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Araştırma / *Research Article*

Albumin, Globulin and Albumin-Globulin Ratio as a Predictor of Mortality, Morbidity After Fontan Operations

Fontan Ameliyatları Sonrası Mortalite ve Morbidite Prediktörü Olarak Albumin, Globulin ve Albumin-Globulin Oranı

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ABSTRACT

Objective: *Assessment of the albumin, globulin score and albumin to globulin ratio (AGR) as a predictor of mortality and morbidity in patients who underwent Fontan procedure.*
Method: *In a retrospective study, we evaluated serum albumin, globulin concentrations, and albumin- globulin ratio of 56 children who underwent Fontan procedure. Patients divided into two groups. Group 1 consisted of 44 patients who were discharged, and Group 2 consisted of 12 patients who died after surgery. Patients' preoperative and postoperative serum albumin, globulin and albumin globulin rates (AGR) were measured. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of the postoperative albumin and AGR to predict mortality.*
Results: *Twelve patients exited soon after surgeries. Postoperative albumin, and globulin values did not differ between groups, however postoperative labumin, and albumin/globulin ratios differed significantly between groups (p=0.002, and p=0.03, respectively). Cut-off value of 3,46 for postoperative albumin became an independent predictor of mortality, with 79% sensitivity, and 83% specificity. A cut-off value of 1.67 became an independent predictor for AGR with 75% sensitivity, and 89% specificity. Postoperative albumin levels below 3.46 mg/dL were associated with 11 -fold increase in the risk of mortality (OR 11; % 95CI 0,27-1,10; p=0.002).*
Conclusion: *Postoperative albumin and AGR are a convenient and effective tool to predict the overall mortality and morbidity in patients undergoing Fontan operations.*

Keywords: *Fontan procedure, albumin, globulin, albumin-globulin ratio, mortality, morbidity*

ÖZ

Amaç: *Fontan prosedürü uygulanan hastaların albümin, globülin skoru ve albümin-globülin oranının (AGR) mortalite ve morbidite prediktörü olarak değerlendirilmesi.*
Yöntem: *Retrospektif bir çalışmada, Fontan prosedürü uygulanan 56 çocuğun serum albümini, globülin konsantrasyonları ve albümin-globülin oranı değerlendirildi. Hastalar 2 gruba ayrıldı. Grup 1 taburcu olan 44 hastadan, Grup 2 ise ameliyattan sonra ölen 12 hastadan oluşuyordu. Mortalite ve morbiditeyi öngörmek için postoperatif albümin ve AGR'nin optimum kesim seviyeleri belirlendi.*
Bulgular: *Ameliyat sonrası yoğun bakımda 12 hasta kaybedildi. Ameliyat sonrası albümin ve globülin değerleri gruplar arasında farklılık göstermedi, ancak ameliyat sonrası albümin ve albümin-globülin oranı gruplar arasında anlamlı olarak farklı bulundu (sırasıyla, p=0.002, p=0.03) Ameliyat sonrası albümin, 3,46 değerinde bir kesim değeri kullanarak, %79 duyarlılık ve %83 özgüllük ile mortalite için bağımsız bir prediktör olmuştur. 1.67 değerinde bir kesim değeri kullanılarak, ameliyat sonrası AGR % 75 duyarlılık ve %89 özgüllük ile mortalite için bağımsız bir prediktör olmuştur. Ameliyat sonrası albümin <3.46, mortalite riskinde onbir kat bir artışla ilişkiliydi (OR 11; % 95CI 0,27-1.10; p=0.002), Postoperatif AGR <1.67, mortalite riskinde dört kat artışla ilişkiliydi (OR 4.4; % 95CI 0.016-0.78; p=0.04).*
Sonuç: *Postoperatif albümin ve AGR, Fontan ameliyatı geçiren hastalarda genel mortalite ve morbiditeyi öngörmede kullanışlı ve etkili bir araçtır.*

Anahtar kelimeler: *Fontan ameliyatı, albümin, globülin, albümin-globülin oranı, mortalite, morbidite*

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INTRODUCTION

The Fontan operation is the final common surgical palliative treatment for patients with a single ventricle. Advance in surgical and postoperative management have led to hospital survival rates up to 98% [1,2]. Despite low mortality, the causes and distribution of these mortalities are still poorly defined. Also, these patients are under risk for postoperative morbidity which prolongs hospital stay.

Serum total protein is composed of albumin and globulin. Serum albumin concentration is considered as a classic parameter of nutritional assessment [4]. Although malnutrition is an important factor in the regulation of albumin production, serum albumin concentration is influenced by various non-nutritional factors such as inflammation, infection, hepatic failure, and dilution from volüme overload, thus impairing its validity as a nutritional parameter in patients who have an acute-phase response and metabolic stress [3,4].

Postoperative hypogammaglobulinemia has been described in children and adults undergoing cardiac surgery with cardiopulmonary bypass (CPB). Potential causes may include hemodilution, destruction of immunoglobulin (Ig) by CPB, and extravasation into the interstitial space due to systemic inflammation and capillary leak syndrome [5,6].

Previous studies have demonstrated that hypoalbuminemia was associated with impaired survival in pediatric cardiac patients [4,7]. However, up to now no study investigated the effects of albumin and globulin in patients who underwent Fontan procedure. Therefore, in our study our aim was to asses of the albumin, globulin score and albumin to globulin ratio (AGR) as a predictor of mortality and morbidity in patients who underwent Fontan procedure.

MATERIAL and METHODS

In a retrospective study, we evaluated serum albumin, globulin concentrations, and albumin- globulin ratio of 56 children who underwent Fontan procedure. The protocol of the study was approved by ethics committee of our hospital. Patients divided into two groups. Group 1 consisted of 44 patients who were discharged, and Group 2 consisted of 12 patients who died after surgery. All patients underwent an extracardiac conduit (ECC) Fontan operation.

Demographic data including gender, weight, and age of the patients, and intraoperative data including operation time, cardiopulmonary bypass time, cross-clamp time were recorded. Patients' postoperative serum albumin, globulin and albumin-globulin ratio were measured The albumin globulin rates (AGR) were calculated using the following formula: AGR= Albumin /(Total Protein-Albumin).

Cardiac Catheterization

Hemodynamic cardiac catheterization with the aid of angiography was performed for all patients before their Fontan procedure. Moderate sedation was provided during procedure. Pulmonary, systemic blood flow and pulmonary, systemic vascular resistances were calculated. Data related to mean pulmonary artery pressure, common atrial pressure, transpulmonary gradient, end-diastolic pressure, and pulmonary vascular resistance were collected.

Anesthesia and Surgical Procedure

All patients had been operated by the same surgical team. Our anesthesia protocol was standard for all the patients. Standard monitoring started with ECG and pulse oximetry followed by IV administration of fentanyl (5 µg/kg), rocuronium (1 mg/kg) and midazolam (0.1 mg/kg) for anesthesia induction. Tracheal intubation, right radial artery, and right jugular vein cannulation were performed for continuous arterial and central venous pressure monitoring. Then induction of inhalation anesthesia was initiated with sevoflurane, and bolus doses of fentanyl, rocuronium, and midazolam were repeated during operations.

Cardiopulmonary bypass is achieved with an aortic cannula and venous cannulas inserted into superior vena cava (SVC), inferior vena cava (IVC). The IVC is transected, and the RA oversewn and the polytetrafluoroethylene graft is anastomosed to the distal IVC. The graft is anastomosed to the right pulmonary artery. These anastomoses are performed during bypass procedure on beating heart. If valve repair is necessary, the heart was arrested at standstill using cardioplegia. Then, at the end of the procedure, the patients are weaned from cardiopulmonary bypass. A transthoracic, intraatrial monitoring line is placed. In case of higher intraatrial pressure, the fenestration procedure was performed.

Statistical analysis

Normally distributed continuous variables were expressed as mean ± standard deviation (SD) or median values with an interquartile range if not normally distributed. Categorical variables were expressed as numbers and percentages. Demographic characteristics, perioperative variables, and calculated values were compared using an independent samples t-test or the Mann-Whitney U test for continuous variables and a chi-square test or Fisher's exact test for categorical variables. Correlations were assessed using Pearson's correlation test. Receiver-operating characteristic (ROC) curve analysis was used to determine the optimum cut-off levels of the postoperative albumin and AGR to predict mortality. The odds ratios (ORs) and 95% confidence intervals (CIs) were estimated with different logistic regression models that were created to determine independent predictors of mortality.

Statistic analysis was performed with SPSS version 20.0 (SPSSInc., Chicago, IL, USA).

RESULTS

Fifty-six children with single ventricle who underwent Fontan procedure were enrolled in the study. The patients divided into two groups. Group 1 consisted of survived and group 2 exited patients.. Demographics, preoperative and postoperative blood test results, and operative characteristics of patients are summarized in Table 1. Twelve patients died during the intensive care unit stay following surgery. Preoperative albumin and globulin values were not different between groups but postoperative albumin values, and albumin-globulin ratios were found to be significantly different between groups (respectively, p=0.002, p=0.03) Neither the preoperative albumin, globulin nor the postoperative globulin values were associated with mortality, but the reduced postoperative albumin (p=0.002) and decreased albumin-globulin ratio (p=0.03) was found to be associated with an increased risk of death (Table 1). The rates of cardiopulmonary bypass

Table 1. Baseline characteristics.

	Grup 1	Grup 2	P
Patient Characteristics			
Age (years)	6.28±4.39	6.50±5.5	0.89
Male (%)	52.8%	41.7%	0.3
Opertive Data			
CPB time(min)	111.17±28.5	135.3±34.7	0.02
Cross clamp (%)	38.9%	41.7%	0.56
Fenestration (%)	16.7%	25%	0.68
Preoperative blood results			
Albumin	3.93±0.46	3.89±0.63	0.29
Globulin	2.32±0.37	2.28±0.43	0.31
Albumin-Globulin Ratio	1.72±0.33	1.70±0.42	0.49
Postoperative blood results			
Albumin	3.81±0.67	3.12±0.45	0.002
Globulin	1.86±0.47	1.88±0.51	0.91
Albumin-Globulin Ratio	2.16±0.59	1.76±0.51	0.03

(CPB) surgeries performed, and their operative times were higher in the patients who died (p=0.02).

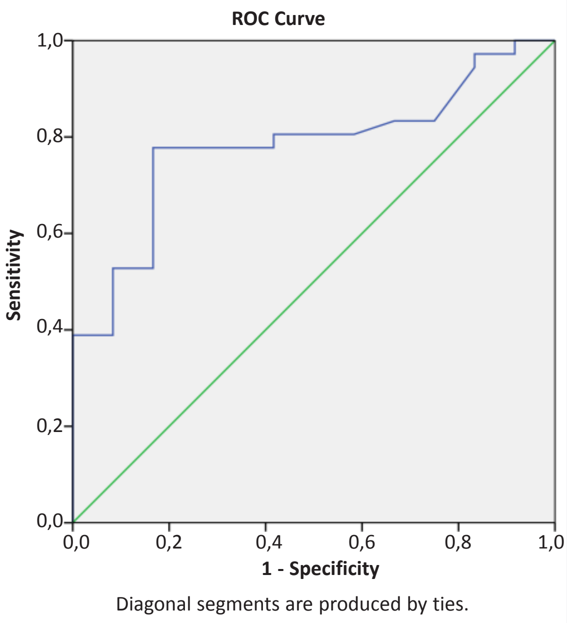

Figure 1. The receiver-operating characteristic (ROC) curve analysis of postoperative albumin for mortality prediction.

The ROC curves for the albumin were correlated with mortality following surgery. The area under curve (AUC) for the postoperative albumin was 0.78 (95% CI 0.64 - 0.92; p=0.004) (Figure 1).

Using a cut-off value of 3.46 mg/dL, postoperative albumin predicted mortality with a sensitivity of 79% and specificity of 83%. When the study population was divided into two groups using a cut-off value of 3.46 mg/dL, the OR for patients with albumin values higher than 3.46 mg/dL was calculated as 10.5 (95% CI 2.29 - 48.2; p=0.03). Besides, a decreased albumin was not associated with prolonged hospital and ICU stay.

The ROC curves for the AGR was associated with mortality following surgery. The area under curve (AUC) for the postoperative AGR was 0.76 (95% CI 0.58 - 0.95; p=0.007) (Figure 2).

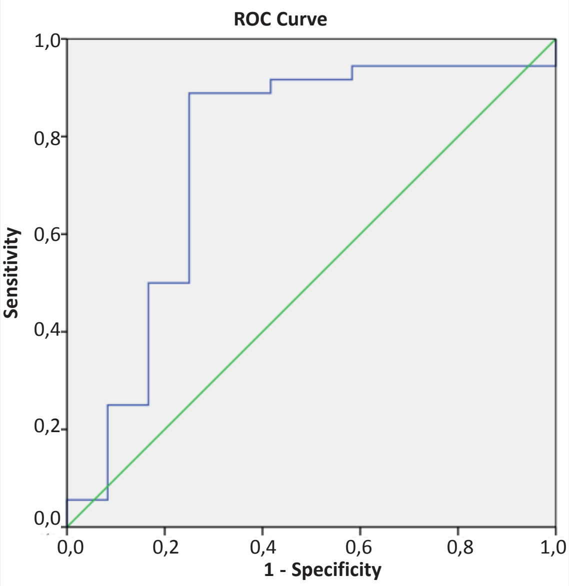

Figure 2. The receiver-operating characteristic (ROC) curve analysis of albumin to globulin ratio for mortality prediction.

Using a cut-off value of 1.67, the postoperative AGR predicted mortality with a sensitivity of 75% and specificity of 89%. When the study population was divided into two groups using a cut-off value of 1.67, the OR for patients with AGR higher than 1.67 was calculated as 18.6 (95% CI 3.71 - 9.27; p=0.0001). In addition, a decreased AGR was associated with prolonged hospital stay (p=0.04).

The statistical relation between albumin values, AGR, and mortality, ICU/hospital stay was shown in Table 2.

Table 2. The correlation of Mortality/morbidity with albumin and AGR.

	Albumin		AGR	
	r	p	r	p
Mortality	-0.44	0.002	-0.58	0.0001
CPB time (min)	-0.38	0.007	-0.19	0.21
Prolonged ICU stay (day)	-0.1	0.49	-0.16	0.26
Prolonged hospital stay (day)	-0.06	0.71	-0.25	0.08

In addition, lower albumin values were associated with mortality (p=0.001). But prolonged ICU and

Table 3. Patient characteristics and outcomes with regard to the Albumin.

	Albumin		
	≤3.46	>3.46	P
Age	6.79±5.51	5.93±3.99	0.53
Male (%)	38.9%	60%	0.06
Mortality (%)	55.5%	6.67%	0.001
Prolonged ICU stay (>2 days)	62,5%	25%	0.09
Prolonged hospital stay (>10 days)	75%	35.1%	0.15

Table 4. Patient characteristics and outcomes with regard to the AGR.

	AGR		
	≤1,67	>1,67	P
Age	8.69±5.3	5.46±4.1	0.06
Male (%)	60%	30.8%	0.001
Mortality (%)	69%	8.57%	0.001
Prolonged ICU stay (>2 days)	75%	28.1%	0.12
Prolonged hospital stay (>10 days)	100%	40.6%	0.04

hospital stay were not significantly different between the patients (Table 3), However, the lower AGR values were associated with mortality and prolonged hospital stay (respectively p=0.001 and p=0.04) (Table 4).

When the risk factors for mortality and morbidity were evaluated, in terms of albumin and AGR, significant differences were found between two groups (respectively p=0.001, p=0.001). However, hospital stay times of patients were not different between two groups, but ICU stay times significantly differed between groups, and they were associated with prolonged hospital stay (p=0.04).

In a subgroup of the patients, in a univariate analysis, postoperative albumin cut-off value of 3.46 mg/dL was found to be a strong independent predictor of mortality OR 20.7; 95%CI 0.27-1.1; p=0.0001). Besides , postoperative AGR cut-off value of 1.67 was a robust independent predictor of mortality OR 24; 95CI % 0,016-0,78; p=0.0001). In similar multivariate models, the postoperative albumin of <3.46 mg/dL was associated with a eleven-fold increase in the risk of mortality (OR 11; 95% CI 0,27-1,10; p=0.002), the postoperative AGR<1.67 was associated with a four-fold increase in the risk of mortality (OR 4.4; 95% CI 0.016-0.78; p=0.04) (Table 5).

Table 5. Multivarate predictors of mortality.

Variables	OR	%95CI	P
Albumin	11	0,27-1,10	0.002
AGR	4,4	0,016-0,78	0.04
CPB time	5,8	-44,4 - -3,97	0.02

DISCUSSION

In this study, we demonstrated that postoperative albumin and albumin globulin ratio have potential predictors of early mortality after Fontan operations.

Fontan physiology has been called paradoxical because systemic venous hypertension is imposed with concomitant pulmonary artery hypotension [8]. This hemodynamic compromise underlies many potential previously described late complications, including arrhythmias, heart failure, tromboembolism, hepatic dysfunction, protein-losing enteropathy, and worsening cyanosis [9]. Despite these recognized causes of mortality, mortality outcomes remain incompletely defined [10].

Major surgery is followed by an important metabolic stress response, which is closely related to adverse outcomes [11,12]. Several perioperative interventions allow modulation of an excessive stress response, some of them having an important positive impact on clinical outcomes [12-14]. Therefore, a reliable prediction of surgical stress response is of high interest. The ideal marker has to be easy to measure, available early in the perioperative course, and inexpensive. It should be strongly correlated with the extent of surgical trauma and be a reliable predictor of complications and prolonged hospital stay. So far, no such parameter is available [12,15].

Concerning postoperative albumin values, the transcapillary flow of plasma proteins secondary to the endothelial lesion is the main underlying mechanism to explain hypoalbuminemia. In the initial stage of the inflammatory process, there is an increase in permeability of the microcirculation, allowing greater transcapillary flow of plasma protein [4,16]. This event may be important in the postoperative period of cardiac surgery because the contact of blood with the surface of cardiopulmonary bypass tubes may produce an endothelial lesion that in turn is a triggering factor of the systemic inflammatory reactions [4,17].

According to Warren et al. two phases of inflammatory response related to cardiopulmonary bypass exist. In the early phase, the contact of blood with the artificial surfaces of the cardiopulmonary bypass circuit triggers several humoral (complement system, pro-inflammatory cytokines, coagulation system) and cellular (leucocytes, vascular endothelial cells, platelets) inflammatory cascades. The later phase is characterized by ischemia-reperfusion injury and endotoxemia, which leads to an endothelial injury with release of reactive oxygen species and alterations of the microcirculation [18,19].

Serum albumin is a type of negative acute-phase protein whose levels decrease during inflammatory reactions [20]. Therefore, in patients who have prolonged CPB time, inflammatory process may also explain the decrease in albumin value. In this case, the sequential measurement of postoperative serum albumin values may guide us about the severity of the inflammatory process. In our patients, we found a significant negative correlation between CPB durations and postoperative albumin values. Leita et al. [4] and Redy et al. [21] discussed the positive correlation between mortality and morbidity after cardiovascular surgery such as prolonged hospital stay with hypoalbuminemia. In a retrospective analysis, postoperative hypoalbuminemia was considered to be predictive of increased length of ICU stay and 28-day mortality in adult patients after cardiopulmonary bypass surgery [22]. Kapoor et al. showed that serum albumin values are used in the early prediction of postoperative mortality and morbidity following cardiac surgery performed for total correction of congenital heart disease [23]. In another study it has been showed that the postoperative decrease in albumin was associated with an increased risk of mortality and morbidity [24]. In other study, postoperatively decreased albumin and globulin had been associated with mortality and morbidity [25]. In this study, in postoperative group of low albumin (<3,46) mortality and morbidity rates were higher than group with higher albumin levels (>3.46).

Albumin-globulin ratio reflects the ratio between the albumin and nonalbuminous proteins such as including globulins, acute phase reactants, cytokines, and other inflammatory proteins). Therefore, the lower AGR represents either low albumin values, high nonalbuminous protein values, or both. While hypoalbuminemia was a predictor of adverse outcomes, elevated non-albumin proteins such as globulin, acute phase reactants were also found to be predictors of adverse outcomes [26,27]. Bhatia et al. demonstrated that only low albümin but also high globülin levels were associated with higher adverse outcomes in cardiovascular patients[28]. In our study, CPB was used for all patients and globulin values of all patients decreased, and globulin values were higher in Group 2 than Group 1. The specific mechanism of hypoglobulinemia after CPB is not fully clear. As smaller proteins than globulins albumin can be found in the extravascular space even in physiologic conditions. Decreased vascular integrity leads to increased permeability and vascular leakage, which may result in decrease in protein levels including albumin. Some authors have attributed these changes to hemodilution during CPB [29]. The results suggested that previous adult and pediatric studies showing an immediate reduction in IgG that may persist several days post- CPB [30]. Potential sources of losses of IgG may be increased capillary permeability or extravasation to the interstitial space due to losses in urine, pleura or peritoneal fluid.

CONCLUSION

In conclusion, the present study suggests that post-operative albumin and AGR are convenient and effective tools to predict the overall mortality and morbidity rates in patients undergoing Fosntan operations. Further larger-scale prospective studies are required to validate this finding and to investigate other prognostic indicators in Fontan operations.

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