Influence of preoperative serum albumin levels on postoperative complications in cardiac surgery

Influência dos níveis séricos da albumina pré-operatória em complicações pós-operatórias de cirurgias cardíacas

Influencia de los niveles preoperatorios de albúmina sérica en las complicaciones postoperatorias de la cirugía cardíaca

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Abstract
Objective: Verify whether lower preoperative serum albumin levels in cardiac surgery patients increase the incidence of acute kidney injury (AKI), pneumonia, postoperative stay in hospital and mortality. Methodology: A hundred and eighty-five medical records of patients that underwent cardiac surgery between January 2014 and December 2017 were surveyed. The albumin levels were compared between the group that presented at least one of the complications listed above and the group where that complication was not observed. The KDIGO criterion was used to define AKI. Pneumonia diagnosis was established based on clinical, radiologic and laboratory results. The postoperative time in hospital was considered increased when the patient had to stay for a period longer than 8 days. The mortality rate was defined by deaths that occurred up to 30 days after the surgery. Results: Albumin levels ≤3.87 mg/dL were associated to an increase in the risk to develop AKI (p= 0,0072). Albumin values ≤3.91 also increased the chance to have pneumonia (p= 0.0001). However, albumin was not statistically significant to predict mortality and increase in the postoperative stay in hospital. Conclusion: Serum albumin levels that were lower than or equal to 3.91 mg/dL and 3.87 mg/dL increased, respectively, the chances of developing both pneumonia and acute kidney injury after cardiac surgery. No significant results were obtained regarding albumin levels influence on postoperative stay in hospital or mortality.
Keywords: Hypoalbuminemia; Thoracic surgery; Acute Kidney Injury; Pneumonia.

Resumo
Objetivo: Verificar se os níveis séricos mais baixos de albumina pré-operatória em pacientes submetidos à cirurgia cardíaca aumentam a incidência de lesão renal aguda (LRA), pneumonia, tempo de internamento pós-operatório e mortalidade. Metodologia: Foram analisados 185 prontuários de pacientes submetidos à cirurgia cardíaca entre janeiro de 2014 até dezembro de 2017. Os níveis de albumina foram comparados entre o grupo que apresentou pelo menos uma complicação das citadas acima e o grupo onde a mesma não foi observada. Para definir LRA, foi utilizado

o critério KDIGO. O diagnóstico de pneumonia foi estabelecido através aspectos clínicos, radiológicos e laboratoriais. O tempo de internamento pós-operatório foi considerado aumentado quando houve permanência superior a 8 dias. Definiu-se mortalidade pela morte hospitalar em até 30 dias após a cirurgia. Resultados: Níveis de albumina ≤3,87 mg/dL foram associados ao aumento de risco de desenvolvimento de LRA (p= 0,0072). Valores de albumina ≤3,91 também aumentaram a chance de pneumonia (p= 0,0001). A albumina não foi estatisticamente significante em predizer mortalidade e aumento de tempo de internamento pós-operatório. Conclusão: Níveis de albumina sérica menores ou iguais a 3,91 mg/dL e 3,87 mg/dL elevaram, respectivamente, a chance de desenvolver pneumonia e lesão renal aguda após cirurgia cardíaca. Não se obteve resultados significativos entre níveis de albumina, dias de internamento pós-operatório e mortalidade.
Palavras-chave: Hipoalbuminemia; Cirurgia torácica; Lesão Renal Aguda; Pneumonia.

Resumen
Objetivo: Comprobar si los niveles preoperatorios de albúmina sérica en pacientes sometidos a cirugía cardíaca aumentan la incidencia de lesión renal aguda (LRA), neumonía, duración de la estancia postoperatoria y mortalidad. Metodología: Se analizaron 185 historias clínicas de pacientes sometidos a cirugía cardíaca desde enero de 2014 hasta diciembre de 2017. Los niveles de albúmina se compararon entre el grupo que presentó al menos una complicación de las mencionadas anteriormente y el grupo en el que no se observó. Para definir la LRA, se utilizaron los criterios KDIGO. El diagnóstico de neumonía se estableció mediante aspectos clínicos, radiológicos y de laboratorio. Se consideró que la estancia hospitalaria postoperatoria aumentó cuando hubo una estancia superior a 8 días. La mortalidad se definió por la muerte intrahospitalaria en los 30 días siguientes a la cirugía. Resultados: Los niveles de albúmina ≤3,87 mg/dL se asociaron con un mayor riesgo de desarrollar IRA (p= 0,0072). Los valores de albúmina ≤3,91 también aumentaron la probabilidad de neumonía (p= 0,0001). La albúmina no fue estadísticamente significativa para predecir la mortalidad y el aumento de la estancia postoperatoria. Conclusión: Los niveles de albúmina sérica inferiores o iguales a 3,91 mg/dL y 3,87 mg/dL aumentaron, respectivamente, la probabilidad de desarrollar neumonía y lesión renal aguda tras la cirugía cardíaca. No se obtuvieron resultados significativos entre los niveles de albúmina, los días de estancia hospitalaria postoperatoria y la mortalidad.
Palabras clave: Hipoalbuminemia; Cirugia torácica; Lesão Renal Acuda; Neumonía.

1. Introduction

Cardiac surgeries are major operations, which are expensive and generate great organic repercussions to the patients. However, they are very frequent in Brazil, where around 102 thousand of these surgeries are carried out every year. The most frequent cardiac surgery is the coronary artery bypass graft (CABG), followed by valve repair, aneurysmectomy and atrial septal defect (ASD) correction (Laizoet al., 2010). Patients undergoing these surgeries need a period of permanence in the intensive care unit and hospital stay, whose duration depends on their clinical evolution (Soares et al., 2011). Two very frequent complications, which are responsible for extending the hospital stay period and increasing morbimortality, are the acute kidney injury (AKI) and pneumonia (Soares et al., 2011). AKI is the most frequent cardiac surgery postoperative complication. Its incidence after this kind of surgery is from 19% to 36%, when diagnosed through the criteria proposed by the KDIGO (Kidney Disease: Improving Global Outcomes) (Hoste & Vandenberghe, 2017; Sampaio et al, 2013). Regarding pneumonia, according to previous studies, it occurs in between 5.7% to 9.9% of the patients (Diretrizes brasileiras para tratamento das pneumonias adquiridas no hospital e das associadas à ventilação mecânica, 2007; Ortiz et al., 2010).

There are several preoperative risk factors involved in the postoperative morbimortality increase in cardiac surgeries. To predict these risks, the European System for Cardiac Operative Risk Evaluation (EuroSCORE II) is currently one of the most used system. This score presents 17 preoperative risk factors to classify the patients into four groups, namely, low risk (score <2), moderate risk (score between 2-4), high risk (score >4) and very high risk (score >6) (Lisboa et al., 2014).

Although many preoperative risk factors are used to calculate the EuroSCORE II, they do not include the patients' nutritional condition, which might also be correlated to the individuals' socioeconomic condition (Lisboa et al., 2014). The indicator usually used to evaluate that condition is the serum albumin. Normal concentrations of this protein are around 3.5 mg/dL and 5.0 mg/dL, and they depend on the complex balance between its hepatic synthesis

and elimination through the kidneys and intestines (Levitt & Levitt, 2016). Albumin plays several roles in the organism such as the maintenance of the colloid osmotic pressure, the blood acid-base balance, and the transport of drugs and liposoluble physiological substances that include fat acids, hormones and small ions (Vincent et al., 2014).

Previous studies concluded that low preoperative serum albumin levels in general and cardiac surgeries correlate with an increase in morbidity and mortality rates. Another study that evaluated risk factors associated to the prognostic of adults admitted in hospital with pneumonia concluded that low serum albumin levels were considered useful severity parameters in the clinical conduction of infections (Khannaet al., 2018).

Therefore, this study aims to verify whether lower preoperative serum albumin levels in patients undergoing cardiac surgery increase the incidence of acute kidney injury, pneumonia, time of postoperative stay in hospital and mortality. In addition, to determine at which cut-off point serum albumin becomes a risk factor for the development of each of the postoperative complications listed above.

2. Methodology

Type of Study

This is an observational analytical study of the retrospective case-control type. The study started after approval by the Human Research Ethics Committee of the State University of Ponta Grossa (protocol number 2.623.899). A retrospective analysis of data stored in the data base of the Cardiac Surgery Service at the Santa Casa Hospital in Ponta Grossa/PR was carried out. This data is collected prospectively.

Sample Inclusion Criteria

All patients that underwent cardiac surgery performed by one surgeon only in the period from January 2014 to December 2017 were included, totalling 263 patients.

Exclusion Criteria

Seventy-five patients were excluded for not having serum albumin dosage up to 30 days before the surgery and 3 for early death (within 48 hours after surgery). The final sample included 185 cases.

Groups of Study

The 185 medical records were divided into four pairs of case-control groups, and the case groups contained patients that developed only one specific complication (AKI, pneumonia, increased hospital stay or death), and the controls included all the other patients that did not develop such complication.

Independent Variables

The values of preoperative serum albumin collected up to 30 days before surgery were used, following the same criteria as the ones employed in previous studies (Gibbset al., 1999). The final score in EuroSCORE II was also used as an independent variable (Nashef et al., 2012).

Dependent variables

AKI was diagnosed using the KDIGO criteria, which defines it as a condition in which the patient presents at least one of the three following characteristics:

(1) Increase of at least 0.3 mg/dL in serum creatinine within 48 hours;

(2) Increased serum creatinine of at least 1.5 times in relation to the patients' basal value within 7 days;

(3) Urinary debt lower than 0.5 mL/kg/h in 6 hours (Kidney, 2012).

This criterion was used for having demonstrated higher sensitivity to detect AKI when compared to other criteria in previous studies (Luo et al., 2014).

Pneumonia was defined by clinical, radiological and laboratory findings, which included:

(1) presence of new pulmonary infiltrate, or progressive or consolidation or cavitation;

(2) at least two of the following criteria: fever (temperature over 38°C) without another defined cause, leukopenia (<4.000 cel/mm³) or leukocytosis (12.000 cel/mm3), or the appearance of purulent tracheal secretions and recorded medical diagnosis (Diretrizes brasileiras para tratamento das pneumonias adquiridas no hospital e das associadas à ventilação mecânica, 2007).

Days of postoperative stay in hospital was presented as a continuous variable, starting the count as of the moment of the surgery up to hospital discharge or death.

Surgical mortality was defined as the death for any cause that occurred up to 30 days after the surgery.

Statistical analysis

The whole sample was tested for normality, and the continuous variables were demonstrated through mean or median, and the categorical ones, through absolute number or percentage.

The receiver operating characteristic (ROC) curve was used to determine the levels of preoperative serum albumin considered to be the values that better balanced the sensitivity and specificity of each dependent and dichotomous variable investigated (AKI, pneumonia and mortality). These values, when statistically significant ($p< 0.05$), were used in those situations as the albumin cut-off point to turn it into a dichotomous variable, and then obtain an odds ratio, through the use of logistic regression, between it and each of the variables cited above. Seeking to set an odds ratio between albumin and days of hospital stay, univariate regression was used. To transform the albumin into a dichotomous variable in this case, its referential levels were used to divide it into below 3.5 mg/dL and over or equal to 3.5 mg/dL. This procedure was necessary because it was not possible to establish its best value by using the ROC curve, since days of stay in hospital were presented as a continuous variable. The EuroSCORE II was always used along with the albumin in the logistic and univariate regressions with the purpose of assessing the patients' risk.

To carry out the statistical calculation, the software MedCalc® version 14.8.1 was used. Significant values were those where *p* was lower than 0.05.

3. Results

Out of the 185 patients investigated, 62.7% (n=116) were men, while 37.3% (n=69) were women, aged between 15 and 83 years old, therefore, mean age 58.79 years. The most recurrent cardiac surgery was CABG 60.54% (n=112), followed by valve repair 35.13% (n=65), ASD correction 3.24% (n=6), and cardiac tumor ressection 1% (n=2). The albumin level global mean was 3.98 mg/dL. The albumin and EuroSCORE II mean values of each pair in the case-control group can be seen in Table 1.

Table 1. Albumin and EuroSCORE II means among patients that presented postoperative complications or not.

	Mean Albumin (mg/dL)	Mean EuroSCORE II	Total (n=185) (%)
AKI			
Yes	3.79	2.40	52 (28.1)
No	4.06	2.33	133 (71.9)
P	0.0016	0.044	
Pneumonia			
Yes	3.63	3.01	23 (12.4)
No	4.03	2.26	162 (87.6)
P	0.001	0.186	
Hospital stay			
>8 days	3.92	2.74	42 (22.7)
≤ 8 days	4.01	2.23	143 (77.3)
P	0.51	0.09	
Mortality			
Yes	3.86	3.14	22 (11.9)
No	4.01	2.27	163 (88.1)
P	0.28	0.02	
Total	3.98	2.35	185

AKI = Acute Kidney Injury. Source: Authors.

The ROC curve result between albumin and AKI is shown in Graph 1 and demonstrates that albumin levels ≤ 3.87mg/dL were more accurate to predict AKI (AUC= 0.649; CI= 0.576 to 0.718; p=0.001). This albumin value was used to transform it into a dichotomous variable (≤3.87 or >3.87), and the logistic regression results with AKI and EuroSCORE II are seen in Table 2. The ROC curve also demonstrated that albumin values ≤2 mg/dL presented 100% sensitivity to AKI, while levels ≥ 4.8 presented 100% specificity.

Graph 1. ROC curve between albumin and AKI evidencing the best accuracy point.
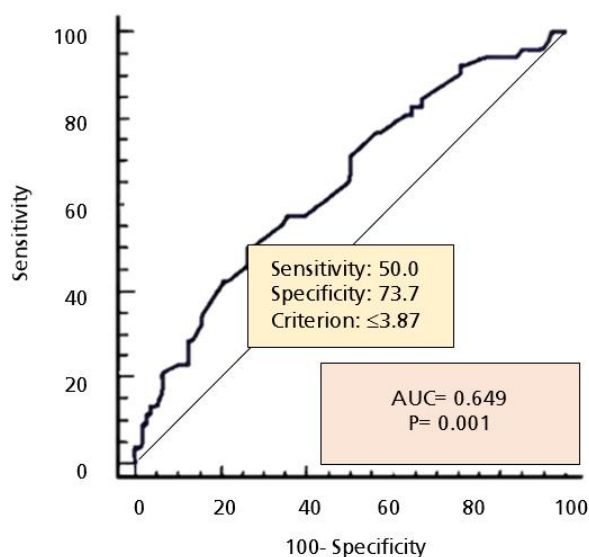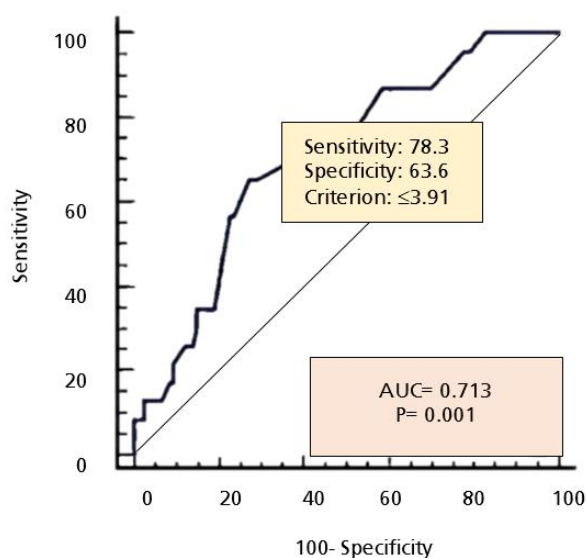

*AUC: Area Under the Curve. Source: Authors.

Table 2. Chances of developing different complications according to the serum albumin levels.

	Albumin (mg/dL)	OR	IC	P
AKI	≤ 3.87	2.94	1.49 – 5.80	0.0072
Pneumonia	≤ 3.91	6.01	2.11 –17.12	0.0004
Hospital stay	<3.5	1.46	0.73 – 5.89	0.2769
Mortality	<3.5	1.75	0.43 – 7.11	0.4296

AKI = Acute Kidney Injury. Source: Authors.

The ROC curve between albumin and pneumonia is presented in Graph 2 and demonstrated that albumin values below 3.91 mg/dl presented better accuracy to predict pneumonia (AUC= 0.713; CI: 0.642 to 0.777; p< 0.001). Through this value, the serum albumin was turned into dichotomous (≤3.91 or >3.91), and the logistic regression results with pneumonia and EuroSCORE II are shown in Table 2. The ROC curve also revealed that albumin levels ≤2 mg/dL were 100% sensitive to predict pneumonia, while those ≥ 4.4 mg/dL were 100% specific.

Graph 2. ROC curve between albumin and pneumonia demonstrating the best accuracy value.

*AUC: Area Under the Curve. Source: Authors.

The sample patients presented, on average, an 8-day postoperative stay in hospital and other data related to this variable is found in Table 2. The regression between postoperative stay in hospital, albumin and EuroSCORE II did not obtain a statistically significant result (p= 0.2769) (Table 2).

The albumin mean among patients that survived surgery was higher than the mean of deaths, however, the association between albumin and mortality was not statistically significant (p= 0.4296) (Tables 1 and 2).

4. Discussion

This paper evidenced the importance of serum albumin to determine the increase in AKI and pneumonia incidence, when the levels are ≤ 3.87 mg/dL and ≤ 3.91 mg/dL respectively, however, no impact was found on postoperative stay in hospital or mortality.

According to Gibbset al., (1999), the serum albumin level might be affected by several factors such as trauma and surgical stress, but it remains as a predictive factor in the surgical prognostic, for being a marker of more severe diseases and malnutrition, in addition to possibly having a protective effect on several biological systems. Albumin dosage has better value in the nutritional evaluation of a patient than anthropometric markers, for its capability to detect protein-calorie malnutrition, which many times is not accompanied by weight loss and, therefore, it is not usually detected clinically, despite being significantly related to increased morbimortality.

Malnutrition or protein-calorie malnutrition might result from an increase in the energy and protein consumption resulting from the stress of the base pathology or an infectious process and, if the amount consumed is not resupplied with a suitable diet, depletion of the visceral reserves and organic dysfunction might occur, including bad gastrointestinal absorption, worsened immune response and reduction in the hepatic production of albumin and other plasma proteins. Albumin intravenous replacement in these cases is not usually effective because the albumin is quickly degraded and the replacement does not correct the underlying cause, which worsens the postoperative prognostic (Gibbset al., 1999).

Albumin is then one of the factors used to evaluate the patients' nutritional state (Gonçalveset al., 2016). It seems relevant to emphasize that for the higher incidence of malnutrition in patients of unfavorable socioeconomic conditions, that population has been studied for presenting higher indices of postoperative cardiovascular complications, both in cardiac surgeries and other procedures. A study carried out by Koch *et al*. demonstrated that socioeconomically deprived patients, mostly Afro-descendants and women, presented worse prognostics, higher number of comorbidities and reduction in the survival rate within 10 years after surgery (Koch et al., 2010).

AKI is currently the most common cause of cardiac surgery postoperative complications, occurring in 5-42% of these procedures worldwide and varying according to the place and population assisted. This is associated to an increase in morbidity, mortality, longer intensive care unit permanence and hospital stay, in addition to increasing the cost of hospital care (Wang & Bellomo, 2019). Considering the patients that present postoperative AKI, 2-6% end up requiring hemodialysis and, from those, 64% will depend on permanent dialysis. Another proved fact is that AKI increases mortality within 10 years after surgery (Thieleet al., 2015; Hanoura et al. (2018). Thus it becomes clear that cardiac surgery postoperative AKI deeply affects the patient's prognostic and future life quality.

The AKI in this study, as defined by the KDIGO criterion, affected 28.11% of the patients, a result that is very close to the 25% found by Hanoura et al. (2018) in a recently published study. When analyzing the odds ratio, we found out that albumin levels ≤ 3.87 mg/dL increased 1.94 times the chance to develop AKI when compared to the group with albumin levels higher than this (CI: 1.49 to 5.80, p= 0.0072). Engelman *et al. (1999)* concluded in a similar study that preoperative albumin levels below 3.5 mg/dL presented a two-fold increase in the chance of AKI development, (OR *2.0; CI 1.3-3.2; p= 0002)*. This study also revealed that 100% of the patients with albumin ≤ 2 mg/dL developed AKI, while no patient with albumin levels > 4.8 mg/dL experienced this complication. Similar results were not found in the literature, but they might be important for comparison with future studies.

Pneumonia, in turn, affects from 1.2 to 9.7% of the patients that undergo cardiac surgery and is considered the most common infection in these cases, whose main etiological agents are *Enterobacteriaceae, Pseudomonas aeruginosa* and *Acinetobacter* spp. During the period of hospital care, the development of pneumonia is a determining factor for higher mortality rates, increase in the mechanical ventilation period, which also impacts the cost of hospital care (Ibañez et al., 2015; Ailawadi et al., 2017). Other aspects also observed were decrease in survival within 5 years after surgery and increase of 2 weeks in hospital stay (Ibañez et al., 2015; Ailawadi et al., 2017).

Pneumonia affected 12.4% of the patients, resulting in around 9.8% as found by Ortiz et al. (2010) in their study involving patients that underwent CABG. Moreover, patients with albumin levels ≤ 3.91 mg/dL presented 6 times more chance of developing this infection when compared to those presenting higher albumin levels (6.01; CI: 2.11 to 17.12 p=0.0004). This increased risk was also reported by Rapp-Kesek *et al. (2004).*, who concluded in their study involving 886 patients, that values below 3.7 mg/dL increased the risk of this infection (OR, 2.1; 95% CI: 0.9 to 7.8 p=0.01). Higher values found in this work, might be due to the higher cut-off point of albumin levels considered. Another finding was that when albumin levels were ≤2 mg/dL, all patients developed pneumonia, whereas the same outcome was not observed when the albumin levels were over 4.4 mg/dL. These results were not seen in previous studies, however, they might stimulate further studies on this factor.

Despite the mean albumin of patients that stayed less than 8 days in hospital being higher than the mean albumin of those that had a longer hospital stay, no statistical significance was found when albumin was used to predict increase in postoperative hospital stay, which was also observed in the studies by Koertzenet al., (2013) and la Cruz et al. (2011).

The mean albumin of patients that survived surgery was also higher than that of patients who died. Despite this protein serum concentration difference between the groups, albumin levels <3.5 mg/dL were not significantly associated in this study to an increase in mortality when compared to the group with levels ≥3.5 mg/dL. De la Cruz et al. (2011) found the same result in their study involving 588 patients that underwent myocardial revasculatization. Montazerghaem & Safaie Nezhad (2014) developed a study in which they concluded that preoperative albumin values <2,5 mg/dL are an independent risk factor for mortality (OR 2.0; CI: 1.3 to 3.0; *p* = 0.002), however, values between 2.5 and 3.5 mg/dL did not increase death risk (p=0.6). This set of data indicated that only more severe hypoalbuminemia can increase the risk of postoperative death.

As previously mentioned, preoperative albumin was seen to be related to an increase in AKI and pneumonia incidence in the postoperative period of cardiac surgeries. Whether albumin is the cause or effect of these complications has not been fully clarified yet, which might be explained by the several functions that this protein has in the human body, its systemic metabolism or even due to the high degree of variability of its levels. Further studies should seek to define this information in order to reduce postoperative complications. Limitations of this study include the fact that the patients were not divided into groups, such as valvular or coronarian patients. Moreover, it was not discussed other important aspects, like, for example, blood transfusion or bypass and clamping times.

5. Conclusion

In this study, preoperative serum albumin levels ≤3,87 mg/dL and ≤ 3,91 mg/dL showed a 1.94 times increase of the patients' chance to develop acute kidney injury, and 6.01 times the risk of developing pneumonia, respectively. No significant results were obtained between albumin levels, days of hospital stay and mortality. There is still a need for further work in this area, and studies can be developed to evaluate the incidence of complications in patients with low serum albumin levels in other types of surgeries.

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