Cardiology in the Young

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Original Article

Cite this article: Henry BM, Borasino S, Ortmann L, Figueroa M, Rahman AKMF, Hock KM, Briceno-Medina M, and Alten JA (2019) Perioperative serum albumin and its influence on clinical outcomes in neonates and infants undergoing cardiac surgery with cardiopulmonary bypass: a multi-centre retrospective study. *Cardiology in the Young* **29**: 761–767. doi: 10.1017/S1047951119000738

Received: 24 August 2018
Revised: 1 March 2019
Accepted: 2 March 2019
First published online: 4 June 2019

Key words:
Human serum albumin; hypoalbuminemia; cardiac surgery; post-operative outcomes

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Perioperative serum albumin and its influence on clinical outcomes in neonates and infants undergoing cardiac surgery with cardiopulmonary bypass: a multi-centre retrospective study

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Abstract

Hypoalbuminemia is associated with morbidity and mortality in critically ill children. In this multi-centre retrospective study, we aimed to determine normative values of serum albumin in neonates and infants with congenital heart disease, evaluate perioperative changes in albumin levels, and determine if low serum albumin influences post-operative outcomes. Consecutive eligible neonates and infants who underwent cardiac surgery with cardiopulmonary bypass at one of three medical centres, January 2012–August 2013, were included. Data on serum albumin levels from five data points (pre-operative, 0–24, 24–48, 48–72, 72 hours post-operative) were collected. Median pre-operative serum albumin level was 2.5 g/dl (IQR, 2.1–2.8) in neonates versus 4 g/dl (IQR, 3.5–4.4) in infants. Hypoalbuminemia was defined as <25th percentile of these values. A total of 203 patients (126 neonates, 77 infants) were included in the study. Post-operative hypoalbuminemia developed in 12% of neonates and 20% of infants; 97% occurred in the first 48 hours. In multivariable analysis, perioperative hypoalbuminemia was not independently associated with any post-operative morbidity. However, when analysed as a continuous variable, lower serum albumin levels were associated with increased post-operative morbidity. Pre-operative low serum albumin level was independently associated with increased odds of post-operative hypoalbuminemia (OR, 3.67; 95% CI, 1.01–13.29) and prolonged length of hospital stay (RR, 1.40; 95% CI, 1.08–1.82). Lower 0–24-hour post-operative serum albumin level was independently associated with an increased duration of mechanical ventilation (RR, 1.35; 95% CI, 1.12–1.64). Future studies should further assess hypoalbuminemia in this population, with emphasis on evaluating clinically meaningful cut-offs and possibly the use of serum albumin levels in perioperative risk stratification models.

Hypoalbuminemia is associated with morbidity and mortality across many critically ill cohorts.[1] In adult cardiac surgical patients, both pre-operative and post-operative hypoalbuminemia have consistently been associated with organ dysfunction, increased ICU resource utilisation, and increased mortality.[2] In paediatric ICU patients, admission albumin level was independently associated with a longer duration of mechanical ventilation, increased length of hospital stay, and higher mortality.[3,4] Few studies have evaluated the impact of hypoalbuminemia in children with cardiac disease.[5–7] In a mixed cohort of adult and paediatric cardiac surgical patients, albumin level decreased after cardiopulmonary bypass and was associated with post-operative morbidity and mortality.[6] Leite et al.[7] demonstrated in 30 paediatric cardiac surgical patients that pre- and post-operative albumin <3 g/dl has a univariate association with mortality, post-surgical infection, and longer length of hospital stay. To date, no studies have evaluated serum albumin level as an independent predictor of morbidity after paediatric cardiac surgery.

This multi-centre study was designed with the following aims: (1) to determine the baseline range of serum albumin levels in neonates and infants with CHD, (2) to determine the impact of cardiac surgery with cardiopulmonary bypass on post-operative serum albumin levels, and (3) to evaluate the association of serum albumin levels with post-operative outcomes.

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We hypothesised that post-operative hypoalbuminemia is common in this population and would be associated with increased morbidity.

Materials and methods

A multi-centre retrospective collaborative study was performed with data collected from three paediatric cardiac centres: Children's Hospital of Alabama, Children's Mercy Hospital, and Le Bonheur Children's Hospital. The study was performed in compliance with U.S. Good Clinical Practice Guidelines and the 2008 revised version of the Helsinki Declaration of 1975. All three centres' institutional review boards approved this study and waived the need for informed consent. All consecutive patients <1 year of age who underwent cardiac surgery with cardiopulmonary bypass for a CHD between January 2012 and August 2013 with at least one post-operative albumin level measured were included in this study. Patients placed on extracorporeal membrane oxygenation in the operating room were excluded from the analysis. Data were collected from patient medical records in which an albumin level was drawn for clinical indication, or per local clinical guidelines, at up to five perioperative time-points: pre-operative, 0–24, 24–48, 48–72, and 72 hours.

Perioperative albumin and steroid administration

At all centres, 100 ml of 25% albumin was added to the prime of the cardiopulmonary bypass circuit. All patients at centres 1 and 2 received modified ultrafiltration at the end of cardiopulmonary bypass; centre 3 did not utilise modified ultrafiltration. At all centres, 5% albumin was routinely given to augment preload and cardiac output in the post-operative period. Low albumin levels were not routinely augmented with 25% albumin in the study time period at any site. All neonates included in the study received perioperative steroids, while all infants did not.

Clinical variables

The following pre- and post-operative variables were collected: gender, age (neonate <30 days, infant ≥30 days), race, genetic syndrome and/or significant congenital anomaly other than heart defect, pre-operative mechanical ventilation, pre-operative need for inotropes (catecholamines and milrinone), the Society of Thoracic Surgeons–European Association for Cardio–Thoracic Surgery mortality category,[8] cardiopulmonary bypass time, aortic cross-clamp time, operating room fluid balance, prophylactic peritoneal dialysis, and delayed sternal closure.

Outcomes

The primary goal was to report the normative levels of pre- and post-operative serum albumin and the prevalence of pre- and post-operative hypoalbuminemia. The thresholds for hypoalbuminemia in neonates and infants is <2.5 g/dl, while the thresholds for clinically important hypoalbuminemia in critically ill children are not well defined, with authors using cut-offs such as 3.3,[9] 3,[4–5] and 2.5 g/dl.[10] Hypoalbuminemia was defined as <25th percentile of the pre-operative albumin value stratified for neonates and infants. The following post-operative outcomes were considered: post-operative albumin level and prevalence of hypoalbuminemia, length of mechanical ventilation in hours and prolonged mechanical ventilation (defined as mechanical ventilation >75th percentile), length of hospital stay and prolonged hospital stay (defined as >75th percentile), infection (positive culture from blood, urine, or wound), peak creatinine, net fluid balance at 24 hours and between 24 and 48 hours, lowest total protein, chylothorax, presence of catecholamine at 24 hours, post-operative steroids administration, and duration of chest tube drainage in hours.

Statistical analysis

Descriptive statistics (means, standard deviations, medians, interquartile ranges, and frequency distributions, all percentages) were used to summarise exposure and outcome variables. The chi-square, Fisher exact, Mann–Whitney U, Student's t, or Kruskal–Wallis tests were performed, as appropriate, for the analyses of initial univariate primary and secondary outcomes. The generalised linear mixed models with logit link were employed to assess the risk factors associated with the duration of mechanical ventilation, prolonged mechanical ventilation, length of hospital stay, and prolonged length of hospital stay. To increase the likelihood that hypoalbuminemia occurred before the outcomes of interest, analyses of the association of post-operative hypoalbuminemia with outcomes were performed utilising the 0–24-hour albumin level.

To account for the correlations between study subjects due to the clustering nature of patients within hospitals, a generalised linear mixed models method was applied. To quantify the effects of risk factors, odds ratio and relative risks with their 95% confidence intervals were estimated. Prior to any multivariate analyses, a stepwise initial variable selection was performed. Only variables with a p-value ≤0.15 were included in the multivariate models. The limited sample size of infants precluded multivariate analyses for some outcomes. All hypothesis tests were two-tailed with a p-value <0.05 indicating statistical significance. All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA). No imputation was utilised to replace missing values. The multivariate analyses of the potential outcomes with covariates involving pre-operative albumin (n = 114), post-operative albumin within 0–24 hours (n = 195), and post-operative hypoalbuminemia (n = 200) were based on available data.

Results

Patients

A total of 203 patients across the three cardiac centres met the inclusion criteria. Among the cohort, 126 (62%) were neonates. Patient characteristics are summarised in Table 1. A summary of aggregate outcomes of interest, stratified by age, are presented in Supplementary Table 1. Not all included patients had a complete set of albumin-level data. The following sample sizes were available for each time-point of albumin-level data collection : pre-operative, n = 114; 0–24 hours post-operative, n = 195; 24–48 hours, n = 172; 48–72 hours, n = 167; >72 hours, n = 34.

Serum albumin level

The median serum albumin levels at four perioperative time-points are presented in Figure 1. The neonatal cohort had significantly lower albumin at all time-points. The median pre-operative albumin level was 2.5 g/dl (IQR, 2.1–2.8) in neonates versus 4 g/dl (IQR, 3.5–4.4) in infants. The median albumin levels in neonates were significantly higher post-operatively than pre-operatively at 0–24, 24–48, and 48–72 hours (p ≤ 0.001), while in infants they were significantly higher only at 0–24-hour time-point (p = 0.04) (Fig 2).

https://doi.org/10.1017/S1047951119000738 Published online by Cambridge University Press

Table 1. Comparison of patient characteristics with and without hypoalbuminemia within the first 72 hours after surgery

Characteristics	All patients (n = 200)*	Post-operative HA: yes (n = 31)	Post-operative HA: no (n = 169)	p-Value
Male, n (%)	120 (60)	16 (52)	104 (62)	0.30
Age group at surgery, n (%)				0.09
Neonate	124 (62)	15 (48)	109 (65)	
Infant	76 (38)	16 (52)	60 (36)	
Race, n (%)				0.04
Black	45 (23)	11 (36)	34 (20)	
White	136 (68)	15 (48)	121 (72)	
Other	19 (10)	5 (16)	14 (8)	
Genetic syndrome/congenital anomaly, n (%)	57 (29)	11 (36)	46 (27)	0.39
Pre-operative mechanical ventilation, n (%)	58 (29)	10 (32)	48 (28)	0.66
Pre-operative inotropes, n (%)	17 (9)	6 (19)	11 (7)	0.02
Pre-operative hypoalbuminemia, n (%)	24/113 (21)	8/20 (40)	16/93 (17)	0.02
STAT category, n (%)				0.84
STAT 1, 2, 3	91 (46)	15 (48)	76 (45)	
STAT 4, 5	108 (54)	16 (52)	92 (55)	
CPB time, minutes	115 (77–146)	127 (82–150)	113 (75–144)	0.31
ACC time, minutes	55 (37–69)	58 (45–71)	54 (36–69)	0.33
OR fluid balance, ml/kg	37 (0–127)	0 (0–123)	39 (0–126)	0.47
Peritoneal dialysis, n (%)	62 (31)	12 (39)	50 (30)	0.31
Delayed sternal closure (yes), n (%)	79 (40)	12 (39)	67 (40)	0.92

ACC = aortic cross-clamp; CPB = cardiopulmonary bypass; HA = hypoalbuminemia; OR = operating room; STAT = the Society of Thoracic Surgeons–European Association for Cardio–Thoracic Surgery Score.
Data presented are median with interquartile range. p-Values compares patients with versus without hypoalbuminemia.
*Three subjects had no post-operative albumin within 72 hours and were excluded from this table.

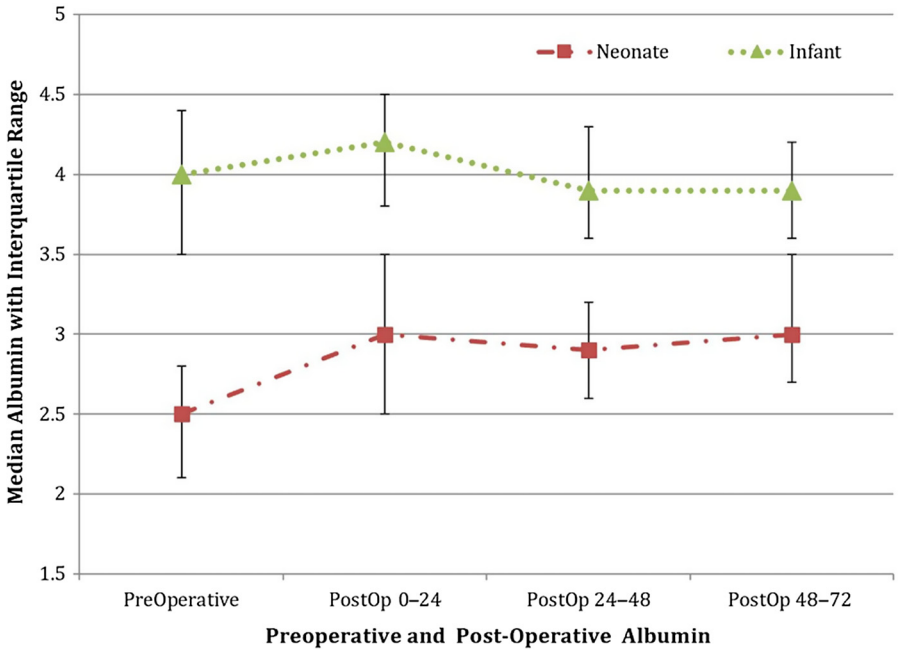

Figure 1. Pre-operative and post-operative serum albumin levels.

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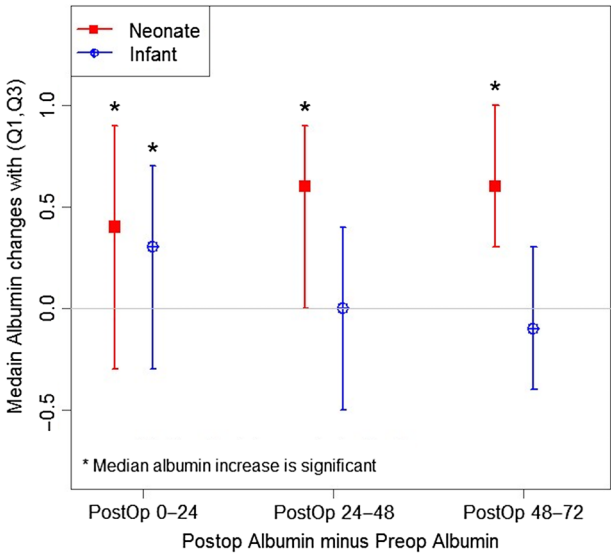

Figure 2. Changes in serum albumin between pre-operative and post-operative time-points.
*When Bonferroni correction was applied to control the type 1 error for multiple comparison of post-operative versus pre-operative albumin for neonates, median albumin levels were still significantly higher post-operatively than pre-operatively with a critical p-value .05/3 = 0.0167.

There were no differences in albumin levels or patterns at any time-point among the three cardiac centres except for post-operative 0–24 hours in neonates; centre 3 had lower 0–24-hour albumin levels compared with pre-operative, while the other two centres had higher albumin levels at this time-point compared with pre-operative.

Based on the a priori criteria (<25th percentile of the aggregate pre-operative albumin value), hypoalbuminemia was defined as a serum albumin <2.1 g/dl for neonates and <3.5 g/dl for infants. Accordingly, 15 (12%) neonates and 16 (20%) infants developed post-operative hypoalbuminemia. Most, 30/31 (97%), developed hypoalbuminemia in the first 48 post-operative hours.

Risk factors for post-operative hypoalbuminemia

Table 1 presents the univariate associations of patient characteristics and perioperative variables with the presence of hypoalbuminemia in the first 72 post-operative hours. Post-operative peritoneal dialysis was not associated with hypoalbuminemia. Patients with pre-operative hypoalbuminemia had over twice the rate of post-operative hypoalbuminemia compared with those without pre-operative hypoalbuminemia. After multivariate analysis, including the demographic and exposure variables in Table 1, pre-operative hypoalbuminemia remained independently associated with the presence of post-operative hypoalbuminemia (OR, 3.67; 95% CI, 1.01–13.29; p = 0.05). Of the 24 subjects who had pre-operative hypoalbuminemia, 16 had normal albumin levels post-operatively, while 8 persisted with hypoalbuminemia. However, there were no statistically significant differences in outcomes between those that persisted with hypoalbuminemia and those that did not (data not shown).

Pre-operative albumin level and outcomes

Age-stratified outcomes in patients with/without pre-operative hypoalbuminemia are shown in Table 2. Pre-operative hypoalbuminemia was associated with the length of hospital stay in both neonates and infants. In neonates only, pre-operative hypoalbuminemia was also associated with the duration of post-operative mechanical ventilation. After multivariate analysis, no outcome variable in Table 2 was independently associated with pre-operative hypoalbuminemia.

When considering albumin as a continuous variable, a lower pre-operative albumin level was associated with multiple worse outcomes in univariate analysis (Supplementary Table 2). Among these outcomes, only hospital length of stay was independently associated with a lower pre-operative albumin level (RR, 1.40; 95% CI, 1.08–1.82; p = 0.01) in multivariate analysis controlling for the risk factor variables in Table 1.

Post-operative albumin level and outcomes

Overall and age-stratified outcomes in patients with/without post-operative hypoalbuminemia are depicted in Table 3. Hypoalbuminemia was associated with prolonged mechanical ventilation in both age cohorts. In neonates, hypoalbuminemia was additionally associated with longer durations of post-operative length of hospital stay and post-operative mechanical ventilation. After multivariate analysis, post-operative hypoalbuminemia in both age cohorts was not independently associated with any of the clinical outcomes depicted in Table 3.

Neonates with prolonged hospital length of stay had a significantly lower 0–24-hour post-operative albumin level than the rest of the neonatal cohort: 2.8 g/dl (95% CI, 2.2–3.4) versus 3.2 g/dl (95% CI, 2.6–3.5), p = 0.04. In infants with prolonged mechanical ventilation, the 0–24-hour post-operative albumin level was lower than all other infants: 3.8 g/dl (95% CI, 3.5–4.3) versus 4.2 g/dl (95% CI, 3.9–4.6), p < 0.01. The mean albumin level was significantly lower in patients who received any post-operative 5% albumin administration from 0–24 hours, 3.3 versus 3.6 g/dl, p = 0.03. The albumin levels were not significantly different between any of the dichotomous outcomes in Table 3 (data not shown).

When considered as a continuous variable, in univariate analysis, a lower 0–24-hour post-operative albumin level was associated with worse outcomes for almost all variables evaluated (Supplementary Table 2). After multivariate analysis, including patient characteristics from Table 1, a lower 0–24-hour post-operative albumin remained independently associated with an increased duration of mechanical ventilation (RR, 1.35; 95% CI, 1.12–1.64; p < 0.01) (Table 4). This association persisted when multivariate analysis was performed in the neonate cohort only (data not shown). Increased duration of chest tube drainage in neonates was the only other outcome from Supplementary Table 2 associated with lower albumin level in multivariate analyses (data not shown).

Discussion

In this retrospective multi-centre cohort, we established normative pre-operative serum albumin levels for neonates and infants undergoing congenital heart surgery with cardiopulmonary bypass across three cardiac surgery centres. Median pre-operative albumin level was 2.5 g/dl (IQR, 2.1–2.8) in neonates and 4 g/dl (IQR, 3.5–4.4) in infants. Neonatal value was lower than what has been reported for healthy term neonates, 3.0 g/dl.[11] Albumin level rose significantly from pre-operative level in the first 24 hours; the aggregate infant albumin level remained relatively stable during the post-operative period, while the albumin level in neonates

https://doi.org/10.1017/S1047951119000738 Published online by Cambridge University Press

Table 2. Pre-operative hypoalbuminemia and age-stratified post-operative outcomes

	Neonates (n = 62)			Infants (n = 52)		
Outcomes	HA: yes(n = 12)	HA: no(n = 50)	p-Value	HA: yes (n = 12)	HA: no (n = 40)	p-Value
MV, hours	144 (93–200)	78 (48–140)	0.05	9 (7–25)	10 (7–21)	0.96
HLOS, days	44 (24–76)	26 (14–40)	0.04	15 (12–38)	8 (5–19)	0.03
Prolonged MV,* n (%)	5 (42)	9 (18)	0.11	4 (33)	8 (20)	0.43
Prolonged HLOS,** n (%)	4 (33)	11 (22)	0.46	5 (42)	11 (28)	0.35
Infection, n (%)	3 (25)	10 (20)	0.70	1 (8)	1 (3)	0.41
Mortality, n (%)	1 (8)	5 (10)	0.99	0 (0)	0 (0)	1.00
Peak creatinine, mg/dl,	0.8 ± 0.3	0.8 ± 0.3	0.66	0.5 ± 0.1	0.4 ± 0.2	0.78
Net fluid balance, 0–24 hours, ml/kg	28 ± 56	94 ± 644	0.45	−3 ± 58	21 ± 42	0.21
Lowest total protein, g/dl	4.3 ± 0.8	4.7 ± 0.8	0.16	6.1 ± 0.8	6.1 ± 0.7	0.86
Chylothorax, n (%)	3 (25)	9 (18)	0.69	1 (8)	2 (5)	0.55
Catecholamines, 24 hours, n (%)	10 (83)	36 (72)	0.71	1 (8)	2 (5)	0.55
Stress dose steroids, n (%)	8 (67)	14 (28)	0.02	1 (8)	4 (10)	0.99
Duration of chest tube drainage, hours	103 (80–164)	68 (48–147)	0.34	42 (38–54)	42 (33–61)	0.97

HA = hypoalbuminemia; HLOS = hospital length of stay; MV = mechanical ventilation.
Data presented as median with interquartile range or mean ± standard deviation.
*Neonate >184 hours, infant >22 hours.
**Neonate >46 days, infant >17 days.

Table 3. Association of post-operative hypoalbuminemia with age-stratified outcomes

	Neonates (n = 124)			Infants (n = 76)		
Outcomes	HA: yes (n = 15)	HA: no (n = 109)	p-Value	HA: yes (n = 16)	HA: no (n = 60)	p-Value
MV, hours	120 (95–264)	83 (48–163)	0.01	13 (5–54)	9 (7–19)	0.56
HLOS, days	42 (25–93)	27 (18–41)	0.03	12 (6–50)	7 (6–15)	0.24
Prolonged MV,* n (%)	7 (47)	23 (22)	0.04	7 (44)	10 (17)	0.02
Prolonged HLOS, n (%)**	6 (40)	24 (22)	0.12	6 (38)	12 (20)	0.14
Infection, n (%)	2 (13)	16 (15)	0.99	1(6)	1 (w)	0.38
Mortality, n (%)	1 (7)	10 (9)	0.99	1(6.)	0 (0)	0.21
Peak serum creatinine, 0–72 hours (ml/kg)	0.70 – 0.17	0.80 – 0.31	0.09	0.45 – 0.17	0.44 – 0.17	0.81
Net fluid balance, 0–24 hours (ml/kg)	54 – 40	59 – 438	0.89	-6 – 60	20 – 38	0.11
Lowest total protein, g/dl	4.1 – 0.5	4.6 – 0.8	0.02	5.5 – 0.7	6.2 – 0.7	<0.01
Chylothorax, n (%)	5 (33)	17 (16)	0.09	1 (6)	4 (7)	0.99
Catecholamines at 24 hours, n (%)	15 (100)	81 (74)	0.02	3 (19)	1 (2)	0.03
Stress dose steroids, n (%)	6 (40)	21 (19)	0.07	2 (13)	9 (15)	0.99
Duration of chest tube drainage, hours	112 (96–288)	94 (59–192)	0.16	48 (38–88)	42 (37–63)	0.23

HA = hypoalbuminemia; HLOS = hospital length of stay; MV = mechanical ventilation.
Data presented as median with interquartile range.
*Neonate >184 hours, infant >22 hours.
**Neonate >46 days, infant >17 days.

appeared to rise for the first 72 hours post-operatively. It is important for cardiac ICU clinicians to understand "normal" age-specific pre-operative serum albumin levels in children with critical CHD, such that outliers who are potentially at risk for increased morbidity can be identified. When defined as <25th percentile of age-specific baseline (pre-operative) albumin level, post-operative hypoalbuminemia was present in 12% of neonates and 20% of infants. When utilising these cut-offs, neither pre-operative nor early post-operative hypoalbuminemia was independently associated with any important post-operative outcome. However, as a continuous variable, a lower early post-operative albumin level was observed to be a marker of increased severity of illness and had an independent association with worse outcomes.

The aetiology of hypoalbuminemia in critically ill patients is multifactorial, developing likely through a combination of decreased synthesis, increased degradation, dilutional effects of resuscitation

https://doi.org/10.1017/S1047951119000738 Published online by Cambridge University Press

Table 4. Multivariate analysis of variables associated with the duration of mechanical ventilation

Duration of mechanical ventilation	RR (95% CI)	p-Value
0–24-hour post-operative albumin level*	1.35 (1.12–1.64)	<0.01
Post-operative infection	2.27 (1.44–3.56)	<0.01
Neonatal age	1.57 (1.05–2.35)	0.03
Catecholamines at 24 hours	2.14 (1.43–3.19)	<0.01
Delayed sternal closure	2.24 (1.61–3.12)	<0.01

CI = confidence interval; RR = relative risk.
*Per one unit decrease in serum albumin from mean albumin of 3.46 g/dl.

fluids, or loss into the interstitial tissues as a result of capillary leak syndrome and inflammation.[1,12] Albumin functions as the main constituent of intravascular oncotic pressure, which may be of extra significance during cardiopulmonary bypass -induced hemodilution.[13] The primary symptoms of hypoalbuminemia are related to tissue/organ oedema and resultant organ dysfunction, in addition to acid–base dysregulation due to a loss of plasma buffer.[9,12,14] Albumin also serves a variety of other important microcirculatory roles, including a reservoir for nitric oxide, free radical scavenger, anti-inflammatory and anti-apoptotic properties, platelet aggregation inhibition, and preservation of erythrocyte morphology during cardiopulmonary bypass.[15–17] Thus hypoalbuminemia may also contribute to microcirculatory dysfunction and tissue injury associated with cardiopulmonary bypass.

In this study, when serum albumin was analysed as a continuous variable, lower pre-operative albumin levels were independently associated with prolonged post-operative length of hospital stay. Pre-operative and admission hypoalbuminemia have been associated with increased morbidity and ICU resource utilisation for adult cardiac surgical and paediatric ICU patients.[3,13] In pre-operative infants, lower albumin is likely most often a consequence of protein malnutrition, plus/minus heart failure. Malnutrition at the time of surgery is associated with worse post-operative outcomes in patients with CHD.[18] For infants with pre-operative hypoalbuminemia, treatment and/or prevention of the underlying protein malnutrition or heart failure, as opposed to albumin supplementation, is likely to have a bigger impact on improving post-operative outcomes.

Like the few other studies in the literature that evaluated the association of serum albumin levels on the outcomes in this population,[6,7] we found that post-operative hypoalbuminemia had a univariate association with morbidity. However, in this multi-centre cohort of predominantly neonates, there was no independent association between post-operative hypoalbuminemia and morbidity, despite the larger sample size. Perhaps our a priori definition of hypoalbuminemia does not depict a clinically meaningful threshold for hypoalbuminemia-related morbidity. However, we also explored the 3.3,[9] 3,[4–5] and 2.5 g/dl [10] thresholds as suggested by other investigators with, again, no differences in findings from multivariate analyses (data not shown). In fact, in our neonatal cohort, half of all albumin levels fell below the traditional cut-off levels for hypoalbuminemia (<2.5 g/dl).[19] Nonetheless, when analysed as a continuous variable, a lower albumin level in the first 24 hours did have an independent association with increased duration of post-operative mechanical ventilation. We believe these findings reflect the overall condition of the patient, with more acutely ill patients suffering worse systemic inflammatory response, fluid overload (and serum albumin dilution), and increased serum albumin translocation into the interstitial space.

Variation in perioperative fluid management will impact post-operative albumin levels. Increased patient fluid removal via modified ultrafiltration, peritoneal dialysis, or aggressive diuresis will hemo-concentrate the patient and increase the albumin level, while increasing levels of fluid overload will lower serum albumin concentration. In these clinical situations in which the total body albumin content does not change, it is likely that outcome differences, if any, are driven by the impact of fluid balance on the physiology of the patient – as opposed to the direct impact of the albumin level. Fluid overload has previously been associated with an increased duration of mechanical ventilation after paediatric cardiac surgery.[20] In this study, one centre did not perform modified ultrafiltration. The median immediate post-operative albumin levels at this centre were significantly lower than in the other two centres, despite similar pre-operative and ICU discharge albumin levels, highlighting that transient hypoalbuminemia may develop as a result of differential fluid management. As reported by Ootaki et al, modified ultrafiltration after cardiopulmonary bypass is associated with a significant increase in serum albumin levels in children.[21] Nonetheless, although not powered to adequately discriminate, there were no apparent differences in outcomes evaluated among the study centres (data not shown).

It is unknown if exogenous albumin supplementation in critically ill patients with anasarca would improve (or worsen) mechanical ventilation outcomes. Perhaps, targeting fluid overload, which has a clear association with post-operative morbidity, should be the predominant intervention, as opposed to supplementation with exogenous albumin. We proffer that, while low albumin alone may not be independently causing morbidity, it may contribute to fluid overload via low oncotic pressure. As such, post-operative hypoalbuminemia should alert the clinician to the potential presence of a more inflamed patient at risk of post-operative morbidity.

This study was limited by bias inherent to its retrospective design. Albumin levels across all five collection time-points were not available for all patients, limiting the inclusion of all patients in all multivariate analyses and, thus, the conclusions that can be drawn from them. As such, analyses of some outcomes may have been in part dependent on albumin levels obtained after the outcome of interest. As this was a retrospective study, clinicians at the study centres ordered albumin levels at their own discretion. Future prospective studies with standardised sampling time windows should be performed to confirm these results.

Fluid management and exogenous albumin administration at these three centres may not be consistent with other paediatric cardiac centres, limiting external validity of our results. Future multi-centre studies with large sample sizes, which can control for variation in site-specific fluid management therapies such as modified ultrafiltration, albumin resuscitation, and early peritoneal dialysis, are needed to determine the independent impact of albumin on post-operative outcomes.

There are several limitations related to our outcome measures. The administration of post-operative steroids as an outcome may be biased as a result of treatment thresholds for each provider that do not necessarily correlate with severity of illness. Inotrope utilisation also may not strongly correlate with the severity of illness, and the use of "presence of catecholamine at 24 hours" as a post-operative outcome may have overestimated the severity of illness by potentially equating children on low-dose epinephrine with those receiving multiple higher-dose catecholamines. Unfortunately, more granular inotrope data were not available. Though peak creatinine levels may not always accurately delineate the severity of kidney injury, data were not available to calculate

https://doi.org/10.1017/S1047951119000738 Published online by Cambridge University Press

acute kidney injury stage using standard guidelines. Additionally, there was tremendous variation in the duration of mechanical ventilation across centres; thus the definition of prolonged mechanical ventilation in this study may not be reflective of patients treated at other centres.

Low serum albumin levels were found to be independently associated with specific outcomes, while our a priori cut-offs for hypoalbuminemia were not, suggesting that the applied criteria may not be sensitive enough to detect clinically meaningful outcomes or were confounded by other factors, including unmeasured ones.

In conclusion, perioperative hypoalbuminemia is common in both neonates and infants, but is not independently associated with post-operative morbidity. However, when analysed as a continuous variable, lower serum albumin levels were associated with increased post-operative morbidity. Pre-operative and post-operative serum albumin levels have distinct prognostic values. Future studies should further assess hypoalbuminemia in this population, with emphasis on evaluating clinically meaningful cut-offs and possibly the use of serum albumin levels in perioperative risk stratification models.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951119000738

Acknowledgements. None.

Financial Support. This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Conflict of Interest. None.

Ethical Standards. The authors assert that all activities contributing to this work comply with the ethical standards of the U.S. Good Clinical Practice Guidelines and the 2008 revised version of the Helsinki Declaration of 1975, and has been approved by the institutional review boards of Children's Hospital of Alabama, Children's Mercy Hospital, and Le Bonheur Children's Hospital.

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