- RCA在人工肝治疗肝衰竭患者中的应用
  - ✓ 非高危出血肝衰竭患者：DPMAS+PE、CPEFA
  - ✓ 高危出血肝衰竭患者
  - ✓ 深静脉导管封管

慢加急性肝衰竭及其治疗方案

ACLF临床特征：

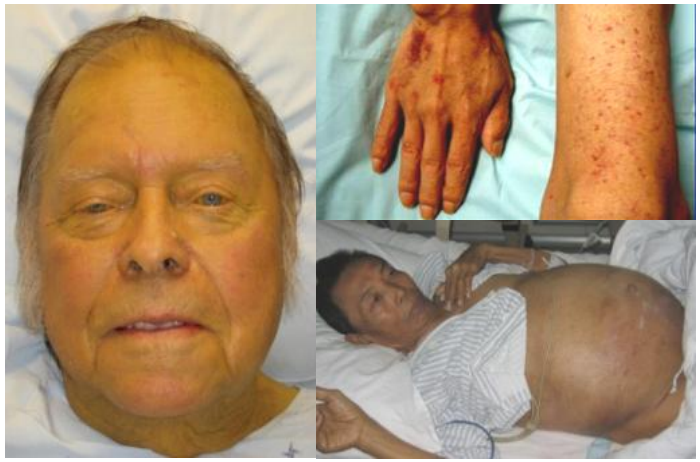
⑴ 慢性肝病急性加重；

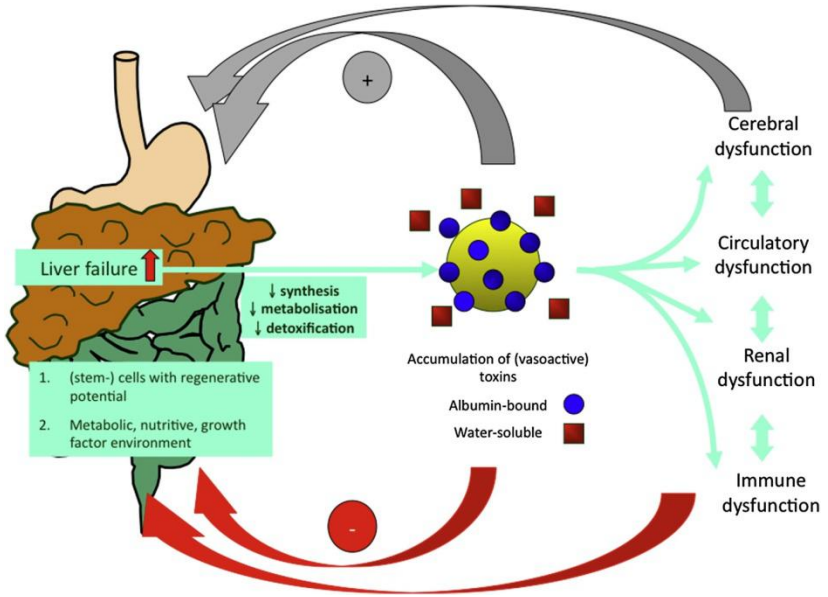
⑵ 极度乏力、严重消化道症状；

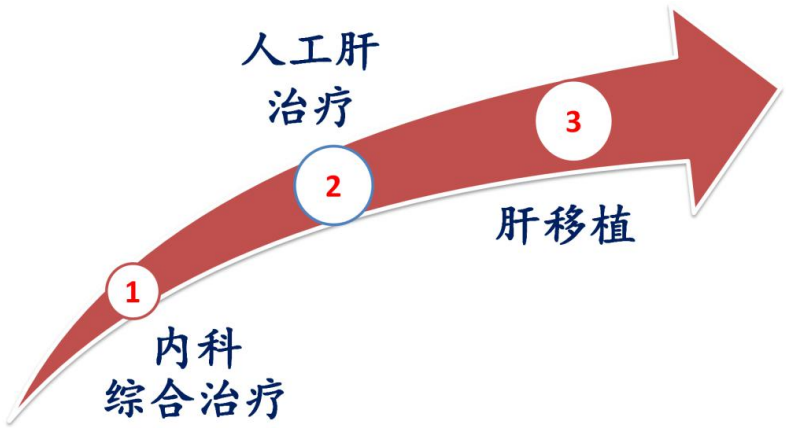
⑶ TB≥10mg/dl或每日上升≥1mg/dl；

⑷ PTA≤40%或INR≥1.5；

⑸ 伴或不伴肝性脑病和(或)腹水等并发症。







Sarin SK, et al. Nat Rev Gastroenterol Hepatol. 2016 Mar;13(3):131-49.
Nevens F, et al. Best Pract Res Clin Gastroenterol. 2012 Feb;26(1):17-26.

人工肝支持系统（ALSS）概念

体外循环装置
血液净化技术

清除各种有害物质
补充蛋白质和凝血因子
维持内环境稳定

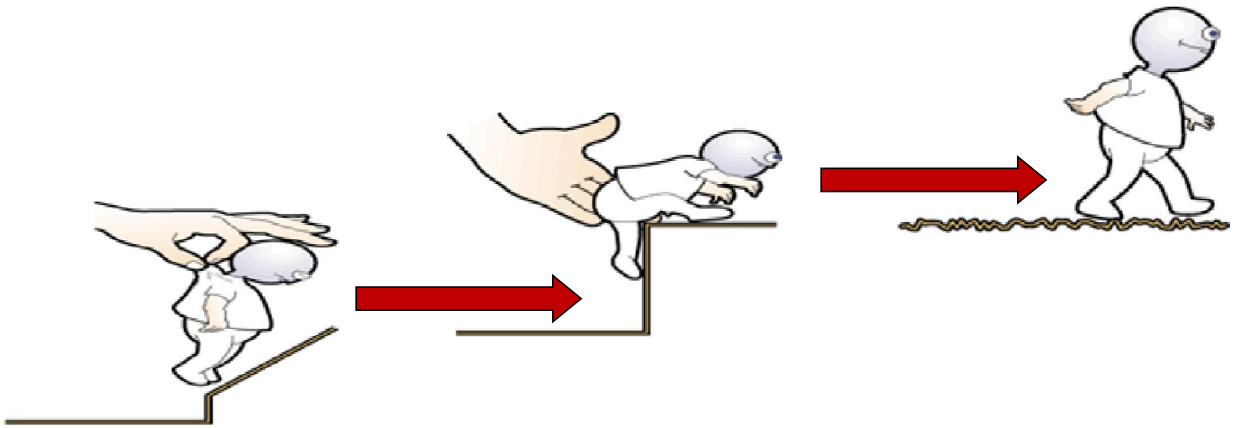
暂时替代
肝脏功能

（1）
肝细胞再生
肝功能恢复

（2）
等待肝移植

Buy time

Bridge

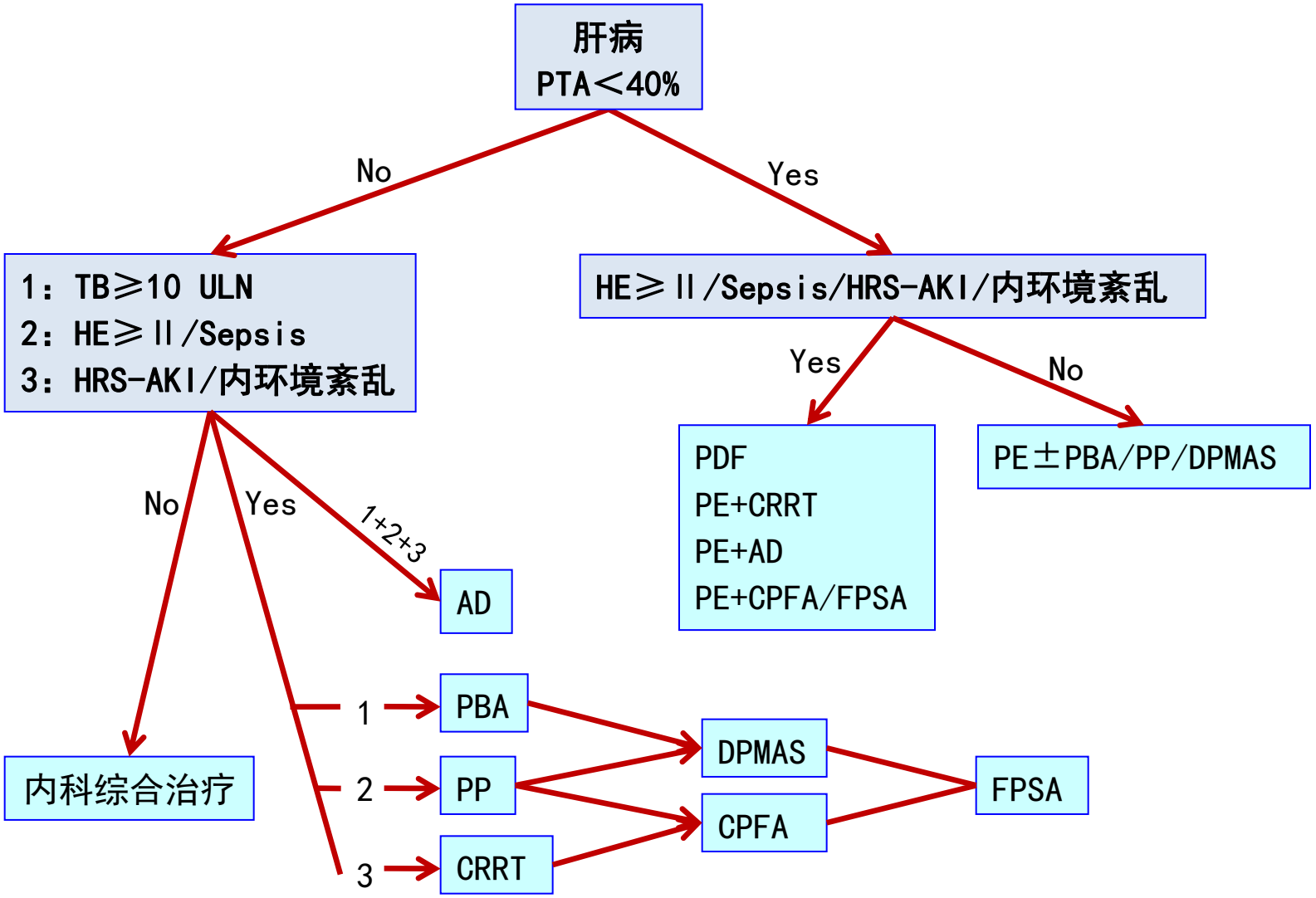


非生物型人工肝治疗肝衰竭指南(2016年版). 中华临床感染病杂志,2016,09(2): 97-103.

ALSS模式

- **血浆置换PE(±CRRT)**
  - ✓ 血浆置换PE
  - ✓ 血浆置换联合血液滤过PERT
  - ✓ 选择性血浆置换FPE
  - ✓ 血浆透析滤过PDF
  - ✓ 双重滤过血浆置换DFPP
- **血浆吸附PA(±CRRT)**
  - ✓ 配对血浆滤过吸附CPFA
    成分血浆分离吸附FPSA(Prometheus system)
  - ✓ 血浆胆红素吸附/血浆灌流PBA/PP
  - ✓ 双重血浆分子吸附系统DPMAS
- **白蛋白透析AD**
  - ✓ 分子吸附再循环系统MARS
  - ✓ 连续白蛋白净化系统CAPS
  - ✓ 单次通过白蛋白吸附SPAD

ALSS模式选择：参考病理生理

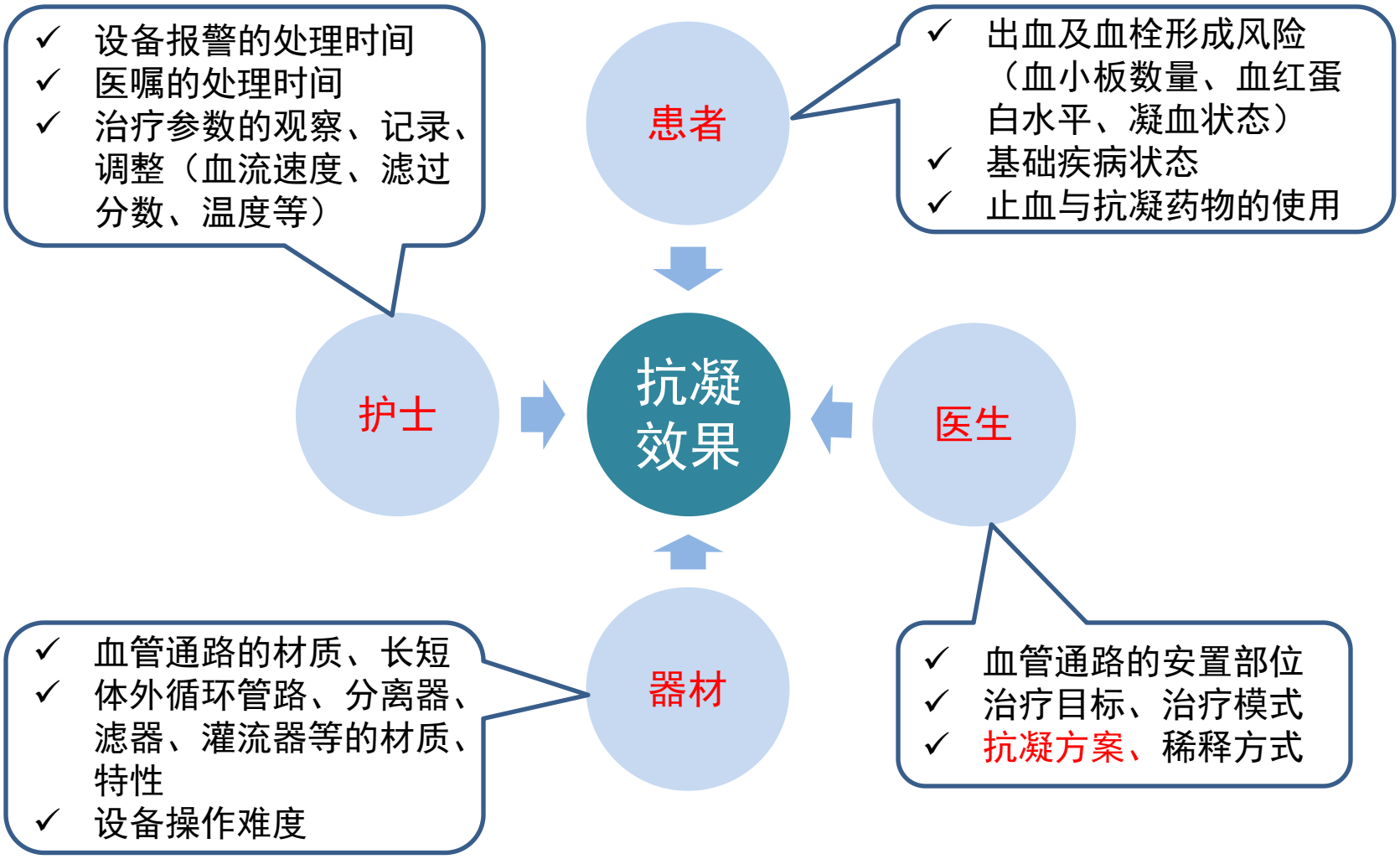


郭利民. 中华临床感染病杂志, 2017, 10(2):113-118.

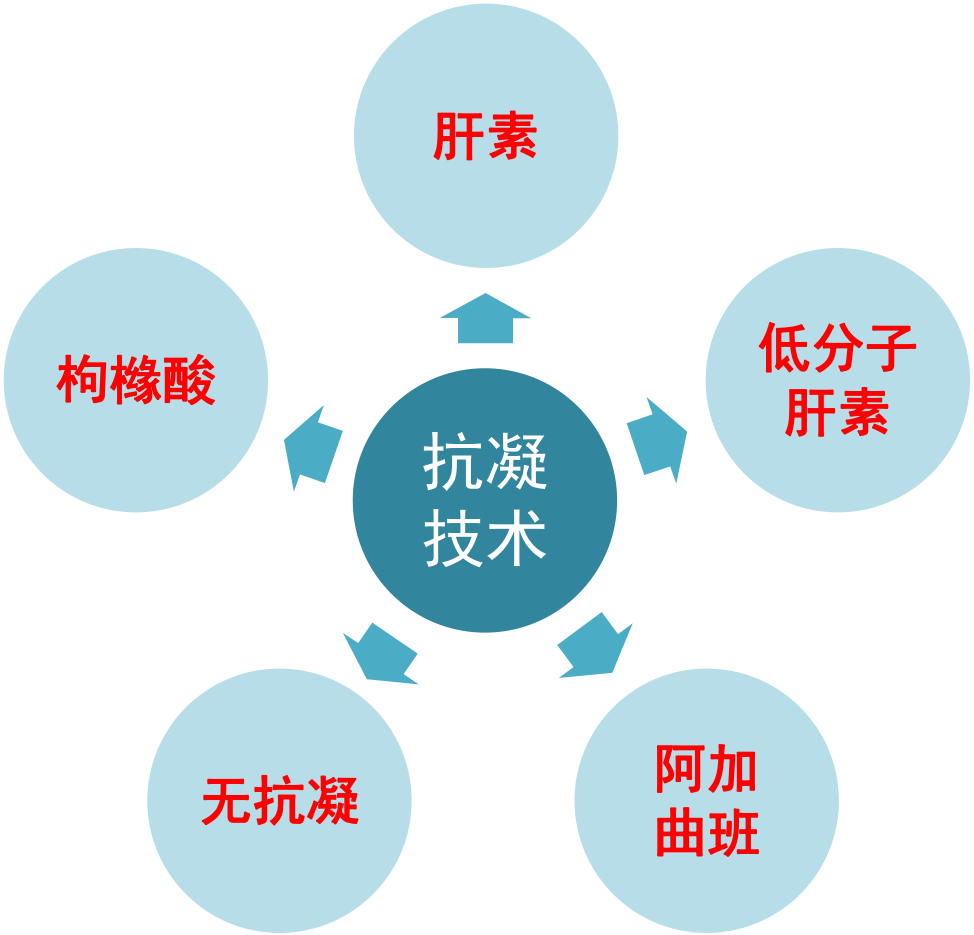
有修改

血液净化治疗必然面临体外循环装置凝血

抗凝效果的影响因素


患者
✓ 出血及血栓形成风险（血小板数量、血红蛋白水平、凝血状态）
✓ 基础疾病状态
✓ 止血与抗凝药物的使用
护士
✓ 设备报警的处理时间
✓ 医嘱的处理时间
✓ 治疗参数的观察、记录、调整（血流速度、滤过分数、温度等）
抗凝效果
医生
✓ 血管通路的安置部位
✓ 治疗目标、治疗模式
✓ 抗凝方案、稀释方式
器材
✓ 血管通路的材质、长短
✓ 体外循环管路、分离器、滤器、灌流器等的材质、特性
✓ 设备操作难度

血液净化常用抗凝技术



肝素抗凝

- ✓ 原理：与抗凝血酶Ⅲ结合，加速灭活Ⅱa、Ⅹa等
  抑制血小板的黏附聚集
- ✓ 代谢：网状内皮系统（主要），肾脏（较少）
- ✓ 用法：首剂30U/kg，维持5-10U/kg·h
- ✓ 监测：APTT or ACT：1.5-2ULN

优势	劣势
经典、成熟 效果明显 监测方便（APTT/ACT） 半衰期短（30min-3h） 可被鱼精蛋白中和 价低	出血风险大 可诱发肝素相关性血小板减少症HIT 依赖抗凝血酶Ⅲ，危重病人多缺乏 药代动力学多变，需要监测 肝素抵抗、过敏 高脂血症、骨质疏松、脱发等

低分子肝素抗凝

- ✓ 原理：分离自普通肝素，与抗凝血酶Ⅲ结合，加速灭活Ｘａ
  抑制血小板的黏附聚集
- ✓ 代谢：肾脏（主要），网状内皮系统（少量）
- ✓ 用法：首剂15-30U/kg，维持5-10U/kg·h
- ✓ 监测：抗Ｘａ因子浓度0.25-0.35U/ml

优势	劣势
药代动力学稳定，可不监测 抗凝效果较可靠 HIT较少	出血风险较大 肾功能衰竭时易蓄积 仅部分被鱼精蛋白中和 依赖抗凝血酶Ⅲ，危重病人多缺乏 半衰期长（2-5h） 价高 抗Ｘａ因子浓度不易监测 高脂血症、骨质疏松、脱发等

（低分子）肝素抗凝适应症

- 既往无肝素/低分子肝素过敏史
- 既往无HIT
- 没有活动性出血
- 无严重异常的血脂与骨代谢
- 抗凝血酶Ⅲ活性在50%以上
- 血小板数量基本正常，凝血功能正常或轻度异常

KDIGO Clinical Practice Guideline for Acute Kidney Injury (2012)

阿加曲班抗凝

- ✓ 原理：高选择性直接凝血酶抑制剂，直接灭活 IIa
- ✓ 代谢：肝脏
- ✓ 用法：1-2μg/kg·min
- ✓ 监测：APTT or ACT：1.5-2ULN

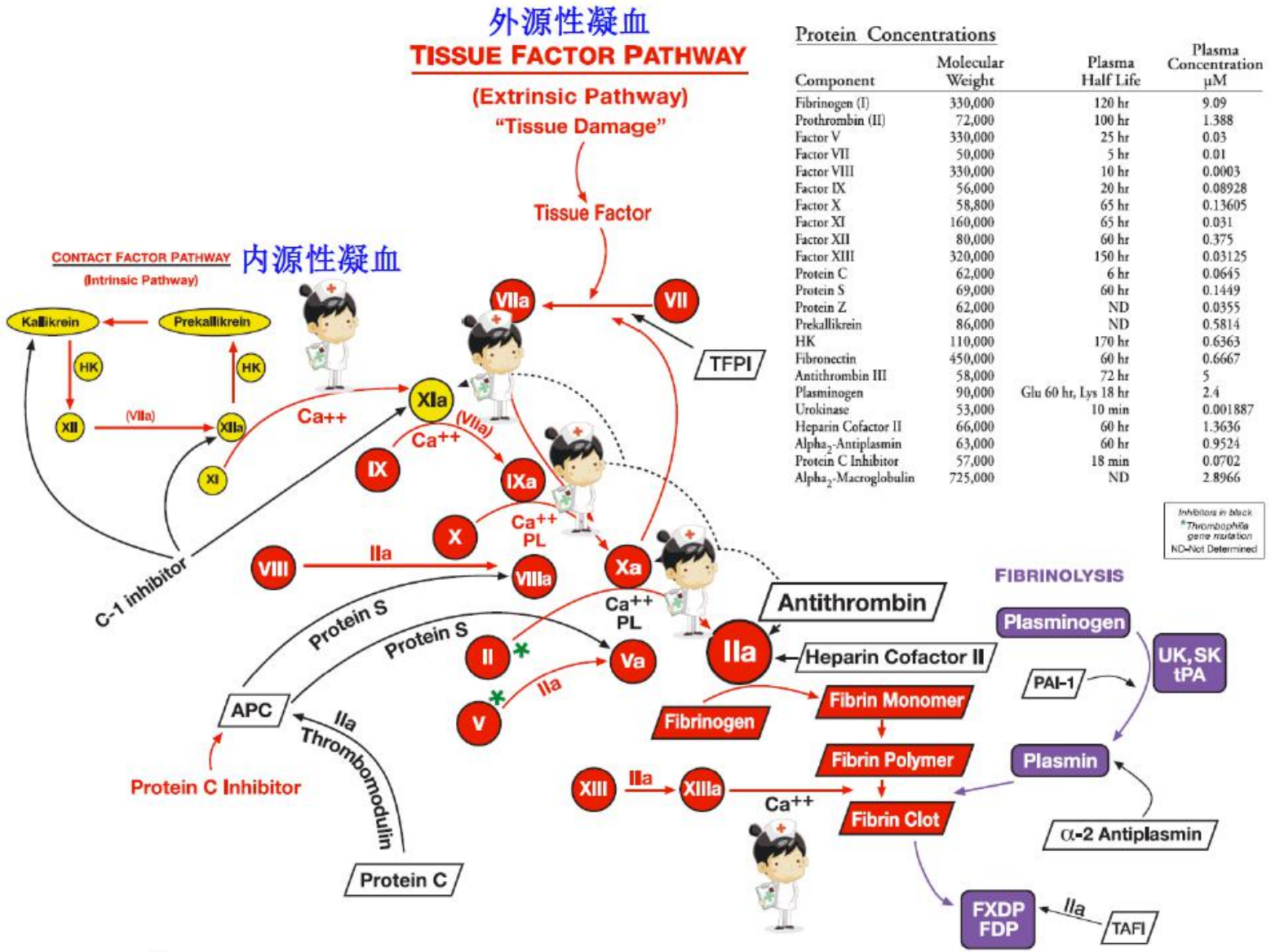
优势	劣势
半衰期短（30-60min） 监测方便（APTT/ACT）	肝功能衰竭时容易出血 无特异性拮抗剂

无抗凝

- ✓ 原理：患者出血倾向、体外循环高流速、前稀释、盐水冲洗
- ✓ 用法：盐水200ml冲洗管路，0.5-1h/次；前稀释
- ✓ 监测：无

优势	劣势
出血风险低	难以避免凝血 损耗血红蛋白、血小板 额外容量负荷 降低治疗效率，治疗目标难达到 护士工作量巨大

枸橼酸抗凝：螯合Ca^{2+}

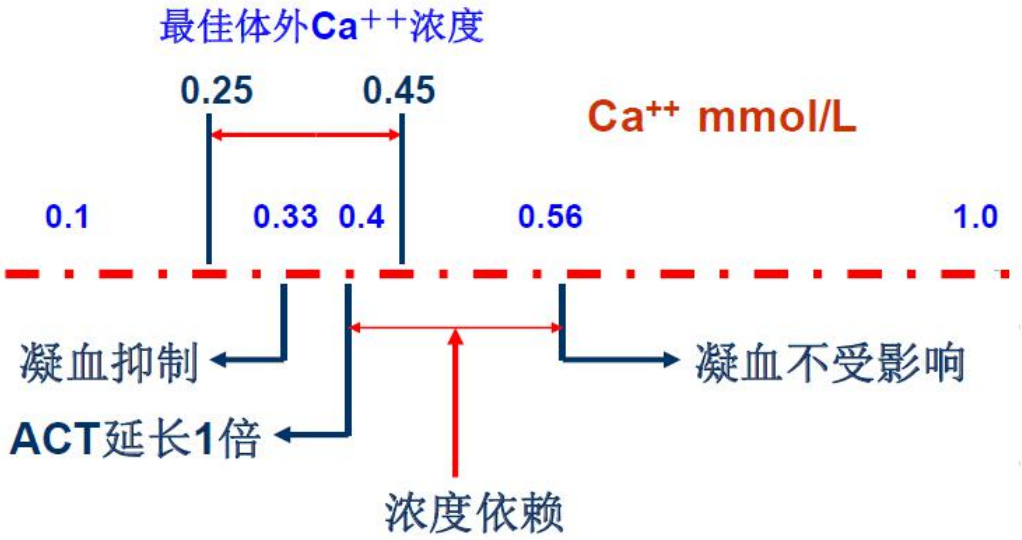


Protein Concentrations

Component	Molecular Weight	Plasma Half Life	Plasma Concentration μM
Fibrinogen (I)	330,000	120 hr	9.09
Prothrombin (II)	72,000	100 hr	1.388
Factor V	330,000	25 hr	0.03
Factor VII	50,000	5 hr	0.01
Factor VIII	330,000	10 hr	0.0003
Factor IX	56,000	20 hr	0.08928
Factor X	58,800	65 hr	0.13605
Factor XI	160,000	65 hr	0.031
Factor XII	80,000	60 hr	0.375
Factor XIII	320,000	150 hr	0.03125
Protein C	62,000	6 hr	0.0645
Protein S	69,000	60 hr	0.1449
Protein Z	62,000	ND	0.0355
Prekallikrein	86,000	ND	0.5814
HK	110,000	170 hr	0.6363
Fibronectin	450,000	60 hr	0.6667
Antithrombin III	58,000	72 hr	5
Plasminogen	90,000	Glu 60 hr, Lys 18 hr	2.4
Urokinase	53,000	10 min	0.001887
Heparin Cofactor II	66,000	60 hr	1.3636
$Alpha_2$-Antiplasmin	63,000	60 hr	0.9524
Protein C Inhibitor	57,000	18 min	0.0702
$Alpha_2$-Macroglobulin	725,000	ND	2.8966

Inhibitors in black
Thrombophilia gene mutation
ND=Not Determined

局部枸橼酸抗凝（RCA）



- ✓ 用法：引血端泵入枸橼酸钠，体外抗凝
  回血端泵入葡萄糖酸钙，恢复体内凝血功能
- ✓ 监测：体外：Ca_{ion} 0.2-0.4mmol/L（有效）
  体内：Ca_{ion} 1.0-1.2mmol/L（安全）

James MF, et al. J Cardiothorac Vasc Anesth. 2004 Oct;18(5):581-6.

RCA并发症

- ✓ 枸橼酸蓄积

  总钙增高，离子钙不变或降低，

  严重时AG增高的代谢性酸中毒

- ✓ 代谢性碱中毒

  1mmol枸橼酸根 → 3mmol HCO_3^-

- ✓ 低钙血症

  补钙不足，或枸橼酸蓄积

- ✓ 高钙血症

- ✓ 高钠血症

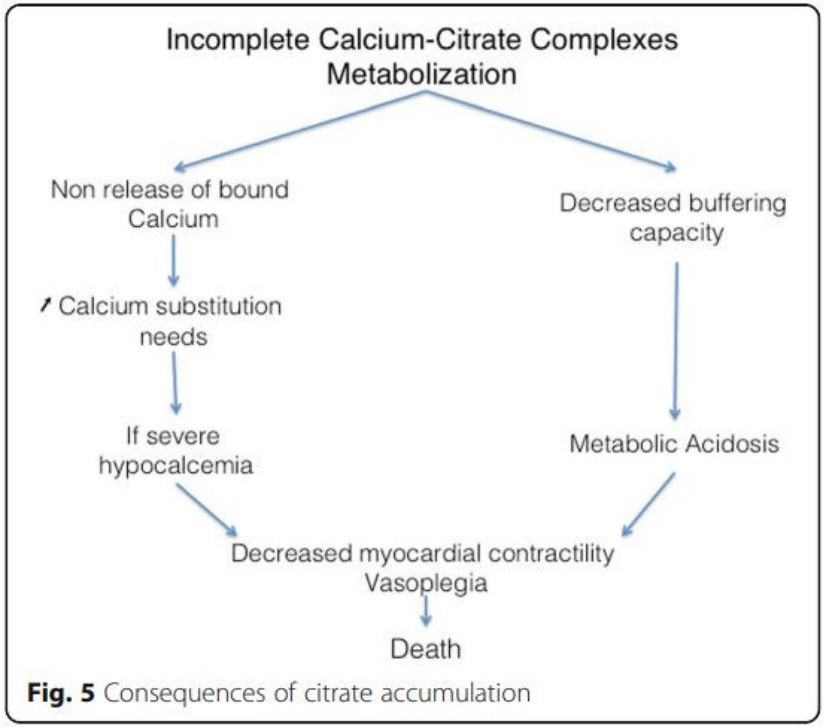


Fig. 5 Consequences of citrate accumulation

Schneider AG, et al. Crit Care. 2017 Nov 19;21(1):281.

RCA禁忌症

- 严重低氧血症（PO_2＜60mmHg）
- 组织灌注差（大剂量升压药物血压仍＜80/40mmHg）
- 肝功能异常（TB＞2ULN ）

↓

代谢枸橼酸能力降低，枸橼酸蓄积风险增高

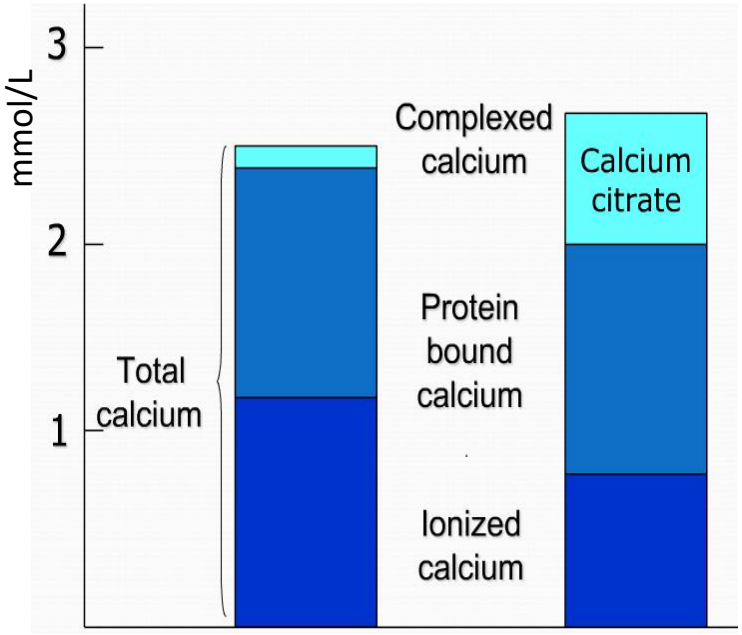
↓

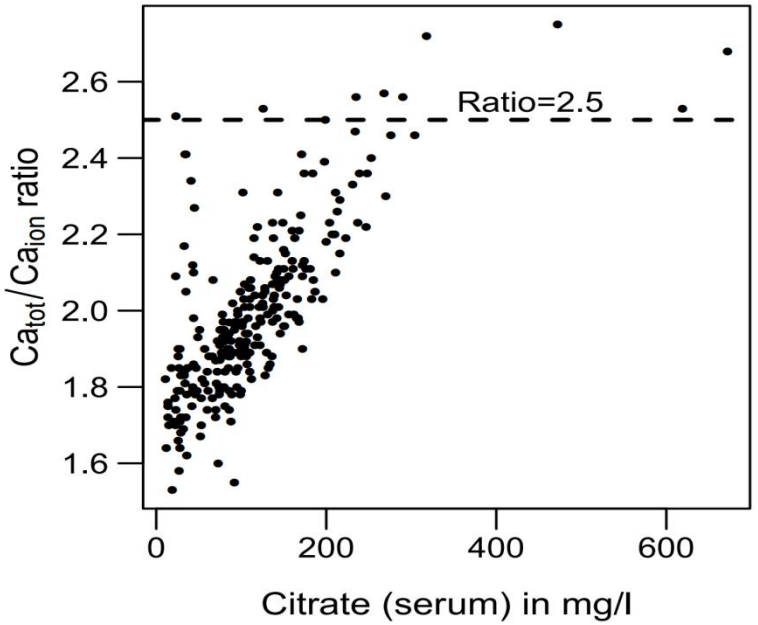
相对禁忌症：任意1条

绝对禁忌症：任意2条或3条

KDIGO Clinical Practice Guideline for Acute Kidney Injury (2012)

枸橼酸蓄积





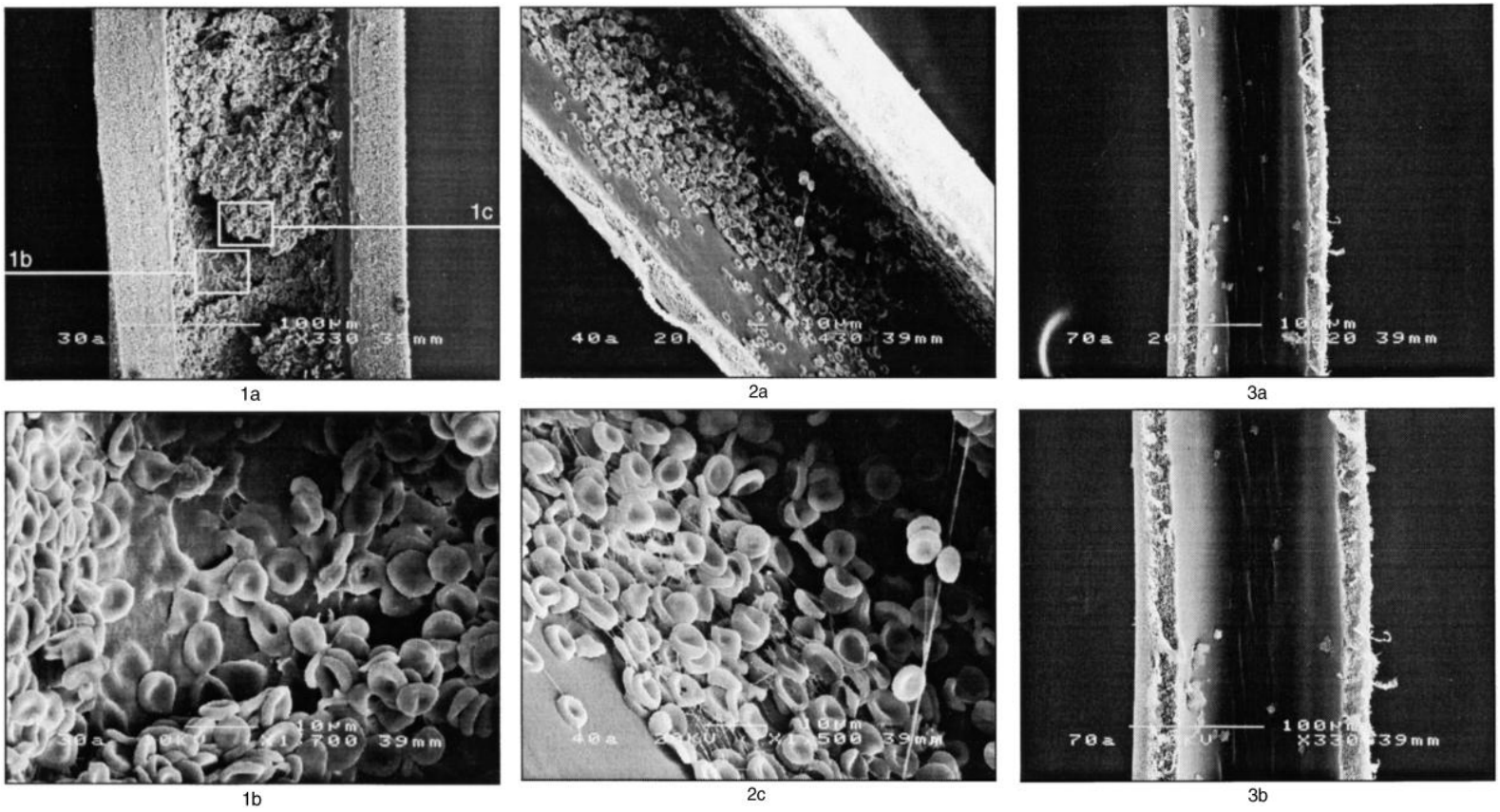
Ca_{tot}/Ca_{ion}比值与血枸橼酸水平有良好的相关性

Ca_{tot}/Ca_{ion}≥2.5提示枸橼酸蓄积

Khadzhynov D, et al. J Crit Care. 2014 Apr;29(2):265-71.
Schultheiß C, et al. Crit Care. 2012 Aug 22;16(4):R162.

RCA：组织相容性更好

肝素抗凝　　低分子肝素抗凝　　RCA

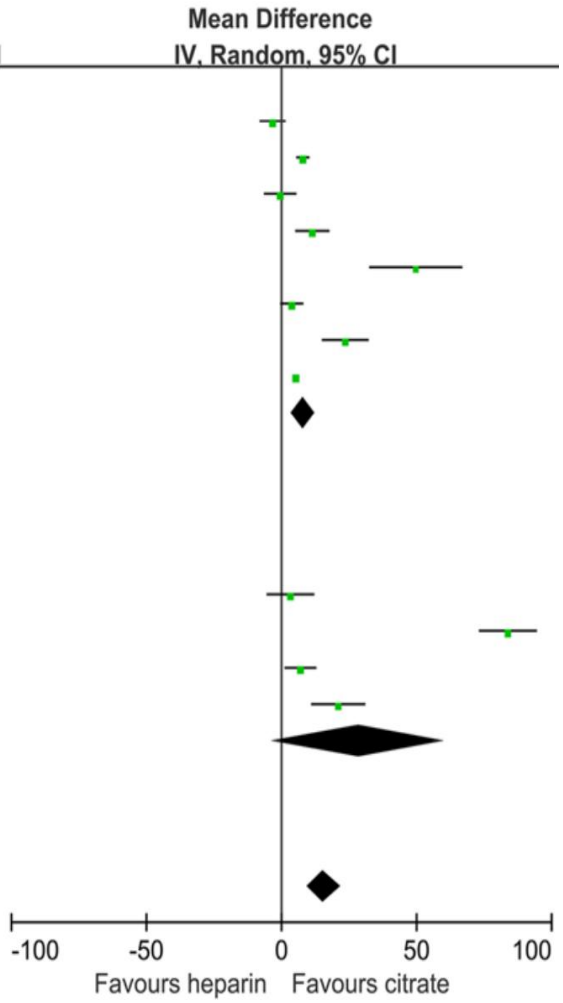


Hofbauer R, et al. Kidney Int. 1999 Oct;56(4):1578-83.

RCA：体外循环管路寿命更长

RCA vs. 肝素抗凝

Study or Subgroup	Citrate Mean	SD	Total	Heparin Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
CVVH								
Betjes et al 2007 NL	39	15.7	70	42.3	13.6	72	9.0%	-3.30 [-8.14, 1.54]
Cui W et al 2011 CN	28.2	4.2	23	20.3	4.3	23	9.4%	7.90 [5.44, 10.36]
Fealy et al 2007 AU	16.2	4.2	10	16.7	8.8	10	8.7%	-0.50 [-6.54, 5.54]
Hetzel et al 2011 DE	37.5	23	87	26.1	19	81	8.7%	11.40 [5.04, 17.76]
Monchi et al 2004 BE	84.7	42.2	26	35	14.4	23	5.6%	49.70 [32.44, 66.96]
Oudemans-vanStraaten et al 2009 NL	28.5	15.2	97	24.7	15.9	103	9.1%	3.80 [-0.51, 8.11]
Schilder et al 2014 NL	57.8	34.2	66	34.2	11.8	73	8.1%	23.60 [14.92, 32.28]
Yang ST et al 2014 CN	19.7	4.3	81	14.4	2.6	53	9.5%	5.30 [4.13, 6.47]
Subtotal (95% CI)			**460**			**438**	**68.0%**	**8.18 [3.86, 12.51]**
Heterogeneity: $Tau^2 = 29.13$; $Chi^2 = 65.99$, df = 7 ($P < 0.00001$); $I^2 = 89\%$								
Test for overall effect: $Z = 3.71$ ($P = 0.0002$)								
CVVHDF								
Brain et al 2014 AU	34	32	96	30.7	35	125	8.0%	3.30 [-5.57, 12.17]
Kutsogiannis et al 2005 CA	125.5	29.1	36	41.7	16.9	43	7.5%	83.80 [73.04, 94.56]
Lin XM et al 2007 CN	27	12.2	27	20	9.1	23	8.8%	7.00 [1.08, 12.92]
Stucker et al 2015 CH	49	29	54	28	23	49	7.7%	21.00 [10.94, 31.06]
Subtotal (95% CI)			**213**			**240**	**32.0%**	**28.60 [-3.52, 60.73]**
Heterogeneity: $Tau^2 = 1053.41$; $Chi^2 = 167.12$, df = 3 ($P < 0.00001$); $I^2 = 98\%$								
Test for overall effect: $Z = 1.74$ ($P = 0.08$)								
Total (95% CI)			**673**			**678**	**100.0%**	**15.69 [9.30, 22.08]**
Heterogeneity: $Tau^2 = 112.07$; $Chi^2 = 275.51$, df = 11 ($P < 0.00001$); $I^2 = 96\%$								
Test for overall effect: $Z = 4.81$ ($P < 0.00001$)								
Test for subgroup differences: $Chi^2 = 1.52$, df = 1 ($P = 0.22$), $I^2 = 34.4\%$								



Liu C, et al. Crit Care. 2016 May 13;20(1):144.

RCA：出血与HIT减少、低钙血症增加

RCA vs. 肝素抗凝

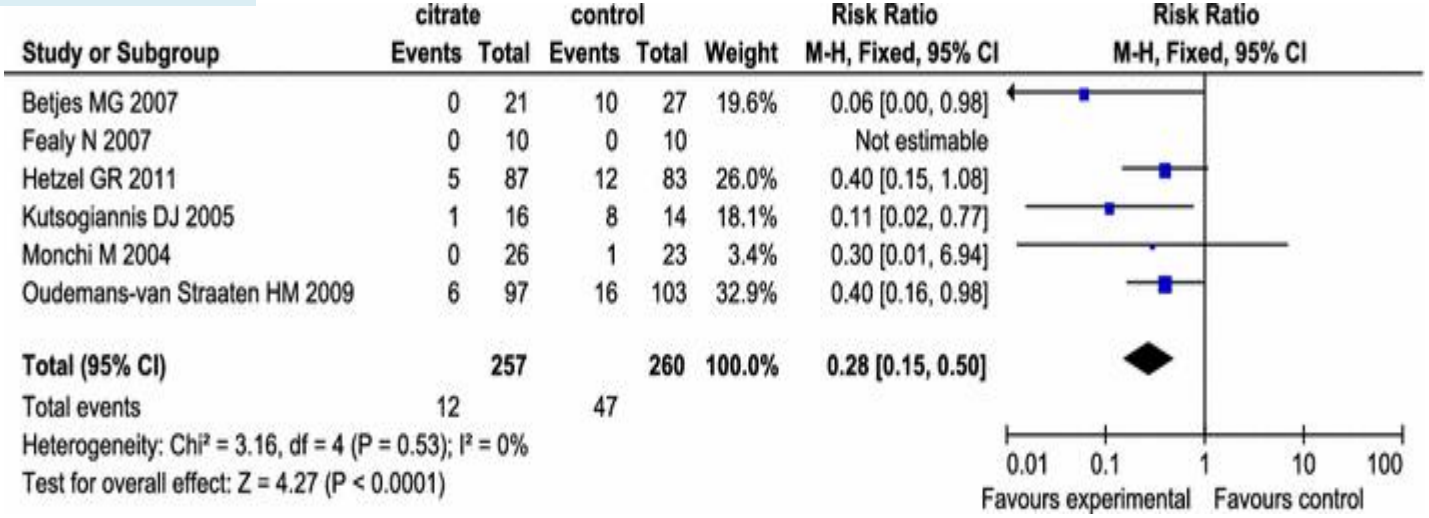


Table 2 Direct comparison of regional citrate with heparin on adverse events

Adverse events	No. of studies	No. of patients		RR(95%CI)	Heterogeneity	Test for effect (p value)
		Citrate	Heparin		I^2 (p value)	
Bleeding events	10 (11, 13, 24, 25, 27, 28, 29, 32, 33, 34)[a]	405	405	0.31(0.19, 0.51)	0% (0.56)	<0.00001
	3 (12, 26, 31)[b]	140	138	0.23 (0.03, 1.97)	0% (0.75)	0.18
HIT	5 (11, 12, 13, 28, 33)	409	415	0.41 (0.19, 0.87)	0% (0.73)	0.02
Metabolic alkalosis	7(11, 13, 24, 27, 28, 29, 34)	289	301	0.84 (0.47, 1.49)	40% (0.14)	0.55
Hypocalcemia	7 (11, 24, 27, 28, 29, 33, 34)	310	311	3.96 (1.50, 10.43)	0% (1.00)	0.005

CI confidence interval, *HIT* heparin induced thrombocytopenia, *RR* relative risk, [a] citrate versus systemic heparin; [b] citrate versus regional heparin

Liu C, et al. Crit Care. 2016 May 13;20(1):144.
Zhang Z, et al. Intensive Care Med. 2012 Jan;38(1):20-8.

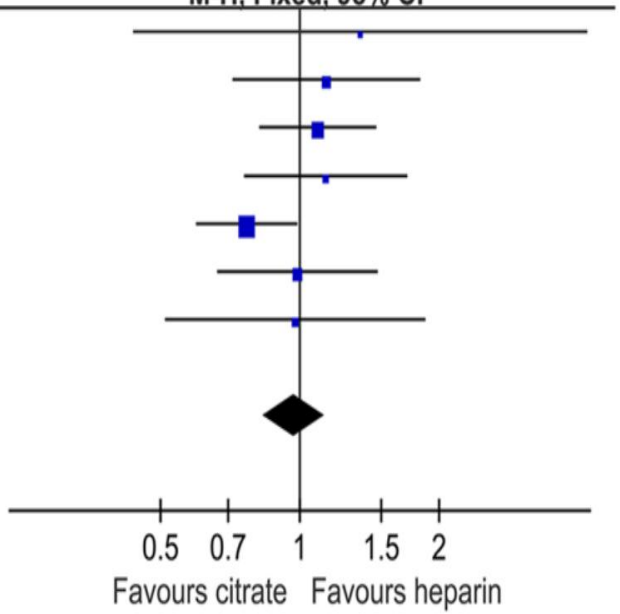
RCA：病死率未增减

RCA vs. 肝素抗凝

Study or Subgroup	Citrate Events	Citrate Total	Heparin Events	Heparin Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Brain et al 2014 AU	7	19	3	11	2.0%	1.35 [0.44, 4.18]
Gattas et al 2015 AU	28	105	25	107	13.3%	1.14 [0.72, 1.82]
Hetzel et al 2011 DE	47	87	41	83	22.6%	1.09 [0.82, 1.46]
Kutsogiannis et al 2005 CA	13	16	10	14	5.7%	1.14 [0.76, 1.71]
Oudemans-vanStraaten et al 2009 NL	47	97	65	103	33.9%	0.77 [0.60, 0.99]
Schilder et al 2014 NL	27	65	29	69	15.1%	0.99 [0.66, 1.47]
Stucker et al 2015 CH	14	54	13	49	7.3%	0.98 [0.51, 1.87]
Total (95% CI)		**443**		**436**	**100.0%**	**0.97 [0.84, 1.13]**
Total events	183		186			

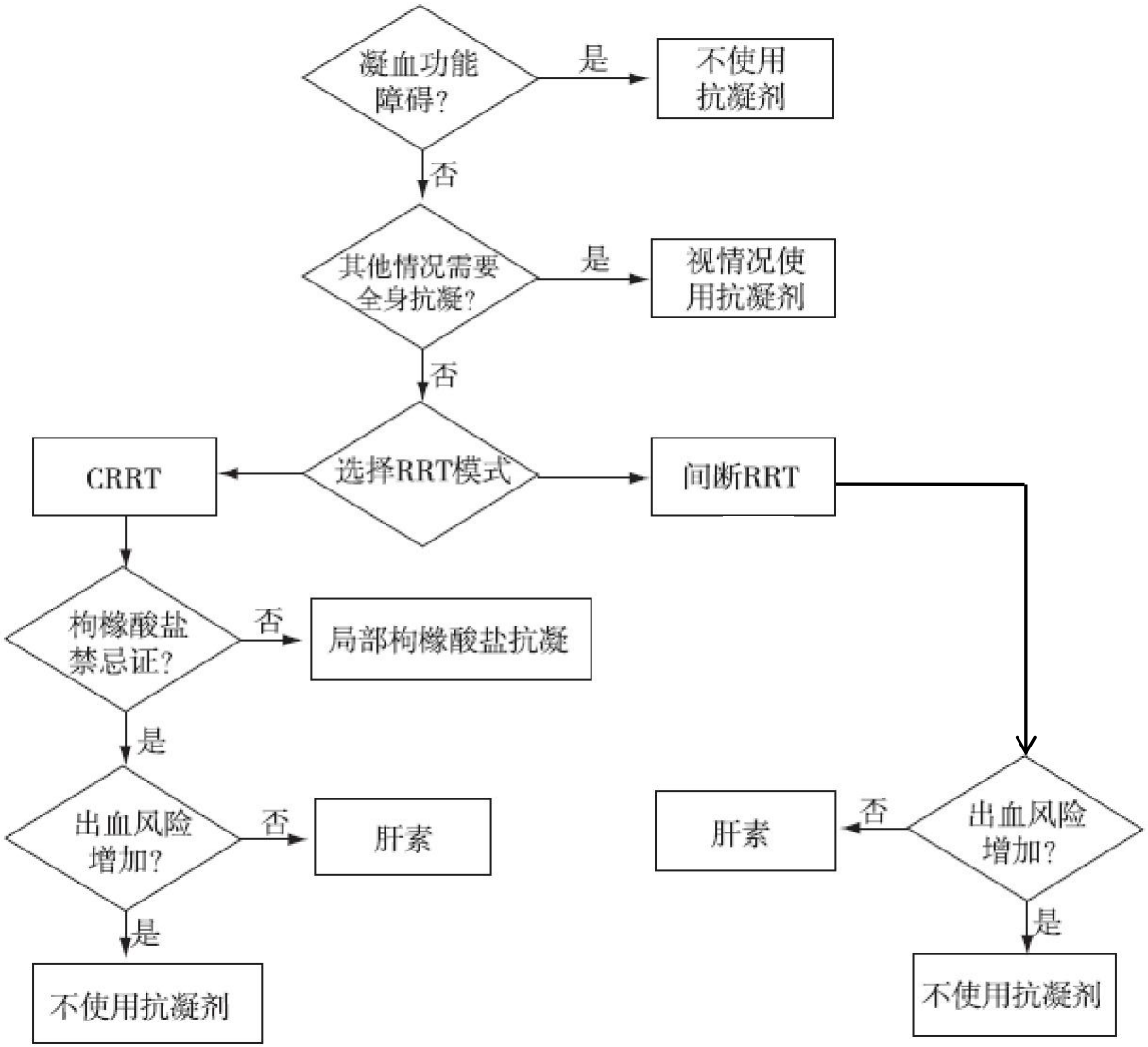
Heterogeneity: $Chi^2 = 5.33$, $df = 6$ ($P = 0.50$); $I^2 = 0\%$

Test for overall effect: $Z = 0.36$ ($P = 0.72$)



Liu C, et al. Crit Care. 2016 May 13;20(1):144.

RCA在血液净化治疗中的地位

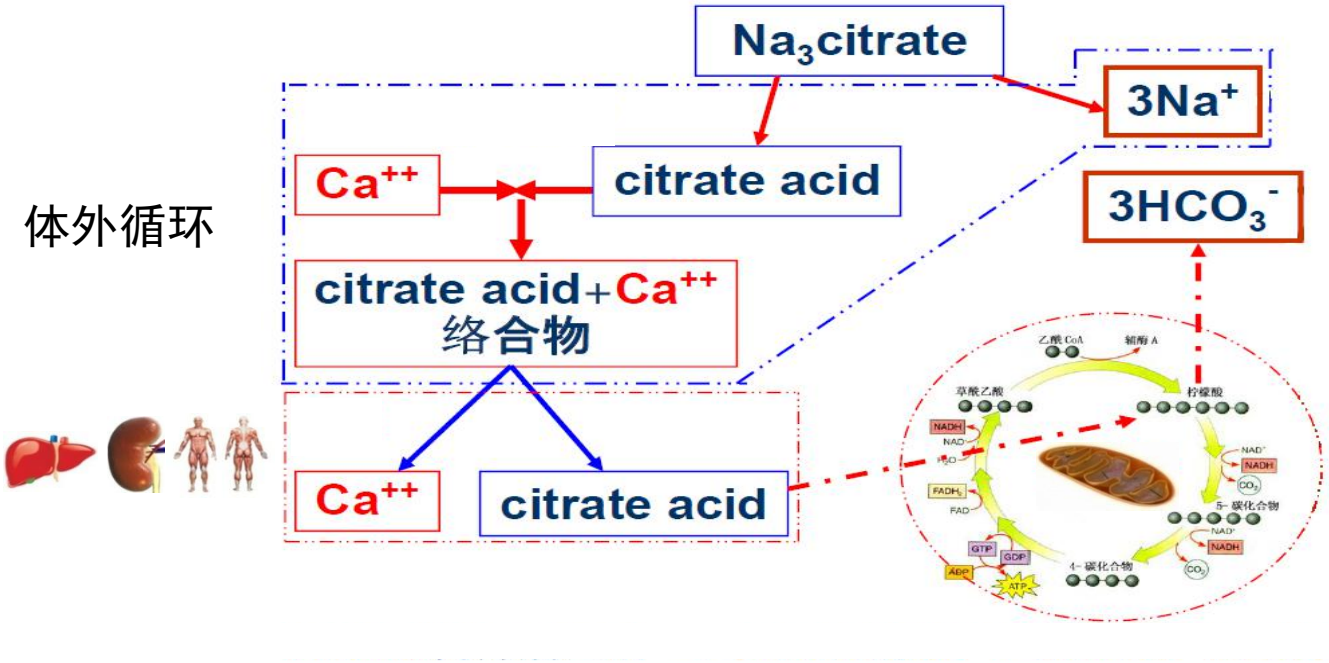


KDIGO Clinical Practice Guideline for Acute Kidney Injury (2012)

肝衰竭患者能耐受枸橼酸蓄积吗？

枸橼酸代谢：健康人

体外循环



$$Na_3(C_6H_5O_7) + 3H_2CO_3 \leftrightarrow 3NaHCO_3 + C_6H_8O_7 \rightarrow 6CO_2 + 4H_2O$$

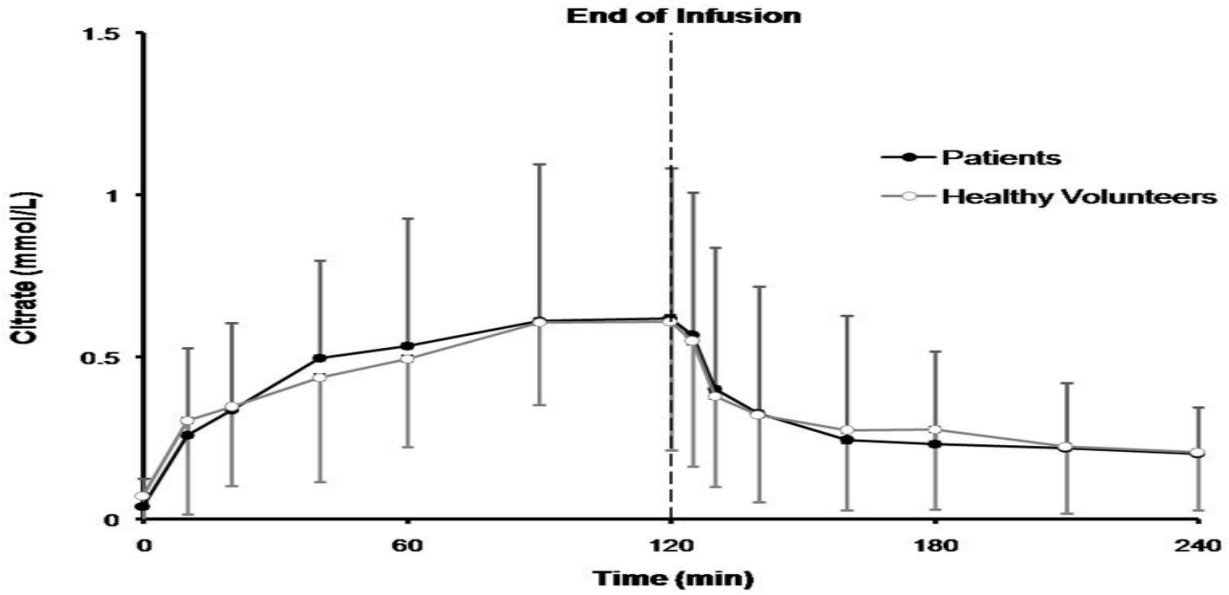
正常人体，枸橼酸钠只需30min即可代谢完全（半衰期约5min）

Kutsogiannis DJ, et al. Am J Kidney Dis. 2000 May;35(5):802-11.
Schneider AG, et al. Crit Care. 2017 Nov 19;21(1):281.

枸橼酸代谢：非肝病重症患者

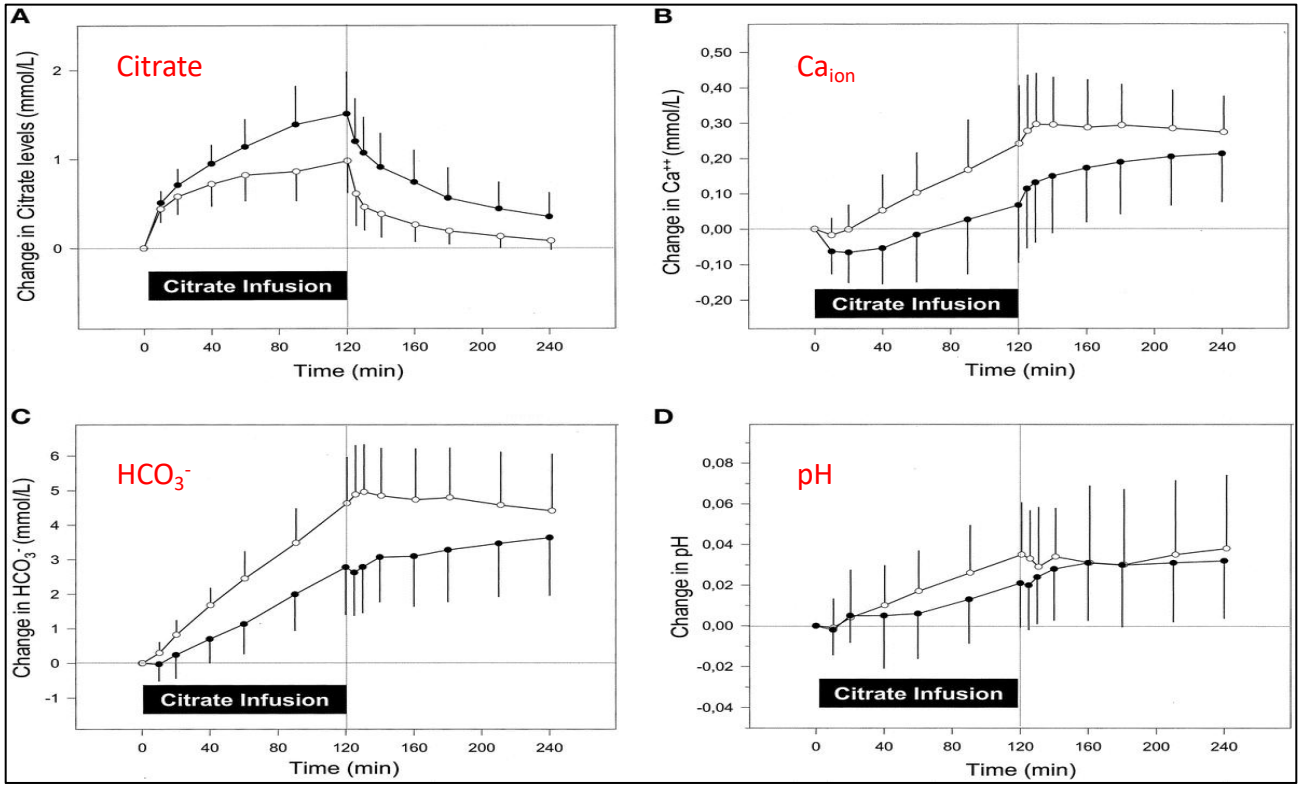
Table 3 Citrate pharmacokinetics.

	Critically Ill Patients with AKI (n=12)	Healthy Patients (n=12)	*p* value
AUC_{0-t} (mmol·min/L)	79.7±95.5	69.9±66.6	0.60
AUC_{0-inf} (mmol·min/L)	86.8±113.8	87.5±95.5	0.95
t_{max} (min)	110.0±18.1	106.6±21.7	0.78
Vd (L)	21.0±19.5	50.6±21.7	0.09
Cl_{body}(ml/min)	648.0±347.0	686.6±353.6	0.62
$C_{baseline}$ (mmol/L)	0.01±0.13	0.02±0.04	0.42
C_{max} (mmol/L)	0.62±0.46	0.56±0.45	0.25
Total dose (mmol)	63.7±9.1	57.1±10.5	0.13



Zheng Y, et al. PLoS One. 2013 Jun 18;8(6):e65992.

肝硬化失代偿患者能耐受枸橼酸蓄积吗？



●Cirrhotic patients

○Noncirrhotic patients

Citrate anticoagulation seems feasible even in patients with decompensated cirrhosis. Metabolic consequences of citrate infusion were not different between groups in this study but may be more pronounced in prolonged infusion.

Kramer L, et al. Crit Care Med. 2003 Oct;31(10):2450-5.

急性肝衰竭患者能耐受枸橼酸蓄积吗？

Wien Klin Wochenschr. 1997 Feb 28;109(4):123-7.

Impairment of citrate metabolism in acute hepatic failure.

Apsner R[1], Schwarzenhofer M, Derfler K, Zauner C, Ratheiser K, Kranz A.

Author information

Abstract

AIMS: To compare the utilization of citrate employed as anticoagulant in patients with acute hepatic failure and subjects with normal liver function.

PATIENTS AND METHODS: Three patients in acute hepatic failure and normal renal function were studied during therapeutic plasma exchange with citrate containing fresh frozen plasma. Six patients receiving immunapheresis or LDL-apheresis anticoagulated with citrate served as controls. Determinations of serum citrate concentrations, of ionized calcium and blood pH were performed before, during, and after the extracorporeal treatment. Total body clearance and elimination half life were calculated in a two compartment model.

RESULTS: Preinfusion citrate levels were higher in the patients with acute hepatic failure than in the controls (n.s.). The citrate level rose to 1.73 +/- 0.2 mmol/l in the liver patients versus 0.99 +/- 0.1 mmol/l in the healthy subjects ($p < 0.03$). Total body clearance was markedly reduced in patients with acute hepatic failure (3.31 +/- 0.03 ml/kg/min) as compared with the controls (6.34 +/- 0.16 ml/kg/min) ($p < 0.02$), the elimination half life (t/2 k1e) was prolonged (49.7 +/- 5.4 vs. 32.9 +/- 1.02 min, $p < 0.05$). In the controls blood pH rose from 7.4 +/- 0.01 to 7.45 +/- 0.01 ($p < 0.05$) after citrate infusion, whereas in the liver patients no rise in pH was observed, again reflecting the impairment of citrate metabolism. Ionized calcium was lower in the patients with acute hepatic failure at the beginning (1.01 +/- 0.05 vs. 1.21 +/- 0.04 mmol/l, $p < 0.05$) and the end (0.68 +/- 0.02 vs. 0.93 +/- 0.04 mmol/l, $p < 0.05$) of the citrate infusion.

CONCLUSIONS: Citrate metabolism is severely impaired and the plasmatic calcium stores are reduced in acute hepatic failure and, thus, the risk of adverse effects is high. Therapeutic infusions of citrate should be restricted in patients with acute hepatic failure and, if necessary, therapy should be closely monitored by repeated measurements of ionized calcium to avoid the development of potentially hazardous hypocalcemia.

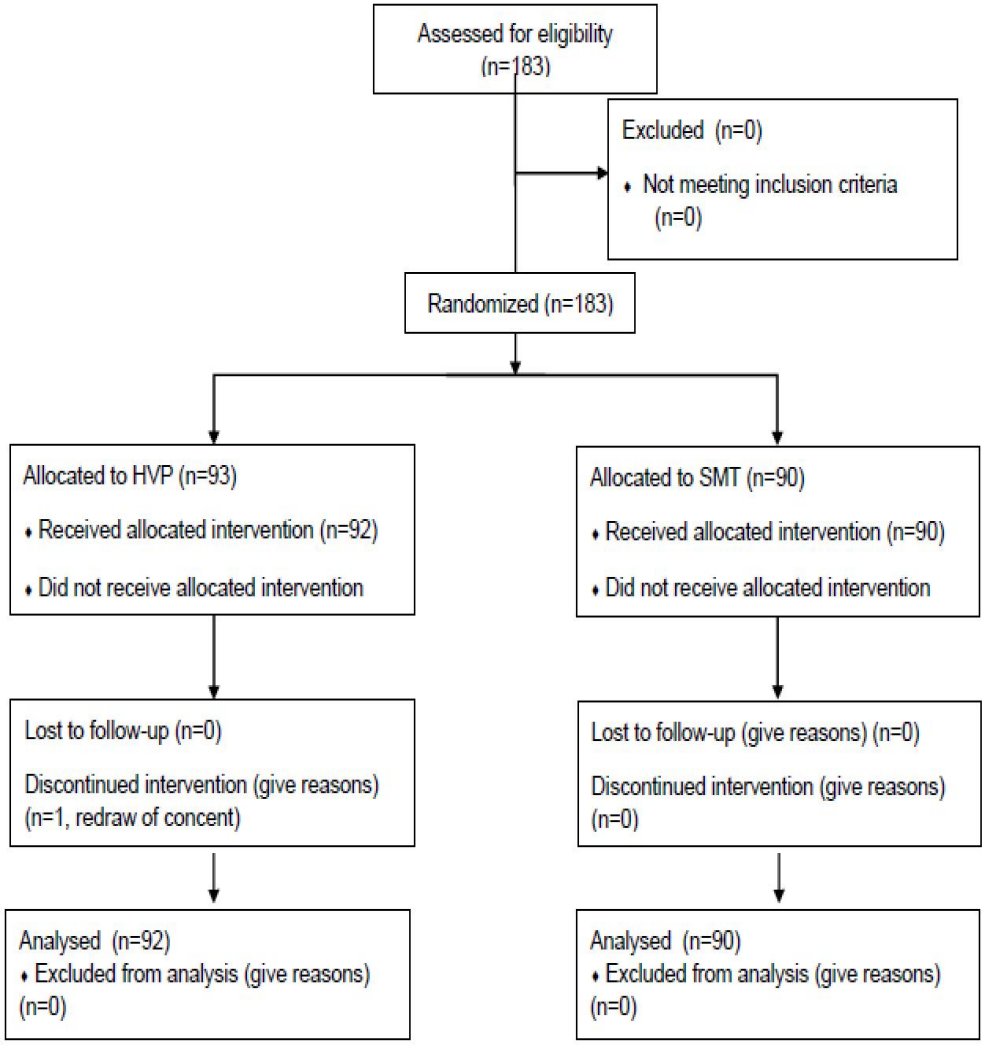
Apsner R, et al. Wien Klin Wochenschr. 1997 Feb 28;109(4):123-7.

PE（9000-9300mL/次）治疗ALF：效果评价

plasma 9-9.3L
(0.33 ± 0.12 L/kg)

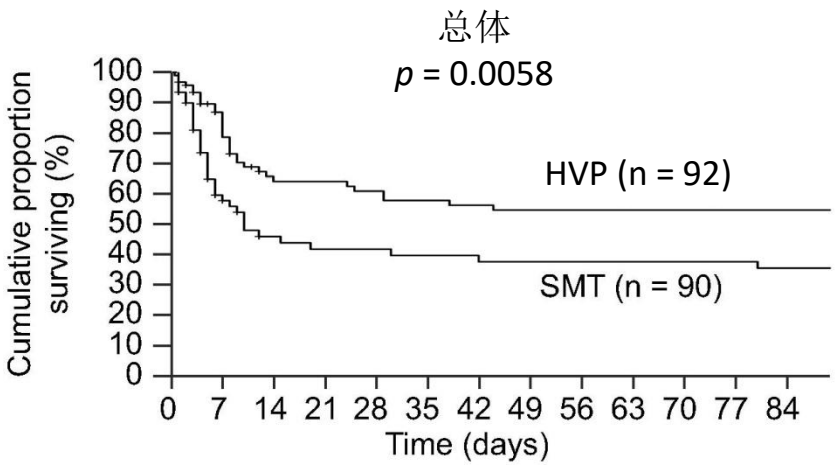
Times：2.4±0.8

随访：90d



Larsen FS, et al. J Hepatol. 2016 Jan;64(1):69-78.

PE（9000-9300mL/次）治疗ALF：提高生存率



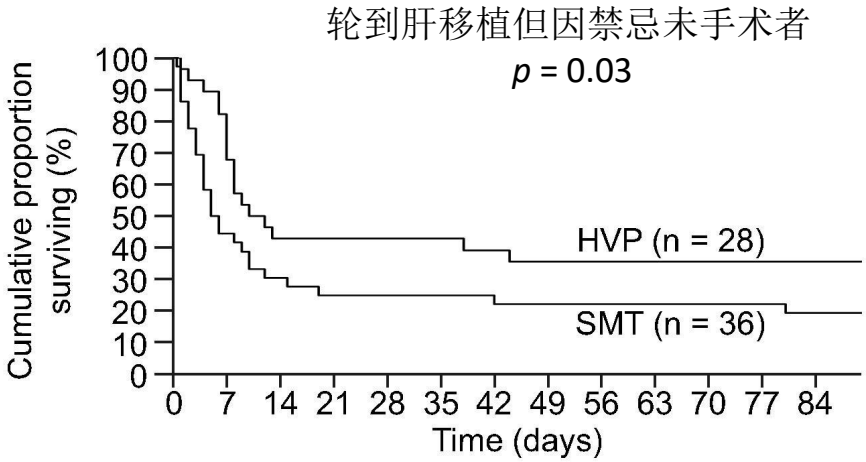


Table 2. Changes in clinical variables and blood gases in patients treated with plasma exchange (HVP) *vs.* control group at baseline (day 0) to day 7.

		SMT (n = 90)		HVP (n = 92)		
	Day	Median	IQR	Median	IQR	*p* value
Temperature (°C)	0	36.7	[36.0-37.3]	36.8	[35.9-37.5]	0.74
	1	36.7	[36.1-37.6]	36.9	[35.8-37.6]	0.55
	2	36.9	[35.8-37.5]	36.8	[36.2-37.5]	0.90
	3	37.9	[36.0-37.7]	37.2	[36.4-38.0]	0.24
	7	37.3	[36.4-37.9]	37.7	[36.5-38.0]	0.43
MAP (mmHg)	0	75	[69-85]	75	[70-88]	0.66
	1	75	[69-84]	90**	[80-100]	<0.0001
	2	74	[68-80]	85**	[75-100]	<0.0001
	3	75	[65-85]	88#	[74-100]	<0.001
	7	80	[68-92]	80	[70-94]	0.51
NA (µg/kg/min) divided by 100	0	5	[0-10]	4	[0-10]	0.51
	1	5	[0-10]	0**	[0-3]	<0.0001
	2	5#	[0-16]	0**	[0-2]	<0.0001
	3	4	[0-14]	0**	[0-0]	<0.0001
	7	1	[0-14]	0#	[0-3]	0.06
ICP (mmHg)	0	9	[7-12]	15	[7-21]	0.17
	1	14#	[12-22]	9	[8-13]	0.04
	2	15#	[7-18]	11	[10-20]	0.95
	3	9	[5-25]	12	[8-16]	0.84
	7	12	[4-22]	12	[7-20]	0.95
Heart rate (beats/min)	0	95	[82-106]	98	[86-112]	0.20
	1	97	[82-110]	96	[85-110]	0.98
	2	99	[85-110]	91*	[80-100]	0.01
	3	100#	[88-113]	97	[88-113]	0.10
	7	99	[90-110]	90#	[82-106]	0.30
PaO_2 (kPa)	0	12.5	[10.4-14.8]	13.1	[11.1-15.6]	0.17
	1	12.3	[10.8-15.6]	11.9#	[10.4-14.4]	0.16
	2	12.3	[10.7-13.8]	11.8#	[10.4-14.3]	0.43
	3	11.6	[10.8-13.5]	11.9#	[10.7-14.0]	0.76
	7	12.0	[10.6-13.2]	11.7#	[10.4-13.4]	0.97
$PaCO_2$ (kPa)	0	4.69	[4.10-5.12]	4.59	[4.03-5.25]	0.66
	1	4.69	[4.08-5.29]	4.95**	[4.49-5.76]	0.01
	2	4.78	[4.11-5.48]	5.02**	[4.60-5.80]	0.01
	3	4.88	[4.41-5.30]	5.10*	[4.39-5.75]	0.06
	7	4.70#	[4.30-5.33]	4.87#	[4.30-5.58]	0.34
PaO_2/FiO_2	0	302	[197-376]	306	[229-397]	0.40
	1	284	[192-364]	271#	[197-341]	0.57
	2	280	[201-353]	273#	[205-357]	0.93
	3	273	[200-355]	258#	[188-374]	0.97
	7	260	[187-339]	259	[164-367]	0.89

MAP, mean arterial pressure; NA, noradrenalin infusion rate; PaO_2, arterial partial pressure for oxygen; $PaCO_2$, arterial partial pressure for carbon dioxide.
#*p* <0.05 compared to day 0 (baseline) within the same randomized group.
**p* <0.001 compared to day 0 (baseline) within the same randomized group.
***p* <0.0001 compared to day 0 (baseline) within the same randomized group.
p values in the table compares HVP with SMT.

Larsen FS, et al. J Hepatol. 2016 Jan;64(1):69-78.

慢加急性肝衰竭患者能耐受枸橼酸蓄积吗？

Hindawi
Canadian Journal of Gastroenterology and Hepatology
Volume 2018, Article ID 4909742, 10 pages
https://doi.org/10.1155/2018/4909742

Clinical Study

Good Tolerance of Citrate Accumulation due to Plasma Exchange among Patients with Acute-on-Chronic Liver Failure: A Prospective, Observational Study

Ma YJ, et al. Can J Gastroenterol Hepatol. 2018 Apr 18;2018:4909742.

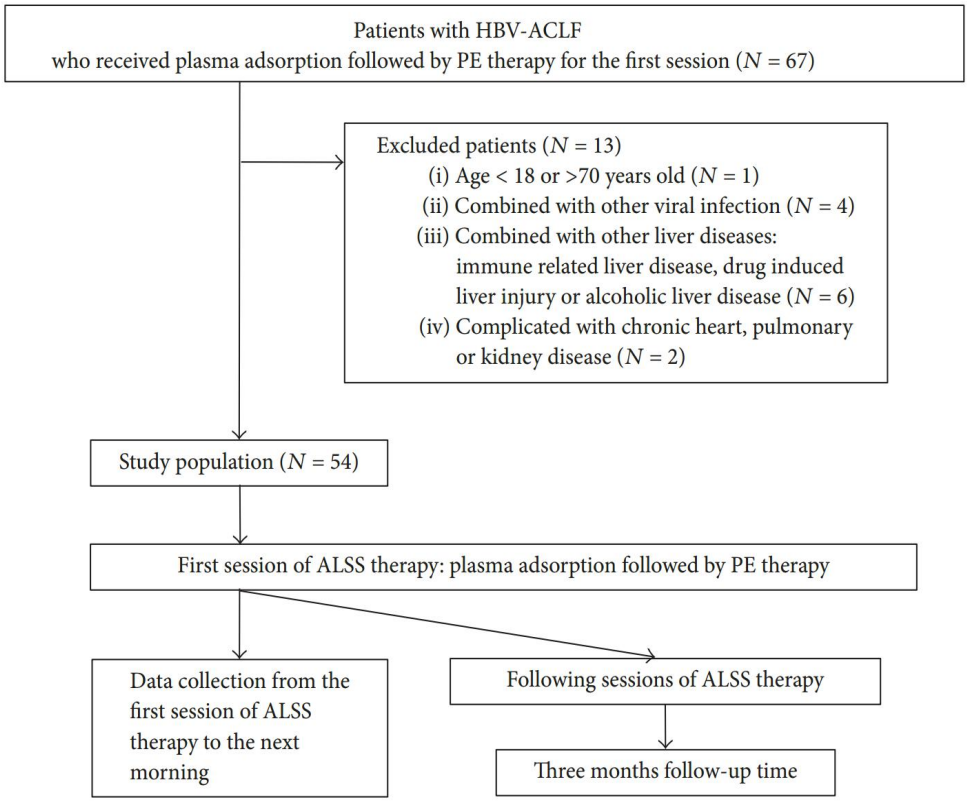


Table 1: Baseline laboratory parameters of patients before the first session of ALSS therapy.

Hemoglobin, g/dL	11.1 ± 2.1
Platelets, $\times 10^9$/L	126 ± 76
White blood cells, $\times 10^9$/L	8.2 ± 6.5
INR	2.0 ± 0.6
Total bilirubin, μmol/L	408.1 ± 137.1
Direct bilirubin, μmol/L	307.2 ± 107.9
Alanine transaminase, IU/L	200 ± 232
Aspartate transaminase, IU/L	177 ± 178
Alkaline phosphatase, IU/L	223 ± 320
gamma-Glutamyl transferase, IU/L	141 ± 276
Albumin, g/L	32.1 ± 4.4
Globulin, g/L	28.2 ± 8.2
Total bile acid, μmol/L	290.7 ± 78.6
Creatinine, μmol/L	101 ± 91
Ammonia, mmol/L	76 ± 35
Sodium, mmol/L	133.9 ± 5.3
Potassium, mmol/L	3.4 ± 0.6
Chloride, mmol/L	97.1 ± 6.4
MELD scores	25 ± 7

Table 3: Disease state during hospitalization and short-term prognosis.

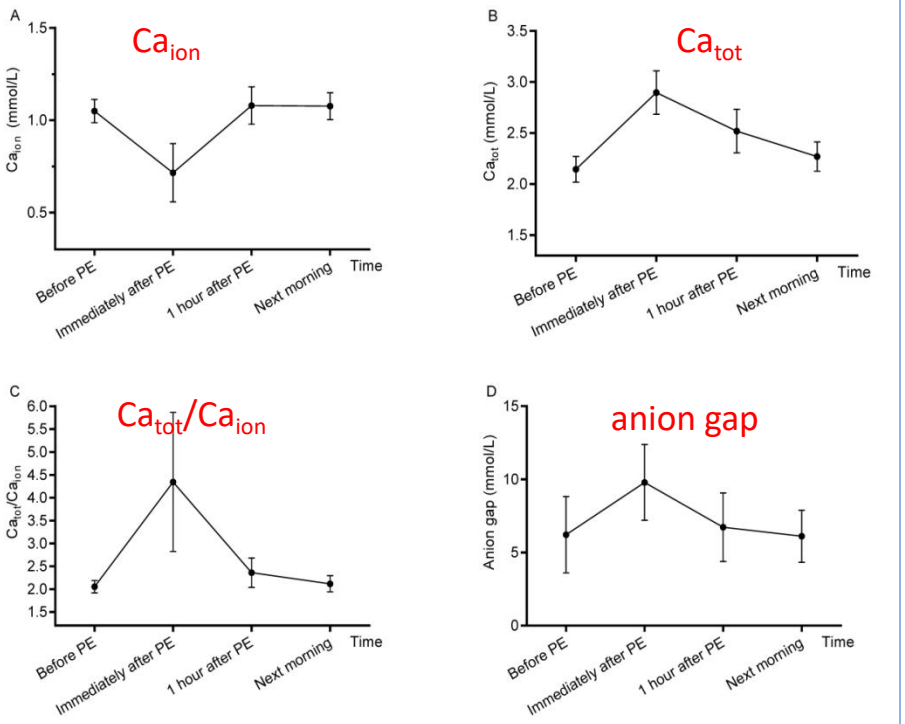
Hospital stay, days	26.0 ± 13.4
Spontaneous bacterial peritonitis, yes/no	30/24
Infection, yes/no	16/38
Hemorrhage, yes/no	7/47
Hepatorenal syndrome, yes/no	12/42
Hepatic encephalopathy, yes/no	15/39
Three-month survival, yes/no*	31/23

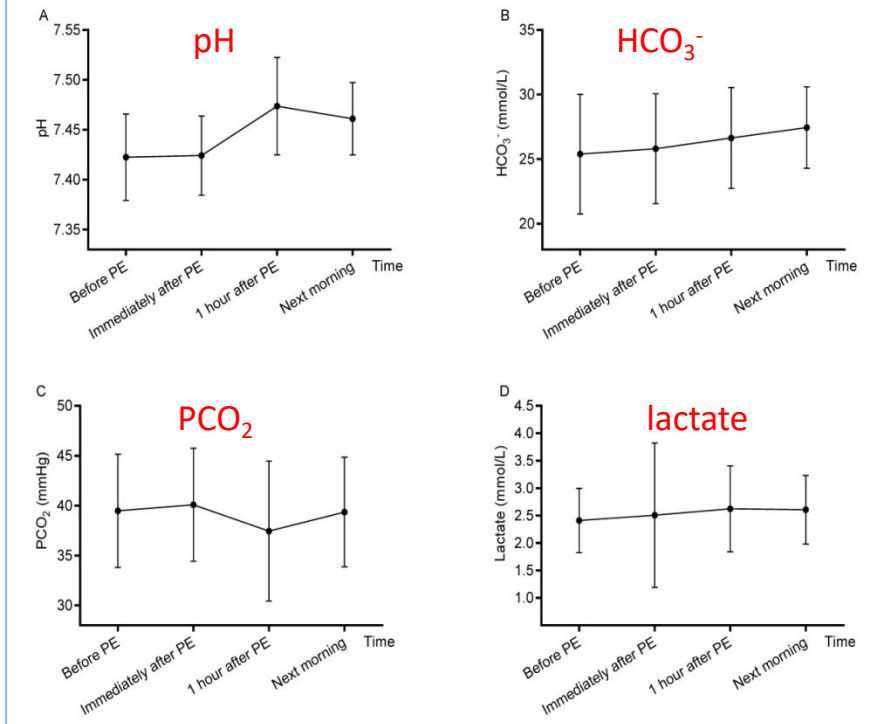
Ma YJ, et al. Can J Gastroenterol Hepatol. 2018 Apr 18;2018:4909742.

Table 4: Calcium and acid-base status during and after ALSS therapy.

Time	Before PE	Immediately after PE	1 hour after PE	Next morning★
Ca_{tot}, mmol/L	$2.15 \pm 0.13^{\S}$	$2.90 \pm 0.21^{\#\S}$	$2.52 \pm 0.21^{\#\S}$	$2.27 \pm 0.14^{\#}$
Ca_{ion}, mmol/L	1.05 ± 0.06	$0.71 \pm 0.16^{\#\S}$	1.08 ± 0.10	1.08 ± 0.06
Ca_{tot}/Ca_{ion}	2.05 ± 0.14	$4.34 \pm 1.52^{\#\S}$	$2.36 \pm 0.32^{\#\S}$	2.10 ± 0.14
$Ca_{tot}/Ca_{ion} \geq 2.5$, yes/no	0/54	$54/0^{\#\S}$	$16/38^{\#\S}$	0/54
Anion gap, mmol/L	6.2 ± 2.6	$9.8 \pm 2.6^{\#\S}$	6.7 ± 2.3	6.1 ± 1.8
pH	$7.42 \pm 0.04^{\S}$	$7.42 \pm 0.04^{\S}$	$7.47 \pm 0.05^{\#}$	$7.46 \pm 0.04^{\#}$
HCO_3^-, mmol/L	$25.4 \pm 4.6^{\triangle}$	25.8 ± 4.3	26.6 ± 3.9	$27.4 \pm 3.2^{\divideontimes}$
PCO_2, mmHg	39.5 ± 5.7	40.1 ± 5.6	37.5 ± 7.0	39.4 ± 5.5
Lactate, mmol/L	2.4 ± 0.6	2.5 ± 1.3	2.6 ± 0.8	2.6 ± 0.6

ALSS, artificial liver support system; PE, plasma exchange; Ca_{tot}, total calcium; Ca_{ion}, ionized calcium; Ca_{tot}/Ca_{ion}, total-to-ionized calcium ratio; HCO_3^-, standard bicarbonate; PCO_2, partial pressure of carbon dioxide. ★The interval time between the time after PE therapy and the next morning is 16.5 ± 1.9 hours. Compared with the data at the time before PE, $^{\divideontimes}p < 0.05$, $^{\#}p < 0.01$, the others, $p > 0.05$. Compared with the data at the next morning, $^{\triangle}p < 0.05$, $^{\S}p < 0.01$, the others, $p > 0.05$. Measurement data are represented as mean ± SD. Enumeration data are represented as frequencies.





Ma YJ, et al. Can J Gastroenterol Hepatol. 2018 Apr 18;2018:4909742.

Table 5: Univariate analysis and multivariate analysis of predictors for citrate accumulation at 1 hour after ALSS therapy.

	Correlation coefficient	p	Regression coefficient	Standard error	p	Odds ratio	95% CI
Gender (male)	0.393	0.003	−2.130	0.938	0.023	0.12	0.02–0.75
Baseline lactate	0.396	0.003	1.710	0.856	0.046	5.53	1.03–29.57
Baseline Ca_{tot}/Ca_{ion}	0.356	0.008	8.632	3.917	0.028	5607.59	2.60–12108390.04
Baseline Ca_{ion}	−0.380	0.005	1.974	8.144	0.809	7.20	0.00–61574425.76
Baseline platelets	−0.368	0.006	0.000	0.006	0.873	1.00	0.99–1.01

PE：乳酸≥2.65mmol/L

(敏感性63%, 特异性84%)

CVVH：乳酸≥3.4mmol/L

(敏感性86%, 特异性86%)

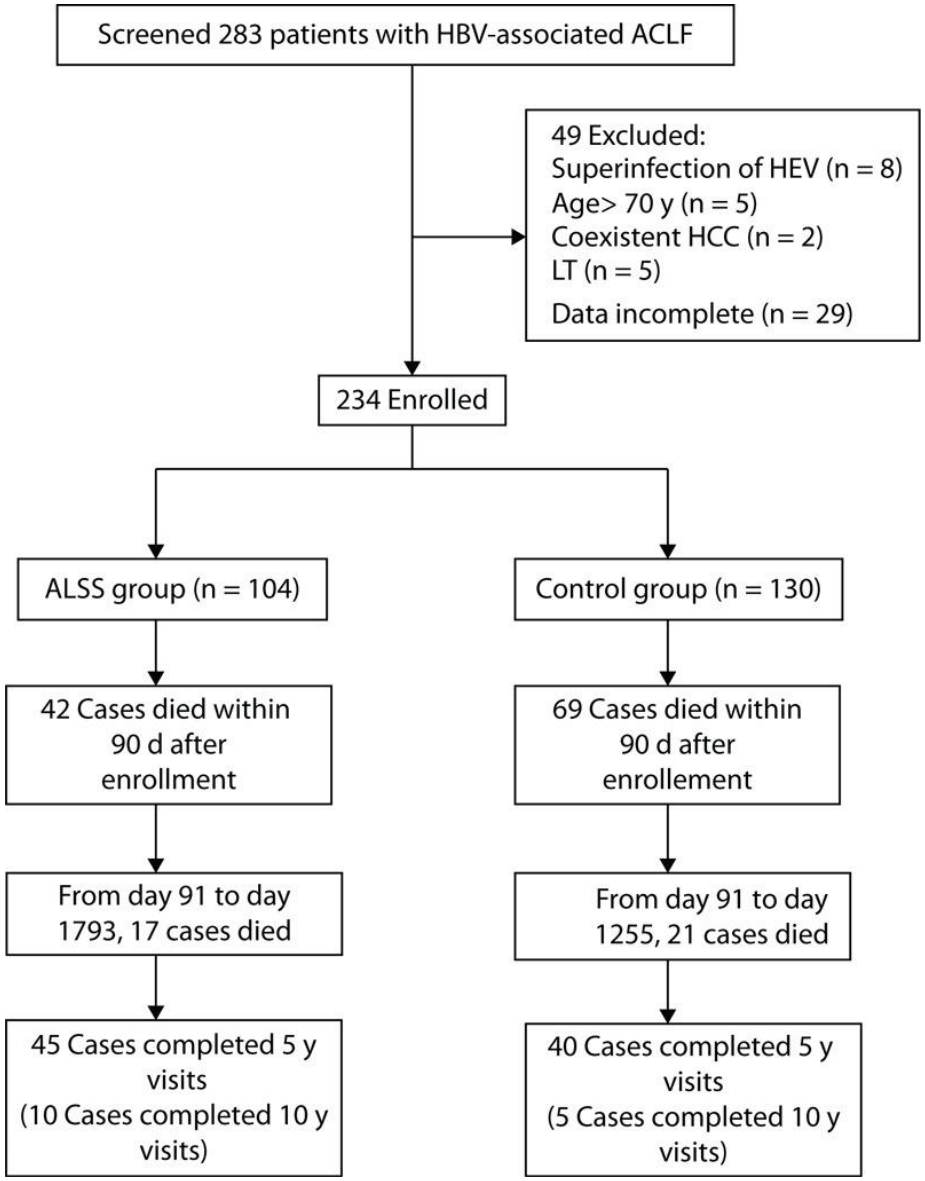
Ma YJ, et al. Can J Gastroenterol Hepatol. 2018 Apr 18;2018:4909742.
Schultheiß C, et al. Crit Care. 2012 Aug 22;16(4):R162.

PE（3500mL/次）治疗ACLF：效果评价

Plasma
3500mL(40-60mL/kg)

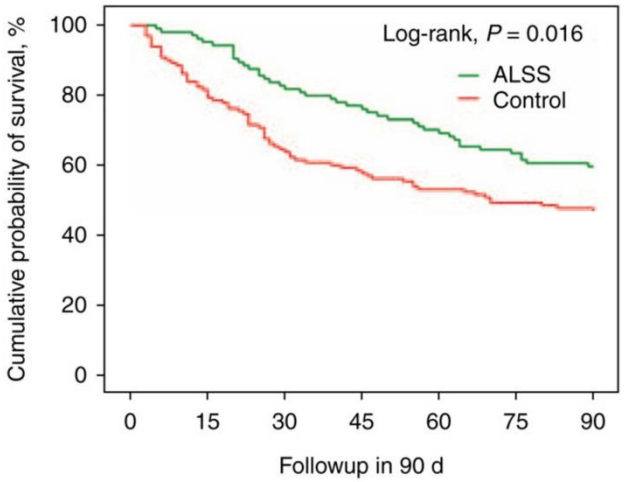
PE：197times
PE+HP：21times(11patients)
PE+HDF：9times(4patients)

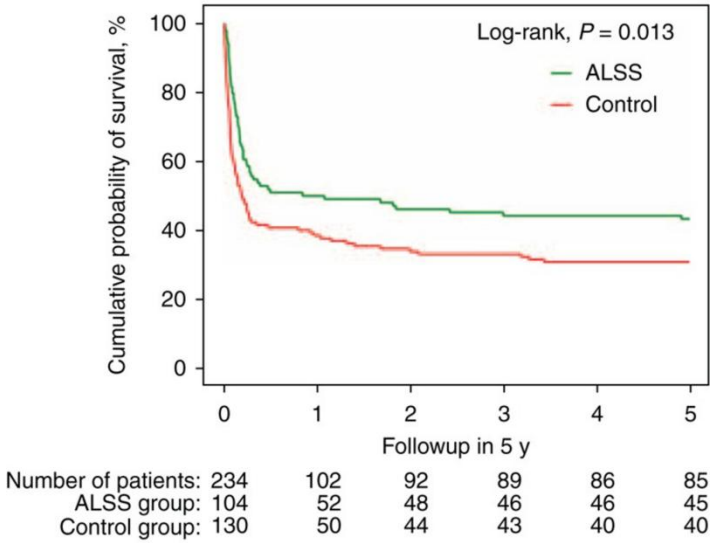
随访：10年

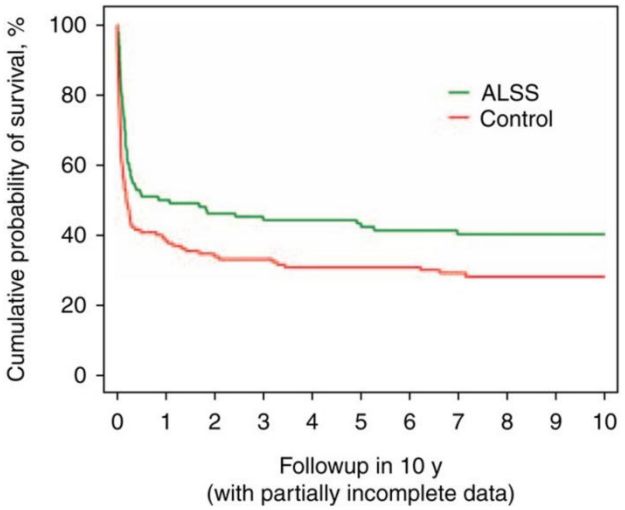


Qin G, et al. Medicine (Baltimore). 2014 Dec;93(28):e338.

PE（3500mL/次）治疗ACLF：提高生存率







Adverse Events During the 90-Day Study Period

Adverse Event	ALSS Group (n = 104)	Control Group (n = 130)	*P* value
Skin rash	28 (26.92%)	9 (6.92%)	<0.01
Hypotension	21 (20.19%)	12 (9.23%)	0.02
Hyperkalemia	19 (18.27%)	16 (12.31%)	NS
Significant bleeding for any source	17 (16.35%)	19 (14.62 %)	NS
Bacteremia	10 (9.62%)	15 (11.54%)	NS
Pneumonia	10 (9.62 %)	17 (13.08%)	NS
Urinary infection	6 (5.77 %)	11 (8.46%)	NS
Respiratory failure	9 (8.65 %)	13 (10%)	NS

Qin G, et al. Medicine (Baltimore). 2014 Dec;93(28):e338.

Journal of Clinical Apheresis 31:149–338 (2016)

临床实践中治疗性单采术应用指南——基于美国血浆置换学会编写委员会的循证策略：第七版

Guidelines on the Use of Therapeutic Apheresis in Clinical Practice—Evidence-Based Approach from the Writing Committee of the American Society for Apheresis: The Seventh Special Issue

ACUTE LIVER FAILURE

Incidence: < 10/1,000,000/yr		**Procedure**	**Recommendation**	**Category**
		TPE	Grade 2B	III
		TPE-HV	Grade 1A	I
No. of reported patients: > 300	**RCT**	**CT**	**CS**	**CR**
TPE	1(120)	1(158)	40(878)	54(73)
TPE-HV	1(182)	NA	NA	NA

TPE-HV: TPE-High Volume, not available in US.

Description of the disease

Acute liver failure (ALF) can develop in a normal liver (known as fulminant hepatic failure [FHF]) or in the setting of chronic liver disease. The most common causes are acetaminophen toxicity and viral hepatitis. Other known causes include ingestion of hepatotoxins/drugs, autoimmune hepatitis, critical illness, neoplastic infiltration, acute Budd–Chiari syndrome, and heat stroke. The mortality rate in FHF is 50–90% due to acute metabolic disturbances, hepatic encephalopathy, and severe coagulopathy; however, following liver transplantation, survival rates improve. Spontaneous recovery from FHF depends on the cause: high recovery rates are observed in fatty liver of pregnancy, acetaminophen ingestion, and hepatitis A; hepatitis B has intermediate prognosis; other drugs and unknown etiologies have a recovery rate < 20%.

Technical notes

Since plasma has citrate as an anticoagulant and there is hepatic dysfunction, whole blood: ACD-A ratio may need to be adjusted accordingly to prevent severe hypocalcemia. Alternatively simultaneous calcium infusion can be used. Calcium supplementation should be strongly considered. Patient should also be monitored for development of metabolic alkalosis. Some groups have performed simultaneous hemodialysis to mitigate this side effect. There is a preference for plasma as a replacement fluid due to moderate to severe coagulopathy; however, use of albumin is acceptable.

Volume treated: TPE: 1–1.5 TPV; TPE-HV: target 15% of ideal body weight **Frequency**: Daily
Replacement fluid: Plasma, albumin

Schwartz J, et al. J Clin Apher. 2016 Jun;31(3):149-62.

肝衰竭患者能耐受枸橼酸蓄积吗？

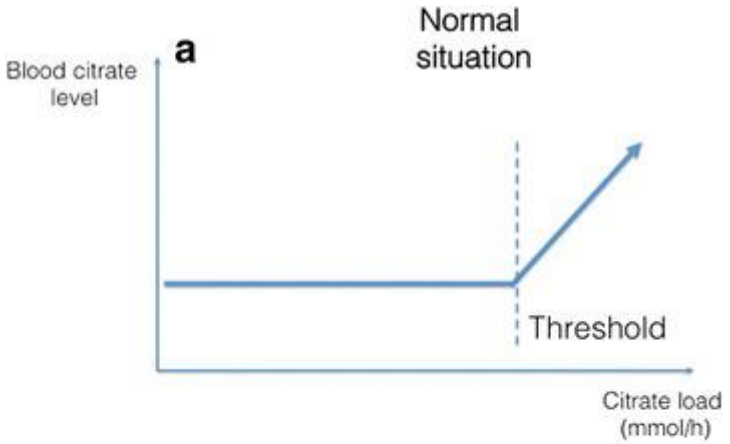
Schneider *et al. Critical Care* (2017) 21:281
DOI 10.1186/s13054-017-1880-1

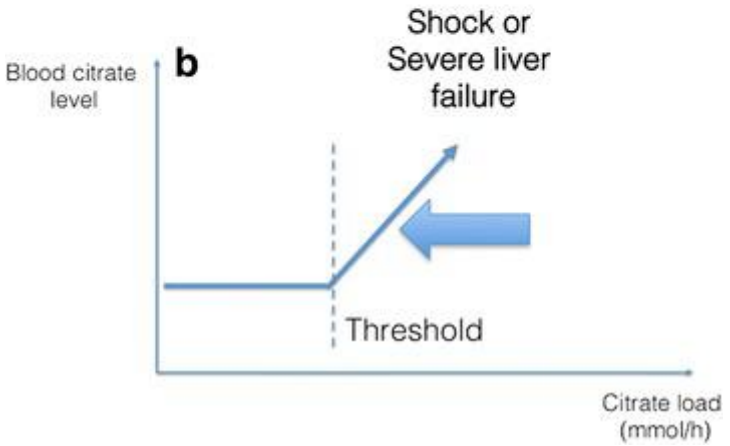
Critical Care

VIEWPOINT Open Access

Complications of regional citrate anticoagulation: accumulation or overload?

Antoine G. Schneider[1,2*], Didier Journois[3] and Thomas Rimmelé[4,5]





Schneider AG, et al. Crit Care. 2017 Nov 19;21(1):281.

肝衰竭患者

人工肝治疗可用局部枸橼酸抗凝吗？

肝衰竭患者血液净化治疗可用局部枸橼酸抗凝吗？

- 既往证据：肝衰竭合并AKI：CVVHD、IHD、SLED
  肝衰竭：MARS、FPSA
- 共 同 点：内含透析技术

问题1：无CRRT技术的血浆吸附与血浆置换治疗，RCA是否可行？

Schultheiß C, et al. Crit Care. 2012 Aug 22;16(4):R162.
Slowinski T, et al. Crit Care. 2015 Sep 29;19:349.
Lahmer T, et al. J Crit Care. 2015 Oct;30(5):1096-100.
Faybik P, et al. Crit Care Med. 2011 Feb;39(2):273-9.
Meijers B, et al. Crit Care. 2012 Feb 3;16(1):R20.
Sentürk E, et al. J Clin Apher. 2010;25(4):195-201.
Klingele M, et al. Crit Care. 2017 Nov 29;21(1):294.

Research Article

Blood Purification

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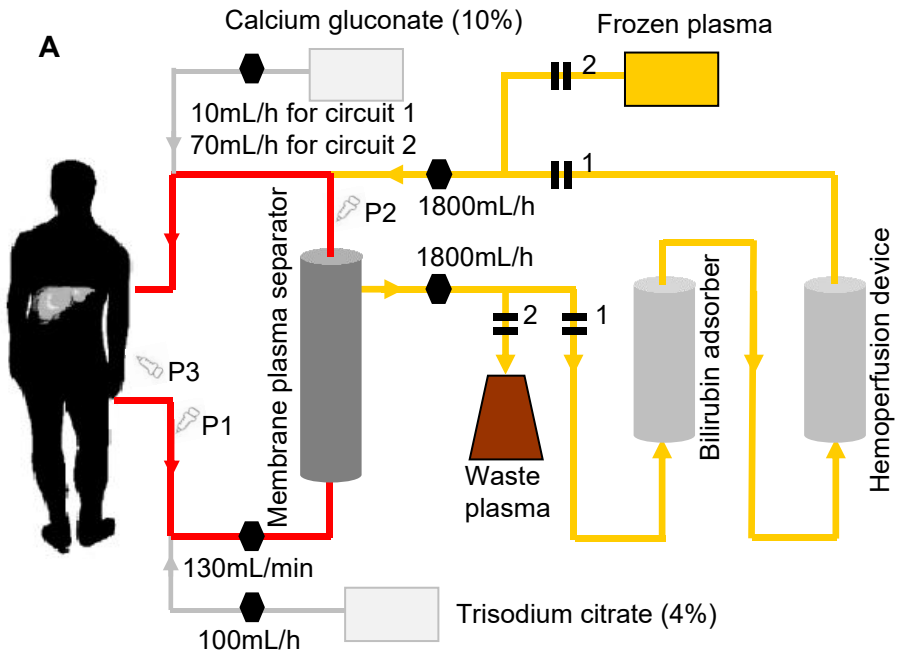
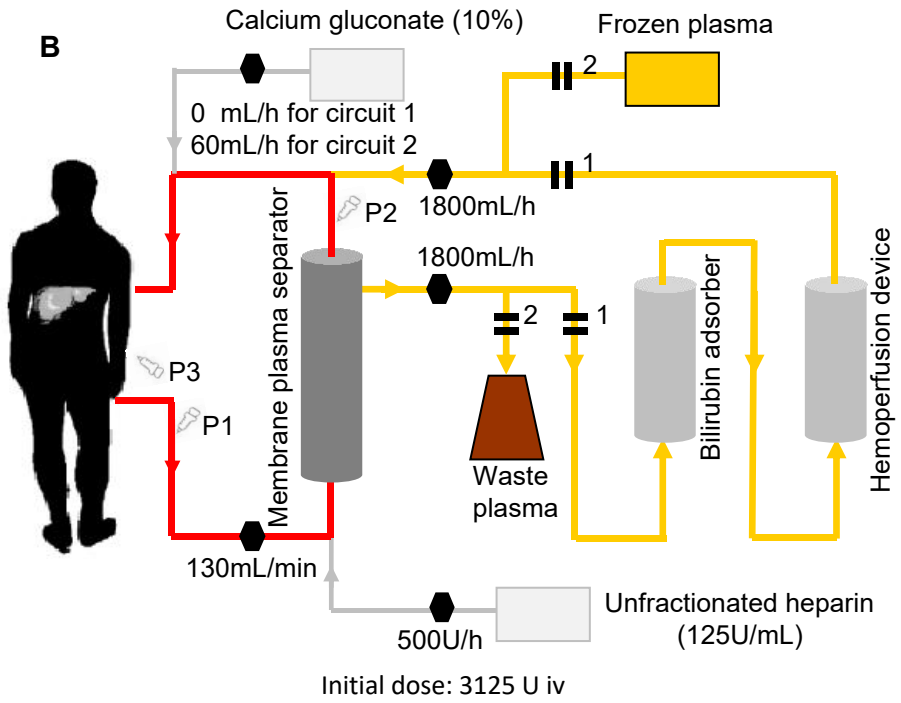
Safety and Efficacy of Regional Citrate Anticoagulation during Plasma Adsorption Plus Plasma Exchange Therapy for Patients with Acute-on-Chronic Liver Failure: A Pilot Study





Ma YJ, et al. Blood Purif. 2019;48(3):223-232.

基本状况

Table 1. Basic characteristics of patients with different methods of anticoagulation before ALSS therapy

	HA group (n=24)	RCA group (n=28)	*p* value
Age(years)	44.8 ± 9.3	48.0 ± 12.1	0.290
Gender (male)	22 (91.7%)	19 (67.9%)	0.036
Liver cirrhosis	15 (62.5%)	18 (64.3%)	0.894
HBV DNA (log IU/mL)	4.6 ± 2.4	4.1 ± 2.1	0.544
MELD scores	27.8 ± 4.8	27.0 ± 4.6	0.501
INR	2.37 ± 0.47	2.27 ± 0.72	0.177
Total bilirubin (μmol/L)	421.8 ± 144.1	414.6 ± 129.2	0.848
Direct bilirubin (μmol/L)	303.3 ± 112.8	312.9 ± 101.6	0.749
Alanine transaminase (IU/L)	221 ± 281	179 ± 217	0.414
Aspartate transaminase (IU/L)	199 ± 231	179 ± 176	0.905
Alkaline phosphatase (IU/L)	154 ± 55	92 ± 34	0.869
γ-glutamyl transferase (IU/L)	68 ± 55	101 ± 128	0.388
Total protein (g/L)	61.8 ± 9.6	59.9 ± 6.3	0.418
Creatinine (μmol/L)	96 ± 43	92 ± 34	0.734
Ammonia (mmol/L)	77 ± 34	78 ± 36	0.927
Sodium (mmol/L)	131.7 ± 4.6	134.3 ± 4.7	0.060
Potassium (mmol/L)	3.56 ± 0.67	3.42 ± 0.54	0.427
Chloride (mmol/L)	97.0 ± 6.4	95.1 ± 6.6	0.653
Hemoglobin (g/L)	111 ± 18	113 ± 21	0.772
Platelets ($\times 10^9$/L)	104 ± 49	104 ± 72	0.457
White blood cells ($\times 10^9$/L)	7.4 ± 2.7	10.0 ± 9.3	0.819

Supplemental table S1. Overview of ALSS therapy with different methods of anticoagulation

	HA group	RCA group	*p* value
Catheter location (internal jugular vein/femoral vein)	16/8	22/6	0.335
Total sessions of ALSS therapy (times)	94	106	/
Mean sessions of ALSS therapy (times per patient)	3.9 ± 2.2	3.8 ± 1.7	0.844
Total duration between the first and the last ALSS therapy (days)	214	213	/
Mean duration between the first and the last ALSS therapy (days per patient)	8.9 ± 7.6	7.6 ± 4.6	0.754

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有效性：RCA不影响治疗效率

Table 2. Comparison of efficacy of different methods of anticoagulation during ALSS therapy

	HA group (n=94)	RCA group (n=106)	*p* value
ALSS therapy (successfully completed)	91 (96.8%)	102 (96.2%)	1.000
Filtration fraction (%)	37.2 ± 3.5	36.4 ± 2.9	0.070
Abnormal pressure parameter	13 (13.8%)	11 (10.4%)	0.453
Suspected clotting of arterial segment	7 (7.4%)	5 (4.7%)	0.417
Suspected clotting of plasma separator	5 (5.3%)	5 (4.7%)	1.000
Suspected clotting of venous segment	5 (5.3%)	3 (2.8%)	0.479
Suspected clotting of plasma separator and venous segment	3 (3.2%)	3 (2.8%)	1.000
APTT before DPMAS therapy (seconds)	69.1 ± 14.7	67.8 ± 12.3	0.665
Extracorporeal APTT at the end of DPMAS therapy (seconds)	162.7 ± 27.2	122.5 ± 29.3	0.000
Reduction rate of total bilirubin (%)	50.2 ± 6.7	48.8 ± 6.3	0.120

The mean level of extracorporeal Ca_{ion} in the RCA group was 0.246 ± 0.063 mmol/L.

An APTT more than 100 seconds is one of the independent predictors of major bleeding in patients with ACLF[#].

Ma YJ, et al. Blood Purif. 2019;48(3):223-232.
[#]Blasi A, et al. Hepatology. 2018;68(6):2325-37.

安全性：RCA不增加病死率、并发症及住院日
—过性枸橼酸蓄积

Table 3. Comparison of clinical outcomes of patients with different methods of anticoagulation

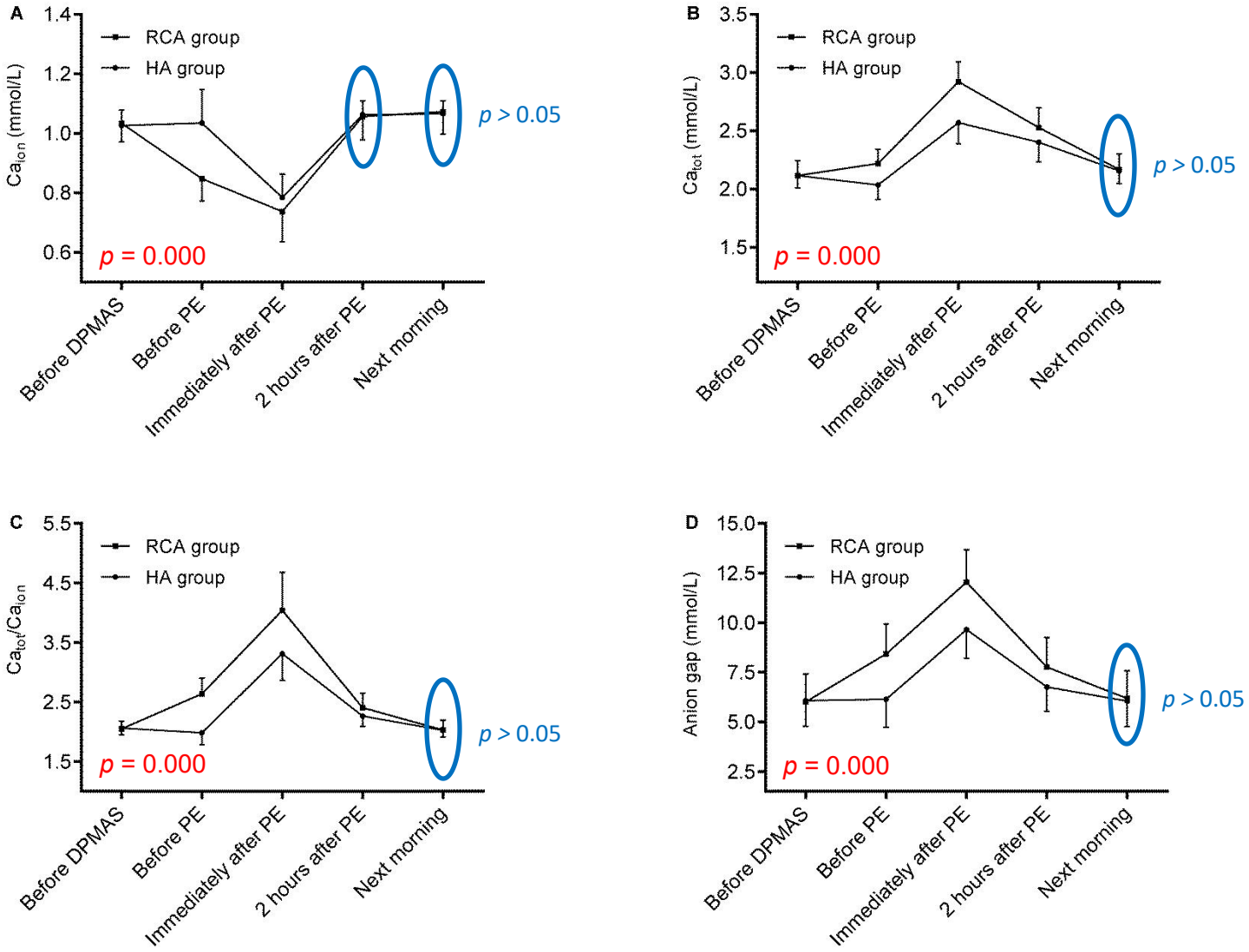
	HA group (n=24)	RCA group (n=28)	*p* value
Hospital stay (days)	28.1 ± 17.4	26.1 ± 14.4	0.594
Infection during hospitalization	15 (62.5%)	22 (78.6%)	0.202
Hemorrhage during hospitalization	4 (20.0%)	4 (16.7%)	0.812
Hepatorenal syndrome during hospitalization	4 (16.7%)	8 (28.6%)	0.310
Hepatic encephalopathy during hospitalization	5 (20.8%)	10 (35.7%)	0.238
Three-month survival	13 (54.2%)	15 (53.6%)	0.966

Table 4. Comparison of safety of different methods of anticoagulation during ALSS therapy

	HA group (n=94)	RCA group (n=106)	*p* value
Mean arterial pressure <65 mmHg	11 (11.7%)	15 (14.2%)	0.607
Fever or rash	22 (23.4%)	28 (26.4%)	0.624
Lip numbness during DPMAS therapy	0 (0.0%)	0 (0.0%)	1.000
Lip numbness during PE therapy	9 (9.6%)	13 (12.3%)	0.544
Lip numbness 2 hours after PE therapy	0 (0.0%)	0 (0.0%)	1.000
Twitch of calf muscles during DPMAS therapy,	0 (0.0%)	0 (0.0%)	1.000
Twitch of calf muscles during PE therapy	1 (1.1%)	3 (2.8%)	0.624
Twitch of calf muscles 2 hours after PE therapy	0 (0.0%)	0 (0.0%)	1.000
Reduction rate of hemoglobin (%)	8.7 ± 5.6	8.5 ± 6.9	0.444
Hemorrhage probably associated with anticoagulation※	3# (3.2%)	0 (0.0%)	0.102
Ca_{tot}/Ca_{ion} ≥2.5 before DPMAS therapy	0 (0.0%)	0 (0.0%)	1.000
Ca_{tot}/Ca_{ion} ≥2.5 at the end of DPMAS therapy	0 (0.0%)	71 (67.0%)	0.000
Ca_{tot}/Ca_{ion} ≥2.5 immediately after PE therapy	94 (100.0%)	106 (100.0%)	1.000
Ca_{tot}/Ca_{ion} ≥2.5 at 2 hours after PE therapy	7 (7.4%)	36 (34.0%)	0.000
Ca_{tot}/Ca_{ion} ≥2.5 in the morning of the next day	0 (0.0%)	0 (0.0%)	1.000

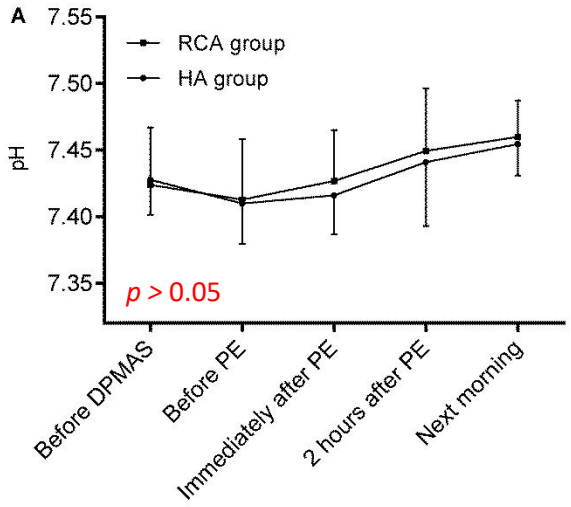
Ma YJ, et al. Blood Purif. 2019;48(3):223-232.

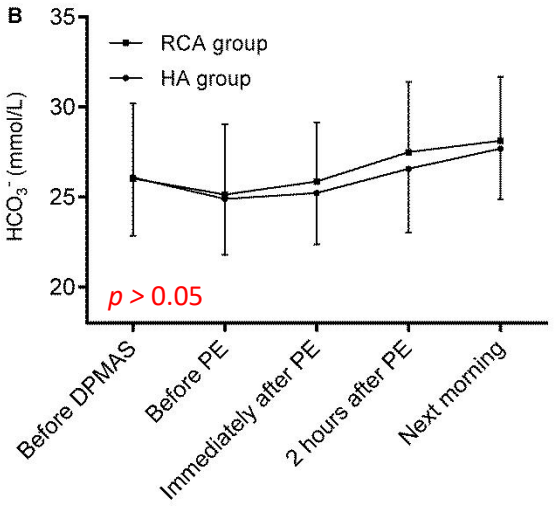
钙、枸橼酸蓄积、阴离子间隙：一过性改变

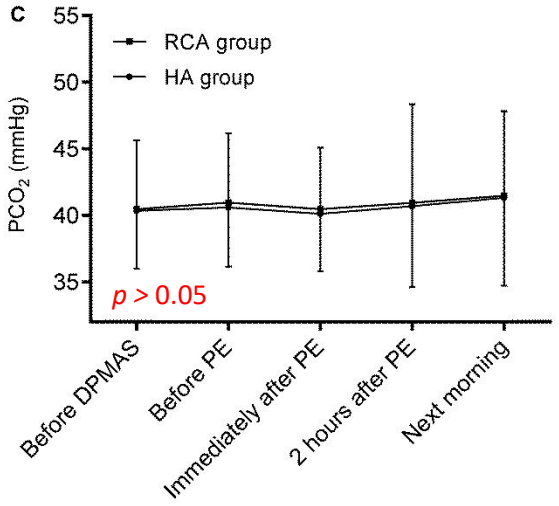


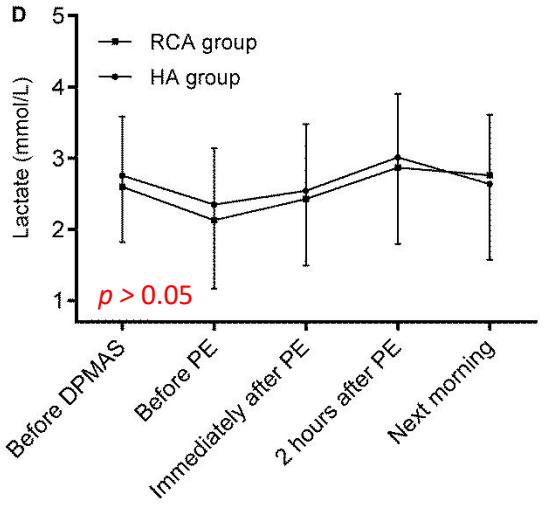
Ma YJ, et al. Blood Purif. 2019;48(3):223-232.

酸碱状态：代谢性碱中毒趋势









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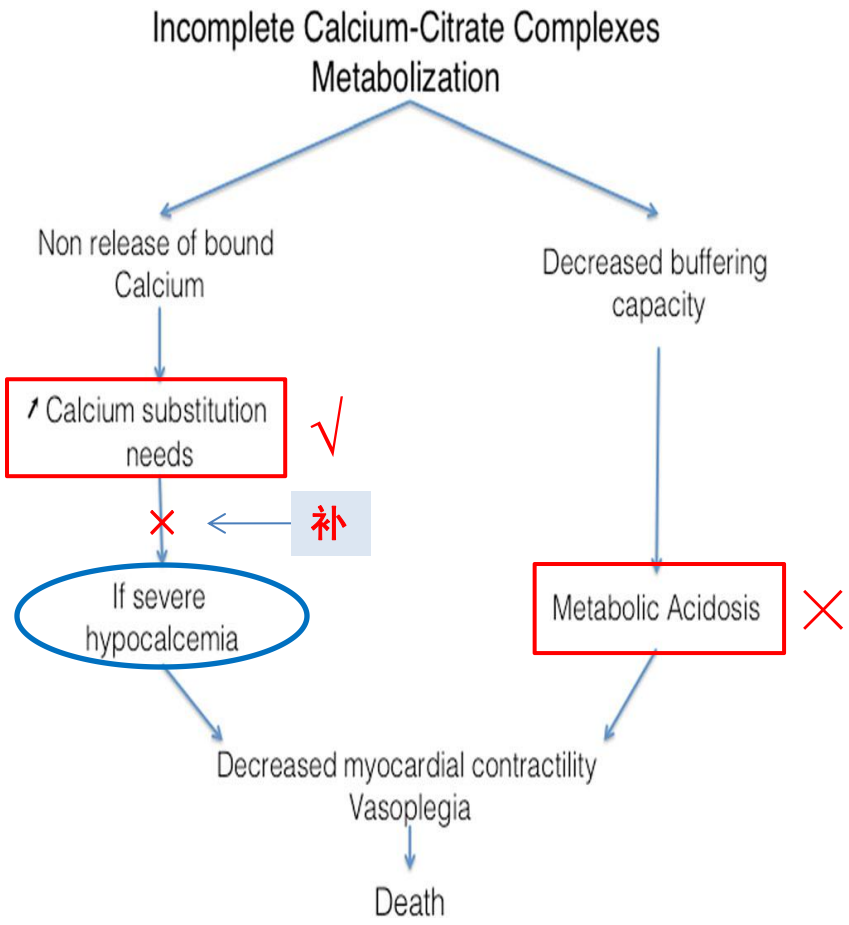
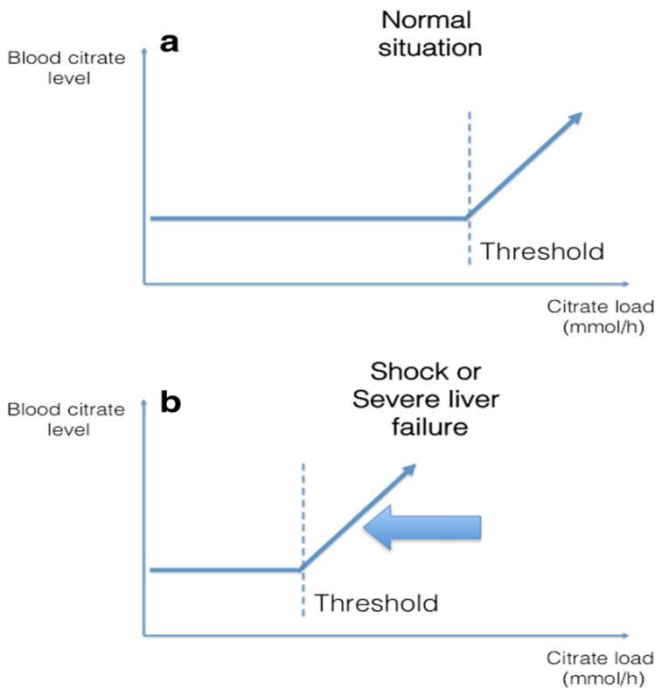
关注Ca_{ion}与Ca_{tot}/Ca_{ion}





Schneider AG, et al. Crit Care. 2017 Nov 19;21(1):281.

肝衰竭患者血液净化治疗可用局部枸橼酸抗凝吗？

- 既往证据：肝衰竭合并AKI：CVVHD、IHD、SLED
  肝衰竭：MARS、FPSA
- 共 同 点：内含透析技术

问题1：无CRRT技术的血浆吸附与血浆置换治疗，RCA是否可行？

可行

Schultheiß C, et al. Crit Care. 2012 Aug 22;16(4):R162.
Slowinski T, et al. Crit Care. 2015 Sep 29;19:349.
Lahmer T, et al. J Crit Care. 2015 Oct;30(5):1096-100.
Faybik P, et al. Crit Care Med. 2011 Feb;39(2):273-9.
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Sentürk E, et al. J Clin Apher. 2010;25(4):195-201.
Klingele M, et al. Crit Care. 2017 Nov 29;21(1):294.
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我科DPMAS+PE模式RCA基础处方

- 设备：后稀释CVVH模式，零超滤
  血流速度130ml/min
  血浆速度1500ml/h（25ml/min）
- 抗凝：4%枸橼酸钠110～120ml/h
  补钙：PA阶段13～15ml/h、PE阶段74～80ml/h
- 治疗：血浆吸附2h，血浆置换1h（血浆1500ml）
  HCT≥40%时采取措施降低FF
- 监测：治疗30min测体内、体外Ca_{ion}，治疗结束后测体内Ca_{ion}
  全程关注低钙表现，保持体内Ca_{ion}≥0.8mmol/L
  避免增加体外循环凝血的非抗凝因素

RCA的PA+PE治疗：哪些患者经历更久的枸橼酸蓄积？

Table 1. Basic characteristics of patients before ALSS therapy

	Total (N=126)	Non-CA (N=92)	CA (N=34)	*p* value
Gender (male)	99(78.6%)	77(83.7%)	22(64.7%)	0.021
Age(years)	46.3±11.3	45.9±11.5	47.3±10.9	0.549
Catheter location (internal jugular vein/femoral vein)	77/49	53/39	24/10	0.185
MELD score	25.0±6.3	25.2±6.7	24.3±5.1	0.504
INR	1.99±0.70	1.84±0.61	2.37±0.79	0.000
TB (μmol/L)	436.9±134.1	431.4±127.3	451.8±152.0	0.449
DB (μmol/L)	324.3±102.7	326.8±97.1	317.3±117.7	0.645
ALT (IU/L)	181±201	179±194	187±224	0.858
AST (IU/L)	163±150	168±152	151±143	0.580
ALP (IU/L)	187±229	192±249	172±165	0.654
GGT (IU/L)	108±189	121±216	71±71	0.188
TBA (μmol/L)	283.0±78.5	284.7±76.2	278.5±85.2	0.696
TP (g/L)	60.4±9.0	60.8±9.1	59.2±8.8	0.378
Alb (g/L)	32.1±4.6	32.3±4.9	31.6±3.9	0.462
Scr (μmol/L)	95±67	87±63	114±75	0.074
NH_3 (mmol/L)	93±46	91±41	98±57	0.418
Na^+ (mmol/L)	133.7±4.8	134.4±4.5	131.6±5.1	0.003
K^+ (mmol/L)	3.40±0.64	3.34±0.65	3.56±0.60	0.091
Cl^- (mmol/L)	97.0±5.6	97.8±4.8	94.7±7.0	0.023
HCT (vol%)	40.3±6.0	41.4±5.91	37.3±5.4	0.001
Hb (g/L)	115±22	119±21	107±23	0.007
PLT ($\times 10^9$/L)	119±73	132±75	84±57	0.000
WBC ($\times 10^9$/L)	7.9±5.2	7.7±4.4	8.6±6.8	0.379
Osm (mmol/L)	264.8±9.1	266.0±7.6	259.0±10.4	0.000
Ca_{tot} (mmol/L)	2.15±0.16	2.14±0.16	2.17±0.17	0.378
Ca_{ion} (mmol/L)	1.037±0.090	1.045±0.093	1.014±0.080	0.080
Ca_{tot}/Ca_{ion}	2.08±0.20	2.06±0.22	2.15±0.13	0.037
AG (mmol/L)	7.4±2.7	7.7±2.5	6.8±2.9	0.122
Lac (mmol/L)	2.8±1.4	2.7±1.5	2.9±1.2	0.635
pH	7.429±0.039	7.424±0.034	7.441±0.049	0.035
HCO_3^- (mmol/L)	25.7±4.2	25.7±3.3	25.8±6.0	0.871
pCO_2 (mmHg)	39.5±5.5	40.0±4.7	38.4±7.0	0.227

Unpublished data

RCA的PA+PE治疗：哪些患者经历更久的枸橼酸蓄积？

Table 2. Predictors for Citrate Accumulation

	Correlation Coefficient	*p* value	Regression Coefficient	Standard Error	*p* value	Odds ratio	95% CI
 Gender (male)	-0.21	0.021	-1.85	0.75	0.014	0.16	0.04～0.69
Hb	-0.24	0.007	0.05	0.03	0.170	1.05	0.98～1.12
PLT	-0.29	0.001	-0.01	0.01	0.124	0.99	0.98～1.00
 INR	0.34	0.000	1.40	0.64	0.029	4.05	1.16～14.16
Scr	0.17	0.051	0.01	0.01	0.021	1.01	1.00～1.02
Na	-0.26	0.003	-0.01	0.10	0.914	0.99	0.81～1.21
K	0.15	0.091	0.47	0.48	0.330	1.60	0.62～4.11
Cl	-0.24	0.006	0.02	0.09	0.846	1.02	0.86～1.21
Hct	-0.30	0.001	-0.18	0.14	0.179	0.83	0.64～1.09
Osm	-0.39	0.000	-0.10	0.06	0.094	0.91	0.81～1.02
Ca_{ion}	-0.16	0.080	1.77	4.46	0.692	5.86	0.00～36752.45
Ca_{tot}/Ca_{ion}	0.19	0.037	2.62	1.91	0.170	13.79	0.33～584.88
AG	-0.14	0.122	-0.20	0.20	0.318	0.82	0.56～1.21
pH	0.19	0.035	2.60	10.01	0.795	13.48	0.00～4512118714.04
pCO_2	-0.13	0.147	-0.01	0.10	0.923	0.99	0.82～1.20

Table 3. Predictive value of INR for Citrate Accumulation

Predictor	AUC	95% CI,	Value	Sensitivity	Specificity
INR	0.708	0.613～0.803	2.225	55.9%	79.3%
			1.5	94.1%	33.7%
			2.0	64.7%	63.0%
			2.5	32.4%	83.7%

Unpublished data

肝衰竭患者血液净化治疗可用局部枸橼酸抗凝吗？

- 既往证据：肝衰竭合并AKI：CVVHD、IHD、SLED
  肝衰竭：MARS、FPSA
- 共 同 点：内含透析技术

- 新 证 据：肝衰竭：DPMAS + PE(无CRRT技术)

问题2：含CRRT技术的配对血浆置换滤过吸附CPEFA治疗，RCA是否可行？

Schultheiß C, et al. Crit Care. 2012 Aug 22;16(4):R162.
Slowinski T, et al. Crit Care. 2015 Sep 29;19:349.
Lahmer T, et al. J Crit Care. 2015 Oct;30(5):1096-100.
Faybik P, et al. Crit Care Med. 2011 Feb;39(2):273-9.
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Klingele M, et al. Crit Care. 2017 Nov 29;21(1):294.
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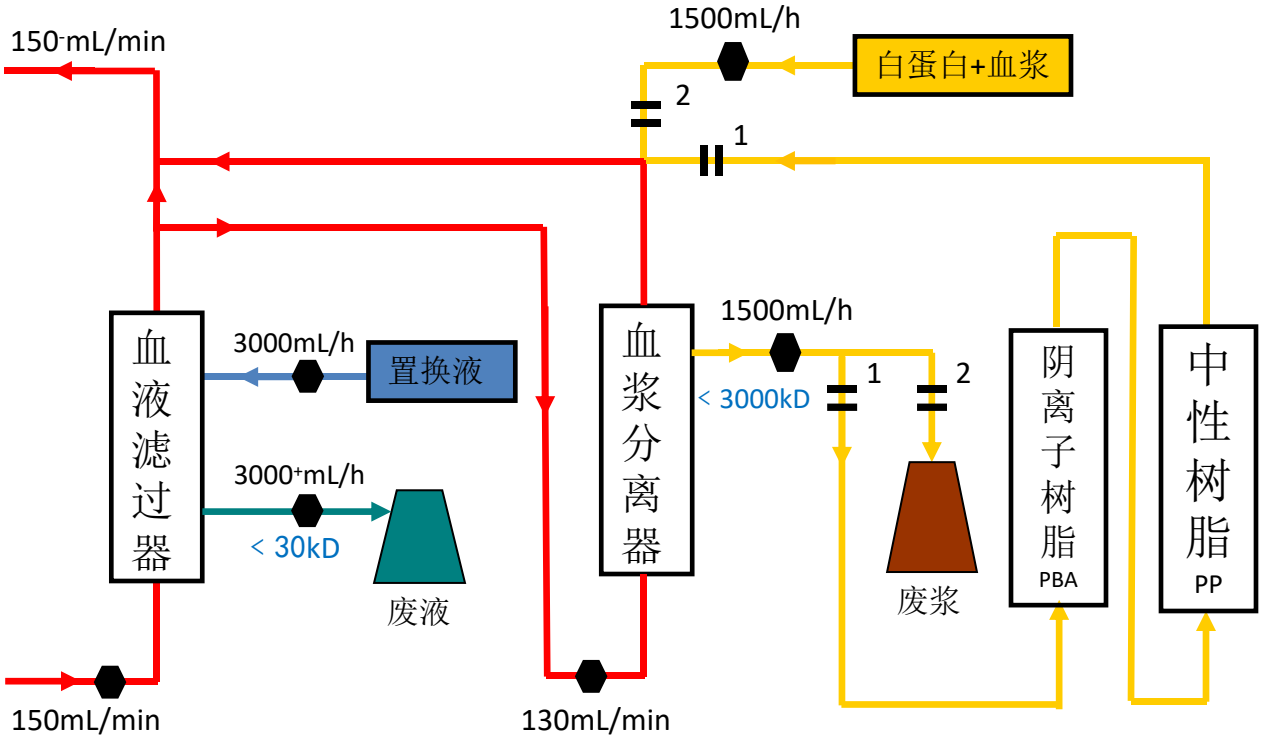
RCA-CPEFA



- ✓ 技术：CRRT的同时DPMAS[1]序贯PE[2]，8h，酌情超滤
- ✓ 应用：肝衰竭并发HE Ⅱ～Ⅳ，或HRS-AKI内科治疗无效者
- ✓ 抗凝：4%枸橼酸钠180～190ml/h

  补钙：DPMAS阶段13～15ml/h、PE阶段74～80ml/h

CPEFA治疗肝衰竭：临床效果

表1. CPEFA治疗前基线特征

	Total (N=16)
Gender (male)	13(81.3%)
Age(years)	33～69
Catheter location (internal jugular vein/femoral vein)	14/2
Antibiotic therapy	10(62.5%)
HE Ⅱ～Ⅳ	12(75.0%)
HRS-AKI	7(43.8%)
MELD score	26～47
INR	1.92～4.86
TB (μmol/L)	284.2～749.7
Scr (μmol/L)	55～537

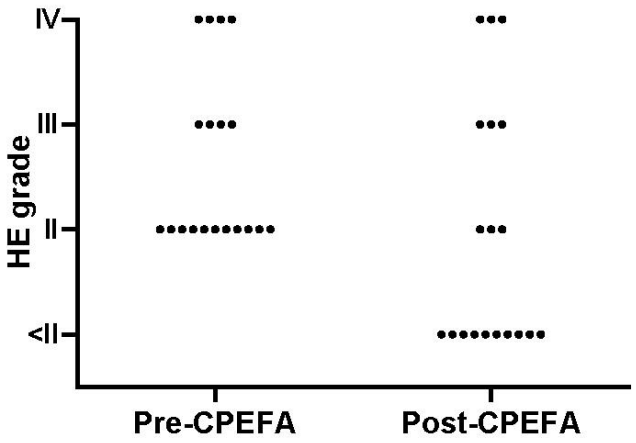


图2. CPEFA治疗前后HE程度变化(n=19)

注：12例HE Ⅱ～Ⅳ，CPEFA 19人次后，10例HE＜Ⅱ

表2. CPEFA治疗前后病情变化

	（治疗前-治疗后即刻）/治疗前 (%) (n=39)	（治疗前-治疗后第二天晨）/治疗前 (%) (n=39)
Hemoglobin	11.9±4.5	4.7±3.7
MELD score	16.4±7.3	9.7±6.5
INR	15.1±8.8	8.7±6.1
TB	40.2±8.7	15.3±7.8
Scr	23.4±9.4	16.2±8.7

ALSS：1～9次/人，共71人次，其中：
CPEFA：1～5次/人，共39人次
DPMAS+PE：3～6次/人，共32人次

转归：6活、1 LT、9逝

Unpublished data

CPEFA治疗肝衰竭：RCA的有效性与安全性

体外Ca_{ion}：0.223±0.118 mmol/L

第2天晨体内Ca_{tot}：2.28±0.14 mmol/L

无出血并发症

表3. RCA在CPEFA治疗中的有效性

	RCA-CPEFA (n=39)
ALSS therapy (successfully completed)	38 (94.9%)
Abnormal pressure parameter	5 (12.8%)
Suspected clotting of arterial segment	0 (0.0%)
Suspected clotting of plasma separator	2 (5.1%)
Suspected clotting of venous segment	2 (5.1%)
Suspected clotting of plasma separator and venous segment	1 (2.6%)

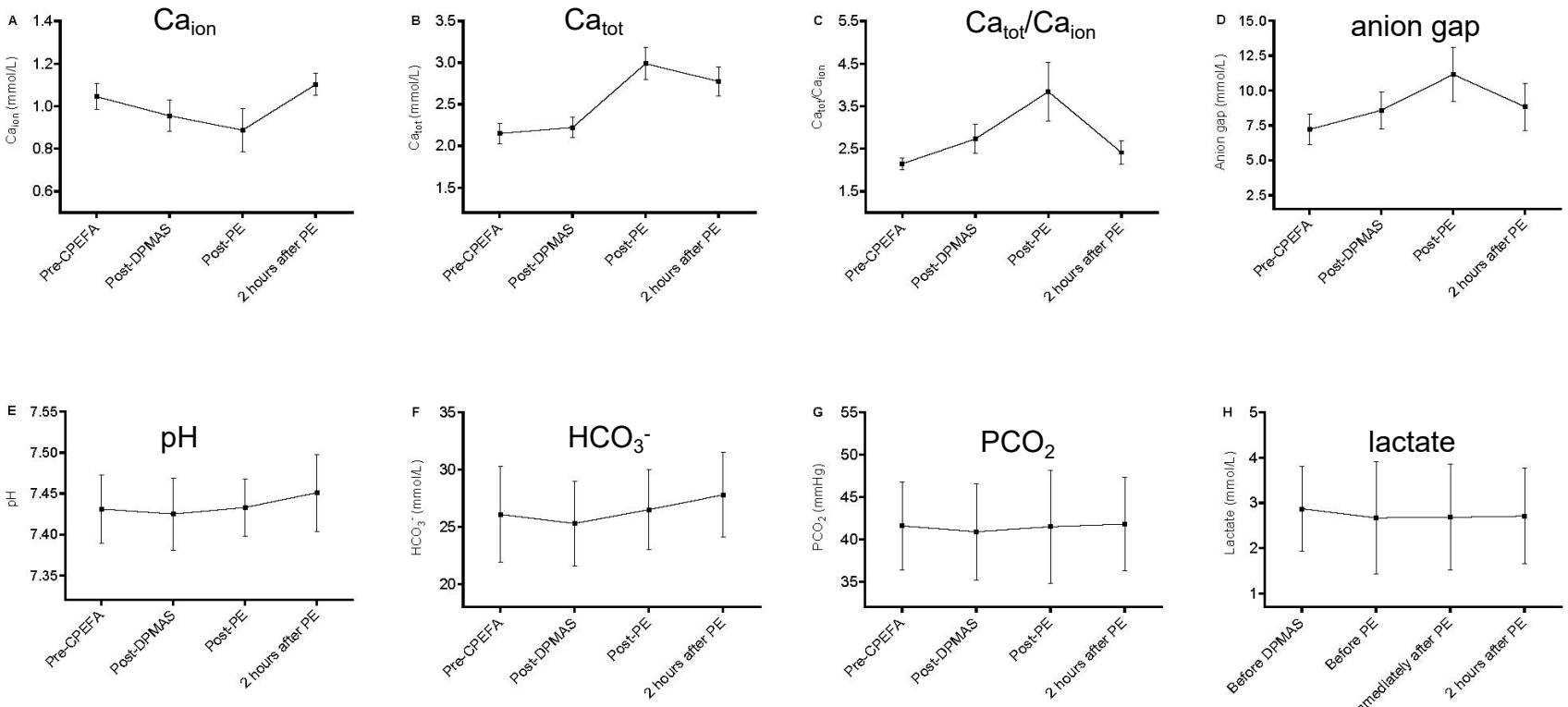


图3. CPEFA治疗前后内环境变化

Unpublished data

高危出血肝衰竭患者

人工肝治疗可用局部枸橼酸抗凝吗？

Swartz出血风险评估

出血危险度分级	出血倾向
极高危	活动性出血
高危	活动性出血停止时间＜3天 手术、创伤后时间＜3天
中危	活动性出血停止时间3-7天 手术、创伤后时间3-7天
低危	活动性出血停止时间＞7天 手术、创伤后时间＞7天

Swartz RD, et al. Kidney Int. 1979 Oct;16(4):513-8.

RCA行PA+PE治疗高危出血肝衰竭患者

- 乙肝相关性慢加急性肝衰竭：7例
  - ✓ TB：435.9～689.3μmol/L
  - ✓ INR：1.68～3.02
  - ✓ MELD：19～33
- 影像学证实的肝硬化：5例
- 高危出血风险：
  - ✓ 脑出血1例
  - ✓ 消化道出血5例
  - ✓ 反复内痔出血1例

表 1　人工肝治疗前实验室检查结果及人工肝治疗的即时效果

指标	治疗前结果	下降率 (%)	
		治疗前与后	治疗前与第2天晨
血红蛋白 (g/L)	100 ± 15	10.8 ± 6.8	3.0 ± 6.4
血小板 ($\times10^9$/L)	75 ± 39	22.4 ± 21.0	20.7 ± 15.0
白细胞 ($\times10^9$/L)	7.61 ± 4.34	1.8 ± 22.3	12.0 ± 22.3
INR	2.40 ± 0.43	24.1 ± 12.2	15.3 ± 13.5
总胆红素 (μmol/L)	390.7 ± 140.1	48.7 ± 5.8	13.4 ± 19.5
直接胆红素 (μmol/L)	275.5 ± 104.5	48.3 ± 6.0	16.3 ± 9.8
谷丙转氨酶 (IU/L)	121 ± 105	35.6 ± 9.3	25.7 ± 16.0
谷草转氨酶 (IU/L)	122 ± 87	38.6 ± 7.3	16.7 ± 9.4
碱性磷酸酶 (IU/L)	150 ± 49	28.4 ± 6.8	7.5 ± 13.1
谷氨酰胺转肽酶 (IU/L)	58 ± 50	29.1 ± 18.9	16.3 ± 24.8
白蛋白 (g/L)	32.6 ± 4.3	7.1 ± 9.0	-0.3 ± 9.6
球蛋白 (g/L)	30.0 ± 8.3	15.5 ± 10.5	11.8 ± 7.7
总胆汁酸 (μmol/L)	298.8 ± 74.8	18.5 ± 15.3	27.3 ± 12.7
肌酐 (μmol/L)	74 ± 23	5.3 ± 12.6	2.5 ± 19.2
血氨 (mmol/L)	69 ± 31	13.5 ± 34.3	-28.7 ± 61.0
钠 (mmol/L)	131.1 ± 5.3	-3.2 ± 2.4	-2.1 ± 2.1
钾 (mmol/L)	3.44 ± 0.52	-8.8 ± 9.3	-6.3 ± 12.7
氯 (mmol/L)	95.4 ± .7.7	1.2 ± 6.7	0.2 ± 5.6
MELD评分	26 ± 4	24.9 ± 7.8	11.7 ± 10.5

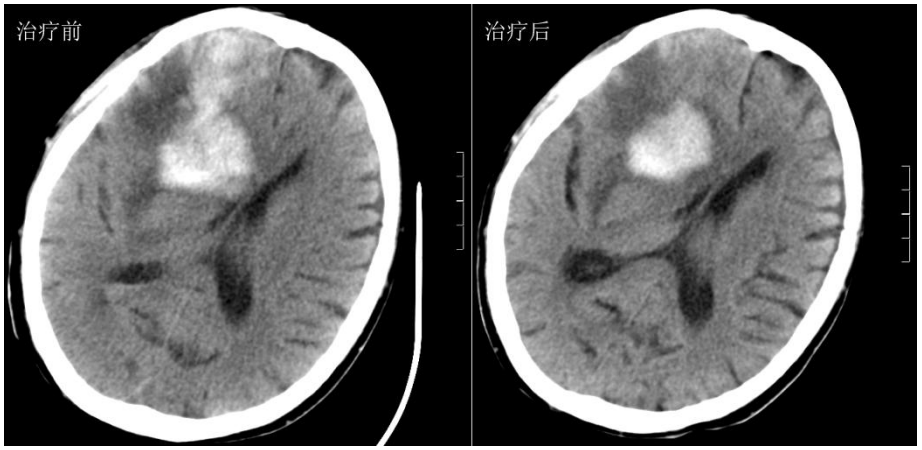
7例患者分别完成2～5次RCA的PA+PE治疗，总计24例次

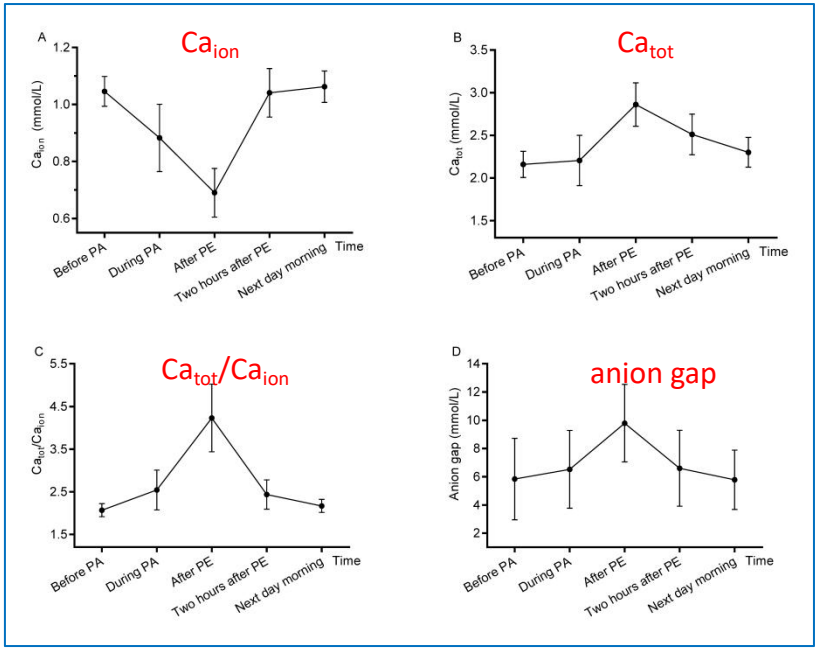
马元吉, 等. 世界华人消化杂志.2018; 26(3): 165-173.

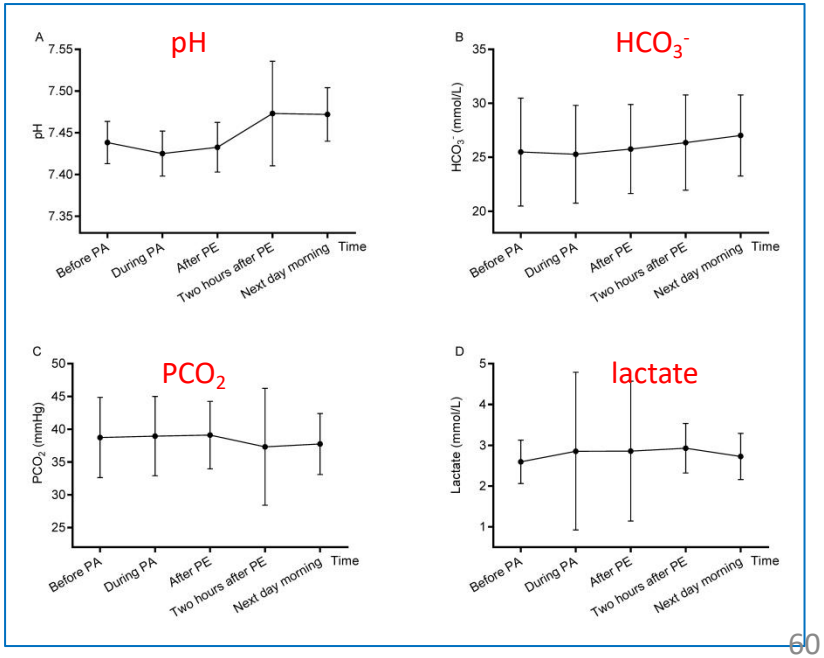
RCA行PA+PE治疗高危出血肝衰竭患者

无新发出血
原出血未恶化
2例好转出院
5例死于其他并发症

脑出血患者
人工肝治疗（4次）
前后头部影像变化
（间隔9天）







马元吉, 等. 世界华人消化杂志.2018; 26(3): 165-173.

肝衰竭患者

血液净化治疗可用局部枸橼酸抗凝吗？

Patel and Wendon *Critical Care* 2012, **16**:153
http://ccforum.com/content/16/5/153

CRITICAL CARE

COMMENTARY

Regional citrate anticoagulation in patients with liver failure - time for a rethink?

Sameer Patel[1] and Julia Wendon[2,*]

Patel S, et al. Crit Care. 2012 Sep 17;16(5):153.

深静脉导管可用枸橼酸封管吗？

枸橼酸封管：有效保持导管功能

枸橼酸 vs. 肝素

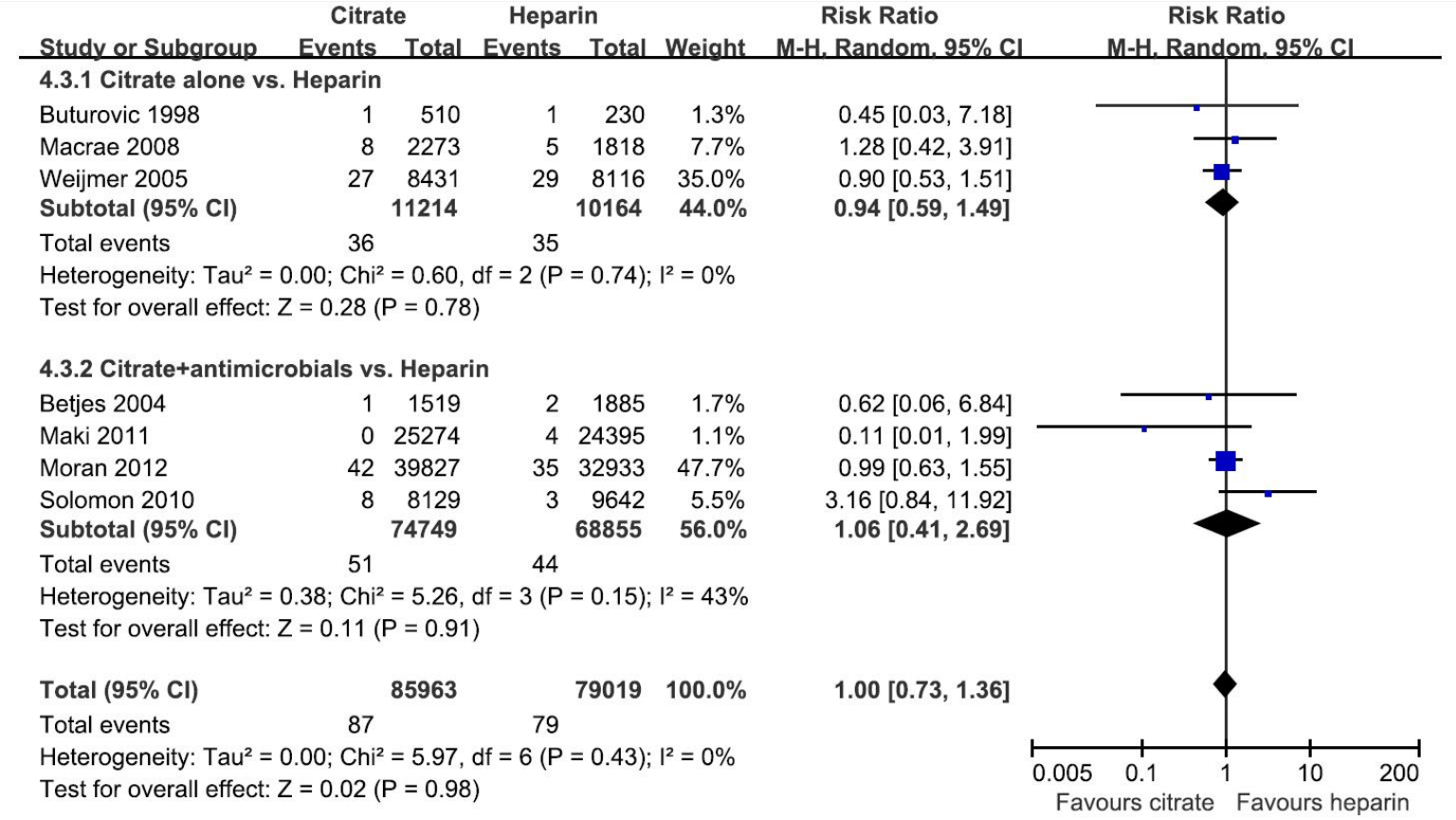
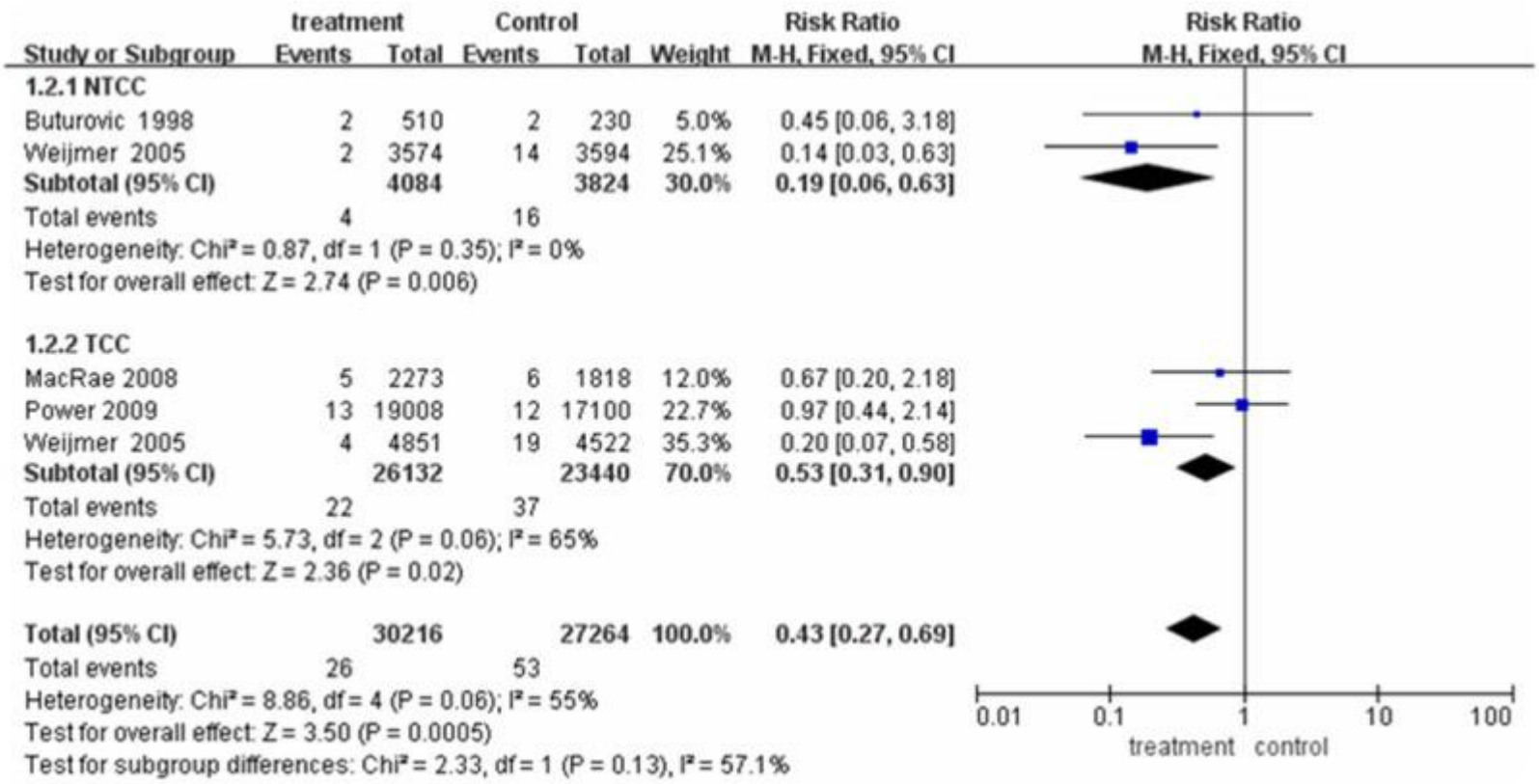


Figure 6. Catheter removal for poor flow per catheter-day. The analysis was stratified by the type of citrate lock. Risk ratio (RR) < 1.0 favors the citrate lock. Abbreviations: CI, confidence interval; M-H, Mantel-Haenszel.

Zhao YL, et al. Am J Kidney Dis. 2014 Mar;63(3):479-90.

枸橼酸封管：减少导管相关性血流感染

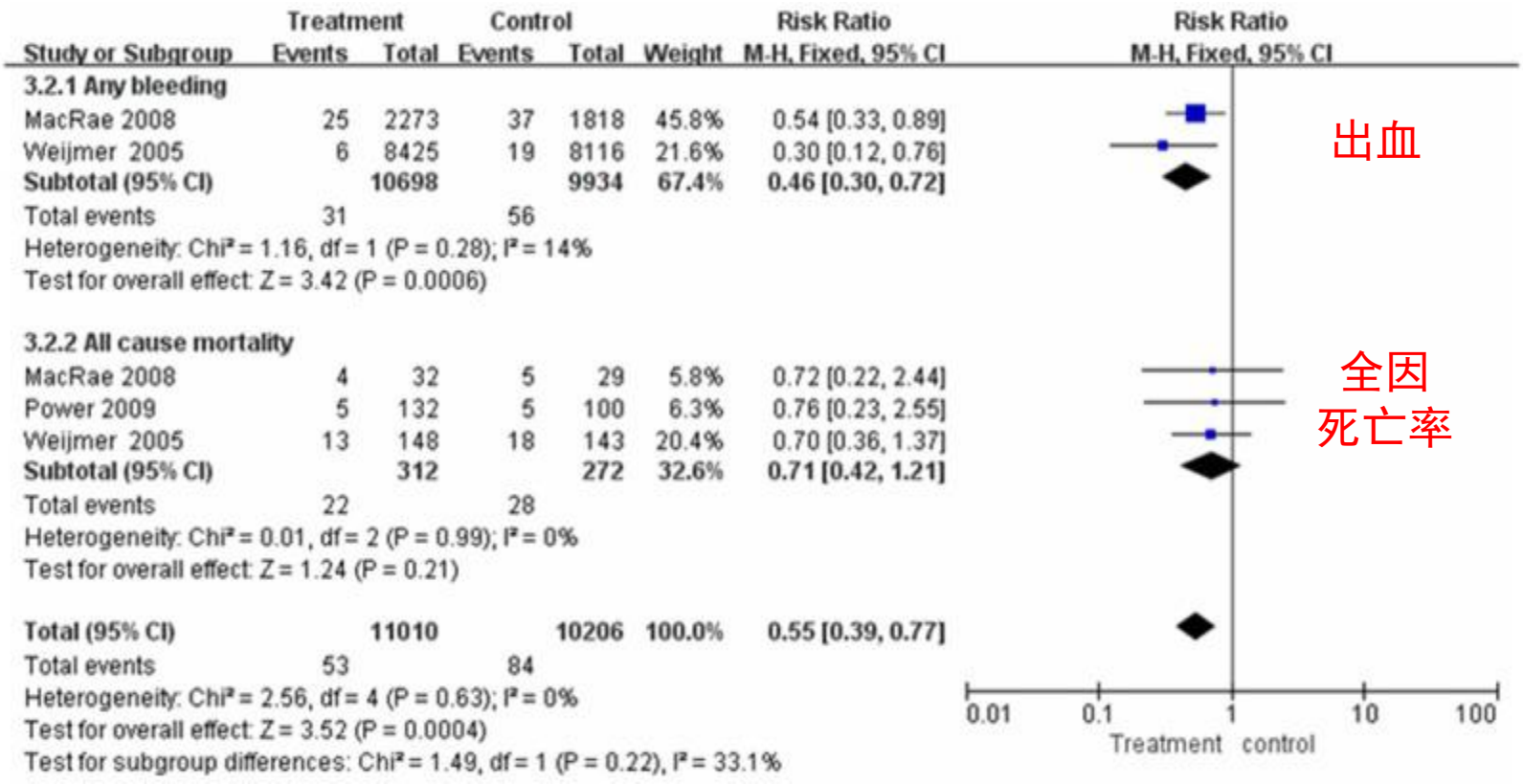
枸橼酸 vs. 肝素



Liu JR, et al. Int J Clin Exp Med. 2015 Aug 15;8(8):11985-95.

枸橼酸封管：减少出血

枸橼酸 vs. 肝素



Study or Subgroup	Treatment Events	Treatment Total	Control Events	Control Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Any bleeding						
MacRae 2008	25	2273	37	1818	45.8%	0.54 [0.33, 0.89]
Weijmer 2005	6	8425	19	8116	21.6%	0.30 [0.12, 0.76]
Subtotal (95% CI)		**10698**		**9934**	**67.4%**	**0.46 [0.30, 0.72]**
Total events	31		56			
Heterogeneity: Chi² = 1.16, df = 1 (P = 0.28); I² = 14%						
Test for overall effect: Z = 3.42 (P = 0.0006)						
3.2.2 All cause mortality						
MacRae 2008	4	32	5	29	5.8%	0.72 [0.22, 2.44]
Power 2009	5	132	5	100	6.3%	0.76 [0.23, 2.55]
Weijmer 2005	13	148	18	143	20.4%	0.70 [0.36, 1.37]
Subtotal (95% CI)		**312**		**272**	**32.6%**	**0.71 [0.42, 1.21]**
Total events	22		28			
Heterogeneity: Chi² = 0.01, df = 2 (P = 0.99); I² = 0%						
Test for overall effect: Z = 1.24 (P = 0.21)						
Total (95% CI)		**11010**		**10206**	**100.0%**	**0.55 [0.39, 0.77]**
Total events	53		84			
Heterogeneity: Chi² = 2.56, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 3.52 (P = 0.0004)						
Test for subgroup differences: Chi² = 1.49, df = 1 (P = 0.22), I² = 33.1%						

Liu JR, et al. Int J Clin Exp Med. 2015 Aug 15;8(8):11985-95.

枸橼酸封管：其他优势

Table 2. Comparison of outcomes of incident catheters per study period

Outcome	Heparin	Citrate	*P*-value
CVC exchange 导管更换频率	2.98/1000	1.65/1000	0.01
Proportion with at least one exchange	83%	67%	0.006
TPA rate 溶栓比例	5.49/1000	3.3/1000	0.002
Hospitalization admit	0.59/1000	0.28/1000	0.49
Hospital days 住院时间	4.12/1000	1.36/1000	<0.001
Mean hospitalization days	8.62	3.34	0.016

Lok CE, et al. Nephrol Dial Transplant. 2007 Feb;22(2):477-83.

枸橼酸封管：肝衰竭病人

表 1　两组患者基线资料

	肝素封管（n=19）	枸橼酸封管（n=22）
年龄（岁）	46.3±8.3	48.7±11.7
男性	17（89.5%）	18（81.8%）
HBV DNA(lgIU/L)	5.0±2.4	4.2±2.2
MELD 评分	26.6±4.5	27.4±4.8
INR	2.3±0.5	2.3±0.8
血小板计数（$\times10^9$/L）	104.8±50.6	101.2±72.5
血红蛋白（g/L）	111.7±18.3	111.2±22.9
白细胞（$\times10^9$/L）	7.6±2.7	10.2±9.5
总胆红素（μmol/L）	389.4±137.5	412.0±134.2
白蛋白(g/L)	30.8±4.9	32.4±3.3
肌酐（μmol/L）	91.8±41.0	95.6±36.3
置管部位（颈内静脉）	14（73.7%）	17（77.3%）

HBV DNA：乙型肝炎病毒脱氧核糖核酸；MELD 评分：终末期肝病模型评分；INR：凝血酶原时间国际标准化值；两组对比，P>0.05。

表 2 两组封管前后 APTT 变化

	例次	封管前（秒）	封管后 2 h（秒）	封管后次日晨（秒）
肝素封管组	79	70.2±15.3	89.8±43.1[②④]	67.8±14.2
枸橼酸封管组	80	73.9±12.8	65.6±12.2[②③⑥]	70.0±13.6

与封管前比：[①]P< 0.05，[②]P< 0.01；与次日晨比：[③]P< 0.05，[④]P< 0.01；两组对比：[⑤]P< 0.05，[⑥]P< 0.01；其余的 P>0.05。

其他：两组患者疾病转归无统计学差异。
两组患者留置导管期间的出血、血栓、导管相关性感染及导管功能等的差异无统计学意义。

*实用肝脏病杂志*接收

枸橼酸封管优于肝素封管

	枸橼酸钠封管	肝素钠封管
凝血功能影响	无影响	APTT明显延长
出血风险	无影响	明显增加
HIT	无影响	有
生物相容性	佳	一般
抗菌效能	高	低
血栓发生几率	相当	相当

4%枸橼酸钠3ml封管：安全、有效

小　结

- 肝衰竭患者仍有较强的代谢枸橼酸能力
- RCA在血液净化治疗中有其独特抗凝优势
- 人工肝治疗肝衰竭：有CRRT技术——RCA可行

  无CRRT技术——RCA可行
- 枸橼酸封管：1周1次安全有效（无针密闭输液接头）

谢 谢 !