

ALBUMIN-BILIRUBIN SCORE AS A PREDICTOR OF HIGHER VASOACTIVE INOTROPIC SCORE IN PEDIATRIC PATIENTS UNDERGOING VENTRICULAR SEPTAL DEFECT REPAIR: A RETROSPECTIVE STUDY

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ABSTRACT

Introduction: A complex pathophysiological interaction exists between the heart and the liver. Recently, the Albumin Bilirubin (ALBI) Score, originally devised for liver disease has now found a prognostic role in cardiac diseases. Hence, our study aimed to evaluate if the ALBI score can predict high inotropic requirements in pediatric patients undergoing ventricular septal defect (VSD) closure surgery.

Methods: Data from 228 patients who underwent surgical VSD closure was screened retrospectively, out of which 158 patients were analyzed and included in our study by dividing into 2 groups based on the maximum Vasoactive Inotropic Score (VIS) in the first 24 hours postoperatively. Baseline demographic, echocardiographic, laboratory, intraoperative, and postoperative data was collected. The cutoff value of the preoperative ALBI score was calculated.

Results: Out of 158 patients, 49(31.01%) were in the high VIS group. While on univariate regression analysis, serum albumin, bilirubin, Serum Glutamate Oxaloacetic transaminase (SGOT), Serum Glutamic Pyruvate transaminase (SGPT), ALBI score, duration of surgery, Systolic Pulmonary Artery Pressure (sPAP) and Left Ventricle (LV) size were statistically significant, however ALBI score (odds ratio [OR]:11.008, 95% confidence interval (CI):2.998-17.220, $p=0.002$), duration of surgery (OR:1.011, 95% CI:1.002-1.020, $p=0.018$) and sPAP (OR:1.134, 95% CI:1.040-1.236, $p=0.005$) emerged to be statistically significant variables on multivariate regression analysis. The cutoff for ALBI score was -2.51(sensitivity=69.4%, specificity=57.8%).

Conclusion: In pediatric patients undergoing surgical VSD closure, ALBI score can emerge as a risk predictive tool for high postoperative inotropic requirement and be incorporated in preoperative assessment owing to its simplicity, easy availability, and application.

Keywords: Albumin, Bilirubin, Cardiac surgery, Echocardiography, Ventricular septal defect

KEY POINTS

1. ALBI score is a composite score comprising serum albumin and serum bilirubin that was originally utilized as a prognostic indicator in various liver ailments.
2. Recently its role has been extrapolated in various cardiac diseases owing to intricate interactions between the liver and heart.
3. In past studies in adult patients with cardiac disease affecting the dynamics of the right heart, ALBI score has emerged as a predictor of morbidity and mortality.
4. There exists a dearth in the literature of the application of ALBI score in pediatric patients, hence we aimed to evaluate whether it is of any clinical significance in isolated surgical VSD closure.
5. We found in our study that ALBI score may be used as a risk predictive tool for high VIS in pediatric patients undergoing surgical VSD closure.

INTRODUCTION

The surgical closure of ventricular septal defect (VSD) is the most common pediatric cardiac procedure performed all over the world. Surgical intervention is reserved for larger defect sizes, left ventricular volume overload (LVVO), and pulmonary arterial hypertension (PAH) as these eventually lead to congestive heart failure (CHF) with back pressure effects, failure to thrive, irreversible PAH and development of Eisenmenger Syndrome [1]. Hence it becomes imperative to identify various risk factors that may be associated with complications and unfavorable outcomes following surgical VSD closure for prognostication, timely management, and long-term follow-up of the patient [2,3]. This assumes importance in the wake of recent findings highlighting substantial morbidity after VSD closure [4]. Factors such as low weight, syndromic association, prolonged bypass time and high Vasoactive Inotropic Score (VIS) have been found to increase the duration of postoperative mechanical ventilation (DO-MV) and length of Intensive Care Unit (LOS-ICU) stay, but there is a paucity of literature focusing on hematological factors predicting complications after surgical VSD closure. In this context, studies have found elevated serum bilirubin and liver enzyme levels in congenital heart disease (CHD) including VSD. Similarly, serum albumin is a prognosticator in various cardiovascular diseases including CHDs [5,6]. The ALBI score, a composite score that includes serum albumin and bilirubin was originally devised as a prognostic tool for patients with hepatocellular carcinoma and now finds a place in the prognostication of various cardiac diseases [7]. Given the predisposition to PAH in VSD patients, we wished to evaluate if ALBI score can predict higher inotropic requirement i.e. high VIS in children undergoing VSD repair.

METHODS

This retrospective study was conducted at our tertiary care referral center after obtaining approval from our institutional ethics committee (IEC/ABVIMS/RMLH/1504). Data from 158 patients between the ages of 6 months to 2 years who underwent surgical VSD repair between the period of 1st January 2019 to 31st December 2023 was analyzed from the hospital record archive files with a waiver of informed consent requirements.

Patients with complex cardiac anomalies, children with genetic syndromes, history of previous pulmonary artery banding, hepatic dysfunction [Serum Glutamic oxaloacetic transaminase (SGOT) and Serum Glutamic Pyruvic Transaminase (SGPT) greater than twice the baseline], renal dysfunction [Increase in serum creatinine by ≥ 0.3 mg/dl from baseline (≥ 26.5 $\mu\text{mol/L}$) within 48 hours], systemic hypoalbuminemic disorders, anemia with Hb < 10 g/dl, unavailability of preoperative investigations < 48 hours before surgery, child on mechanical ventilation and active infection were excluded from the study.

The baseline demographic data that included gender, age, weight, and body surface area (BSA) along with the history of CHF and previous mechanical ventilation (MV) were noted. Preoperative echocardiographic data like the size of VSD, systolic pulmonary artery pressure (sPAP), left atrium (LA), left ventricle (LV), and right ventricle (RV) dimensions were recorded and preoperative laboratory data comprised of baseline hemoglobin, total and differential leucocyte count, serum total bilirubin, liver enzymes, blood urea, serum creatinine, and serum albumin. The ALBI score was calculated as $(\text{Albumin} \times -0.085) + (\log_{10} \text{bilirubin} \times 0.66)$, where albumin is measured in g/L and bilirubin in $\mu\text{mol/L}$.

Intraoperatively duration of surgery, cross-clamp time, blood and blood product transfusion were recorded, while postoperatively data collected was VIS score, postoperative DO-MV, and LOS-ICU. VIS was calculated as $(\text{dopamine} [\mu\text{g/kg/min}] \times 100 + \text{milrinone} [\mu\text{g/kg/min}] \times 100 + \text{norepinephrine} [\mu\text{g/kg/min}] \times 100 + \text{vasopressin} [\text{units/kg/min}] \times 10000)$. Based on the VIS score empirically taken as 15 as the cutoff, patients were distributed into two groups [8,9]. VIS_{max} which is defined as the maximum VIS score observed on the post operative day one i.e. within 24 hours after surgery was noted.

The surgical procedure was performed following a standard institutional protocol on the conduct of anesthesia and cardiopulmonary bypass (CPB). After standard premedication to allay anxiety and parental separation, the patients were induced with Inj. Fentanyl 10 mcg/kg and Inj. Vecuronium 0.1 mg/kg given intravenously and intubated with appropriate endotracheal tube (ETT) size followed by femoral arterial and right internal jugular central venous line insertion. All patients were mechanically ventilated employing a volume-controlled ventilation mode with a targeted arterial partial pressure of Carbon dioxide within 35-45 mmHg. The CPB circuit was primed with leuco-reduced packed red blood cell, albumin, crystalloid (plasmalyte A), mannitol, sodium bicarbonate and heparin. Heparin (4mg/kg) was given intravenously to attain activated clotting time > 400 seconds. Following aortic and bicaval cannulation, CPB at a pump flow rate of 150-200ml/kg/min was instituted, maintaining hematocrit of 25-28%, moderate hypothermia (rectal temperature 28°-32° C) and perfusion pressure of 30-50 mmHg. Del Nido cold blood cardioplegia given through aortic root. Anesthesia was maintained with i.v. narcotic and muscle relaxant. Arterial blood gas analysis was performed at regular intervals.

VSD was closed with Dacron patch by pledgeted 5-0 prolene suture. Intravenous infusion of appropriate inodilator or/and vasopressors depending on hemodynamics were instituted to facilitate weaning from CPB. Modified Ultrafiltration was performed after completion of CPB. Heparin was reversed with a slow infusion of protamine (1 mg for 100U of heparin) over 10-15 minutes. Patients were shifted to ICU for elective mechanical ventilation, to be extubated once extubation criteria was satisfied.

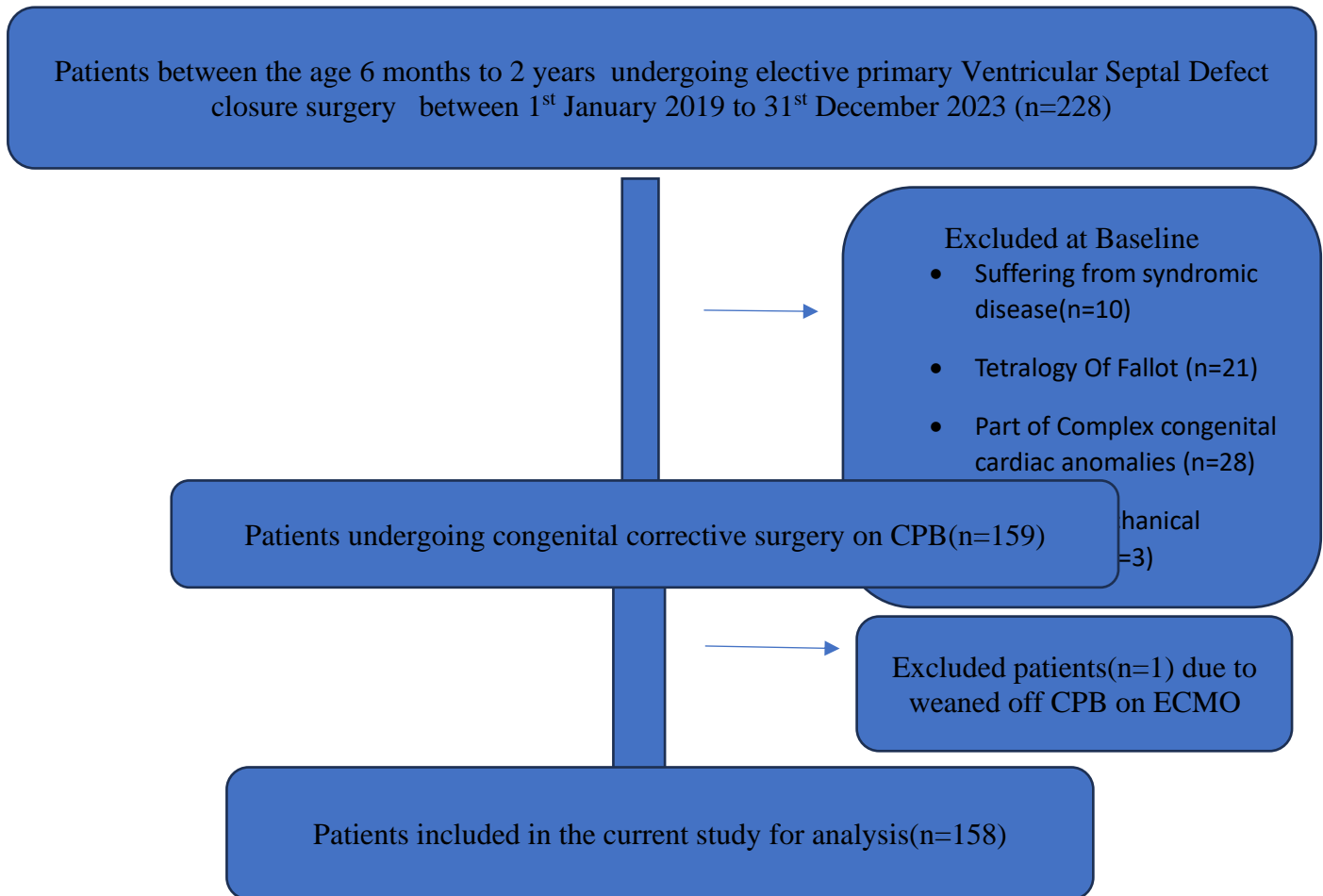


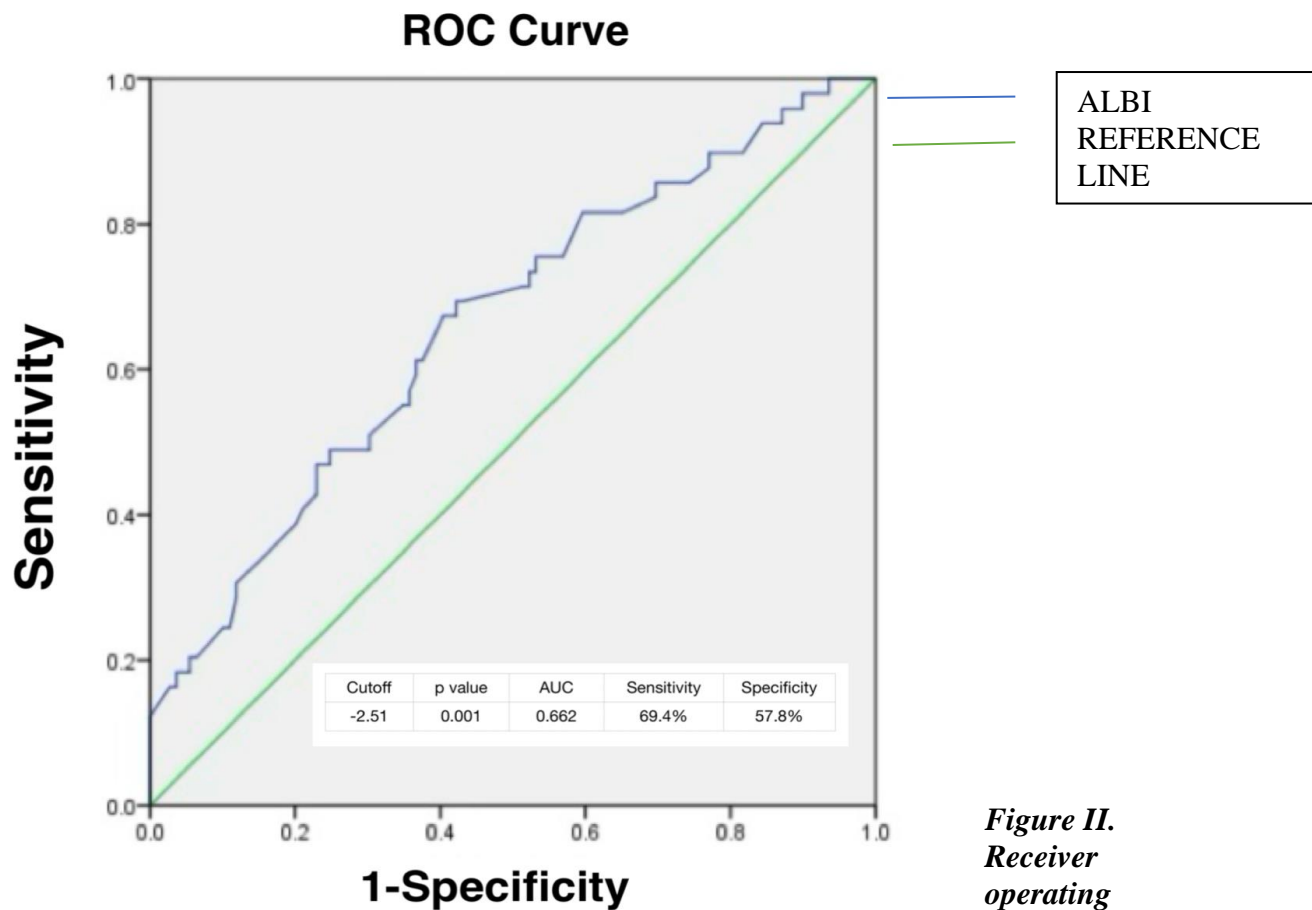
Figure 1. Patients selection flow chart

CPB=Cardiopulmonary bypass

ECMO=Extracorporeal membrane oxygenation

Statistical Analysis

For descriptive statistics dividing the patients into high versus low VIS score, continuous variables are expressed as Mean, Median and Standard Deviation. On applying Shapiro Wilk's test data was not found to be normally distributed and therefore, compared across the groups using the non-parametric Mann-Whitney U test. Categorical variables were expressed as number of patients and percentage of patients and compared across the groups using Pearson's Chi Square test for Independence of Attributes/Fisher's Exact Test as appropriate. Association between continuous variables are captured by Spearman's Rank Correlation Coefficient since the data does not follow normal distribution. Multivariate analysis done using Multivariate Binary Logistic Regression. The statistical software SPSS version 25 has been used for the analysis.



Diagonal segments are produced by ties

characteristic (ROC) analysis of optimal ALBI score alongside the cutoff value, area under the curve (AUC), sensitivity and specificity

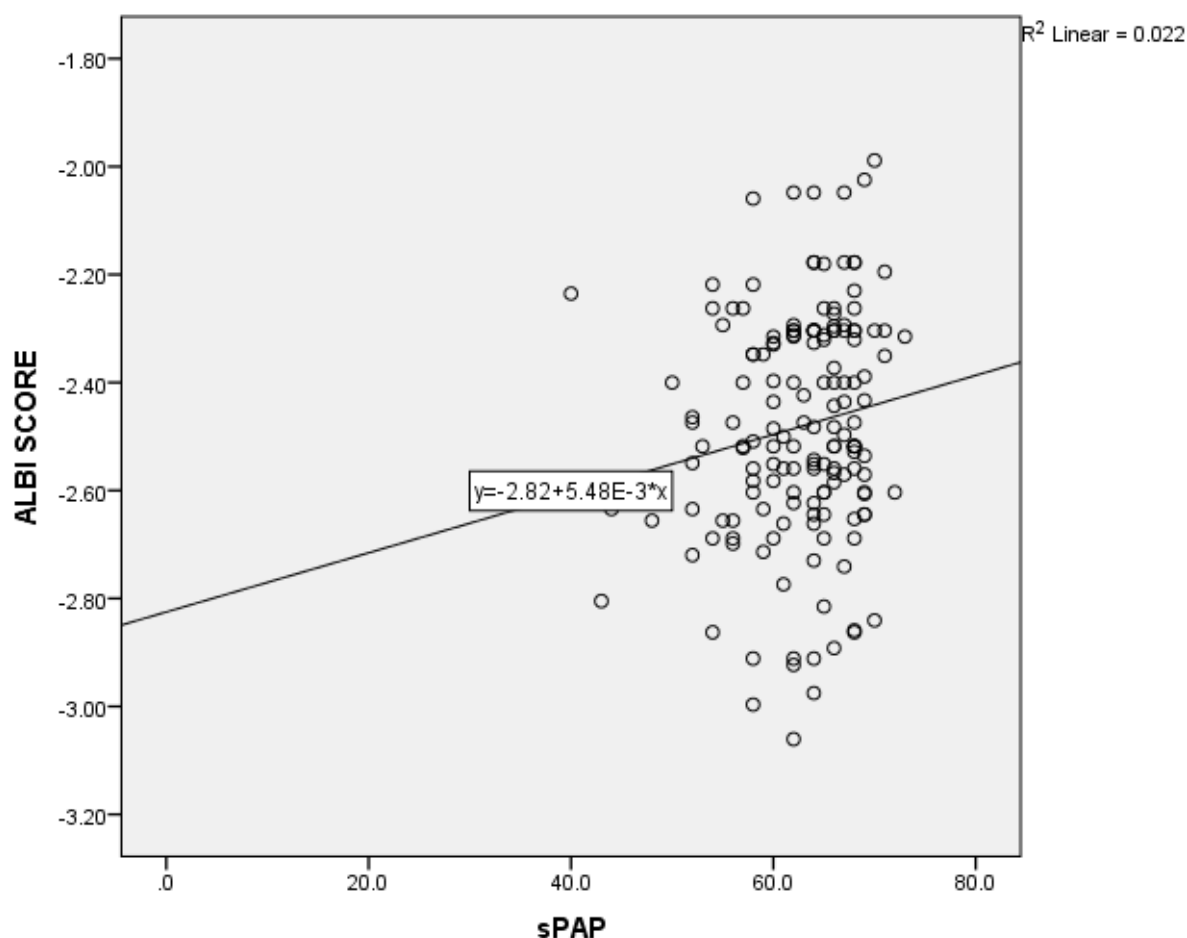


Figure III. Correlation between Albumin-Bilirubin (ALBI) score and Systolic Pulmonary Artery Pressure (sPAP).

Results

A total of 228 patients' data between the age of 6 months to 2 years undergoing primary VSD closure was collected. After applying exclusion criteria, data of 158 patients was ultimately analyzed in our study. The groups were divided based on VIS score (Group 1 had a VIS score ≤ 15 while Group 2 had a VIS score > 15). Group 1 with a VIS score of ≤ 15 consisted of 109 patients while Group 2 with a VIS score > 15 comprised 49 patients. No statistical difference was found between the two groups in the demographic parameters like sex, age, weight and Body Surface Area (BSA) as well as history of MV and CHF as depicted in **Table I**.

On univariate regression analysis, serum albumin, serum bilirubin, ALBI score, serum SGOT, and SGPT, duration of surgery, echocardiographic parameters sPAP, and LV size were statistically significant (**Table I**). However, on subsequent multivariate regression analysis ALBI score (odds ratio [OR]:11.008, 95% confidence interval (CI):2.998-17.220, $p=0.002$), duration of surgery (OR:1.011, 95% CI:1.002-1.020, $p=0.018$) and sPAP (OR:1.134, 95% CI:1.040-1.236, $p=0.005$) emerged to be statistically significant variables predicting a high VIS score following VSD closure surgery (**Table II**). Following a ROC curve analysis, a cutoff value of -2.51 with an area under the curve (AUC) of 0.662 was found for ALBI score with a sensitivity of 69.4% and specificity of 57.8% predicting a high VIS score (> 15) (**Figure II**). Consequently, 57.8% of patients in Group 1

accounted for ALBI score less than the cutoff value of -2.51 while 69.39% of patients in Group 2 displayed an ALBI score more than the cutoff value and this difference was statistically significant($p=0.002$).

It was also found that patients with higher VIS score had prolonged DO-MV (Mean \pm SD=28.67 \pm 5.27) and LOS-ICU (Mean \pm SD=81.88 \pm 15.25) and the DO-MV was statistically significant between the two groups ($p=0.002$).

Spearman's Rank Correlation Coefficient was used to evaluate any correlation between ALBI score and preoperative echocardiographic parameters. Out of all the echocardiographic parameters, only sPAP showed a weak positive correlation ($p=0.058$) (Table II, Figure III)

Table I. Comparison of demographics, preoperative laboratory parameters, intraoperative parameters, preoperative echocardiographic parameters and postoperative parameters between the low and high VIS groups.				
Parameter		VIS\leq15	VIS$>$15	p- value
		N (%) or mean\pmSD/median		
SEX	MALE	63(57.8)	24(48.98)	0.303
	FEMALE	46(42.2)	24(48.98)	
CHF	YES	52(47.7)	30(61.22)	0.115
	NO	57(52.29)	19(38.77)	
MV	YES	28(26.41)	16(32.65)	0.366
	NO	81(74.3)	33(67.34)	
BLOOD TRANSFUSION	YES	82(75.23)	41(83.67)	0.237
	NO	27(24.77)	8(16.33)	
AGE		1.32 \pm 1.44/0.92	0.94 \pm 0.67/0.75	0.056
BSA		0.39 \pm 0.15/0.33	0.35 \pm 0.12/0.33	0.076
WEIGHT		7.65 \pm 4.00/6.20	6.30 \pm 2.36/6.00	0.057
PREOPERATIVE LABORATORY PARAMETERS				
Hb		10.79 \pm 0.60/10.80	10.85 \pm 0.41/10.90	0.226
TLC		10664.95 \pm 700.85/10700.00	10857.14 \pm 486.91/10800.00	0.089
UREA		26.98 \pm 10.78/24.00	28.04 \pm 14.01/24.00	0.871
CREATININE		0.31 \pm 0.12/0.30	0.29 \pm 0.12/0.30	0.486
SGOT		43.65 \pm 8.14/43.00	39.78 \pm 6.42/40.00	0.006*
SGPT		28.22 \pm 6.17/28.00	30.71 \pm 5.85/31.00	0.016*

ALBUMIN	40.93±2.21/41.00	39.8±2.66/39	0.015*
BILIRUBIN	29.56±5.41/30.00	32.9±4.91/35	<0.001*
ALBI SCORE	-2.52±0.2/-2.52	-2.39±0.21/-2.4	0.001*
INTRAOPERATIVE PARAMETERS			
TOTAL BYPASS TIME	109.10±39.79/100.00	113.61±36.20/109.00	0.267
CLAMP TIME	61.23±18.51/61.00	63.53±22.71/63.00	0.787
DURATION OF SURGERY	142.40±45.36/130.00	158.98±36.89/155.00	0.002*
PREOPERATIVE ECHOCARDIOGRAPHIC PARAMETERS			
SIZE OF VSD	8.48±1.54/8.50	8.04±1.84/8.00	0.224
sPAP	61.56±6.20/62.00	65.27±3.75/66.00	<0.001*
LV SIZE	24.72±2.36/24.10	23.75±1.63/24.00	0.022
LA SIZE	21.04±1.89/21.00	20.69±1.54/21.00	0.453
RV SIZE	32.00±2.86/31.50	31.38±3.06/31.38	0.071
POSTOPERATIVE PARAMETERS			
DO-MV	24.67±5.27/26.00	26.17±13.18/22.00	0.002*
LOS-ICU	73.98±18.01/70.00	81.88±15.25/80.00	0.005

*p-value<0.05 is statistically significant.

CHF=Congestive Heart Failure; MV=Mechanical Ventilation; Hb=Hemoglobin; TLC=Total leucocyte count; SGOT=Serum Glutamic Oxaloacetic Transaminase; SGPT=Serum Glutamic Pyruvate Transaminase; ALBI=Albumin-Bilirubin; VSD=Ventricular Septal Defect; Spap =Systolic Pulmonary Artery Pressure; LV=Left Ventricle; LA=Left Atrium; RV=Right Ventricle; DO-MV=Duration of Mechanical Ventilation; LOS-ICU=Length of Stay Intensive Care Unit.

VIS=Vasoactive Inotropic Score ; SD=Standard Deviation.

Table II. Univariate and Multivariate Analysis of Parameters Predicting VIS						
Parameter	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	p value	OR	95% CI	p Value
PATIENT PARAMETERS						
BSA	0.081	0.004-1.608	0.076			
WEIGHT	0.872	0.770-0.989	0.057			
AGE			0.056			

LABORATORY PARAMETERS						
Hb	1.224	0.661-2.265	0.226			
TLC	1.000	1.000-1.001	0.089			
UREA	1.007	0.980-1.036	0.871			
CREATININ E	0.259	0.014-4.684	0.486			
SGOT	0.931	0.886-0.979	0.006*			
SGPT	1.070	1.010-1.132	0.016*			
ALBUMIN	0.813	0.699-0.946	0.015*			
BILIRUBIN	1.134	1.055-1.219	<0.001*			
ALBI SCORE	23.434	3.757- 27.182	0.001*	11.009	12.998- 17.220	0.002*
INTRAOPERATIVE PARAMETERS						
TOTAL BYPASS TIME	1.003	0.994-1.012	0.267			
CLAMP TIME	1.006	0.989-1.023	0.787			
DURATION OF SURGERY	1.009	1.001-1.016	0.002*	1.011	1.002- 1.020	0.018*
PREOPERATIVE ECHOCARDIOGRAPHIC PARAMETERS						
SIZE OF VSD	0.848	0.688-1.045	0.224			
Spap	1.159	1.069-1.257	<0.001*	1.134	1.040- 1.236	0.005*
LV SIZE	0.798	0.670-0.951	0.022			
LA SIZE	0.894	0.736-1.086	0.453			
RV SIZE	0.923	0.811-1.050	0.071			
POSTOPERATIVE PARAMETERS						
DO-MV	0.988	0.957-1.020	0.002*			
LOS-ICU	1.013	0.993-1.034	0.005			

*p-value<0.05 is statistically significant.

OR=Odd's ratio; CI=Confidence Interval; VIS=Vasoactive Inotropic Score.

CHF=Congestive Heart Failure; MV=Mechanical Ventilation; Hb=Hemoglobin; TLC=Total leucocyte count; SGOT=Serum Glutamic Oxaloacetic Transaminase; SGPT=Serum Glutamic Pyruvate Transaminase; ALBI=Albumin-Bilirubin; VSD=Ventricular Septal Defect; sPAP =Systolic Pulmonary Artery Pressure; LV=Left Ventricle; LA=Left Atrium; RV=Right Ventricle; DO-MV=Duration of Mechanical Ventilation; LOS-ICU=Length of Stay Intensive Care Unit.

TableIII. Correlation between ALBI and preoperative echocardiographic parameters.			
Spearman's rho	SIZE OF VSD	Correlation Coefficient	0.044
		p Value	0.581
	sPAP	Correlation Coefficient	0.151
		p Value	0.058
	LV SIZE	Correlation Coefficient	-0.067
		p Value	0.402
	LA SIZE	Correlation Coefficient	0.072
		p Value	0.367
	RV SIZE	Correlation Coefficient	-0.108
		p Value	0.177

*p-value<0.05 is statistically significant.

LA=Left Atrium; LV=Left Ventricle; RV=Right Ventricle; sPAP =Systolic Pulmonary Artery Pressure

VSD=Ventricular Septal Defect

DISCUSSION

There is ample literature to suggest that high VIS predicts adverse outcomes and increased mortality following pediatric cardiac surgery [9,10]. In our study, the incidence of $VIS_{max} > 15$ was 31.01%. ALBI score (AUC 0.662 OR=11.008 CI:2.998-17.220, $p=0.002$), duration of surgery and sPAP emerged as significant predictors of high VIS following VSD closure surgery.

In pediatric cardiac patients, there is still a paucity of easily available risk predictive tools. Recent literature evaluates the prognostic role of Neutrophil-Lymphocyte Ratio (NLR), Platelet-Leucocyte Ratio (PLR) and Red Blood cell Distribution Width (RBDW) in predicting outcomes following pediatric cardiac surgery [11,12,13]. NLR, PLR and RBDW have been evaluated as easily available hematological prognostic factors but there exist gaps considering lack of availability of uniform cut off values and limited evidence of their direct impact on poor outcomes in the pediatric age group.

Considering the involvement of liver in CHD due to hemodynamic derangements, either due to backward failure caused by venous congestion, from forward failure of the systemic ventricle, or hypoxemia in CHD, we sought to examine if ALBI score can be used a prognosticator in pediatric cardiac surgery thereby adding an incremental value to the formal indices [14]. Liver function tests may be affected in CHD patients with mild hyperbilirubinemia and hypoalbuminemia serving as a marker of congestive liver structural and functional abnormality [15]. While serum bilirubin and serum albumin may be a predictor of increased morbidity and mortality following cardiac surgery, the recently devised ALBI Score that combines the former two may be a more advantageous, easily measurable, and cost-effective tool in predicting outcomes after cardiac surgery. It has increasingly been found to detect insignificant liver dysfunction over the Child-Pugh and the Model for End Stage Liver Disease (MELD) Scores [7]. Its use has been extrapolated as a prognostic factor in cardiac diseases [13]. In the study by Evlice et al, ALBI score emerged to be a potential indicator of increased liver congestion in adult patients with isolated ostium secundum atrial septal defect [18]. However, its utilization in pediatric patients with CHD remains unexplored.

Han et al. found an increase in in-hospital mortality among patients with HF by 8.2% for every 0.1-point increase in ALBI score (OR 1.082; 95% CI 1.052 to 1.114; $p<0.001$), and even enhancing the predictive potential of NT-pro-BNP [17]. ALBI score's cutoff value was -2.32 (specificity=0.630, sensitivity=0.632) in their study which is commensurate with the cut-off value found in our study (-2.51 ; sensitivity=69.4%, specificity=57.8%). Similarly in acute heart failure, ALBI score (OR 2.11, 95% CI: 1.60-2.79, $p<0.001$) is considered to be a suitable marker of fluid overload and prognosis [6]. This assumes importance in children with VSD who are also predisposed to CHF due to venous congestion.

Evlice et al. also showed a significant correlation between the preoperative echocardiographic parameters and the ALBI score (sPAP $r=0.803$, $p<0.001$) [17]. Similarly, Duman et al. demonstrated that ALBI score was a strong variable in predicting hospital mortality ($p<0.001$), and AKI ($p=0.28$) following valvular surgery in adults. They also demonstrated a positive correlation ($r: 0.245$, $P=0.004$) between ALBI score and pulmonary artery pressure [19]. The authors attributed the latter to right heart failure and liver congestion. In our study, though both sPAP and ALBI score significantly predicted high VIS score independently, with a cutoff value of ALBI closer to that found in the Duman et al. study (-2.44 vs -2.51), sPAP and ALBI score are only weakly positively correlated with each other (Spearman's correlation coefficient (r): 0.151, $P=0.058$). This finding emphasizes that ALBI score can independently predict adverse outcome i.e. high VIS, irrespective of high pulmonary artery pressures. However, this further needs to be evaluated in the light of dearth of literature on hepatic dysfunction secondary to VSD.

To the best of our knowledge, this is one of the initial studies exploring the risk predictive potential of the ALBI score in pediatric population undergoing cardiac surgery. ALBI score in itself demonstrates residual liver function

reserve but there are no recommendations for using ALBI score in preoperative assessment of patients with CHD. However, the accruing literature suggests ALBI may be a simple, inexpensive and easily available biochemical parameter that may have prognostic importance in CHD especially VSD considering the intricacies of heart and liver interaction.

LIMITATIONS

This study's limitations include its retrospective design and observational nature which affected by systematic errors. Additionally, being a single-center study only a small number of patients were available for study which restricted the power of our analysis. A comprehensive right heart echocardiographic evaluation could not be obtained due to retrospective nature of the study. Our findings were restricted to the perioperative period and we did not examine long term morbidity and mortality. What we need are more prospective studies conducted in multiple centers with better power to elucidate the risk prediction prowess of ALBI score in the pediatric population since establishing a direct causal relationship is beyond the scope of this study.

FUTURE DIRECTIONS

Considering the simplicity, non-invasive nature and feasibility, ALBI score may be utilized as a prognostic parameter in congenital heart disease owing to its representation of both backward as well as forward failure. However, further research may be undertaken establishing its correlation with other hematological factors as well as studying the impact of post operative ALBI score on outcomes in pediatric cardiac surgery.

CONCLUSION

Our study demonstrates the use of the ALBI score as a risk predictive tool in patients undergoing cardiac surgery in the pediatric subgroup.

According to our analysis, ALBI score may be an important preoperative risk assessment tool in pediatric patients undergoing surgical VSD closure. This score may have an incremental value to other predictors of poor outcomes following pediatric cardiac surgeries.

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