The efficacy and safety of regional citrate anticoagulation centrifugal plasma exchange is equivalent to those of systemic heparin anticoagulation membrane plasma exchange in patients with liver failure: a single center retrospective cohort study

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Research Article

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Abstract

Background: The purpose of this study is to compare with the efficacy and safety of regional citrate anticoagulation centrifugal plasma exchange and systemic heparin anticoagulation membrane plasma exchange in patients with liver failure.

Methods: This study was a single center and retrospective study. All enrolled liver failure patients were treated with therapeutic plasma exchange. The patients treated by regional citrate anticoagulation centrifugal plasma exchange were defined as RCA group and those treated by systemic heparin anticoagulation membrane plasma exchange were defined as heparin group, respectively. Survival and clinical characteristics, including patients' age, gender, total bilirubin, serum creatinine, international normalized ratio, platelet count, types of liver failure, arterial blood gas analysis, the model for end-stage liver disease (MELD) score, and occurrence of complications were compared between the two groups. Survival analyses of two groups and subgroups classified by MELD score were performed by Kaplan-Meier method and were compared by the log-rank test.

Results: There were 69 patients enrolled in this study, 51 patients in RCA group and 18 patients in heparin group respectively. In overall patients, the 28-day mortality rate was 41% in RCA group and 39% in heparin group ($P > 0.05$). The 90-day mortality rate was 59% in RCA group and 50% in heparin group ($P > 0.05$). MELD best-fit value is 30, and area under the ROC curve is 0.7208 in the transplantation free patients with liver failure in both RCA group and heparin group. There was no significant difference in the occurrence of complications between the two groups.

Conclusions: In conclusion, our study demonstrates that the efficacy and safety of regional citrate anticoagulation centrifugal plasma exchange is equivalent to those of systemic heparin anticoagulation membrane plasma exchange in patients with liver failure. RCA plasma exchange at an interval of 48 hours in patients with acute or acute-on-chronic liver failure may be an effective in reducing the occurrence of the complication of citrate accumulation. RCA centrifugal plasma exchange treatment can achieve a good prognosis and well tolerance, especially in MELD<30 patients with liver failure.

Background

Liver failure in the context of either acute liver failure (ALF) or acute on chronic liver failure (ACLF) is associated with high mortality in the absence of a liver transplantation. Therapeutic plasma exchange (TPE) has been considered to be a promising and effective bridging therapy in patients with liver failure to liver transplantation or spontaneous regeneration [1]. Plasma exchange can be performed either by membrane separation or centrifugal separation. Systemic heparin anticoagulation membrane TPE is a common TPE treatment method in patients with liver failure [2]. In recent years, regional citrate anticoagulation (RCA) has become a favorable alternative to heparin in patients at risk from excessive bleeding. However, there are few studies about regional citrate anticoagulation centrifugal TPE treatment in patients with liver failure, due to the risk of citrate accumulation and toxicity might be increased in

patients with liver failure because of the impaired citrate metabolism in the citric acid cycle, which is mainly processed in the liver. A previous study demonstrate that despite the occurrence of significant citrate accumulation when continuous renal replacement therapy (CRRT) using RCA in patients with liver failure, the effects of citrate accumulation are not as severe as might have been expected [3]. Regional citrate anticoagulation in patients with liver failure maybe a time for a rethink [4]. However, more evidences on the use of citrate anticoagulation are warranted in patients with liver failure.

The purpose of this study is to compare with the efficacy and safety of regional citrate anticoagulation centrifugal plasma exchange and systemic heparin anticoagulation membrane plasma exchange in patients with liver failure. Furthermore, this study will look for the prognostic parameter's threshold of plasma exchange therapy in patients with liver failure.

Methods

Patients' selection, study cohort and processing

This study was a single center and retrospective study. All consecutive liver failure patients were treated with TPE at the Department of Infectious Diseases, Huashan Hospital, Fudan University, Shanghai, China from January 2014 to December 2021. Acute liver failure is generally defined as development of hepatic encephalopathy within 4 weeks of onset of jaundice. The diagnosis of ACLF was based on the criteria formalized by consensus recommendations of the Asian Pacific association for the study of the liver[1]. Since the basic premise in ACLF is to identify patients with chronic liver disease or cirrhosis presenting as acute liver failure, the time frame for liver failure was kept as 4 weeks. Acute on chronic liver failure is defined as coagulation abnormality with an INR ≥ 1.5 and total bilirubin ≥ 10mg/dL in this study. Exclusion criteria were: patients aged less than 14 years; patients coinfected with human immunodeficiency virus; pregnancy and lactation; the patients were treated without TPE. The patients treated by regional citrate anticoagulation centrifugal plasma exchange were defined as RCA group and those treated by systemic heparin anticoagulation membrane plasma exchange were defined as heparin group, respectively. The study was performed in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Huashan Hospital, Fudan University.

Clinical Characteristics And Outcome Parameters

Clinical characteristics and outcome parameters
Clinical characteristics including age, gender, total bilirubin, serum creatinine, international normalized ratio (INR), platelet count, types of liver failure and arterial blood gas analysis, were obtained from patients' medical records. All patients were evaluated by the model for end-stage liver disease (MELD) as a prognostic scoring system. MELD score was calculated as follows: 9.6×ln[creatinine (mg/dL)] + 3.8×ln[bilirubin (mg/dL)] + 11.2×ln(INR) + 6.4 (etiology: 0 if cholestatic or alcoholic, 1 otherwise).

Laboratory values less than 1.0 are set to 1.0 for the purposes of the MELD score calculation. The maximum serum creatinine considered within the MELD score equation is 4.0 mg/dl[5].

Tpe And Anticoagulation

TPE was performed regional citrate anticoagulation centrifugal separation plasma exchange (cTPE) machine (FRESENIUS KABI COM.TEC, Germany) or systemic heparin anticoagulation membrane separation plasma exchange (mTPE) machine (KURURAY KM8900, Japan). The plasma exchange volume was 1500ml ~ 3000ml calculated according to body weight and hematocrit. The blood flow was 35ml/min ~ 40ml/min in cTPE and 100ml/min ~ 150ml/min in mTPE or adjusted according to patient's conditions. Anticoagulant Citrate Dextrose Solution A (ACDA, Shanghai Blood Biomedical Technology Co., Ltd.) was infused immediately in arterial line port automatically with the dose per milliliter of whole blood by machine setting in cTPE. The first dose of heparin was 0.3 ~ 0.5mg/kg and maintained at 8mg/h was infused immediately in venous line port automatically with the dose per milliliter of whole blood by machine setting in mTPE.

Statistical analysis

Statistical analyses were performed with the Graphpad 9.3.1 (Graphpad Software, San Diego, CA). Variables were expressed as mean ± standard deviation or median (range) unless otherwise specified. Survival probabilities were estimated by means of Kaplan-Meier method and were compared by the log-rank test. The performance of prognostic scores on the prediction of mortality was assessed by the receiver operating characteristic curve (ROC curve). Differences in the parameters were compared using the unpaired parametric t-test, paired parametric t-test or nonparametric Mann-Whitney U test as needed. A 2-tailed P value of < 0.05 was considered statistically significant.

Results

The baseline characteristics of the liver failure patients treated with TPE

Finally, there were 69 patients enrolled in this study, 51 patients in RCA group and 18 patients in heparin group respectively. All patients were Asian. Table 1 shows the baseline characteristics at enrollment of overall patients during the first day after hospital admission.

Table 1
Baseline characteristics of patients with liver failure

Characteristics	RCA group N = 51	Heparin group N = 18	*P* value
Age, years	47 ± 14	47 ± 17	0.9755
Male sex, n (%)	41(80%)	11(61%)	0.1208
Total Bilirubin, μmol/L	355.2(178.7 ~ 928.9)	308.9(185.8 ~ 493.7)	0.0921
Serum Creatinine, μmol/L	66(18 ~ 403)	57(30 ~ 214)	0.2118
INR	2.04(1.50 ~ 4.19)	2.13(1.55 ~ 4.18)	0.3401
Platelet count, $\times 10^9$/L	92(27 ~ 256)	106(56 ~ 283)	0.2300
Types of liver failure, ALF/ACLF	15/36	6/12	0.7722
MELDs	27(22 ~ 44)	27(22 ~ 35)	0.7709

Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).

In RCA group, there were 15 acute liver failure patients, 8 patients were caused by drug, 3 patients were caused by acute hepatitis E virus, 1 patient was caused by acute hepatitis B virus, and 3 patients were unknown etiology. There were 36 acute on chronic liver failure patients, 32 patients had chronic hepatitis B virus, 1 patient had alcoholic liver disease, 2 patients had autoimmune hepatitis, and 1 patient had Wilson's disease. 14 patients underwent liver transplantation in the end.

In heparin group, there were 6 acute liver failure patients, 3 patients were caused by drug, 1 patient was caused by autoimmune hepatitis, and 2 patients were unknown etiology. There were 12 acute on chronic liver failure patients, 9 patients had chronic hepatitis B virus, 2 patients had alcoholic liver disease, and 1 patient had cirrhosis with unknown etiology. No one underwent liver transplantation in the end.

There was no statistical significance of the age, gender, total bilirubin, serum creatinine, INR, platelet count, types of liver failure and MELD between the RCA group and the heparin group.

Table 2 shows the baseline characteristics of the patients with liver failure who didn't have a liver transplantation in the end. There were 37 patients in RCA group, and 18 patients in heparin group. The INR was significantly lower in RCA group than that in heparin group. However, there was no statistical significance of the age, gender, total bilirubin, serum creatinine, platelet count, types of liver failure and MELD between the RCA group and the heparin group.

Table 2
Baseline characteristics of transplantation free patients with liver failure

Characteristics	RCA group N = 37	Heparin group N = 18	*P* value
Age, years	48 ± 15	47 ± 17	0.8551
Male sex, n (%)	29(78%)	11(61%)	0.2082
Bilirubin, μmol/L	358.0(184.1 ~ 928.9)	308.9(185.8 ~ 493.7)	0.0635
Creatinine, μmol/L	66(18 ~ 210.0)	57(30 ~ 214)	0.1815
INR	1.88(1.50 ~ 3.96)	2.13(1.55 ~ 4.18)	0.0267
Platelet count, 10^9/L	96(27 ~ 256)	106(56 ~ 283)	0.4002
Types of liver failure, ALF/ACLF	14/23	6/12	0.7755
MELDs	27(22 ~ 34)	27(22 ~ 35)	0.2574

Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).

Outcome Of Liver Failure Patients Treated With Tpe

In overall patients, the 28-day mortality rate was 41% in RCA group and 39% in heparin group ($P > 0.05$, Fig. 1A). The 90-day mortality rate was 59% in RCA group and 50% in heparin group ($P > 0.05$, Fig. 1B).

In transplantation free patients, the 28-day mortality rate was 32% in RCA group and 39% in heparin group ($P > 0.05$, Fig. 2A). The 90-day mortality rate was 43% in RCA group and 50% in heparin group ($P > 0.05$, Fig. 2B).

Accuracy of the MELD in predicting 28-day mortality of the transplantation free liver failure patients was calculated. MELD best-fit value is 30, and area under the ROC curve is 0.7208 in the transplantation free patients with liver failure in both RCA group and heparin group (Fig. 3A). MELD best-fit value is 30, and area under the ROC curve is 0.7033 in the transplantation free patients with liver failure in RCA group (Fig. 3B). Therefore, the transplantation free patients with liver failure were divided into two groups: MELD ≥ 30 group and MELD < 30 group. The 28-day mortality rate was 25% in MELD < 30 group and 73% in MELD ≥ 30 group ($P = 0.0002$, Fig. 4A). The 90-day mortality rate was 32% in MELD < 30 group and 100% in MELD ≥ 30 group ($P < 0.0001$, Fig. 4B).

Safety Of Tpe Treatment

In RCA group, 134 sessions TPE were performed, with an average of 3 sessions per patient. There were 10 times complications: 5 patients with rashes, 1 patient with shiver, 1 patient with shock and 3 patients with aggravation of hepatic encephalopathy. In heparin group, 46 sessions TPE were performed, with an average of 3 sessions per patient. There were 4 times complications: 2 patients with shock and 2 patients with aggravation of hepatic encephalopathy. There was no significant difference in the occurrence of complications between the two groups ($P = 0.6561$).

The arterial blood gas before RCA and after RCA plasma exchange treatment were analyzed (Table 3). The concentrations of calcium, chloride, hemoglobin, hematocrit, and ionized calcium before RCA plasma exchange treatment were significantly higher than those after RCA plasma exchange treatment. The concentrations of glucose, lactate, actual HCO_2, standard HCO_2, PH, extracellular base excess, base excess, anion gap, total calcium, and total calcium/ionized calcium before RCA plasma exchange treatment were significantly lower than those after RCA plasma exchange treatment.

Table 3
Arterial blood gas before RCA and after RCA plasma exchange treatment

Characteristics	Before RCA	After RCA	*P* value
Sodium, mmol/L	134.7 ± 4.045	134.6 ± 3.455	0.8586
Potassium, mmol/L	3.101 ± 0.4204	3.034 ± 0.3694	0.2374
Chloride, mmol/L	99.66 ± 4.274	96.06 ± 4.270	< 0.0001
Glucose, mmol/L	7.890(4.620 ~ 17.29)	10.50(6.720 ~ 21.99)	0.0020
Lactate, mmol/L	2.060(0.2000 ± 3.270)	2.535 (1.800 ± 5.810)	0.0018
Hemoglobin, g/dl	11.05 ± 2.014	10.42 ± 2.073	< 0.0001
Actual HCO_2, mmol/L	23.80(17.20 ~ 26.60)	25.15(19.10 ~ 28.40)	0.0003
Standard HCO_2, mmol/L	24.10(19.40 ~ 31.00)	25.30(21.20 ~ 27.90)	0.0117
PH	7.432 ± 0.03000	7.448 ± 0.02042	0.0194
Oxygen saturation, %	98.10(93.60 ~ 99.10)	98.30(95.50 ~ 99.80)	0.2779
Hematocrit, %	37.60(22.20 ~ 45.50)	34.40(20.80 ~ 44.70)	< 0.0001
Oxygen partial pressure, KPa	14.42 ± 2.737	14.23 ± 2.190	0.6791
Carbon dioxide partial pressure	4.708 ± 0.6280	4.739 ± 0.5595	0.3236
Extracellular base excess, mmol/L	-0.5500(-7.100 ~ 2.600)	1.150(-4.800 ~ 4.700)	0.0004
Base excess, mmol/L	-0.4000(-6.100 ~ 2.500)	1.150(-3.900 ~ 4.400)	0.0007
Anion gap, mmol/L	14.80(5.300 ~ 19.80)	17.60(4.100 ~ 21.90)	< 0.0001
Ionized calcium, mmol/L	1.090(0.8400 ~ 1.210)	0.8900(0.7300 ~ 1.040)	< 0.0001
Total calcium, mmol/L	2.154 ± 0.2272	2.600 ± 0.2700	< 0.0001
Total calcium/ionized calcium	1.970(1.730 ~ 3.190)	2.840(2.200 ~ 3.710)	< 0.0001
Blood ammonia, mmol/L	32.00(9.000 ~ 92.00)	29.00(9.000 ~ 71.00)	0.7769
Continuous variables were presented as mean ± standard deviation. Non-normal distribution data were presented as median (range).			

The median total calcium/ionized calcium value at the time before RCA plasma exchange was 1.97 (range from 1.73 to 3.19), and that after RCA plasma exchange was 2.84 (range from 2.20 to 3.71). The total calcium/ionized calcium value after RCA plasma exchange was significantly higher than that before RCA plasma exchange ($P < 0.0001$). The concentration of total calcium after RCA plasma exchange (2.600 ± 0.2700 mmol/L) was significantly higher than that before RCA plasma exchange (2.154 ± 0.2272 mmol/L, $P < 0.0001$), as well as that at 24 hours after RCA plasma exchange (2.230 ± 0.1747 mmol/L, $P =$

0.0007) was also significantly higher than that before RCA plasma exchange. However, there was no significant difference between the concentrations of total calcium before RCA plasma exchange and that at 48 hours after RCA plasma exchange (2.183 ± 0.09220 mmol/L, *P* = 0.6807).

Discussion

In this single center retrospective study, we found that there was no difference in survival rate and complications between RCA centrifugal plasma exchange and systemic heparin anticoagulation membrane plasma exchange in patients with liver failure. The best cut-off value of MELD score for plasma exchange treatment in patients with liver failure is MELD = 30. This cut-point may help identify patients with liver failure at high risk of mortality, prompting more aggressive management, such as liver transplantation. We demonstrated that, as expected, significant citrate accumulation did occur, predicted using the total calcium to ionized calcium ratio, but more interestingly that the effects of citrate accumulation were not as severe as expectation. That the patients with liver failure treated by RCA plasma exchange was well tolerated with citrate accumulation seems to somewhat dispel the concept that RCA is contraindicated in patients with liver failure.

In 2020, The Kidney Disease: Improving Global Outcomes (KDIGO) published a new guideline on the controversies in acute kidney injury, and the recommendation from 2012 to use regional citrate anticoagulation for CRRT in patients who do not have a contraindication remains supported by existing data [6]. In adult patients with acute kidney injury, there is no difference in mortality between the regional citrate and heparin treated groups. However, regional citrate is more efficacious in prolonging circuit life span and reducing the risk of bleeding and should be recommended as the priority anticoagulant for critically ill patients who require CRRT [7]. It has been thought that severe liver failure was listed as one of the contraindications of citrate anticoagulation, regarding the potential citrate accumulation and the subsequent metabolic complications. But in recent years, some studies have found that CRRT or intermittent renal replacement therapy using RCA might be safe and effective in liver failure patients with a prolonged filter lifespan. The increased risk of citrate accumulation most likely could be well addressed by careful monitoring and timely strategy-adjusting [8, 9].

At the end of the last century, some artificial liver support systems, including Molecular Adsorbent Recirculating System, Single-Pass Albumin Dialysis system, and therapeutic plasma exchange alone or combined with plasma adsorption or high flux CRRT, began to develop with the aim of being used as supportive therapy until liver transplantation[10]. RCA can be an effective and safe method of anticoagulation during Molecular Adsorbent Recirculating System therapy [11]. Another study found that the probability of filter survival in the RCA group was 94% and in the heparin group 82% during Molecular Adsorbent Recirculating System therapy (P = 0.204) [12]. RCA provides safe and effective anticoagulation for pediatric liver failure patients requiring extracorporeal liver support with albumin-assisted dialysis[13]. Citrate accumulation is well tolerated by ACLF patients who receive plasma exchange centered therapy without filtration and dialysis [14]. RCA might be safe and effective in ACLF patients receiving plasma adsorption plus plasma exchange therapy [15]. However, there are few studies about regional citrate

anticoagulation centrifugal TPE treatment in both ALF and ACLF patients. Our research provides new evidence that RCA can be well tolerated in both ALF and ACLF patients despite raised citrate accumulation, compared with heparin group.

In this study, we found that the MELD score cut-off value was 30 for plasma exchange treatment in patients with liver failure and area under the ROC curve was 0.7208. A retrospective study found that the hepatitis B virus infection related liver failure patients with MELD score ≤ 26.6 had high negative predictive values of longer duration of citrate accumulation, treated with double plasma molecular adsorption system plus plasma exchange therapy with RCA [16].

In this study, we used total calcium/ionized calcium ratio ≥ 2.5, instead of using citrate concentration to indirectly evaluate the presence of citrate accumulation [17]. The total calcium/ionized calcium, the median value was 2.84, after RCA plasma exchange was significantly higher than that before RCA plasma exchange ($P < 0.0001$). Despite the occurrence of significant citrate accumulation when TPE using RCA in patients with liver failure, there was no difference in survival rate between RCA group and heparin group. Therefore, the effects of citrate accumulation are not as severe as might have been expected. There was no significant difference between the concentrations of total calcium before RCA plasma exchange and that at 48 hours after RCA plasma exchange. This is an indirect indicator demonstrate that the patients with liver failure still have a certain ability to metabolize citrate. It means that a 48 hours interval of RCA plasma exchange may be effective in reducing complications.

Our study has several limitations. First, there may be bias in a single-center retrospective study and some data are incomplete. Second, we do not compare with other prognostic scoring systems, such as MELD-sodium, Child-Turcotte-Pugh, sequential organ failure assessment score (SOFA), and so on. Because we use the MELD scoring system more often to decide whether or not to have a liver transplant, based on our previous data [18–21]. Last, the cut-points generated from this study should be validated by others cohort.

Conclusions

In conclusion, our study demonstrates that the efficacy and safety of regional citrate anticoagulation centrifugal plasma exchange is equivalent to those of systemic heparin anticoagulation membrane plasma exchange in patients with liver failure. RCA plasma exchange at an interval of 48 hours in patients with acute or acute-on-chronic liver failure may be an effective in reducing the occurrence of the complication of citrate accumulation. RCA centrifugal plasma exchange treatment can achieve a good prognosis and well tolerance, especially in MELD < 30 patients with liver failure.

Abbreviations

ACLF: acute on chronic liver failure; ALF: acute liver failure; CRRT: continuous renal replacement therapy; INR: international normalized ratio; KDIGO: Kidney Disease: Improving Global Outcomes; MELDs: model

for end-stage liver disease score; RCA: regional citrate anticoagulation; ROC curve: receiver operating characteristic curve; TPE: therapeutic plasma exchange.

Declarations

Ethics approval and consent to participate

The study was performed in accordance with the Helsinki Declaration and was approved by the Ethical Committee of Huashan Hospital, Fudan University. The consent to participate is not applicable.

Consent for publication

Not applicable.

Availability of data and materials

All data generated or analyzed during this study are from published articles.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

XFZ and JQL contributed equally to this work. XFZ, YW, YZ, QMG, QZ and JMZ1 performed TPE treatment; JQL, TTL, KKY, CH, NL and JMZ1 contributed to clinical data collection; JMZ1 performed statistical analyses and manuscript writing; XFZ, JMZ1, QL and WHZ contributed to the study idea; JMZ2 and RX revise the manuscript critically. JMZ1 is corresponding to Jian-Ming Zheng and JMZ2 is corresponding to Ji-Ming Zhang. All authors read and approve the final manuscript.

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References

1. Sarin SK, Choudhury A, Sharma MK, Maiwall R, Al Mahtab M, Rahman S, et al. Acute-on-chronic liver failure: consensus recommendations of the Asian Pacific association for the study of the liver (APASL): an update. Hepatol Int. 2019; 13(4):353–90.
2. Maiwall R, Sarin SK. Plasma Exchange in Acute and Acute on Chronic Liver Failure. Semin Liver Dis. 2021; 41(4):476–94.
3. Schultheiß C, Saugel B, Phillip V, Thies P, Noe S, Mayr U, et al. Continuous venovenous hemodialysis with regional citrate anticoagulation in patients with liver failure: a prospective observational study. Crit Care. 2012; 16(4):R162.
4. Patel S, Wendon J. Regional citrate anticoagulation in patients with liver failure–time for a rethink?. Crit Care. 2012; 16(5):153.
5. Wiesner R, Edwards E, Freeman R, Harper A, Kim R, Kamath P, et al. Model for end-stage liver disease (MELD) and allocation of donor livers. Gastroenterology. 2003; 124(1):91–6.
6. Ostermann M, Bellomo R, Burdmann EA, Doi K, Endre ZH, Goldstein SL, et al. Controversies in acute kidney injury: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Conference. Kidney Int. 2020; 98(2):294–309.
7. Liu C, Mao Z, Kang H, Hu J, Zhou F. Regional citrate versus heparin anticoagulation for continuous renal replacement therapy in critically ill patients: a meta-analysis with trial sequential analysis of randomized controlled trials. Crit Care. 2016; 20(1):144.
8. Zhang W, Bai M, Yu Y, Li L, Zhao L, Sun S, et al. Safety and efficacy of regional citrate anticoagulation for continuous renal replacement therapy in liver failure patients: a systematic review and meta-analysis. Crit Care. 2019; 23(1):22.
9. Pourcine F, Vong LVP, Chelly J, Rollin N, Sy O, Jochmans S, et al. Sustained low-efficiency dialysis with regional citrate anticoagulation for patients with liver impairment in intensive care unit: A single-

center experience. Ther Apher Dial. 2021; 25(2):211–7.
10. García Martínez JJ, Bendjelid K. Artificial liver support systems: what is new over the last decade?. Ann Intensive Care. 2018; 8(1):109.
11. Faybik P, Hetz H, Mitterer G, Krenn CG, Schiefer J, Funk GC, et al. Regional citrate anticoagulation in patients with liver failure supported by a molecular adsorbent recirculating system. Crit Care Med. 2011; 39(2):273–9.
12. Dyla A, Mielnicki W, Bartczak J, Zawada T, Garba P. Effectiveness and Safety Assessment of Citrate Anticoagulation During Albumin Dialysis in Comparison to Other Methods of Anticoagulation. Artif Organs. 2017; 41(9):818–26.
13. Lion RP, Tufan Pekkucuksen N, Srivaths P, Desai MS, Arikan AA. The Safety and Efficacy of Regional Citrate Anticoagulation in Albumin-Assisted Liver Dialysis for Extracorporeal Liver Support in Pediatric Patients. Blood Purif. 2019; 47(1–3):23–7.
14. Ma Y, Xu Y, Chen F, Wang Y, Bai L, Tang H. Good Tolerance of Citrate Accumulation due to Plasma Exchange among Patients with Acute-on-Chronic Liver Failure: A Prospective, Observational Study. Can J Gastroenterol Hepatol. 2018; 2018:4909742.
15. Ma Y, Chen F, Xu Y, Wang M, Zhou T, Lu J, et al. 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. Blood Purif. 2019; 48(3):223–32.
16. Ma Y, Chen F, Liu C, Xu Y, Wang M, Zhou T, et al. A novel predictive score for citrate accumulation among patients receiving artificial liver support system therapy with regional citrate anticoagulation. Sci Rep. 2020; 10(1):12861.
17. Link A, Klingele M, Speer T, Rbah R, Pöss J, Lerner-Gräber A, et al. Total-to-ionized calcium ratio predicts mortality in continuous renal replacement therapy with citrate anticoagulation in critically ill patients. Crit Care. 2012; 16(3):R97.
18. Li N, Huang C, Yu KK, Lu Q, Shi GF, Zheng JM. Validation of prognostic scores to predict short-term mortality in patients with HBV-related acute-on-chronic liver failure: The CLIF-C OF is superior to MELD, CLIF SOFA, and CLIF-C ACLF. Medicine (Baltimore). 2017; 96(17):e6802.
19. Huang C, Yu KK, Zheng JM, Li N. Steroid treatment in patients with acute-on-chronic liver failure precipitated by hepatitis B: A 10-year cohort study in a university hospital in East China. J Dig Dis. 2019; 20(1):38–44.
20. Li Q, Lu Q, Zhu MQ, Huang C, Yu KK, Huang YX, et al. Lower level of complement component C3 and C3a in the plasma means poor outcome in the patients with hepatitis B virus related acute-on-chronic liver failure. BMC Gastroenterol. 2020; 20(1):106.
21. Yang Q, Zhou Z, Yang X, Chen Y, Liu A, Zhang B, et al. Latent Cytomegalovirus Reactivation in Patients With Liver Failure: A 10-Year Retrospective Case-Control Study, 2011–2020. Front Cell Infect Microbiol. 2021; 11:642500.

Figures

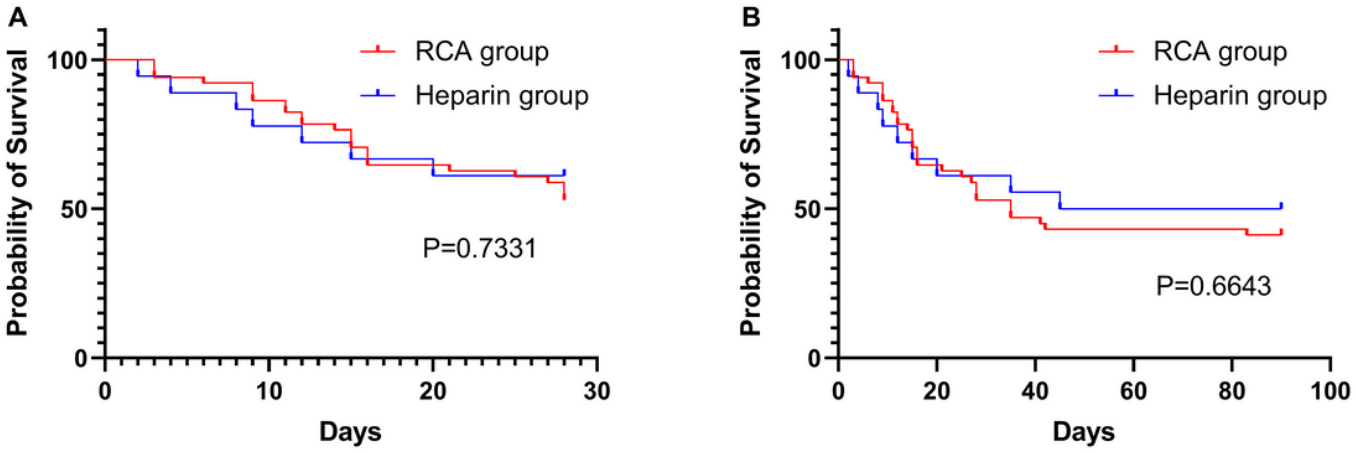

Figure 1

A comparison of cumulative overall survival between the RCA group and the heparin group. A comparison of cumulative overall survival, using the Kaplan-Meier curve, between the RCA group and the heparin group (A) at day 28 (P = 0.7331) and (B) at day 90 (P = 0.6643).

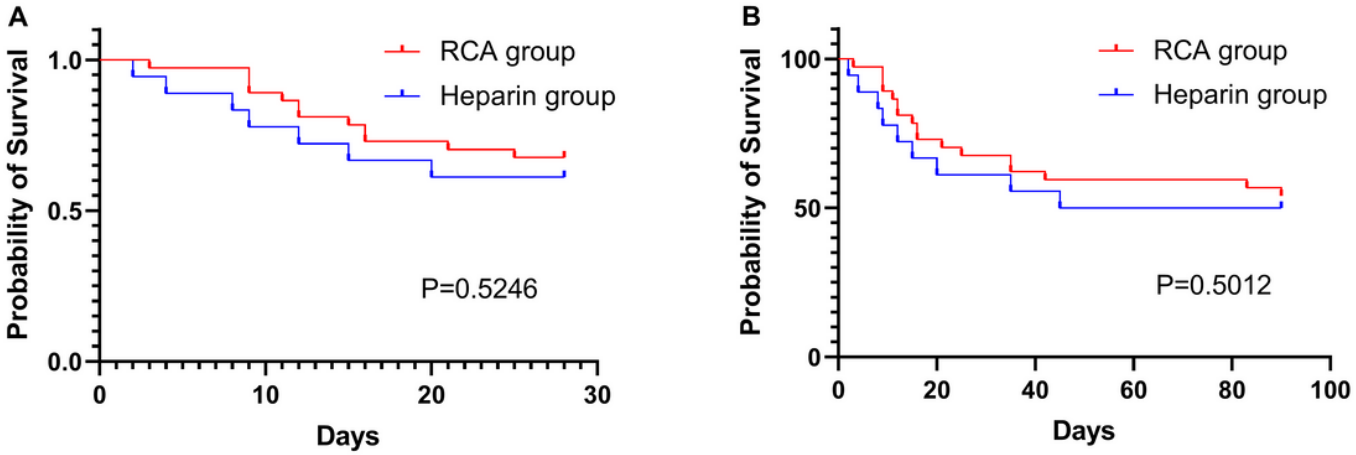

Figure 2

A comparison of cumulative spontaneous survival between the RCA group and the heparin group. A comparison of cumulative spontaneous survival, using the Kaplan-Meier curve, between the RCA group and the heparin group (A) at day 28 (P = 0.5246) and (B) at day 90 (P = 0.5012).

Figure 3

Accuracy of the MELD in predicting 28-day mortality of the spontaneous patients with liver failure. MELD best-fit value is 30, and area under the ROC curve is 0.7208 in the transplantation free patients with liver failure in both RCA group and heparin group (A). MELD best-fit value is 30, and area under the ROC curve is 0.7033 in the transplantation free patients with liver failure in RCA group (B).

Figure 4

A comparison of cumulative spontaneous survival between MELD≥30 group and the MELD<30 group. A comparison of cumulative spontaneous survival, using the Kaplan-Meier curve, between the MELD≥30 group and the MELD<30 group (A) at day 28 (P = 0.0002) and (B) at day 90 (P < 0.0001).