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Albumin Level and Stroke. Potential Association Between Lower Albumin Level and Cardioembolic Aetiology

F. J. Alvarez-Perez,[1,2] M. Castelo-Branco,[1,2] and J. Alvarez-Sabin[3]

[1]*Department of Medicine, Research Center in Health Sciences, Faculty of Health Sciences, Beira Interior University, Covilhã, Portugal*

[2]*Stroke Unit, Hospital of Covilhã, Portugal*

[3]*Neurovascular Unit, Department of Neurology, Hospital Universitari Vall d'Hebron, Universitat Autonoma de Barcelona, Spain*

ABSTRACT

Background: Lower level of albumin was related to worse prognosis of stroke and clinical trials showed that albumin therapy reduced mortality. However, stroke is heterogeneous and differences in the baseline concentration of albumin among subtypes of stroke were not assessed. The aim was to assess albumin level in patients with ischemic stroke classified by mechanism. *Methods*: Prospective controlled clinical study, including 200 patients with ischemic stroke and 50 controls. Patients were classified following Trial of ORG 10172 in Acute Stroke Treatment criteria. Plasma levels of albumin, fibrinogen, D-dimer, and C-reactive protein were assessed during 48 hr after admission. The National Institutes of Health Stroke Scale (NIHSS) on admission, in-hospital mortality, and Rankin score on discharge were recorded. Dependence was defined as mRS>2. *Results*: Patients with cardioembolic stroke showed significantly higher D-dimer and lower albumin. Mortality was related to higher NIHSS, higher D-dimer, lower albumin, and cardioembolic aetiology. Dependence was strongly related to lower albumin and higher NIHSS. *Logistic regression*: The cardioembolic aetiology (OR 0.101, 95% CI 0.010–1.007, $p = .051$) and the higher NIHSS score (OR 0.871, 95% CI 0.758–1.002, $p = .053$) were related to mortality; NIHSS (OR 1.560, 95% CI 1.323–1.838, $p < .0001$) and older age (OR 1.052, 95% CI 1.012–1.093, $p = .010$) were independently related to dependence. *Discussion*: Patients with cardioembolic stroke showed lower albumin and higher risk of mortality than non-cardioembolic ones. Lower mean level of albumin was related to mortality and dependence in all patients. Reduced albumin may be a marker of chronic systemic inflammation, which may be the mechanism for cardiopathy and bad outcome of stroke. In addition, direct effects on ischemic tissue were suggested in experimental models.

KEYWORDS: Albumin, D-dimer, fibrinogen, prognosis, stroke

BACKGROUND

Albumin is a multifunctional, non-glycosylated plasma protein synthesized primarily in the liver. Raised level of albumin is related to hemoconcentration and reduced level is associated with malnutrition and chronic inflammatory diseases, representing a negative acute-phase protein (Quinlan, Martin, & Evans, 2005). Previous studies have shown that patients with lower level of albumin had a higher risk of developing atrial fibrillation or coronary heart disease and had a worse prognosis after ischemic stroke. In both the situations, reduced albumin may be a marker of chronic systemic inflammation, which is the final mechanism (Danesh, Collins, Appleby, & Peto, 1998; Dziedzic, Slowik, & Szczudlik, 2004; Mukamal, Tolstrup, Friberg, Gronbaek, & Jensen, 2006). Experimental studies involving a rat model of ischemic stroke showed that albumin had neuroprotective effects. Authors suggested several mechanisms: hemodilution; antioxidant effect (albumin is the main oxygen radical trapping, exceeding that of vitamin E); maintenance of endothelial permeability and transport ability; inhibition of endothelial cell apoptosis; reduction of oedema in cerebral ischemic tissue; regulation of astrocyte metabolism and mitogenic

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Address correspondence to Francisco José Álvarez Pérez, Research Center in Health Sciences, Beira Interior University, Infante D. Henrique Avenue, 6200-506, Covilhã, Portugal. E-mail: franciscoplus@hotmail.com

activity (Belayev, Busto, Zhao, Clemens, & Ginsberg, 1997; Belayev, Liu, Zhao, Busto, & Ginsberg, 2001; Belayev, Zhao, & Pattany, 1998; Halliwell & Gutteridge, 1990; He & Curry, 1993; Nadal, Fuentes, Pastor, & McNaughton, 1995; Tabernero, Medina, Sanchez-Abarca, Lavado, & Medina, 1999; Zoellner, Hofler, & Beckmann, 1996). Consistent with this evidence, first clinical trials using albumin therapy showed that it reduced mortality at least by 10% and suggested that exogenous albumin may be neuroprotective if it is administered during acute phase of stroke (Goslinga, Eijzenbach, & Heuvelmans, 1992). The results of Albumin in Acute Stroke (ALIAS) pilot trial showed that therapy with high-dose albumin in patients with acute ischemic stroke is safe and has a dose-dependent association with the probability of good outcome (Ginsberg, Hill, Palesch, Ryckborst, & Tamariz, 2006; Palesch, Hill, Ryckborst, Tamariz, & Ginsberg, 2006). The multicenter, randomized, and placebo-controlled efficacy trial is ongoing (U.S. National Institute of Health, n.d.). However, stroke is a heterogeneous condition with specific pathways for developing ischemia. In this regard, studies assessing biomarkers showed different roles for inflammation and thrombogenesis depending on the mechanism (Idicula, Waje-Andreassen, Brogger, Naess, & Thomassen, 2009; Montaner, Perea-Gainza, & Delgado, 2008). As albumin is a negative marker of inflammation, its baseline plasma level and the effect of its exogenous administration during acute may be different according to stroke's etiopathology. Therefore, the main aim of the present study was to assess albumin level in patients with diagnosis of acute ischemic stroke classified by mechanism and the secondary aim was to correlate albumin and others variables with mortality and functional outcome of patients.

PATIENTS AND METHODS

This was a prospective clinical study, which included 200 patients consecutively admitted to Stroke Unit (SU) of a teaching hospital with diagnosis of ischemic stroke and 50 controls without evidence of cerebrovascular disease from Neurology outpatient consultation. Patients were consecutively included and classified following Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria to reach 50 patients of each aetiological subgroup, excluding the category of "other aetiology" of stroke (Adams, Bendixen, & Kappelle, 1993). Patients were excluded when one of the following criteria was present: evolution of stroke for more than 24 hr or unknown when patient arrived in emergency department; diagnosis of haemorrhagic stroke; presence of fever and/or signs of active infection on admission; presence of anaemia on the first analysis performed in the emergency department, following WHO definition of anaemia when hemoglobin was lower than 13 g/dl in males or 12 g/dl in females; previous diagnosis of active chronic liver disease; active malignant neoplasm or monoclonal gammopathy diagnosed before admission or during in-hospital evaluation; evidence of venous thromboembolic disease on admission; fibrinolytic or anticoagulant treatment; diagnosis of "other aetiology" of stroke.

Evaluation of Patients

Demographic variables, pathologic antecedents, and cardiovascular risk factors were recorded on admission. Analytic parameters were determined in two separate venous samples. The first sample was obtained in the emergency department to determine haemogram, basic biochemistry, C-reactive protein (CRP), and fibrinogen. The second sample was obtained during 48 hr after admission to determine lipids profile, the D-dimer level, and plasma proteinogram.

Following the SU protocol, arterial blood pressure, heart rate, oximetry, tympanic temperature, and ECG were semi-intensively monitored during the first 48 hr after admission. Clinical severity of stroke on admission was assessed using the National Institute of Health Stroke Scale (NIHSS). All patients were clinically classified by Oxfordshire Community Stroke Project (OCSP) in total anterior carotid infarction (TACI), partial anterior carotid infarction (PACI), lacunar infarction (LACI), and posterior infarction (POCI) (Bamford, Sandercock, Dennis, Burn, & Warlow, 1991). To classify the mechanism of stroke, the protocol of paraclinical examinations included transthoracic echocardiogram and carotid eco-Doppler and transcranial Doppler studies. Additional examinations, as transesophageal echocardiogram, Holter monitoring of blood pressure or heart rate, hypercoagulability and autoimmunity analysis, and vascular imaging were performed when indicated. Modified Rankin scale (mRS) was calculated on discharge and dependence was defined as mRS $>$ 2. The in-hospital mortality was also recorded.

A SU Informed Consent Form was obtained from patients or their relatives. The present study was approved by the Ethics Commission of the hospital.

Laboratory Methods

Fibrinogen concentration was quantitatively determined in plasma by the Clauss method using the Hemos IL Fibrinogen-C Kit (Beckman Coulter), which uses an excess of thrombin to transform the fibrinogen in fibrin in diluted plasma. Normal range used in the laboratory is 203–472 mg/dl. The D-dimer concentration was quantitatively measured in plasma using an automatized latex turbidimetric immunoassay kit (D-dimer Kit,

Beckman Coulter). This assay uses a suspension of latex particles with a monoclonal antibody against the D-dimer dominion of soluble fibrin derivates. Normal range is 0–255 ng/ml. Plasmatic concentration of CRP was quantitatively determined using the latex-enhanced turbidimetric immunoassay technique (COBAS INTEGRA C-Reactive Protein, Roche Diagnostics GMBH). Normal range is 0–0.75 mg/dl. A plasma proteinogram (albumin, α-, β-, and γ-globulins) was performed by electrophoresis on agarose. Later, albumin was quantified using a densitometer. Normal range is 3.90–4.60 g/dl.

Statistics

The licensed statistical software SPSS (version 15.0) was used to elaborate the database and analyze the data. Assumption of normal distribution of continuous variables was assessed by the Kolgomorov–Smirnov test. Continuous quantitative variables were compared using the Student's t-test for those normally distributed and Mann–Whitney U test for nonparametric ones. Comparisons among subtypes of ischemic stroke and clinical syndromes of OCSP classification were performed by one-way ANOVA for normally distributed variables, and by the Kruskal–Wallis test for non-normally distributed ones. Following ANOVA and the Kruskal–Wallis tests, post-hoc analyses were applied to significantly different variables using the Tukey and the Mann–Whitney U-tests, respectively. Qualitative variables were compared using the X^2 test.

Two models of logistic regression (forward stepwise method) were performed to predict in-hospital mortality and dependence on discharge. At each step, each variable not in the model was assessed as to its contribution to the model, and the most significant variable was added to the model. The process continued until no variable, not in the model, made a significant contribution. Both the models included significantly related variables after univariate analysis and their overall fit of the model was assessed with the Hosmer and Lemeshow test. In all analyses a bilateral alpha level inferior or equal to 0.05 was chosen to define statistical signification.

RESULTS

Characteristics of Patients

Patients were included between November 2007 and September 2009. During this period 469 patients were admitted to SU with diagnosis of stroke. Main causes for exclusion were haemorrhagic stroke (N = 72), evolution greater than 24 hr or unknown (N = 49), fibrinolysis (N = 35), lack of second sample of the analytic study (N = 31), signs of infection on admission (N = 21), diagnosis of neoplasm (N = 20), anticoagulant therapy (N = 16), presence of anaemia (N = 12), diagnosis of monoclonal gammopathy (N = 10), recent surgery (N = 2), and diagnosis of stroke of "other aetiology" (N = 1).

Controls were recruited between January 2008 and March 2009. The diagnoses of controls were as follows: mild cognitive impairment/Alzheimer's disease (N = 18), idiopathic or non-vascular secondary epilepsy (N = 8), essential tremor (N = 7), primary headache tension or migraine type (N = 6), Parkinson's disease and other parkinsonian syndromes (N = 6), mononeuropathy, idiopathic dysgeusia, idiopathic syncope, peripheral vertigo, generalized anxiety disorder (N = 1).

As the NIHSS score and levels of fibrinogen, D-dimer, and CRP followed a nonparametric distribution, the Kruskal–Wallis and the Mann–Whitney U-tests were applied. Age, albumin, and cholesterol followed a normal distribution, and the comparisons were done using ANOVA and the Student's t-test.

Both groups showed a similar distribution by sex and age. As expected, the prevalence of cardiovascular risk factors was significantly higher in patients. Controls showed values of all analytical parameters in the normal range. The Table 1 summarizes the demographical characteristics, cardiovascular risk factors, and laboratory variables in controls and patients.

Patients by Subtype of Stroke

Patients with cardioembolic stroke were significantly younger than patients with atherothrombotic and lacunar infarcts ($p < .0001$ and $p = .023$, respectively). Males predominated in the atherothrombotic subtype when it was compared with others ($p = .003$ versus cardioembolic, $p = .041$ versus lacunar, and $p = .025$ versus undetermined). Clinical severity on admission was significantly higher in patients with cardioembolic stroke compared with patients with atherothrombotic ($p = .05$) and lacunar ($p = .013$) stroke.

Fifty-five patients had TACI syndrome, 55 had PACI, 71 had LACI, and 18 had POCI. Older age ($p = .040$, ANOVA test), atrial fibrillation ($p = .002$, X^2 test), higher D-dimer level ($p = .041$, Kruskal–Wallis test), and lower albumin level ($p = .001$, ANOVA test) were related to TACI syndrome.

Prevalence of diabetes mellitus was higher in patients with lacunar and undetermined stroke. Differences were significant when they were compared with patients with cardioembolic stroke ($p = .021$ and.004 versus lacunar and undetermined strokes, respectively). Atrial fibrillation was the most frequent cardiac condition in the cardioembolic subtype ($p < .0001$ versus others subtypes), followed by ischemic heart disease associated with left ventricular hypo/akinesia. Prevalence of smoking and

TABLE 1. Demographical characteristics, cardiovascular risk factors, and biochemical parameters in stroke patients and controls

	Patients (N = 200)	Controls (N = 50)	*p*
Age (years)	72 ± 11.5	69.2 ± 9.9	.107*
Male	104 (52%)	21 (42%)	.206
NIHSS on admission	4 (2–9)†		
Hypertension	153 (85.5%)	26 (52%)	<.0001
Atrial fibrillation	43 (21.7%)	0	<.0001**
Diabetes mellitus	48 (24.2%)	8 (16%)	.213
Coronary heart disease	22 (11.2%)	6 (12%)	.868
HF with EF < 50%	5 (2.5%)	0	.586**
Previous stroke	42 (21.2%)	0	.001**
Smoking	54 (30.7%)	11 (22.9%)	.293
Alcohol consumption	58 (33%)	14 (29.2%)	.618
Total cholesterol (mg/dl)	188.3 ± 47.3	201.5 ± 41.4	.086*
LDL cholesterol (mg/dl)	112.5 ± 41.7	121.4 ± 32.6	.183*
Fibrinogen (mg/dl)	323 (286–381.5)	281 (255–319.5)	<.0001***
D-dimer (ng/ml)	272.5 (181.2–471.5)	190.5 (140–240.5)	<.0001***
C-reactive protein (mg/dl)	0.36 (0.19–0.77)	0.18 (0.08–0.30)	<.0001***
Albumin (mg/dl)	4 ± 0.5	4.4 ± 0.2	<.0001*

Notes: *Normal continuous variables are expressed as mean ± standard deviation and comparisons were done using the Student's t-test. Dichotomic variables are expressed as N (%) and comparisons between cases and controls were done with the X^2 test or the Fisher exact test (**).

***Nonparametric continuous variables are expressed as median (interquartilic range) and comparisons were done with the Mann–Whitney U test.

alcohol abuse were higher in patients with stroke related to large vessel disease when compared with patients with cardioembolic ($p < .0001$ for both risk factors), lacunar ($p = .001$ and.086 for smoking and alcohol consumption, respectively), and undetermined ones ($p < .0001$ and.003 for smoking and alcohol consumption, respectively).

Patients with atherothrombotic and lacunar strokes showed the highest levels of total and low-density lipoprotein (LDL) cholesterol. Differences were significant when patients with atherothrombotic stroke were compared with patients with cardioembolic ($p = .001$ and.002 for total cholesterol and LDL cholesterol, respectively) and undetermined stroke ($p = .007$ and.022 for total cholesterol and LDL cholesterol, respectively).

Patients with cardioembolic stroke showed significantly lower mean level of albumin than patients with atherothrombotic ($p = .044$), lacunar ($p = .002$), and undetermined ($p = .010$) subtypes. The highest median level of fibrinogen was found in patients with cardioembolic stroke followed by atherothrombotic ones, but differences among subtypes were nonsignificant. Patients with cardioembolic stroke had the highest median level of D-dimer, followed by those with undetermined stroke. Differences were significant when patients with cardioembolism were compared with other subtypes ($p < .0001$ versus atherothrombotic and lacunar, and $p = .002$ versus undetermined). Median level of CRP was higher in patients with atherothrombotic stroke, followed by patients with cardioembolism. Differences were significant when patients with atherothrombotic stroke were compared with lacunar ($p = .010$) and undetermined ($p = .003$) stroke. Table 2 summarizes the demographical characteristics, NIHSS, cardiovascular risk factors, and biochemical parameters in patients classified by mechanism of stroke.

Outcome

Seven patients died during in-hospital period (3.5%), five with cardioembolic stroke, one with atherothrombotic stroke, and one with undetermined stroke. On discharge, 119 patients were dependent (59.5%), 30 with cardioembolic stroke (60%), 27 with atherothrombotic (54%), 24 with lacunar (48%), and 38 with undetermined stroke (76%). In-hospital mortality was related to the higher NIHSS score on admission, cardioembolic aetiology, higher median levels of fibrinogen and D-dimer, and lower albumin mean level. Dependence on discharge was strongly related to the higher NIHSS score and lower mean level of albumin. Other variables associated with worse functional outcome were older age, female gender and higher median levels of fibrinogen, D-dimer, and CRP. Table 3 summarizes the relationship between demographical, clinical, and biochemical variables and between in-hospital mortality and dependence status on discharge.

The first model of logistic regression used in-hospital mortality as dependent and included the NIHSS score, age, levels of D-dimer, CRP and albumin, cardioembolic aetiology, and diabetes mellitus as covariables. None of the variables was independently related to mortality, and only the cardioembolic aetiology (OR 0.101,

TABLE 2. Demographical characteristics, cardiovascular risk factors, and biochemical parameters in stroke patients classified by stroke subtype

	Cardioembolic (N = 50)	Atherothrombotic (N = 50)	Lacunar (N = 50)	Undetermined (N = 50)	*p*
Age (years)	76.9 ± 7.6	66.7 ± 12.5	70.6 ± 11.9	73.9 ± 10.9	<.0001*
Male	20 (40%)	35 (70%)	25 (50%)	24 (48%)	.021
NIHSS on admission	6 (2–14)	4 (2–8)	4 (2–6)	6 (2–10)	.067**
Hypertension	41 (83.7%)	38 (77.6%)	36 (73.5%)	38 (76%)	.660
Atrial fibrillation	36 (72%)	0	0	5 (10%)	<.0001
Diabetes mellitus	5 (10%)	12 (24%)	14 (28.6%)	17 (34%)	.039
Coronary heart disease	6 (12.5%)	4 (8%)	5 (10%)	7 (14%)	.791
HF with EF < 50%	5 (10%)	0	0	0	.001
Peripheral arteriopathy	2 (4.1%)	4 (8.2%)	1 (2%)	3 (6%)	.553
Previous stroke	12 (24%)	9 (18%)	7 (14%)	14 (28.6%)	.333
Smoking	7 (14%)	26 (53%)	12 (24%)	9 (18%)	<.0001
Alcohol consumption	5 (10%)	24 (47%)	17 (34%)	12 (24%)	<.0001
Total cholesterol (mg/dl)	170.8 ± 40.9	207.2 ± 49.9	198.2 ± 49	177.3 ± 40.4	<.0001*
LDL cholesterol (mg/dl)	98.9 ± 37	128 ± 45	119.1 ± 42	104.3 ± 36.7	.001*
Fibrinogen (mg/dl)	340 (293–408.5)	325 (287–374)	322.5 (270–389.5)	312 (280.5–352)	.397**
D-dimer (ng/ml)	500 (235.5–674.8)	218 (156.8–406)	224.5 (162–281)	283 (182.3–394)	<.0001**
C-reactive protein	0.36 (0.24–0.97)	0.58 (0.24–1.09)	0.32 (0.16–0.68)	0.33 (0.18–0.51)	.013**
Albumin (mg/dl)	3.8 ± 0.5	4 ± 0.4	4.1 ± 0.5	4.1 ± 0.5	.002*

Notes: Dichotomic variables are expressed as N (%) and comparisons were done with the X^2 test (**).
*Normal continuous variables are expressed as mean ± standard deviation and comparisons were done using ANOVA.
Nonparametric continuous variables are expressed as median (interquartilic range) and comparisons were done with the Kruskal–Wallis test. (**)

95% CI 0.010–1.007, $p = .051$) and the higher NIHSS score on admission (OR 0.871, 95% CI 0.758–1.002, $p = .053$) showed a weak association. The second model used dependence status on discharge as dependent and included the NIHSS score, age, levels of D-dimer, CRP and albumin, and diabetes mellitus as covariables. The NIHSS score on admission (OR 1.560, 95% CI 1.323–1.838, $p < .0001$) and older age (OR 1.052, 95% CI 1.012–1.093, $p = .010$) were independently related to dependence.

DISCUSSION

The present study confirmed the presence of specific analytical modifications during the acute phase of ischemic stroke. Levels of parameters used as positive

TABLE 3. Demographical characteristics, cardiovascular risk factors, and biochemical parameters of patients compared by in-hospital mortality and dependence on discharge

	Dead (N = 7)	Alive (N = 193)	*p*	Dependent (N = 119)	Independent (N = 81)	*p*
Age (years)	78.4 ± 5.3	71.8 ± 11.6	.132*	74 ± 11.5	69.1 ± 10.8	.002*
Male	2 (28.6%)	102 (52.8%)	.264**	55 (46.2%)	49 (60.5%)	.047
NIHSS on admission	15 (7–20)	4 (2–8)	.001***	7 (4–12)	2 (1–4)	<.0001***
Cardioembolic aetiology	5 (71.4%)	46 (23.8%)	.005	30 (25.2%)	21 (25.9%)	.909
Hypertension	6 (85.7%)	147 (77.4%)	.603	92 (78.6%)	61 (76.3%)	.693
Atrial fibrillation	4 (57.1%)	39 (20.4%)	.041**	28 (23.9%)	15 (18.5%)	.364
Diabetes mellitus	0	48 (25.1%)	.199**	32 (27.4%)	16 (19.8%)	.220
Coronary heart disease	0	22 (11.6%)	0.227**	7 (6%)	15 (18.8%)	.005
HF with EF < 50%	1 (14.3%)	4 (2.1%)	.167**	4 (3.4%)	1 (1.2%)	.650**
Peripheral arteriopathy	0	10 (5.3%)	1.000**	2 (3.4%)	6 (7.5%)	.322**
Previous stroke	2 (28.6%)	40 (20.9%)	.641**	26 (22.2%)	16 (19.8%)	.676
Smoking	2 (28.6%)	52 (30.8%)	1.000**	29 (28.2%)	25 (34.2%)	.388
Alcohol consumption	2 (28.6%)	56 (33.1%)	1.000**	28 (27.2%)	30 (41.1%)	.060
Fibrinogen (mg/dl)	375 (324–458)	320 (283–377.5)	.030***	330 (292–402.5)	315.5 (274–350)	.039***
D-dimer (ng/ml)	636 (515–1.047)	264 (180–429)	.003***	313 (189.5–546)	240 (171–332)	.009***
C-reactive protein	0.69 (0.36–0.95)	0.34 (0.19–0.77)	.075***	0.40 (0.22–0.88)	0.31 (0.16–0.56)	.007***
Albumin (mg/dl)	3.4 ± 0.4	4 ± 0.5	.006*	3.9 ± 0.5	4.2 ± 0.4	<.0001*

Notes: *Normal continuous variables are expressed as mean ± standard deviation and comparisons were done using the Student's t-test.
**Dichotomic variables are expressed as N (%) and comparisons were done with the X^2 test or the Fisher Exact test.
***Nonparametric continuous variables are expressed as median (interquartilic range) and comparisons were done with the Mann–Whitney U test.

markers of inflammation (fibrinogen and CRP) and markers of thrombotic activity (D-dimer) were significantly higher in patients versus controls, whereas the negative marker of inflammation (albumin) was significantly lower. These differences were probably related to specific biochemical modifications developed after the ischemic episode. However, the long half-life of albumin and the lack of association between TACI syndromes and positive acute phase parameters suggest that they may also be associated with stroke's mechanism. The half-life of albumin is approximately 21 days. In this study its plasmatic concentration was measured during first 72 hr after stroke. Then, its baseline level reflects previous nutritional and inflammatory states, but it does not represent a negative acute phase response (Quinlan et al., 2005). The presence of TACI syndrome was used to estimate the largest lesion of the middle cerebral artery territory (Pittock et al., 2003). Considering the limitations of this approach, the lack of association between fibrinogen and CRP and TACI syndromes suggests that raised levels of these inflammatory parameters are not the only acute response to ischemia. The association found between higher D-dimer level and TACI syndromes may be explained considering the greater prevalence of atrial fibrillation in this group. In patients with chronic atrial fibrillation, the raised level of D-dimer characterizes the intracardiac prothrombotic activity and it may be used as a predictor of embolic risk (Lyp, Lowe, Rumley, & Dunn, 1995).

The profile of the analytical modifications found in the patients was different depending on the mechanism of the stroke. As previously reported, patients with cardioembolic stroke had higher level of D-dimer, a marker of prothrombotic activity, and patients with atherothrombotic strokes showed greater total and LDL cholesterol and CRP (Grau, Weimar, & Buggle, 2001; Heuschmann, Kolominsky-Rabas, & Misselwitz, 2004; Imamura, Doi, & Arima, 2009; Ladenvall et.al., 2006; Lyp et al., 1995; Montaner et al., 2008).

The main finding of the present study was the association between lower mean level of albumin and cardioembolic aetiology of stroke. The most frequent causes of cardioembolism in the present series were atrial fibrillation and coronary heart disease. This result is not surprising because both conditions were related to lower level of albumin in previous epidemiological studies (Danesh et al., 1998; Mukamal et al. 2006). The reduced level of albumin may indicate the presence of systemic chronic inflammation, which is related to endothelial dysfunction and cardiovascular disorders. This fact was supported by the finding of lymphomononuclear infiltrates and necrosis of myocytes on biopsy of the right atrial septum in patients with refractory lone atrial fibrillation (Frustaci et al., 1997). Although the present study did not assess molecular mechanisms, it is possible that the inflammatory pathways implied in cardiopathies are different than those implied in atherosclerotic stroke. This is suggested by the association found between higher level of the positive inflammatory marker CRP and the atherothrombotic subtype of stroke, as reported previously (Ladenvall et.al., 2006).

The present study found a relatively low mortality rate. This may be related to the exclusion of patients with severe systemic diseases or signs of infection on admission, presenting a higher risk of systemic complications during acute phase. Mortality was associated with greater NIHSS score on admission, cardioembolic aetiology of stroke, higher median levels of fibrinogen and D-dimer, and lower mean level of albumin. Dependence on discharge was related to older age, severity of stroke on admission, higher median levels of fibrinogen, D-dimer and CRP, and lower mean concentration of albumin. These findings support the results of previous studies, which associated cardioembolic aetiology, severity of stroke on admission, lower albumin level, and higher levels of fibrinogen and D-dimer with bad outcome (del Zoppo, Levy, & Wasiewski, 2009; Di Napoli, Papa, & Bocola, 2001; Grau et al., 2001; Heuschmann et al., 2004; Idicula et al., 2009; Turaj, Slowik, & Dziedzic, 2006).

The relationship between lower mean level of albumin and higher risk of mortality and bad outcome may be explained by two mechanisms (Idicula et al., 2009). First, low albumin level is associated with chronic systemic inflammation and/or previous malnutrition, and both conditions were related to bad outcome after stroke (Dávalos, Ricart, & Gonzalez-Huix, 1996; del Zoppo et al., 2009; Di Napoli et al., 2001; Turaj et al., 2006). The sustained endothelial inflammation may aggravate the consequences of stroke by promoting cellular processes, which increase the tissue damage, and activating the cascade of coagulation to occlude microcirculation and reduce cerebral perfusion (del Zoppo et al., 2009; Di Napoli et al., 2001; Turaj et al., 2006). Second, experimental models of brain ischemia suggested that the exogenous supplementation of albumin was neuroprotective. The precise mechanisms are not completely clarified, but it has been suggested that albumin therapy has anti-oedema effect, can neutralize lysophosphatidylcholine molecules (generated by circulating phospholipase A_2 and with pro-inflammatory effects), or vials may be contaminated with plasmatic alpha 1-acid glycoprotein, protein that reduced brain oedema in a rat model of stroke (Belayev et al., 1997, 1998, 2001; Halliwell et al., 1990; He & Curry, 1993; Nadal et al., 1995; Tabernero et al., 1999; Zoellner et al., 1996).

After logistic regression analysis, only cardioembolic aetiology and the higher NIHSS score on admission were weakly related to mortality, and the higher NIHSS

score on admission and older age were independently related to mRS > 2 on discharge. These associations are similar to previously reported in the German Stroke Registers Study. The authors discussed that the higher clinical severity and worse prognosis in patients with cardioembolic stroke were related to the greater volume of infarction (Grau et al., 2001; Heuschmann et al., 2004).

In summary, lower mean level of albumin was related to cardioembolic aetiology of stroke. Moreover, lower concentration of albumin was associated with worse prognosis and mortality after univariate analysis, although the strength of this association disappeared when clinical variables were considered. Probably, lower albumin level represents chronic inflammation, which is a risk factor for embolic cardiopathies and worse outcome after stroke. However, a reduction of the presumed neuroprotective effects of albumin on ischemic tissue may be relevant in these patients. Clinical trials may help to clarify whether the administration of exogenous albumin is a therapeutic option for all patients with stroke or only for selected patients with severe cardioembolic stroke and/or low level of albumin on admission.

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