Bilirubin Adsorption Versus Plasma Exchange for Hyperbilirubinemia in Patients After Cardiac Surgery: A Retrospective Study

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Abstract

Objective: Hyperbilirubinemia after cardiac surgery increases in-hospital mortality and is associated with poor prognosis. Our present study aimed to compare the efficacy of bilirubin adsorption (BA) and plasma exchange (PEX) in patients with hyperbilirubinemia after cardiac surgery.

Methods: We retrospectively included patients who underwent BA treatment or PEX treatment due to severe hyperbilirubinemia after cardiac surgery in our center from 2015 to 2020. We collected examinations of urine and liver function before and after treatment and compared the in-hospital mortality and morbidity between two treatment groups.

Results: A total of 56 patients were enrolled in this study, 14 patients received BA treatment and 42 patients received PEX treatment. BA group provided a statistically significant reduction in the TBil ($p=0.016$) and DBil ($p=0.036$) compared to PEX group. The in-hospital mortality was 85.7% (48/56) in the whole group, BA group had lower mortality than PEX group (71.4% vs. 90.5%, $p=0.078$). BA group showed better circulatory support, including lower risks of IABP (21.4% vs. 52.4%, $p=0.044$), ECMO (21.4% vs. 50.0%, $p=0.061$), re-intubation (64.3% vs. 40.5%, $p=0.122$) and ventricular arrhythmias (64.3% vs. 45.2%, $p=0.217$). The in-hospital mortality was still lower in BA treatment group than PEX treatment group (71.4% vs. 100%, $p=0.049$) in matched cohort.

Conclusions: BA treatment had higher removal ability of bilirubin in patients with hyperbilirubinemia and could reduce the mortality and risks of poor clinical outcomes compared to PEX treatment. BA treatment should be considered as an effective treatment method for patients with higher TBil level or Dbil level.

Introduction

Cardiac surgery with cardiopulmonary bypass (CPB) could lead to different degrees of liver damage. In a previous series of reports, the rate of hyperbilirubinemia was reported around 8.6% to 40%(1-3). Hyperbilirubinemia significantly increases the risk of mortality and morbidity (4). The most serious level of liver damage is acute liver failure (ALF). ALF usually develops into multiple organ dysfunction syndrome (MODS) after cardiac surgery. The rate of MODS combination with ALF is relatively low (4.7%), while it could increase the mortality rate up to 90%(5, 6).

Current treatments for ALF or hyperbilirubinemia include plasma exchange (PEX), molecular adsorbent recirculating system (MARS), extracorporeal blood purification and bilirubin adsorption (BA). All of these methods for the treatment are based on their ability to remove endotoxin, cytokines and bilirubinemia from blood which could replace the detoxification function and create conditions for liver cell regeneration.

PEX is a non-biological artificial liver support system and has been one of the effective methods for the treatment of ALF. It was recommended that PE treatment can be used in the early stage of viral hepatitis and liver failure. BA is an important part of the artificial liver support system, which could overcome

adverse reactions such as plasma dosage restrictions, plasma allergies and blood transfusion infection. It provides another option for treatment of ALF and hyperbilirubinemia.

Multiple processes participate in ALF in patients after cardiac surgery, including CPB, low cardiac output syndrome and elevation of venous pressure etc. Therefore, it still remains controversial which treatment for ALF after cardiac surgery has better clinical outcomes. Furthermore, there were only a few clinical studies with limited sample size on this question. PEX and BA had been used in our center for treatment of ALF after cardiac surgery since 2015. We designed this retrospective study to compare the effectiveness in patients with ALF after cardiac surgery between BA and PEX treatment.

Methods

Study population

From 2015 to 2020, 11483 adult patients underwent cardiac surgery in our center, 56 patients among them were diagnosed AFL or hyperbilirubinemia after cardiac surgery, 14 patients received BA treatment and 42 patients received PEX treatment. This study was obtained from Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College (2020-249-01). The requirement to obtain informed consent from the patient was waived, and all authors had full control of the data and information in this study.

Indications

We diagnosed ALF depend on following criteria(7-9): onset was acute with II degree hepatic encephalopathy; Extremely weak with gastrointestinal symptoms such as anorexia, abdominal distension, nausea and vomiting; The jaundice progresses quickly with total bilirubin (TBil) $\geq 10 \times$ Upper limit of normal (ULN) or daily increasing data $\geq 17.1 \mu\text{mol/L}$. Patients with ALF usually had hyperbilirubinemia and developed into multiple organ dysfunction (MODS) after cardiac surgery. We divided the 56 cases into two groups: 14 cases with BA treatment and 42 cases with PEX treatment.

Treatment approach

The vascular access was obtained via a double-lumen hemodialysis catheter, introduced into the femoral, jugular or subclavian vein. Blood anti-coagulation was controlled using unfractionated heparin (target clotting time of 140-200 s).

In the BA treatment device, using PF 2000N (Gambro Dialysatoren GmbH) as plasma filter, BS330 (Jafron Biomedical Co., Ltd, China) as bilirubin absorption column (Jafron Biomedical Co., Ltd, China), HA330-II (Jafron, China) as disposable hemoperfutor and Diapact CRRT system (Fresenius Medical Care, Germany) as a machine performing the performing the procedure, the following parameters were set: Blood flow rate 120-150 ml/min; Plasma flow rate 30 ml/min; Average duration of treatment 4 h; Average amount of plasma 6 L.

In the PEX treatment device, using PF 2000N (Gambro Dialysatoren GmbH) as plasma filter and Diapact CRRT system (Fresenius Medical Care, Germany) as a machine performing the procedure, the following parameters were set: Blood flow rate 120-150 ml/min; Plasma flow rate 25 ml/min; Average duration of treatment 2 h; Average amount of plasma 3 L.

Statistical analysis

Data analysis was performed using SPSS for Windows version 22 (IBM Corporation, Armonk, NY). Generally, continuous variables were stated as mean $\pm$ standard deviation. Categorical variables are stated as absolute numbers and proportions (n, %). Differences in categorical variables were analyzed using the χ^2 test. Differences in continuous variables were tested by t-test or Mann-Whitney U-test. To overcome the selection bias in our study, we chose a matched cohort of 28 cases (14 cases with BA treatment and 14 cases with PE treatment) with similar conditions before treatment. Some bias could exist in our study. Adjustment for indication bias was further assessed using a matched cohort. In matched cohort, the PEX subjects were selected for each case and matched for sex, age ($\pm$ 2 years) and EuroSCORE II ($\pm$ 1 %). Differences were considered as significant at $p < 0.05$.

Results

Preoperative and intraoperative variables are listed in Table 1. The mean age of all patients was 66.0 ± 10.6 years. Most patients were male (41/56, 73.2%) and had cardiac insufficiency (NYHA class III/IV, 55/56, 98.2%). Patients in BA treatment Group had higher risks of surgery mortality with higher EuroScore II score than PEX treatment Group ($p = 0.006$). All patients had no history of chronic renal failure or liver disease. Baseline liver function and renal function had no difference between two groups. The type of cardiac operation showed no differences among two groups. The mean cardiopulmonary bypass time and aortic cross-clamp were 225.9 ± 80.7 and 164.9 ± 60.7 minutes, respectively. BA treatment group presented longer bypass time and cross-clamp time, while there were no differences between two groups.

The baseline total bilirubin (TBil) level of all patients before treatment was 306.0 ± 100.7 $\mu\text{mol/L}$; Direct bilirubin (DBil) level was 174.0 ± 68.3 $\mu\text{mol/L}$. Before adsorption or exchange, DBil ($p = 0.040$) levels were much higher in BA treatment group than PEX treatment group. Bilirubin adsorption treatment provided a statistically significant reduction in the TBil ($p = 0.016$) and DBil ($p = 0.036$) compared to plasma exchange treatment. The details of TBil and DBil before and after BA/PE treatment are shown in Table 2.

Serum aminotransferase levels reflecting hepatocyte cytolysis syndrome also had significantly improved: Aspartate aminotransferase (AST) and Alanine aminotransferase (ALT) levels were both decreased after BA or PEX treatment (Table 2). Since the majority of patients with AFL received renal replacement therapy before BA or PEX treatment for MODS, the baseline serum creatinine and blood urea nitrogen (BUN) levels were not very serious: the serum creatinine level was 112.3 ± 43.4 $\mu\text{mol/L}$ and BUN level was 14.5 ± 6.0 mmol/L. After BA or PE treatment, the serum creatinine level was 86.8 ± 27.8 $\mu\text{mol/L}$ and BUN level was 12.1 ± 3.7 mmol/L (Table 2). The improvement of renal function indicated both two treatments could eliminate the water-soluble toxic substances.

The in-hospital mortality was 85.7% (48/56) in the whole group, BA group had lower mortality than PEX group (71.4% vs. 90.5%, $P=0.078$). BA treatment showed better circulatory support, including lower risks of IABP (21.4% vs. 52.4%, $p=0.044$), ECMO (21.4% vs. 50.0%, $p=0.061$), re-intubation (64.3% vs. 40.5%, $p=0.122$) and ventricular arrhythmias (64.3% vs. 45.2%, $p=0.217$). One of the main efficacy criteria of treatment therapy was its impact on maintaining homeostasis. BA treatment could reduce the incidence of hepatic encephalopathy (35.7% vs. 71.4%, $p=0.017$) and septic shock (35.7% vs. 52.4%, $p=0.280$). The peak lac adsorption ($p=0.004$) and vasoactive inotropic score (VIS) ($p=0.002$) after treatment was both lower in BA treatment group than PEX treatment group. The detailed early outcomes were listed in Table 3.

After matching, a total of 28 cases were enrolled in analysis (14 in BA treatment group and 14 in PEX treatment group). The in-hospital mortality was lower in BA treatment group than PEX treatment group (71.4% vs. 100%, $P=0.049$). The circulatory supports were similar between two groups, including the usage of IABP, ECMO, re-intubation and ventricular arrhythmias. BA treatment group had advantages of maintaining homeostasis, reflecting on the lower incidence of hepatic encephalopathy (35.7% vs. 92.9%, $p=0.002$), lower VIS score ($P=0.013$) and lac levels ($P=0.045$) after treatment. BA treatment group also showed better efficacy on removing toxins, it provided a statistically significant reduction in TBil, DBil, ALT, AST, Serum Creatinine, BUN and C-creative protein. The results of matched cohort were listed in Table 4.

Discussion

Hyperbilirubinemia after cardiac surgery has been known for a long time, despite demonstrable improvements in surgical techniques and perioperative care over the last decade, hepatic dysfunction still remains a serious postoperative complication(10, 11). Relevant factors about hyperbilirubinemia after cardiac surgery included(4, 12-14): (1) Hepatic ecchymosis due to high pressure of right atrium; (2) Non-pulsatile flow in CPB and its associated risk of regional malperfusion causing liver ischemic damage; (3) Massive transfusion; (4) Hemolysis caused by cardiotomy suction, the membrane oxygenator and various other elements of CPB; (5) Postoperative infection. Different methods were used to treat hyperbilirubinemia such as molecular adsorbent recirculating system (MARS), plasma exchange (PEX) and bilirubin adsorption (BA), it was still unclear which treatment strategy was more useful for patients with hyperbilirubinemia after cardiac surgery(15). We presented a retrospective analysis of prospectively collected data that compared BA treatment with PEX treatment in hyperbilirubinemia after cardiac surgery. This study demonstrated that (I) BA treatment could be considered as an effective strategy for the reduction of TBil and DBil in patients with post-operative hyperbilirubinemia. (II) The BA could reduce in-hospital mortality and risks of poor outcomes compared to PEX.

Several studies have reported that the incidence of hyperbilirubinemia after cardiac surgery was between 10% and 40%(4, 16, 17), which has been consistent since the first report in 1967(2). In our center, the incidence of hyperbilirubinemia was 0.48% which was similar to previous studies. Most patients suffered severe cardiac disease with NYHA class III/IV(18), valvular surgery and valvular surgery as well as CABG

were the most common surgery types. These findings were similar to previous studies, complicated valve surgery procedure caused more frequent postoperative hyperbilirubinemia (4, 12, 18-20). Therefore, the severity and complexity of valve surgery might be important predictive factor for the incidence of postoperative hyperbilirubinemia.

When hyperbilirubinemia turned to acute liver failure, a large amount of endotoxin, cytokines and other pathogenic factors, especially those close to albumin were accumulated in plasma. The combined toxin was difficult to pass through traditional blood purification treatments such as hemodialysis. These toxins played a key role in the development of liver failure and could cause hemodynamics and hepatorenal syndrome. It has been proved that short-term mortality depends on high levels of bilirubin (21) and low levels of bilirubin could facilitate hepatocyte regeneration. High levels of bile acids may induce apoptosis and cell necrosis of hepatocytes and retard hepatic regeneration (22). In addition, bilirubin has neurotoxic and encephalopathic effects (23). Based on these reasons, the removal of bilirubin seems to be an important therapeutic target. BA treatment and PEX treatment are both effective therapies for hyperbilirubinemia (24, 25). Plasma exchange therapy can remove a variety of toxins, supply coagulation factors and regulate immune function. Bilirubin adsorption works through resin adsorbent which has acceptable capacity for toxins such as bilirubin and cytokines. In our study, we found that BA treatment had higher removal ability of TBil and DBil compared to PEX treatment, while the removal ability of ALT, AST and serum creatinine was similar between two treatments. The following rate limiting factors influenced the removal ability of albumin-binding toxins: (1) plasma ion strength and PH value(26); (2) the possible loss of albumin due to its binding to the absorber columns (27); (3) the molar ratio of bilirubin to albumin (28). Since the 20-fold higher molar ratio of serum bilirubin to albumin compared to the respective dialysate (26, 29) and the loss of albumin with time due to its binding to the filter (27).

Our findings demonstrated that postoperative hyperbilirubinemia resulted in significantly increased in-hospital mortality, as the mortality was up to 85.7%, which was much higher than reported early mortality between 19% and 25%(3, 18). Patients in our study were all critical patients with severe congestive heart disease, most of them were NYHA class III/IV. EuroSCORE II scores showed that these patients suffered huge risks of mortality and complications. Indeed, patients in our study were almost acute liver failure with MODS, the mortality of MODS after cardiac surgery was reported up to 90%(5, 6). Acute liver failure combined with MODS could cause the disorder of internal environment and hemodynamically unstable. In this study, most patients suffered poor clinical outcomes, especially in the usage of IABP, ECMO, CRRT etc. Almost all patients died of MODS.

There were limited studies about the optimal techniques for bilirubin removal and no direct comparison exists between BA and PEX in patients after cardiac surgery. Recently, Chen X and his colleagues draw a conclusion that BA treatment was an effective and safe method for hyperbilirubinemia in patients after cardiac surgery(30). Our study added evidence that BA treatment not only had a higher removal ability of bilirubin but also could lower the mortality and risks of poor clinical outcomes in patients with hyperbilirubinemia after cardiac surgery. Moreover, PEX treatment needed a large amount of plasma or albumin which could be confined to limitations of plasma and patients with rare blood type. BA treatment

had advantage in this aspect, it can adsorb bilirubin in a competitive binding way compared to albumin. After the free bilirubin in plasma is adsorbed, the bilirubin bound to plasma albumin is partially dissociated and then adsorbed, albumin and coagulation factors could be protected in this way.

Study Limitations

This study was a retrospective study with limited study cases in one center. Missing data for other possible factors, such as the amount of bleeding, postoperative central venous pressure and coagulation function may limit our findings. We tried to compare two treatment therapies more clearly according to a matched cohort. However, factors that affect assignment to treatment and outcomes but that cannot be observed could not have been accounted for in the matched cohort. These hidden biases might have remained in matched cohort and led to some statistical errors. Furthermore, the treatment timing for different therapies were not discussed in this study, we thought it needed larger amount of sample size and prospective studies to explain.

Conclusion

BA treatment had higher removal ability of bilirubin in patients with hyperbilirubinemia and could reduce the mortality and risks of poor clinical outcomes compared to PEX treatment. BA treatment should be considered as an effective treatment method for patients with higher TBil level or Dbil level.

Abbreviations

CABG: Coronary artery bypass grafting

CPB: Cardiopulmonary bypass

ACC: Aortic cross-clamp

AST: Aspartate aminotransferase

ALT: Alanine aminotransferase

GGT: Gamma-glutamyl transpeptidase

TBil: Total bilirubin; DBil: Direct bilirubin

LDH: Lactate dehydrogenase

NYHA: New York Heart Association

BUN: Blood urea nitrogen

Lac: Arterial lactate

CRRT: Continuous renal replacement therapy

IABP: Intra-aortic balloon pump

ECMO: Extracorporeal Membrane Oxygenation

Declarations

Authors' contributions

Dong-jin Wang and Hai-long Cao were major contributors to the conception of the study and revised the manuscript; Ke Pan, He Zhang, Kai Zhong, Hai-tao Zhang, Zhong Chen, Ze-shi Li, Man Xie , Su-ping Gu and Tuo Pan collected the data; Ke Pan and He Zhang wrote the manuscript; all authors contributed to the conception of the study; Tuo Pan, Ke Pan and He Zhang corrected the statistical analysis. All authors read and approved the final manuscript

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained from Medical Ethics Committee of Affiliated Nanjing Drum Tower Hospital, Nanjing University Medical College (2020-249-01), and conducted according to the principles in the Declaration of Helsinki.

Consent for publication

All authors have read and approved the manuscript for publication.

Competing interests

The authors declare that they have no competing interests.

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References

1. Welbourn N, Melrose DG, Moss DW. Changes in serum enzyme levels accompanying cardiac surgery with extracorporeal circulation. *J Clin Pathol.* 1966;19(3):220-32.
2. Lockey E, McIntyre N, Ross DN, Brookes E, Sturridge MF. Early jaundice after open-heart surgery. *Thorax.* 1967;22(2):165-9.
3. Collins JD, Bassendine MF, Ferner R, Blesovsky A, Murray A, Pearson DT, et al. Incidence and prognostic importance of jaundice after cardiopulmonary bypass surgery. *Lancet.* 1983;1(8334):1119-23.
4. Wang MJ, Chao A, Huang CH, Tsai CH, Lin FY, Wang SS, et al. Hyperbilirubinemia after cardiac operation. Incidence, risk factors, and clinical significance. *J Thorac Cardiovasc Surg.* 1994;108(3):429-36.
5. Daas M, Plevak DJ, Wijdicks EF, Rakela J, Wiesner RH, Piepgras DG, et al. Acute liver failure: results of a 5-year clinical protocol. *Liver Transpl Surg.* 1995;1(4):210-9.
6. Gerth HU, Pohlen M, Pavenstadt H, Schmidt H. [Extracorporeal liver support of liver failure]. *Z Gastroenterol.* 2017;55(4):383-93.
7. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet.* 1993;342(8866):273-5.
8. Bernal W, Wendon J. Acute liver failure. *N Engl J Med.* 2013;369(26):2525-34.
9. Jalan R, Yurdaydin C, Bajaj JS, Acharya SK, Arroyo V, Lin HC, et al. Toward an improved definition of acute-on-chronic liver failure. *Gastroenterology.* 2014;147(1):4-10.
10. Olsson R, Hermodsson S, Roberts D, Waldenstrom J. Hepatic dysfunction after open-heart surgery. *Scand J Thorac Cardiovasc Surg.* 1984;18(3):217-22.
11. Michalopoulos A, Alivizatos P, Geroulanos S. Hepatic dysfunction following cardiac surgery: determinants and consequences. *Hepatogastroenterology.* 1997;44(15):779-83.
12. Hosotsubo KK, Nishimura M, Nishimura S. Hyperbilirubinaemia after major thoracic surgery: comparison between open-heart surgery and oesophagectomy. *Crit Care.* 2000;4(3):180-7.
13. Gregoretti S. Suction-induced hemolysis at various vacuum pressures: implications for intraoperative blood salvage. *Transfusion.* 1996;36(1):57-60.
14. Garcia MJ, Vandervoort P, Stewart WJ, Lytle BW, Cosgrove DM, 3rd, Thomas JD, et al. Mechanisms of hemolysis with mitral prosthetic regurgitation. Study using transesophageal echocardiography and fluid dynamic simulation. *J Am Coll Cardiol.* 1996;27(2):399-406.
15. Szczepiorkowski ZM, Shaz BH, Bandarenko N, Winters JL. The new approach to assignment of ASFA categories—introduction to the fourth special issue: clinical applications of therapeutic apheresis. *J Clin Apher.* 2007;22(3):96-105.
16. Scott BB, McCormack MC, Austen WG. Commentary on: Compact Fat Grafting: A Novel Method to Improve Graft Retention Through Modulation of Adipocyte Size. *Aesthet Surg J.* 2021.
17. Chu CM, Chang CH, Liaw YF, Hsieh MJ. Jaundice after open heart surgery: a prospective study. *Thorax.* 1984;39(1):52-6.

18. Nishi H, Sakaguchi T, Miyagawa S, Yoshikawa Y, Fukushima S, Saito S, et al. Frequency, risk factors and prognosis of postoperative hyperbilirubinemia after heart valve surgery. *Cardiology*. 2012;122(1):12-9.
19. Lau GT, Tan HC, Kritharides L. Type of liver dysfunction in heart failure and its relation to the severity of tricuspid regurgitation. *Am J Cardiol*. 2002;90(12):1405-9.
20. Mastoraki A, Karatzis E, Mastoraki S, Kriaras I, Sfirakis P, Geroulanos S. Postoperative jaundice after cardiac surgery. *Hepatobiliary Pancreat Dis Int*. 2007;6(4):383-7.
21. Lopez-Velazquez JA, Chavez-Tapia NC, Ponciano-Rodriguez G, Sanchez-Valle V, Caldwell SH, Uribe M, et al. Bilirubin alone as a biomarker for short-term mortality in acute-on-chronic liver failure: an important prognostic indicator. *Ann Hepatol*. 2013;13(1):98-104.
22. Chamuleau RA, Aronson DC, Frederiks WM, Bosman DK, Smit JJ, Maas MA, et al. Liver regeneration after partial hepatectomy in rats with defective bilirubin conjugation or biliary excretion. *Dig Dis Sci*. 1991;36(4):510-2.
23. Lee JY, Kim SB, Chang JW, Park SK, Kwon SW, Song KW, et al. Comparison of the molecular adsorbent recirculating system and plasmapheresis for patients with graft dysfunction after liver transplantation. *Transplant Proc*. 2010;42(7):2625-30.
24. Onodera K, Sakata H, Yonekawa M, Kawamura A. Artificial liver support at present and in the future. *J Artif Organs*. 2006;9(1):17-28.
25. Li LJ, Yang Q, Huang JR, Xu XW, Chen YM, Fu SZ. Effect of artificial liver support system on patients with severe viral hepatitis: a study of four hundred cases. *World J Gastroenterol*. 2004;10(20):2984-8.
26. Gong D, Cruz D, Ronco C. Depurative capacity of molecular adsorbent recycling system (MARS): A focus on bilirubin removal. *Int J Artif Organs*. 2008;31(10):875-81.
27. Gong D, Ji D, Ren B, Tao J, Xu B, Ronco C, et al. Significant decrease in dialysate albumin concentration during molecular adsorbent recirculating system (M.A.R.S.) therapy. *Int J Artif Organs*. 2008;31(4):333-9.
28. Steiner C, Sen S, Stange J, Williams R, Jalan R. Binding of bilirubin and bromosulphthalein to albumin: implications for understanding the pathophysiology of liver failure and its management. *Liver Transpl*. 2004;10(12):1531-8.
29. Schaefer B, Schaefer F, Engelmann G, Meyburg J, Heckert KH, Zorn M, et al. Comparison of Molecular Adsorbents Recirculating System (MARS) dialysis with combined plasma exchange and haemodialysis in children with acute liver failure. *Nephrol Dial Transplant*. 2011;26(11):3633-9.
30. Chen X, Li L, Bai M, Sun S, Chen X. Bilirubin adsorption for the treatment of severe hyperbilirubinemia after cardiac surgery: A retrospective cohort study. *Int J Artif Organs*. 2021:391398821997841.

Tables

Table 1. Baseline and Characteristics			
Variable	Bilirubin adsorption (n=14)	Plasma exchange (n=42)	P value
Age (year)	62.2±14.9	67.2±8.5	0.125
Gender (male, %)	10, 71.4%	31, 73.8%	0.862
Weight (kg)	64.4±10.4	62.4±8.6	0.477
NYHA class (n, %)			0.329
I	0	0	
II	0	1, 2.3%	
III	6, 42.8%	23, 54.8%	
IV	8, 57.2%	18, 42.9%	
EuroSCORE II	30.5±17.5	20.9±7.6	0.006
Previous Medical History (n,%)			
Acute Myocardial infarction	5, 35.7%	9, 21.4%	0.285
Diabetes Mellitus	7, 50.0%	11, 26.2%	0.099
Chronic Renal Failure	0	0	—
Hypertension	11, 78.6%	24, 26.2%	0.151
Liver Disease	0	0	—
Smoking	5, 35.7%	11, 26.2%	0.495
Type of cardiac operation (n,%)			
CABG	1, 7.1%	4, 9.5%	
Valvular surgery	5, 35.7%	14, 33.3%	
CABG + Valvular surgery	4, 28.6%	13, 31.0%	
Aortic surgery	4, 28.6%	11, 26.2%	
CPB time	251.1±79.7	218.1±80.4	0.20
ACC time	187.8±65.1	157.8±58.2	0.12
Pre-operation liver function			
ALT	29.0(13.4-58.7)	25.0.3 (17-51.3)	0.813
AST	34.1(20.2-109.4)	30.5(17.9-37.6)	0.348

GGT	102.8±70.9	74.1±38.2	0.225
TBil	23.3±15.1	18.3±9.9	0.157
DBil	10.3±7.3	9.6±6.4	0.715
LDH	230.9±116.5	183.4±83.4	0.176
Serum albumin	38.7±4.8	38.8±3.5	0.906
Pre-operation Serum Creatinine	115.9±77.5	95.4±53.8	0.276
Mean±SD	Median (Interquartile range)		
CABG: Coronary artery bypass grafting	CPB: Cardiopulmonary bypass		
ACC: Aortic cross-clamp	AST: Aspartate aminotransferase		
ALT: Alanine aminotransferase	GGT: Gamma-glutamyl transpeptidase		
TBil: Total bilirubin	DBil: Direct bilirubin		
LDH: Lactate dehydrogenase	NYHA: New York Heart Association		

Table 2. Hepatorenal function after treatment			
Variable	Bilirubin adsorption (n=14)	Plasma exchange (n=42)	P value
Before adsorption/exchange			
ALT	68.6(40.3-139.5)	56.1(40.3-82.0)	0.635
AST	83.6(55.9-110.5)	91.3(5.9-169.5)	0.669
GGT	103.8±76.3	87.6±60.7	0.422
TBil	329.8±115.1	298.1±95.6	0.311
DBil	206.2±80.8	163.2±60.9	0.040
LDH	555.5(418.5-1142.2)	497.5(164.7-636.2)	0.204
Serum Creatinine	123.7±55.9	108.7±38.4	0.265
BUN	15.8±7.0	14.1±5.7	0.367
C-creative protein	138.8±52.1	142.6±50.8	0.871
Child-Pugh Classification (n, %)			0.501
A	0	3, 7.1%	
B	7, 50.0%	21, 50.0%	
C	7, 50.0%	18, 42.9%	
After adsorption/exchange			
ALT	40.5(31.3-66.8)	42.1(32.9-86.8)	0.383
AST	67.0(63.9-80.5)	76.3(65.1-88.8)	0.372
GGT	81.7±67.2	107.6±90.2	0.331
TBil	187.8±66.5	237.9±196.6	0.016
DBil	106.1±42.6	143.4±71.5	0.036
LDH	418.6±146.8	440.0±170.0	0.675
Serum Creatinine	75.2±15.3	90.8±30.1	0.136
BUN	11.2±2.9	12.4±3.9	0.334
C-creative protein	106(81.5-124.5)	112.0(78.0-145.0)	0.393
Mean±SD	Median (Interquartile range)		
LDH: Lactate dehydrogenase	AST: Aspartate aminotransferase		

ALT: Alanine aminotransferase	GGT: Gamma-glutamyl transpeptidase
TBil: Total bilirubin	DBil: Direct bilirubin
BUN: Blood urea nitrogen	

Table 3. Outcomes			
Variable	Bilirubin adsorption (n=14)	Plasma exchange (n=42)	P value
Death (n, %)	10, 71.4%	38, 90.4%	0.078
CRRT (n, %)	12, 85.7%	30, 71.4%	0.285
IABP (n, %)	3, 21.4%	22, 52.4%	0.044
ECMO (n, %)	3, 21.4%	21, 50.0%	0.061
Re-intubation (n, %)	9, 64.2%	17, 40.5%	0.122
Septic shock (n, %)	5, 35.7%	22, 52.4%	0.280
Ventricular arrhythmias (n, %)	9, 64.2%	19, 45.2%	0.217
Hepatic encephalopathy (n, %)	5, 35.7%	30, 71.4%	0.017
Peak VIS after adsorption/exchange	51.5±12.2	65.1±15.6	0.002
Peak lac adsorption/exchange (mmol/L)	8.4±2.1	10.6±2.3	0.004

Lac: arterial lactate

Table 4. Outcomes and hepatorenal function in matched cohort			
Variable	Bilirubin adsorption (n=14)	Plasma exchange (n=14)	P value
Death (n, %)	10, 71.4%	14, 100.0%	0.049
CRRT (n, %)	12, 85.7%	12, 85.7%	—
IABP (n, %)	3, 21.4%	8, 57.15%	0.060
ECMO (n, %)	3, 21.4%	3, 21.4%	—
Re-intubation (n, %)	9, 64.2%	10, 71.4%	0.500
Septic shock (n, %)	5, 35.7%	4, 28.6%	0.500
Ventricular arrhythmias (n, %)	9, 64.2%	6, 42.9%	0.225
Hepatic encephalopathy (n, %)	5, 35.7%	13, 92.9%	0.002
Peak VIS after adsorption/exchange	47.3±5.9	62.9±19.8	0.013
Peak lac adsorption/exchange (mmol/L)	8.4±2.2	10.1±2.1	0.045
After adsorption/exchange			
ALT	28.9(19.4-64.0)	42.1(32.9-94.0)	0.021
AST	58.0(46.6-74.5)	76.3(60.3-101.7)	0.012
GGT	69.0(20.0-118.5)	79.0(30.0-125.3)	0.667
TBil	162.9±76.3	235.2±82.9	0.024
DBil	90.4±35.2	139.1±53.5	0.009
LDH	394.5±127.8	435.1±161.7	0.467
Serum Creatinine	80.1±11.9	107.8±22.8	0.001
BUN	10.3±2.8	14.5±4.3	0.010
C-creative protein	83.5±15.8	151.6±49.2	0.018