Nutritional status of outpatients with systemic immunoglobulin light-chain amyloidosis[1–3]

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ABSTRACT

Background: Maintenance of a good nutritional status is associated with prolonged survival in many chronic diseases. To date, the nutritional status of outpatients with immunoglobulin light-chain (AL) amyloidosis has not been evaluated.

Objective: The aims of this study were to obtain information regarding the nutritional status of AL amyloidosis outpatients and to investigate its prognostic role.

Design: One hundred six consecutive patients with histologically confirmed AL amyloidosis were enrolled. Anthropometric, biochemical, and clinical variables were measured. The Kaplan-Meier method was used to calculate survival. A Cox proportional hazard model was constructed to evaluate the prognostic effect of the nutritional variables.

Results: Unintentional weight loss (median: 11.3%; range: 2.6–34% of usual nonedematous body weight) was documented in 58 subjects (54.7%). Body mass index (BMI; in kg/m^2) was <22 in 25 subjects (23.6%). Serum prealbumin was <200 mg/L (lower reference limit) in 26 patients (24.5%). A multivariate analysis showed that the percentage weight loss was significantly greater in patients with than in those without cardiac involvement ($P = 0.03$), and it also differed significantly by New York Heart Association class ($P = 0.02$) and Eastern Cooperative Oncology Group performance status ($P = 0.001$). Cardiac involvement ($P = 0.008$), hematologic response to therapy ($P = 0.013$), BMI ($P = 0.001$) and serum prealbumin ($P = 0.001$) were independent predictors of survival.

Conclusions: Malnutrition is a prominent clinical feature of patients with AL amyloidosis. Appropriate nutritional evaluation that comprises the easily measurable nutritional variables associated with survival should be an integral part of the clinical assessment of AL amyloidosis outpatients. *Am J Clin Nutr* 2006;83:350–4.

KEY WORDS Amyloidosis, outpatients, nutritional status, weight loss, prognosis, survival

INTRODUCTION

Systemic amyloidoses are disorders of protein conformation and metabolism resulting in tissue deposition of insoluble fibrils that cause vital organ dysfunction (1). In immunoglobulin light-chain (AL) amyloidosis, the fibrils are composed of the *N*-terminal fragment of a monoclonal light-chain. AL amyloidosis is the most common type of systemic amyloidosis in Western countries; its estimated incidence is 8.9 per million person-years (2). The prognosis of patients with AL amyloidosis is mainly dependent on the presence of cardiac involvement and by response to chemotherapy aimed at suppressing the plasma cell clone producing the amyloidogenic light chain (3, 4). AL amyloidosis is a systemic disease that can involve the heart, kidneys, liver, gastrointestinal tract, and the peripheral and autonomic nervous systems. The clinical manifestations of the disease include anorexia, dysphagia, dysgeusia, vomiting, diarrhea, malabsorption, and weight loss (4-7). Hence, the nutritional status of AL amyloidosis patients is likely to be impaired, and this impairment can have a multifactorial etiology.

To date, weight loss has been reported to be a predictor of survival in 2 retrospective studies (4, 6). A study from the Mayo Clinic involved 474 AL amyloidosis patients: weight loss was reported in 52% of the subjects (median loss: 10.4 kg; range: 0.9–91 kg), and the amount of weight loss during the first year after diagnosis was found to have a significant influence on survival (4). The study by Hayman et al (6) included 19 patients with AL amyloidosis and clinical and laboratory evidence of malabsorption syndrome. Weight loss was documented in all of the subjects (median loss: 13.6 kg; range: 0.9–60.8 kg) and was found to influence survival: the 6 patients with a weight loss ≤ 9.1 kg had a median survival of 22 mo from the time of initial diagnosis, whereas the 13 subjects with a weight loss > 9.1 kg had a median survival of only 10 mo after diagnosis (6). The Mayo Clinic group also evaluated a series of 98 patients with hepatic AL amyloidosis: an average weight loss of 10.4 kg was documented in 72% of the subjects (7). In a large study by a group in Boston, 42.7% of 232 patients with cardiac AL amyloidosis had an unintentional weight loss ≥ 4.5 kg (8).

To the best of our knowledge, the nutritional status of a patient with AL amyloidosis has been assessed, by means of recorded

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TABLE 1
Clinical characteristics of the subjects[1]

	Value
Age (y)	60 (28–78)[2]
Monoclonal protein in serum or urine or both	
λ	79 (74.5)[3]
κ	21 (19.8)
Biclonal	6 (5.7)
Amyloid organ involvement	
1	47 (44.3)
>2	59 (55.7)
Kidney involvement	79 (74.5)
Cardiac involvement	64 (60)
Liver involvement	25 (24)
Gastrointestinal tract involvement	3 (2.8)
Proteinuria (g/24 h)	2.9 (0–39.8)
Urine protein loss > 3 g/24 h	52 (49)
Serum creatinine (mg/L)	12 (4–147)
> 12 mg/L[4]	51 (48.1)
> 20 mg/L	29 (27.3)
Dialysis	8 (7)
Peripheral edema	58 (55)
Ascites	0 (0)
Treatment at enrollment	86 (81.1)
High-dose dexamethasone-based therapy	53 (50)
Thalidomide	20 (18.9)
Autologous stem cell transplant	7 (6.6)
Other	6 (5.6)
Newly diagnosed patients not receiving any treatment at enrollment	20 (18.9)
Hematologic response to therapy	55 (63.9)[5]

[1] $n = 106$.
[2] Median; range in parentheses (all such values).
[3] n; percentage in parentheses (all such values).
[4] Upper reference limit.
[5] Percentage of treated patients.

weight and serum albumin, transferrin, and prealbumin, in only one case-report study. That study reported that malnutrition and heart failure had dominated the clinical course of a hospitalized 39-y-old woman affected by multiple myeloma and AL amyloidosis, leading to her death (9). The aims of the current, prospective study were to obtain information regarding the nutritional status of a representative sample of AL amyloidosis outpatients and to investigate its prognostic role.

SUBJECTS AND METHODS

Subjects

One hundred six consecutive AL amyloidosis outpatients [60 (56.6%) males], evaluated at the Center for Amyloidosis of the University Hospital San Matteo of Pavia, Italy, were enrolled into the study over a 6-mo period. All patients had a histologic diagnosis of amyloidosis, and a monoclonal component was detected in the serum or urine (or both) with the use of high-resolution agarose gel immunofixation electrophoresis. The clinical characteristics of the patients are shown in **Table 1**. Kidney involvement was defined as proteinuria > 0.5 g/24 h, and cardiac involvement was defined as mean ventricular wall thickness > 12 mm at echocardiography in the absence of other cardiac causes (10). Liver involvement was defined as either serum alkaline phosphatase > 418 U/L (ie, > 1.5 times the institutional upper reference limit of 279 U/L), a total liver span >15 cm in the absence of heart failure, or both (10). Gastrointestinal tract involvement was defined as direct biopsy verification with symptoms (10), and a hematologic response to therapy was defined as a reduction of > 50% in the serum and urine monoclonal component (10). None of the patients was taking dietary supplements or being treated with enteral or parenteral nutrition.

Oral informed consent was obtained from all subjects. The study was approved by the institutional review board of the IRCCS Policlinico San Matteo.

Measurements

Measurements were carried out by a single specialist in clinical nutrition, and variables related to nutritional status were recorded during the routine clinical examination at the Center for Amyloidosis. The following clinical variables were recorded: presence of anorexia, dysphagia, dysgeusia, vomiting (considered as the occurrence of ≥2 episodes during the week before the clinical examination), and diarrhea (considered as ≥3 loose or watery stools in at least two 24-h periods during the week before the clinical examination). The patients were questioned about unintentional weight loss and usual nonedematous body weight before the onset of signs or symptoms of the disease. Weight loss and percentage weight loss were calculated on the basis of the recorded weight; the duration of weight loss was determined.

Performance status was assessed according to the Eastern Cooperative Oncology Group performance status scale (11), and patients with cardiac involvement were classified according to the New York Heart Association classification (12). Body mass index (BMI; in kg/m^2) and mid-arm muscle circumference (MAMC) were determined. Height and weight were measured while the subjects were barefoot and lightly dressed. Body weight was measured to the nearest 0.1 kg on a balance-beam platform scale (Wunder, Milan, Italy). Height was measured to the nearest centimeter by using a stadiometer (Wunder) at head level while the subjects were barefoot and were standing with the feet together. BMI was calculated (13). Midarm circumference was measured to the nearest centimeter by wrapping a plastic flexible tape at the median point between the acromion and the olecranon on the nondominant side of the body. Three measurements of triceps skinfold thickness were made according to the international recommendations (14) by using a calibrated caliper accurate to 0.2 mm (Harpenden skinfold caliper; John Bull British Indicators Ltd, London, United Kingdom) and then averaged. MAMC was calculated (14) and compared with sex- and age-matched percentiles (15).

The biochemical markers serum albumin, prealbumin, and transferrin were measured with the use of an immunonephelometric method (Dade Behring, Marburg, Germany).

Statistical analysis

All statistical analyses were performed with STATA statistical software [version 8.2; STATA Corp, College Station, TX (16)]. Patient survival was defined as the time between the date of enrollment and the date of death from any cause or the date of last contact or last known to be alive. Correlations were assessed by calculating Spearman's correlation coefficient. Differences among the groups of subjects were assessed by using Student's t test and one-way analysis of variance. Scheffe's test was used for post hoc pairwise comparison. The test for trend was also applied. For the purpose of the analyses, percentage weight loss was

TABLE 2
Differences within the nutritional variables according to the presence of symptoms[1]

	Subjects	BMI	MAMC	Serum prealbumin	Weight loss
	n (%)	*kg/m²*	*cm*	*mg/L*	*%*
Dysgeusia					
Yes	36 (34)	23.0 ± 3.2[2]	22.9 ± 2.5	245 ± 90	13.2 (5.8–18.2)[3]
No	70 (66)	25.3 ± 3.4	24.6 ± 3.3	260 ± 88	0.0 (0.0–6.5)
P[4]		0.002	0.010	0.44	0.005
Anorexia					
Yes	33 (31.1)	22.6 ± 3.2	22.2 ± 2.8	229 ± 93	15.1 (7.0–19.9)
No	74 (68.9)	25.4 ± 3.2	24.8 ± 3.0	266 ± 86	0.0 (0.0–6.3)
P		< 0.001	< 0.001	0.047	< 0.001
Vomiting					
Yes	18 (17)	22.5 ± 3.8	21.9 ± 2.6	272 ± 109	11.9 (6.8–21.8)
No	88 (83)	24.9 ± 3.3	24.5 ± 3.1	251 ± 84	0.0 (0.0–8.4)
P		0.006	0.010	0.36	0.1
Dysphagia					
Yes	15 (14.1)	21.9 ± 3.2	22.0 ± 3.3	225 ± 95	18.5 (15.1–24.2)
No	91 (85.9)	24.9 ± 3.3	24.3 ± 3.0	260 ± 87	0.0 (0.0–7.8)
P		0.001	0.009	0.17	< 0.001
Diarrhea					
Yes	9 (8.5)	22.9 ± 3.2	23.2 ± 3.7	176 ± 68	16.4 (9.2–22.4)
No	97 (91.5)	24.6 ± 3.5	24.1 ± 3.1	262 ± 87	2.7 (0.0–9.7)
P		0.16	0.42	0.005	0.040

[1] MAMC, midarm muscle circumference.
[2] $\bar{x}$ ± SD (all such values).
[3] Median; 25th–75th percentiles in parentheses (all such values).
[4] Student's *t* test (all such values); percentage weight loss data were log transformed (skewed distribution).

log transformed (skewed distribution). Multivariate general linear regression was used to assess the association of cardiac involvement, New York Heart Association classification, and Eastern Cooperative Oncology Group performance status with percentage weight loss (log transformed) after control for the other nutritional variables. Because of the multicollinearity between these clinical characteristics, 3 different models were fitted. Backward selection was performed; values of $P = 0.1$ were used to remove variables.

Kaplan-Meier cumulative survival was computed. The Cox proportional hazard model was used to identify independent predictors of death. Hazard ratios and their 95% CIs were computed. A two-sided P value of < 0.05 was adopted as statistically significant.

RESULTS

At the time of this writing, 26 (24.5%) subjects have died after a median follow-up of 10.6 mo (range: 1–31.8 mo); overall median survival was not reached. Median follow-up of living patients was 29.6 mo (range: 1–36.5 mo). Differences within the nutritional variables according to the presence of symptoms are reported in **Table 2**. Median BMI was 24.5 (range: 17.5–33.7); BMI was > 30 in 8 patients (7.5%), $> 25 < 30$ in 38 (35.8%), < 22 in 25 (23.6%), and < 18.5 in 3 (2.8%). BMI was correlated with the percentage weight loss ($r = -0.43$, $P < 0.001$) and MAMC ($r = 0.69$, $P < 0.001$). Percentage weight loss, MAMC, and serum prealbumin stratified by BMI categories of < 22 or ≥ 22 are reported in **Table 3**.

Median MAMC was 24.1 cm (range: 17.7–32.5 cm). MAMC was below the sex- and age-matched 10th percentile in 29 patients (27.3%). MAMC was correlated with percentage weight loss ($r = -0.41$, $P < 0.001$) and serum prealbumin ($r = 0.22$, $P = 0.02$). Serum prealbumin was < 200 mg/L (reference range: 200–400 mg/L) in 26 patients (24.5%) and was correlated with serum creatinine ($r = 0.35$, $P < 0.001$). Serum albumin was < 35 g/L (reference range: 35–52 g/L) in 67 patients (63.2%) and was correlated with proteinuria ($r = -0.72$, $P < 0.001$) and serum transferrin ($r = -0.52$, $P < 0.001$). Serum transferrin was < 2.0 g/L (reference range: 2.0–3.6 g/L) in 56 patients (52.8%) and was correlated with proteinuria ($r = -0.30$, $P = 0.002$).

Unintentional weight loss [median: 8 kg; range: 2–30 kg (ie, median: 11.3%; range: 2.6–34% of usual nonedematous body weight)] was documented in 58 patients (54.7%) within the previous 2–72 mo (median: 12 mo). Mean weight loss/y was 10.9 ± 1.3 kg and mean percentage weight loss/y was 14.8 ± 1.5% of usual nonedematous body weight. Unintentional weight loss was found in 45 (70.3%) of the 64 patients with cardiac involvement.

TABLE 3
Percentage weight loss, midarm muscle circumference (MAMC), and serum prealbumin stratified by BMI category[1]

	BMI ≥ 22 ($n = 81$)	BMI < 22 ($n = 25$)	P[2]
Percentage weight loss (%)	0.0 (0.0–7.4)[3]	16.4 (6.3–20.5)	< 0.001
MAMC (cm)	25 ± 2.8[4]	20.8 ± 2.1	< 0.001
Serum prealbumin (mg/L)	267 ± 88	215 ± 81	0.01

[1] BMI measured in kg/m².
[2] Student's *t* test; percentage weight loss data were log transformed (skewed distribution).
[3] Median; 25th–75th percentile in parentheses (all such values).
[4] $\bar{x}$ ± SD (all such values).

TABLE 4
Percentage weight loss according to the presence or absence of cardiac involvement, New York Heart Association (NYHA) classification, and Eastern Cooperative Oncology Group (ECOG) performance status

		P		
	Weight loss	ANOVA	Test for trend	Adjusted[1]
	%			
Cardiac involvement		0.04	NA	0.03
Yes ($n = 64$)	7.2 (0.0–16.6)[2]			
No ($n = 42$)	0.0 (0.0–4.2)			
NYHA classification[3]		0.03	0.01	0.02
No heart involved ($n = 42$)	0.0 (0.0–4.2)			
I ($n = 28$)	1.3 (0.0–11.8)			
II ($n = 20$)	6.6 (3.5–16.2)			
III ($n = 16$)	16.0 (8.2–24.6)			
ECOG performance status[4]		< 0.001	< 0.001	0.001
0 ($n = 29$)	0.0 (0.0–4.1)			
1 ($n = 48$)	1.3 (0.0–12.4)			
2 ($n = 19$)	9.1 (5.9–19.0)			
3 ($n = 10$)	16.0 (10.3–26.3)			

[1] Adjusted for BMI, midarm muscle circumference, and serum albumin, prealbumin, and transferrin in a multivariate regression model on log-transformed percentage weight-loss data.
[2] Median; 25th–75th percentiles in parentheses. Data were log transformed for the purpose of the analyses (skewed distribution).
[3] Post hoc pairwise comparison between NYHA classes (Scheffe's test): no heart involvement versus NYHA class III, $P = 0.03$; other comparisons were not significant.
[4] Post hoc pairwise comparison between ECOG performance status classes (Scheffe's test): 0 versus 2, $P = 0.01$; 0 versus 3, $P = 0.001$; other comparisons were not significant.

In 31 patients (29.2%), 26 of whom had cardiac involvement, weight loss was > 7.5% of usual nonedematous body weight, and it occurred over a period of > 6 mo. In 6 patients (5.6%), weight loss was > 7.5% of usual nonedematous body weight, and it occurred over a period of ≤6 mo.

Percentage weight loss variations according to the presence of cardiac involvement and performance status are shown in **Table 4**. Patients with BMI < 22 (**Figure 1**) and those with serum prealbumin concentration below the lower reference limit (**Figure 2**) had a significantly shorter survival than did other patients.

The multivariate Cox regression analysis (**Table 5**) showed that the presence of cardiac involvement, hematologic response to chemotherapy, BMI, and serum prealbumin were independent predictors of survival. Serum albumin and serum transferrin were not significantly associated with survival.

DISCUSSION

The current study shows that malnutrition is a prominent clinical feature of patients with AL amyloidosis, particularly those with cardiac involvement. The proportion of subjects with cardiac AL amyloidosis who had lost weight was significantly higher in our study (70.3%) than in that by Dubrey et al (42.7%; 8). Furthermore, we found that patients with cardiac involvement

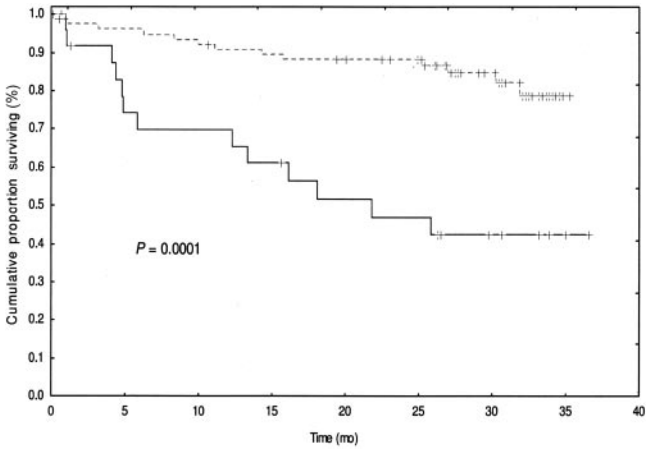

FIGURE 1. Survival stratified by BMI (in kg/m^2) categories of <22 (solid line; $n = 25$) or ≥22 (dashed line; $n = 81$) with the use of Kaplan-Meier survival analysis. Each drop in a probability curve indicates ≥1 event in that group. Vertical lines indicate censored patients, ie, those who reached the end of their follow-up without dying.

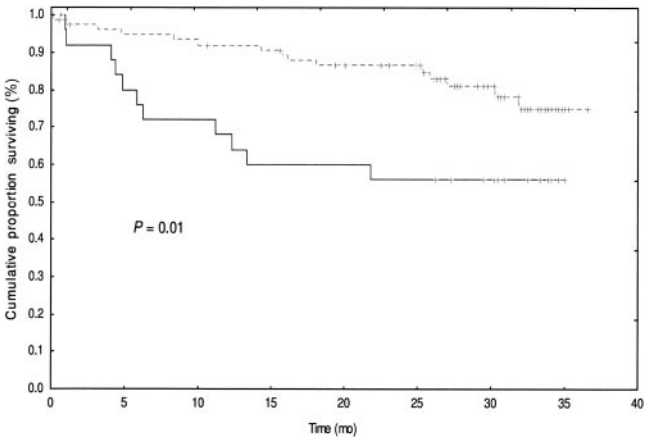

FIGURE 2. Survival stratified by serum prealbumin categories of <200 (solid line; $n = 26$) or ≥200 (dashed line; $n = 80$) mg/L with the use of Kaplan-Meier survival analysis. Each drop in a probability curve indicates ≥1 event in that group. Vertical lines indicate censored patients, ie, those who reached the end of their follow-up without dying.

TABLE 5
Multivariate Cox proportional hazard model[1]

Independent variable	Hazard ratio (95% CI)	*P*
Cardiac involvement	6.1 (1.58, 23.25)	0.008
Hematologic response to therapy[2]	0.26 (0.09, 0.75)	0.013
BMI (kg/m^2)	0.75 (0.64, 0.88)	0.001
Serum prealbumin	0.86 (0.79, 0.94)	0.001
Serum albumin	0.46 (0.20, 1.06)	0.068
Serum transferrin	1.0 (0.99, 1.00)	0.842

[1] $n = 106$.
[2] Available in 81 treated patients.

had lost significantly more weight than did the other patients and that weight loss was associated with functional impairment in terms of performance status. According to the definition of cardiac cachexia, we identified almost 40% of patients with cardiac involvement as cachectic (17).

The nutritional status of AL amyloidosis patients can be satisfactorily described with simple measurements and laboratory tests that can be performed easily in nonreferral centers and can become part of the routine evaluation of these patients. BMI and serum prealbumin concentration emerged as important prognostic determinants, and the multivariate analysis showed that their effect on survival was independent from the presence of cardiac amyloidosis and from a hematologic response to chemotherapy. Although maintenance of a good nutritional status is known to be associated with prolonged survival in many chronic and progressive diseases (18, 19), malnutrition continuese to be often unrecognized and untreated (20, 21). Moreover, the lack of internationally accepted thresholds for the anthropometric and biochemical variables used to define nutritional status in specific clinical populations can cause confusion and potentiate the problem. To date, raw weight loss has been the only nutritional variable considered in the evaluation of AL amyloidosis patients, and it has been assessed retrospectively.

With the simple tools adopted, we estimated that almost one-quarter of AL amyloidosis outpatients were malnourished. These data cause concern, especially if we consider that none of the patients was receiving any nutritional support at the time of enrollment. Supportive treatment and a careful follow-up play an important role in the care of the fragile AL amyloidosis patients (3). It is likely that appropriate and closely monitored nutritional support could improve the survival of patients with AL amyloidosis, by rendering them able to undergo aggressive treatments, by reducing the incidence of complications, notably infections, or by doing both. This hypothesis is worth further investigation. Another interesting field for further investigation is the role of cardiac involvement in the development of body wasting in AL amyloidosis, which would include the evaluation of the metabolic, neuroendocrinologic, and immunologic abnormalities linked to cachexia (22).

Dietary intake was not assessed in this study. Nevertheless, the symptoms referred by the patients had a significant effect on the recorded nutritional variables, and we strongly suspect that the subjects who reported anorexia, dysphagia, and dysgeusia had insufficient protein-energy intakes. However, the assessment of food intake may provide additional information with regard to the risk of developing malnutrition, may allow the identification of specific nutritional deficits, and is essential for plannning targeted nutritional interventions. Hence, it should be included in future studies.

RC and GM participated in the design of the study; RC, GP, CV, BC, PR, FL, and GM participated in the clinical evaluation of the patients; RC, GP, CV, BC, FL, and GM participated in data collection; RC, GP, HC, and GM participated in the analysis and interpretation of the data; and RC, GP, and CK participated in writing the manuscript. None of the authors had a personal or financial conflict of interest.

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