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Hepatopathy and acute kidney injury Following Corrective Cardiac Surgery with cardiopulmonary bypass pump in Pediatric with Congenital Heart Defects

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Abstract

BACKGROUND: Congenital heart defects (CHDs) are common anomalies in children. Cardiopulmonary bypass (CPB) is widely used in cardiac surgeries, but it is associated with complications. Liver and kidney injuries frequently occur during CPB. This study aimed to evaluate liver and kidney damage in pediatric patients with CHDs undergoing cardiac surgery with CPB.

METHODS: This retrospective study examined 51 patients with CHDs who underwent cardiac surgery with CPB at Vali-Asr and Razi hospitals in Birjand, Iran. The study period spanned from 2013 to 2019. Patient information was extracted from hospital records and compiled into checklists, which included demographic data, disease severity, liver function tests, cardiac ejection fraction, and serum levels of hematocrit, direct and indirect bilirubin, albumin, total protein, and creatinine.

RESULTS: Among the patients, 52.9% were male and 47.1% were female, with a mean age of 37 months. A total of 78.4% had cyanotic CHDs.

After surgery, the levels of AST, ALT, and ALKP increased significantly ($P < 0.001$), while the levels of indirect bilirubin, albumin, and total protein decreased ($P < 0.001$). The cardiac ejection fraction also improved following surgery ($P < 0.001$). However, changes in creatinine and direct bilirubin were not significant. Notably, AST levels were markedly higher in deceased patients compared to survivors.

CONCLUSION: This study revealed significant alterations in liver enzyme levels in patients undergoing cardiac surgery using CPB, potentially indicating liver damage during the procedure. Furthermore, elevated postoperative AST levels were associated with a higher risk of mortality.

Keywords: Liver Function Tests; Congenital Heart Defects; Cardiopulmonary Bypass, Hepatopathy; Transaminases; Acute Kidney Injury

Introduction

Congenital heart defects (CHDs) are among the most common congenital anomalies and contribute to pediatric mortality. These conditions account for 10–25% of stillbirths. The prevalence of CHDs is approximately 1 in 120 live births, affecting millions of individuals worldwide[1].

While the cause of many CHDs remains unknown, abnormal embryogenesis of the heart plays a significant role. These conditions often result from a combination of genetic and acquired factors. Genetic disorders—such as Down syndrome, DiGeorge syndrome, trisomy 13 and 18, Holt–Oram syndrome, and Alagille syndrome-along with environmental influences, including maternal diabetes and congenital rubella, contribute to CHD occurrence[2,3].

Treatment options for CHDs include pharmacotherapy, catheter-based procedures, and open-heart surgery. Catheter-based interventions are less invasive and preferred for conditions such as atrial septal defects (ASDs), whereas more severe and complex defects require open-heart surgery[4].

Cardiopulmonary bypass (CPB) is a type of extracorporeal circulation used in cardiac surgeries, including those for repairing congenital heart defects (CHDs). In this method, the patient's blood is pumped into a machine outside the body, where it is oxygenated using an oxygenator and then recirculated into the vessels[5]. This technique has enabled successful repairs in newborns and infants with CHDs.

Adequate tissue perfusion and oxygenation are crucial for organ function before, during, and after cardiac surgery with CPB. However, CPB has limitations; alterations in blood concentration can result in complications affecting various organs, including the liver and kidneys. Approximately 25% of patients undergoing cardiac surgery with CPB experience gastrointestinal issues, such as bleeding, hyperbilirubinemia, pancreatitis, acute cholecystitis, intestinal inflammation, and ischemia[6-8].

Liver disorders (hepatopathy) may also occur, ranging from mild to severe, with a mortality rate of approximately 25%. In cases progressing to liver failure, mortality can reach 80–90%. Hepatic complications related to CPB are multifactorial and result from factors such as decreased cardiac output, impaired hepatic perfusion due to intraoperative hypotension or reduced cardiac output, non-pulsatile flow during bypass, compromised blood flow, elevated catecholamine levels, and the release of inflammatory mediators during the bypass procedure[9].

Comparative analyses between coronary artery bypass grafting (CABG) using CPB (on-pump CABG) and off-pump techniques reveal notable differences. While liver metabolic function remains consistent across both methods, on-pump procedures carry an exclusive risk: liver ischemia. This highlights the importance of considering CPB as a significant factor in hepatic complications during cardiac surgeries[10].

Given the high prevalence of congenital heart defects in children and the potential organ complications associated with cardiac repair surgeries using CPB, this study aimed to explore alterations in liver function following cardiac surgery with CPB.

Method and Patients

Patients

This retrospective study, approved by the Ethics Committee of Birjand University of Medical Sciences in Birjand, Iran (Ethics Code: IR.BUMS.REC.1399.540), involved pediatric patients with congenital heart defects (CHDs). The study focused on patients who were candidates for heart surgery with cardiopulmonary bypass (CPB) at Vali-Asr and Razi hospitals between September 3, 2013, and September 3, 2019.

Patient data were de-identified to ensure confidentiality, eliminating the need for informed consent. Participants were selected using a census method. The inclusion criteria encompassed CHD patients who underwent cardiac surgery with CPB during the study period. Exclusion criteria applied to patients with congenital syndromes such as Turner syndrome, Down syndrome, and trisomies, as well as those lacking essential tests in their hospital records, patients with CHDs coexisting with other liver and kidney diseases, and those with advanced CHDs that had led to liver failure.

Definitions and methods

In this study, we focused on CHDs that require surgical intervention due to their significant impact on children's health. CPB plays a critical role in cardiac surgery, particularly in procedures involving CHDs. During CPB, the patient's heart and lungs are temporarily bypassed. The use of CPB in cardiac surgery is commonly referred to as the "on-pump" method, in contrast to "off-pump" surgeries, in which the heart continues to beat without bypass. CPB creates a stable environment for intricate heart procedures, ensuring adequate oxygenation and circulation throughout surgery[5].

Various factors before, during, and after surgery significantly influence postoperative complications. These factors include age, nutritional status, CHD severity and type, the presence of accompanying disorders or abnormalities, the duration of surgery, the length of CPB use, and the risk of post-surgical infections. All these elements affect the patient's prognosis[11.]

During cardiac surgery, the liver is one of the affected organs, leading to a condition known as cardiac surgery-associated hepatopathy. This condition is characterized by postoperative cholestasis, elevated biomarkers such as bilirubin and gamma-glutamyl transferase (GGT), and impaired liver synthesis-marked by reduced production of albumin and/or coagulation factors. Sonographic changes in the liver may or may not be present during the postoperative period[12].

Serum creatinine (SCr) is a key renal function test used to evaluate acute kidney injury (AKI) following cardiac surgery. AKI is defined as an acute increase in SCr to ≥50% above baseline. In pediatric patients, the pediatric Risk, Injury, Failure, Loss, End-Stage (pRIFLE) criteria are used to assess AKI severity:

- Mild: SCr increase between 1.5 and 2 times baseline
- Moderate: SCr increase between 2 and 3 times baseline
- Severe: SCr increase ≥3 times baseline[13]

In this study, liver function tests included alkaline phosphatase (ALKP) and serum transaminases specifically aspartate aminotransferase (AST) and alanine aminotransferase (ALT). Additionally, serum albumin and total protein levels were assessed as indicators of liver synthesis, while serum creatinine served as a kidney function test. These measurements were obtained before surgery and 24 hours postoperatively. Echocardiography was performed before and 24 hours after surgery to evaluate changes in cardiac ejection fraction.

Data analysis

We collected demographic, preoperative, and postoperative data for each patient. To assess normal data distribution, we used the Kolmogorov-Smirnov test. For normally distributed data, paired t-tests and independent t-tests were applied. For non-normally distributed data, the Wilcoxon test and Mann-Whitney test were used as non-parametric equivalents.

Logistic regression was employed to explore the relationship between transaminase levels and patient prognosis while controlling for confounding factors. Descriptive results were summarized using central and dispersion indices. A p-value of less than 0.05 was considered statistically significant.

Data analysis was performed using IBM Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Corp., Armonk, NY, USA).

Results

The data were collected from 51 patients with CHDs who underwent surgery with CPB. Upon comparing the hepatopathy and non-hepatopathy groups, no significant differences in preoperative risk factors were observed. Among the examined patients, 27 (52.9%) were male and 24 (47.1%) were female, with ages ranging from 5 days to 12 years (mean age: 37 months).

The majority of the studied population (78.4%; 40 patients) had cyanotic CHDs. Their demographic and cyanotic features are detailed in Table 1.

The mean serum levels of laboratory parameters were compared preoperatively and postoperatively. The mean levels of AST, ALT, ALKP, albumin, total protein, indirect bilirubin, and hematocrit significantly decreased after surgery (P < 0.001). Notably, there was no statistically significant change in the mean serum levels of direct bilirubin or SCr before and after surgery (Table 2).

The cardiac ejection fraction (EF) exhibited a significant increase following surgery (Table 3).

Among the 51 patients studied, 47 (92.2%) survived after surgery, while 4 (7.8%) died. Comparisons revealed that the average postoperative serum transaminase levels (AST and ALT) were higher in patients who died than in those who survived. However, only the mean AST level was significantly elevated in deceased patients compared to survivors (P = 0.042) (Table 4).

Disscusion

In this study, 51 patients were investigated, 78.4% of patients had cyanotic CHDs and 21.6% had non-cyanotic CHDs. The survival rate was 92.2%, while 7.8% of patients unfortunately passed away. Notably, There was a significant correlation between elevated hepatic transaminase levels

Table 1. the Frequency distribution of the patients according to gender, age and cyanotic congenital heart defects

		Frequency (%)	Average age by month (minimum-maximum)
Gender	M	27 (52.9%)	23.66 (2-120)
	F	24 (47.1%)	52.31 (17-144)
Cyanotic CHDs	yes	40 (78.4%)	39.66 (17-144)
	No	11 (21.6%)	28 (4-72)

CHDs: Congenital heart defects

Table 2. Comparison of the average hepatic laboratory factors of the patients before and after surgery
The results of data analysis are reported as mean ± SD, median (Q25-Q75)

	Preoperation	Postoperation	P-value
AST (U/L)	43.18 ± 19.12 39 (31-49)	130 ± 67.60 117 (83-170)	<0.001
ALT (U/L)	25.88 ± 15.73 20 (16-28)	32.78 ± 15.45 30 (21-40)	<0.001
ALKP (U/L)	555.71 ± 230.07 523 (420-625)	311.37 ± 131.73 287 (238-367)	<0.001
Indirect bilirubin (mg/dl)	1.39 ± 0.85 0.5 (0.4-.71)	1.23 ± 1.11 0.9 (0.7-1.2)	<0.001
Direct bilirubin (mg/dl)	0.35 ± 0.28 0.2 (0.1-0.3)	0.28 ± 0.25 0.2 (0.1-0.3)	0.392
Albumin (gr/dl)	4.49 ± 0.56 4.5 (4-5)	4.06 ± 0.48 4 (3.7-4.5)	<0.001
Total protein (gr/dl)	6.30 ± 0.72 6.4 (5.8-6.8)	5.59 ± 0.77 5.60 (4.97-6.03)	<0.001
Hematocrit (%)	36.92 ± 5.96 35.2 (32.9-39)	32.68 ± 6.46 31.3 (29.1-35.5)	<0.001
SCr (mg/dl)	0.53 ± 0.12 0.5 (0.5-0.6)	0.63 ± 0.63 0.5 (0.5-0.6)	0.584

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase
ALKP: Alkaline Phosphatase
SCr: Serum creatinine

Table 3. Comparison of the average ejection fraction of the patients before and after surgery
The results of data analysis are reported as mean ± SD, median (Q25-Q75)

	Preoperation	Postoperation	P-value
Ejection fraction (%)	51.57 ± 6.04 50 (50-55)	57.75 ± 5.13 50 (55-60)	<0.001

Table 4. The comparison of the mortality rate of the patients in terms of serum transaminases after surgery
The results of data analysis are reported as mean ± SD, median (Q25-Q75)

	Died	Survived	P-value
Number of patients	4	47	
ALT (U/L)	36.75 ± 15.24 35.5 (22.75-52)	32.45 ± 15.58 30 (21-39)	0.505
AST (U/L)	220.25 ± 104.94 221.5 (120.75-318.5)	122.40 ± 59.00 117 (76-164)	0.042

ALT: Alanine aminotransferase
AST: Aspartate aminotransferase

in patients who died and those who survived, reinforcing findings from similar studies. There is an evidence that elevated liver function test (LFT) results following cardiac surgery are associated with higher mortality rates.

AST and ALT serve as sensitive indicators for assessing liver damage during both hypothermic and normothermic conditions when using a CPB. In our study, postoperative levels of AST, ALT, and ALKP increased significantly in patients. The changes were significant for AST and ALKP. These alterations in liver enzyme levels influenced by changes in liver blood flow, increasing inflammation in liver tissue, and damage to sinusoidal cells and hepatocytes during CBP[14]. Other factors including increase in duration of CPB (more than 100 minutes), amount of blood transfusion (more than 6 units), hypothermia (less than 32 °C), hypotension and the use of Anesthetic drugs contribute to tissue damage during CBP. These factors can lead to decreased liver blood flow. Mechanistically, elevated calcium concentration in hepatocytes and the development of antigen-antibody immune responses against hepatocytes contribute to these injuries[15].

In a retrospective study, 45% of pediatric patients with hepatopathy and irreversible multiorgan dysfunction passed away. Among these patients, 30% underwent liver transplantation[12]. In our study, postoperative mortality occurred in four patients. We compared the mean levels of serum transaminases (AST and ALT) after surgery in these patients with those in a group of patients who survived. The comparison revealed a significant difference between the two groups, specifically in AST levels. Therefore, an increase in AST levels after surgery may indicate liver damage, which can potentially lead to complications and, in some cases, death.

However, it is important to note that changes in LFTs in pediatric patients with CHD undergoing CPB surgery are not always consistent. These findings suggest that liver function test results may appear normal in some cases, despite abnormalities detected through sonography and/or CT scan imaging[16].

Serum albumin levels serve as an indicator of both liver and kidney dysfunction. In pediatric patients with CHD, hypoalbuminemia may result from factors such as malnutrition or homeostatic disorders[17]. This condition can increase postoperative mortality. Additionally, surgical stress exacerbates hypoalbuminemia. The stress response during surgery affects both the liver and kidneys, leading to decreased albumin production in the liver and increased excretion by the kidneys. The liver, which plays a crucial role in protein synthesis, may prioritize other metabolic processes over albumin production during CPB.

Furthermore, stress can increase the

permeability of the glomerular filtration barrier in the kidneys, resulting in elevated albumin excretion in the urine[18]. During CPB, a blood pump circulates blood through the vessels, potentially causing endothelial injury and resulting in microcapillary leakage of proteins-particularly albumin-into the third space[19].

Hypoalbuminemia increases the risk of bleeding, infections, multiorgan dysfunction, and mortality in postoperative patients. Additionally, the use of hyperoncotic albumin (Albumin 25%) within the first 48 hours after surgery may contribute to AKI[20,21]. In our study, we observed a significant decrease in total serum protein and albumin levels after surgery, and Albumin 5% was prescribed prophylactically to prevent hypoalbuminemia in postoperative patients.

Hemodilution during cardiopulmonary bypass (CPB) surgery is a well-established strategy aimed at minimizing thrombotic events, enhancing oxygen delivery, reducing blood transfusion needs, decreasing hospitalization time, and improving patient outcomes. During hemodilution, the patient's blood is mixed with a volume of fluid (typically a crystalloid or colloid solution) to maintain adequate blood volume. This process dilutes the concentration of red blood cells (RBCs), leading to decreased hematocrit levels. By reducing RBC concentration, the blood becomes less viscous, facilitating smoother flow through the bypass circuit and the patient's tissues. This can help prevent clot formation within the circuit and enhance tissue perfusion. However, excessive hemodilution may have adverse effects, including reduced oxygen-carrying capacity, impaired tissue oxygenation, and increased transfusion requirements. Therefore, maintaining an appropriate balance between hemodilution and adequate oxygen transport is crucial. Monitoring hematocrit levels and adjusting fluid composition during CPB are essential strategies for optimizing patient outcomes[22].

Additionally, CPB triggers a pro-coagulant state, leading to platelet activation, inflammation, thrombin generation, and platelet dysfunction. In pediatric patients with congenital heart disease (CHD), these derangements are more pronounced due to immature coagulation systems, hemodilution, hyperreactive platelets, and cyanosis-associated physiological changes. While heparin administration aims to balance thrombosis risk and bleeding, dosing protocols adapted from adult patients may not be optimal for children. Recent studies emphasize the importance of evidence-based, individualized anticoagulation management during pediatric CPB[23].

Acute kidney injury (AKI) is a common complication following cardiac surgery with CPB. The incidence of AKI related to cardiac surgery with CPB ranges from 9.6% to 40% in children. Serum creatinine (SCr) serves as a sensitive indicator of kidney function, but it typically does not increase until approximately 50% of renal function is lost. The specific pattern of creatinine elevation has significant implications for clinical outcomes, including mortality risk and long-term changes in renal function[24].

In this study, creatinine levels increased in patients after surgery, although this change was not statistically significant. Nonetheless, close monitoring of renal function remains crucial. Identifying and managing AKI promptly can help mitigate potential kidney damage and improve patient outcomes. This may involve implementing strategies such as optimizing preoperative nephrotoxic medication, maintaining hemodynamic stability, ensuring adequate fluid balance, administering diuretics, and considering interventions such as renal replacement therapy if necessary[25].

Ejection fraction (EF) serves as an indicator for evaluating cardiac function, providing valuable insights into the heart's performance both before and after surgical procedures. In our recent study, we observed an improvement in EF following surgery. This increase may result from several factors, including enhanced blood flow, reduced strain on the heart, and improved contractility of the cardiac muscle. Importantly, an elevated EF often indicates improved cardiac function, reflecting the success of the operation[26].

A study demonstrated a significant association between EF improvement and patient outcomes.

For every 5% increase in EF, the risk of death decreases by 20%. Patients with improved EF tend to have better survival outcomes compared to those with worsened or unchanged EF[27].

Conclusion

Hepatopathy and AKI are potential complications in pediatric patients with congenital heart defects undergoing cardiac surgery with a CPB pump. Following CPB, liver enzyme and serum bilirubin levels increased, while albumin and total protein levels significantly decreased. Although serum creatinine levels also increased, the change was not statistically significant. These parameter alterations suggest potential liver damage during CPB.

Therefore, it is crucial to evaluate patients before surgery, implement preventive measures during the procedure, promptly address any damage, and provide postoperative care to monitor recovery. Notably, average AST levels were significantly elevated after surgery in patients who did not survive, indicating a possible predictive factor for postoperative mortality. Further research is necessary to investigate the underlying mechanisms and develop effective interventions for preventing and managing hepatopathy in pediatric patients with congenital heart defects undergoing cardiac surgery.

Limitations

This study had several limitations. First, it was a retrospective study, which may hinder the ability to establish causal relationships. Second, the sample size was small, potentially affecting the generalizability of the findings. Third, being a single-center study, the results may not be universally applicable. Additionally, the absence of Blood Urea Nitrogen (BUN), PT, PTT, GGT, and BS measurements in some patients prevented an accurate assessment of these parameters' impact on evaluating kidney and liver damage caused by cardiac surgery with CPB.

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Conflict of interests

The authors declare no conflict of interest.

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Author's Contributions

Study Conception or Design: FSA, AA
Data Acquisition: SS
Data Analysis or Interpretation: SFRB
Manuscript Drafting: MHS, SS
Critical Manuscript Revision: TC
All authors have approved the final manuscript and are responsible for all aspects of the work.

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