# Primary Systemic Amyloidosis: Clinical and Laboratory Features in 474 Cases

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THE TERM "amyloid" was coined by Matthias Schleiden, a German botanist, in 1838 to describe a normal amylaceous constituent of plants. In 1854, Rudolf Virchow used the term amyloid because the iodine-sulfuric acid test indicated that the substance was similar to cellulose.[1] The term "lardaceous disease" had been used more than 60 years before by Antoine Portal, a French physician, but was popularized by Karl Rokitansky in 1842, when he stated that patients with tuberculosis or syphilis had liver enlargement because of infiltration by a gray, albuminous, gelatinous substance.[40] "Waxy" was used interchangeably with lardaceous in describing the distinctive substance. However, it had been recognized as albuminous rather than fatty by William Budd during the 1840s.[2] Johann Meckel reported that the lardaceous changes were present in the aorta, arteries, and intestinal wall as well as the liver and kidneys. This is the distribution of amyloid that is now recognized as primary. Virchow, in a lecture on April 17, 1858, stated, "Only when we have discovered the means of isolating the amyloid substance, shall we be able to come to any definite conclusion with regard to its nature."[43]

Although amyloidosis was described more than 300 years ago, it was not until 1856 that Wilks described a 51-year-old man with "lardaceous viscera" unrelated to syphilis, osteomyelitis, other osseous disease, or tuberculosis. At autopsy, the patient's heart was enlarged and his spleen was described as hard and lardaceous. The patient had experienced episodes of dropsy for 8 years as well as lardaceous changes in his kidney. This patient probably had primary amyloidosis (AL).[44]

Amyloid seems to be homogeneous and amorphous under the light microscope. The amorphous, hyalinlike appearance of amyloid is misleading because it is a fibrous protein consisting of rigid, linear, nonbranching, aggregated fibrils 7.5 to 10 nm wide and of indefinite length. Each amyloid fibril consists of two to five filaments and is arranged in an antiparallel or cross β-pleated sheet configuration. This arrangement is responsible for the staining and optical features of amyloid. The metachromatic stains such as methyl violet or crystal violet produce typical color changes in amyloid tissue. Congo red is considered the most specific stain, which, when viewed with a polarized light source, produces apple-green birefringence.

The fibrils deposit extracellularly, are insoluble, and generally resist proteolytic digestion. They ultimately lead to disorganization of tissue architecture and the loss of normal tissue elements.

## PATHOGENESIS AND CLASSIFICATION

Amyloid fibrils consist of various proteins such as monoclonal κ or λ light chains in primary amyloidosis (AA) protein A in secondary amyloidosis (AA), transthyretin (prealbumin) in familial or senile systemic amyloidosis, or $\beta_2$-microglobulin ($\beta_2$M) in dialysis-associated amyloidosis (Table 1). All types of amyloid stain positively with Congo red, thioflavin T, or the metachromatic stains and contain amyloid P component. A more complete nomenclature and classification of amyloidosis have been published.[21]

Magnus-Levy[34,35] postulated more than 60 years ago that Bence Jones protein and amyloid were related. Osserman et al[37] proposed in *Seminars in Hematology*, vol 1, that Bence Jones proteins were directly involved in the production of amyloid and that these light chains had a greater affinity for certain tissues. In 1971, Glenner et al[19] showed that amyloid fibrils from a patient with AL were virtually identical to the variable portion of that patient's monoclonal light chain (Bence Jones protein).

The fibrils of AL consist of the N-terminal amino acid residues of the variable portion of a

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**Table 1. Systemic Amyloidosis: Immunohistochemical Identification**

| | Congo Red | Kappa/ Lambda | Protein A | $\beta_2$M | Transthyretin (Prealbumin) |
|---|---|---|---|---|---|
| AL | + | + | − | − | − |
| AA | + | − | + | − | − |
| FMF | + | − | + | − | − |
| AD | + | − | − | + | − |
| AF | + | − | − | − | + |
| SSA | + | − | − | − | + |

Abbreviations: FMF, familial Mediterranean fever; AD, dialysis amyloidosis; AF, familial amyloidosis; SSA, senile systemic amyloidosis.

monoclonal light chain. In AL the light-chain class is more frequently λ than κ (2:1), in contrast to light-chain classes found in multiple myeloma, in which this ratio is reversed. Interestingly, all patients with $\lambda_{VI}$ subgroup have AL. Presumably, some light chains possess features that render them amyloidogenic.

Primary amyloidosis can be divided into (1) AL, and (2) AL with multiple myeloma on the basis of the number of plasma cells in the bone marrow, the amount of monoclonal (M-) protein in the serum and urine, and the presence or absence of skeletal lesions. However, differentiation on the basis of the presence or absence of multiple myeloma is frequently difficult and indeed artificial because the two disorders are both plasma cell proliferative processes with much overlap. In addition, the amyloid fibrils consist of the $NH_2$ terminal amino acid residues of the variable portion of a monoclonal immunoglobulin light chain in both AL and AL with myeloma. The M-protein is a product of the plasma cell, and both conditions represent a clonal plasma cell proliferative process. Also, the presence or absence of multiple myeloma does not influence survival during the first year after diagnosis of AL.[31] Furthermore, therapy for the two conditions is the same. Consequently, it is preferable to consider both categories together as AL.

## EPIDEMIOLOGY

The age- and sex-adjusted annual incidence rate of AL in Olmsted County, Minnesota, was determined to be 0.89 per 100,000 (8.9/million person-years). Applying this rate to the US population, we could expect approximately 2,225 new cases annually. The age-adjusted rate for males was more than twice that for females.[29] Although the age- and sex-adjusted incidence rates were slightly higher from 1970 through 1989 than from 1950 through 1969, there was no significant increase over time.

## MATERIALS AND METHODS

All Mayo Clinic records reporting a histological diagnosis of amyloidosis from January 1, 1981, through December 31, 1992, were reviewed and the data abstracted on sheets suitable for keypunching. The data for multiple visits were recorded on separate sheets. Searches for keypunching and abstracting errors were conducted by computer. Cases without a definite histological diagnosis of amyloidosis were excluded, as were cases of AA, localized amyloidosis, or familial or senile amyloidosis.

All laboratory data were obtained from Mayo Clinic records within 1 month after the histological diagnosis of AL. Patients who came to the Mayo Clinic more than 1 month after the initial diagnosis were excluded from this review. Follow-up letters were written to patients and their physicians for more information. Death certificates were requested when needed. Data from the Mayo Cancer Registry were used for follow-up.

## RESULTS

From January 1, 1981, through December 31, 1992, 1,315 patients with amyloidosis were evaluated at the Mayo Clinic. More than two thirds had AL. Localized amyloidosis was found in 19%. Most of the patients with localized amyloidosis had involvement of the carpal ligament. Secondary amyloidosis and familial amyloidosis were uncommon (Fig 1). During this 12-year period, 918 patients with AL were seen at the

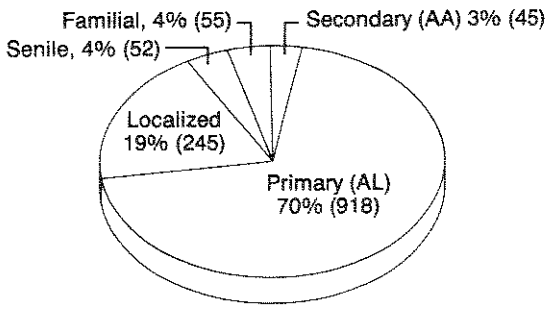


**Fig 1. Types of amyloidosis in 1,315 patients, 1981-1992.**

Mayo Clinic. However, in 444 (48%) the diagnosis was made more than 1 month before or after being seen at the Mayo Clinic, and these patients were excluded from this study. The laboratory and clinical features of the remaining 474 patients are reported in this review.

The diagnosis was made at the Mayo Clinic in 322 patients (68%) and elsewhere in the remaining 152 cases, but the latter group was seen at the Mayo Clinic within 1 month of diagnosis. During 1981 and 1982, 84% of the diagnoses were made at the Mayo Clinic, whereas during the last 2 years (1991 and 1992), 61% were made at the Mayo Clinic. The decline is probably because of increased awareness of AL in the medical community and our prospective therapeutic protocols for AL, which promote referral.

At the time of diagnosis of AL, 78 patients (16%) had monoclonal gammopathy of undetermined significance, 71 (15%) had multiple myeloma, 13 (3%) had smoldering multiple myeloma, 4 (1%) had macroglobulinemia, and 2 (0.5%) had solitary plasmacytoma of bone.

*Age and Sex*

The median age at diagnosis was 64 years, which is similar to that for multiple myeloma and macroglobulinemia. Ninety-nine percent were 40 years or older (Fig 2). None was younger than 30 years.

*Clinical Findings*

Weakness or fatigue and weight loss were the most frequent initial symptoms (Fig 3). Weight loss occurred in more than one half of the patients. The median weight loss was 23 pounds;

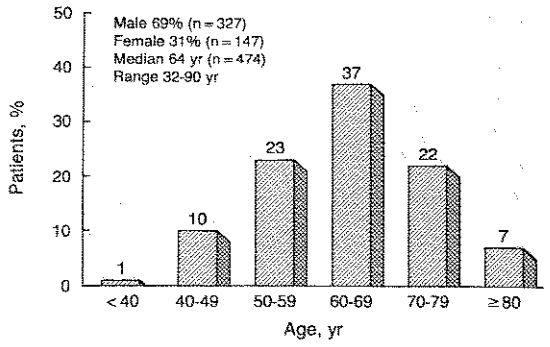


**Fig 2. Age and sex of 474 patients with AL seen at Mayo Clinic within 1 month of diagnosis.**

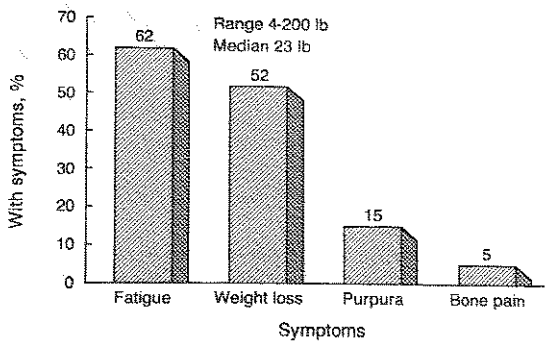


**Fig 3. Symptoms of AL in 474 patients.**

five patients lost more than 100 pounds. Purpura, particularly in the periorbital and facial areas, was noted in 15%. Some patients had seen multiple physicians for periorbital and facial purpura, but the amyloidosis had not been recognized. Gross bleeding was reported initially in only 3%. Skeletal pain was a major symptom in only 5% and was usually related to lytic lesions or fractures associated with multiple myeloma. Dyspnea and pedal edema were frequent in patients with congestive heart failure. Paresthesias, light-headedness, and syncope were often noted in patients with peripheral neuropathy or autonomic neuropathy. In several instances hoarseness or change of voice to a weak, high-pitched, or a deep, husky sound alerted the physician to the possibility of amyloidosis. In these patients the voice frequently became weak late in the day.

A family history of cancer was recorded in 38%, leukemia or lymphoma in 4%, and myeloma in 1% of first-degree relatives. Forty-five patients (9.5%) had suffered in the past or were currently suffering from carcinoma. The most commonly involved organs were prostate (nine cases), breast (seven cases), skin (five cases), and kidney (four cases).

*Physical Findings*

The major initial physical findings are listed in Fig 4. The liver was palpable in almost one fourth of patients, but the edge was palpable more than 5 cm below the right costal margin in only 11%. Splenomegaly was present initially in 5% and extended more than 5 cm below the left costal margin in only one patient. Hepatosplenomegaly was of modest degree in patients with AL. Macroglossia was present initially in fewer

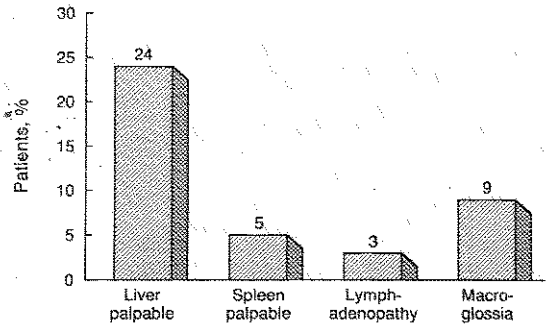


**Fig 4. Physical findings in 474 patients with AL.**

than one tenth of patients. The decreasing prevalence of macroglossia that we have observed during the past 30 years[27,28,30] is most likely a reflection of earlier diagnosis of the disease. Occasionally, the tongue is large and very vascular and causes troublesome bleeding (Fig 5). Increased firmness of the tongue, enlargement of the submandibular structures, and dental indentations are helpful in determining the presence of macroglossia. It is frequently associated with dysphagia and dysarthria and may produce obstructive sleep apnea.

Purpura is a frequent finding and often involves the neck and face, especially the upper eyelids; purpura may be striking after proctoscopy (Fig 6). Purpura may be increased after vomiting or coughing. It can be elicited by minimal trauma such as rubbing the eyelids. The skin is often fragile.

Edema is common and usually results from

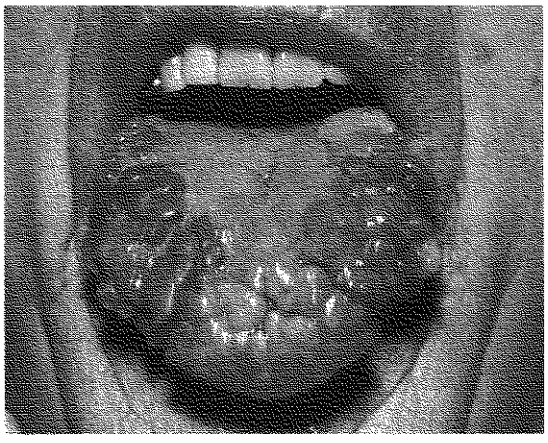

**Fig 5. Macroglossia and increased vascularity of tongue in patient with AL. (Reprinted by permission of Mayo Foundation.[30])**

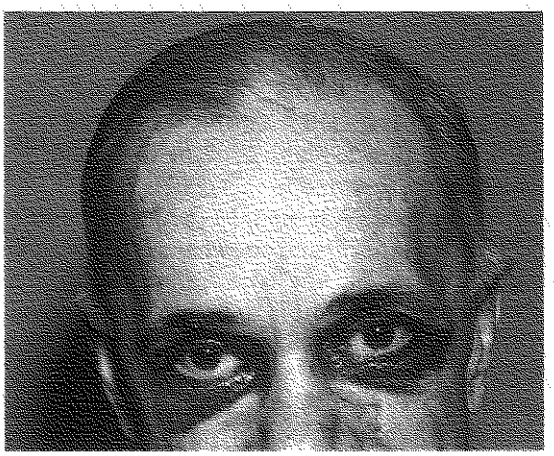

**Fig 6. Postproctoscopic periorbital purpura(PPP). (Reprinted with permission.[28])**

congestive heart failure or nephrotic syndrome. Orthostatic hypotension may be prominent and associated with syncope. Occasionally, patients have difficulty standing. Generalized lymphadenopathy is infrequent but may be the initial manifestation of systemic amyloidosis. Signs of congestive heart failure, nephrotic syndrome, peripheral neuropathy, carpal tunnel syndrome, and malabsorption must be sought during elicitation of the history and performance of the physical examination.

*Syndromes*

The frequency of amyloid syndromes at diagnosis is given in Fig 7. Symptoms of congestive heart failure or nephrotic syndrome or renal insufficiency existed for a median of 3 months before amyloidosis was diagnosed, whereas symptoms of peripheral neuropathy or carpal

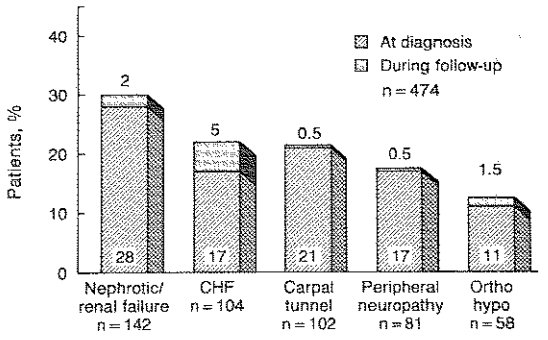


**Fig 7. Frequency of amyloid syndromes at diagnosis of AL. CHF indicates congestive heart failure; Ortho hypo, orthostatic hypotension.**

tunnel syndrome were present for a median of 1 year or more before diagnosis (Table 2). This difference in time before diagnosis in patients with neuropathy probably reflects both a delay by the patients in seeking medical attention and physicians paying little attention to the symptoms. Congestive heart failure developed more often than the other syndromes during the course of the disease. In almost one fourth of patients with congestive heart failure, the condition developed after the histological diagnosis of AL.

The presence of one of these syndromes and an M-protein in the serum or urine is a strong indication of the presence of AL and requires appropriate biopsies for diagnosis.

*Laboratory Findings*

*Hematologic.* Anemia is not a prominent feature in AL (Table 3). Multiple myeloma, renal insufficiency, and gastrointestinal bleeding are the most common causes of anemia. Of 20 patients with hemoglobin values less than 9 g/dL, 12 had multiple myeloma; the remainder had renal insufficiency, melena, or an unrelated cause.

The leukocyte and differential counts were usually normal. Only three patients (0.6%) had a leukocyte value of less than $2 \times 10^9$/L, and 2% had a value of $20 \times 10^9$/L or more. Leukocytosis was not directly related to AL. Thrombocytopenia (platelet count less than $100 \times 10^9$/L) was present initially in 2.6%. Leukopenia and thrombocytopenia, when present, were usually caused by chemotherapy. Thrombocytosis was relatively common; 9% of the patients had platelet values of more than $500 \times 10^9$/L. A common cause of thrombocytosis is functional hyposplenism from amyloid replacement of the spleen.[13]

**Table 2. Time From Diagnosis of Amyloid Syndromes to Diagnosis of AL and From Diagnosis of AL to Diagnosis of Amyloid Syndromes**

| Syndrome | No. | % | Time From Dx Syndrome to Dx AL, Median Mo | Time From Dx AL to Dx Syndrome, Median Mo |
|---|---|---|---|---|
| Nephrotic/renal failure | 142 | 30 | 3 | 0.5 |
| Congestive heart failure | 104 | 22 | 3 | 4 |
| Carpal tunnel | 102 | 21 | 18 | 3 |
| Peripheral neuropathy | 81 | 17 | 11.5 | 27 |
| Orthostatic hypotension | 58 | 12 | 4 | 1 |

Abbreviation: Dx, diagnosis.

**Table 3. Initial Hematologic Laboratory Data in Amyloidosis**

| | No Patients | Value | | |
|---|---|---|---|---|
| | | Median | Range | Other |
| Hemoglobin, g/dL | 474 | 12.9 | 6.6-18.6 | < 10 = 11% |
| Leukocytes, $\times 10^9$/L | 474 | 7.3 | 0.6-31.3 | < 2.0 = 0.6% |
| | | | | > 20 = 2% |
| Platelets, $\times 10^9$/L | 474 | 288 | 4-953 | < 100 = 3% |
| | | | | > 500 = 9% |
| Uric acid, mg/dL | 467 | 6.5 | 2.3-17.5 | ≥ 10 = 8% |
| Calcium, mg/dL | 472 | 9.3 | 5.2-15.8 | > 11 = 2% |
| Cholesterol, mg/dL | 290 | 233 | 51-1,360 | > 500 = 5% |
| | | | | > 300 = 27% |
| Triglycerides, mg/dL | 272 | 132 | 51-2,856 | > 500 = 5% |
| | | | | > 300 = 13% |

This consequence is manifested by the presence of Howell-Jolly bodies.

*Other blood studies.* Hypercalcemia (calcium value more than 11 mg/dL) occurred in only 11 patients (2%) and was caused by multiple myeloma in all 11. The serum cholesterol value was elevated in almost one half of the patients, and the triglyceride value was increased (more than 200 mg/dL) in 29%. Four patients had a triglyceride level of more than 1,000 mg/dL. One patient presented with acute pancreatitis associated with hyperlipidemia.

The carotene value was low (less than 48 μg/dL) in 6% of patients. Most of these patients had malabsorption caused by autonomic neuropathy. The serum $B_{12}$ level was less than 190 μg/L in only 5% of patients. One patient had pernicious anemia.

*Renal and liver function.* Renal insufficiency was present in almost one half of patients at the time of diagnosis; 20% had a serum creatinine value of 2.0 mg/dL or more (Table 4). Proteinuria was present at diagnosis in 73%. The serum alkaline phosphatase level was increased in one

**Table 4. Serum Creatinine Value at Diagnosis of Amyloidosis**

| | % 327 Males | % 146 Females | Total (n = 473), % |
|---|---|---|---|
| Normal* | 49 | 53 | |
| Elevated, mg/dL | | | |
| 1.3-1.9 | 29 | | 25 |
| 1.0-1.9 | | 30 | |
| ≥ 2.0 | 22 | 17 | 20 |
| Range, mg/dL | 0.6-11.7 | 0.4-14.6 | 0.4-14.6 |
| Median, mg/dL | 1.3 | 0.9 | 1.1 |

*Normal values (mg/dL) are < 1.3 for males and < 1.0 for females.

Table 5. Liver Function in Amyloidosis

| | No. Patients | Value | | |
|---|---|---|---|---|
| | | Median | Range | Other |
| Alkaline phosphatase, U/L (normal, <250) | 468 | 169 | 79-3,660 | >250 = 26% |
| AST U/L (normal, <31) | 470 | 27 | 9-351 | >31 = 34%<br>>100 = 3% |
| Bilirubin, mg/dL | | | | |
| Direct | 466 | 0.1 | 0-11.3 | >0.3 = 8% |
| Total | 466 | 0.6 | 0.1-15.7 | >1.1 = 11%<br>>2 = 3% |
| Serum albumin, g/dL | 463 | 2.9 | 0.8-4.6 | <3 = 51%<br><2 = 12% |
| Prothrombin time, seconds | 332 | 12 | 9-33 | >13 = 16% |

Abbreviation: AST, aspartate aminotransferase.

fourth. The serum glutamic-oxaloacetic transaminase value was increased in only one third. Hyperbilirubinemia was an infrequent finding, but when present it indicated a short survival. Hypoalbuminemia was common, and the albumin level was less than 2 g/dL in 12% (Table 5). The prothrombin time was elevated in only one sixth of patients (Table 5).

*Serum proteins.* The serum protein electrophoretic pattern showed a localized band or spike in 48% of the patients. When present, it was modest in size (median value, 1.4 g/dL) (Fig 8). Only 7% had an M-spike of 3 g/dL or more. Hypogammaglobulinemia was found in one fifth of patients (Table 6).

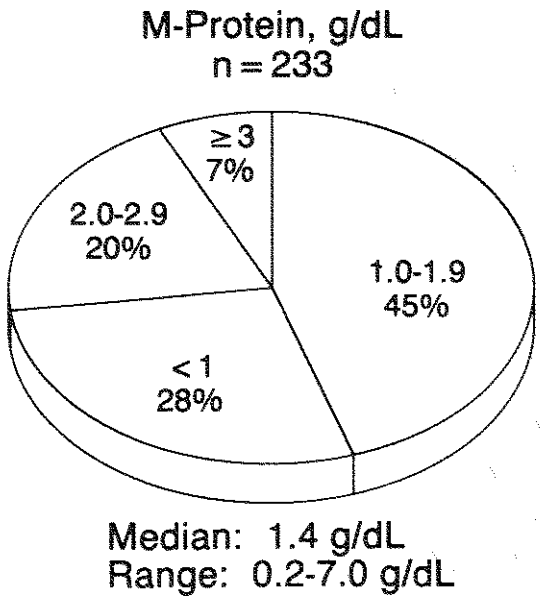


Fig 8. Size of serum M-protein in AL by cellulose acetate electrophoresis.

Table 6. Serum Protein Electrophoretic Pattern in Amyloidosis

| | Total % 463 |
|---|---|
| Hypogammaglobulinemia | 20 |
| Normal | 31 |
| γ Band | 38 |
| β Band | 10 |
| Polyclonal | 1 |
| Total | 100 |

M-spike: median, 1.4 g/dL (233 patients).

Immunoelectrophoresis of the serum showed an M-protein in 72% of patients (Fig 9). Only 48% had a monoclonal intact immunoglobulin, and 24% had a free monoclonal light chain in the serum (Bence Jones proteinemia). λ Light chains were noted in the serum of 70% of patients with an M-protein; this figure contrasts with that for patients with multiple myeloma, in whom only one third have λ light chains.

*Urinary proteins.* Ninety percent of patients had an albumin component shown by electrophoresis of an adequately concentrated urine specimen. The globulin peak was often small and not recognizable as an M-protein. Immunoelectrophoresis and immunofixation are necessary to detect the monoclonal light chain in this setting. In 443 patients the total urinary protein value ranged from 0.1 to 24.1 g/24 hours (median, 1.2 g/24 h). Thirty-six percent excreted 3.0 g/24 hours or more (Fig 10). An M-spike was

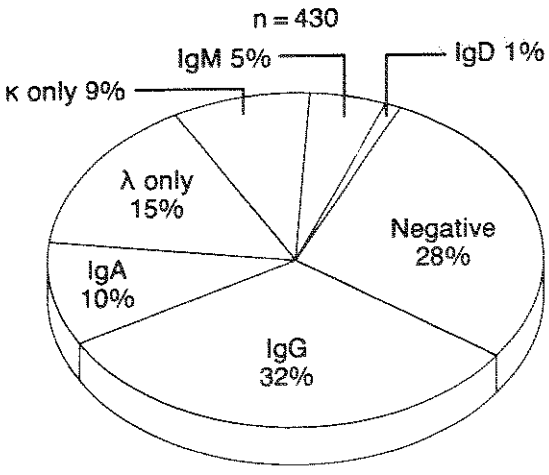


Fig 9. Type of serum M-protein in AL by immunoelectrophoresis or immunofixation.

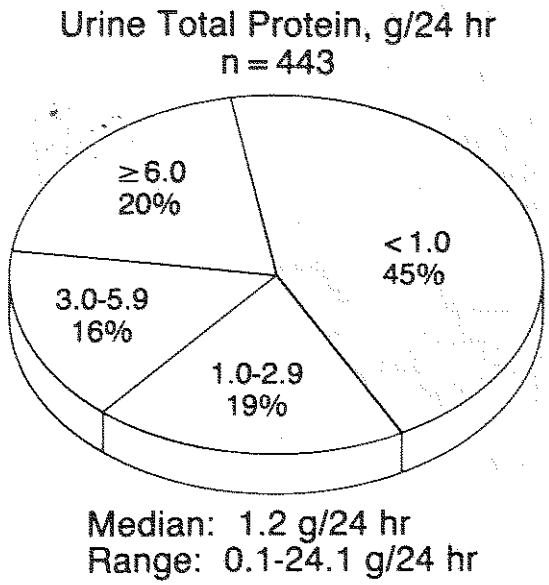


Fig 10. Urine total protein per 24 hours in AL.

detected in the urine in 285 patients, but the size of the M-protein was small (Fig 11).

Immunoelectrophoresis and/or immunofixation of an adequately concentrated urine specimen showed a monoclonal light chain in 73% of patients; 68% of those with a monoclonal light chain were λ (Fig 12). The prevalence of an M-protein in the serum or urine did not differ significantly among those with congestive heart failure, orthostatic hypotension, nephrotic syndrome, or peripheral neuropathy.

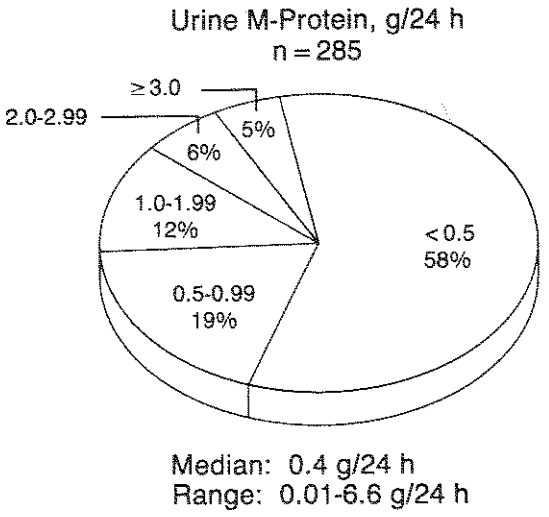


Fig 11. Size of urine M-protein in AL.

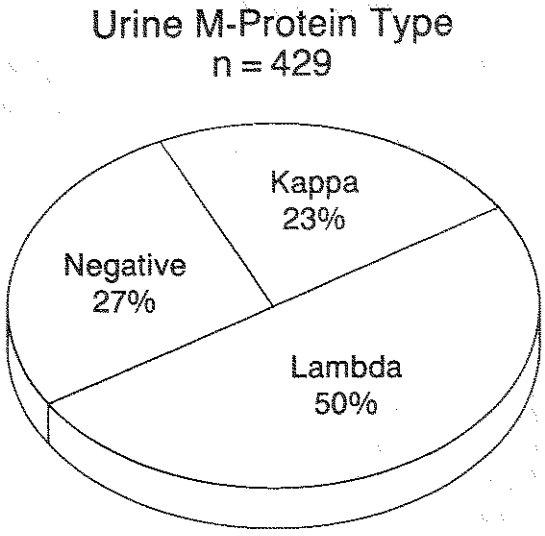


Fig 12. Urine M-protein type in AL.

An M-protein was found in the serum or urine in 89% of patients (in whom both tests were performed) at the time of diagnosis of AL (Fig 13). Twenty of 43 patients without an M-protein in the serum or urine had positive immunohistochemical stains or evidence of monoclonal proliferation of plasma cells in the bone marrow. Seven other patients had an M-protein in their serum or urine 30 days before or after the diagnosis. The remainder had typical features of AL.

*Bone marrow.* Sixty percent of patients had less than 10% plasma cells in the marrow; 18% had 20% or more plasma cells (Table 7). Of the

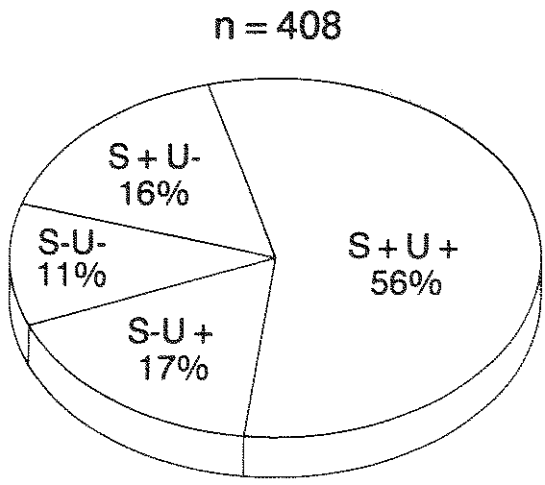


Fig 13. Serum (S) and urine (U) M-protein in AL.

**Table 7. Bone Marrow Plasma Cells in Amyloidosis (n = 391)**

| Plasma Cells (%) | % Patients |
|---|---|
| ≤5 | 44 |
| 6-9 | 16 |
| 10-19 | 22 |
| ≥20 | 18 |
| Total | 100 |
| Median, 7; range, 1-95 | |

72 patients with 20% or more plasma cells, 45 had unmistakable features of multiple myeloma including osteolytic lesions (22 cases), M-spike 3 g/dL or more (5 cases), urine M-protein value more than 2 g/24 h (9 cases), or hemoglobin value less than 10 g/dL (9 cases) (Table 8). Eighty-six patients had 10% to 19% bone marrow plasma cells. Osteolytic lesions were found in seven patients, a serum M-protein value more than 3 g/dL in two, a urine M-protein value more than 2 g/24 h in eight, and hemoglobin value less than 10 g/dL in five. Of the 71 patients with multiple myeloma present at diagnosis, 67 had 10% or more plasma cells in the marrow. In addition, nine patients with 10% or more bone marrow plasma cells had osteoporosis or compression fractures.

*Bone lesions.* Roentgenograms were normal in 71% of patients. Lytic lesions were found in 39 patients, fractures in 8, and osteoporosis in 11. All 39 patients with lytic lesions had multiple myeloma.

### *Organ System Involvement*

*Cardiac and circulatory.* The heart is often involved in patients with AL. Congestive heart failure was present in 17% of our patients at the time of diagnosis and developed during the course of the disease in an additional 5% (Fig 7).

Electrocardiography frequently shows either low voltage in the limb leads or characteristics consistent with anteroseptal infarction (loss of anterior forces), but there is no evidence of myocardial infarction at autopsy.[41] Arrhythmias, including atrial fibrillation, atrial or junctional tachycardia, ventricular premature complexes, or heart block, are common electrocardiographic features.[39]

Echocardiography is a valuable technique for the detection and evaluation of amyloid heart disease. The major echocardiographic features are increased thickness of the left and right ventricular walls, abnormal myocardial texture (granular sparkling), atrial enlargement, valvular thickening and regurgitation, pericardial effusion, and abnormal diastolic and, ultimately, systolic ventricular function. Restriction is associated with marked shortening of the deceleration time and development of cardiac symptoms.[23]

We found a relationship between increasing thickness of the ventricular wall and septum (0.5 × thickness of free wall left ventricle in diastole plus 0.5 × thickness of ventricular septum) and prevalence of congestive heart failure. Patients with greater wall thickness (that is, infiltration of amyloid) also had a higher frequency of associated echocardiographic abnormalities such as left atrial enlargement, granular sparkling, and reduced systolic function. The median duration of survival was 2.4 years for patients with ventricular septal thicknesses of 12 mm or less, whereas it was only 0.4 year for patients with thickness of 15 mm or more.[7]

Serial echocardiography is also useful for documenting the progression of disease. Congestive heart failure, arrhythmias, or both developed or worsened in 14 of 27 patients with cardiac AL who had serial echocardiographic studies. These 14 patients had significant increases in left ventricular wall thickness and in left atrial size and a decrease in fractional ventricular shortening. Thirteen patients without clinical progression showed no significant echocardiographic changes.[8]

Doppler echocardiographic assessment of diastolic function in AL shows impressive abnor-

**Table 8. Characteristics of Patients With Amyloidosis and Multiple Myeloma**

| Bone Marrow Plasma Cells | | Myeloma Features, No. Patients | | | | |
|---|---|---|---|---|---|---|
| % | No. Patients | Hemoglobin, < 10 g/dL | Lytic Lesions* | Serum M-spike, ≥ 3.0 g/dL | Urine M-protein, ≥ 2 g/24 h | Total |
| ≥20 | 72 | 9 | 22 | 5 | 9 | 45 |
| 10-19 | 86 | 5 | 7 | 2 | 8 | 22 |

*Nine additional patients had osteoporosis or compression fractures.

**Table 9. Echocardiographic Features of Amyloidosis (n = 157)**

| Feature | % |
|---|---|
| Normal | 35 |
| Diastolic Dysfunction | 18 |
| Systolic Dysfunction | 5 |
| Diastolic and Systolic Dysfunction | 16 |
| Abnormal (nonspecific) | 26 |

malities. Early cardiac amyloidosis is characterized by abnormal relaxation, whereas advanced involvement (mean wall thickness of 15 mm or more) is characterized by restrictive hemodynamics. The most common diastolic abnormality is a short deceleration time consistent with restriction in the advanced stages of the disease. Thickening of the valves is usually seen. Valvular regurgitation is common, but the degree is mild and rarely of clinical significance.

Results of echocardiography were abnormal in almost two thirds of our patients at the time of diagnosis (Table 9). Almost one half of patients had septal thickness of 15 mm or more (Table 10). The median duration of survival was 7 months for patients with left ventricular septal thickness of 15 mm or more and 26 months for those with thickness less than 15 mm ($P = .0003$) (Fig 14). The ejection fraction was normal in 80%. The median duration of survival was 15 months for those with a normal ejection fraction (more than 55%) and 3 months for those with an ejection fraction less than 40% ($P = .0027$) (Fig 15). Ejection fraction was less than 30% in only eight (2%) patients. Amyloid infiltration is frequently misinterpreted as concentric left ventricular hypertrophy. All patients with biopsy-proven AL should have an echocardiographic study.

Hypertrophic obstructive cardiomyopathy or constrictive pericarditis may be difficult to differentiate from AL. Intermittent claudication of the jaw was reported in almost 10% of patients with AL.[16] Arm and calf claudication may also occur. Orthostatic hypotension was found at the

**Table 10. Septal Thickness in Amyloidosis (n = 121)**

| Thickness (mm) | % |
|---|---|
| ≤ 11 | 24 |
| 12-14 | 29 |
| 15-19 | 36 |
| ≥ 20 | 11 |
| Median, 14; range, 8-22 | |

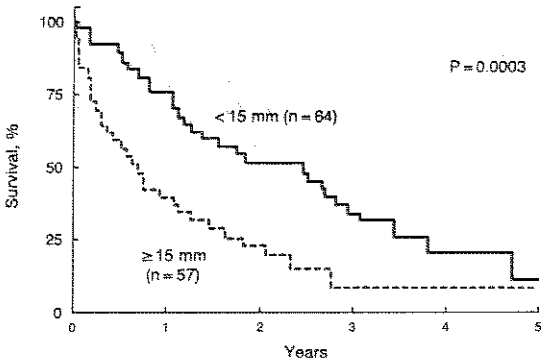


**Fig 14. Survival in AL, by septal thickness.**

time of diagnosis in 11% of our patients (Fig 7). It was usually caused by involvement of the autonomic nervous system. Orthostatic hypotension may be severe enough to produce lightheadedness and syncope preventing ambulation.

*Renal.* Involvement of the kidneys is very common in AL and is one of the major clinical problems. Nephrotic syndrome or renal failure was present in 28% of our patients at diagnosis and developed in 2% during the course of their disease (Fig 7 and Tables 2 and 4). The laboratory features of the 118 patients with nephrotic syndrome are shown in Table 11. Amyloid is first deposited in the mesangium of the glomerulus and later extends along the basement membrane. The degree of proteinuria does not correlate with the extent of amyloid deposition in the kidney. The kidneys may be enlarged but are often of normal size or even contracted and smaller than normal. Hypertension may develop as renal failure progresses.

Nephrogenic diabetes insipidus, adult Fanco-

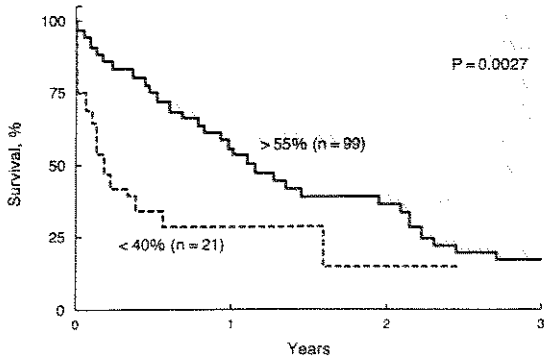


**Fig 15. Survival in AL, by ejection fraction.**

**Table 11. Laboratory Features of Nephrotic Syndrome With Protein Value > 3 g/24 h in Amyloidosis (n = 118)**

| Factor | No Patients | Value | | |
|---|---|---|---|---|
| | | Median | Range | Other |
| Urine protein, g/24 h | 118 | 7.0 | 3-24 | ≥ 10 = 31% |
| Serum albumin, g/dL | 116 | 2.1 | 0.8-3.8 | ≤ 2 = 47% |
| | | | | ≤ 1 = 3% |
| Creatinine, mg/dL | 118 | 1.3 | 0.6-8.5 | ≥ 2 = 25% |
| Serum cholesterol, mg/dL | 100 | 312 | 149-1,360 | > 500 = 16% |
| | | | | > 300 = 55% |
| Triglycerides, mg/dL | 93 | 228 | 61-2,865 | > 500 = 12% |
| | | | | > 300 = 27% |

ni's syndrome, priapism, and renal vein thrombosis have been reported in patients with AL.

Kidney biopsy specimens that have the appearance of minimal-change glomerulopathy must be carefully stained for amyloid in adults because minimal deposits of amyloid may be overlooked. Immunotactoid glomerulopathy[25] must be differentiated from amyloid. Light-chain deposits may be seen in addition to amyloid fibrils.[3]

*Gastrointestinal.* Histological involvement of the gastrointestinal tract occurs in most patients with AL but is usually asymptomatic. Radiographic abnormalities include decreased peristalsis and thickening of the mucosa. A malabsorption pattern is uncommon.[4] Malabsorption occurs in less than 5% of patients.

Motor dysfunction of the gastrointestinal tract may result from extensive mucosal deposition of amyloid but is much more often attributable to autonomic dysfunction. In some instances, apparent mechanical bowel obstruction may actually represent pseudo-obstruction, for which surgical treatment is not helpful and actually dangerous. Ascites may occur.

Macroglossia occurs in about 10% of patients. It may interfere with eating and may be severe enough to obstruct the airway. Recurrent hemorrhagic bullae of the oral cavity are not uncommon. Loss of taste has been noted.

Symptomatic gastric amyloidosis occurs in about 1% of patients and is usually manifested by hematemesis or nausea and vomiting. Amyloidosis of the stomach may present as a gastric mass resembling a carcinoma.[36]

The liver is frequently involved by amyloidosis and was palpable initially in one fourth of our patients. Elevation of the serum alkaline phosphatase value occurs in one fourth of patients, but hyperbilirubinemia and liver failure are uncommon.[12] Spontaneous rupture of the spleen may be the initial manifestation.

*Respiratory.* Although histological evidence of AL in the lung is common, it is usually asymptomatic.[5] Chest radiography shows an interstitial infiltration or a reticular nodular pattern but is not diagnostic. Amyloid may infiltrate the alveolar septa and produce dyspnea. Diffuse interstitial pulmonary amyloidosis has also been described. Tracheobronchial involvement or solitary pulmonary nodules remain localized and do not progress to systemic amyloidosis.[6]

*Neurological.* Sensorimotor peripheral neuropathy occurred initially in 17% of our patients (Fig 7 and Table 2). The neuropathy is usually distal, symmetric, and progressive. Dysesthetic numbness may be extremely troublesome. The lower extremities are involved earlier and more severely than the upper. Autonomic dysfunction may be a prominent feature and is often manifested by orthostatic hypotension, diarrhea, or impotence. Axonal degeneration with predominant involvement of the small myelinated and unmyelinated fibers is seen histologically. Cranial neuropathy is rare but may be the initial manifestation of AL.[42]

Carpal tunnel syndrome was the initial presenting finding in 21% of our patients with AL. One must consider the possibility of AL in any patient with carpal tunnel symptoms and an M-protein in the serum or urine. However, elderly patients may present with carpal tunnel syndrome in which the amyloid consists of normal transthyretin (prealbumin) rather than κ or λ light chains. In these patients, systemic amyloidosis rarely develops.[32]

*Miscellaneous.* Petechiae, ecchymoses, papules, plaques, nodules, tumors, bullous lesions, alopecia, and dystrophy of the nails are common in AL.[38] Amyloidosis involving periarticular structures can closely resemble seronegative rheumatoid arthritis. Deposits of amyloid in the periarticular areas of the shoulder may produce pain, swelling, and prominence (shoulder pad sign). Extensive deposits of amyloid may produce pseudohypertrophy of skeletal muscles. Large amyloid deposits (amyloidomas) may present as large tumors in the mediastinum or retroperitoneum.[26]

Bleeding may be a major complication of AL. In addition to the isolated deficiency of factor X, a decrease of vitamin K–dependent clotting factors, increased antithrombin activity, increased fibrinolysis, and intravascular coagulation may all contribute to bleeding. Prolongation of the thrombin time occurs in about 40% of patients with AL.[9]

## DIAGNOSIS

AL was diagnosed before death in 98% of our 474 patients. The possibility of AL must be considered in every patient who has an M-protein in the serum or urine and who also has nephrotic syndrome or renal insufficiency, congestive heart failure, sensorimotor peripheral neuropathy, carpal tunnel syndrome, hepatomegaly, or idiopathic malabsorption. Any patient older than 30 years who has an unexplained nephrotic syndrome or renal insufficiency should have electrophoresis, immunoelectrophoresis, and immunofixation of the serum and urine performed. The presence of a monoclonal light chain in the urine of a person with nephrotic syndrome is almost always caused by AL or light-chain deposition disease.

AL diagnosis requires the demonstration of amyloid deposits in tissue (Fig 16). Congo red produces an apple-green birefringence under polarizing light and is the most commonly used stain. AL, senile systemic amyloidosis, familial amyloidosis, and localized amyloidosis are all resistant to potassium permanganate, whereas secondary amyloidosis typically loses its affinity for Congo red and its polarization characteristics after pretreatment with potassium permanganate, but exceptions occur and the technique is unreliable. The best approach to classification is the use of antisera to protein A, κ, λ, transthyretin (prealbumin), and $\beta_2$M.[33] In some patients, staining results with Congo red or the metachromatic stains are negative but electron microscopy shows typical amyloid fibrils. The diagnoses in these instances must be evaluated carefully.

A bone marrow aspiration and biopsy should be performed initially to determine the number of plasma cells and whether they are monoclonal (producing κ or λ light chains). We found that 11 of 13 patients with AL but no detectable monoclonal immunoglobulin in the serum or urine had a clonal excess of plasma cells in the bone marrow.[11] Virtually all patients with AL have an M-protein in the serum or urine or a monoclonal population of plasma cells in the bone marrow. The bone marrow biopsy specimen should be stained for amyloid because stain results were positive in 56% of our patients.

The next diagnostic procedure should be abdominal fat aspiration; the aspirate was positive in 80% of patients in our series. The specimen must be stained properly with Congo red and interpreted by an experienced pathologist.[18] We found that in 170 (89%) of our 191 patients who had both bone marrow and subcutaneous fat biopsies performed, one or both stained positive. Rectal biopsy results were positive in only one of seven patients with negative results from fat and bone marrow examination.

If biopsy results of these sites are negative, tissue should be obtained from a suspected involved organ such as the kidney, liver, heart, or sural nerve. In our experience, a renal biopsy is usually unnecessary. Renal biopsy has a high

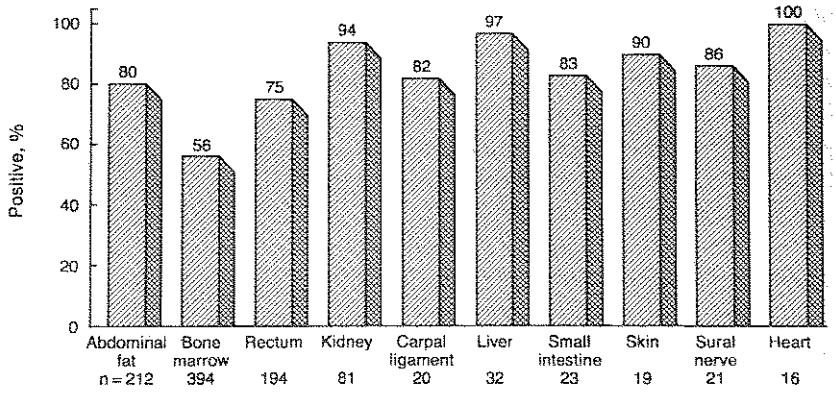


**Fig 16. Results of biopsy in AL.**

incidence of positive findings (Fig 16), but the procedure is more difficult than subcutaneous fat, bone marrow, or rectal biopsies. The frequency of hematuria after renal biopsy is not greater in patients with AL than in patients without AL. It should be kept in mind that a negative renal biopsy result does not exclude AL. Of our five patients with negative kidney biopsy results, three had unrelated renal disease, one had myeloma of the kidney, and one had nephrotic syndrome, presumably caused by AL.

Results of liver biopsy are almost always positive (Fig 16), but the procedure may cause bleeding and in rare instances the liver has ruptured. However, we have seen bleeding in only two of more than 80 patients with AL who underwent needle biopsy of the liver. In both patients the bleeding resolved with bed rest. Our patient with a negative liver biopsy had a history of alcohol abuse. Tissue obtained at carpal tunnel decompression should be stained for amyloid; immunohistochemical staining with κ, λ, and transthyretin antisera is necessary. The sural nerve is an excellent source of biopsy material in patients with peripheral neuropathy (Fig 16). However, this source is appropriate only if the peripheral neuropathy is severe because a sural nerve biopsy will result in loss of local sensation. Three of our patients with peripheral neuropathy had negative sural nerve biopsy results; one of these had an atypical motor neuropathy that was probably unrelated to the AL. Endomyocardial biopsy results are always positive in our experience and the test is associated with little risk.

Congo red is a more reliable stain than methyl violet, crystal violet, or thioflavin T. Electron microscopy may be necessary for the identification of the typical fibrils. Nonamyloid fibrillar glomerulopathy such as immunotactoid glomerulopathy must be distinguished from amyloidosis.[24] Light-chain deposition disease must also be differentiated from AL.[3]

$^{123}$I-labeled serum amyloid P component can be used for locating and monitoring the extent of systemic amyloidosis.[20] Increased uptake of technetium-99m–pyrophosphate is not reliable.[10]

*Prognosis and Survival*

The mean duration of survival after diagnosis in an earlier Mayo Clinic series of 81 patients seen between 1935 and 1959 was 4.9 months.[27] In a Mayo Clinic series of 193 patients seen between 1960 and 1972, the median duration of survival after histological diagnosis of amyloid was 14.7 months for patients with AL and 4 months for those with AL and myeloma.[28] The median duration of survival for 229 patients with AL seen at the Mayo Clinic within 1 month of histological diagnosis from 1970 through 1980 was 12 months; less than one fourth were alive at 3 years.[30]

In the current series of 474 patients with AL seen within 1 month of diagnosis, the median duration of survival was 13.2 months (Fig 17). Seven percent survived for 5 or more years, and only 1% were alive at 10 years. Survival varied greatly among the various syndromes (Fig 17 and Table 12). For example, the median duration of survival was 4 months for the 80 patients presenting with congestive heart failure. The groups were arranged in a hierarchical fashion; that is, patients were placed only in the first group in which the syndrome occurred. Thus, none of the 114 patients who presented with renal disease had either congestive heart failure or orthostatic hypotension but some may have had peripheral neuropathy. The 40 patients with peripheral neuropathy had no evidence of congestive heart failure, orthostatic hypotension, or nephrotic syndrome at diagnosis and had a median duration of survival of 26 months. Death in these patients was usually the result of subsequent cardiac or renal failure.

The presence of congestive heart failure was an important prognostic finding. The median duration of survival was 4 months for the 80 patients presenting with congestive heart failure and 16 months for the 394 patients without congestive heart failure ($P < .0001$) (Fig 18).

Death was attributed to cardiac involvement from congestive heart failure or arrhythmias in 48% of 285 patients who had died. The actual percentage of cardiac deaths is probably higher because some patients whose death was ascribed to AL almost certainly had a terminal cardiac arrhythmia. Death was attributed to infection in 8% and renal failure in 6%.

Multivariate analysis was applied to data

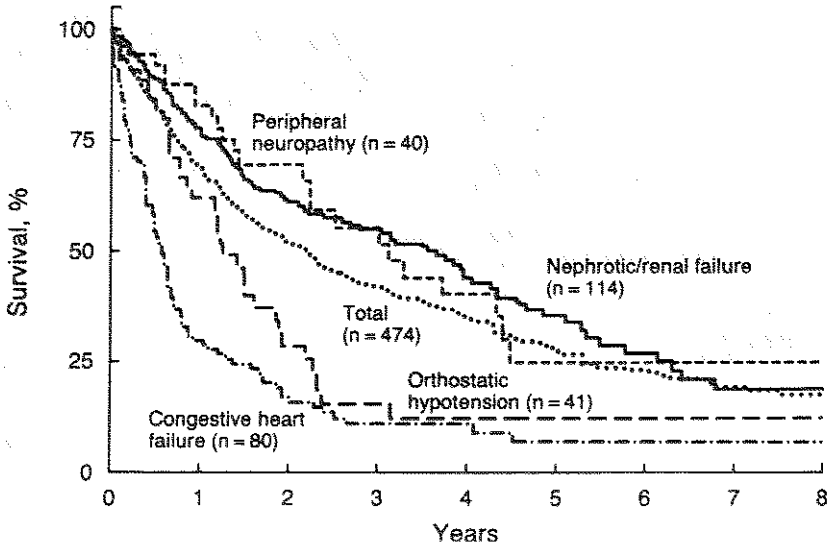


**Fig 17. Survival in AL, by syndrome, arranged hierarchically.**

from 168 patients with AL seen at the Mayo Clinic from 1970 through 1980 in whom all laboratory and clinical studies were performed within 1 month of diagnosis. The proportional-hazards method of Cox identified four variables that had a significant influence on survival during the first year, congestive heart failure, urinary light chain, hepatomegaly, and amount of weight loss. The proportional-hazards model identified elevated serum creatinine value, diagnosis of multiple myeloma, presence of orthostatic hypotension, and serum M-protein as having a highly significant adverse influence on survival in patients who lived 1 year after diagnosis.[31]

The $\beta_2$M level is a useful prognostic factor. Median duration of survival was 33 months in AL patients with a level less than 2.7 μg/mL and 11 months for those with an elevated level. When the analysis was restricted to patients with normal renal function, those with an elevated $\beta_2$M level also had a significantly shortened survival.[15] Thus, the impact of $\beta_2$M level on survival was independent of the serum creatinine level. We have also shown that a plasma cell labeling index greater than 0% predicted a survival disadvantage (14.1 months *v* 30.9 months) ($P < .05$) in 103 AL patients without myeloma.[14] Patients with a normal serum creatinine level and urinary protein value less than 2 g/24 h at diagnosis are unlikely to require dialysis.[17] We have shown that Doppler echocardiographic studies are helpful for predicting outcome in patients with cardiac AL. The 1-year survival of patients with an initial deceleration time of 150 milliseconds or less was 55%, whereas 90% lived for more than 1 year when the deceleration time was more than 150 milliseconds ($P < .01$).[22]

**Table 12. Survival in Amyloidosis, Hierarchical**

| | No. | % | Years | Months |
|---|---|---|---|---|
| Congestive heart failure | 80 | 17 | 0.3 | 4 |
| Orthostatic hypotension | 41 | 9 | 1.0 | 12 |
| Nephrotic | 114 | 24 | 1.4 | 16 |
| Peripheral neuropathy | 40 | 8 | 2.1 | 26 |
| Total group | 474 | | 1.1 | 13 |

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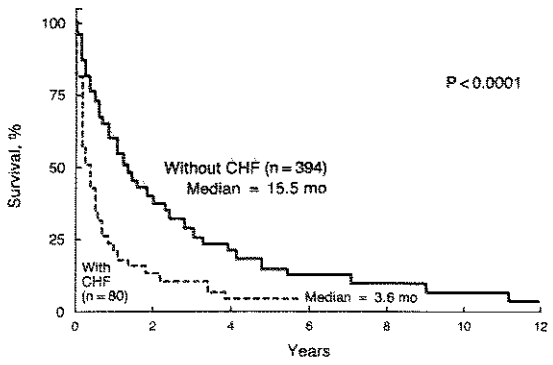


**Fig 18. Survival in AL, by presence of CHF.**

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