RHEUMATOLOGY

doi:10.1093/rheumatology/kev322
Advance Access publication 10 September 2015

Concise report

Serum prealbumin is an independent predictor of mortality in systemic sclerosis outpatients

Veronica Codullo[1], Emanuele Cereda[2], Catherine Klersy[3], Ilaria Cavazzana[4], Claudia Alpini[5], Chiara Bonardi[2], Annalisa Turri[2], Franco Franceschini[4], Riccardo Caccialanza[2], Carlomaurizio Montecucco[1] and Roberto Caporali[1]

Abstract

Objective. Serum prealbumin is a recognized marker of malnutrition, but its role in the prognosis of patients with SSc has not yet been investigated. The aim of the present multicentre prospective study was to investigate the association between prealbumin and mortality, independent of clinical features, in a cohort of SSc outpatients.

Methods. Patients were followed up according to standard clinical guidelines with visits at least every 6 months. Data collected included records of skin and internal organ involvement, survival and causes of death.

Results. During a median follow-up of 48 months [interquartile range (IQR) 25–58], 34/299 patients (11%) died. In univariable survival analysis, age; male sex; lung, gastrointestinal or multiple visceral organ involvement (two or more); co-morbidities (two or more) and low serum prealbumin were significant predictors of mortality. In bivariable Cox models, alternatively adjusted for significant predictors, prealbumin was independently and significantly associated with the outcome. Mortality rates were particularly influenced by low prealbumin in patients without significant co-morbidities or multiple organ involvement.

Conclusion. In SSc patients, low serum prealbumin is an independent predictor of mortality, particularly in those without significant internal organ involvement. Further research on this nutritional marker is warranted.

Key words: systemic sclerosis, serum prealbumin, mortality.

Rheumatology key messages

- Low serum prealbumin predicts mortality in SSc independent of other significant risk factors.
- Mortality rates are influenced by prealbumin in SSc without significant co-morbidities or organ involvement.
- Interventional trials in SSc should establish the effect of modifying prealbumin status on mortality.

Introduction

Recent studies have shown that malnutrition is a frequent co-morbidity in SSc, with a prevalence ranging from 15 to 55%, depending on the method of assessment and case population. Several factors appear to contribute to this picture, particularly gastrointestinal symptoms, disease subset, activity or disability [1–3]. The negative prognostic impact of malnutrition in acute and chronic diseases is well established [4], but evidence in SSc is still limited. Krause *et al*. [1] recently found that the impairment of body composition predicts survival; in their study, however, the independent prognostic value of nutritional derangements was not investigated in combination with other predictors. Changes in body composition are likely to reflect disease severity and activity and potential interactions between these components in outcome prediction could not be excluded. Also, the combined assessment of nutritional parameters and disease activity was shown to

[1]Division of Rheumatology, University of Pavia, [2]Nutrition and Dietetics Service, [3]Service of Biometry and Statistics, Fondazione IRCCS Policlinico San Matteo, Pavia, [4]Unit of Rheumatology and Clinical Immunology, Spedali Civili Hospital in Brescia and [5]Clinical Biochemistry, Fondazione IRCCS Policlinico San Matteo, Pavia, Italy

Submitted 9 December 2014; revised version accepted 4 August 2015

Correspondence to: Roberto Caporali, Division of Rheumatology, Fondazione IRCCS Policlinico San Matteo, University of Pavia, Piazzale Golgi 19, 27100 Pavia, Italy. E-mail caporali@smatteo.pv.it

CLINICAL SCIENCE

improve the evaluation of mortality risk in SSc [5]. Our group recently showed that serum prealbumin is a marker of malnutrition in SSc [3], but its role in the prognosis has not yet been investigated. The aim of the present prospective study was to investigate the association between prealbumin and mortality, independent of clinical features, in a cohort of SSc outpatients.

Methods

Study design

We report the analysis of a multicentre cohort study of outpatients affected by SSc followed at two University Hospitals: IRCCS Policlinico San Matteo Foundation (Pavia, Italy) and Spedali Civili Hospital (Brescia, Italy). Part of the Pavia cohort ($n = 160$) has been previously analysed in both cross-sectional and prospective studies [3, 5]. In brief, all consecutive SSc patients satisfying LeRoy's criteria for SSc [6] attending the outpatient clinics of the Rheumatology Unit of both institutions from September 2006 to September 2012 were screened for study inclusion. Exclusion criteria were patient's refusal, age <18 years and acute complications. All patients underwent a complete clinical assessment and serum collection. Data included demography (sex and age), age at onset (date of the first non-Raynaud's symptom), disease duration, limited/diffuse disease subset (LeRoy's criteria) [6], modified Rodnan skin score, visceral involvement (according to the EULAR Scleroderma Trials and Research group recommendations) [7], disease activity (active disease was defined as a score $\geqslant 3$) [8] and other co-morbidities. Finally, fasting (8–12 h in post-absorptive state) venous blood samples were drawn for full investigation of the autoantibody profile (EliA, Phadia, Germany) and the assessment of serum prealbumin (immunonephelometric method; Dade Behring, Eschborn, Germany). Reduced prealbumin serum levels were defined as values <200 mg/l [9]. Anthropometric nutritional parameters (BMI and weight loss), which were already investigated by our group [3, 5], were not included in the present analysis due to colinearity with serum prealbumin. The multicentre cohort study was approved by the local institutional ethics committees (IRCCS Policlinico San Matteo Foundation and Comitato Etico Provinciale della Provincia di Brescia) and written informed consent was obtained. Ethical approval for the cohort was extended to include this subanalysis.

Statistical analysis

Patient survival was defined as the time between the date of enrolment and the date of death from any cause or the date of last contact or last known to be alive. Kaplan–Meier cumulative survival was computed. The Cox proportional hazard model was used to evaluate non-collinear predictors of death. Associations between mortality and clinical features and prealbumin were initially investigated in univariable models. Then, multivariable analysis was used to control the effect of prealbumin for other known clinical risk factors. The effect modification of prealbumin by clinical features was assessed with a test on interaction. The Harrell's C statistic was computed for model validation. Hazard ratios (HRs) and their 95% CIs were computed, as well as the incidence rate per 100 patients/year. A two-sided P-value <0.05 was deemed to be significant. All statistical analyses were performed using STATA 13.1 statistical software (StataCorp, College Station, TX, USA).

Results

In this multicentre study, a total of 299 patients with SSc were enrolled: 239 at the Rheumatology Unit in Pavia and 60 in Brescia. The demographic and clinical characteristics of the population are presented in Table 1.

After a median follow-up of 48 months [interquartile range (IQR) 25–58], 34 patients (11%) had died. Causes of death were SSc-related causes [$n = 30$; 28 with pulmonary complications (fibrosis or pulmonary hypertension) and 2 with severe gastrointestinal involvement], neoplastic complications ($n = 3$; 2 lung and 1 oesophageal carcinomas) and hepatic cirrhosis ($n = 1$). In the univariable analysis (Table 1), age, male sex, lung and gastrointestinal involvement, presence of multiple (two or more) visceral organ involvement, presence of co-morbidities (two or more) and low serum prealbumin were significant predictors of mortality, with higher HRs for lung or multiple visceral organ involvement [5 (95% CI 2.45, 10.34) and 3.94 (2.01, 7.74), respectively; both $P < 0.0001$].

Due to the relatively small number of events, no multivariable analysis could be performed and relevant SSc clinical predictors in univariable analysis were alternatively included in bivariable models in order to test the independent association between serum prealbumin and mortality (Table 2). In models alternatively adjusted for single factors (age; male sex; lung or gastrointestinal involvement; multiple visceral organ involvement and two or more co-morbidities, including kidney or hepatic failure; HCV infection and autoimmune hypothyroidism; medication with steroids or NSAIDs), low serum prealbumin retained a significant association with mortality. In particular, it was the only significant predictor when combined with demographic parameters (age and sex), HCV infection, medications and gastrointestinal involvement. In the other models, both prealbumin and either multiple co-morbidities, lung involvement or multiple visceral organ involvement were independently associated with death. Mortality rates (per 100 patients/year) in pre-specified groups by disease predictors and prealbumin are also shown in Table 2. Again, models with the best fit (and higher Harrell's C statistics) were those including lung or multiple visceral organ involvement [Harrell's C 0.76 (95% CI 0.68, 0.84) and 0.75 (0.66–0.83), respectively].

Discussion

The present multicentre study shows that serum prealbumin is a predictor of mortality in SSc patients independent of other significant disease-related risk factors. These findings support the importance of the nutritional domain

TABLE 1 Demographic, clinical and nutritional characteristics of the population with univariable HR for mortality

Characteristic	Population ($n = 299$)	Univariable HR (95% CI)	*P*-value
Age, mean (S.D.), years	61 (11.8)	3.49 (1.62, 7.54)	0.001
Male, *n* (%)	39 (13)	3.68 (1.68, 8.03)	0.001
Disease duration, median (IQR), months	77 (13–118)	1.06 (0.85, 1.3)	0.617
Disease subset (diffuse), *n* (%)	51 (17)	1.31 (0.57, 3)	0.523
Skin thickness (mRSS), median (IQR)	7 (2–10)	—	—
DAS (0–10), median (IQR)	1.5 (0.5–2.5)	1.13 (0.94, 1.36)	0.207
Active disease (score $\geqslant 3$), *n* (%)	54 (18)	1.98 (0.94, 4.17)	0.071
Serologic pattern			
Anti-centromere positive, n (%)	164 (55)	0.70 (0.26, 1.87)	0.476
Anti-topoisomerase-I positive, n (%)	49 (16)	2.43 (0.93, 6.32)	0.069
Other, n (%)	78 (26)	1.5 (0.52, 4.28)	0.454
Negative, n (%)	7 (2)		
Lung involvement, *n* (%)	94 (31)	5 (2.45, 10.34)	$\leqslant 0.001$
Gastrointestinal involvement, *n* (%)	166 (56)	2.15 (1.03, 4.5)	0.043
Kidney involvement, *n* (%)	9 (3)	1 (0.14, 7.3)	0.997
Multiple visceral organs involvement ($\geqslant 2$), *n* (%)	69 (23)	3.94 (2.01, 7.74)	$\leqslant 0.001$
Co-morbidities			0.025
None, *n* (%)	135 (45)		
1, *n* (%)	119 (39)	–2.26 (0.96, 5.32)	–0.06
$\geqslant 2$, *n* (%)	48 (16)	3.42 (1.35, 8.7)	0.01
Prealbumin, mean (S.D.), mg/l	259 (140)		
<200 mg/l, *n* (%)	58 (20)	3 (1.52, 5.97)	0.002

Disease activity has been calculated according to the criteria defined by the European Scleroderma Study Group [8] (score 0–10). HR: hazard ratio; IQR: interquartile range; mRSS: modified Rodnan skin score.

and the need to assess nutritional status and its biomarkers in every SSc patient. Malnutrition is not uncommon in SSc [1–3]. Furthermore, its presence has been strongly associated with active disease and low serum prealbumin levels [3]. BMI alone was found to be unrelated to mortality, while impaired nutritional status according to body composition analysis was found to predict mortality [1]. Also, the combined assessment of nutritional parameters and disease activity was shown to improve the evaluation of mortality risk [5]. However, the independent association between nutritional derangements and mortality has never been an object of investigation. In the present study, low serum prealbumin conferred elevated HRs in the survival analysis, which remained statistically significant even after adjusting for other known risk factors in SSc. An association between reduced prealbumin and adverse outcomes has been detected in several other chronic diseases [9–11], but this is the first report to describe it in SSc.

Serum prealbumin is reasonably considered a nutritional marker. However, many conditions appear to affect its serum levels, such as protein-calorie intake, organ dysfunction (e.g. liver or kidney), medications (glucocorticoids and/or high-dose NSAIDs), hormonal disorders (e.g. hypothyroidism) and inflammation, differently and synergistically acting on the balance between synthesis and catabolism [12, 13]. With respect to SSc, it is reasonable to believe that prealbumin mirrors the status of body protein stores and the metabolically active components of the body, which in turn are likely to be affected by chronic low-grade inflammation [14] and have been associated with outcome more strongly than BMI [15]. However, although no association was found between prealbumin levels and most of the aforementioned factors, including ESR (data not shown), we were unable to fully explore this hypothesis. We did not collect information on CRP levels or abnormal liver disease and it would be interesting to investigate how these parameters correlate with prealbumin and compare to it in predicting outcome. Our population showed a low median disease activity score and it is likely that CRP levels were low in this sample, which is probably not powered enough to rule out the influence of CRP alone on the outcome or in combination with other predictors. Furthermore, mortality was unrelated to disease activity in our study. On the other hand, despite the fact that models with the best fit (higher Harrell's C statistic) were those including prealbumin and lung or multiple visceral organ involvement, in our analysis, rates of mortality were especially influenced by prealbumin levels in patients without significant organ involvement or co-morbidities, drawing attention to a potential underestimation of the prognosis in the absence of a severe and co-morbid clinical picture. Indeed, there was a striking difference (more than 3-fold in both cases) among incidence rates of mortality in those without significant organ involvement or with no or just one co-morbidity but with different prealbumin concentrations (>200 mg/l or <200 mg/l), arguing in favour of the added value of prealbumin in these cases and their prognostic stratification. Importantly, prealbumin levels are subject to change

Table 2 Mortality prediction by low serum prealbumin and corresponding incidence rates for prealbumin groups in the presence of other risk factors

Bivariable models	HR (95% CI)	*P*-value	*P*-value for interaction	Harrell's C (95% CI)	Incidence rates per 100 persons/year (95% CI)	
Prealbumin and co-morbidities						
Prealbumin, <200 mg/l	3.41 (1.70, 6.85)	0.001	0.805	0.68	Prealbumin >200 mg/l and co-morbidities <2	1.8 (1.1, 3.1)
					Prealbumin <200 mg/l and co-morbidities <2	5.9 (3.3, 10.8)
Co-morbidities ⩾2	2.58 (1.21, 5.49)	0.014		(0.59, 0.78)	Prealbumin >200 mg/l and co-morbidities ⩾2	4.5 (2.2, 9.5)
					Prealbumin <200 mg/l and co-morbidities ⩾2	16.5 (5.3, 51.3)
Prealbumin and lung involvement						
Prealbumin, <200 mg/l	2.62 (1.32, 5.22)	0.006	0.512	0.76	Prealbumin >200 mg/l and no lung involvement	1.3 (0.63, 2.5)
					Prealbumin <200 mg/l and no lung involvement	2.3 (0.7, 7.1)
Lung involvement	4.73 (2.30, 9.74)	<0.001		(0.68, 0.84)	Prealbumin >200 mg/l and lung involvement	5.1 (2.9, 8.9)
					Prealbumin <200 mg/l and lung involvement	15.3 (8.5, 27.6)
Prealbumin and GI involvement						
Prealbumin, <200 mg/l	2.75 (1.38, 5.50)	0.004	0.464	0.69	Prealbumin >200 mg/l and no GI involvement	1.4 (0.6, 3.1)
					Prealbumin <200 mg/l and no GI involvement	5.6 (2.1, 14.9)
GI	1.90 (0.90, 4.01)	0.091		(0.61, 0.78)	Prealbumin >200 mg/l and GI involvement	3.2 (1.9, 5.4)
					Prealbumin <200 mg/l and GI involvement	7.6 (4.1, 14.1)
Prealbumin and multiple visceral organs involvement						
Prealbumin, <200 mg/l	2.71 (1.36, 5.40)	0.005	0.602	0.75	Prealbumin >200 mg/l and visceral organs involved <2	1.4 (0.8, 2.6)
					Prealbumin <200 mg/l and visceral organs involved <2	4.6 (2.2, 9.7)
Visceral organs involved ⩾2	3.72 (1.89, 7.32)	<0.001		(0.66, 0.83)	Prealbumin >200 mg/l and visceral organs involved ⩾2	6.1 (3.3, 11.3)
					Prealbumin <200 mg/l and visceral organs involved ⩾2	13.8 (6.6, 28.9)

GI: gastrointestinal; HR: hazard ratio.

with nutritional interventions [16], and nutritional support may be effective in improving not only nutritional status, but also patient outcome [17].

The main limitation of our longitudinal study is the small number of events that occurred during the follow-up, a factor that clearly hampers the statistical power of our analyses. It could not be excluded that a larger sample size and a longer follow-up would allow identification of an even stronger independent prognostic value of serum prealbumin. In this view, prealbumin probably represents a more sensitive serological nutrition-related biomarker, offering a reliable prognostic stratification of SSc patients. Another limitation of our study is that the effect of variables acting during the follow-up has not been considered. The possibility of nutritional interventions altering prealbumin status and possibly positively influencing the prognosis remains to be evaluated with a specific trial. Finally, evidence is confined to SSc patients.

In conclusion, low serum prealbumin seems a useful prognostic marker in SSc patients, independent of established clinical factors. Therefore we suggest further research on this parameter and that nutritional assessment should be part of the clinical workup of every SSc patient. Thus clinical nutrition trials are warranted in order to investigate the role of nutritional support on patient's outcome.

Funding: No specific funding was received from any funding bodies in the public, commercial or not-for-profit sectors to carry out the work described in this article.

Disclosure statement: The authors have declared no conflicts of interest.

References

1 Krause L, Becker MO, Brueckner CS *et al*. Nutritional status as marker for disease activity and severity predicting mortality in patients with systemic sclerosis. Ann Rheum Dis 2010;69:1951–57.

2 Baron M, Hudson M, Steele R *et al*. Malnutrition is common in systemic sclerosis: results from the Canadian scleroderma research group database. J Rheumatol 2009;36:2737–43.

3 Caporali R, Caccialanza R, Bonino C *et al*. Disease-related malnutrition in outpatients with systemic sclerosis. Clin Nutr 2012;31:666–71.

4 Norman K, Pichard C, Lochs H, Pirlich M. Prognostic impact of disease-related malnutrition. Clin Nutr 2008;27:5–15.

5 Cereda E, Codullo V, Klersy C *et al*. Disease-related nutritional risk and mortality in systemic sclerosis. Clin Nutr 2014;33:558–61.

6 LeRoy EC, Black C, Fleischmajer R *et al*. Scleroderma (systemic sclerosis): classification, subsets and pathogenesis. J Rheumatol 1988;15:202–5.

7 Walker UA, Tyndall A, Czirjak L *et al*. Clinical risk assessment of organ manifestations in systemic sclerosis: a report from the EULAR Scleroderma Trials and Research group database. Ann Rheum Dis 2007; 66:754–63.

8 Valentini G, Bencivelli W, Bombardieri S *et al*. European Scleroderma Study Group to define disease activity criteria for systemic sclerosis. III. Assessment of the construct validity of the preliminary activity criteria. Ann Rheum Dis 2003;62:901–3.

9 Caccialanza R, Palladini G, Klersy C *et al*. Nutritional status of outpatients with systemic immunoglobulin light-chain amyloidosis 1. Am J Clin Nutr 2006;83:350–4.

10 Rambod M, Kovesdy CP, Bross R, Kopple JD, Kalantar-Zadeh K. Association of serum prealbumin and its changes over time with clinical outcomes and survival in patients receiving hemodialysis. Am J Clin Nutr 2008;88:1485–94.

11 Devakonda A, George L, Raoof S *et al*. Transthyretin as a marker to predict outcome in critically ill patients. Clin Biochem 2008;41:1126–30.

12 Caccialanza R, Palladini G, Klersy C *et al*. Serum prealbumin: an independent marker of short-term energy intake in the presence of multiple-organ disease involvement. Nutrition 2013;29:580–2.

13 Muangchan C, Harding S, Khimdas S *et al*. Association of C-reactive protein with high disease activity in systemic sclerosis: results from the Canadian Scleroderma Research 13 Group. Arthritis Care Res 2012;64:1405–14.

14 Roubenoff R, Roubenoff RA, Ward LM, Holland SM, Hellmann DB. Rheumatoid cachexia: depletion of lean body mass in rheumatoid arthritis. Possible association with tumor necrosis factor. J Rheumatol 1992;19:1505–10.

15 Volpato S, Romagnoni F, Soattin L *et al*. Body mass index, body cell mass, and 4-year all-cause mortality risk in older nursing home residents. J Am Geriatr Soc 2004;52: 886–91.

16 Ingenbleek Y, Young V. Transthyretin (prealbumin) in health and disease: nutritional implications. Annu Rev Nutr 1994;114:495–533.

17 Stratton RJ, Elia M. Encouraging appropriate, evidence-based use of oral nutritional supplements. Proc Nutr Soc 2010;69:477–87.