

## Hypoalbuminemia seems to be associated with a higher rate of hospitalization in hemodialysis patients

A hypoalbuminemia parece estar associada a uma maior taxa de hospitalização nos pacientes em hemodiálise

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### ABSTRACT

**Introduction:** Anemia, inflammation and hypoalbuminemia are frequent disorders among patients underwent hemodialysis. There are few national data, particularly from Northeast region where anemia and malnourished were common findings, analyzing the association between these conditions and clinical outcomes. **Objective:** The aim of this study was to evaluate the impact of the presence of anemia, inflammation and hypoalbuminemia on clinical outcomes (death and hospitalization) of hemodialysis patients. **Methods:** In this prospective observational study 221 adult patients were evaluated, considering the presence of anemia (hemoglobin  $\leq$  10 g/dL), inflammation (C-reactive protein (CRP)  $\geq$  0,5 mg/dL) and hypoalbuminemia (albumin  $<$  3,8 g/dL) at baseline. Clinical outcomes were recorded over 13 months. **Results:** The occurrence of hospitalization and death did not differ between the groups with and without anemia or inflammation. Patients with hypoalbuminemia had more hospitalizations, and the presence of hypoalbuminemia was associated with shorter hospitalization event-free time ( $p = 0.008$ ). There was a trend of shorter hospitalization event-free time among patients with increased PCR ( $p = 0.08$ ). There was no correlation between albumin and CRP levels. The presence of anemia, inflammation and hypoalbuminemia were not associated with lower survival. Adjusting for confounders, hypoalbuminemia was a predictor of hospitalization in hemodialyzed patients. **Conclusion:** The presence of hypoalbuminemia, but not anemia or inflammation, was able to predict hospitalization in hemodialysis patients.

**Keywords:** anemia; dialysis; hypoalbuminemia; inflammation.

### RESUMO

**Introdução:** Anemia, inflamação e hypoalbuminemia são complicações frequentemente observadas em pacientes submetidos à hemodiálise crônica. Existem poucos dados nacionais que avaliam a associação dessas condições à morbidade e mortalidade especialmente considerando a região nordeste do país onde a ocorrência de anemia e desnutrição é elevada. **Objetivo:** O objetivo desse estudo foi avaliar o impacto da presença da anemia, inflamação e hypoalbuminemia sobre os desfechos clínicos (óbito e hospitalização) de pacientes sob hemodiálise. **Método:** Trata-se de um estudo de coorte prospectivo observacional com pacientes pre avaliados 221 pacientes adultos, considerando-se os valores de hemoglobina, proteína C reativa (PCR), albumina sérica no início do estudo. A ocorrência de hospitalização e óbito foi computada em um seguimento aproximado de 13 meses. **Resultados:** A ocorrência de hospitalização e óbito não diferiu entre os grupos com e sem anemia (Hb  $\leq$  10g/dL) ou inflamação (PCR  $\geq$  0,5mg/dL). Houve um maior número de hospitalização entre os pacientes com hypoalbuminemia. A albumina não apresentou correlação com os níveis séricos de PCR. Observou-se um menor tempo livre de hospitalização entre os pacientes com hypoalbuminemia ( $p = 0,008$ ), houve uma tendência de menor tempo livre de hospitalização entre os pacientes com PCR aumentado ( $p = 0,08$ ), e a anemia não se relacionou com o tempo livre de hospitalização. Não houve diferença na sobrevida em relação à presença de anemia, inflamação e hypoalbuminemia. A análise de regressão de Cox apontou a hypoalbuminemia como fator independente relacionado à hospitalização, mesmo após ajustes para idade, presença de diabetes, PCR e hemoglobina. **Conclusão:** A hypoalbuminemia, e não anemia ou inflamação, mostrou-se um marcador independente de hospitalização em pacientes submetidos à hemodiálise.

**Palavras-chave:** anemia; diálise; hypoalbuminemia; inflamação.

## INTRODUCTION

Despite the technological advances of recent decades, the morbidity and mortality of patients undergoing hemodialysis remains very high.<sup>1-3</sup> National data is scarce. Sesso *et al.*<sup>4</sup> reported that the annual mortality rate was 17.9% and the monthly hospitalization rate was 5.8%. Several are the factors associated with this high prevalence; among them we stress anemia, inflammation and hypoalbuminemia.<sup>5-7</sup>

Anemia is an often-found complication in patients with chronic kidney disease (CKD), especially in those undergoing dialysis. The 2012 data from the Brazilian Society of Nephrology census showed that 34.4% of hemodialysis patients had anemia.<sup>4</sup> This condition is associated with cardiovascular alterations, and a marked increase in the risk of hospitalization and mortality.<sup>5,6,8,9</sup> Similarly to anemia, inflammation is a common complication of CKD.<sup>10</sup> Studies suggest that the levels of proinflammatory cytokines are 8 to 10 times higher in chronic renal failure patients when compared to healthy individuals.<sup>11</sup> C-reactive protein (CRP) is considered a good marker of inflammation in this population and is associated with the progression of atherosclerosis and cardiovascular events, being an independent predictor of hospitalization and mortality.<sup>12,13</sup> Albumin, a protein that increases in the acute phase of inflammation, has been consistently considered a marker of inflammation in that population.<sup>14</sup> However, the decrease in albumin concentration may represent an inadequate nutrient intake, also being a nutritional status indicator.<sup>15,16</sup>

In fact, in some studies, adequate nutritional supplementation improves hypoalbuminemia and clinical outcome.<sup>17</sup> The International Society of Renal Nutrition and Metabolism considers hypoalbuminemia, defined by a serum albumin value < 3.8 g/dL, a marker of nutritional risk.<sup>18,19</sup> Hypoalbuminemia has been associated with an increased risk of morbidity and mortality in patients undergoing hemodialysis.<sup>18,19</sup>

There is very little data on people on dialysis in the North and Northeast of Brazil, which have different socioeconomic characteristics of other regions in the country. A recent study of patients on dialysis in Sao Luiz do Maranhao showed that the incidence of anemia and hypoalbuminemia were well above the national average.<sup>20</sup> The role of these complications in outcomes in populations of the North and Northeast regions has not yet been established. The

objective of this study was to evaluate the impact of anemia, inflammation and hypoalbuminemia on the occurrence of hospitalization and death in patients undergoing hemodialysis in two centers in Maceio, in the Brazilian Northeast.

## METHODS

The study population consisted of a convenience sample, in which all adult patients (n = 275) in the hemodialysis programs of the Ribamar Vaz Nephrology Institute of the Santa Casa de Maceio Hospital (INRV-SCMM) and the Kidney Disease Center of the Sanatorium Hospital (CDR-Sanatorium) were invited to participate. Inclusion criteria were age > 18 years and being on dialysis for more than three months, and the exclusion were: patients who were absent on the day of collection (n = 2) and those with active infection in the blood collection date (n = 5), or those refused to participate in the study (n = 47). Of the 221 patients who participated in the study, 11 (4.9%) had temporary catheter at the start of the study. Water treatment and capillaries reuse followed the standards set by the Brazilian legislation in the two dialysis centers throughout the study period.

## STUDY DESIGN

In this prospective observational study, patients with CKD on hemodialysis programs were followed up for approximately 1 year. Clinical and demographic data and erythropoietin and intravenous iron doses were collected from medical records of patients and from a structured medical interview at baseline. Data on the occurrence of events were evaluated monthly by medical records. Hospitalization was defined as a hospital stay for a period exceeding 12 hours.

## LABORATORY EVALUATION

Routine examinations of dialysis centers were used in the study, collected during the second dialysis in the week before the session. From the whole blood samples we evaluated: hemoglobin (Hb), serum ferritin (turbidity), transferrin saturation (TSAT), ultrasensitive C-reactive protein (CRP, immunochemiluminescence - Immulite, DPC-Biermann DPC, Hessen, Germany) and serum albumin (immunoturbidimetry), at the beginning of the follow-up period. Anemia was considered when Hb < 10 g/dL<sup>21</sup> and hypoalbuminemia as albumin < 3.8 g/dL.<sup>19</sup> Inflammation was assessed both by the

presence of increased CRP ( $\geq 0.5$  mg/dL)<sup>22</sup> alone, or together with hypoalbuminemia.

#### STATISTICAL ANALYSIS

The data was expressed as mean and standard deviation or median and interquartile range. Comparisons between groups were made by the Student's *t* and the Mann-Whitney tests, according to the characteristics of the variables. Chi-square or Fisher tests were used to compare proportions when appropriate. A Univariate analysis with the Spearman correlation test was used to assess the relationship between CRP and albumin. Hospitalization-free time and death were estimated by the Kaplan-Meier method and compared by the long-rank test. The Cox regression analysis was used to assess whether anemia, inflammation and hypoalbuminemia were independently associated to hospitalization. The model was adjusted for age and diabetes and the associations were described by hazard ratios and a 95% confidence interval. A *p* value  $<0.05$  was considered statistically significant. The analyses were performed using the SPSS for Windows (Version 18 SPSS Inc., Chicago, IL).

#### RESULTS

The clinical and demographic characteristics of the 221 patients are shown in Table 1. Most of the patients were middle-aged man, one third of them being diabetic and the mean dialysis duration was 7 years. The population was made up of low-income families, and 80% earned less than 3 minimum wages/month/family; and 37% received less than one minimum wage/month/family.

At baseline, anemia was present in 36% of patients and 63% had hypoalbuminemia. Inflammation, as assessed by the presence of increased CRP, was present in 49%. However, when assessed by the presence of two markers (hypoalbuminemia and increased CRP), it was present in 33% of the patients.

Upon comparing patients with and without anemia, we found that those with anemia were younger [47 (34-58) *vs.* 52 (40-63) years, *p* = 0.02] and there was no difference between the groups in terms of gender, presence of diabetes, dialysis time, CRP, and albumin. When comparing patients with inflammation (with high CRP

**TABLE 1** BASELINE DEMOGRAPHIC, CLINICAL AND LABORATORY CHARACTERISTICS OF THE PATIENTS

Variable	Total
N	221
Age (years)	50 (38-63)
Male gender	130 (59%)
Time in hemodialysis (years)	7 (4-9)
Diabetes	64 (29%)
Kt/V	1.4 (1.2-1.6)
Ferritin (ng/dl)	424.8 (212.5-560)
Transferrin saturation (%)	29.8 $\pm$ 10.6
Hemoglobin (g/dl)	10.6 $\pm$ 1.9
C-Reactive Protein (mg/dl)	1.0 (0.19-1.29)
Albumin (g/dl)	3.6 (3.4-3.9)

Median (interquartile range); mean  $\pm$  standard deviation.

and concomitant hypoalbuminemia) and those without inflammation, we found that those with inflammation were older [57 (40-67) *vs.* 50 (36-61) years, *p* = 0.01] and there was no difference between the groups in terms of gender, presence of diabetes, dialysis duration and Hb. When we compared the patients with and without increased CRP, those with CRP  $\geq 0.5$  mg/dL were older [54 (42-65) *vs.* 46 (34-57) years, *p* < 0.001], there were no other differences between the groups. There was no difference between patients with normal albumin and hypoalbuminemia as to age, gender, presence of DM, duration of dialysis and CRP. There was no correlation between CRP concentrations and albumin (*r* = -0.1, *p* = 0.14).

The doses of erythropoietin were higher in patients with anemia, when compared to those without anemia [12,000 Units/week (12000-12000) *vs.* 8,000 Units/week (0-12000), *p* < 0.00], while the iron doses did not differ [200 mg/month (0-800) *vs.* 200 mg/month (0-800), *p* = 0.73]. The doses of erythropoietin and iron were not different in patients with and without increased CRP [12,000 units/week (0-12000) *vs.* 8000 units/week (0-12000), *p* = 0.25]; and [200mg/month (0-800) *vs.* 200 mg/month (0-800), *p* = 0.97], respectively; and in patients with and without hypoalbuminemia [8,000 units/week (0-12000) *vs.* 8,000 units/week (0-12000), *p* = 0.72]; and 200 mg/month (0-800) *vs.* 200mg/month (0-800), *p* = 0.14], respectively.

The patients were followed for about 13 months (389  $\pm$  35 days). There were 71 hospitalizations

in this period: 25 (35.2%) from cardiovascular disease; 23 (32.4%) due to infection and 23 (32.4%) for other causes. The mean hospital stay was 4 (2-8) days. During the study, there were 7 deaths, all in hospitalized patients: 1 (14.3%) from cardiovascular disease, 4 (57.1%) due to infection and 2 (28.6%) from other causes. During the study, 4 patients were transplanted and 3 were transferred to another dialysis center.

Hospitalization and death among patients vis-à-vis the presence or absence of anemia, increased CRP and hypoalbuminemia are shown in Table 2. Hospitalization was significantly higher in patients with hypoalbuminemia, but there was no difference between patients with anemia or increased CRP. There was no difference in mortality in relation to anemia, increased CRP or hypoalbuminemia. It is noteworthy that the doses of erythropoietin and iron did not differ when comparing hospitalized patients with their non-hospitalized counterparts, [12,000 units/week (0-12000) vs. 8,000 units/week (0-12000),  $p = 0.32$ ]; and [200mg/month (0-800) vs. 200 mg/month (0-800),  $p = 0.97$ ], respectively. There was also no difference between patients who died or those who did not die [12,000 units/week (8000-12000) vs. 8,000 units/week (0-12000),  $p = 0.85$ ]; and [200mg/month (100-800) vs. 200mg/month (0-800),  $p = 0.92$ ], respectively.

Patients with albumin < 3.8 g/dL had a shorter hospital-free time ( $p = 0.01$ ), there was a trend of less hospitalization-free time among patients with increased CRP ( $p = 0.08$ ). Anemia was not associated with hospitalization-free time (Figure 1). There was no difference in survival in relation to anemia, increased CRP and hypoalbuminemia (Figure 2).

The Cox analysis showed only hypoalbuminemia as an independent factor related to hospitalization, even after adjusting for age, presence of diabetes, anemia and inflammation (Table 3). In the Cox regression analysis, anemia, increasing CRP and hypoalbuminemia were not determinants of death.

## DISCUSSION

In the present study in which a population of CKD patients subjected to hemodialysis in Maceio was evaluated, we found that hypoalbuminemia, and not anemia or inflammation, was an independent factor associated with hospitalization in one year follow up. The occurrence of death was not related to anemia, inflammation or hypoalbuminemia.

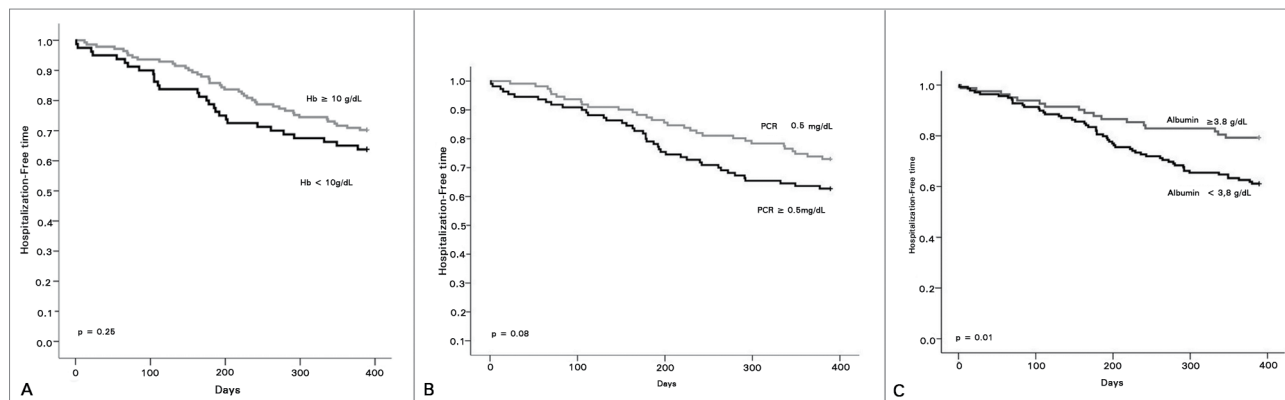
**TABLE 2** HOSPITALIZATION AND DEATH IN THE GROUPS OF PATIENTS WITH AND WITHOUT ANEMIA, INFLAMMATION AND HYPOALBUMINEMIA

Anemia	Hb < 10 g/ dL	Hb ≥ 10 g/ dL	<i>p</i>
	N = 80	N = 141	
Hospitalization	29 (36%)	42 (30%)	0.32
Óbito	4 (5%)	3 (2%)	0.24
Inflammation	PCR ≥ 5 mg/dL	PCR < 5 mg/dL	<i>p</i>
	N = 108	N = 113	
Hospitalization	41 (38%)	30 (26.5%)	0.10
Death	5 (4,6%)	2 (1.8%)	0.24
Hypoalbuminemia	Alb < 3,8 g/dL	Alb ≥ 3.8 g/ dL	<i>p</i>
	N = 139	N = 82	
Hospitalization	54 (39%)	17 (21%)	< 0.001
Death	5 (3.6%)	2 (2.4%)	0.63

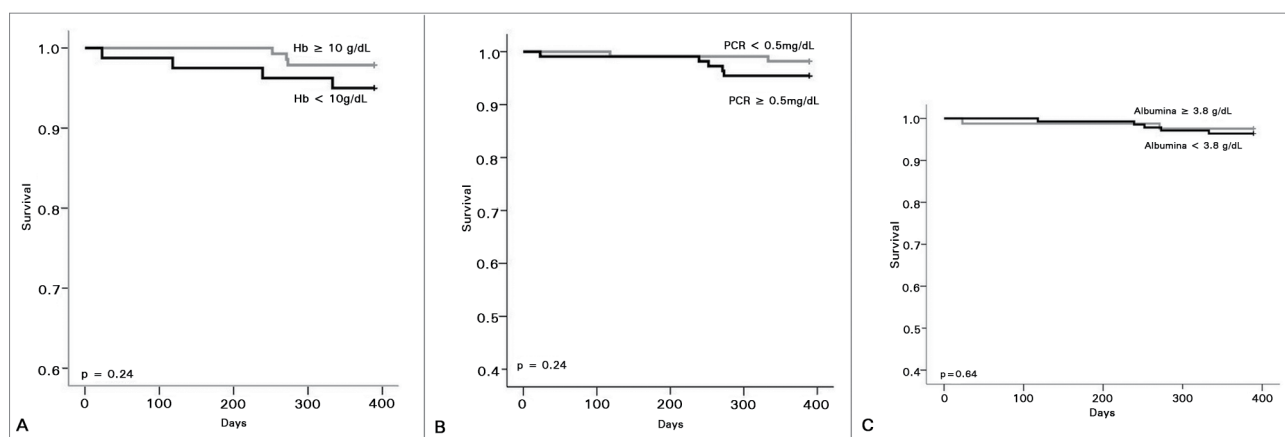
The prevalence of anemia described in the 2012 census by the Brazilian Society of Nephrology (SBN) was 34% in patients on dialysis, considering Hb < 11 g/dL in the definition of anemia. In this study, a similar prevalence has been described, but anemia was considered only when Hb < 10 g/dL. Using the same criteria above, this same prevalence would be 54%, higher than the national average, and closer to what was found in a recent study in another Northeastern capital (63.6%).<sup>20</sup> Intriguingly, patients with anemia were younger - a fact that may partly explain the lack of association between anemia and hospitalization or death in this study. This result differs from national and international data,<sup>5,6,8,9,23</sup> and we could not find an explanation for this finding.

Inflammation was present in about 50% of the study population, a prevalence similar to that described in national studies that point to increased CRP in 38-59% of patients on hemodialysis.<sup>7,10</sup> It is noteworthy that there is still no consensus on the concentration of CRP from which inflammation is defined in uremic patients.<sup>21</sup> Wanner *et al*<sup>24</sup> suggested that a CRP > 0.5 mg/L should be considered abnormal in this population. Furthermore, CRP levels fluctuate significantly over time in the same patient, and sequential samples appear to be more effective than single samples to identify a population with inflammation.<sup>22</sup> Inflammation has been associated with worse outcomes in numerous studies.<sup>12,13,25</sup> In this study, there was a trend towards shorter

**Figure 1.** Hospitalization-free time in patients with and without anemia (A), inflammation (B) and hypoalbuminemia (C).



**Figure 2.** Comparison of survival between patients with and without anemia (A), inflammation (B) and hypoalbuminemia (C).



**TABLE 3** COX REGRESSION ANALYSIS FOR FACTORS ASSOCIATED WITH HOSPITALIZATION

	Hazard Ratio	Confidence Interval (95%)	p
Albumin < 3.8 g/dl	2.10	1.21 - 3.63	0.01
Age (years)	1.00	0.99 - 1.02	0.43
Diabetes	1.35	0.78 - 2.33	0.28
Hb > 10 g/dl	1.37	0.84 - 2.23	0.20
PCR ≥ 0.5 mg/dl	1.44	0.88 - 2.34	0.14

hospitalization-free time in patients with increased CRP. The low occurrence of death and the measurement of CRP only may be possible explanations for not having observed a relationship between inflammation and mortality in this population.

The prevalence of hypoalbuminemia in hemodialysis patients in Brazil varies from 15 to 85.3%. This wide variability can be partially explained by the value used to define hypoalbuminemia and the characteristics of the populations studied. In the 2012 SBN census, the incidence of hypoalbuminemia in hemodialysis patients was 15.2%, considering a

serum albumin < 3.5 g/dL.<sup>4</sup> In a study carried out in another Northeastern Brazilian capital, with most patients (87%) belonging to socioeconomic classes C, D and E, it was reported that 85.3% of patients had albumin < 4.0 g/dL.<sup>20</sup> In our study the occurrence was high, 63% considering serum albumin < 3.8 g/dL and it would have been 33% (data not shown), if we had considered albumin < 3.5 g/dL. This high incidence, higher than the national average, can be associated with the low income of the population studied and the extended time on dialysis.

Hypoalbuminemia was the only factor associated with hospitalization in this study. Although albumin is a protein of the acute phase of inflammation, we found no relation between the concentration of albumin and CRP, which may suggest that in this population, hypoalbuminemia is reflecting an unfavorable nutritional status. Unfortunately other nutritional parameters were not available to enable an accurate diagnosis of the nutritional status of this population. In a recent study, patients with albumin < 3.8 g/dL who received early nutritional intervention

had a longer hospitalization-free time.<sup>17</sup> However, the nutritional intervention had no effect on mortality.<sup>17</sup> The increased risk of mortality seems to be associated with lower serum levels of albumin (< 2.5 g/dL).<sup>26</sup>

Despite the relatively small sample size, short follow-up and a third of hospital admissions not being related to infection or cardiovascular disease, this study was able to identify hypoalbuminemia as a marker of morbidity in a characteristic population of Northeastern Brazil. A better characterization of nutritional parameters and serial measurements of CRP or measurement of other markers of inflammation would enable a better understanding of the clinical significance of low serum albumin in this population.

This study showed hypoalbuminemia, and no anemia or increased CRP as an independent risk marker for hospitalization in patients undergoing hemodialysis.

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