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Original

Hypoalbuminemia and other prognostic factors of mortality at different time points after ischemic stroke

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Abstract

Objective: **The aim of this study was to investigate whether hypoalbuminemia and other risk factors for mortality after stroke have the same or different short (1 month), medium (3 months), long (1 year) or very long term (5 years) prognostic value.**

Subjects/methods: **clinical and analytical data from 254 patients admitted to our Hospital with an ischemic stroke and followed up prospectively for 2 years were collected with a prospective standard protocol. Additional data up to 5 years were obtained from Clinical and Laboratory Registries of the Hospital, a mailed questionnaire, a phone call and the Council Registry of Mortality. Risk factors for mortality at different time points were calculated with logistic regression and Cox proportional hazard analyses.**

Results: **The following factors were significantly associated with mortality at one month: cardioembolic mechanism, hypoalbuminemia, glycemia, age, low diastolic arterial pressure and Canadian Scale, at three months: previous stroke and Barthel index at discharge, at one year: previous dementia and Barthel index at three months and at five years: age, Canadian Scale score at discharge and low cholesterol at admission. Cox regression analysis considering survival time showed hypoalbuminemia at admission (hazard ratio (HR) 2; p = 0.03), age (HR 1.06; p < 0.00), previous dementia (HR 2; p < 0.00), cardioembolic mechanism (HR 2; p < 0.00) and severity on the Canadian Neurological Stroke Scale (HR 1.2; p < 0.00) to be independently associated with mortality.**

Conclusion: **Mortality after ischemic stroke seems to depend on different factors along time. Hypoalbuminemia at admission is an independent factor for short term (acute) and global mortality. Other risk factors for global mortality were previous dementia, cardioembolic mechanism and severity on the Canadian Neurological Stroke Scale at admittance.**

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Key words: *Hypoalbuminemia. Mortality. Ischemic stroke. Stroke registry. Inflammation. Risk factor. Prognosis.*

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HIPOALBUMINEMIA Y OTROS FACTORES PRONÓSTICOS DE MORTALIDAD EN DISTINTOS PERIODOS TRAS UNA TROMBOSIS ISQUÉMICA

Resumen

Objetivo: **El propósito del estudio era investigar si la hipoalbuminemia y otros factores de riesgo de mortalidad tras un ictus tenían el mismo valor pronóstico tras un ictus a corto (1 mes), medio (3 meses), largo (1 año) o muy largo plazo (5 años).**

Métodos: **Se estudiaron 254 pacientes ingresados en nuestro hospital con ictus isquémico y seguidos prospectivamente durante dos años con un procolo estándar de forma prospectiva. Se recogieron datos adicionales hasta 5 años de las Historias Clínicas, los datos del laboratorio, un cuestionario enviado por correo, una llamada telefónica y la revisión de los Registros de Mortalidad de los ayuntamientos. Los factores de riesgo de mortalidad en cada periodo se calcularon con regresión logistica y el modelo de riesgos proporcionales de Cox.**

Resultados: **Se asociaron de forma significativa con la mortalidad al mes el mecanismo cardioembólico, la hipoalbuminemia, la glucemia al ingreso, la edad, la presión arterial diastólica más baja y la puntuación en la Escala Canadiense. A los tres meses, la existencia de ictus previos y el índice de Barthel al alta. Al año la existencia previa de demencia y el índice de Barthel a los 3 meses y a los cinco años la edad, la puntuación en la escala Canadiense al alta y un colesterol menor al ingreso. El análisis de regresión de Cox considerando el tiempo de supervivencia, mostró una asociación independiente con la mortalidad de la hipoalbuminemia al ingreso ((HR) 2; p = 0,03), la edad (HR 1,06; p < 0,00), la demencia previa (HR 2; p < 0,00), el mecanismo cardioembólico (HR 2; p < 0,00) y la severidad según la escala Canadiense (HR 1.2; p < 0,00).**

Conclusión: **La mortalidad tras un ictus isquémico parece depender de distintos factores según el tiempo transcurrido.**

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Palabras clave: *Hipoalbuminemia. Mortalidad. Ictus isquémico. Registro de ictus. Inflamación. Factores de riesgo. Pronóstico.*

Introduction

Hypoalbuminemia is a predictive factor for several clinical outcomes (recurrences, functional recovery and medical complications) and mortality in patients with stroke.[1-12] Recent studies have renewed the interest about the influence of hypoalbuminemia on mortality and the use of albumin in acute stroke.[13-18] Our study was performed several years ago on a cohort of ischemic stroke patients but it can be of interest because of the long follow-up period and the number of risk factors considered. The main purpose of this study was to investigate if hypoalbuminemia at admission was an independent risk factor for mortality in patients with an ischemic stroke considering an overall five years follow- up period and at different time points in between.

Materials and methods

All patients who were admitted to the Hospital Severo Ochoa with a diagnosis of stroke between May 1, 1994 and September 30, 1995 were included in a systematic Stroke Registry. The catchment area of the Hospital covered an estimated population of 347.551 inhabitants. The definition of stroke of "Ad Hoc Committee on Cerebrovascular Diseases"[19] was used for case selection. Transient ischemia, subaracnoid hemorrhage were excluded from the Registry and patients without CT or albumin at admission were excluded from this study.

A standard protocol was applied in all patients including *complete medical history:* age, sex, educational level, smoking, alcohol ingestion, previous pulmonar, hepatic, renal, gastrointestinal and thyroideal illnesses, cardiac insufficiency, cerebrovascular events (previous stroke, transient ischemia and their number); atrial fibrillation, flutter, hypertension (documented previously and/or two readings of systolic ≥ 140 mmHg and/or diastolic pressure ≥ 90 mmHg), diabetes (documented previously, a casual glucose value > 200 mg/dl or 2 determinations > 126 mg/dl or treatment with diet, oral medications, insulin or both), peripheral arteriopathy, obesity, ingestion of drugs and their number; *clinical data:* systolic and diastolic blood pressure, urinary incontinence (UI) and epileptic crisis), *neurological examination:* coma status, dementia diagnosed by a neurologist according to the DSM-III-R criteria, the Canadian Neurological Stroke Scale (CNSS),[20] Short Portable Mental Status Questionnaire (SPQSM),[21] Barthel Index (BI)[22] and Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE);[23] *blood chemistry:* serum albumin, glucose, cholesterol, creatinine, urea, triglycerides, total proteins, globulin, calcium, uric acid and C reactive protein (CRP); *haematological tests:* hematocrit, median corpuscular value (MCV), leukocyte and thrombocyte count, median corpuscular haemoglobin (MCH), globular sedimentation rate (GSR); *CT scan* of the brain and 12- lead *electrocardiogram.* Blood tests were obtained at admission between 24 and 48 hours after arrival at emergency room. Albumin was analysed as a continous parameter and stratified by cuartiles (< 3.5, 3.5-3.8, 3.8-4.1, > 4.1 g/dl), terciles (< 4.2, 4.2-4.4, > 4.4 g/dl), intervals, < 3.5 *vs* ≥ 3.5 g/dl and ≤ 2.9, 3-3.4, ≥ 3.5 g/dl and the ratio albumin/ globulin < 1.45 as described in previous studies.[9-12] Stroke was classified according to clinical data as cardioembolic in patients with valvulopathy or atrial fibrillation and thrombotic in the others; and according to CT images as lacunar (< 1.5 cm diameter in the penetrating arteries), non lacunar (> 1.5 cm), hemorrhagic if partial hemorrhagic content and non specified (normal image).

At discharge and 3, 6, 12 and 24 months visits, vital status, recurrences, CNSS, BI, anticoagulation, recurrences, respiratory or urinary infections, deep venous thrombosis, peripheral arteriopathy, cardiac insufficiency or ischemic cardiopathy were registered. At *three months visit,* systolic and diastolic blood pressure, SPQSM, BI, IQCODE, a blood test (albumin, glucose, cholesterol, LDL and HDL-cholesterol, creatinine, urea, triglycerides, total proteins, GSR, calcium, uric acid, hematocrit, MCV, leukocyte and thrombocyte recount, MCH and prothrombin time) and proteinuria were assessed. *Between 2 and 5 years of follow-up,* data about recurrences, cardiac insufficiency, ischemic cardiopathy, urinary infections, pneumonia, deep venous thrombosis, peripheral arteriopathy or macrovascular complications were obtained from Clinical Registries in Hospital, laboratory computers, a mailed questionnaire and a phone call. Student s *t*- test was used to compare quantitative variables and chi-square or Fisher test for comparison of frequencies. Pearsons s correlation coefficients were calculated between variables. The independent association of factors with survival was examined at every time point (1 month, 3 months, 1 year and 5 years after stroke) with forward stepwise Multiple regression considering only those patients alive at the corresponding time. Cox regression analysis including lost cases and considering the global time was done to ascertain the relationship of albumin to death. Data were analyzed using SPSS (Stadistical Package for Social Sciences. Windows version, release 10.0.6. Chicago. SPSS. 1999). All results were adjusted for age. $P < 0.05$ was considered as the statistical level of significance.

Results

The Registry recruited 326 patients. Intracerebral hemorrhages (n = 35), patients without CT or albumin (n = 31) and cases lost to follow-up (n = 6) were excluded. Therefore, 254 patients (87 %), 50 % male, were analysed in this study: 111 of them (44 %) died during follow up. Twenty, 14, 20 and 58 patients died

Table I
Differential clinical features of patients who died one month after stroke

	OR (95% CI)	*Dead (n = 20)*	*Survivor (n = 234)*	*p*
Age	1.1 (1.05-1.2)	81.5 ± 7	69 ± 13	0.000
Cardiopathy	6 (2- 16)	75%	32%	0.002
Atrial fibrillation	3 (1.008- 7.5)	40%	16%	0.048
DBP at admission (mmHg)	0.96 (0.93- 0.99)	81 ± 18	91 ± 17	0.035
Embolic mechanism	3 (1.1- 8)	45%	17%	0.03
Coma at admission	11 (3- 49)	25%	6%	0.001
Canadian* scale score on admission 0 to 7 > 7	0.6 (0.5- 0.8) 5 (1.1-25) 0.2 (0.04-0.9)	4 ± 2.2	7 ± 2	0.000
Barthel Index**	1.13 (1.05- 2)	77 ± 32	94 ± 15	0.001
Canadian* scale score at discharge	0.5 (0.3- 0.8)	4 ± 2	8 ± 2	0.002
Urea (mg/dl) (n = 188)	1.04 (1.02-1.07)	72 ± 31	43 ± 18	0.003
Calcemia (mg/dl) (n = 183)	0.08 (0.02-0.4)	8.4 ± 0.4	9.2 ± 0.5	0.002
Albumin (g/dl)	7 (2.5-19)	3.2 ± 0.5	3,8 ± 0.4	< 0.001
Total proteins (g/dl)	0.3 (0,1-0,6)	6,3 ± 0.5	6,8 ± 0.6	0.04
Cholesterol (mg/dl)	0.98 (0.97-0.99)	174 ± 49	220 ± 50	< 0,001
Glycemia (mg/dl)	1.01 (1.004-1.02)	177 ± 77	126 ± 52	< 0.002

Data are mean ± standard deviation or percentage.
*Inverse value of the Canadian Scale.
**Inverse value of the Barthel Index before admission.
Figures in brackets indicate the number cases when data were not available for the whole sample.
OR: Odds ratio; DBP: Diastolic blood pressure.

in the first month, between one and three months, between three months and one year and between one and five years, respectively. Patients who died during follow up were significantly older (78 ± 9 *vs* 64 ± 13, OR: 1.1 (1.09-1.2), p < 0.000), took more medications (2.5 ± 2 *vs* 1.8 ± 2, OR: 1.2 (1.04-1.4), p = 0.01), had previously dementia more often (30 (27%) *vs* 6 (4%), OR: 4 (1.6-11), p = 0.003), had more often antecedents of stroke (25 (22.5%) *vs* 12 (8%), OR: 4 (1.7-10), p = 0.002), cardiopathy (52 (47%) *vs* 37 (26%), OR: 2 (1.1-4), p = 0.02), nephropathy (15 (13.5%) *vs* 8 (5.5%), OR: 3 (1.2-9.6), p = 0.02), cardiac insufficiency (14 (13%) *vs* 5 (3.4%), OR: 1.1 (1.09-1.2), p < 0.000), and atrial fibrillation (31 (28%) *vs* 14 (10%), OR: 3 (1.3-6), p = 0.01) than those who survived. They scored worse in Barthel Index previous to admission (87 ± 24 *vs* 98 ± 7.5, OR: 0.97 (0.94-0.99), p = 0.01), Canadian Scale at admission (5 ± 2 *vs* 8 ± 2, OR: 0.7 (0.6-0.8), p < 0.000), Barthel Index at discharge (42 ± 35 *vs* 78 ± 30, OR: 0.98 (0.97-0.99), p < 0.000) and Canadian Scale at discharge (6 ± 2 *vs* 8 ± 2, OR: 0.7 (0.6-0.8), p < 0.000). They had more urinary incontinence at admission (71 (65%) *vs* 29 (20%), OR: 4 (2-7), p < 0.000), and at discharge (30 (28%) *vs* 13 (9%), OR: 3 (1.2-6), p = 0.02). They had at admission a lower albumin (3.6 ± 0.5 *vs* 3.9 ± 0.3, OR: 0.3 (0.15-0.6), p = 0.001, and cholesterol (203 ± 56 *vs* 228 ± 46, OR: 0.99 (0.98-0.99), p = 0.01) and a higher glucose (141 ± 63 *vs* 122 ± 49, OR: 1.008 (1.002-1.013), p = 0.008) and creatinine (1.3 ± 1.2 *vs* 1 ± 0.2, OR: 4 (1.2-15), p = 0.02).

Patients with atrial fibrillation were more frecuently women (67.5%, p = 0.01), older (6 ± 2 years p = 0.001) and with more severe strokes at admission (CNSS 5.8 ± 2.6 *vs* 6.8 ± 2.4, p = 0.007).

Short term mortality (at one month)

Table I shows the variables associated with mortality at one month in univariate analyses. When these variables were introduced into a logistic regression analysis with 249 cases, cardioembolic mechanism (p = 0,01 = hypoalbuminemia (p = 0,02), glycemia (p < 0,001), age (p = 0,02), low diastolic arterial pressure (p = 0,01) and Canadian Scale score (p = 0,04) were significantly associated with mortality at one month (table VI).

Medium term mortality (between 1 and 3 months)

Table II shows the variables associated with mortality between 1 and 3 months in univariate analyses. When these variables were introduced into a logistic regression analysis with 233 cases, previous stroke (p = 0,009) and Barthel index at discharge (p < 0,0001) were significantly associated with mortality (table VI).

Table II
Differential clinical features of patients who died between one and three months after stroke

	OR (95% CI)	*Dead (n = 14)*	*Survivor (n = 220)*	*p*
Canadian Scale score at admission	0.7 (0.6-0.9)	5 ± 2	7 ± 2	0.02
Canadian Scale score at discharge	0.6 (0.5-0.8)	5 ± 2	8 ± 2	0.001
Barthel Index previous to admission	0.9 (0.95-0.98)	76 ± 35	95 ± 12	0.004
Barthel Index at discharge	0.9 (0.89- 0.97)	12 ± 13	68 ± 34	0.001
SPMSQ score*	0.7 (0.6-0.9)	8 ± 6	15 ± 4	0.01
IQCODE score**	1.05 (1.003- 1.1)	65 ± 13	56 ± 8	0.04

Data are mean ± standard deviation.
*SPMSQ: short portable mental status questionnaire.
**IQCODE: informant Questionnaire on Cognitive Decline in the Elderly.

Table III
Differential clinical features of patients who died between three months and one year after stroke

	OR (95% CI)	*Dead (n = 20)*	*Survivor (n = 200)*	*p*
Coma at admission	10 (1.2-88)*	10%	1 %	0.03
IQCODE score* at 3 months (n = 180)	1.1 (1.07-1.2)	79 ± 11	62 ± 10	0.000
IQCODE score* at admission (n = 199)	1.07 (1.03-1.1)	65 ± 14	55 ± 7	0.02
Previous Barthel Index	0.95 (0.92-0.98)	82 ± 19	96 ± 11	0.001
Barthel Index at discharge	0.96 (0.95-0.98)	33 ± 30	72 ± 32	0.000
Barthel Index at three months	0.95 (0.94-0.97)	22 ± 33	78 ± 31	0.016
SPMSQ score** at 3 months (n = 173)	0.8 (0.7-0.9)	9 ± 6	16 ± 4	0.001
Canadian Scale score at admission	0.7 (0.6 -0.8)	5 ± 3	7 ± 2	0.005
Canadian Scale score at discharge	0.8 (0.7-0.9)	6.5 ± 2.5	8 ± 2	0.04
SPMSQ score** at admission (n = 164)	0.7 (0.6-0.8)	10 ± 4	15 ± 4	0.001
Total proteins at admission (g/dl) (n = 150)	0.3 (0.1- 0.6)	6.7 ± 0.4	6.8 ± 0.6	0.001
Hematocrit at admission (%) (n = 145)	0.8 (0.7-0.9)	43 ± 5	41 ± 7	0.004

Data are mean ± standard deviation or percentage.
Figures in brackets indicate the number of cases when data were not available for the whole sample.
OR: Odds ratio.
*IQCODE: informant Questionnaire on Cognitive Decline in the Elderly.
**SPMSQ: short portable mental status questionnaire.

Long term mortality (between 3 and 12 months)

Table III shows the variables associated with mortality between 3 and 12 months in univariate analyses. When these variables were introduced into a logistic regression analysis with 219 cases, previous dementia (p = 0,02) and Barthel index at three months (p < 0,000) were significantly associated with mortality (table VI).

Very long term mortality (between 1 and 5 years)

Table IV shows the variables associated with mortality between 1 and 5 years in univariate analyses. When these variables were introduced into a logistic regression analysis with 198 cases, age (p < 0.0001), Canadian Scale score at discharge (p < 0,001) and low cholesterol at admission (p < 0,002) were significantly associated with mortality (table VI).

Relationship between hypoalbuminemia and overall mortality

The mean value of serum albumin of patients who died during the follow up (3.6 ± 0.5) was significantly lower than in those who survived (3.9 ± 0.4, $p < 0.001$). When serum albumin was dichotomized according to a cut off previously used in the literature, patients with albumin < 3.5 g/dl among those who died (34 %) were significantly more frequent than among survivors (12.5%), $p = 0.007$). In contrast, total proteins, globulin and the ratio albumin/ globulin < 1.45 did not differ between groups.

In the *Kaplan-Meier Analysis,* 56 patients with an albumin at admission < 3.5 g/dl (38 died and 18 censored), and 198 patients with albumin at admission ≥ 3.5 g/dl (73 died and 125 censored) had a median survival of 873 ± 105 days and 1,373 ± 48 days respectively (Log-Rank 23.5, $p < 0.001$). The Kaplan- Meier

Table IV
Differential clinical features of patients who died between one and five year after stroke

	OR (95% CI)	*Dead (n = 58)*	*Survivor (n = 142)*	*p*
Barthel Index at discharge	0.98 (0.97-0.99)	55 ± 34	79 ± 29	0.02
Canadian Scale score at admission	0.8 (0.7-0.9)	6 ± 2	8 ± 2	0.003
Canadian Scale score at discharge	0.7 (0.6-0.9)	7 ± 2	8 ± 2	0.001
IQCODE score* at 3 months (n = 166)	1.06 (1.02-1.10)	69 ± 12	59 ± 8	0.003
SPMSQ score** at 3 months (n = 165)	0.88 (0.8- 0.9)	13 ± 4	17 ± 4	0.005
Barthel Index at 3 months	0.98 (0.97-0.99)	62 ± 35	84.5 ± 27	0.01
Cholesterol at 3 months (n = 138)	0.98 (0.97-0.99)	217 ± 53	245 ± 41	0.003
Albumin at 3 months (g/dl) (n = 44)	0.2 (0.07-0.7)	3.4 ± 0.8	4 ± 0.5	0.01
Hematocrit at 3 months (%) (n = 136)	0.8 (0.7-0.9)	41 ± 6	44 ± 4	0.002
HDL-cholesterol at 3 months (n = 92)	0.94 (0.90- 0.98)	42 ± 17	55 ± 21	0.003

Data are mean ± standard deviation.
Figures in brackets indicate the number of cases were data were not available for the whole sample.
OR: Odds ratio.
*IQCODE: informant Questionnaire on Cognitive Decline in the Elderly.
**SPMSQ: short portable mental status questionnaire.

Table V
Risk factors for the overall mortality. Cox Regression Model

		p	*OR*	*95% CI*
Age	0.06	0.000	1.06	1.04-1.09
Cardioembolic mechanism	0.7	0.001	2	1.3-3
Canadian Scale score at admission	-0.2	0.000	0.8	0.7-0.9
Reverse of albumin at admission	0.5	0.03	2	1.06-3
Previous Dementia	0.8	0.000	2	1.4-3.3

OR: Odds ratio.

Survival Analysis of the 239 patients alive at three months, showed a median survival of 1,483 ± 39 days in the 221 cases with albumin > 3.5 g/dl (151 censored and 70 died) *vs* 1,157 ± 172 days in the 18 patients with albumin ≤ 3.5 g/dl (7 censored and 11 died) (Log Rank: 7, p = 0.006).

260 patients were included (254 analysed and 6 lost during the follow-up) in the *Cox Regression Analysis* model considering time of follow up. Factors independently associated to long term mortality in the Cox Regression Analysis are shown in table V. The risk of dying is double for each descent of 1 g/dl of plasmatic albumin at admission (95 % CI 1.12-3, $p = 0.01$).

Discussion

Stroke is the leading cause of mortality in women and the second one in men in Spain. The identification of mortality risk factors could allow us to take clinical decisions, including treatment, advice, design of clinical essays and selection of individuals who might benefit from intensified therapy. A systematic review showed that 75% of articles published describing predictor models of mortality after a stroke were not internally valid and 80% of the rest had selection bias.[24] Prospective longitudinal studies in ischemic stroke patients, frequently include few variables[25] and differ in them[26,27] and in the patient characteristics[28] making difficult the comparison. This study includes numerous variables in a big sample followed prospectively during five years. Only 4.5% of all the elegibles patients (291 cases) had not a computerized tomography and were excluded. Only 2% of patients were lost due to the prospective follow-up and the telephone contact as well as the Death Registry examination. The number of patients died at five years is similar to other studies (between 45 and 61%).[29]

In this study, short term mortality is related to severity (as measured with the Canadian Scale), age, albumin, glycemia, diastolic blood pressure (DBP) and the cardioembolic mechanism (CM). Relationship between acute mortality and age, neurological impairment, severity at admission,[30-32] CM,[33] and hyper-

Table VI
Risk factors for mortality at different time points. Logistic regression analysis

		E.T.	Wald	gl	Sig	OR	95% CI
A. Mortality at one month							
Cardiembolic mechanism	1.7	0.7	6	1	0.01	5.5	1.4-22
Albumin*	1.4	0.6	5	1	0.02	4	1.3-14
Age	0.1	0.04	6	1	0.02	1.1	1.02-1.2
Glycemia	0.02	0.006	11	1	0.001	1.02	1.008-1.03
DBP at admission	-0.4	0.02	6	1	0.01	0.96	0.92-0.99
Canadian Scale score at admission	-0.3	0.1	4	1	0.04	0.7	0.5-0.9
B. Mortality between one and three months							
Previous Stroke	1.9	0.7	7	1	0.009	7	1.6-29
Barthel index at discharge	-0.1	0.02	12	1	0.000	0.9	0.89-0.96
Constant	-0.9	0.5	4	1	0.04	0.3	
C. Mortality between three months and one year							
Previous Dementia	1.5	0.6	6	1	0.02	4.5	1.3-15
Barthel Index at three months (reverse)	0.04	0.009	23	1	0.000	1.04	1.02-1.06
D. Mortality between one and five years							
Age	0.09	0.02	9	1	0.000	1.09	(1.05-1.13)
Canadian Scale at discharge	0.3	0.09	11	1	0.001	0.7	(0.6-0.8)
Cholesterol at admission < 192 mg/dl	1.2	0.4	9	1	0.002	3	(1.5-7)
Constant	-5.3	1.6	11	1	0.001		

*Reverse albumin value at admission.
DBP: Diastolic blood pressure.
A) At one month: 249 cases (98%): 20 died, 234 survived. Model correctly predicts 92.4%.
B) Between one and three months: 234 cases (99,6%): 14 died, 220 survived. Model correctly predicts 95%.
C) Between three months and one year: 220 cases (99,5%): 20 died, 200 survived. Model correctly predicts 91,3%.
D) Between one year and five years: 200 cases (99%): 58 died, 142 survived. Model correctly predicts 71%.

glycemia,[34,35] has been previously described. We don't find a relationship with a higher systolic blood pressure but a lower diastolic one, posibly because night falls would worse the ischemic process. Plasmatic albumin inversely related to mortality as in other studies[36] increasing mortality four times for each g/dl that it diminishes at admission.

There are few mortality studies at three months. Similarly to others, 13% of patients died at 3 months.[31] In the one month survivors, factors most significantly associated to mortality at three months were having a previous stroke and the functional dependence at discharge measured as the Barthel Index score. Functional outcome has also been related to hypoalbuminemia at admission in some studies.[37] The NIH-Stroke functional scale at admission, comparable to Barthel Index has shown predictive value on mortality at three months by others.[38,39]

Long term mortality. As in the Oxfordshire Community Stroke Project[29] in our study died 21% at a year and 9% between 3 months and one year. In survivors at one year previous dementia and functional status at 3 months have shown predictors of mortality as in previous studies.[40-42]

Very long term mortality (between 1-5 y). Independent variables on mortality are age, severity of stroke at discharge (Canadian Scale score) and a cholesterol at admission lower than 192 mg/dl (quartile 25). Other authors that excluded patients died in previous periods found age a risk factor also.[26] Severity of stroke at admission was related to mortality at very long term excluded patients died at one month in the Olmsted County Study.[33]

Previously published studies considering survivors only for study of long term mortality find usually cardiopathy antecedents, atrial fibrillation and cardioembolic mechanism to be a prognostic factor.[24,27] In our study, it doesn t remain significant after adjusting by age.

Variables significant for mortality at long term in other studies as The Perth Community Stroke Study,[26] or the Northern Manhattan Stroke Study,[27] ceased to be so in ours when adjusting for others as cholesterol or severity.

Severity, hyperglycemia and previous cardiopathy were predictors of mortality at one month in the Hankey meta-analysis. In survivors at one month, predictors for long term mortality were severity, age and previous cardiopathy.[24] In our study, previous dementia is more important than previous cardiopathy in the long term mortality. Collins published a study analyzing patients for mortality after a stroke at short, medium and long term similarly to ours. It is not strictly comparable because an exclusion criteria was having a previous stroke and there were no data of severity at admission.[43]

The only analytical parameter statistically significant to predict mortality in our seria of patients is

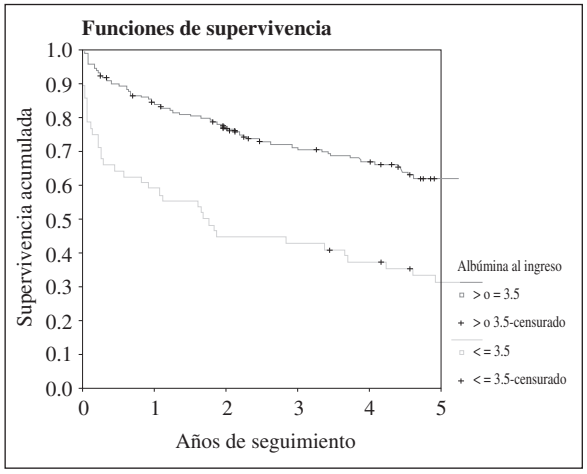

Fig. 1.—Kaplan-Meier curves correspondint to albumin categories at admission.

albumin concentration at admission as an absolute value, but not divided in the intervals previously described by others[8,10,12,44] nor the albumin/globulin ratio.[45] There are three mechanism of albumin descent in different pathologies:

Inflammation: Citokines increase vascular permeability to albumin owed to changes in the interstitial matrix.[46] Other acute phase reactants have been shown to predict hypoalbuminemia in patients with different illnesses.[47] Treatment should be focused on diminishing inflammatory response[48] being hypoalbuminemia a stress and illness severity marker.

Dilution: an stroke as an acute illness conveys an incapacity to eliminate water and salt excess with increased extracellular volume. This is the only case in which intravenous albumin would be indicated followed by diuretics.[48] It has to be emphasized the care in using albumin after the recently published ALIAS Multicenter Clinical Trial.[13,14] We are waiting hopefully the results of the second part of that trial.

Previous malnutrition: malnutrition in patients admitted to the hospital, especially if they are hemiparetic or disphagic, conveys a cardiac, respiratory, hepatic and renal deterioration, a pancytopenia owed to medular aplasia, impaired inmune function with an increased susceptibility to infections, a delay in healing and a cognitive impairment.[49]

Most clinicians associate hypoalbuminemia to malnutrition, but except for albumin and weight, no other nutritional variables drop during the hospital stay after an ischemic stroke[50] and owing to its long half-life (14-20 days) and low daily exchange (< 5%), it is not a good marker of hepatic damage nor acute malnutrition.

Today, it seems clear that albumin concentration in patients with serious illnesses doesn't reflect just the nutritional status but can be an inespecific marker of graveness[7,47] that can condition coagulation[51] and metabolic alterations.[52] Its reduction depends on the severity of the illness and its duration.[48] In patients with stroke a higher mortality in patients with hypoalbuminemia without other markers of malnutrition[8] has been described.

The other risk factors we find in our study have been widely described previously associated to mortality: age has been found a risk factor of mortality in most other studies because it means more associated cardiovascular risk factors,[53] medical complications;[29] cardioembolic stroke,[38,39] severity (CNSS)[54] and previous dementia.[50]

Our study weaknesses include not being able to access to the Death certificates in some cases, so lacking the cause of mortality and not having collected anthropometric measurements. Our strengths are the long prospective follow-up, the different ways to obtain very long term data and the amount of variables considered.

In conclusion, we found mortality after an ischemic stroke dependent on different factors depending of the period of time considered.

Hypoalbuminemia at admission is an independent factor for overall mortality.

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