Alpha 1-acid glycoprotein is an independent predictor of in-hospital death in the elderly

Olivier F. Henry[1], Jacques Blacher[2], Jacqueline Verdavaine[1], Monique Duviquet[3], Michel E. Safar[2]

[1]Service de Médecine Gériatrique, Hôpital Emile Roux, AP-HP, Limeil-Brévannes, France
[2]Service de Médecine Interne, Hôpital Broussais, AP-HP, Paris, France
[3]Service de Médecine Gériatrique, Hôpital Charles Richet, AP-HP, Villiers-Le-Bel, France

Address correspondence to: M. Safar, Service de Médecine Interne, Hôpital Broussais, AP-HP, 96, rue Didot, 75014 Paris, France. Fax: (+33) 1 45 43 38 94. Email: michel.safar@brs.ap-hop-paris.fr

Abstract

Objectives: to determine the contribution of the two acute phase proteins alpha 1-acid glycoprotein, and C-reactive protein to the prediction of overall mortality in hospitalised elderly patients.
Design: prospective cohort study.
Setting: a department of geriatric medicine of Charles Richet Hospital, in the Paris-Ile de France area.
Subjects: 433 consecutive patients (mean age 84 ± 7 years) admitted for rehabilitation in a department of geriatric medicine.
Methods: clinical and laboratory examinations were performed at baseline. Follow-up ended at hospital discharge or death. Prognostic factors of survival were identified using Cox proportional hazards regression model.
Results: compared with the survivor group, the mean serum levels of both C-reactive protein and alpha 1-acid glycoprotein at baseline were higher in the deceased group (44 ± 51 mg/l *versus* 22 ± 34 mg/l and 1691 ± 69 mg/l *versus* 1340 ± 456 mg/l respectively; $P < 0.001$ for each). Baseline levels of albumin and prealbumin were significantly lower in patients who died than in patients who survived. In multivariate analysis, alpha 1-acid glycoprotein (but not C-reactive protein), previous stroke, previous heart failure, and age emerged as the only parameters significantly and independently related to overall mortality.
Conclusion: this study shows that the increase in plasma levels at admission of two acute-phase proteins, alpha 1-acid glycoprotein and C-reactive protein, were associated with in-hospital mortality in a population of hospitalised elderly patients. Furthermore, associations of overall mortality with inflammation differed among the markers and only alpha 1-acid glycoprotein entered the multivariate prediction model. Our findings support the hypothesis that alpha 1-acid glycoprotein may be superior to C-reactive protein in mortality risk assessment strategies for elderly patients.

Keywords: *elderly, inflammation, C-reactive protein, alpha 1-acid glycoprotein, mortality*

Introduction

Several simple physical and commonly performed biochemical tests have been able to predict functional decline or mortality among those without disability at baseline [1, 2]. Powerful predictors of mortality in several studies are represented by nutritional markers, most notably serum albumin and serum prealbumin [2–5].

Numerous studies have shown that the synthesis of albumin and prealbumin decreases during inflammation, as do their serum concentrations, and that these changes occur entirely independently of nutritional state [6, 7]. It is therefore uncertain whether the prognostic value of low serum albumin among older persons reflects inflammation or whether there is an independent effect of serum albumin, perhaps due to nutritional or other factors [8]. Recent research has focused on inflammatory markers that reflect underlying pathological processes that may contribute to increasing the risk of mortality in the elderly.

Increased levels of C-reactive protein (CRP) and interleukin-6 (IL6) have been associated with cardiovascular diseases (CVD) and with a high risk of all-cause mortality in older people [9–14]. Nevertheless, several studies suggest that the risk predicted by the level of CRP is less accurate in the elderly [13] and that other 'acute phase reactants' may be more adequate inflammatory predictors of mortality than CRP [14, 15].

A few population-based studies have investigated the association between circulating levels of alpha 1-acid glycoprotein (AGP), also called orosomucoid, and the risk of all-cause mortality [15–17]. To our knowledge, there are no data evaluating the respective contribution of AGP and CRP in the overall and cardiovascular risk of older patients.

Thus the goal of the present study is (i) to assess whether increased plasma levels of AGP is predictive of all-cause mortality in the elderly, potentially independently of confounders; and (ii) to determine whether AGP is a better predictor of all-cause mortality than plasma protein and/or CRP.

Methods

Study cohort

Between October 1995 and May 1998 the data of 580 patients admitted consecutively to the department of geriatric medicine at the Charles Richet Hospital (in the Paris-Ile de France area) were prospectively collected. These patients were admitted for rehabilitation after infectious disease, CVD (including heart failure, atrial dysrythmia, coronary artery disease, stroke, and peripheral artery disease), recent orthopaedic or non-orthopaedic surgery, dementia or pressure ulcers. Most of these patients were transferred from acute wards. The length of hospital stay was relatively long (mean duration: 104 days), due to many of the patients having multiple chronic conditions or functional deterioration along with poor socio-economic conditions, as is commonly observed in France. Factors with real or potential influence on acute-phase protein levels, such as recent infection, were not deemed a reason for exclusion. However, patients who needed palliative care and patients with cognitive impairment and/or other disease processes that would not permit them to give informed consent or baseline information and who had no available family or proxy respondent were excluded ($n=147$). Thus 433 subjects (345 women and 88 men) participated in the study. Their mean age was 84 ± 7 years [±1 standard deviation (SD)].

On admission, the baseline evaluation included a clinical examination and routine biochemistry analyses. Cognitive status was assessed by the Mini Mental State Examination (MMSE) [18]. The questionnaire completed at inclusion included information on gender, age, weight, history of cardiovascular events, history of diabetes mellitus, previous diseases, MMSE level, inability to walk, urinary incontinence, use of medication and number of prescribed drugs. In all cases, the information confirmed that of relatives and/or that of medical records from previous hospitalisation.

Patient recruitment was closed in May 1998 and follow-up ended in June 1999. For each patient, follow-up ended at hospital discharge or death. The mean patient follow-up was 104 ± 131 days. At the end of the follow-up, 351 patients had survived and 82 had died.

Classification of patients

The presence of diseases was based on a past diagnosis with medication prescribed or on clinical examinations. The details of the clinical management of these patients have previously been described elsewhere [19]. A past and/or present history of CVD was present in 253 patients and absent in 180 patients. The diagnosis of dementia was based on DSM-IV criteria (American Psychiatric Association, 1994). One hundred and twenty seven subjects showed signs of dementia, most commonly caused by Alzheimer's disease or vascular dementia involving multiple infarcts within the brain. One hundred and ninety-eight patients were unable to walk and 219 suffered from urinary incontinence. Drug treatment, including hypnotic, antidepressant and anti-psychotic agents, was prescribed to 174 patients for neuropsychological disorders and/or sleep disturbance.

Biological determinations

Venous blood samples were drawn within three days following admission and were obtained from subjects after an overnight fast. In all patients the samples were taken 15 to 21 days after the acute initial diagnosis – that is, after the patients had been transferred from acute wards. CRP, AGP and prealbumin were measured by use of an immunonephelemetry method (Cobas Mira, Denmark). Albumin was measured by use of a colorimetric method (Albumine kit, Biomérieux, France). The upper limits of the reference intervals considered by our laboratory are 10 mg/l for CRP and 1200 mg/l for AGP. Total cholesterol was measured using a Technicon Chem assay (Technicon Instruments, Paris, France).

Statistical analysis

Data are expressed as means $\pm$ SD. Student's *t*-test was used for comparison of normally distributed continuous variables. Differences in frequency were tested by chi-square analysis. Univariate associations between variables were assessed by Pearson's correlations. Prognostic factors of survival were identified using the Cox proportional hazards regression model. The assumption of proportional hazards over time was verified before the analyses were performed and was met by all covariates. The assumption concerning linearity of continuous

covariates was also verified before analysis. Adjusted hazard ratios (HR) were determined from models involving all prognosis-related parameters as the exponent raised to the power of the respective regression coefficient, along with 95% confidence limits. Survival curves were estimated using the Kaplan-Meier product-limit method and compared by the Mantel (log-rank) test. Statistical analysis was performed using NCSS 6.0.21 software. A P value < 0.05 was considered significant. All tests were two-sided.

Results

The population was divided in two groups of patients: survivor and dead according to their vital status at hospital discharge. Baseline characteristics and laboratory findings on admission are shown in Table 1. Dysrythmia, pressure ulcers, inability to walk and urinary incontinence were significantly more prevalent in the deceased group. Baseline levels of albumin and prealbumin were significantly lower in patients who died than in patients who survived. Compared with the survivors group, the mean serum levels of both CRP and AGP at baseline were respectively 2-fold and 1.3-fold higher in the deceased patients group. At admission, CRP concentrations ranged from 1–284 mg/l and AGP concentrations ranged from 295–4308 mg/l. Two hundred and twenty individuals (50%) had CRP values > 10 mg/l, which is the cut-off point generally considered to be associated

Table 1. Characteristics of the study population at admission according to vital status at hospital discharge

Parameters	Survivors ($n=351$)	Dead ($n=82$)	P
Age (years)	84 ± 7	87 ± 7	0.002
Gender (% female)	80	80	0.99
Mini mental status (/30)	19 ± 7	15 ± 8	0.007
Body weight (kg)	58 ± 14	53 ± 15	0.031
Drugs number at admission (n)	3.9 ± 2.3	3.8 ± 2.4	0.73
Totality of previous CV disease (%)	61	61	0.90
Dysrhythmia (%)	14	24	0.016
Congestive heart failure (%)	10	17	0.12
Coronary artery disease (%)	12	7	0.31
Hypertension (%)	37	28	0.14
Prior brain infarction (%)	7	12	0.19
Dementia (%)	28	34	0.35
Diabetes mellitus (%)	7	4	0.41
Infectious disease at admission (%)	6	12	0.52
Pressure ulcers (%)	8	22	< 0.001
Inability to walk (%)	41	66	< 0.001
Urinary incontinence (%)	45	75	< 0.001
Length of hospitalisation (days)	92 ± 104	157 ± 204	< 0.001
C-reactive protein (mg/l)	22 ± 34	44 ± 51	< 0.001
Alpha 1-acid glycoprotein (mg/l)	1340 ± 456	1691 ± 69	< 0.001
Albumin (g/l)	37 ± 4	35 ± 4	< 0.001
Prealbumin (mg/l)	200 ± 62	165 ± 67	< 0.001
Plasma total cholesterol (mmol/l)	5.0 ± 1.3	5.0 ± 1.8	0.98

with significant inflammation [5], and 60% had AGP values > 1200 mg/l (normal value for laboratory $\leqslant$ 1200 mg/l). There were statistically significant differences between CRP and AGP levels according to presence or absence of pressure ulcers, inability to walk and urinary incontinence ($P < 0.001$ for all comparisons). In contrast, there was no difference for CRP and AGP levels according to presence or absence of any other prevalent disease including CVD (data not shown).

The correlation matrix (Table 2) shows the linear relationships between age, CRP, AGP, prealbumin and albumin. Note the weak age-dependency of all parameters except AGP which is not significantly associated with age. Note also the strong positive correlation between CRP and AGP.

Multivariate analysis of the relationships among clinical features, biological data, and the risk of death showed that four variables significantly and independently entered the prediction model: age, AGP, previous stroke and previous heart failure. Serum albumin and serum prealbumin entered the prediction model of mortality only after removal of inflammatory parameters. The hazard ratios of death along with 95% confidence intervals for the independent prognostic variables are given in Table 3. AGP emerged as the strongest all-cause mortality-predicting parameter. Figure 1 shows the probabilities of survival in the study population according to the level of AGP divided into tertiles. Comparison between survival curves was highly significant (chi square = 16.59; $P < 0.001$).

Discussion

The salient finding of this study was that the increase in plasma levels at admission of both CRP and AGP was associated with in-hospital mortality in a population of hospitalised elderly patients. Furthermore, associations of overall mortality with inflammation differed among the markers and only AGP entered the multivariate prediction model.

In the multivariate prediction analysis, we clearly showed that hypoalbuminemia disappeared as a risk factor, when AGP or CRP was in the model. Only AGP and not CRP persisted in the multivariate prediction model as a strong and independent predictor of overall mortality. CRP increased significantly with age, but no significant correlation was observed between age and AGP. It was somewhat expected that the age-dependency of CRP was significant in our cohort because IL-6 has been shown to increase with age, even in the elderly [20–22]. Furthermore, studies of ageing have shown that markers of chronic inflammation, such as low albumin, high IL-6 and high CRP, increase with age [22] and are associated with incident disability [20, 23] as well as cardiovascular [5, 11, 13] and total mortality [10, 11, 13, 14]. Our data confirm these results and suggest that increased inflammatory

Table 2. Correlation matrix between age and inflammatory parameters (Pearson correlation coefficients and *P* values)

	Age (years)	CRP (mg/l)	AGP (mg/l)	Prealbumin (mg/l)	Albumin (g/l)
Age (years)		R=0.13 (*P*=0.007)	R=0.09 (*P*=0.07)	R=−0.15 (*P*=0.002)	R=−0.23 (*P*<0.001)
CRP (mg/l)			R=0.69 (*P*<0.001)	R=−0.43 (*P*<0.001)	R=−0.24 (*P*<0.001)
AGP (mg/l)				R=−0.36 (*P*<0.001)	R=−0.23 (*P*<0.001)
Prealbumin (mg/l)					R=0.42 (*P*<0.001)
Albumin (g/l)					

CRP=C-reactive protein; AGP=Alpha 1-acid glycoprotein.

Table 3. Adjusted hazard rates of all-cause mortality per increment of prognosis variables. Adjustments were made on all the parameters in this table

Prognostic variable	Z value	Adjusted HR (95% CI)	P value
Alpha 1-acid glycoprotein (per 100 mg/l)	5.28	1.12 (1.08–1.16)	*P*<0.001
Previous stroke (yes *vs* no)	2.79	2.79 (1.35–5.70)	*p*=0.005
Previous heart failure (yes *vs* no)	2.75	2.29 (1.27–4.15)	*p*=0.006
Age (per 1 year)	2.17	1.04 (1.01–1.08)	*p*=0.030

HR=Hazard ratios; CI=Confidence interval.

AGP: Alpha 1-acid glycoprotein
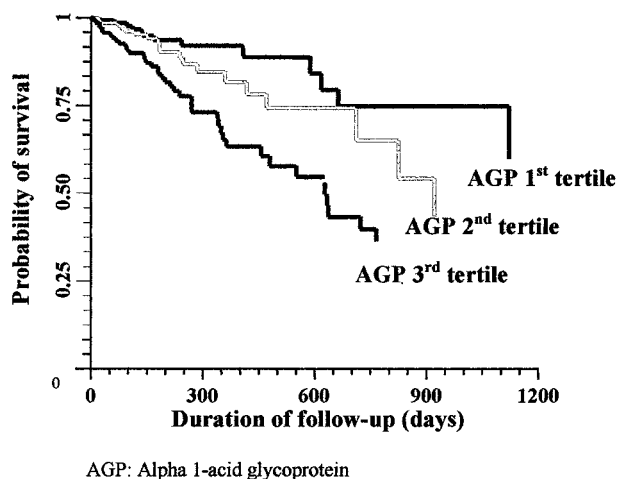
Figure 1. Probabilities of survival in the study population according to the level of AGP divided into tertiles. Comparison between survival curves was highly significant (chi square=16.59; *P*<0.001).

markers are related to both age and inflammation and may not be solely a phenomenon of physiological ageing [24]. The differing relationships between CRP and AGP with both age and mortality may be related to differential influences of cytokines on transcriptional regulation of these proteins [6].

In this study, besides the inflammatory markers, overall mortality risk was significantly and independently increased in the presence (or the past history) of cardiovascular disease involving stroke and congestive heart failure. One important unresolved question is whether chronic arterial inflammation is causally related to the development of cardiovascular disease or a marker of existing disease, or both. In accordance with previous findings in which inflammatory markers were not specifically related to cardiovascular mortality [11, 13,

14, 16], we may hypothesise that in elderly persons with important co-morbidity, episodic or chronic inflammation plays a causal role not only in vascular damage but also in various disease mechanisms, including frailty and CVD [25]. It is noticeable that hypertension did not predict mortality in our population. In a recent longitudinal study in the elderly, cardiovascular mortality was influenced only by one factor, aortic pulse wave velocity, but not high blood pressure [26]. This study did not include determination of inflammatory markers. Because in end-stage renal disease aortic pulse wave velocity was shown to be strongly correlated with CRP, further longitudinal studies are needed better to elucidate the relationships between inflammatory markers, aortic rigidity and cardiovascular mortality risk [27].

The principal limitations of the present study are related to design and population. First, MMSE scores were relatively low in our population (mean MMSE score: 18.5±7/30) which indicated that clinical characteristics were difficult to assess in our elderly patients. However, when a full medical history with complete clinical evaluation was not obtained from our patients, they were excluded. Second, despite the fact that we have no measurements except weight by which to assess nutritional status, the present observations do not differ substantially from those previously published [2–4] where hypoalbuminemia and/or hypoprealbuminemia predicted overall mortality. It is worth noting that in the present study 30 subjects had pressure ulcers and 18 patients were in a period of infectious disease recovery, two conditions which might influence nutritional status. Third, our elderly patients should be considered 'survivors'. For that reason they cannot be representative of the totality of elderly individuals. This also explains the relatively disproportionate number of women, which is relatively common in France [15, 19]. Fourth, the choice of overall mortality instead of

cardiovascular mortality as primary end-point in our study has probably limited the power of the reported inflammation-prognosis association. However, because of the high prevalence of co-morbidity in our cohort, cause of death is most of the time very difficult to determine, and therefore use of cardiovascular mortality as the primary end-point was not possible in the present study.

In conclusion, our results suggest that there are important relations between age, inflammation, and mortality in hospitalised elderly patients. AGP measurements may be useful for identification of high-risk people and the role of increased CRP production with ageing remains to be fully clarified. Whether the acute-phase protein production profile observed in the data represents an age-related failure of immune regulation remains to be determined.

Key points

- Elderly hospitalised patients have commonly elevated levels of both CRP and AGP.
- The increase of these two acute phase proteins is associated with in-hospital mortality.
- AGP and not CRP is a strong and independent predictor of overall mortality.

Acknowledgements

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