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Original Article

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Renal involvement in systemic amyloidosis*

An Italian collaborative study on survival and renal outcome

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Abstract

Background. Few data are available from large population-based studies on survival and renal outcome of patients with renal involvement and different types of systemic amyloidosis.

Methods. Two hundred and ninety of over 373 patients affected from systemic amyloidosis with renal involvement diagnosed in Italy between January 1995 and December 2000 were followed from diagnosis to death or until the last available clinical control. Eighty-three patients were excluded from analysis either because the amyloid type remained undetermined or they were lost at follow-up. Clinical and laboratory information was collected according to the different types of amyloidosis using a specific form which included renal function with 24 h proteinuria at diagnosis and at the end of follow-up, the type and the date of onset of dialysis and the kind of treatment they underwent.

Results. The median time of follow-up was 24 months in primary (AL) amyloidosis (range: 1–88 months), 16 months in AL with associated multiple myeloma (MM + AL: range 1–76 months), 30 months in reactive (AA) amyloidosis (range: 1–99 months) and 52 months in patients with familial forms (AF: range 14–82 months). Patients with AL showed a significantly shorter survival than AA. Despite no significant differences of renal outcome or survival on dialysis being observed between the two groups, a lower renal survival with a higher number of patients who progressed to end-stage renal disease (ESRD) was observed in patients with AA. Overall survival was markedly improved in patients with AL who underwent a specific therapy (conventional chemotherapy or autologous stem cell transplantation (ASCT)) even in the absence of a positive kidney response. Multivariate analysis showed cardiac involvement and specific therapy to significantly influence survival in AL whereas age, serum creatinine (sCr) and heart involvement significantly affected survival in AA. In both groups, sCr and heart involvement were the most relevant predictors for renal outcome, together with urinary protein excretion, in patients with AA.

Conclusions. Our results show a worse survival in AL due to the higher prevalence of heart involvement in this group and emphasize that a specific therapy significantly prolongs survival and slows the progression of renal disease in patients with AL. We suggest that a late nephrological referral is likely the cause of the higher sCr found at presentation in patients with AA and probably accounts for the lower renal survival observed in the short term in these patients. At the time being, renal transplantation and ASCT are still rare therapeutic options for renal patients affected from systemic amyloidosis.

Keywords: AA amyloidosis; AL amyloidosis; renal amyloidosis; renal outcome; survival

Introduction

Renal involvement is quite common in systemic amyloidosis of any type [1]: AL (primary or immunoglobulin light chain associated) [2–4], AA (secondary or reactive to chronic inflammation) [5,6] or AF (heredofamilial) [7]. However, data on survival and renal outcome of patients with renal amyloidosis are usually limited to patients either with AL or AA type [2,6,8]. Unfortunately, no epidemiological data are available from a large cohort of patients suffering from different types of systemic amyloidosis and renal involvement.

In addition, dated and scarce is the information concerning the incidence and prevalence of AL and AA amyloidosis among the causes of end-stage renal disease (ESRD). Indeed, in 1989 the combined report on regular dialysis and transplantation in Europe reported that amyloidosis was

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responsible for 1.6% of all patients with ESRD starting dialysis in that year and that three quarters of these patients suffered from AA due to chronic inflammatory diseases, among which rheumatoid arthritis was the most prevalent [9]. Although the frequency of the disease in the different European registries of renal biopsies is well known [10,11], since then no data have ever been published about the relative frequency of AA and AL with the exception of our recent report which showed a clear prevalence of AL [12].

At that time, however, the characterization of amyloid deposits was essentially based on major clinical and laboratory criteria such as a history of long-standing inflammatory process or the presence of a monoclonal component (MC), either in serum or urine, while the screening for heredofamilial forms had not yet been introduced into clinical practice [13].

In regard to AL, survival has greatly improved from the 13.2 months described by Kyle *et al.* in 474 patients from the Mayo Clinic in 1995 [3] to 46 months reported by Palladini *et al.* in 645 patients followed at Pavia Amyloid Centre in 2003 [4]. In both studies, renal involvement occurred in about two-thirds of the overall population examined with 18% of patients reported by Palladini *et al.* who progressed to ESRD and dialysis after a median time of only 7.5 months [8].

Survival was markedly influenced in both series by heart involvement [3,4].

Few studies addressed survival of patients with AA amyloidosis. Gertz *et al.* described a median survival of 24 months in 1991 [5], Joss *et al.* reported an almost doubled figure in 2000 [6] and Lachman *et al.* recently reported as much as 10 years median survival in a large cohort of patients in the UK [14]. None of these studies described a significant heart involvement. To date, only two papers have described the clinical course and outcome of patients with systemic amyloidosis on dialysis [15,16].

Diagnostic approach and treatment has greatly improved in the past years both for AL and for underlying diseases responsible for AA providing new opportunities to improve survival and renal outcome. In particular, autologous stem cell transplantation (ASCT) has become more common for patients with AL as well as renal or heart transplantation in cases with severe organ failure [2,17]. However, no one knows the current policy of different nephrological or internal medicine centres towards these emerging treatments as well as the results in terms of either renal or haematologic response. For this reason, we have set up a retrospective survey throughout Italy on survival and renal outcome of patients with different types of systemic amyloidosis and renal involvement.

Patients and methods

The clinical and laboratory records of 373 patients with biopsy-proven systemic amyloidosis with renal involvement diagnosed in Italy between January 1995 and December 2000 were retrospectively reviewed for follow-up analysis.

Patients were collected from 45 major renal units representing 35% of all nephrological centres associated to the Italian Society of Nephrology (SIN) and from three internal medicine and one haematology units associated to the Italian Society of Amyloidosis (SIA) (see the appendix).

All patients had evidence of amyloid deposits on renal biopsy or, according to criteria for non-invasive diagnosis of amyloidosis [18], at an alternate site such as abdominal fat tissue (AFT), provided they showed typical signs of renal involvement (UPE $>$ 0.5 g/day and/or renal insufficiency) and did not have diabetic nephropathy. Amyloid cardiomiopathy was diagnosed when typical features of diastolic dysfunction, granular sparkling of myocardial texture and increased interventricular septum thickness on echocardiography occurred in the absence of other potential causes of left ventricular hypertrophy. Detailed characteristics of the population have been reported elsewhere [12].

Inclusion criteria

All patients with the characterization of amyloid deposits and at least one clinical control after diagnosis were included in the study.

Eighty-three out of 373 patients (22% of the overall population) were excluded from analysis at follow-up either because the type of amyloidosis remained undetermined ($n = 26$) or because they were lost at follow-up ($n = 57$). Of these, 39 were AL 5 with an associated multiple myeloma (AL + MM) and 18 were AA. Two hundred and ninety patients were finally selected for follow-up analysis: 167 (57%) were affected from AL, 31 (11%) from AL + MM, 86 (30%) from AA and 6 (2%) from AF. Characteristics of the selected patients are reported in Table 1.

Data collection

Follow-up ranged from diagnosis to death or until the last available clinical control.

Data were collected from December 2001 to December 2003 and included the date of last clinical control and eventual of death with the relative serum creatinine (sCr) and UPE, cause of death, date of onset and type of dialysis and therapy options including ASCT and kidney transplantation. Therapy of patients affected from AL was carefully recorded according to whether they received only a supportive or a specific therapy. Specific therapy included conventional chemotherapy used for an adequate period of time (at least 6 months) or ASCT. Consequently, AL patients who underwent a specific therapy were arbitrarily considered to have fulfilled minimum criteria for potentially effective therapy (treated group) regardless of the type of conventional therapy they actually followed and were compared to patients who either did not follow any specific treatment or followed it inadequately (untreated group).

Because of the many different therapeutic schedules used in patients with AA and the poor drug information available, it was impossible to analyse the results in this group of patients. All patients underwent a supportive therapy for both renal insufficiency and/or nephrotic syndrome.

Cardiac involvement was present in 56 patients with AL (33%) and in 12 with AA (14%). Nine patients, 5 AL and 4 AA, had more than two organs involved.

Survival and renal outcome were calculated separately for AL, AL + MM and AA.

Table 1. Characteristics of patients

	AL	AL + MM	AA	AF	Total
Patients (%)	167 (57.6%)	31 (10.7%)	86 (29.7%)	6 (2.1%)	290
Follow-up (months)	24 (*1–88*)	16 (*1–76*)	30 (*1–99*)ˆ	52 (*14–82*)	25 (*1–99*)
Gender (M/F)	93/74	19/12	36/50	3/3	151/139
Age (years)	66 (34–87)	67 (41–88)	62 (19–86)	63 (53–68)	65 (19–88)
Serum creatinine (mg/dl)	1.2 (0.6–10.3)	1.1 (0.5–9.7)	1.6 (0.5–12.4) ˆ	2.0 (1.4–3.4)	1.3 (0.5–12.4)
UPE (g/24h)	4.9 (0–20)	2.3 (0–20)	5.0 (0.5–29.8)	1.6 (0–4)	4.8 (0–29.8)
Heart involvement	56 (33%)	14(45%)	12 (14%)	0/6	82 (29%)
Dialysis (%)°	59 (22%)	7 (3%)	37 (14%)	1 (0.3%)	104 (39%)
Renal transplantation	1	0	0	0	1
Treated patients	70	12	35	0	117
ASCT*	18	1	0	0	19

Data are referred at the time of diagnosis and are reported as medians with range. ˆ$P < 0.01$ versus AL. (°)% refers to 263 patients evaluated for renal outcome.
*ASCT: autologous stem cell transplantation.

The cause of death was systematically investigated and registered in order to differentiate the conditions directly or indirectly related to the disease from those certainly unrelated. Deaths were recorded as 'unknown' whenever the cause was not reported.

Statistics

All data are presented as medians with range. Differences between groups were evaluated using Mann–Whitney *U*-test for unpaired data or χ^2 analysis when necessary. Linear regression analysis was used to evaluate the rate of decline of renal function (1/sCr) versus time. Survival curves were derived from the Kaplan–Meier method using the Cox regression analysis to determine the variables affecting survival and log-rank test to evaluate the differences between the curves. A $P < 0.05$ was considered significant.

Results

Patient survival

The overall median time of observation was 25 months (range: 1–99 months) with 24 months for AL (range: 1–88 months), 16 months (range: 1–76 months) for AL + MM, 30 months for AA (range: 1–99 months) and 52 months for AF (range: 14–82 months).

AA had a significantly longer follow-up as compared to AL (30 months versus 24, $P < 0.01$).

AL showed a median age of 65 years (range: 34–87 years) with a slight prevalence of male gender while AA showed a similar age but with a prevalence of females (Table 1).

At the end of follow-up, 140 patients (48% of the entire population) were dead. Among these, 87 were AL (62%), 18 (13%) had MM + AL and 34 were AA (24%). Among the AF, only one patient died and for a cause unrelated to the disease. One hundred and fifty patients were still alive at the end of follow-up: 80 were AL (53%), 52 (35%) AA, 13 (9%) MM + AL and 5 (3%) AF.

The causes of death are reported in Table 2. Thirty-four deaths remained unknown and 17 were certainly not referable to amyloidosis. The remaining deaths are reported in detail and were ascribed directly or indirectly to amyloidosis.

Median survival was significantly longer in AA (79 months) than in patients with AL (37 months, $P = 0.008$) (Figure 1) with a cumulative survival at 2 years of 74% in AA and 65% in AL. Approximately 51% of patients with AA and 36% of patients with AL were still alive after 5 years. In both groups, survival was dramatically shorter in the case of heart involvement: 21 versus 57 months in AL and 21 versus 79 months in AA (Figure 2).

Table 2. Causes of death in 140 patients with renal amyloidosis

	AL	AL+MM	AA	AF	Total
Deaths	87 (62.1%)	18 (12.8%)	34 (24.3%)	1 (0.7%)	140 (48.2)
Unknown causes of death	24	3	7	0	34
Deaths unrelated to amyloidosis	11	0	5	1	17
Deaths related to amyloidosis	52	15	22	0	89
Cachessia (or disease progression)	10	10	7		27
Heart disease	31	4	5		40
Infections	3		3		6
ASCT* complications	4				4
Miscellaneous	4	1	7		12

*ASCT: autologous stem cell transplantation.

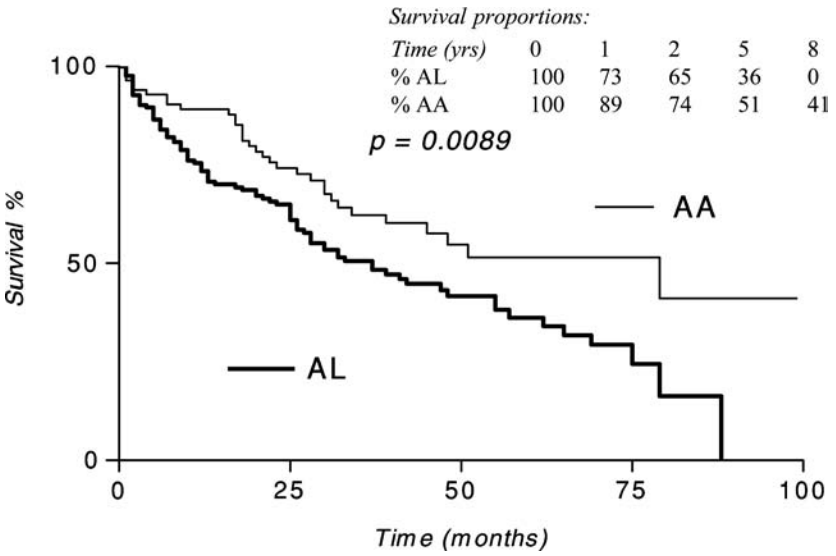

Fig. 1. Survival of 167 AL (37 months) and 86 AA patients (79 months) according to the Kaplan–Meier method.

Patients with an associated MM showed a shorter (28 months), although not significant, median survival than AL.

Analysis of factors influencing survival in the overall population of patients showed that the different types of amyloidosis, age, heart involvement and sCr significantly affected survival. However, when the above factors were examined using a Cox regression model, the role of the different types of amyloidosis was no longer evident and only age, sCr and heart involvement remained significantly correlated to patient survival (Table 3). When multivariate analysis was carried out in AL, only heart involve-

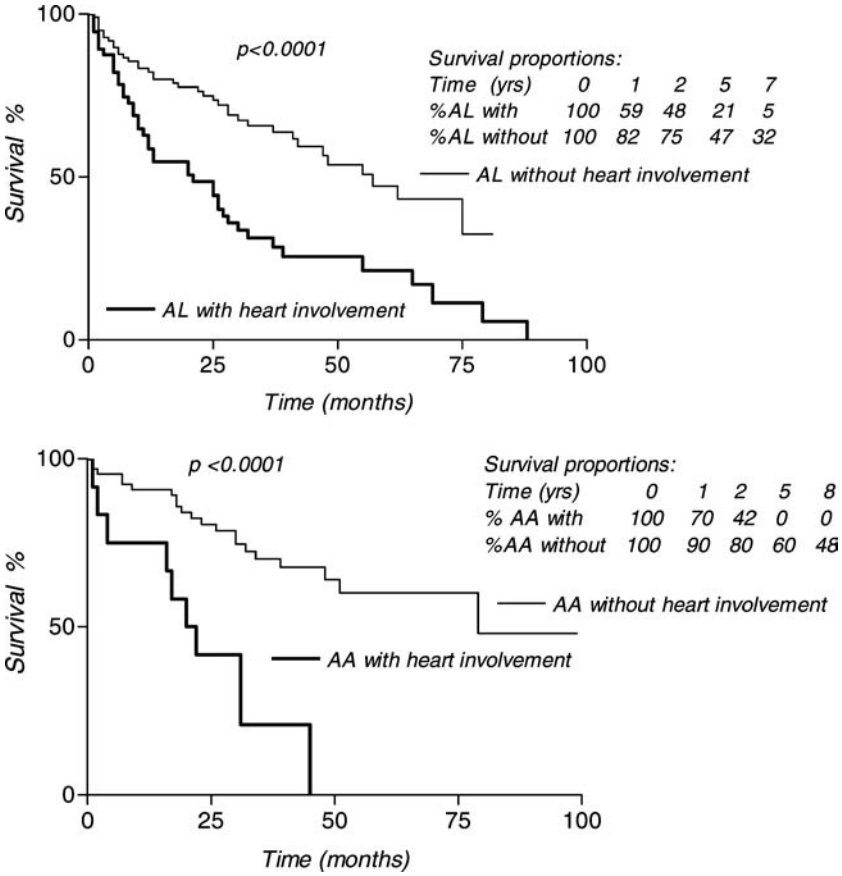

Fig. 2. *Top*: survival of 159/167 AL patients; 56 with heart involvement (median survival 21 months); 103 without heart involvement (median survival 57 months). *Bottom*: survival of 74/86 AA patients: 12 with heart involvement (median survival 21 months), 81 without heart involvement (median survival 79 months), according to the Kaplan–Meier method.

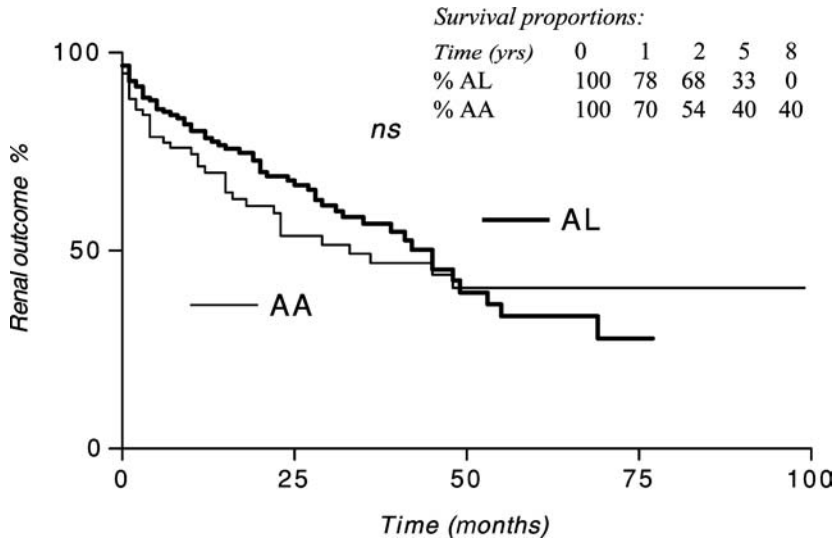

Fig. 3. Renal outcome of 152 AL patients (45 months) and 78 AA patients (33 months) according to the Kaplan–Meier method.

ment (HR 2.78, $P = 0.000$) and specific therapy (HR 0.40, $P < 0.02$) were found to significantly affect survival (Table 3). The strong influence of specific therapy on survival is clearly demonstrated by the corresponding survival curve (Figure 5, top). The kappa/lambda ratio (data not reported) did not influence the survival as well as age and sCr despite both of them showing a significant influence when examined alone. Multivariate analysis in AA showed age (HR 1.05, $P = 0.002$) and heart involvement (HR 3.4, $P = 0.002$) and sCr (HR 1.27, $P = 0.001$) as major predictors of poor survival in these patients (Table 3). Gender and UPE did not show a significant influence in both groups.

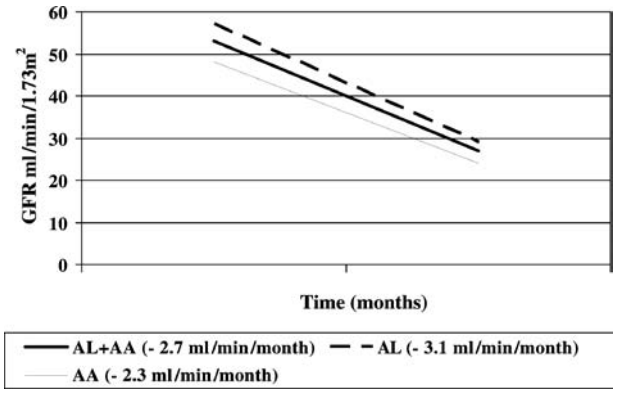

Fig. 4. The mean rate of decline of renal function according to simplified MDRD equation [19].

Renal outcome

Renal outcome was calculated using the time interval between diagnosis and the beginning of dialysis (kidney death). All patients who died before reaching ESRD were regularly 'censored'.

Renal survival curves in both AL and AA are shown in Figure 3. Despite a shorter median survival in AA (33 versus 45 months) no significant differences were observed between the two curves, which, in the long run, tended to overlap and even to show a better trend in AA. By the end of the study, patients with an associated MM did not reach a median value thus showing a better renal outcome than AL (data not reported).

Patients with AL showed a slightly faster, although not significant, decline of renal function than patients with AA (Figure 4).

When the Cox regression analysis was applied to the factors potentially affecting renal outcome in AL such as age, gender, heart involvement, sCr, UPE, kappa/lambda ratio

Table 3. Multivariate analysis of factors affecting survival

	Overall population (AL + AA)		AL		AA	
	(HR 95% C.I.)	*P*	(HR 95% C.I.)	*P*	(HR 95% C.I.)	*P*
Type (AL/AA)	1.13 (0.71–1.78)	0.5				
Age	1.03 (1.01–1.05)	0.001	1.01(0.98–1.04)	0.7	1.05 (1.01–1.08)	0.002
Gender	1.18 (0.80–1.74)	0.3				
Heart involvement	2.22 (1.46–3.36)	0.000	2.78(1.59–4.85)	0.000	3.4(1.5–7.4)	0.002
Creatinine	1.14 (1.03–1.25)	0.006	1.03(0.88–1.21)	0.6	1.27(1.10–1.47)	0.001
Therapy			0.40(0.23–0.71)	0.02		

Table 4. Multivariate analysis of factors affecting renal outcome

	AL		AA	
	HR (95% C.I.)	*P*	HR (95% C.I.)	*P*
Age	0.98 (0.95–1.01)	0.2	1.02 (0.99–1.05)	0.06
Heart involvement	1.79 (0.94–3.41)	0.07	2.8 (1.13–7.07)	0.02
Creatinine	1.47 (1.25–1.72)	0.000	1.83 (1.44–2.32)	0.000
UPE	1.06 (0.98–1.15)	0.1	1.13 (1.05–1.21)	0.001
Therapy	0.69 (0.35–1.36)	0.2		

and specific therapy, only sCr showed to be a strong predictor of renal failure (HR 1.47, $P = 0.000$) while therapy and type of MC lost the influence found at univariate analysis (Table 4).

When the same analysis was performed in AA, sCr (HR 1.8, $P = 0.000$), UPE (HR 1.1, $P = 0.001$) and heart involvement (HR 2.8, $P = 0.02$) were found to significantly influence the renal outcome (Table 4).

Fifty-nine out of 152 patients with AL (39%) developed ESRD and started a dialysis programme. Of these, 51 entered a regular treatment on haemodialysis (HD) while 8 started a programme on peritoneal dialysis (PD). Correspondingly, 37 patients out of 78 with AA (47%) developed ESRD and had to begin a dialytic therapy: 33 on HD and 4 on PD. Noteworthy, a few patients were already on dialysis at the time of diagnosis (5 in AL and 4 in AA).

Patients with AA showed a significantly higher sCr (Table 1) at diagnosis than patients with AL and starting earlier the dialitic therapy (Figure 3).

In both groups, patients who developed ESRD showed a significantly higher sCr at presentation with no differences concerning UPE and in AL kappa/lambda ratio (Table 5).

Concerning renal outcome in AF, three patients showed a progression of renal disease, one of whom had to start peritoneal dialysis, and three did not show any significant changes.

When death or dialysis were considered as clinical endpoints, age, sCr and heart involvement were the major predictors of a poor outcome (Table 6).

Table 6. Comparison between patients who died or entered dialysis versus patients alive without dialysis at the end of the study

	Dialysis or death	Alive without dialysis	*P*
Patients (*n*)	175	101	
Age (years)	68 (19–88)	62 (23–86)	<0.002
Serum creatinine (mg/dl)	1.4 (0.5–12.4)	1.1 (0.5–7.1)	<0.0001
UPE (g/24 h)	5.0 (0.1–29.8)	4.5 (0.5–16.0)	0.12
Male	56%	44.5%	ns
Cardiac involvement	38%	16%	<0.001
AL	62%	56%	ns
AL + MM	12%	10%	ns
AA	26%	34%	ns

Data are expressed as medians with range.

Response to treatment

Seventy patients out of 167 fulfilled criteria for specific therapy.

AL patients who underwent a specific therapy ('treated patients') showed a marked improvement of both overall and renal survival (Figure 5) despite a poor kidney response.

When the analysis was adjusted for other variables, therapy was found to significantly affect only overall survival. Renal response was considered improved whenever a 50% decrease in UPE occurred in the absence of a 25% increase of sCr concentration [18].

According to the above-mentioned criteria only 10 out of 70 patients who were treated improved ('14% of

Table 5. Characteristics of patients according to dialysis

	AL (n = 152)		AA (n = 78)	
	HD	No HD	HD	No HD
Patients (n)	59 (*39%*)	93 (*61%*)	37 (*47%*)	41 (*53%*)
HD/PD	51/8		33/4	
Pts on dialysis at diagnosis	5		4	
Age (range)	64 (*43–80*)	66 (*34–83*)	68 (*19–82*)	58 (*23–86*)
Gender (M/F)	32/27	50/43	14/23	18/23
Serum creatinine (mg/dl)	1.8^ (0.6–10.3)	1.1* (0.6–7.1)	2.7 (0.7–12.4)	1.2** (0.5–7.5)
UPE (g/24 h)	5.3 (0.1–21.4)	5 (0.5–17)	6.0 (1.6–28.8)	4.9 (0.5–20)
k / λ ratio	1:3	1:5		
Death rate	37/59 (63%)	36/93 (39%)	25/37 (67%)	7/41 (17%)

Data are referred at the time of diagnosis and are reported as medians with range.
Statistically significant differences within each group (*P = 0.0003, **p = 0.0002) and between the groups on dialysis (^p = 0.05).

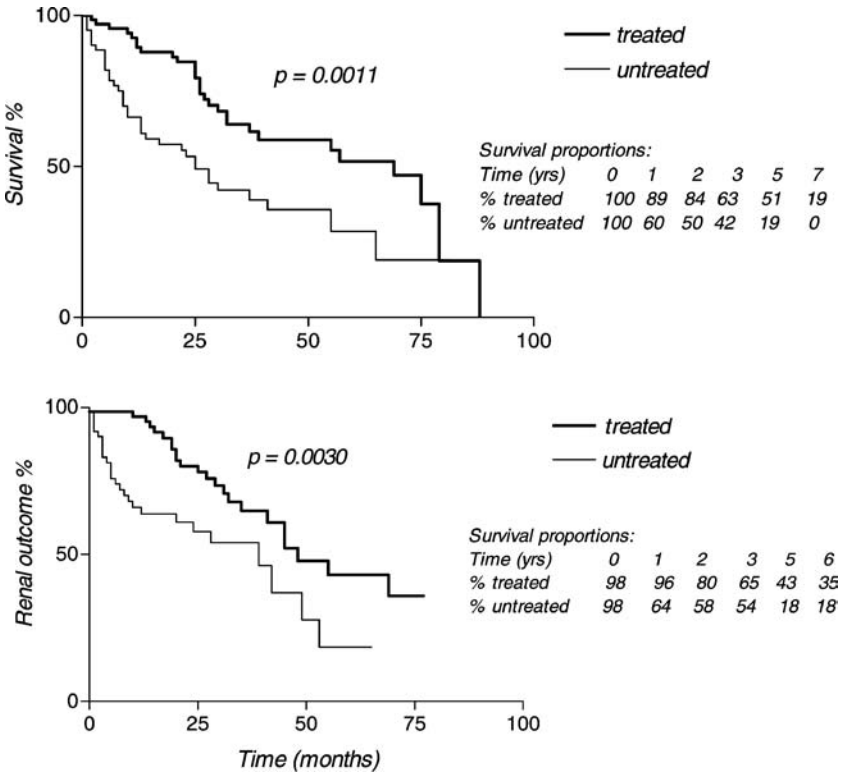

Fig. 5. *Top*: survival of 134/167 AL patients according to whether or not they underwent a specific chemotherapy: treated ($n = 70$, median survival 69 months) versus untreated ($n = 64$, median survival 25 months). *Bottom*: renal outcome of 134/152 AL patients: treated ($n = 70$, median survival 48 months) versus untreated ($n = 64$, median survival 39 months), according to the Kaplan–Meier method.

responders') as opposed to 47 who showed a disease progression and to 13 who did not show any significant changes ('not responders'). In as many as 64 patients there was no evidence of a specific therapeutic intervention ('untreated patients').

Among specific therapy, 19 patients, including one with MM, underwent ASCT, 33 followed a conventional alkylating-based regimen of melphalan plus prednisone, 10 followed melphalan plus high-dose dexamethasone, 3 underwent VAD regimen (vincristine, adriamycin and dexamethasone) and 5 followed various combinations of chemotherapic agents including thalidomide in 3 patients and iododoxorubicin in 2.

Kidney response after ASCT was slightly better than that observed after conventional chemotherapy. Four patients improved, 4 did not show significant changes and as many as 11 showed disease progression, 6 of whom starting a regular dialysis treatment. The median time of survival after ASCT was 28 months and 6 out of 19 patients died. One AL patient underwent renal transplantation and was referred with a still functioning graft 47 months after transplantation.

Dialysis

Median survival on dialysis was 11 months in AL and 17 in AA but the difference was not significant. In consideration of the low number of PD as compared to HD patients (12 versus 84), we could not compare the survival analysis of the two groups which, however, showed the same median time of survival of 6.5 months. As a consequence, we compared AL patients on dialysis (HD + PD) with the corresponding group of AA (HD + PD). Although we did not find significant differences, cumulative survival at 12 months was 48% for AL compared to 75% for AA. After 5 years, survival dropped to 18% in AL and 12% in AA (Figure 6). Mortality rate was 77% in PD and 63% in HD, with only two deaths occurring in the first month after the beginning of dialysis. Dialysis significantly affected survival in AA but not in AL patients ($P = 0.0005$, data not reported).

The mortality rate on dialysis showed an estimated 67% for AA and 63% for AL. Heart disease was the major cause of death in both groups regardless of the type of treatment they followed (PD or HD).

Discussion

Our results show a longer survival in patients affected from AA as compared to AL amyloidosis with no significant differences according to renal outcome.

To date, no studies have been reported which compared in the same cohort patients affected from AL and AA amyloidosis with the exception of a recent work by Cazalets *et al.* who reported a longer survival in AL as compared to AA [22].

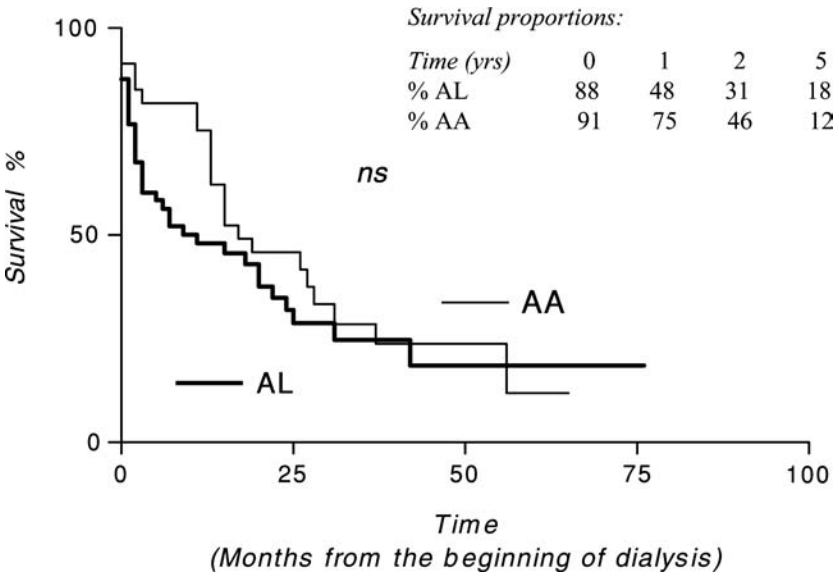

Fig. 6. Survival on dialysis (HD and PD) of 59 AL patients (median survival 11 months) versus 37 AA patients (median survival 17 months) according to the Kaplan–Meier method.

AL amyloidosis

Kyle *et al.* studying 474 patients with AL reported a median survival of 13.2 months with half of them presenting with renal failure at diagnosis [3]. Unfortunately, no data are reported about renal outcome and survival on dialysis. The authors stated that elevated sCr at presentation had an adverse influence on survival in patients who lived at least 1 year after diagnosis. In a later study concerning 153 patients, the same authors found a median survival of 25.6 and 14.9 months respectively according to whether sCr at diagnosis was below or over 1.3 mg/dl. In contrast, survival was not correlated to UPE but rather to lambda light chain found in urine [20].

Data reported from the Italian Society for Amyloidosis showed in patients with AL either a 34- or 50-month survival according to whether or not they showed a "dominant" renal involvement [21].

In 2004 the same group reported, among 409 patients presenting with renal involvement, as many as 18% who progressed to ESRD after a median time of only 7.5 months.

Multivariate analysis showed younger age, UPE, sCr at diagnosis and haematologic response to treatment to independently affect the progression towards ESRD. Unfortunately, no data were reported on patient survival on dialysis [8].

In contrast to other reports [2,8,21,22], we did not find sCr at presentation to affect the overall survival in AL, and we were unable as well to confirm proteinuria as a predictive factor of renal outcome. In addition, we could not confirm that patients with a urinary lambda light chain had a lower survival. On the other hand, we confirmed the negative role played by heart involvement [2–4] and by an associated MM [25].

Despite our renal response, which was actually very poor (14% of responders) if compared to 49% of haematologic responders reported by Palladini *et al.* [8], our results confirmed the effectiveness of a specific therapeutic approach (either conventional or ASCT) as compared to supportive therapy in order to prolong survival and reduce the progression towards ESRD in keeping with previous studies which proved the beneficial use of alkylating agents [24,25].

Indeed, the use of alkylating agents may account for the improved survival and renal outcome of our patients on a specific therapy. It is feasible that, in the absence of a kidney response, this beneficial effect may depend on some haematologic response whose prevalence and entity however remains unknown. It is possible that the poor kidney response observed in our study may depend on a more advanced organ damage and/or on a poor selection of patients in particular of those who underwent ASCT.

Actually, functional improvement of the organs involved has been reported after the haematologic response but only in a portion of responsive patients [23].

Until recently, haematologic response could only be evaluated by few specialized laboratories and such information could not be available in large retrospective studies. In the last few years, however, a new assay for serum-free light chain analysis has allowed a safe and reliable method to detect and monitor the haematologic response [26].

Concerning renal transplant, older age, the presence of renal failure and/or of cardiac involvement have certainly reduced the opportunities for this choice in many of our patients.

AA amyloidosis

Survival appears greatly improved in our study as compared to 24.5 months reported by Gertz and Kyle [5] and to 52.9 months recorded by Joss *et al.* with only 18 months of renal survival [6]. Renal failure and a low serum albumin at diagnosis were the most important predictors for a poor outcome in these studies. In addition, Joss *et al.* also found

UPE to have a significant influence on the progression of renal disease [6]. Recently, Torregrosa *et al.* reported in a group of patients without dialysis a survival of only 67% and 53% at 12 and 24 months, respectively [27]. Patients with AA seem to show a shorter renal survival with a higher number of patients who develop ESRD, in spite of an apparently slower decline of renal function. These differences however, are not significant and are largely dependent on the worse renal function found in these patients at the time of presentation, and in turn, a likely consequence of patients' late referral [12].

Cardiac disease was the second cause of death in spite of a relatively low incidence of heart involvement (14%) compared to patients with AL or MM (37% and 51% respectively) [12,3,4].

Indeed, the heart is far more frequently involved in AL amyloidosis, amyloid cardiomiopathy being rarely extensive in AA and almost never resulting in heart failure [3,13].

Recently, Lachmann *et al.* [7] identified several abnormalities in 222 patients with AA amyloidosis who underwent echocardiography but only in two cases were they characteristic for amyloidosis.

Because of the retrospective character of our study and the different causes responsible for amyloidosis, the therapeutic regimens employed in the different centres were not comparable. In addition, pre- and post-treatment SAA concentrations, a basic marker of disease activity, were not available at the time of the study and could not be used to evaluate the response to treatment.

Gillmore *et al.* suggested that treatment in AA should be guided by frequent determinations of serum SAA concentrations which can usually provide invaluable prognostic information [28].

Dialysis

To date, only two studies have been published on patients with systemic amyloidosis on chronic dialysis. The first one, published by Moroni *et al.* in 1992 [15], concerned 43 patients with biopsy-proven renal amyloidosis of whom 27 affected from AA and 16 from AL, and the second one, published by Martinez-Vea *et al.* [16], concerned 48 patients of whom 11 were affected from AL and 37 from AA.

Both of them reported a prevalence of patients with AA with a median cumulative survival (AL + AA) of 25 and 52 months, much longer than that observed in our study either in AL or AA (11 and 17 months respectively). Younger age may account for the longer survival observed in their patients, another possible explanation also being the exclusion in both studies of patients who died within the first year and likely affected from a more severe disease. Conversely, Torregrosa *et al.* have recently reported in patients with AA a lower survival rate than that observed in our study (42% versus 75%) after 12 months of dialysis [27].

However, in agreement with our results, Moroni *et al.* did not find any difference in survival at any time during dialysis between patients with AL and with AA as well as between patients on haemo- or peritoneal dialysis [15].

Concluding remarks

Our results point to heart involvement and to treatment as the major factors affecting survival and renal outcome. The higher prevalence of heart involvement likely accounts for the shorter survival observed in AL. In contrast, the higher sCr at presentation found in AA can account for the differences observed in renal outcome between patients with AA and AL. These findings raise the problem of a late nephrological referral in AA and call for an improved cooperation between rheumatologists, internists and nephrologists. Our results emphasize in AL the protective influence on survival and renal outcome of a specific therapeutic approach and strengthen the need for an early diagnosis together with a wider and more careful application of current therapies including kidney transplantation and ASCT.

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Conflict of interest statement. None declared.

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Appendix List of participating centres to the study

City	Hospital	Chief	Referring
Ancona	Umberto I	V Mioli	E Fanciulli
Aosta	Ospedale Regionale	S Aloatti	A Gaiter
Arezzo	S. Maria	M Sasdelli	D Bizzarri
Avellino	S. Giuseppe Moscati	W De Simone	S Iannaccone
Bagno a Ripoli (FI)	Ospedale S. Maria Annunziata	F Pizzarelli	S Nigrelli
Bari	Policlinico	FP Schena	C Manno
Bassano del Grappa (VI)	Ospedale Civile S. Bassiano	A Fabris	MV Pellanda
Bergamo	Ospedali Riuniti	G Remuzzi	T Bertani
Bologna	Malpighi	A Santoro	S Pasquali
Bologna	S. Orsola	S Stefoni	GM Frascà
Bolzano	Azienda Sanitaria di Bolzano	W Huber	P Riegler
Brescia	Ospedali Civili	P Maiorca	G Gregorini
Cagliari	G. Brotzu	P Altieri	A Pani G Dessì
Castelfranco Veneto (TV)	Presidio Ospedaliero	C Cascone	C Abaterusso
Cremona	Istituti Ospitalieri	F Malberti	P Pecchini
Cuneo	S. Croce	M Formica	C Pino
Florence	Azienda Ospedaliero-Universitaria Careggi	M Salvadori	F Bergesio
Florence	Nuovo Ospedale S. Giovanni di Dio	PL Tosi	G Monzani F Manescalchi
Genoa	S. Martino	G Cannella	D Mulas
Genoa	Università	G De Ferrari	S Garibotto
Lecco	A. Manzoni	F Locatelli	C Pozzi
Lodi	Maggiore	E Imbasciati	M Farina
Lucca	Ospedale Campo di Marte	A Antonelli	R Giusti
Milan	S. Carlo Borromeo	G Colasanti	F Ferrario
Milan	Maggiore	C Ponticelli	G Banfi
Milan	Istituto Clinico Humanitas	G Graziani	G Graziani
Modena	Policlinico	A Albertazzi	L Furci
Montefiascone (VT)	Ospedale di Montefiascone U.O. Ematologia	M Montanaro	M Montanaro L Scaramucci
Naples	Università Federico II	VE Andreucci	B Cianciaruso
Palermo	Dipartimento di Medicina Interna	G Cerasola	M Li Vecchi
Pavia	Fondazione S. Maugeri	A Salvadeo	L Semeraro
Perugia	R. Silvestrini	U Buoncristiani	R Brugrano
Pisa	S. Chiara	P Rindi	V Batini
Ravenna	S. Maria delle Croci	M Fusaroli	M Santostefano A Fabbri

City	Hospital	Chief	Referring
Reggio Calabria	Melacrino	C Zoccali	C Martorano
Reggio Emilia	Arcispedale S. Maria Nuova	PP Borgatti	R Rustichelli
Rimini	Infermi	L Cagnoli	L Cagnoli
Rome	Policlinico Umberto I	G Stirati	G Pecci
Rome	Fatebenefratelli-Isola Tiberina	MG Chiappini	M Di Girolamo
Rome	S. Pertini	A Paone	M Galliani
Torino	Don Bosco	F Quarello	G Rollino
Torino	Mauriziano Umberto I	M Bruno	M Manganaro
Torino	Molinette	GP Segoloni	L Besso
Torino	CMID Ospedale L. Einaudi	D Roccatello	D Roccatello
Trento	S. Chiara	C Rovati	C Comotti
Trieste	Ospedale di Cattinara	GO Panzetta	S Savoldi M Carraro
Udine	S. Maria Misericordia	D Montanaro	G Boscutti
Verona	Civile Maggiore	G Maschio	P Bernich
Vimercate (MI)	Ospedale di Vimercate	A Sessa	M Righetti