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Serum Prealbumin Levels on Admission as a Prognostic Marker in Stroke Patients Treated with Mechanical Thrombectomy

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Keywords
Prealbumin · Acute stroke · Mechanical thrombectomy · Modified Rankin scale · Mortality

Abstract
Introduction: Prealbumin is a marker of malnutrition and inflammation. It has been associated with poor prognosis in cardiovascular disease, but less is known in stroke patients. Our objective was to evaluate the association of prealbumin levels at admission with prognosis in patients with stroke treated with mechanical thrombectomy. ***Methods:*** Retrospective study of a prospective database of consecutive patients treated with mechanical thrombectomy. Clinical, radiological, and blood parameters including serum prealbumin, and prognostic variables such as respiratory infection, in-hospital mortality, and the modified Rankin scale at 3 months were collected. ***Results:*** We included 319 patients between 2018 and 2019. Prealbumin levels were significantly lower in patients older than 80 years, women, patients with a prestroke Rankin score >2, a glomerular filtrate rate <60 mL/min, and in those with atrial fibrillation. Regarding prognostic variables, prealbumin levels were not associated with respiratory infection. Low prealbumin levels were associated with poor functional prognosis (Rankin score >2), in-hospital mortality, and 3-month mortality. In multivariate analysis, prealbumin was an independent risk factor associated with mortality at 3 months, OR 0.92 [0.86–0.98], p = 0.019. ***Conclusion:*** Lower prealbumin levels at admission behaved as an independent predictor of long-term mortality in patients treated with mechanical thrombectomy. These results should be replicated in other cohorts.

Introduction

Prealbumin (also known as transthyretin) is a low-weight protein synthesized in the liver. Its normal plasma levels range from 17 to 42 mg/dL. This molecule participates as a transport protein, being a marker of malnutrition and liver disease, but also of acute inflammation.

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In previous studies, it has been demonstrated that low prealbumin concentrations are associated with poor prognosis in patients with heart disease [1, 2]. However, there are few studies that correlate prealbumin levels and prognosis in stroke patients [3, 4]. The aim of this study was to evaluate the association between serum prealbumin levels at admission and functional prognosis and mortality in patients with acute ischemic stroke treated with mechanical thrombectomy (MT).

Methods

Patients' Selection and Data Collection

We conducted a single-center retrospective study from a prospective database of consecutive patients with acute ischemic stroke treated with mechanical thrombectomy in our hospital between January 2018 and December 2019. Inclusion of data in this prospective database has been approved by the Ethic Committee of our center. Baseline characteristics of all patients were registered, including age, gender, vascular risk factors, previous comorbidities such as stroke or heart disease, toxic habits, and premorbid functional basal status. We recorded data about the clinical presentation of stroke (NIHSS), radiological findings, and analytical results at the time of admission and in the first 24 h after admission. We recorded serum prealbumin levels in the first 24 h after admission. During follow-up, we registered the presence of post-thrombectomy complications, respiratory infections, and rates of mortality during hospitalization. After discharge, an in-person visit or a telephonic interview with the patient or their caregiver was made to evaluate functional status using the modified Rankin scale (mRS). Laboratory personnel that measured prealbumin levels were blinded to clinical outcomes, and investigators that assessed clinical outcomes at 3-month post-stroke were also unaware of prealbumin levels at the moment of outcome evaluation).

Statistical Analysis

Quantitative variables were expressed as mean (SD) in cases of normal distribution or median (interquartile range [IQR]) otherwise. Qualitative variables were expressed as frequencies (percentages). Bivariate comparisons were made using the *t* test or Mann-Whitney U test for quantitative variables and the χ^2 test for categorical variables. Taking median prealbumin levels of the sample, baseline characteristics were compared between patients with prealbumin levels ≤17 mg/dL and those with prealbumin levels >17 mg/dL.

The main objective of our study was to evaluate the association between serum prealbumin levels at admission and the degree of functional dependence and mortality at 3 months after discharge. We used the mRS to evaluate the degree of dependence, a mRS <3 being a marker of good outcome. As secondary outcomes, we also evaluated the association of prealbumin levels and respiratory infection or mortality during hospitalization. We constructed a multivariate logistic regression model for each outcome including prealbumin levels as a continuous variable, including covariates related to prealbumin levels in the univariate analysis with a $p < 0.05$ and also including known variables related with outcome in stroke patients (such as a NIHSS or ASPECTS scale). Also, we constructed a ROC curve analysis to approximate a cutoff point of prealbumin levels more associated with prognosis. We used IBM SPSS Statistics program, version 19.0.

Results

Between January 1, 2018, and December 31, 2019, we collected data from 319 patients admitted to our hospital presenting an acute ischemic stroke (mean age 74 years, 50% women, median NIHSS 16), all of whom received endovascular treatment with mechanical thrombectomy.

Baseline Characteristics

Baseline characteristics of the whole sample and comparing those with prealbumin levels higher, lower or equal than 17 mg/dL are represented in Table 1. Patients with lower prealbumin levels were significantly older, more frequently women, had more often a prestroke mRS >2, a glomerular filtration rate (GFR) <60 mL/min and harbored more atrial fibrillation diagnosis (AF). There were no differences in body mass index among those with higher or lower prealbumin levels. Active smokers were more frequently found in the group of higher prealbumin levels (26.3 vs. 4.2%), probably due to age and gender differences among groups. Levels of total cholesterol, LDL-cholesterol, and triglycerides were positively correlated with prealbumin levels (Spearman coefficients 0.41, 0.34, and 0.27, respectively, $p < 0.001$) but lipid levels were not significantly associated with functional prognosis or mortality in our sample.

Stroke severity at admission, ASPECTS score in baseline CT, site of vessel occlusion, use of prior alteplase, TOAST ethology, and recanalization rates were similar among those with higher or lower prealbumin levels (Table 1). TOAST ethology was also similar among groups of prealbumin levels, with 51% of cardioembolic etiology in our sample.

Follow-Up and Prognosis

Clinical follow-up was conducted during hospitalization and 3 months after stroke. During hospitalization, respiratory infection was diagnosed in 53 patients (16.6%) and there was no statistically significant association with prealbumin levels (mean prealbumin levels in the group without respiratory infection of 19.1 ± 5.5 mg/dL vs. 17.74 ± 5.7 mg/dL) in the group with respiratory infection ($p = 0.104$). 13 out of 319 patients (4.1%) presented symptomatic intracranial hemorrhage (SICH). There were no differences between those patients with lower or higher

Table 1. Baseline characteristics

	Total (n = 319)	Prealbumin levels ≤17 (n = 142)	Prealbumin >17 (n = 177)	p value
Median age (±SD), years	73.93 (±13.78)	81 (±10.68)	72 (±14.59)	0.000
Age >80 years, *n* (%)	155 (48.59)	93 (65.49)	62 (35.03)	0.000
Gender (female), *n* (%)	159 (49.84)	89 (62.7)	70 (39.5)	0.000
High blood pressure, *n* (%)	205 (64.67)	96 (62.6)	109 (62.3)	0.324
Diabetes mellitus, *n* (%)	74 (23.20)	37 (26.1)	37 (20.9)	0.279
Dyslipidaemia, *n* (%)	158 (49.53)	64 (45.1)	94 (53.1)	0.154
Atrial fibrillation, *n* (%)	152 (48.25)	84 (59.6)	68 (39.1)	0.000
Ischemic heart disease, *n* (%)	49 (15.46)	23 (16.3)	26 (14.8)	0.706
Previous stroke, *n* (%)	56 (17.55)	30 (21.1)	26 (14.7)	0.133
BMI (mean±SD)	27.64 (±4.77)	28 (±6.25)	27.30 (±3.85)	0.422
GRF <60, *n* (%)	109 (34.71)	57 (41)	52 (29.7)	0.037
Premorbid mRS >2, *n* (%)	68 (21.32)	42 (29.8)	26 (14.74)	0.001
NIHSS at admission (median [p25/p75])	16 [11–20]	17 [12–20]	15 [11–19]	0.443
ASPECTS (median [p25/p75])	9 [7–10]	9 [8–10]	8 [7–10]	0.759
Affected vessel territory, *n* (%)				0.796
Anterior circulation	300 (94.04)	133 (93.7)	167 (94.4)	
Posterior circulation	19 (5.96)	9 (6.3)	10 (5.6)	
Recanalization treatment, *n* (%)				0.151
Combined (IV + MT)	46 (14.42)	16 (11.3)	30 (16.9)	
MT alone	273 (85.58)	126 (88.7)	147 (83.1%)	
Full recanalization (TICI 2b/3), *n* (%)	280 (87.77)	155 (88.03)	125 (87.57)	0.901
SICH, *n* (%)	13 (4.1)	5 (3.5)	8 (4.5)	0.646

Data are presented as frequency (percentage) unless otherwise indicated. SD, standard deviation; IQR, interquartile range; BMI, body mass index; GFR, glomerular filtration rate; mRS, modified Rankin Scale; MT, mechanical thrombectomy; IV, intravenous fibrinolysis; SICH, symptomatic intracranial hemorrhage.

prealbumin levels at admission (3.5 vs. 4.5%, respectively, $p = 0.646$).

In-hospital mortality occurred in 19 (6%) of patients. During 3-month follow-up, mortality occurred in 119 (21.68%) of patients. As shown in Figure 1, a significant association between lower prealbumin levels and mortality during hospitalization and at 3 months was found. A statistical association was also observed between lower levels of prealbumin and a greater dependence at 3 months. In multivariate regression analysis adjusted for age, sex, presence of AF, NIHSS score at admission, ASPECTS score, baseline mRS, and renal glomerular filtration, prealbumin levels at admission emerged as independent predictor of mortality at 3 months (OR 0.92 [0.86 0.98], $p = 0.019$) together with poor prestroke functional status and with ASPECTS score (Table 2). In the ROC curve analysis, AUC was 0.67 [0.60–0.74] (<0.01) for 3rd month mortality and a cutoff point of 12 mg/dL or lower (sensitivity 0.25, specificity 0.91) behaved as an independent predictor of 3rd month mortality with an OR of 2.75 (1.21–6.28) in the same multivariate model. However, baseline prealbumin levels was not an independent predictor of other outcomes (in-hospital mortality and functional prognosis mRS <3) in adjusted multivariable regression models.

Table 2. Multivariate analysis: prognostic factors and 3rd month mortality

	3rd month mortality	
	OR [95% CI]	p value
Gender (female)	1.205 [0.613–2.370]	0.589
Atrial fibrillation	1.150 [0.597–2.219]	0.676
NIHSS	1.050 [0.991–1.113]	0.97
ASPECTS	0.753 [0.600–0.945]	0.014
Prealbumin levels	0.922 [0.862–0.987]	0.019
Previous mRS ≤2	0.401 [0.198–0.816]	0.012
GFR	1.456 [0.752–2.819]	0.266
Age (over 80 years)	1.845 [0.854–3.983]	0.119

mRS, modified Rankin Scale; GFR, glomerular filtration rate.

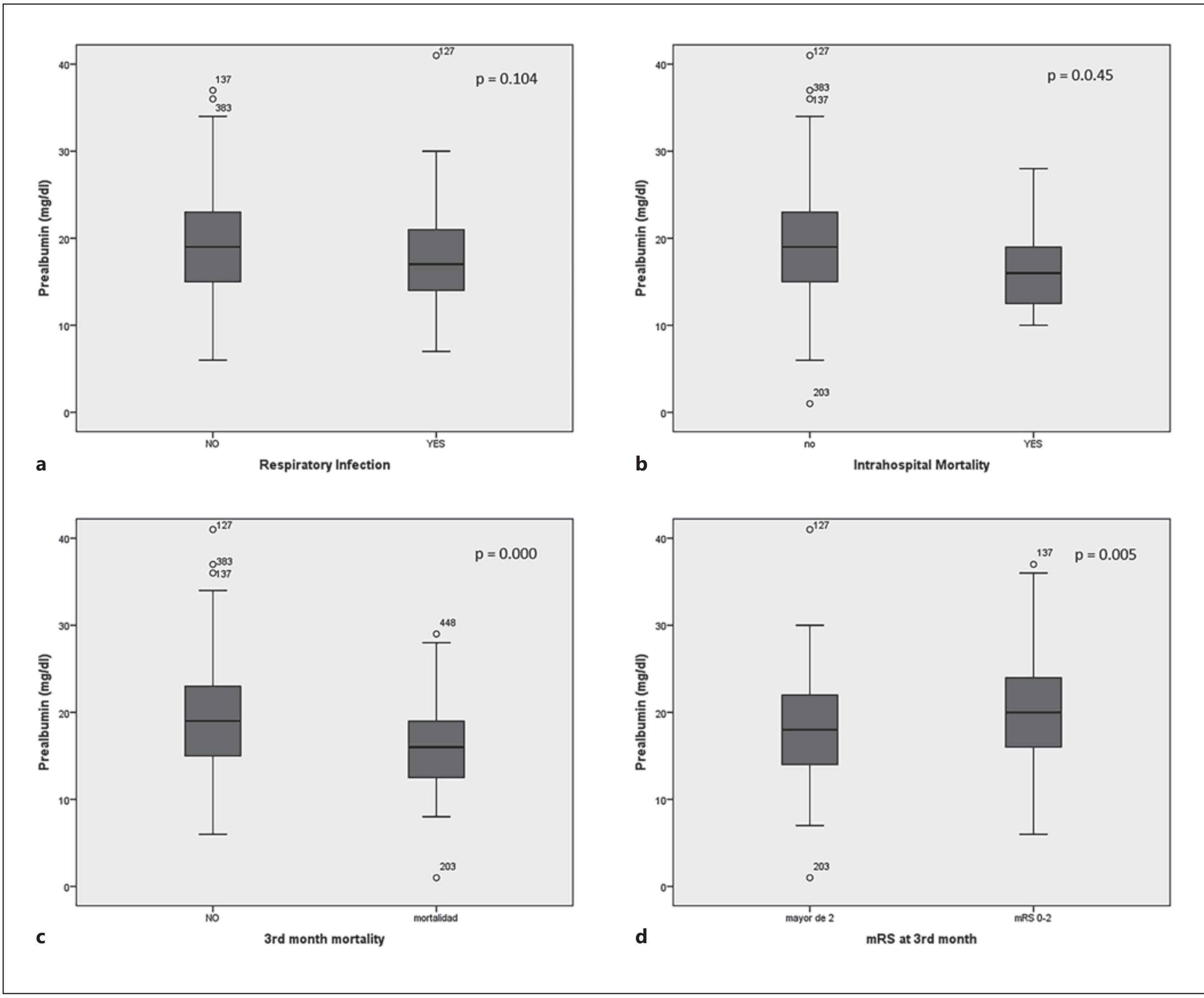

Fig. 1. Association between prealbumin levels at admission and prognostic factors: prevalence of respiratory infection (**a**), rates of intrahospital (**b**) and 3rd month mortality (**c**), and mRS at 3 months (**d**).

Discussion

In our cohort of patients with ischemic stroke treated with mechanical thrombectomy, lower prealbumin levels at admission were independently associated with mortality at 3 months after stroke. Although often related to malnutrition [5, 6] and infections [7], prealbumin levels were not associated with BMI nor respiratory infection in our cohort.

In our study, prealbumin levels were lower in older patients, females, patients with renal impairment and those with worse prestroke functional status. Hence, low prealbumin levels might be a marker of a proinflammatory state or frailty status: prealbumin works as a negative acute-phase protein and its synthesis can be reduced and even suppressed by many of the cytokines who play a role in the inflammatory process. Several of these cytokines, such as TNF-a, play a role in the pathogenesis of atherosclerosis, which has been related to an increase in the risk of poor outcomes in patients with cardiovascular disease [8]. In patients with acute stroke, there's an increase of proinflammatory cytokines due to CNS damage that might contribute to a decrease of prealbumin concentrations [4]. Recently, an association between prealbumin levels and poor outcomes and mortality after contrast-induced renal impairment has been seen since prealbumin has been related to higher systemic inflammation, oxidative stress, and endothelial dysfunction, all of them associated with renal failure and its poorer outcome [8]. Therefore, prealbumin levels are negatively correlated with the presence of inflammatory markers that take part in endothelial damage. This vascular involvement participates in the pathogenesis and prognosis of patients with cardiovascular and cerebrovascular disease.

Ambrosius et al. [3] evaluated the association of low transthyretin levels and a poorer outcome in 81 patients with ischemic stroke. In their sample, patients were slightly younger than in ours (median age. 67 vs. 73.94 years) with a predominance of masculine gender. The same vascular risk factors were found. In this study, levels of prealbumin were checked in the first 24 h of admission, and lower levels of prealbumin were found as an independent risk factor for poor outcome (mRS >3 at 3 months). Zhang et al. [4] studied the effect of lower prealbumin levels in 105 patients suffering from hemorrhagic stroke. Patients were younger than those in our cohort (median age 41.5 years) with a predominance of male patients. There were higher rates of hypertension (76.2 vs. 64.67%) and diabetes mellitus type 2 (35.24 vs. 23.20%). Dyslipidemia rates and BMI were lower in Zhang's cohort. Serum levels of prealbumin were checked at time of admission, and at day 3, 6, 9 and between days 14–21 after admission. In this study, prealbumin levels were significantly lower in patients who developed an infection during hospitalization and was found also to be a risk factor for poor outcomes at time of discharge (measured by the Glasgow Outcome Score [GOS]). In congruence with those studies, we have observed a statistically significant association between prealbumin levels and a greater dependence at 3 months after stroke, despite these differences being not statistically different after multivariate analysis in our cohort (Table 2).

We would like to mention that we observed a statistically significant association between low prealbumin levels and the presence of atrial fibrillation in our patients (Table 1). Most of the patients of our cohort are aged over 80 years, age being the principal risk factor for atrial fibrillation. However, further investigation will be needed to determine the causality between the presence of atrial fibrillation and prealbumin levels.

Our study had some limitations. We did not record other infections different from respiratory infections, and we did not record other inflammatory markers such as CRP levels on admission nor premorbid inflammatory conditions such as cancer or autoimmune diseases that may be related to prealbumin levels. Moreover, we only have the determination of prealbumin levels at admission (baseline), so we cannot evaluate the possible differences in prealbumin levels throughout admission and their prognostic significance. Finally, we did not register the cause of mortality to study its possible association with prealbumin levels.

Conclusion

In view of the results obtained in this study, it can be concluded that low prealbumin levels at admission behave as independent predictors of poor outcome and mortality at 3 months after ischemic stroke treated with mechanical thrombectomy. These results need to be replicated in further cohorts.

Statement of Ethics

This study protocol was reviewed and approved by Comité de ética de la Invetigación de Medicamentos del Principado de Asturias, approval number 2020-254. Our study constitutes a retrospective observational study, therefore, written informed consent was not required.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Elena López-Cancio: methodology and conceptualization of the study, data collection, formal analysis, and writing review & editing. Begoña López: participant investigator (data collection), formal analysis, and original draft writing. Maria Castañón-Apilánez: participant investigator (data collection), formal analysis, and writing review. Javier Molina-Gil, Santiago Fernández-Gordón, Gemma González, Antia Reguera Acuña, José Jiménez, Davinia Larrosa Campo, Montserrat González Delgado, Lorena Benavente Fernández, Maria Rico-Santos, Carmen García-Cabo, and Sergio Calleja Puerta: participant investigator (data collection) and writing review.

Data Availability Statement

All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

References

1 Wang W, Ren D, Wang CS, Li T, Yao HC. High sensitivity C-reactive protein to prealbumin ratio measurement as a marker of the prognosis in acute coronary syndrome. Sci Rep. 2019;9(1):11583–7.

2 Wang W, Wang CS, Ren D, Li T, Yao HC, Ma SJ. Low serum prealbumin levels on admission can independently predict in-hospital adverse cardiac events in patients with acute coronary syndrome. Medicine. 2018;97(30): e11740.

3 Ambrosius W, Michalak S, Kazmierski R, Andrzejewska N, Kozubski W. Predictive value of serum transthyretin for outcome in acute ischemic stroke. PLoS One. 2017;12(6): e0179806.

4 Zhang SQ, Peng B, Stary CM, Jian ZH, Xiong XX, Chen QX. Serum prealbumin as an effective prognostic indicator for de-termining clinical status and prognosis in patients with haemorrhagic stroke. Neural Regen Res. 2017;12(7):1097–1102.

5 Magadan C, Figueroa JF, Muino M, Seijo G, Fernández-Saya B, Cobelo C. Valores de referencia de proteinas marcadoras del estado nutricional: albumina, prealbumina Y transferrina. Rev la Soc Esp Quim Clin. 1992;11(3): 151–5.

6 Zhang Z, Pereira SL, Luo M, Matheson EM. Evaluation of blood biomarkers associated with risk of malnutrition in older adults: a systematic review and meta-analysis. Nutrients. 2017;9(8):E829.

7 Ye S, Lin SP, Wu K, Fan Y, Xu M. Serum prealbumin is a predictive biomarker for stroke-associated infection after an ischemic stroke. Int J Neurosci. 2017;127(7):601–5.

8 You ZB, Lin KY, Zheng WP, Lin CJ, Lin F, Guo TL, et al. Association of prealbumin levels with contrast-induced acute kidney injury in elderly patients with elective percutaneous coronary intervention. Clin Interv Aging. 2018;13:641–9.