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Article

Trends in Survival and Renal Recovery in Patients with Multiple Myeloma or Light-Chain Amyloidosis on Chronic Dialysis

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Abstract

Background and objectives Monoclonal gammopathies (MGs) with renal involvement can lead to ESRD caused by myeloma cast nephropathy (MCN), immunoglobulin light chain amyloidosis (ALA), or light–chain deposition disease (LCDD). Few studies have focused on the prognosis of patients with MG on chronic dialysis. We evaluated the outcomes of patients with MG incident on chronic dialysis in France.

Design, setting, participants, & measurements All incident patients registered in the Renal Epidemiology and Information Network Registry between 2002 and 2011 with ESRD caused by ALA, LCDD, or MCN were included. Patient's survival, censored for renal transplantation, renal recovery, and loss to follow-up, as well as renal outcomes were analyzed and compared with a control group. Risk factors and causes of death were analyzed.

Results We included 1459 patients, comprising 265 (18%) patients with ALA, 334 (23%) patients with LCDD, and 861 (59%) patients with MCN. Median age was 72 years, and 56% were men. Median follow-up was 13.1 months. Renal recovery was observed in 9.1% of patients and more frequent after 2006. Kidney transplantation was rare in this population (2.3%). Among 1272 patients who remained on dialysis, 67% died. Median survival on dialysis was 18.3 months. Main causes of death were malignancies (34.4%), cardiovascular diseases (18%), infections (13.3%), and cachexia (5.2%). Independent risk factors of death were age (hazard ratio [HR], 1.03 per year increase; 95% confidence interval [95% CI], 1.02 to 1.03), frailty (HR, 1.93; 95% CI, 1.58 to 2.36), congestive heart failure (HR, 1.54; 95% CI, 1.23 to 1.93), and dialysis initiation on a central catheter (HR, 1.40; 95% CI, 1.11 to 1.75). Factors associated with a lower risk of death were year of dialysis initiation (HR, 0.95 per year increase; 95% CI, 0.91 to 0.99) and high BP (HR, 0.80; 95% CI, 0.67 to 0.97).

Conclusions Survival of patients with ALA, LCDD, or MCN on chronic dialysis is poor but has improved over time. Progressive malignancy is the main cause of death in this population. Renal recovery has increased since 2006.

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Introduction

Renal involvement of monoclonal gammopathies (MGs) can lead to ESRD. The most frequent causes of ESRD in this setting are myeloma cast nephropathy (MCN), immunoglobulin light chain amyloidosis (ALA), and light–chain deposition disease (LCDD). Multiple myeloma (MM) accounts for 1% of malignant diseases and 12%–15% of hematologic malignancies in Europe, with a three to five per 100,000 annual incidence. Incidence rates increase with age (1) and have remained stable in the last decades (2). ESRD caused by MM represented 1.5% of patients on RRT in the 1986–2005 European Renal Association-European Dialysis and Transplant Association (ERA-EDTA) Registry (3). Dialysis dependence is associated with poor survival in MM (3–5). Recent use of efficacious low–toxicity chemotherapy, such as bortezomib, may have improved the outcome of patients with MM on dialysis. However, although bortezomib increased median time to disease progression of 45% in the general population of patients with MM (6,7), large studies failed to show a benefit in patients on chronic dialysis (3,4). Bortezomib was approved in France in 2004 (8) for patients with MM or ALA and renal failure.

Few studies have addressed specifically the outcome of patients with ALA or LCDD on chronic dialysis. Estimated incidence of ALA was 6–10 per 1 million per year in 2008 in the United Kingdom (9). ESRD occurs in one quarter of patients with renal ALA (10), whose survival depends on cardiac involvement. LCDD, characterized by monoclonal light–chain granular tissue deposition (11,12), is distinct from MM or ALA (13), but outcomes of patients with LCDD have rarely been studied specifically (14).

We report here the characteristics and outcomes of the national cohort of patients with ALA, LCDD, or MCN incident on chronic dialysis registered in the

Renal Epidemiology and Information Network (REIN) Registry over a 10-year period (2002–2011).

Materials and Methods

Patient Population, Data Collection, and Definitions

All incident patients with ESRD related to ALA, LCDD, or MCN registered in the REIN between January 1, 2002 and December 31, 2011 were included. The REIN was founded in 2001 as a tool to provide public health decision support, evaluation, and research related to RRT for ESRD (15). Data are collected at the initiation of RRT (*i.e.*, hemodialysis [HD], peritoneal dialysis, or kidney transplantation [KTR]) for all patients in France and updated annually. Only patients considered as having ESRD by their attending nephrologist are included in the REIN, not patients requiring RRT for AKI. Patients may be included from their first day of RRT if they had previous severe CKD or *a posteriori* in case of absence of recovery after 3 months on dialysis. In both cases, the first day on dialysis is recorded in the registry. Thirty-six dedicated clinical research assistants coordinate data collection and quality control. Eight types of events are reported in the REIN from the first day of RRT: (*1*) KTR, (*2*) registration on the kidney transplant waiting list, (*3*) changes in dialysis setting, (*4*) changes in type of dialysis, (*5*) recovery of renal function, (*6*) loss of follow-up, (*7*) therapy withdrawal, and (*8*) death. If death occurs, the main cause of death is recorded. The National Commission for Information Technology and Privacy approved the data collection conducted by the REIN, and the REIN Scientific Committee approved this study.

Major comorbidities, including frailty (inability to walk without help), and demographic information were collected as well as the following information relative to RRT: dialysis start in emergency, dialysis start on a catheter, primary renal disease, and dialysis settings. Dialysis start in emergency was defined as unplanned first dialysis for a vital risk linked to hyperkalemia, overhydration, acidosis, pericarditis, or severe anemia. Primary renal diseases were coded according to the thesaurus of the French language Society of Nephrology on the basis of the 10th revision of the International Classification of Disease.

Any events were registered from the first day of dialysis to the study's end point on November 13, 2013. The primary outcome examined was the survival of patients on dialysis censored for recovery of renal function, KTR, loss to follow-up, or the end of the study.

Patients with MG were divided in three groups according to primary renal disease codes: ALA, LCDD, and MCN. Patients with other amyloidosis (nonimmunoglobulin light chain) were excluded.

A control population of incident patients with ESRD was selected randomly without any matching from all patients without MG included in the REIN during the same period of time (three or four control patients per one patient with MG).

Aims of the Study

The main objective was to evaluate the survival of patients with MG (ALA, LCDD, or MCN) on chronic dialysis and identify risk factors of death.

Additional objectives were to determine causes of death, disease incidence over time, rates of renal recovery over time, trends in mortality over time, and access to the transplantation waiting list and KTR.

We also compared survival and causes of death between patients with ALA, LCDD, or MCN and between patients with MG and control patients.

Statistical Analyses

For descriptive analyses, results were expressed as frequencies and percentages for categorical variables. Means and SDs or medians and interquartile ranges (IQRs) were used for continuous variables with asymmetric distributions. Groups of patients with MG were compared using chi-squared tests (or Fisher exact tests) for frequencies and ANOVA for continuous variables. Patients with MG and control patients were compared using chi-squared tests for frequencies and t tests for continuous variables. Survival probabilities on dialysis were estimated using the Kaplan–Meier method and compared using the log-rank test for equality of the survival curves. Cumulative incidences of death on dialysis was also analyzed using the competing risks analysis method. Death was the main event. Transplantation and renal recovery were considered as competing events. Equality across groups was tested with Fine and Gray analysis.

Risk factors associated with death were explored with the multivariate Cox model adjusted on mortality risk factor. Age and risk factors with a P value <0.25 in the univariate analysis were included in the Cox model.

For survival analysis comparison between patients with MG and control patients on dialysis, a multivariate Cox analysis was performed after adjustment for age and the risk factors of mortality identified.

In patients with multiple events, the first event was registered. Additional events were only considered in descriptive analysis of subgroups.

Statistical analysis was performed using R and SPSS (SPSS Inc., Chicago, IL) software. P values <0.05 were considered statistically significant.

Results

Characteristics of Patients with MG at the Initiation of RRT

Among 63,349 incident patients registered in the REIN during the study period, 1462 (2.3%) had ESRD related to MG: ALA in 267 (18%), LCDD in 334 (23%), and MCN in 861 (59%). Prevalence of patients with MG was stable (2%–3%) over time.

Patients' characteristics are detailed in Table 1. Sex ratio of men to women was 1.26, and median age was 72.3 years. Dialysis was initiated as an emergency for 45.6% of patients, and 72% started HD on a central venous catheter. Most patients (95%) were treated with HD, mainly in hospital centers (92.6%); 5% were treated with peritoneal dialysis, and there was no preemptive KTR. Comorbid conditions were hypertension (50.1%), congestive heart failure (CHF; 15.9%), diabetes mellitus (11.6%), coronary artery disease (10.8%), chronic lung disease (8%), peripheral vascular disease (5.8%), and cerebrovascular disease (5.6%). Frailty was reported in 22% of patients.

Baseline characteristics differed between the groups (Table 1): patients with ALA were younger, had lower albumin levels, and suffered more frequently from CHF,

Table 1. Baseline characteristics of patients with monoclonal gammopathy and controls at the initiation of RRT in France between 2002 and 2011

Characteristic	ALA (*n*=267)	LCDD (*n*=334)	MCN (*n*=861)	*P* Value	Patients with MG (*n*=1462)	Controls on Dialysis (*n*=5036)	*P* Value
Age (yr), median ± IQR	70.6±14.6	72.3±16	72.9±14.3	<0.001	72.3±15	70.9±22.2	<0.001
Men (%)	172 (64.4)	176 (52.7)	467 (54.2)	<0.01	815 (55.7)	3100 (61.6)	<0.001
Hemodialysis started on catheter (%)	156 (58.4)	226 (67.7)	673 (78.2)	<0.001	1055 (72.2)	2225 (44.2)	<0.001
Missing	19 (7.1)	23 (6.9)	50 (5.8)		92 (6.3)	609 (12.1)	
Dialysis start in emergency (%)	86 (32.2)	133 (39.8)	447 (51.9)	<0.001	666 (45.6)	1310 (26)	<0.001
Missing	20 (7.5)	24 (7.2)	65 (7.5)		109 (7.5)	581 (11.5)	
First treatment modality (%)							
Hemodialysis	254 (95.1)	312 (93.4)	823 (95.6)	0.30	1389 (95)	4324 (85.9)	<0.001
Peritoneal dialysis	13 (4.9)	22 (6.6)	38 (4.4)		73 (5)	565 (11.2)	
Transplantation	0	0	0		0	144 (2.9)	
Diabetes (%)	23 (8.6)	34 (10.2)	113 (13.1)	0.09	170 (11.6)	1937 (38.5)	<0.001
Missing	17 (6.4)	21 (6.3)	48 (5.6)		86 (5.9)	279 (5.5)	
High BP (%)	132 (49.4)	176 (52.7)	424 (49.2)	0.43	732 (50.1)	3647 (72.4)	<0.001
Missing	20 (7.5)	26 (7.8)	59 (6.9)		105 (7.2)	442 (8.8)	
Ever smoker (%)							
Never	135 (50.6)	173 (51.8)	470 (54.6)	0.25	778 (53.2)	2503 (49.7)	<0.001
Current	20 (7.5)	19 (5.7)	39 (4.5)		78 (5.3)	436 (8.7)	
Former	48 (18)	53 (15.9)	127 (14.8)		228 (15.6)	1082 (21.5)	
Missing	64 (24)	89 (26.6)	225 (26.1)		378 (25.9)	1015 (20.2)	
Heart failure (%)	72 (27)	48 (14.4)	112 (13)	<0.001	232 (15.9)	1256 (24.9)	<0.001
Missing	26 (9.7)	31 (9.3)	61 (7.1)		118 (8.1)	478 (9.5)	
Peripheral vascular disease (%)	24 (9)	15 (4.5)	46 (5.3)	0.03	85 (5.8)	961 (19.1)	<0.001
Missing	29 (10.9)	30 (9)	68 (7.9)		127 (8.7)	509 (10.1)	
Coronary artery disease (%)	40 (15)	30 (9)	88 (10.2)	0.04	158 (10.8)	1155 (22.9)	<0.001
Missing	22 (8.2)	31 (9.3)	62 (7.2)		115 (7.9)	495 (9.8)	
Cerebrovascular disease (%)	16 (6)	13 (3.9)	53 (6.2)	0.36	82 (5.6)	503 (10)	<0.001
Missing	26 (9.7)	37 (11.1)	63 (7.3)		126 (8.6)	538 (10.7)	
Chronic lung disease (%)	30 (11.2)	26 (7.8)	61 (7.1)	0.09	117 (8)	584 (11.6)	<0.001
Missing	21 (7.9)	31 (9.3)	68 (7.9)		120 (8.2)	505 (10)	
BMI (kg/m^2), mean±SD	23.2±3.9	23.9±4.5	24.1±4.4	0.07	23.9±4.4	25.8±5.6	<0.001
BMI<20 kg/m^2 (%)	38 (14)	39 (12)	92 (11)	0.63	169 (12)	469 (9.3)	<0.01
Missing	66 (25)	97 (29)	286 (33)		449 (31)	1497 (29.7)	
Albumin (g/dl), mean±SD	2.5±0.9	3.1±0.7	3.2±0.7	<0.001	3.0±0.8	3.3±0.7	<0.001
Albumin <3.0 g/dl (%)	115 (43.1)	76 (22.8)	179 (20.8)	<0.001	370 (25.3)	703 (14)	<0.001
Missing	105 (39.3)	157 (47)	382 (44.4)		644 (44)	2402 (47.7)	
Hemoglobin (g/dl), mean±SD	10.5±2.1	9.7±1.8	9.3±1.7	<0.001	9.6±1.9	10.3±1.8	<0.001
Missing (%)	75 (28)	97 (29)	224 (26)		396 (27)	1352 (26.8)	
Frailty (%)	49 (18.4)	64 (19.2)	209 (24.3)	0.02	322 (22)	768 (15.3)	<0.001
Missing	50 (18.7)	57 (17.1)	174 (20.2)		281 (19.2)	1113 (22.1)	

ALA, immunoglobulin light chain amyloidosis; LCDD, light–chain deposition disease; MCN, myeloma cast nephropathy; MG, monoclonal gammopathy; IQR, interquartile range; BMI, body mass index.

peripheral vascular disease, and coronary artery disease; patients with MCN had lower hemoglobin levels, were more likely to be frail, and started HD more often in emergency on a central catheter.

Comparisons between Patients with MG and Control Patients on Chronic Dialysis

The control group comprised 5036 patients, and their characteristics differed from those of patients with MG (Table 1). Median follow-up was 27 months (IQR, 10–45). Compared with patients with MG (Table 2), more controls received KTR after a shorter dialysis duration. Thus, fewer controls remained on dialysis, despite a lower rate of renal recovery. Among control patients who remained on dialysis, median survival was better (51.6 months; 95% confidence interval [95% CI], 49.6 to 54.1) than in patients with MG ($P<0.001$). Multivariate analysis showed an adjusted hazard ratio (HR) of death of 2.18 [95% CI, 1.93 to 2.46 ($P<0.001$)] in patients with MG compared with controls.

Similarly, cumulative incidence of death using competing risks analysis was lower in control patients than in patients with MG ($P<0.001$).

Cardiovascular mortality was more frequent in the control group, whereas malignancy-related mortality caused by hematologic malignancies and also, solid tumors was less frequent (Table 4).

Survival of Patients with MG

Median follow-up was 13.1 months (IQR, 4–33). Overall, 1272 (87%) patients remained on chronic dialysis, among whom 982 (77.2%) died after median dialysis duration of 8.8 months (IQR, 3–30). Death occurred in 173 (72.4%) patients with ALA, 218 (75.2%) patients with LCDD, and 591 (79.5%) patients with MCN (Table 2). Median survival of patients with MG who remained on dialysis was 18.3 months (95% CI, 16.3 to 19.9). Survival rates at 1, 3, 5, and 8 years were 58%, 34%, 24%, and 18%, respectively (Figure 1A). Survival censored for KTR, renal recovery, loss of follow-up, or end of the study period was better in patients with ALA than in patients with MCN ($P=0.004$ between the three groups) (Figure 1B). Median survival was 28.9 months (95% CI, 23.7 to 34.8) in ALA, 18.4 months (95% CI, 14.9 to 24.1) in LCDD, and 16 months (95% CI, 12.5 to 18.3) in patients with MCN. Survival rates at 1, 3, and 5 years were 66%, 41%, and 26%, respectively, in ALA; 59%, 37%, and 26%, respectively, in LCDD; and 55%, 30%, and 22% in MCN, respectively.

Cumulative incidences of death were also analyzed considering transplantation and renal recovery as competing risks (Figure 2). Similarly, the risk of death was higher in patients with MCN than in patients with ALA ($P=0.04$).

Incidence of Renal Recovery

Renal recovery was reported in 133 (9.1%) patients (Table 2) after median dialysis duration of 5 months (IQR, 2–9). Renal recovery was more frequent in patients with MCN (11.3%) than in patients with LCDD (8.4%) and patients with ALA (3%; $P<0.001$) (Figure 3A). No patient stopped dialysis because of therapy withdrawal. Dialysis was eventually resumed in 20 (15%) of these patients after a median duration of 9 months (IQR, 4–19). Thirty-four (26%) patients died after a period of renal recovery, of which ten had resumed dialysis before dying.

Recovery rate was higher in patients with MG who had started dialysis since January 1, 2006 versus those who had started dialysis before January 1, 2006 ($P<0.001$), whereas no difference was observed in control patients between the two periods (Figure 3B).

Of note, baseline characteristics differed between patients who did and did not recover renal function (Table 3): patients who recovered were more likely to have started dialysis on a catheter in emergency. They were more likely to have diabetes, had a higher body mass index and serum albumin level, and had lower hemoglobin level.

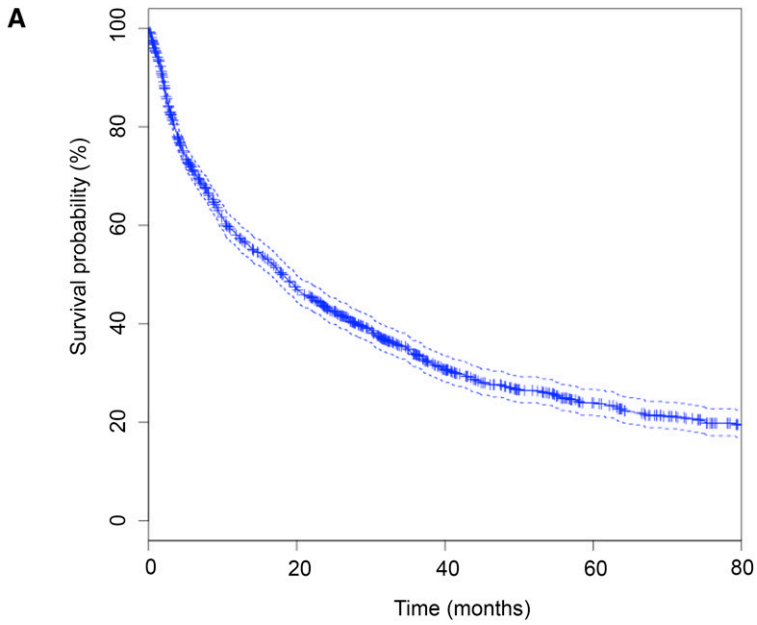
Incidence of KTR

Forty-six (3.1%) patients were registered on the KTR waiting list after a median of 15 months (IQR, 7–34), and 34 (2.3%) patients received a KTR after a median of 32.5 months (IQR, 18–55) on dialysis. Registration on the KTR waiting list was more frequent in patients with ALA (7.5%) than in patients with LCDD (4.5%) and patients with MCN (1.5%; $P<0.001$). KTR was also more frequent in patients with ALA (6.4%) than in patients with LCDD (3.3%) and patients with MCN (0.7%; $P<0.001$). Median follow-up after KTR was 32 months (IQR, 12–59). Only one patient lost KTR function after 9 months and died 8 months after she resumed dialysis.

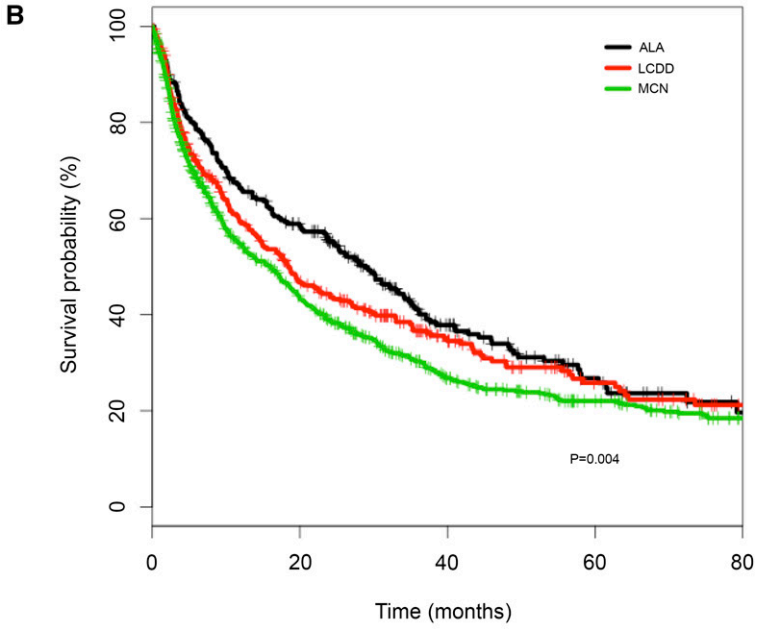
Table 2. Outcomes of patients with monoclonal gammopathy and control patients on chronic dialysis

Events	ALA (n=267)	LCDD (n=334)	MCN (n=861)	P Value	Patients with MG (n=1462)	Controls on Dialysis (n=5036)	P Value
Remained on dialysis (%)	239 (89.5)	290 (86.8)	743 (86.3)	0.39	1272 (87)	3656 (72.6)	<0.001
Death among patients on dialysis (%)	173 (72.4)	218 (72.2)	591 (79.5)	0.67	982 (77.2)	2171 (59.4)	<0.001
Renal recovery (%)	8 (3)	28 (8.4)	97 (11.3)	<0.001	133 (9.1)	246 (4.9)	<0.001
Waiting list registration (%)	20 (7.5)	15 (4.5)	11 (1.3)	<0.001	46 (3.1)	1447 (28.7)	<0.001
Kidney transplantation (%)	17 (6.4)	11 (3.3)	6 (0.7)	<0.001	34 (2.3)	1065 (21.1)	<0.001
Loss of follow-up (%)	3 (1.1)	5 (1.5)	15 (1.7)	0.88	23 (1.6)	69 (1.4)	0.56

ALA, immunoglobulin light chain amyloidosis; LCDD, light–chain deposition disease; MCN, myeloma cast nephropathy; MG, monoclonal gammopathy.



Time (Months)	0	20	40	60	80
Number at risk	1462	593	275	143	69



Time (months)		0	20	40	60	80
Number at risk	ALA	267	145	65	27	9
	LCDD	334	136	64	30	13
	MCN	861	312	146	86	47

Figure 1. | Kaplan–Meier survival analyses of patients with monoclonal gammopathies. (A) Overall survival probability of patients with monoclonal gammopathies (censored for kidney transplantation, renal recovery, and loss of follow-up or end of the study period). (B) Survival probabilities of patients with immunoglobulin light chain amyloidosis (ALA), light–chain deposition disease (LCDD), or myeloma cast nephropathy (MCN) (censored for kidney transplantation, renal recovery, and loss of follow-up or end of the study period).

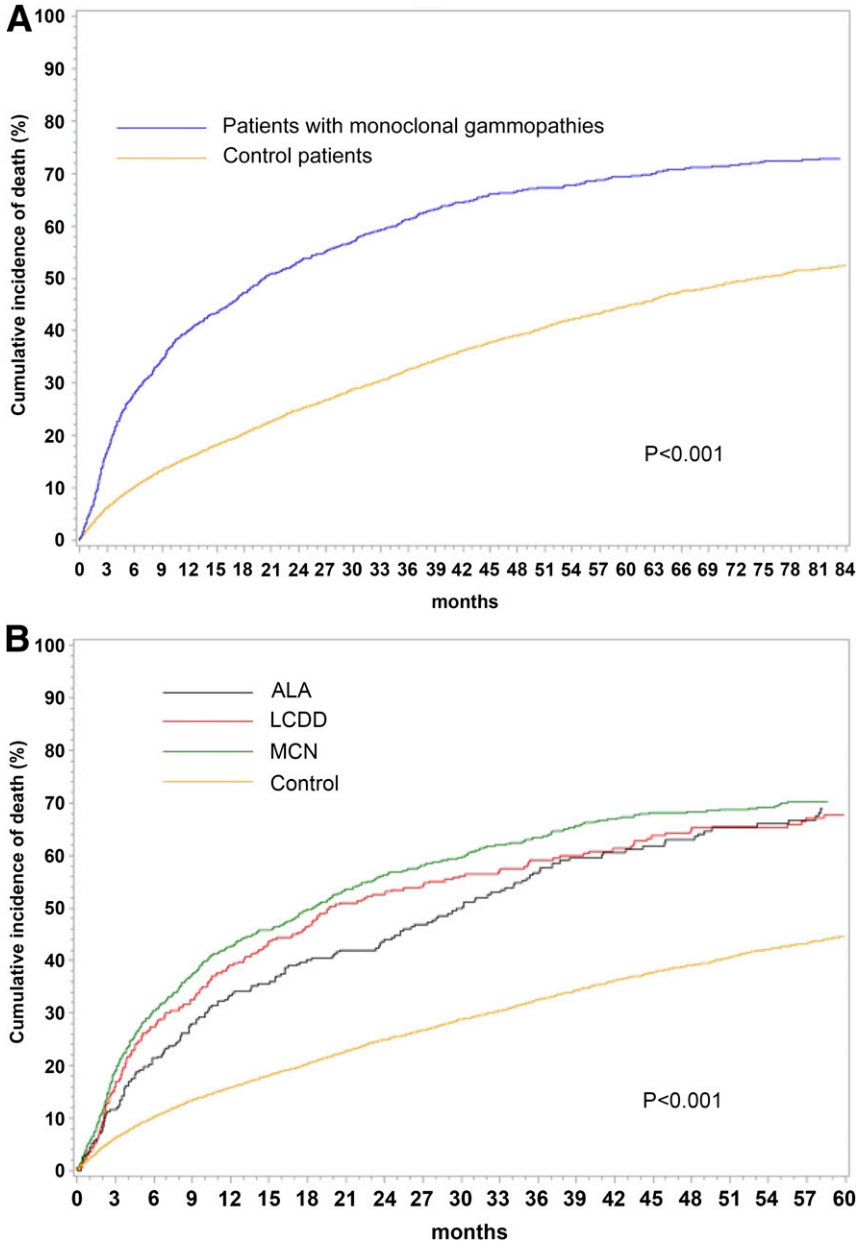


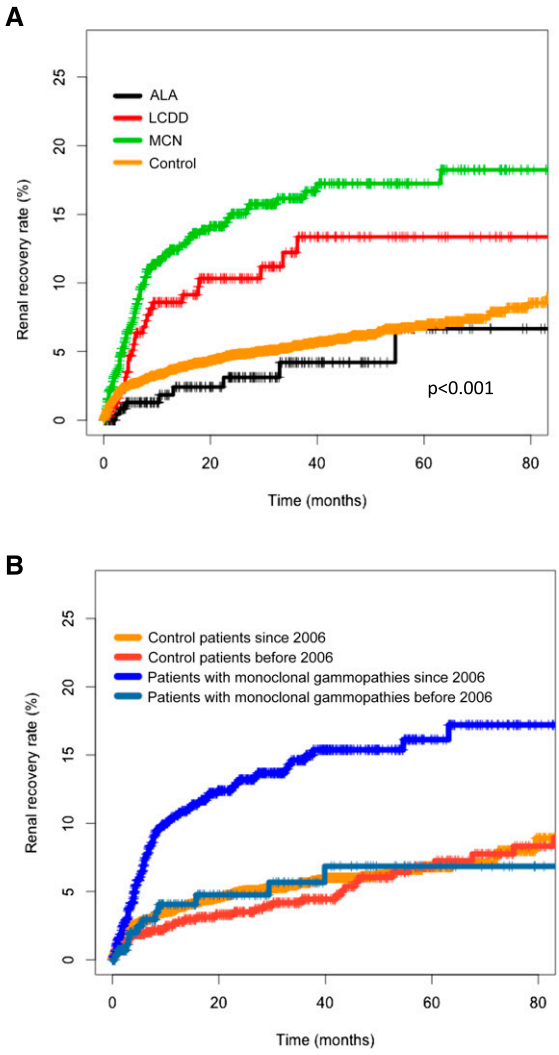
Figure 2. | **Cumulative incidence of death is higher in patients with monoclonal gammopathies than in control patients.** Cumulative incidence of death (considering transplantation and renal recovery as competing risks) in (A) patients with monoclonal gammopathies and control patients on chronic dialysis and (B) patients with AL amyloidosis (ALA), light–chain deposition disease (LCDD), or myeloma cast nephropathy (MCN) and control patients on chronic dialysis.

Principal Causes of Death in Patients with MG on Chronic Dialysis

Main causes of death in patients with MG were malignancy in 338 (34.4%) patients, cardiovascular events in 177 (18%) patients, infectious diseases in 131 (13.3%) patients, and cachexia in 51 (5.2%) patients (Table 4). Cardiovascular events were more frequent in patients with ALA (30.6%) than in patients with LCDD (15.1%) and patients with MCN (15.4%; $P<0.001$), with more frequent sudden death (11.6% versus 5.5% and 7.1%, respectively) and CHF (6.9% versus 1.8% and 1.7%, respectively). Death caused by cachexia was also more frequent in patients with ALA (8.7%) than in patients with LCDD (3.2%) and patients with MCN (4.9%; $P=0.05$).

Risk Factors of Mortality in Patients with MG

Seven parameters were associated with mortality with univariate Kaplan–Meier survival analysis (Table 5): MCN group, HD initiation on a catheter, dialysis start in emergency, CHF, body mass index <20 kg/m^2, frailty, and cardiac arrhythmia. Year of RRT initiation was not significantly associated with mortality in univariate Cox analysis (HR, 0.98%; 95% CI, 0.96 to 1.01; $P=0.13$).



N° at risk	0	20	40	60	80
Control patients since 2006	4178	2590	1239	454	93
Control patients before 2006	858	520	324	213	151
Patients with monoclonal gammopathies since 2006	1161	468	196	85	24
Patients with monoclonal gammopathies before 2006	301	125	79	58	45

ALA: AL amyloidosis; LCDD: light chain deposition disease; MCN: myeloma cast nephropathy; BMI: Body Mass Index

Figure 3. | **Renal recovery rates differ between monoclonal gammopathies and controls and has increased after 2006.** Cumulative incidence of renal recovery in (A) patients with AL amyloidosis (ALA), light–chain deposition disease (LCDD), or myeloma cast nephropathy (MCN) and control patients on chronic dialysis and (B) patients with monoclonal gammopathies and control patients on chronic dialysis before or since January 1, 2006. Patients with monoclonal gammopathies: log–rank *P* value, $P<0.001$; control patients: log–rank *P* value, $P=0.40$).

Four risk factors were independently associated with mortality after multivariate logistic Cox regression analysis: age (HR per year increase, 1.03%; 95% CI, 1.02 to 1.03; $P<0.001$), frailty (HR, 1.93%; 95% CI, 1.58 to 2.36; $P<0.001$), CHF (HR, 1.54%; 95% CI, 1.23 to 1.93; $P<0.001$), and HD initiation on a catheter (HR, 1.40; 95% CI, 1.11 to 1.75; $P=0.004$). Two factors were independently associated with a lower mortality: year of RRT initiation (HR per year increase, 0.95%; 95% CI, 0.91 to 0.99; $P<0.01$) and high BP (HR, 0.80%; 95% CI, 0.67 to 0.97; $P=0.02$) (Table 5).

Discussion

This national cohort study shows that outcome of patients with MG on chronic dialysis is poor but improving over time,

Table 3. Characteristics of patients with monoclonal gammopathy who did and did not recover renal function

Characteristic	Nonrecovery (*n*=1329)	Recovery (*n*=133)	All Patients (*n*=1462)	*P* Value
Age (yr), mean±SD	70.6±11.5	69.7±10.9	70.5±11.5	<0.001
Men (%)	744 (56)	71 (53.4)	815 (55.7)	0.63
Catheter (%)	943 (71)	112 (84.2)	1055 (72.2)	0.004
Missing	87 (6.5)	5 (3.7)	92 (6.3)	
Dialysis start in emergency (%)	593 (44.6)	73 (54.8)	666 (45.6)	0.03
Missing	100 (7.5)	9 (6.8)	109 (7.5)	
First treatment modality (%)				
Hemodialysis	1259 (94.7)	130 (97.7)	1389 (95)	0.19
Peritoneal dialysis	70 (5.3)	3 (2.3)	73 (5)	
Diabetes (%)	144(10.8)	26 (19.5)	170 (11.6)	0.003
Missing	76 (5.7)	10 (7.5)	86 (5.9)	
High BP (%)	674 (50.7)	58 (43.6)	732 (50.1)	0.16
Missing	94 (7.1)	11 (8.2)	105 (7.2)	
Ever smoker (%)				
Never	716 (53.9)	62 (46.6)	778 (53.2)	0.48
Current	73 (5.5)	5 (3.8)	78 (5.3)	
Former	205 (15.4)	23 (17.3)	228 (15.6)	
Missing	335 (25.2)	43 (32.3)	378 (25.9)	
Heart failure (%)	214 (16.1)	18 (13.5)	232 (15.9)	0.52
Missing	107 (8.1)	11 (8.3)	118 (8.1)	
Peripheral vascular disease (%)	80 (6)	5 (3)	85 (5.8)	0.41
Missing	113 (8.5)	14 (10.5)	127 (8.7)	
Coronary artery disease (%)	143 (10.8)	15 (11.3)	158 (10.8)	0.96
Missing	104 (7.8)	11 (8.3)	115 (7.9)	
Cerebrovascular disease (%)	73 (5.5)	9 (6.8)	82 (5.6)	0.65
Missing	113 (8.5)	13 (9.8)	126 (8.6)	
Chronic lung disease (%)	112 (8.4)	5 (3.8)	117 (8)	0.08
Missing	109 (8.2)	11 (8.3)	120 (8.2)	
BMI (kg/m^2), mean±SD	23.8±4.4	24.1±4.3	23.9±4.4	<0.001
BMI<20 kg/m^2 (%)	152 (11.4)	17 (12.8)	169 (12)	0.96
Missing	414 (31.2)	35 (26.3)	449 (31)	
Albumin (g/dl), mean±SD	3.0±0.8	3.2±0.8	3.0±0.8	<0.001
Albumin <3.0 g/dl (%)	332 (25)	38 (28.6)	370 (25.3)	0.62
Missing	601 (45.2)	43 (32.3)	644 (44)	
Hemoglobin (g/dl), mean±SD	9.6±1.9	9.2±1.6	9.6±1.9	<0.001
Missing (%)	368 (27.7)	28 (21)	396 (27)	
Frailty (%)	106 (8)	5 (3.8)		0.11
Missing	258 (19.4)	23 (17.3)	281 (19.2)	

BMI, body mass index.

with an increased rate of renal recovery after January 1, 2006. Survival of patients with ALA was comparable with data from the Australia and New Zealand Dialysis and Transplant Registry, comprising 490 patients with ALA or amyloid A (AA) amyloidosis on chronic dialysis (16), and a smaller French cohort of patients with ALA (17). Survival was better (39 months) in a British cohort of 221 patients with ALA (10) but worse (11 months) in an Italian cohort of 59 patients (18). A mild increase in survival of patients with ALA on dialysis was reported by Gertz and coworkers (19,20) between 1992 (19) and 2009 (20).

Survival was lower in patients with MCN from this cohort, consistent with a Spanish cohort of 28 patients with MM incident on RRT in 1980–2000 (21) and the 10.8-month survival reported in the ERA-EDTA Registry of 2453 incident patients with MM in 1985–2005 (3). Survival did not differ between two time periods (1986–1990 versus 2001–2005) in this large European cohort. Mortality was higher in patients with MG than in controls in this study, such as in data from the US Renal Data System Registry (1992–1997) showing a 2-year mortality of 58% in patients with MM versus 31% in control patients on dialysis (5). A survival of 49 months was reported in an Italian cohort of 63 patients with LCDD and renal involvement, with no association of RRT requirement with mortality (16).

Malignancy was the first cause of death in our study like in the ERA-EDTA Study (3), and there were also similar rates of cardiovascular and infectious causes of death in both studies.

Independent risk factors of mortality were age, frailty, CHF, and dialysis initiation on a catheter. Frailty has already been described as an independent risk factor of mortality in chronic dialysis (22,23), and CHF is a major prognostic factor in patients with ALA (17). The surprising association of high BP at the initiation of dialysis with a reduced risk of death has been reported before in dialysis (24) and could be of particular relevance in patients with ALA, where low BP can be caused by CHF or dysautonomia. The year of RRT initiation was also associated with a lower risk of death,

Table 4. Causes of death in patients with monoclonal gammopathy and control patients on chronic dialysis

Causes of Death	ALA (*n*=173)	LCDD (*n*=218)	MCN (*n*=591)	*P* Value	Patients with MG (*n*=982)	Controls on Dialysis (*n*=2171)	*P* Value
Cardiovascular disease (%)	53 (30.6)	33 (15.1)	91 (15.4)	<0.001	177 (18)	773 (35.6)	<0.001
Sudden cardiac death	20 (11.6)	12 (5.5)	42 (7.1)		74 (7.5)	239 (11)	
Cerebrovascular disease	7 (4)	7 (3.2)	17 (2.9)		31 (3.2)	98 (4.5)	
Congestive heart failure	12 (6.9)	4 (1.8)	10 (1.7)		26 (2.6)	128 (5.9)	
Myocardial infarction	4 (2.3)	3 (1.4)	8 (1.4)		15 (1.5)	122 (5.6)	
Cardiac arrhythmia	3 (1.7)	3 (1.4)	4 (0.7)		10 (1)	41 (1.9)	
Pulmonary embolism	0	1 (0.5)	1 (0.2)		2 (0.2)	12 (0.6)	
Others	7 (4)	3 (1.4)	9 (1.5)		19 (1.9)	133 (6.1)	
Infectious disease (%)	20 (11.6)	33 (15.1)	78 (13.2)	0.58	131 (13.3)	247 (11.4)	0.11
Septicemia	15 (8.7)	17 (7.8)	41 (6.9)		73 (7.4)	146 (6.7)	
Pulmonary infection	2 (1.2)	8 (3.7)	22 (3.7)		32 (3.3)	56 (2.6)	
Peritonitis	0	2 (0.9)	4 (0.7)		6 (0.6)	12 (0.6)	
Others	3 (1.7)	6 (2.8)	11 (1.9)		20 (2)	33 (1.5)	
Malignancy (%)	21 (12.1)	71 (32.6)	246 (41.6)	<0.001	338 (34.4)	188 (8.7)	<0.001
Solid malignancy	20 (11.6)	50 (22.9)	105 (17.8)		175 (17.8)	180 (8.3)	
Hematologic disease	1 (0.6)	21 (9.6)	141 (23.9)		163 (16.6)	8 (0.4)	
Others (%)							
Cachexia	15 (8.7)	7 (3.2)	29 (4.9)	0.05	51 (5.2)	144 (6.6)	0.12
All-causes bleedings	1 (0.6)	4 (1.8)	7 (1.2)	0.05	12 (1.2)	44 (2)	0.11
Hyperkaliemia	0	2 (0.9)	5 (0.8)	0.65	7 (0.7)	17 (0.8)	0.83
Others known causes	29 (16.8)	21 (9.6)	56 (9.5)	0.02	106 (10.8)	295 (13.6)	0.03
Unknown causes	34 (19.7)	47 (21.6)	79 (13.4)	<0.01	160 (16.3)	462 (21.3)	0.001

ALA, immunoglobulin light chain amyloidosis; LCDD, light–chain deposition disease; MCN, myeloma cast nephropathy; MG, monoclonal gammopathy.

with the probability of death decreasing over the years when taking into account patients characteristics in multivariate analysis. This may be linked to global improvement of dialysis care and/or increasing use of more effective chemotherapies.

Renal recovery was not rare in patients with MG, especially patients with MCN, and was higher than in controls. It was more frequent after January 1, 2006, which could be related to the widening use of novel medications, including bortezomib. Indeed, patients with ESRD were excluded from the first studies on bortezomib in MM (25), but bortezomib became broadly used in patients with MM or ALA on dialysis in France after January 1, 2006. In 2007, Chanan-Khan *et al.* (26) reported a 75% response rate in 24 patients on dialysis treated between 2003 and 2005, among which 17% had a renal recovery. In acute MCN, renal recovery was observed after therapy including bortezomib in eight of ten patients requiring dialysis (27) in a Greek cohort and three of 14 patients in a retrospective Italian cohort (28). Recovery rates were lower in our study, probably because only patients with chronic ESRD were included in the REIN. The possible occurrence of late renal recovery, particularly in patients with MM, is noteworthy.

Registration on the KTR waiting list and KTR were rare in our cohort. Higher KTR rates have been reported in ALA (10.2% [29] and 9.4% [16]), with a shorter delay (27.6 months [29]), than in other cohorts. Mortality after KTR was low in our cohort, comparable with the 52% after 55 months observed in a British cohort (29). KTR was anecdotal in 1998 in patients with MG (30), and although it is now considered a therapeutic option in patients in remission, it remained exceptional in patients with MCN from our cohort. Risks of KTR in this population include recurrence of myeloma, monoclonal Ig–mediated graft dysfunction, and infections (31). Similarly, KTR rate in patients with LCDD was very low. A case series of seven patients with LCDD reported a median renal graft survival of 37.2 months, with two deaths caused by the progression of MM 3 months after KTR. Thus, benefit of KTR in patients with LCDD remains uncertain, especially in patients with MM (32).

We acknowledge certain limitations to this study, mainly related to the absence of available data on hematologic disease history and specific treatment in the REIN. Indeed, the REIN is the comprehensive national registry of all patients starting RRT in France, and no disease-specific data is recorded. Moreover, accurate coding of primary renal diagnose could not be verified retrospectively, because no renal biopsy data were available. Indeed, although the French thesaurus seems more comprehensive than the ERA-EDTA Study diagnostic codes (33,34), it might not have corresponded exactly to the evolving classification of MGs. Another pitfall is the possible overlap of MGs: there can be multiple causes of ESRD in a single patient with MM or ALA. Also, patients considered as having ESRD but recovering renal function during the follow-up had, in fact, prolonged AKI. However, such patients were included in the REIN similarly before and after January 1, 2006, and the increase in recovery rate after January 1, 2006 may reflect improvement of prolonged AKI recovery. Patients who recovered renal function were not systematically followed up

Table 5. Risk factors of mortality in patients with monoclonal gammopathy on chronic dialysis

Characteristic	Median Survival (mo) or Hazard Ratio	95% Confidence Interval	Log–Rank *P* Value
Univariate analysis			
Men	17.93	15.51 to 20.39	0.47
Women	18.33	15.87 to 21.7	
ALA	28.92	23.70 to 34.75	Reference
LCDD	18.39	14.85 to 24.10	0.15
MCN	16.00	12.52 to 18.33	0.001
Hemodialysis	18.33	16.36 to 20	0.65
Peritoneal dialysis	15.57	5.54 to 30.39	
No catheter	28.03	23.87 to 32.30	<0.001
Catheter	16.49	13.93 to 18.82	
No dialysis start in emergency	20.23	18.30 to 25.28	<0.01
Dialysis start in emergency	14.85	11.61 to 19.34	
No chronic lung disease	18.43	16.69 to 20.39	0.06
Chronic lung disease	16.23	9.87 to 21.70	
No cerebrovascular disease	18.07	16.22 to 20	0.96
Cerebrovascular disease	19.54	10.43 to 30.07	
No congestive heart failure	19.67	17.93 to 22.75	<0.001
Congestive heart failure	10.16	8.16 to 12.82	
No coronary artery disease	18.59	16.69 to 20.59	0.10
Coronary artery disease	16.23	10.30 to 20.13	
No peripheral vascular disease	18.39	16.36 to 20.23	0.41
Peripheral vascular disease	15.87	9.02 to 22.62	
No diabetes	18.75	16.95 to 20.72	0.26
Diabetes	13.97	9.48 to 19.93	
No high BP	16.69	14.03 to 19.93	0.10
High BP	19.34	17.34 to 23.21	
BMI>20 kg/m^2	24.39	19.90 to 28.66	0.01
BMI<20 kg/m^2	16.62	11.21 to 23.61	
Frailty	5.15	4.07 to 6.82	<0.001
No frailty	23.61	20.49 to 27.38	
No cardiac arrhythmia	18.72	16.49 to 20.72	0.05
Cardiac arrhythmia	17.11	10.49 to 21.70	
Multivariate analysis			
Age per yr	1.03	1.02 to 1.03	<0.001
Frailty	1.93	1.58 to 2.36	<0.001
Congestive heart failure	1.54	1.23 to 1.93	<0.001
Catheter	1.40	1.11 to 1.75	0.004
Year of RRT initiation per yr	0.95	0.91 to 0.99	<0.01
High BP	0.80	0.67 to 0.97	0.02

ALA, immunoglobulin light chain amyloidosis; LCDD, light–chain deposition disease; MCN, myeloma cast nephropathy; BMI, body mass index.

in the REIN Registry after recovery, which is another limitation of this study, because only the outcome of patients with MG who remained on dialysis could be analyzed.

However, our study is the first to analyze together and then, compare between groups the characteristics and outcomes of patients on chronic dialysis with ALA, LCDD, or MCN. Completeness of the REIN Registry is the major strength of this study. Because of participation of all dialysis units in France, all patients on chronic dialysis caused by an MG were included. Another strength is the registration of easily assessable and meaningful clinical settings, like frailty. Last, the evaluation of renal recovery is of particular interest in patients with MG, and factors associated with renal recovery should be further investigated in future studies, especially regarding efficacy of novel chemotherapies.

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Disclosures

None.

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