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Clinical significance of homocysteine in elderly hospitalized patients

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Abstract

Serum homocysteine levels, which increase with age, are now recognized as a vascular risk factor and are related to the development of heart failure and dementia in the elderly. However, relatively low serum homocysteine levels have also been reported to be an adverse prognostic factor in dialysis patients. The objective of the study was to analyze the prevalence, clinical significance, and prognostic value of serum homocysteine levels in patients older than 65 years, admitted to a general internal medicine hospitalization unit. We studied 337 hospitalized patients, 184 males and 153 females, aged 77.2 ± 0.4 years, whose admission was not determined by an acute vascular event. We recorded past vascular events and vascular risk factors. We determined the body mass index (weight in kilograms divided by the square of height in meters), and cholesterol, triglyceride, folate, vitamin B_{12}, and homocysteine levels. We also studied 36 control subjects (18 males and 18 females) of similar age. After discharge, we assessed the survival status of 301 patients by telephone recall. Survival curves were plotted by the method of Kaplan and Meier. Median survival was 1186 days. The 15th (9.6 μmol/L) and 50th (14.4 μmol/L) percentiles, as the lowest and highest cut-off points, were empirically defined as those related to a shorter survival. Serum homocysteine concentration was significantly positively correlated with age and serum creatinine and albumin concentrations, and negatively correlated with serum cobalamin and folate concentrations. The average serum homocysteine concentration for the patients group, as a whole, was 16.5 ± 0.5 μmol/L, not significantly different from the control group, but with a much greater dispersion, as patients with congestive heart failure or cognitive impairment had higher serum homocysteine concentrations, and patients with sepsis, leukocytosis, and hypoalbuminemia had lower concentrations. Malnutrition was associated both with abnormally high and low homocysteine concentrations, and abnormally low and abnormally high homocysteine concentrations were both associated with higher mortality. In conclusion, low homocysteine levels in elderly non–vitamin-supplemented hospitalized patients should not be interpreted as a protective factor in some individuals. Instead, it may be considered as an effect of an inflammatory-malnutrition process associated with a poor prognosis.

1. Introduction

Many case-control and cohort studies have shown a close relationship between hyperhomocysteinemia and vascular diseases such as myocardial infarction, thrombotic stroke, peripheral vascular disease, and venous thrombosis [1-5]. This is, therefore, considered to be a vascular risk factor, in a similar way as hypertension, diabetes, hyperlipidemia, obesity, or tobacco use. Other studies have shown a relationship between homocysteine and congestive heart failure [6-8] and Alzheimer's dementia [9-11]. Most of these studies have been performed either in an apparently healthy general population or after a vascular event such as a myocardial infarction or a cerebral thrombosis. However, the possible significance of serum homocysteine levels in elderly hospitalized patients has been less studied. Studies in the elderly, performed by Ventura et al [12] and Marengoni et al [13], have shown that plasma homocysteine levels are related to age and creatinine, folate, vitamin B_{12}, and serum albumin levels. In these studies, patients with vascular disease or heart failure also presented higher serum homocysteine levels.

Cohort studies have shown that hyperhomocysteinemia is related to an impaired long-term survival [14-16]. However, long-term prognosis related to plasma homocysteine after

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hospitalization has only been analyzed in dialysis patients. Three studies performed in dialysis patients, in which homocysteine is markedly raised (Sirrs et al [17], Suliman et al [18,19], and Kalantar-Zadeh et al [20]), have shown that lower plasma homocysteine levels, but not hyperhomocysteinemia, are related to a higher mortality. This raised mortality seems to be associated with an inflammatory-malnutrition syndrome, related to hypoalbuminemia, a condition frequently seen in dialysis patients [21]. Protein disulfide-bound homocysteine accounts for more than 70% of total homocysteine. Because homocysteine is mainly bound to albumin, hypoalbuminemia could lead to decreased serum homocysteine levels [22]. It has not been determined whether these findings are specific to dialysis patients or could also be valid for general medical patients.

Our objective is to analyze the clinical significance of serum homocysteine levels in elderly patients admitted to a general internal medicine hospitalization unit, where cardiovascular risk factors are highly prevalent and, also, to evaluate the possible long-term prognostic value of low and high serum homocysteine levels compared with other well-known prognostic factors.

2. Methods

Three hundred thirty-seven hospitalized patients, 184 males and 153 females, with a mean age of 77.2 ± 0.4 years (range, 65-101 years) were included. All the patients were hospitalized in the internal medicine unit of the Hospital Universitario de Canarias. Patients were included after evaluation in the emergency department. We did not include patients admitted for an acute vascular event.

2.1. Diseases

Vascular disease and cardiovascular risk factors were recorded according to diagnosis at admission and at discharge: previous cardiovascular diseases such as myocardial infarction 38 (11.3%), ischemic cerebral stroke 65 (19.3%), and peripheral vascular disease 26 (7.7%), as well as cardiovascular risk factors such as arterial hypertension 211 (62,6%), hyperlipidemia 122 (36,2%), obesity (body mass index [BMI] >30 kg/m^2) 68 (22.1%), diabetes mellitus 158 (46.9%), and current or past smoker (27%).

Besides cardiovascular risk factors and past cardiovascular events, the diseases diagnosed at admittance and at discharge are reported in Table 1. Congestive heart failure was diagnosed in 144 patients (42.7%) according to the Framingham criteria [23]; atrial fibrillation in 121 (35.9%); chronic obstructive pulmonary disease (COPD) and/or asthma in 66 (19.6%). A neoplastic disease was diagnosed in 24 patients (7.1%); 13 of them had active cancer, whereas in the other 11 it was a past antecedent without signs of recurrence. We recorded infections (mainly sepsis of respiratory and urinary tract) according to the diagnosis at discharge in 164 patients (49%); mild infections with little clinical significance such as uncomplicated cystitis or acute bronchitis were not included. Cognitive impairment was assessed in 297 of the patients by Pfeiffer test [24,25]; 45 (15.2%) of them had more than 5 points.

Table 1
Diagnosis

Sepsis	164 (48.7)
Lung sepsis	125 (37.1)
Urinary	25 (7.4)
Biliary	9 (2.7)
Abdominal	5 (1.5)
Bone arthritis	4 (1.2)
Cellulitis	15 (4.5)
Other	3 (0.9)
Heart failure	144 (42.7)
Atrial fibrillation	121 (35.9)
COPD and/or asthma	66 (19.6)
Acute renal failure	25 (7.4)
Chronic renal failure	44 (13.1)
Alcoholism (excessive ethanol intake)	41 (12.2)
Chronic liver disease	33 (9.8)
Anemia	52 (15.4)
Acute digestive bleeding	14 (4.2)
Thromboembolic disease	16 (4.7)
Acute confusion (delirium)	36 (10.7)
Dementia	27 (8)
Parkinson's disease	14 (4.2)
Epilepsy	11 (3.3)
Hyperthyroidism	9 (2.7)
Hypothyroidism	14 (4.2)
Connective tissue disease	11 (3.3)
Active cancer	11 (3.3)

Data are expressed as number (percentage).

2.2. Nutritional assessment

We inquired about the regularity of feeding habits, how many meals in a day, how many dishes in a meal, or if dishes are frequently substituted by snacks. All these data were then used to classify dietary habits as good or irregular. Excessive alcohol drinking (more than 80 g/d in men and 40 g /d in women) was reported by 54 patients (16%) (grams of ethanol = volume of beverage [mL] × strength [vol/vol; %] × 0.8). We determined the BMI as weight in kilograms divided by the square of height in meters, the MAC, and the triceps skinfold by a Holtain lipocaliper, and further calculated the midarm muscle area [26]. Anthropometric parameters were compared with those of the adult population of the Western Canary Islands of the same sex and age [27].

Subjective nutritional evaluation included examination of the muscle masses of the upper and lower limbs and of the temporal muscle, defining 2 degrees of atrophy (severe, moderate), and absence of atrophy. We assigned 2, 1, and 0 points to each category. Bichat's fat and subcutaneous fat atrophy were classified in the same way. We therefore defined a subjective nutritional score (SNS) based on the sum of the assigned points. As previously reported, a score of 0 to 2 was considered normal, 3 to 4 points as mild malnutrition, and higher than 4 points as severe malnutrition [28,29].

Table 2
Comparison between patients (373) and control (36) subjects

	Control	Patients	Mann-Whitney *U* test	*P*
Homocysteine (μmol/L)	15.6 ± 0.7	16.5 ± 0.5	0.376	.707 (NS)
Vitamin B_{12}	377 ± 27	570 ± 24	2.822	.005
Folate (ng/L)	10.6 ± 3.8	6.4 ± 0.2	0.7140	.475 (NS)
Hemoglobin (g/dL)	13.5 ± 0.3	11.8 ± 0.1	4.301	.000
Neutrophil count/mm^3	4833 ± 385	7048 ± 236	3.250	.001
lymphocyte count/mm^3	1918 ± 150	1302 ± 44	4.154	.000
Serum albumin (g/dL)	4.1 ± 0.05	3.2 ± 0.03	8.117	.000
Serum creatinine (mg/dL)	0.78 ± 0.05	1.15 ± 0.04	4.465	.000

NS indicates not significant.

2.3. Serum homocysteine and vitamin measurements

After clinical assessment, at 8:00 AM, venous blood from fasting subjects was drawn into Vacutainer silicone tubes. Serum was separated (within 30 minutes) and frozen at −40°C for analysis of homocysteine levels by polarized fluorescence immunoassay (Abbott IMX system, Abbott Laboratories, Abbott Park, IL). Homocysteine artificial increase due to methionine is minimal if the sample is centrifuged within 1 hour [30]. Serum folate levels were determined by ionic capture immunoassay (Abbott AXSYM system) and serum B_{12} levels were determined by microparticle enzyme immunoassay (Abbott AXSYM system). Patients had intravenous hydration only if clinically necessary. Regarding vitamins, in the emergency department, only B_1 was administered, but not folate, B_{12}, or B_6.

As a control group, we studied 36 healthy subjects older than 65 years (aged 74 ± 1 years; 18 males and 18 females) attending for minor surgery, such as small basal cell carcinoma, cataracts, or herniorrhaphy, without a history of vascular events or other current acute diseases and not hospitalized in the last year. The study was approved by the institutional review board; informed consent was obtained from all patients.

2.4. Statistical analysis

Statistical analysis was performed using SPSS software version 12.0 (SPSS, Chicago, IL). As most variables, especially homocysteine and serum vitamins, did not fit the normal distribution, we performed nonparametric tests such as χ^2 test, Mann-Whitney *U* test, Kruskal-Wallis test, and Spearman correlation. To assess if serum homocysteine levels were dependent on factors such as heart failure or dementia, correcting for quantitative variables such as age or vitamins, we performed a covariance analysis with previous logarithmic transformation of these variables. Stepwise multivariate linear regression analysis was performed to discern parameters with an independent predictive value on serum homocysteine. This was also done after logarithmic transformation of the variables.

After discharge, patients were followed by telephone recall. By this way we could assess the survival status (alive or dead) of 301 (nearly 90%) of patients. Survival curves were plotted by the method of Kaplan and Meier, and the log-rank test was performed to assess differences in survival.

The 15th (9.6 μmol/L) and 50th (14.4 μmol/L) percentiles, as the lowest and highest cut-off points, were empirically defined as those related to a shorter survival. To test the hypothesis that both low and high serum homocysteine levels may be related to a shorter survival, we converted serum homocysteine into a categorical variable using the percentile system. We searched for the best cut-off, testing for mortality after dividing the patients into 20, 10 (deciles), 5 (quintiles), and 4 (quartiles) groups. After this, we found that the 15th and 50th percentiles, as lower and upper cut-off points, were the best ones to predict long-term mortality. Multivariate analysis (Cox regression with covariate survival analysis) was performed to discern which parameters yield independent predictive values on survival. All the tests performed were 2-tailed. Results are expressed as means ± SEM.

3. Results

Between January 2002 and April 2004, 337 patients were included. Mean serum homocysteine levels were 16.5 ± 0.5 μmol/L, without differences regarding sex and also without differences compared with the control group (15.6 ± 0.7 μmol/L). However, if we consider 15 μmol/L as the upper limit of normality, 47.2% of patients reached or surpassed this limit. The distribution of serum homocysteine was broader in patients than in controls, with the most extreme values corresponding to patients. Only 2.8% of controls showed a serum homocysteine level higher than 25 μmol/L vs 11% of patients, and 5.6% of controls showed a serum homocysteine level lower than 10 μmol/L vs 15.4% of patients ($P = .029$).

Low serum folate levels (<3 ng/mL) were present in 12.1% and serum B_{12} levels less than 200 pg/mL in 8.9% of the patients. Differences in serum folate and B_{12} levels between patients and controls are shown in Table 2. Besides homocysteine, serum folate levels also correlated negatively with age, leukocyte count, Pfeiffer score, and with subjective nutritional assessment and positively with serum albumin and prealbumin levels (lower serum folate in malnutrition and in dementia).

To investigate which factors serum homocysteine levels depend on, we performed correlation (Spearman ρ) and

regression analyses. Homocysteine correlations were very different in men and women. In male patients, homocysteine correlated with B_{12} (negatively, $P < .001$), neutrophil count (negatively, $P = .003$), blood glucose (negatively, $P = .013$), serum urea nitrogen ($P < .001$), creatinine ($P < .001$), and serum albumin ($P = .002$), whereas in females, it correlated with age ($P = .012$), folate (negatively, $P = .008$)), creatinine ($P = .016$), and midarm muscle area ($P = .036$). After logarithmic transformation of the variables, by stepwise multiple linear regression, we found that serum homocysteine depended, in this order, on B_{12} (negatively), creatinine, folate levels (negatively), serum albumin, and neutrophil count (negatively).

Vascular risk factors and cardiovascular diseases were frequent in patients older than 65 years. Only 33 patients (9.8%) showed no cardiovascular risk factors. We did not find an increase in serum homocysteine levels in relation to vascular risk factors, to past cardiovascular diseases, or atrial fibrillation.

Congestive heart failure, which is highly prevalent (42.7%), was related to an increase in serum homocysteine: 17.8 ± 0.7 μmol/L in patients with heart failure vs 15.5 ± 0.6 μmol/L in patients without heart failure ($P = .005$). The significantly higher serum homocysteine levels persisted after adjustment for sex, age, serum vitamin levels, creatinine levels, and cardiovascular disease. Prevalence of heart failure increased with serum homocysteine levels: from 30% when homocysteine was below the 15th percentile, to 40% between the 15th and 50th percentiles, and to 48% when above the 50th percentile. This relationship was only significant in patients with serum creatinine levels of more than 1 mg/dL ($P = .040$).

Cognitive impairment (5 or more points at the Pfeiffer test) was related to an increase in serum homocysteine: 20.2 ± 1.5 vs 15.8 ± 0.5 μmol/L ($P = .004$). Patients with cognitive impairment were older and showed a worse nutritional status with significantly lower serum folate and albumin levels and a worse SNS. The significantly higher serum homocysteine levels in patients with cognitive impairment persisted after adjustment for age, serum vitamin levels, and ischemic stroke. The prevalence of dementia increased in parallel with serum homocysteine levels: from 11.6% when homocysteine is under the 15th percentile to 21.3% when homocysteine is above the 50th percentile ($P = .007$).

Irregular feeding was reported by 16% of the patients. Subjective nutritional assessment was normal in 28.2%, 33.1% showed mild malnutrition, and 38.7% severe malnutrition. Serum albumin levels were normal (>3.8 g/dL) in 14.3%, mildly impaired (3–3.8 g/dL) in 52.6%, and intensely decreased (<3 g/dL) in 33.1% of the patients. Patients with severe malnutrition also showed lower serum albumin and prealbumin levels.

Both patients with lower and higher serum homocysteine levels showed a more impaired nutritional status (SNS = 4.67 ± 0.4 and 4.57 ± 0.2, respectively) than those with homocysteine between the 15th and 50th percentiles (SNS = 3.69 ± 0.2; $P = .008$); this effect was independent of serum creatinine levels or sepsis. A total of 48% of patients with homocysteine under the 15th percentile presented severe malnutrition, and 45% of those above the 50th percentile, whereas in those between the 15th and 50th percentiles, severe malnutrition was observed only in 25% ($P = .005$).

Patients with homocysteine under the 15th percentile showed lower serum albumin levels ($P = .039$) and higher neutrophil count ($P = .038$) compared with the other 2 groups. Patients with homocysteine above the 50th percentile showed a higher degree of cognitive impairment (21.3%) than the other 2 groups (8.8%) ($P = .009$) and a higher proportion of raised creatinine levels (more than 1.5 mg/dL), 20% vs 11% in the other 2 groups ($P = .003$).

Patients with sepsis showed lower serum homocysteine levels: 15.3 ± 0.5 vs 17.9 ± 0.7 μmol/L ($P = .003$). Sepsis was also related to lower serum folate and albumin levels, higher neutrophil count, and higher serum creatinine. A raised neutrophil count (>5000/mm^3) was also related to lower serum homocysteine levels: 15.7 ± 0.5 vs 17.9 ± 0.8 μmol/L ($P = .023$). Low serum albumin level (<2.5 g/dL, 10th percentile) was also related to lower serum homocysteine levels: 13.1 ± 1 vs 16.8 ± 0.5 μmol/L ($P = .021$). However, patients with high serum albumin levels (>3.8 g/dL, 90th percentile) did not show higher homocysteine levels: 16.9 ± 1.2 vs 16.4 ± 0.5 μmol/L (nonsignificant differences). Serum albumin positively correlated with homocysteine only in patients with infection, but not in noninfected patients. Moreover, decreased serum homocysteine in infected patients occurred despite an older age, decreased serum folate, and increased serum creatinine levels. If we exclude patients with sepsis (49%) or with a neutrophil count of more than 5000/mm^3 (64%), the mean serum homocysteine levels in the remaining 69 cases rise to 19.4 ± 1.1 μmol/L.

Mortality within the first 4 weeks after admission was 5.3%. Long-term survival status was followed by telephone recall in 301 patients. The total group showed a median survival of 1186 days with a 95% confidence interval (CI) between 971 and 1400 days. The relationship between clinical alterations and survival is shown in Table 3. Obesity, hypertension, hyperlipidemia, and diabetes were not associated with an impaired survival. Factors related to a shorter survival were advanced age, low (under the 15th percentile) and high (above the 50th percentile) serum homocysteine levels, malnutrition, serum folate lower than 3 ng/mL, low serum albumin and prealbumin levels, a low lymphocyte count (<1500/mm^3), a neutrophil count of more than 5000/mm^3, Na of less than 132 mmol/L, low systolic and diastolic arterial pressure, a decreased prothrombin activity, cognitive impairment (Pfeiffer score >5), sepsis, and active cancer. Atrial fibrillation and past cardiovascular events were also associated with a lower survival, but not heart failure, or COPD.

The 15th and 50th percentile cut-off points for serum homocysteine were empirically obtained as the best ones related with long-term mortality. We searched for the best

Table 3
The following parameters were associated with a significant shorter survival

Variable	Log-rank test	P
Age >84 y	25.06	.0000
Homocysteine under the 15th percentile vs 15th- 50th percentiles	4.82	.0282
Homocysteine above the 50th percentile vs 15th-50th percentiles	6.77	.0093
Any past cardiovascular event	5.43	.0198
Atrial fibrillation	4.42	.0356
Irregular feeding	16.98	.0000
Serum folate <3 ng/L	19.27	.0000
Impaired SNS (>2 points)	20.20	.0000
BMI <21 kg/m^2	6.72	.0095
Serum cholesterol <100 mg/dL	18.15	.0000
Serum triglyceride <80 mg/dL	5.95	.0147
Serum albumin level <3 g/dL	7.04	.0080
Serum prealbumin level <10 mg/dL	8.35	.0039
Total lymphocyte count <1500/mm^3	17.78	.0000
Neutrophil count >5000/mm^3	8.76	.0031
Hemoglobin <9 g/dL	5.21	.0025
Serum urea nitrogen <6 mg/dL	25.55	.0000
Creatinine <0.6 mg/dL	11.61	.0002
Na <132 mmol/L	15.50	.0001
Systolic arterial pressure <110 mm Hg	11.40	.0007
Diastolic arterial pressure <60 mm Hg	8.92	.0028
Prothrombin activity <70%	10.46	.0012
Cognitive impairment (Pfeiffer score >5)	13.15	.0025
Active cancer	16.90	.0000
Sepsis	4.32	.0377

cut-off points testing survival after dividing the sample into groups of 20, 10 (deciles), 5 (quintiles), and 4 (quartiles) groups with the same number of patients. However, the 15th and 50th percentiles were the most closely related to a shorter survival. With the use of deciles we did not observe a gradual increase in mortality.

In survival analysis with covariates (Cox regression), homocysteine was not included as an independent prognostic factor. When we adjusted survival analysis for subjective nutritional assessment, the prognostic value of low homocysteine levels disappeared. When the homocysteine survival analysis with 15th and 50th percentiles as cut-off points was stratified according to the existence or not of sepsis, the log-rank test was still significant.

Variables with an independent prognostic value in the Cox analysis were low serum urea nitrogen (<6 mg/dL; relative risk [RR], 9.98; 95% CI, 28.9-3.44), active cancer (RR, 5.53; 95% CI, 11.4-2.67), old age (>85 years; RR, 2.47; 95% CI, 3.95-1.54), impaired nutrition with subjective assessment (SNS >2; RR, 2.18; 95% CI, 4.24-1.13), a low lymphocyte count (<1500 mm^3; RR, 2.00; 95% CI, 3.58-1.12), hyponatremia (Na <132 mmol/L; RR, 1.90; 95% CI, 3.15-1.16), and decreased prothrombin activity (<70%; RR, 1.81; 95% CI, 2.86-1.14).

4. Discussion

Although there no consensus about the upper normal limit for serum homocysteine levels in aged patients, we have considered 15 μmol/L as suggested by the American Heart Association [1,10,12,30]. This upper limit reflects more a clinical criteria regarding vascular risk than a simple statistic criteria. With this upper limit we found a high prevalence of hyperhomocysteinemia, 47.2%, similar to the results reported by Ventura et al [12] also in hospitalized patients. However, these results are slightly overestimated, as serum homocysteine levels may be 5% to 10% higher than plasma ones.

We did not find differences between patients and a control group of similar age, without vascular events and not hospitalized, both presenting raised mean values of 16.5 $\pm$ 0.5 and 15.6 $\pm$ 0.7 μmol/L, respectively. This lack of difference suggests 2 considerations. First, the increased homocysteine levels of our apparently healthy nonhospitalized controls (regarding the upper limit) can be only explained by the advanced age of this control group and reflects the great influence of age on homocysteine concentrations. In this sense, Seshadri et al [9] report a mean of 11.5 μmol/L in the group of patients aged 65 to 69 years increasing to 22.3 μmol/L in the group of patients aged 90 to 94 years. Second, why did our patients not show a more increased homocysteine concentrations when compared with the control group? The explanation is that our patients conform a heterogeneous sample, including patients with high and low homocysteine concentrations. The range of serum homocysteine levels was wider in patients than in controls, with more extreme values among the former.

Homocysteine has been reported to increase with age, low serum folate or vitamin B_{12} levels, increased serum urea nitrogen and serum creatinine, cognitive impairment, and heart failure, all of them frequent circumstances among our patients [6-13,32-34]. One of the most frequent causes of a rise in homocysteine is folate deficiency, which may be caused by low local intake. However, a regional survey shows that there is no endemic folate deficiency in the Canary Islands [31], so the folate deficiency of our patients must be attributed to disease and malnutrition. Taken together, these data may explain the high prevalence of hyperhomocysteinemia in elderly patients.

On the other hand, patients with sepsis, a high neutrophil count, or low serum albumin level showed decreased serum homocysteine levels. Hence, the heterogeneous underlying conditions of our patients, which may have an opposite influence on serum homocysteine levels, increasing or lowering them, could explain a mean value that does not differ from that of the control group.

An important concern about hyperhomocysteinemia is its relationship with vascular risk [1-4,6-16]. However, we found that neither patients with past cardiovascular events showed higher homocysteine levels nor patients with one or more vascular risk factors such as hypertension, hyperlipidemia, obesity, or diabetes. The explanation for this lack of relationship may be that our patients are a heterogeneous sample and that homocysteine levels are subjected to diverse and opposing influences, which surpass its relationship with vascular risk and atherosclerosis.

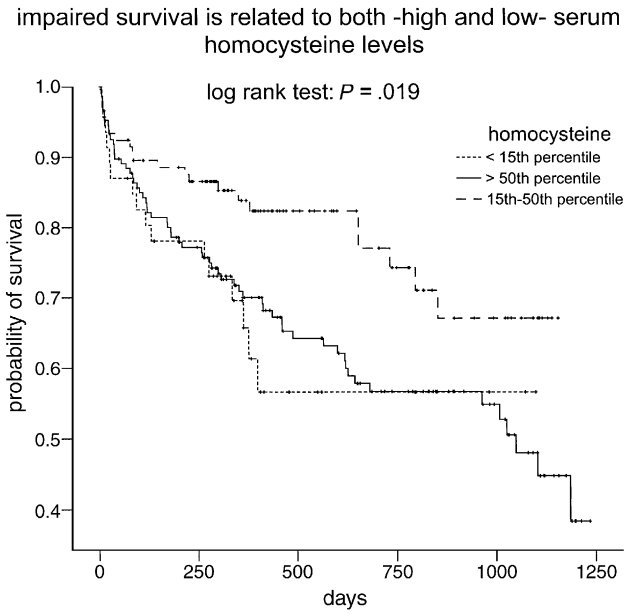

Fig. 1. Low (under the 15th percentile; 47 patients) and high (above the 50th percentile; 106 patients) serum homocysteine levels show an impaired survival when compared with homocysteine concentrations between the 15th and 50th percentiles (148 patients). With multivariate analysis, serum homocysteine levels loose prognostic value, being displaced by nutritional status, which is impaired both at high and low homocysteine concentrations.

Like other authors, over the past few years, we have found raised serum homocysteine levels in patients with heart failure [6-8,12]. It has been suggested that, in heart failure, homocysteine may increase in association with raised serum creatinine because of a low renal blood flow. In our patients, the prevalence of heart failure increases with serum homocysteine levels, but only significantly in patients with serum creatinine level of more than 1 mg/dL. A relationship between hyperhomocysteinemia and dementia has also been reported [9-11]. Our patients with cognitive impairment had elevated serum homocysteine levels. These patients were older and poorly nourished, so they also had lower serum folate levels. However, the relationship between hyperhomocysteinemia and dementia persisted after adjusting for age and serum folate and B_{12} levels.

Which other factors could homocysteine be related to? When assessed by multivariate analysis, serum homocysteine was independently related to B_{12}, creatinine, folate, serum albumin, and neutrophil count. Results for the first 4 factors agree with those of many studies [11-13,32-34]. However, it is remarkable that serum albumin, in some studies, correlated negatively with homocysteine [12,35,36], whereas in others, performed in healthy controls, in patients in dialysis, in hospitalized elderly patients [13,32,37,38], and, in our study, in septic patients this relationship was positive. The difference may be because, in our study, when blood was drawn, in the first days after admittance, many patients had an acute-phase inflammatory process. Half of our patients were admitted for sepsis and, also, more than half had reduced serum albumin levels and a raised neutrophil count. Hence, as septic patients have lower homocysteine levels (despite an older age, lower folate levels, and higher serum creatinine), and, also, because homocysteine correlates with serum albumin and negatively with neutrophil count, we can hypothesize that severe infection decreases serum albumin levels and, in turn, serum homocysteine levels, as serum homocysteine is linked to serum proteins and mainly (70%) to albumin. We can, therefore, consider that low serum homocysteine is related, at least partially, with low serum albumin, suggesting an acute-phase reaction linked to sepsis.

High serum homocysteine levels have been related to long-term impaired prognosis in cohort studies. However, in our elderly sample, we wanted to analyze the relative importance of homocysteine when compared with other factors. Regarding prognosis, besides old age, the main factors related to survival were nutritional ones, such as irregular feeding, subjective nutritional assessment, low serum albumin and prealbumin, low lymphocyte count, low cholesterol and triglyceride, and low folate levels. Moreover, we failed to find any relationship with mortality when we analyzed factors traditionally related to a long-term poor prognosis, such as hypertension, obesity, diabetes, or hyperlipemia. On the contrary, low blood pressure, serum cholesterol of less than 100 mg/dL, triglyceride level of less than 80 mg/dL, or malnutrition was related to a higher mortality. These contradictory results have been defined as "reverse epidemiology" in patients with heart failure, dialysis, and in the elderly, and are mainly explained by malnutrition [39-42]. In epidemiologic studies performed in apparently healthy people, obesity, hypertension, and hyperlipidemia are well-established long-term vascular risk factors. However, once disease develops, and especially at older ages, a preserved nutritional status is of paramount importance for survival. It is not the case that obesity or hypertension change from being poor prognostic factors to being good ones, but that—in the context of disease, old age, and inflammation—the presence of hypotension and malnutrition are all unfavorable conditions.

Homocysteine is related to nutrition and, therefore, may also be related to prognosis. Both patients with low (below the 15th percentile) and high (above the 50th percentile) serum homocysteine showed a shorter survival and, also, a worse nutritional status when assessed by the SNS (Fig. 1). Moreover, among patients with low and high serum homocysteine levels we observed a high proportion of patients with intense malnutrition (48% and 45%, respectively), whereas in the remainder, malnutrition was observed only in 25%.

Over the past few years, Sirrs et al [17], Kalantar-Zadeh et al [20,21], and Suliman et al [18,19] have shown, in dialysis patients, who have especially high serum homocysteine levels, that relatively low homocysteine values are associated with higher mortality. In these studies, malnourished patients showed lower levels of serum albumin and homocysteine, with a positive correlation between both parameters. This effect is explained by a malnutrition-inflammation syndrome,

which is common in dialysis patients, and leads to reduced serum albumin levels, to which homocysteine is mainly bound. Our study shows that both decreased and increased homocysteine levels are related to long-term mortality, with a moderate significance. However, at multivariate analysis, homocysteine looses its predictive value. In our patients, low homocysteine levels were related to sepsis, neutrophilia, malnutrition, and low serum albumin levels. Because sepsis, neutrophilia, low albumin, and malnutrition are all related to a poor prognosis and also to low homocysteine levels, we can explain the impaired outcome of low homocysteine levels. When we adjusted survival for subjective nutritional assessment, the prognostic value of low homocysteine levels disappeared. On the other hand, higher homocysteine levels are also associated with a shorter survival. Higher homocysteine levels were also related to malnutrition, low folate and B_{12} levels, heart failure, cognitive impairment, and impaired renal function. All these factors may explain the association between higher homocysteine levels and shorter survival. Moreover, when we adjusted survival for subjective nutritional assessment, the prognostic value of high homocysteine levels disappeared.

In conclusion, the prognostic value of low homocysteine, first described in dialysis patients, may be extended to elderly hospitalized general medical patients. In these situations, low homocysteine levels should not be interpreted as a marker of low cardiovascular risk, but as a possible marker of a malnutrition-inflammation syndrome related to sepsis, high neutrophil count, and low albumin. Thus, in elderly hospitalized general medical patients, they should not be considered as a protective factor, but, instead, possibly associated with a poor prognosis.

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