

Primary Systemic Amyloidosis: Multivariate Analysis for Prognostic Factors in 168 Cases

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One hundred sixty-eight patients with primary systemic amyloidosis (AL) were identified. Median survival after diagnosis was 12 months and ranged from 4 months for patients presenting with congestive heart failure to 50 months for those presenting with peripheral neuropathy only. Utilizing the proportional-hazards model in a stepwise multivariate fashion to evaluate the simultaneous influence of putative risk factors as of diagnosis revealed that congestive heart failure, urine light chain, hepatomegaly, and multiple myeloma were the major factors adversely affecting survival during the first year after

diagnosis. Serum creatinine, multiple myeloma, orthostatic hypotension, and monoclonal serum protein were the most important variables adversely affecting survival for patients surviving 1 year. These models were used to categorize patients according to the variables in the models into low-, moderate-, and high-risk groups for the first year after diagnosis and separately for subsequent years. The influence of these variables on survival is important in stratification of patients randomized to prospective clinical trials.

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ALTHOUGH amyloidosis has been recognized for more than a century, there has been no analysis of prognostic factors. Amyloid, a substance that appears to be homogeneous and amorphous under the light microscope, consists of rigid, linear, nonbranching aggregated fibrils. The fibrils consist of the variable portion of a monoclonal light chain, are arranged in a β -pleated sheet formation, are insoluble, generally resist proteolytic digestion, and constitute the amyloid deposits that replace and destroy normal tissues. Except for multiple myeloma, which is seen in about one-fifth of the patients with primary amyloidosis (AL), patients have no evidence of preceding or coexisting disease responsible for the amyloidosis.

In two series of patients with primary amyloidosis (AL), the median survival after histologic diagnosis of amyloid was approximately 1 year.^{1,2} This short survival and the lack of an analysis of prognostic factors in primary amyloidosis (AL) prompted us to undertake this study.

MATERIALS AND METHODS

All Mayo Clinic records reporting a histologic diagnosis of amyloidosis from Jan 1, 1970, to Dec 31, 1980, were reviewed, and the data were abstracted on sheets suitable for keypunching. All laboratory data were obtained from Mayo Clinic records within 1 month of the histologic diagnosis of amyloidosis. All parameters were measured in all patients. The data for multiple visits were recorded on separate sheets, and a longitudinal view was obtained. Patients with secondary amyloidosis or with localized, familial, or senile amyloidosis were excluded. Patients with amyloidosis and multiple myeloma were included because differentiation on this basis is often difficult inasmuch as these conditions represent the same fundamental process. In a recent report,³ the presence or absence of myeloma in patients with amyloidosis did not influence survival. All

patients were followed up until death or for at least 1 year after the diagnosis of amyloidosis.

Standard univariate statistical methods were used to summarize the distribution of each of the parameters. Survival curves were estimated by the Kaplan-Meier technique.⁴ The proportional-hazards method of Cox was used to determine the variables that influenced survival separately for the first year after diagnosis and for subsequent years.⁵

RESULTS

One hundred sixty-eight patients with primary systemic amyloidosis (including 40 with multiple myeloma) were identified (Table 1). Amyloidosis was diagnosed on the basis of finding amyloid deposits in tissue by the use of appropriate staining procedures or of demonstrating amyloid fibrils with electron microscopy. Seventy percent of the patients had a positive rectal biopsy. Biopsies of the kidney, small intestine, and sural nerve were positive in 83% to 100% of specimens studied.

Loss of weight was noted in 42% of the patients; the amount of the loss contributed significantly to the prediction of early survival. Among those who lost weight, the loss ranged from 2.3 to 40.9 kg (5 to 90 lb), with a median of 9.1 kg (20 lb). Fatigue was common, being found in 55% of the 168 patients. Purpura was found in 15% and gross bleeding in 9%. Some patients had more than one symptom.

The liver was palpable in one-third of the patients but extended more than 10 cm below the right costal margin in only two. The spleen was palpable in only 4% and was modest in size; none extended >3 cm below the left costal margin. Macroglossia, present in one-fourth of the patients, occasionally constituted the major manifestation of the disease. Lymphadenopathy was infrequent.

The syndromes present at the time primary systemic amyloidosis was diagnosed are listed in Table 2. Nine patients (5.3%) had a malabsorption syndrome. Symptoms of nephrotic syndrome and congestive heart failure existed approximately 1 to 3 months before the diagnosis of amyloidosis, while symptoms of peripheral neuropathy or carpal tunnel syndrome were present for approximately a year before amyloidosis was diagnosed. Congestive heart failure and orthostatic hypotension frequently developed during the patient's illness.

Laboratory studies. Anemia was not a prominent finding, the initial median hemoglobin value being 12.7 g/dL. Of

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Table 1. Age and Sex Distribution of 168 Patients With Primary Systemic Amyloidosis (AL)

Age (yr)	Males	Females	Total	
			No.	%
<40	2	0	2	1
40-49	11	6	17	10
50-59	29	15	44	26
60-69	30	25	55	33
70-79	31	13	44	26
≥80	6	0	6	4
Total*	109 (65%)	59 (35%)	168	100

*Median, 64 years.

the 18 patients with an initial level <10 g/dL, 8 had multiple myeloma, 8 had renal insufficiency, 1 had gastrointestinal bleeding, and 1 had no apparent cause. Leukopenia was found in only 1%, thrombocytopenia in 1%, and thrombocytosis (> 500,000/mm³) in 7%. Renal insufficiency was evident initially in 55% of the males and 59% of the females. Twenty-six percent of the males and 12% of the females had an initial creatinine level > 2.0 mg/dL.

Serum protein findings. More than half of the patients had either hypogammaglobulinemia or a normal serum protein electrophoretic pattern. A localized band or spike was found in 74 patients, and when present, it was usually of only modest size (median, 1.3 g/dL). Immunoelectrophoresis revealed a monoclonal serum protein in 69%. Unexpectedly, 26% of the patients had a free monoclonal light chain in the serum (Bence Jones proteinemia). Lambda light chains predominated (λ in 83 and κ in 31 cases).

Urine protein findings. Proteinuria (routine urinalysis) was found in 80% of the patients. Electrophoresis of concentrated urine revealed a globulin band in two-thirds of the patients and an albumin peak in more than 70%.

Immunoelectrophoresis of an adequately concentrated urine specimen showed a monoclonal light chain in 75% of the patients during their disease. In two-thirds of the patients, the light chains were λ. A monoclonal protein was found in the serum or urine in 89% of the patients.

Other studies. Bone marrow plasma cell counts ranged from 1% to 99%, with a median of 9%. Roentgenograms were

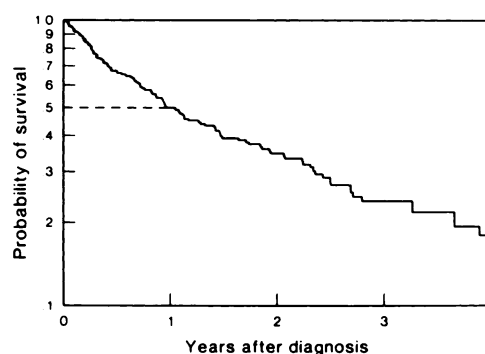


Fig 1. Probability of survival after diagnosis of primary systemic amyloidosis (AL).

normal in 62% of the patients. Osteolytic lesions were found in 15 patients; all had overt multiple myeloma.

Therapy and cause of death. Eighty-four percent of the patients received an alkylating agent some time during their illness. Colchicine was given to 13 patients. Nineteen patients did not receive any therapy. Cardiac involvement accounted for 40% of the deaths, but the percentage was probably higher because many patients who died of “amyloidosis” may have died of cardiac disease. Only 1 patient died of another malignancy—malignant melanoma.

Survival by syndromes. Median survival of the 168 patients after the diagnosis of amyloidosis was 12 months (Fig 1). All patients were followed up, if alive, for at least 1 year, and, as of the last follow-up, 79% had died. In contrast, the estimated median survival from diagnosis of amyloidosis to death for patients presenting with various syndromes ranged from 4 months for those presenting with congestive heart failure to 50 months for those presenting only with peripheral neuropathy (Table 3). Death of patients presenting with only the carpal tunnel syndrome or peripheral neuropathy (or both) was due to eventual involvement of other organs.

Seventeen of the 54 patients presenting with a nephrotic syndrome also had either congestive heart failure or orthostatic hypotension at presentation. Nine of the 54 survived more than 3 years after the diagnosis of amyloidosis, and only 2 of them are now known to have died, 1 of malignant

Table 2. Syndromes at Time of Diagnosis of Primary Systemic Amyloidosis (AL)*

Condition	At or Before Diagnosis of Amyloidosis		Month Before Diagnosis of Amyloidosis		No. After Diagnosis of Amyloidosis	Total	
	No.	%	Median	Range		No.	%
Congestive heart failure	38	23	3.5	0-12	19	57	34
Nephrotic syndrome	54	32	1.5	0-36	6	60	36
Carpal tunnel syndrome	46	27	9.2	0-227	1	47	28
Orthostatic hypotension	23	14	6.2	0-39	9	32	19
Peripheral neuropathy	28	17	12.8	0-58	1	29	17

*Some patients had more than one condition.

Table 3. Survival by Presenting Symptoms of 168 Patients With Primary Systemic Amyloidosis (AL)

	Patients	Median Survival (mo)
Total group	168	12
Hierarchical groups*		
Congestive heart failure	38	4
Orthostatic hypotension	17	12
Nephrotic syndrome	37	16
Carpal tunnel syndrome	28	23
Peripheral neuropathy	11	50

*Patients were placed only in the first group they occurred in. Thus, none of the 37 patients listed as presenting with a nephrotic syndrome had either congestive heart failure or orthostatic hypotension, but some may have had the carpal tunnel syndrome or peripheral neuropathy.

melanoma and 1 of suicide. One patient continues on dialysis more than 12 years after diagnosis. Only 3 patients who had congestive heart failure at presentation survived more than 2 years.

Analysis of survival. Because the assumption of proportional-hazards functions was not satisfied over the entire follow-up period but did hold separately within the first year and subsequently, the proportional-hazards method of Cox was used separately for these two periods in an attempt to evaluate the influence of the variables on survival. Coincidentally, half of our patients were dead at 1 year.

Analysis of survival during the first year. Four variables—congestive heart failure (CHF), urinary light chain (ULC), hepatomegaly, and amount of weight loss—had a highly significant influence on survival during the first year (Table 4). Four other variables (albuminuria, elevated serum creatinine, sex, and myeloma) were significant ($P < 0.05$).

The proportional-hazards model was then employed in a step-wise multivariate fashion to evaluate the simultaneous influence of combinations of the variables. The first three variables that were entered into the model, and their P values on entry, were CHF ($P < 0.0001$), ULC ($P = 0.0001$), and MCS (monoclonal serum protein) ($P = 0.009$).

When the step-wise process was allowed to continue without concern for the implications of the limited data available in some subsets of patients, hepatomegaly and multiple myeloma were identified as having an additional

Table 4. Effect of Individual Variables on Survival Curves

During First Year		After First Year	
Variable	P (log-rank)	Variable	P (log-rank)
Congestive heart failure	.0001	Hemoglobin	.0022
Urinary light chain	.0001	Serum creatinine	.0023
Hepatomegaly	.0002	Myeloma	.0037
Weight loss (amount)	.0055	Monoclonal serum protein	.0370
Electrophoretic pattern of albumin in urine	.0108	Urinary light chain	.0540
Elevated serum creatinine (>2.0 mg/dL)	.0270		
Sex	.0320		
Myeloma	.0420		

Table 5. A Model Involving Five Variables Related to Survival During First Year After Diagnosis of Primary Systemic Amyloidosis (AL)

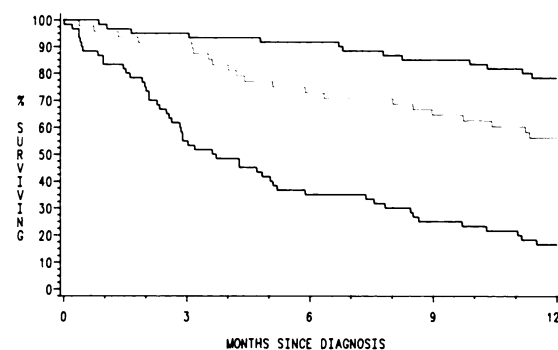
Variable	Coefficient	P Value
Congestive heart failure (CHF)	1.43	<0.0001
Urine light chain (ULC)	0.97	0.0064
Hepatomegaly (HEP)	0.58	0.0106
Multiple myeloma (MM)	0.65	0.0126
Monoclonal serum protein (MCS)	-0.87	0.0008

effect on survival ($P < 0.05$) after the effects of the first three variables had been accounted for.

The possibility that some of these five variables interact with each other in their influence on survival cannot be denied. However, the numbers of patients with combinations of variables is too small to address the question of such potential interactions in a satisfactory manner. The model (Table 5) summarizing the influence of the five variables assumes no interactions among them, and therefore the joint influences predicted by the model are based on the distribution of the individual variables, and predictions are possible, even when data are sparse.

The coefficients of the variables in this model suggest that a diagnosis of CHF is highly detrimental to survival, the presence of ULC somewhat less detrimental, the presence of HEP and MM about equal and even less detrimental, and the presence of MCS actually "protective." This model was used to create a gradient of risk, and three classes of patients were defined according to this gradient. These classes, referred to as low, moderate, and high risk, are defined as (1) low risk: Patients with no factors or MCS alone or MCS and one of HEP, MM, ULC. (2) Moderate risk: Patients with one of HEP, MM, ULC or MCS and two of HEP, MM, ULC or MCS and CHF. (3) High risk: Patients with CHF alone or all factors except CHF or CHF with or without MCS with one or more of HEP, MM, ULC or two or more of HEP, MM, ULC.

When the 168 patients were classified according to these definitions, there were 60 patients in the high-risk group, 70 in the low-risk group, and 48 in the moderate-risk group. The Kaplan-Meier estimates of the survival curves for these three

**Fig 2. Kaplan-Meier estimates of the survival curves for low-, moderate-, and high-risk patients with primary systemic amyloidosis (AL).**

classes are illustrated in Fig 2. The three curves are significantly different ($P < 0.0001$, log-rank test) and demonstrate a clear classification of the patients into three groups according to likelihood of surviving 1 year after a diagnosis of amyloidosis.

Analysis of survival after 1 year. The proportional-hazards model was also used to identify variables whose value at diagnosis influenced the rate of subsequent mortality among the 84 patients who survived 1 year after diagnosis (Table 4). Hemoglobin level, serum creatinine level, and presence of multiple myeloma have a highly significant influence on survival ($P < 0.005$), with MCS and ULC being of borderline significance.

As before, the proportional-hazards model was used in a step-wise multivariate fashion to evaluate the simultaneous influence of several variables on survival and/or to evaluate the influence of a variable after the influence of other variables has been taken into account.

In the modeling process, hemoglobin and serum creatinine levels appeared to be surrogates of each other, and the final model ($P < 0.0001$) included serum creatinine, multiple myeloma, orthostatic hypotension, and monoclonal protein in the serum (Table 6). Although no interactions were found to be significant, the sample size limits our ability to detect them. As before (in reference to year 1), the model is used to establish a gradient of risk, and three classes of patients are defined on the basis of the values of the four variables at the time of the diagnosis of amyloid and referred to as low, moderate, and high risk. These classes are (1) low risk: Serum creatinine ≤ 2.0 and no risk factors (MM, OH, MCS); (2) moderate risk: Serum creatinine 2.0 to 6.5 and no risk factors or serum creatinine < 2.0 and either MM or MCS; (3) high risk: Serum creatinine > 6.5 and no risk factors or serum creatinine > 2.0 and either MM or MCS or OH alone or two or more of MM, MCS, OH.

Of the 84 patients who survived 1 year after the diagnosis of amyloid, 14 were in the low-risk group, 38 in the moderate-risk group, and 32 in the high-risk group. Figure 3 illustrates the estimated survival curves (Kaplan-Meier) for these three groups. The curves differ significantly ($P < 0.0001$, log-rank test).

DISCUSSION

In three series comprising almost 500 cases of primary systemic amyloidosis (AL) from the Mayo Clinic, the median survival was 14.7 months or less.^{1,2,6} Daniels and Hewlett⁷ reported that the median survival of patients with

Table 6. Variables Affecting Survival After First Year Following the Elimination of Hemoglobin in Cases of Primary Systemic Amyloidosis (AL)

Variable	Coefficient	P Value
Serum creatinine	0.21	0.0001
Multiple myeloma (MM)	1.07	0.0014
Orthostatic hypotension (OH)	1.75	0.0007
Monoclonal serum protein (MCS)	1.04	0.0065

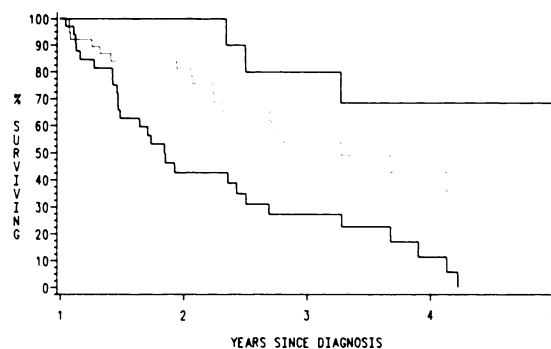


Fig 3. Kaplan-Meier estimates of the survival curves for low-, moderate-, and high-risk patients with primary systemic amyloidosis (AL) who survived 1 year after diagnosis.

primary amyloidosis was 5 months, while in another series,⁸ no patients with primary amyloidosis (AL) survived more than 12 months after diagnosis. In a series of 32 patients with primary systemic amyloidosis with or without myeloma, the median survival was 14 months.³ In 1976, Pruzanski and Katz⁹ reported a mean survival of 28 months for 26 patients with primary amyloidosis who had died.

The median survival from diagnosis of amyloidosis to death among the current series of 168 patients presenting with associated syndromes ranged from 4 months in those presenting with congestive heart failure to 50 months in those presenting only with peripheral neuropathy. It should be pointed out that the patients presenting only with peripheral neuropathy or the carpal tunnel syndrome who died usually did so from subsequent cardiac or renal involvement. In fact, cardiac involvement accounted for the deaths of 40% of the patients who died.

The median survival of the 168 patients in our series was 12 months. The major risk factor for survival during the first year was the presence of congestive heart failure. The presence of hepatomegaly, urinary light chain, and multiple myeloma also had an adverse effect on survival during the first 12 months. The presence of a monoclonal protein appeared to have a "protective" effect on survival but only during the first year. An explanation of this phenomenon is not readily available. Utilization of these variables allowed us to categorize the patients into low risk, moderate risk, or high risk the first year after diagnosis. Patients in the high-risk group had a median survival of 3.5 months, in contrast to more than 1 year for those in the low- or moderate-risk groups.

Utilization of the proportional-hazards model in a step-wise multivariate fashion revealed that after the first year, patients with more severe systemic amyloidosis had died and that serum creatinine levels, multiple myeloma, orthostatic hypotension, and monoclonal serum protein in the urine were the most important variables affecting survival. Patients in the high-risk group had a median survival of 10 months after the first year (total, 22 months), whereas the median survivals in the low- and moderate-risk groups exceeded 28 months after the first year (total, 40 months). It should be emphasized that the significant variables influencing survival dur-

ing the first year after diagnosis—congestive heart failure, urinary light chain, hepatomegaly, and loss of weight—had a negligible role in affecting survival after the first year.

This study permits a more accurate assessment of survival at the time of diagnosis of primary systemic amyloidosis. The influence of these variables on survival is important in the

stratification of patients randomized to prospective clinical trials.

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