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ABSTRACT

The International Staging System(ISS) -calculated from serum albumin and beta-2 microglobulin(β2m)- is an established prognostic marker in multiple myeloma(MM), which has also been suggested to account for survival among general senior population. Our objective was to examine long-term survival of older women free of MM according to baseline ISS. The study included 230 community-dwelling healthy older women without known MM from the EPIDOS cohort(mean±SD, 80.4±3.4years). Serum albumin and β2m were measured at baseline, and used to calculate the ISS *a posteriori*. Abnormal ISS was defined as ISS=2 or ISS=3, although ISS=1 was considered normal. The vital status was sought after a mean follow-up of 17.6±0.2years(range, 16.8-18.3). Age, body mass index, mean arterial pressure, diabetes mellitus, hypertension, coronary heart disease, stroke, use corticosteroids, number of drugs daily taken, smoking, physical activity, fall history, bone mineral density, and creatinine clearance were used as potential confounders. All participants died during the 17-year follow-up. Compared to women with normal ISS, those with abnormal ISS(n=24) had shorter survival time(4.9±4.3 versus 8.7±5.2years, P=0.001) and died earlier(85.6±4.8 versus 89.1±5.6years old, P=0.003). Survival time after blood test correlated with both serum albumin(r=0.16, P=0.015) and β2m(r=-0.27, P<0.001). Cox regression revealed that abnormal ISS was associated with mortality(adjusted HR=3.03, P<0.001). Kaplan-Meier distributions showed that participants with abnormal ISS died earlier than those with normal ISS(log-rank P<0.001). In conclusion, community-dwelling older women with abnormal ISS had shorter survival time than the others, suggesting that ISS could be considered as a universal prognostic “aging system” rather than a specific MM “staging system”.

Keywords: albumin; beta-2 microglobulin; Multiple Myeloma International Staging System; prognosis; survival; older adults

HIGHLIGHTS

- The ISS combines concentrations of albumin and beta-2 microglobulin.
- The ISS may be a prognostic staging system unspecific of MM.
- Older adults with abnormal ISS had 44%-shorter survival time over 17 years.
- The ISS may serve as a potent prognostic marker in the general senior population.

INTRODUCTION

The first step of any efficient geriatric care relies on the early identification of older adults most vulnerable to stress, who are at greater risk of failure of usual coping mechanisms, with consequent lower survival chance. This screening is yet limited by the difficulty of implementation into clinical practice due to the time consumption of standard validated tools [1,2]. A simple and easily accessible blood test is thus desirable to improve the feasibility of the screening for older adults with limited life expectancy in daily clinical practice.

There is ample evidence that serum albumin (SA) and beta-2 microglobulin (β2m) are both biological prognostic biomarkers of survival [3-5]. The combination of SA and β2m constitutes a potent staging system in multiple myeloma (MM)[6-10], with a higher prognostic value compared to all other markers including gene expression profiles [9]. In 2005, this SA/β2m combination was internationally recognized as the MM international staging system (ISS)[10]. However and importantly, it was proposed that the ISS may actually take into account more the age-related comorbidity burden of MM older patients than the intrinsic malignancy of the MM clone [11]. Decreased SA and increased β2m reflect declines across multiple physiologic systems and may account for the comorbidity burden among older adults [11]. This suggests that the ISS should not be considered as a specific MM staging system, but rather as an "aging system", i.e. a universal prognostic biomarker in older adults.

We hypothesized that the ISS could predict survival time in general senior population. We had the opportunity to examine the association of ISS with survival time in a sample of healthy women aged ≥75years from the large representative community-based EPIDémiologie de l'OStéoporose (EPIDOS) cohort. The objective of this historical, longitudinal cohort study was to examine long-term survival of older women according to baseline ISS.

MATERIALS AND METHODS

We studied 230 participants without known MM, a subset recruited from 1992 to 1994 in the EPIDOS study, a French large observational prospective multicenter cohort study designed to evaluate risk factors for hip fractures among healthy community-dwelling women aged 75 years and older [12]. The present analysis considered data from all women who had: i) full data on serum measures; and ii) full data on mortality up to October 1, 2010.

All study participants had a blood test at the time of inclusion. Sera were stored at -100°C until analyses were performed in a sample of women drawn using a random number table that generated in an unpredictable, haphazard a sequence of number corresponding to the number of participants included in the study [13]. SA (g/L) and β2m (mg/L) concentrations were determined using automated standard laboratory methods at the University Hospital of Lyon, France. The ISS was scored in 3 stages as previously described [10]: stage 1 defined as β2m<3.5mg/L with SA≥3.5g/dL; stage 2 defined as β2m between 3.5-5.5mg/L with any SA level, or β2m<3.5mg/L with SA<3.5g/L; stage 3 defined as β2m≥5.5mg/L. Abnormal ISS was defined as ISS=2 or ISS=3, and ISS=1 was considered normal.

Mortality data were collected either via telephone or through a search of the French national death registry CépiDC [Centre d'épidémiologie sur les causes médicales de décès] up to October 1, 2010 [14]. The survival time was calculated between the date of recruitment in the EPIDOS study and the date of death or end of the follow-up.

All participants had a full examination consisting of clinical examination and structured questionnaires on socio-demographic data, health status, and physical functioning. Age, body mass index, mean arterial pressure, diabetes mellitus, hypertension, coronary heart disease, history of stroke, current use of corticosteroids, number of drugs taken per day, smoking, regular practice of physical activity, history of falls in preceding 6 months, whole-body bone mineral density, and estimated glomerular filtration rate (estimated from the Cockcroft-Gault

formula: [[(140-age$_{years}$)x weight] / creatinine$_{mol/L}$] x 1.04) were measured and used as potential confounders.

The study was conducted in accordance with the ethical standards set by Helsinki declaration (1983). The EPIDOS study was approved by the local ethics committee. All participants gave written informed consents.

Statistical analysis

The participants' baseline characteristics were summarized using means and standard deviations or frequencies and percentages, as appropriate. Participants were separated into 2 groups according to ISS at baseline (i.e., normal ISS versus abnormal ISS). Firstly, between-group comparisons were performed using the independent samples *t*-test or Chi-square test, as appropriate. Secondly, three consecutive Cox regression models were used to examine the associations of mortality (dependent variable) with SA, β2m and abnormal ISS adjusted on baseline characteristics (independent variables). The models produce a survival function that provides the probability of death at a given time for the characteristics supplied for the independent variables. Third, the elapsed time to death was studied by survival curves computed according to the Kaplan-Meier method and compared by the log-rank test. P-values<0.05 were considered statistically significant. All statistics were performed using SPSS (version 19.0; SPSS, Inc., Chicago, IL).

RESULTS

All 230 participants (mean age at baseline, 80.4±3.4years) died during the follow-up (mean, 17.6±0.2years; range, 16.8-18.3years). As shown in Table 1, women with abnormal ISS (n=24) had shorter survival time than those with normal ISS (4.9±4.3 versus 8.7±5.2years; P=0.001) and died earlier (mean age of death, 85.6±4.8 versus 89.1±5.6years; P=0.003). Survival time after blood test correlated positively with SA concentration (r=0.16, P=0.015),

and negatively with serum β2m concentration (r=-0.27, P<0.001) (Figure 1). Cox regression models revealed an inverse association between SA and mortality (fully adjusted hazard ratio (HR)=0.96, P=0.036) and a positive association between β2m and mortality (fully adjusted HR=1.30, P=0.004) (Table 2). Abnormal ISS was also associated positively with mortality (HR=2.29, P<0.001), even after adjustment for potential confounders (fully adjusted HR=3.03, P<0.001) (Table 2). Consistently, Kaplan-Meier distributions showed in Figure 2 that participants with abnormal ISS had shorter survival time than those with normal ISS (log-rank P<0.001).

DISCUSSION

Our results show that abnormal ISS predicted, irrespective of studied potential confounders, shorter long-term survival time in community-dwelling healthy older women.

To the best of our knowledge, we provide here the first evidence of the prognostic value of the ISS in general senior population. This finding is consistent with previous studies reporting that SA and β2m are both biological prognostic factors of survival [3-5]. Numerous epidemiological studies have showed an association between lower SA concentrations and increased morbid-mortality [3,4,15,16]. The estimated increase in the odds of death ranges from 24% to 56% for each 2.5 g/L decrement in SA concentration [3]. This association predicts overall and cause-specific mortality including cardiovascular mortality. Several biological mechanisms have been suggested to explain the association of lower SA concentrations with increased mortality [3]. First, a protective effect of SA is likely based on its potential nitrovasodilator effect, which could modulate cardiovascular diseases processes. Another protective mechanism may be related to a significant antioxidant effect of SA in blood and extracellular fluids. SA enhances the removal of reactive oxygen species involved in the pathogenesis of numerous diseases such as atherosclerosis. SA may also be directly

beneficial by increasing the ability of serum to bind potential toxins. Finally, SA is an inhibitor of human endothelial apoptosis and lower SA concentrations may result in a general increased vascular permeability leading to tissue damage [3,4,16]. Like SA, higher β2m has been associated with increased morbi-mortality while aging, independent of any history of MM [5,17-21]. Firstly, greater levels of serum β2m have been reported in healthy older adults compared to younger ones [18,21]. Secondly, β2m is an established biomarker of disease activity not only in malignancies and chronic renal dysfunction, but also in autoimmune affections and infections [17,19-21]. Thus, an increase in serum β2m concentration reflects pathological aging across multiple physiologic systems. In line with this, increased β2m concentrations were used as a marker of frailty phenotype in geriatric inpatients [20]. Thirdly, a strong association has been reported among older adults between increased serum β2m concentration and higher rate of all-cause mortality, specifically cardiovascular mortality [5]. All these findings suggest that the combination of SA with β2m adequately explores the balance of inflammation proteins and constitutive proteins, and may reflect the physiological reserves available to the senior, making it an “aging system”.

Some limitations of our study should be considered. Firstly, the study cohort was restricted to relatively vigorous older women with interest in personal health issues who may be unrepresentative of older adults in general. Secondly, although we were able to control for important characteristics that could modify the association between ISS and mortality, residual potential confounders such as the presence of inflammatory systemic diseases or the causes of deaths might still be present. Thirdly, data were recorded before 2000. It is possible, though unproven, that the profiles and the risks of the participants have changed since then, as well as the implementation and enforcement of various prevention programs. The present results show thus trends that would better be confirmed by an independent survey in another cohort.

In conclusion, abnormal ISS predicted shorter survival time in community-dwelling healthy older women. Further studies with different cohorts are warranted to corroborate this finding, and assess the value of the ISS as an “aging system” and a universal marker of frailty phenotype in older adults.

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CONFLICT OF INTEREST

All other authors state that they have no conflicts of interest with this paper.

CONTRIBUTIONS OF THE AUTHORS

Annweiler has access to all the study data, takes responsibility for the accuracy of the analysis, and has authority over manuscript preparation and the decision to submit the manuscript for publication.

- Study concept and design: Annweiler.
- Acquisition of data: Schott.
- Analysis and interpretation of data: Annweiler, Pouzoullic.
- Drafting of the manuscript: Annweiler, Pouzoullic.
- Critical revision of the manuscript for important intellectual content: Schott, Sánchez-Rodríguez, Bataille.

- Statistical analysis: Annweiler.
- Obtaining funding: Schott.
- Administrative, technical, or material support: Schott.
- Supervision: Annweiler.

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Table 1. Characteristics and comparison of participants separated into two groups based on the International Staging System* (n=230)

	Whole sample (n = 230)	International Staging System		P-value †
		Normal* (n = 206)	Abnormal* (n = 24)	
Age, years	80.4±3.4	80.3±3.5	80.6±2.7	0.711
Body mass index, kg/m^2	25.5±4.4	25.5±4.5	25.7±3.6	0.848
Mean arterial pressure, mmHg	106.4±12.4	106.8±12.4	102.9±12.3	0.144
History of diabetes mellitus, n (%)	15 (6.5)	15 (7.3)	0 (0.0)	0.170
History of arterial hypertension, n (%)	107 (46.5)	94 (46.1)	13 (54.2)	0.453
History of coronary heart disease, n (%)	48 (20.9)	39 (19.0)	9 (37.5)	**0.035**
History of stroke, n (%)	12 (5.2)	9 (4.4)	3 (12.5)	0.092
Use corticosteroids, n (%)	8 (3.5)	8 (3.9)	0 (0.0)	0.325
Number of drugs taken per day	5.1±3.0	5.0±2.9	6.5±3.9	**0.022**
Smoking, n (%)	28 (12.2)	26 (12.7)	2 (8.3)	0538
Regular physical activity‡, n (%)	116 (50.4)	105 (51.2)	11 (45.8)	0.618
History of falls in preceding 6 months, n (%)	57 (24.8)	50 (24.4)	7 (29.2)	0.609
Whole-body mineral density, g/cm^2	0.98±0.09	0.98±0.09	0.97±0.08	0.560
Serum albumin concentration, g/L	45.1±4.5	45.5±4.3	42.2±5.2	**0.001**
Serum beta-2 microglobulin concentration, mg/L	2.49±0.96	2.26±0.50	4.46±1.55	**<0.001**
Estimated glomerular filtration rate‖, mL/min	51.3±15.9	52.3±15.8	41.3±14.1	**0.006**
Survival time after blood test, years	8.3±5.2	8.7±5.2	4.9±4.3	**0.001**
Age of death, years	88.8±5.6	89.1±5.6	85.6±4.8	**0.003**

Data presented as mean±standard deviation where applicable. *: normal ISS defined as ISS=1; abnormal ISS defined as ISS=2 or ISS=3; †: comparisons between participants with normal ISS and participants with abnormal ISS based on independent samples *t*-test or Chi-square test, as appropriate; ‡: at least one hour recreational physical activity (walking, gymnastics, cycling, swimming or gardening) per week for the past month or more; ‖: calculated from the Cockcroft formula; P-value significant (i.e., <0.05) indicated in bold.

Table 2. Hazard ratios of mortality (dependent variable) according to serum albumin concentration, serum beta-2 microglobulin concentration, and abnormal International Staging System at baseline (independent variables)*(n=230)

	Mortality								
	Model 1			Model 2			Model 3		
	HR	95%CI	P-Value	HR	95%CI	P-Value	HR	95%CI	P-Value
Serum albumin concentration	0.97	[0.94-1.00]	0.063	0.97	[0.93-1.00]	0.069	0.96	[0.92-0.99]	**0.036**
Serum beta-2 microglobulin concentration	1.30	[1.15-1.48]	**<0.001**	1.35	[1.17-1.55]	**<0.001**	1.30	[1.09-1.55]	**0.004**
Abnormal International Staging System	2.29	[1.49-3.53]	**<0.001**	2.87	[1.79-4.59]	**<0.001**	3.03	[1.72-5.33]	**<0.001**

HR: hazard ratio; CI: Confidence interval; Model 1: unadjusted Cox model; Model 2: Model 1 + adjustment for age, body mass index, mean arterial pressure, diabetes mellitus, hypertension, coronary heart disease, stroke, use corticosteroids, number of drugs per day, smoking, regular physical activity, history of falls in preceding 6 months, whole-body bone mineral density; Model 3: Model 2 + adjustment for estimated glomerular filtration rate; *: separate regression analyses were conducted for each model; HR significant (i.e. $P < 0.05$) indicated in bold.

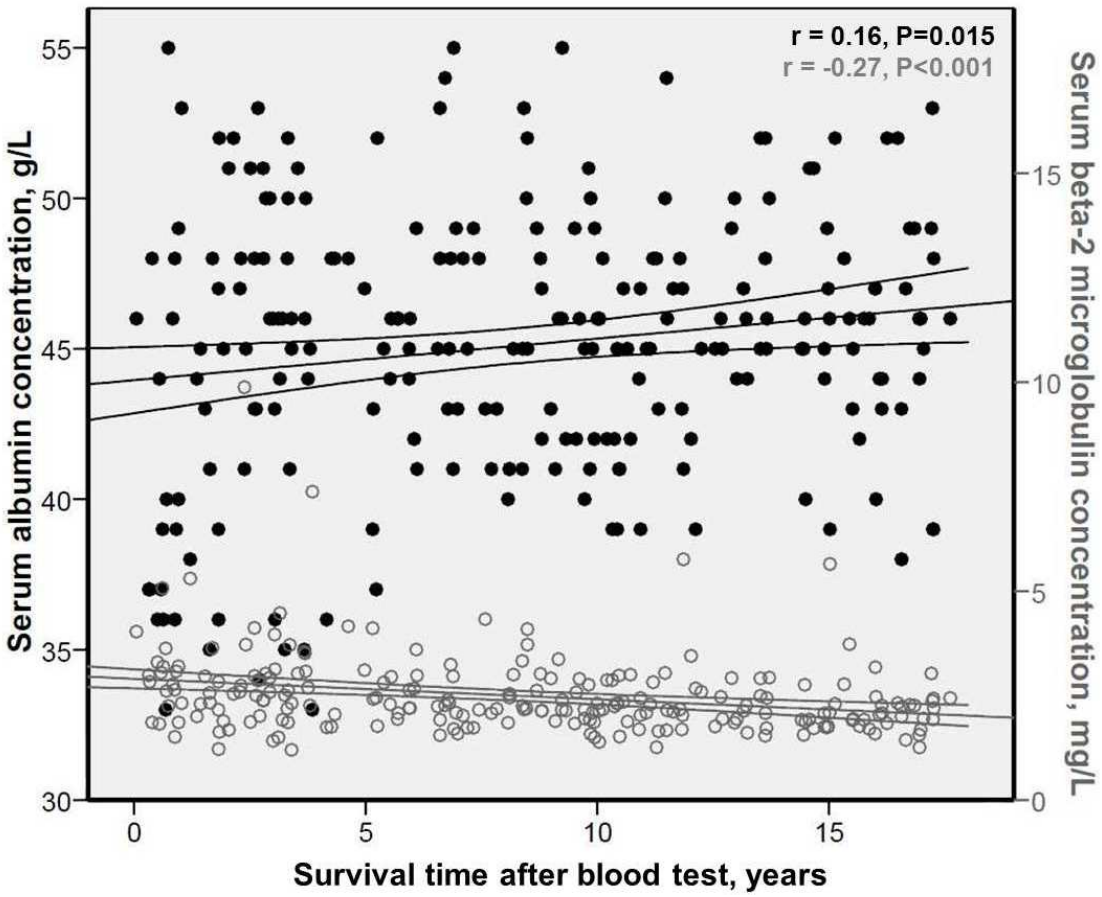

Figure 1. Relationships between survival time and serum concentrations of albumin and beta-2 microglobulin.

The tick lines are the best-fit linear regression lines, and the thin lines at the top and bottom are the limits of the 95% confidence intervals.

● Survival time on serum albumin

○ Survival time on serum beta-2 microglobulin

━ Survival time on serum albumin

━ Survival time on serum beta-2 microglobulin

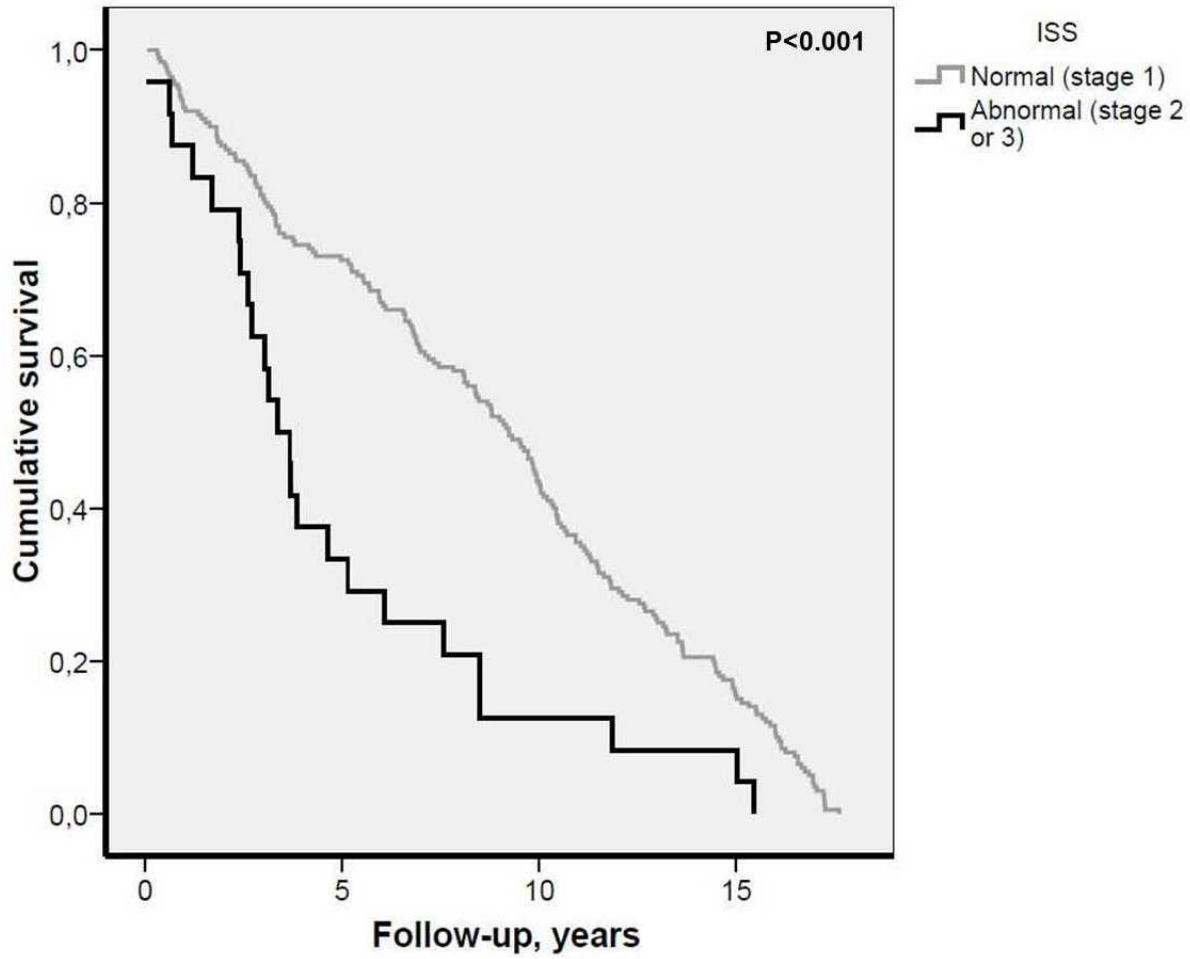

Figure 2. Kaplan-Meier estimates of the cumulative probability of participants' survival according to the International Staging System (ISS) (n=230)