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## ORIGINAL ARTICLE

# Kidney involvement in hereditary transthyretin amyloidosis: a cohort study of 103 patients

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## ABSTRACT

**Background.** Hereditary transthyretin amyloidosis (ATTRv) is a disabling and life-threatening disease that primarily affects the nervous system and heart. Its kidney involvement has not been systematically studied, particularly in non-V30M mutations, and is not well known to nephrologists.

**Methods.** We conducted a retrospective study describing the kidney phenotype of all prevalent patients with ATTR mutations, with neurological or cardiac involvement or presymptomatic carriers, followed up in two university hospitals from the South of France between June 2011 and June 2021.

**Results.** A total of 103 patients were included, among whom 79 were symptomatic and 24 were presymptomatic carriers. Patients carried 21 different ATTR mutations and 54% carried the V30M mutation. After a mean follow-up of  $7.9 \pm 25.7$  years, 30.4% of the symptomatic patients had developed chronic kidney disease (CKD) and 20.3% had a urinary protein:creatinine ratio  $\geq 0.5$  g/g. None of the presymptomatic carriers had CKD or proteinuria. In a multivariate analysis, late onset of symptoms (after 60 years), the V122I mutation and proteinuria were significantly associated with CKD. The median CKD-free survival in symptomatic patients was estimated at 81.0 years (interquartile range 77.1–84.9). It did not differ between V30M and non-V30M patients, but was lower in patients with the V122I mutation. The average age of the onset of CKD was  $69.3 \pm 13.0$  years. In one 38-year-old V30M female who presented a kidney-predominant phenotype, treatment with patisiran resulted in remission of the nephrotic syndrome.

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**Conclusion.** CKD affects almost one-third of patients with symptomatic ATTRv. The role of ATTRv per se in the development of CKD in this population remains to be determined, but some patients may benefit from specific therapies.

**Keywords:** ATTR, chronic kidney disease, hereditary transthyretin amyloidosis, kidney amyloidosis, proteinuria

## INTRODUCTION

Hereditary transthyretin amyloidosis (ATTRv) is a systemic autosomal dominant genetic disease. Transthyretin (TTR), also called prealbumin, is one of the most abundant circulating proteins; 90% of TTR is synthesized by the liver. More than 120 mutations in the TTR gene have been described, of which at least 15 are associated with documented kidney involvement [1]. TTR mutations result in a decrease in the interactions between the four subunits of the protein tetramer. Monomers aggregate into amyloid fibrils that deposit in tissues and impair their functions [2].

It should be pointed out that wild-type TTR can also cause amyloidosis, called 'senile ATTR amyloidosis', with predominantly cardiac involvement in elderly subjects, related to the deposition of fibrils derived from unmutated TTR.

ATTRv has variable penetrance and expressivity and usually becomes symptomatic in adulthood, with heterogeneity in the clinical presentation and clinical course. This phenotypic variability often leads to diagnostic difficulty or delay, especially in countries where the disease is not considered endemic. The main clinical manifestation is a rapidly progressive sensorimotor and autonomic polyneuropathy. Other manifestations are cardiac, cerebral, ocular, gastrointestinal and renal [3].

Worldwide, the prevalence of the disease is estimated at 0.56–1 per 10<sup>6</sup> inhabitants, with a higher prevalence in Portugal, Sweden and Japan, where patients most often carry the V30M mutation (substitution of a valine by a methionine at position 30) [4, 5].

Although rare, ATTRv is a disabling and life-threatening disease and early diagnosis is crucial. Survival from amyloid disease onset has been estimated in the literature at 7–12 years [6, 7]. The last decade has seen the development of effective, innovative therapies. Liver transplantation, which was the first-line treatment, is now being largely replaced by less invasive treatments such as the tetramer stabilizer tafamidis or the gene silencing molecules patisiran and inotersen [6, 8, 9]. A promising therapy using CRISPR-Cas9 *in vivo* hepatic gene editing is also under development [10]. There are no specific data on kidney outcomes in patients with kidney amyloidosis under gene silencing therapies.

Kidney involvement of ATTRv is not well known and has been poorly studied. A large Portuguese cohort described proteinuria in one-third of patients and end-stage kidney disease (ESKD) in 11% [1]. However, these data only concern patients with the V30M mutation the main mutation encountered in Portugal. In France, due to a more important intermingling of the population, the mutations are more diverse [11, 12]. Patients with a TTR gene mutation other than V30M may actually present kidney involvement [1, 13], and they are still under represented in the literature.

Our main objective was to study chronic kidney disease (CKD) and proteinuria prevalence in a French retrospective cohort of patients with TTR mutations, symptomatic or not, followed up in the Neurology, Cardiology and Nephrology Departments in the university hospitals of Marseille and Nîmes in the South of France.

## MATERIALS AND METHODS

### Design of the study

This is a retrospective cohort study. The inclusion period was from 1 June 2011 to 1 June 2021.

### Study population

We included all prevalent patients carrying a mutation causing ATTRv, symptomatic or not, followed up in the Neurology, Cardiology and Nephrology Departments in the university hospitals of Marseille and Nîmes.

The data included in this study were anonymized, approved by the local ethics committee and registered at the Health Data Portal of Assistance Publique-Hôpitaux de Marseille (PADS 21-038).

### Objectives

Our primary objective was to evaluate the prevalence of CKD and proteinuria in patients with a TTR mutation. Our secondary objectives were to study the survival without CKD, from birth to the last follow-up, in patients with a TTR mutation and to describe factors associated with CKD in this population.

### Definitions

Estimated glomerular filtration rate (eGFR) was calculated with the 2021 Chronic Kidney Disease Epidemiology Collaboration formula [14]. CKD was defined as an eGFR <60 mL/min/1.73 m<sup>2</sup> confirmed after 3 months. The presence of significant proteinuria was defined by a urinary protein:creatinine ratio (UPCR) ≥0.5 g/g.

Neurological involvement of ATTRv was defined by the presence of clinical symptoms of neuropathy (dysesthesias, carpal tunnel syndrome, motor deficits) associated with an impairment of electrochemical skin conductance evaluated by Sudoscan (Impeto Medical, Paris, France) or electromyogram (EMG). The severity of the neuropathy was assessed through the functional score of polyneuropathy disability (PND), representing walking capacity [15].

Cardiac involvement of ATTRv was defined by the presence of characteristic features of myocardial amyloid infiltration on transthoracic echocardiography (TTE) or on magnetic resonance imaging (MRI).

Patients were defined as symptomatic if they carried an ATTRv mutation and were symptomatic. Amyloid disease onset was defined as the beginning of symptoms, which could be, in addition to neurological and cardiac involvement, weight loss, fatigue, gastrointestinal disorders or ocular manifestations.

Patients were defined as presymptomatic if they carried an ATTRv mutation and were not symptomatic, with no neurological or cardiac involvement.

We defined high blood pressure (BP) as >140/90 mmHg.

Table 1. Patients' characteristics

Parameters	Symptomatic patients (n = 79)	presymptomatic carriers (n = 24)
Gender ratio (male:female)	2.1:1	1:1
Mutation V30M, n (%)	42 (53.2)	14 (58.3)
Other mutations, n (%)	37 (46.9)	10 (41.7)
V122I	8 (10.1)	0 (0)
F64L	4 (5.1)	4 (16.7)
S77Y	3 (3.8)	1 (4.2)
E89Q	3 (3.8)	2 (8.3)
Other	14 (17.7)	3 (12.5)
Type 2 diabetes, n (%)	6 (7.6)	0 (0)
High BP, n (%)	23 (29.1)	0 (0)
Body mass index, mean ± SD	24.5 ± 4.6	24.8 ± 4.8
Age at the onset of symptoms, mean ± SD	58.1 ± 16.5	NA
At the diagnosis of ATTR amyloidosis		
Neuropathy, n (%)	58 (73.4)	NA
Cardiac amyloidosis, n (%)	35 (44.3)	NA
CKD (eGFR <60 mL/min/1.73 m <sup>2</sup> ), n (%)	13 (16.5)	NA
Proteinuria (UPCR ≥0.5 g/g), n (%)	9/54 (16.1)	0 (0)
At The Last Assessment		
Age (years), mean ± SD	64.0 ± 15.1	43.8 ± 12.9
Neurological involvement, n (%)	72 (91.1)	0 (0)
Cardiac involvement, n (%)	43 (54.4)	0 (0)
Elevated level of BNP or NT-proBNP, n (%)	24/73 (32.9)	0/18 (0)
With cardiac involvement	23 (55.8)	0/18 (0)
Without cardiac involvement	1/30 (3.3)	0/18 (0)
Elevated level of troponin I or troponin T hs, n (%)	37/73 (50.7)	0/15 (0)
With cardiac involvement	33 (76.7)	0/15 (0)
Without cardiac involvement	4/30 (13.3)	0/15 (0)
Proteinuria (UPCR ≥0.5 g/g), n (%)	12/59 (20.3)	0/16 (0)
CKD KDIGO 1	2/59 (3.3)	
CKD KDIGO 2	1/59 (1.7)	
CKD KDIGO 3A	11 (13.9)	
CKD KDIGO 3B	9 (11.4)	
CKD KDIGO 4	1 (1.3)	
CKD KDIGO 5	3 (3.8)	
CKD (eGFR <60 mL/min/1.73 m <sup>2</sup> ), n (%)	24 (30.4)	0 (0)
ESKD on maintenance hemodialysis, n (%)	2 (2.5)	0 (0)
Kidney biopsy, n (%)	2 (2.6)	0 (0)
Liver transplantation, n (%)	6 (7.6)	NA
First-line treatment with tafamidis, n (%)	50 (63.3)	NA
First-line treatment with patisiran or inotersen, n (%)	11 (13.9)	NA
Deaths, n (%)	8 (10.1)	0 (0)
Age of death (years), mean ± SD	74.2 ± 11.3	NA

Elevated BNP or NT-proBNP: BNP >100 ng/L or NT-proBNP >450 ng/L before 50 years, >900 ng/L between 50 and 75 years, >1800 ng/L after 75 years. Elevated troponin I or troponin T hs: troponin I >0.05 pg/L or troponin T hs >14 ng/L. KDIGO, Kidney Disease: Improving Global Outcomes; NA, not applicable.

### TTR gene analyses

All patients gave their informed consent to genetic studies prior to this study. Direct Sanger sequencing of the TTR gene's full coding region was performed on DNA from mononuclear blood cells. Only TTR mutations known to be responsible for ATTRv according to the Human Gene Database and <http://www.amyloidosismutations.com/mut-attr.php> were considered in this work.

### Statistical analysis

Categorical values were expressed as number (percentage) and quantitative values were expressed as mean ± standard deviation (SD).

Patients' characteristics were reported as a descriptive cross-sectional analysis at the last assessment during the follow-up. Factors associated with CKD were identified using odds ratio (OR) calculations with Fisher's exact test, followed by a multivariate analysis with a logistic regression model.

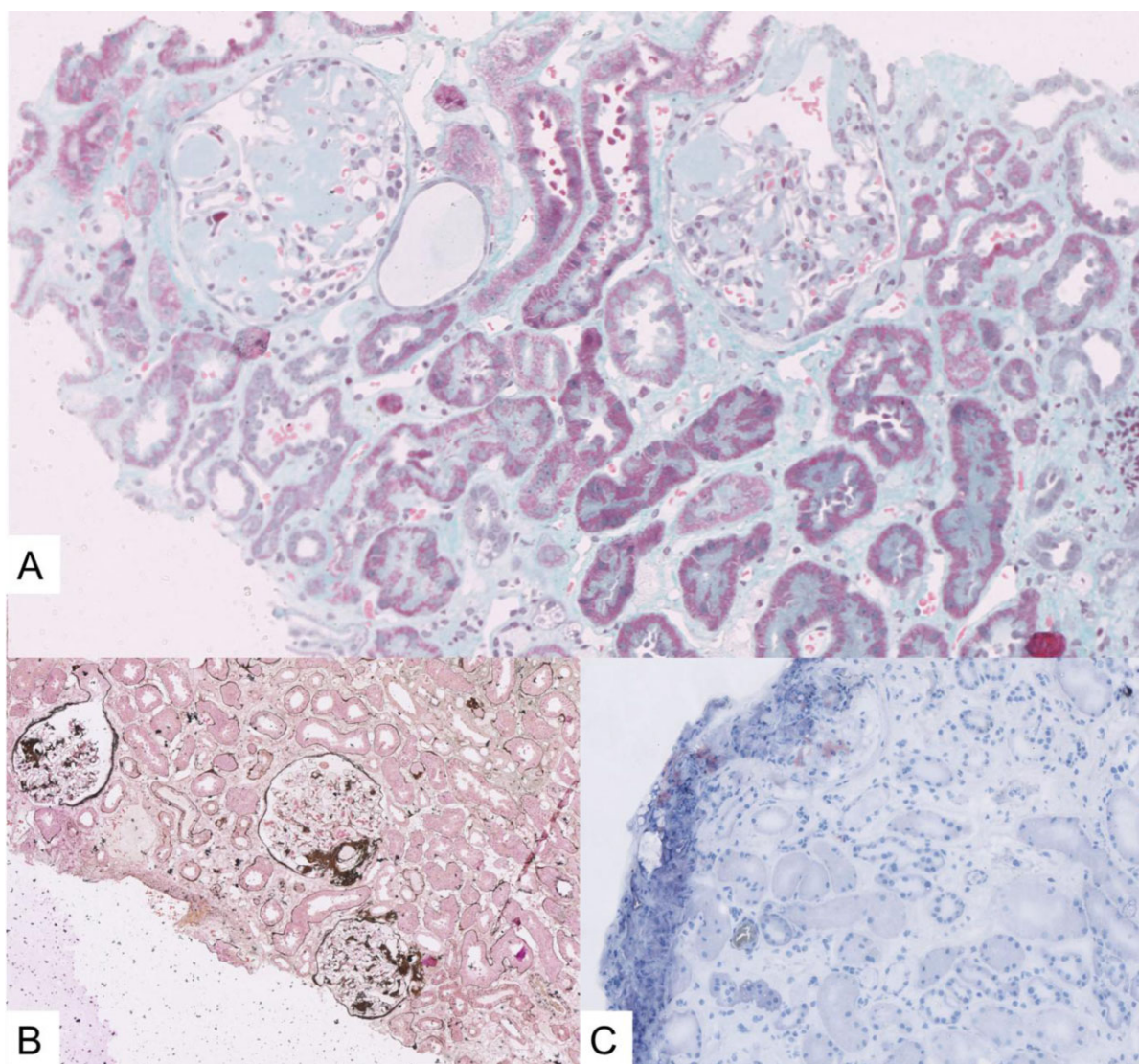
CKD-free survival was determined by the Kaplan-Meier method. Comparison of the CKD-free survival according to TTR mutations was performed with the logrank test.

## RESULTS

### Population

Overall, 103 patients were included in the analysis, of whom 79 had symptomatic ATTRv and 24 were presymptomatic TTR





**FIGURE 1:** Light microscopy results of kidney biopsy performed in two patients. (A) Patient 1: Masson's trichrome staining showed large nodular mesangial glomerular deposits. (B) Patient 2: silver staining showed segmental mesangial glomerular and distal vascular deposits (at the vascular pole of the glomeruli). (C) Patient 2: Congo-red staining showed glomerular and vascular deposits and confirmed the amyloid nature of these deposits.

mutation carriers. The main characteristics of the population are shown in Table 1. The majority of patients were male (64.1%). The mean age at the last assessment was  $64.0 \pm 15.1$  years. Patients carried 21 different ATTR mutations and 54% carried the V30M mutation. In the 79 patients with symptomatic ATTRv amyloidosis, the male:female ratio was 2.1:1 (1.6:1 in V30M patients and 2.3:1 in patients with a TTR gene mutation other than V30M). A total of 58 (73.4%) had predominant neurological involvement and 21 (26.6%) had predominant cardiac involvement at diagnosis. At the time of their last assessment, 72 (91.1%) patients had neurological involvement and 26 (32.9%) had cardiac involvement. The different organ involvements of V30M and V122I patients are summarized in the Supplementary data, Table S1. A total of 50 (63.3%) patients received first-line treatment with tafamidis, 11 (13.9%) received first-line treatment with patisiran or inotersen and 6 (7.6%) were liver transplant recipients. The mean follow-up since diagnosis was  $7.9 \pm 25.7$  years. During the follow-up, 12 patients died, at a mean age of  $73.6 \pm 11.1$  years.

### Prevalence of kidney involvement

Among the 79 symptomatic patients, 13/79 (16.5%) had CKD at the time of diagnosis of ATTRv, 9/56 (16.1%) had significant proteinuria and 1/56 (1.7%) had a nephrotic syndrome.

At the last assessment, 24/79 (30.4%) patients had CKD, 2/79 (2.5%) had developed ESKD and were on maintenance hemodialysis and 12/59 (20.3%) had proteinuria. The two patients who developed ESKD carried the V30M mutation for one and the V122I mutation for the other. Two patients had kidney biopsies, one for a nephrotic syndrome (this case is detailed below) and the other for the discovery of glomerular proteinuria while he was on inotersen. Both kidney biopsies showed glomerular and vascular amyloid deposits (Fig. 1).

Initial symptoms in the 24 CKD patients are summarized in the Supplementary data, Table S2.

Of the 24 presymptomatic carriers, none had proteinuria or CKD and 0/12 had a urine albumin:creatinine ratio  $\geq 30$  mg/g.

Table 2. Risk factor of CKD among patients with symptomatic ATTR

A. Multivariate analysis						
Parameters	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)	Model 4, OR (95% CI)	Model 5, OR (95% CI)	Model 6, OR (95% CI)
Age at amyloidosis onset >60 years	4.9 (1.5–20.5)	4 (1.2–12.7)	27.6 (3.3–3596)	4.2 (1.3–13)	4.1 (1.2–12.9)	3.1 (1.4–7.9)
V122I mutation	60.6 (6.2–8334)					3.1 (1.7–8.2)
High BP		3.1 (1.1–9.2)				0.1 (0.9–1.9)
Proteinuria			77 (8.1–10 494)			3.9 (1.4–9.7)
Neuropathy with PND score $\geq 2$				2.1 (0.7–6.1)		
Cardiac amyloidosis					2.1 (0.7–6.1)	

B. Univariate analysis			
Parameters	CKD (n = 24)	No CKD (n = 55)	OR (95% CI)
Female	7	17	0.9 (0.3–2.6)
Age >65 years	17	27	2.5 (0.9–7.0)
Age at amyloidosis onset >50 years	20	33	3.3 (1.05–11.1)
Age at amyloidosis onset >60 years	19	24	4.9 (1.6–15.1)
V30M mutation	12	30	0.8 (0.3–2.2)
V122I mutation	8	0	57.2 (6.5–7540)
High BP	12	11	4.0 (1.4–11.3)
Type 2 diabetes	3	3	2.5 (0.5–13.3)
Neuropathy with PND score $\geq 2$	13/22	16	2.9 (1.1–7.8)
Cardiac amyloidosis	17	25	2.9 (1.1–8.1)
Proteinuria	9/17	3/44	15.4 (3.4–69.6)

ORs were calculated with the Fisher's exact test for the univariate analysis and with a logistic regression model for the multivariate analysis. We used a penalized logistic regression model for the mutation V122I parameter. The presence of high BP, diabetes, neuropathy with a PND score  $\geq 2$ , cardiac amyloidosis and proteinuria was considered at the time of CKD onset in patients with CKD or at the last assessment in patients without CKD.

Overall, CKD was observed in 24/103 (23.3%) patients of the global cohort. A total of 9.5% of patients <40 years of age, 11.5% between 40 and 60 years, 32.6% between 60 and 80 years and 40.0% >80 years had CKD.

### Factors associated with CKD

Comparison between the 24 symptomatic patients with CKD and the 55 symptomatic patients without CKD is detailed in Table 2.

In univariate analysis, late onset of symptoms, i.e. after 50 years [OR 3.3 [95% confidence interval (CI) 1.05–11.1]] and *a fortiori* after 60 years [OR 4.9 (95% CI 1.6–15.1)] were associated with CKD. High BP [4.0 (95% CI 1.4–11.3)], proteinuria [OR 15.4 (95% CI 3.4–69.6)], presence of cardiac involvement [OR 2.9 (95% CI 1.1–8.1)] and presence of severe neuropathy with a PND score  $\geq 2$  [OR 2.9 (95% CI 1.1–7.8)] were also associated with CKD. The V122I mutation was strongly associated with CKD [OR 57.2 (95% CI 6.5–7540)] and not the V30M mutation. Age >65 years and diabetes were not significantly associated with CKD in this population, but only six patients were diabetic (Table 2A).

In multivariate analysis adjusted for age of onset >60 years, high BP [OR 3.1 (95% CI 1.1–9.2)], the V122I mutation [OR 60.6 (95% CI 6.2–8334)] and proteinuria [OR 77 (95% CI 8.1–10494)] were strongly associated with CKD. In a final model taking into account age of onset >60 years, high BP, the V122I mutation and proteinuria, these factors remained statistically associated with CKD, except for high BP (Table 2B).

### Survival without CKD

CKD-free survival in the 79 symptomatic patients, from birth to the last assessment of kidney function, is reported in

Fig. 2A. Median CKD-free survival was 81.0 years (interquartile range 77.1–85.0). The average age of onset of CKD was  $69.3 \pm 13.0$  years. Among the 24 patients with CKD, the mean duration between the onset of symptoms of amyloidosis and CKD was  $1.9 \pm 3.7$  years. CKD-free survival was significantly lower in the symptomatic patients with the V122I mutation (logrank test;  $P = .006$ ) than in patients with other mutations (Fig. 2B, C).

### Nephrotic syndrome as an initial manifestation of ATTRv amyloidosis

One 38-year-old female carrying the V30M mutation, who had remained asymptomatic until then, presented in June 2020 with a nephrotic syndrome (serum albumin 23 g/L, UPCr 3.5 g/g, lower limb edema) with normal kidney function. Her family history is presented in Fig. 3A. Kidney biopsy showed massive Congo red-positive amyloid deposits that showed apple-green birefringence under polarized light (Fig. 1A). Anti-TTR antibody fixation was not detected by immunohistochemistry, but repeat genetic analyses confirmed the exclusive heterozygous mutation of V30M (with no other amyloid-related genetic mutation) and proteomic analysis by mass spectrometry of micro dissected glomeruli confirmed the presence of TTR in the amyloid deposits. She had no cardiac involvement of ATTRv (normal MRI) and a stage 1 neuropathy (discrete paresthesia, normal EMG, altered Sudoscan). She was treated with angiotensin-converting enzyme inhibitors and diuretics without remission of the nephrotic syndrome after 5 months. In November 2020, a treatment with patisiran [small interfering RNA (siRNA)] was initiated, with progressive remission of the nephrotic syndrome (Fig. 3B). Diuretics were discontinued in April 2021. Kidney function remained normal.



## DISCUSSION

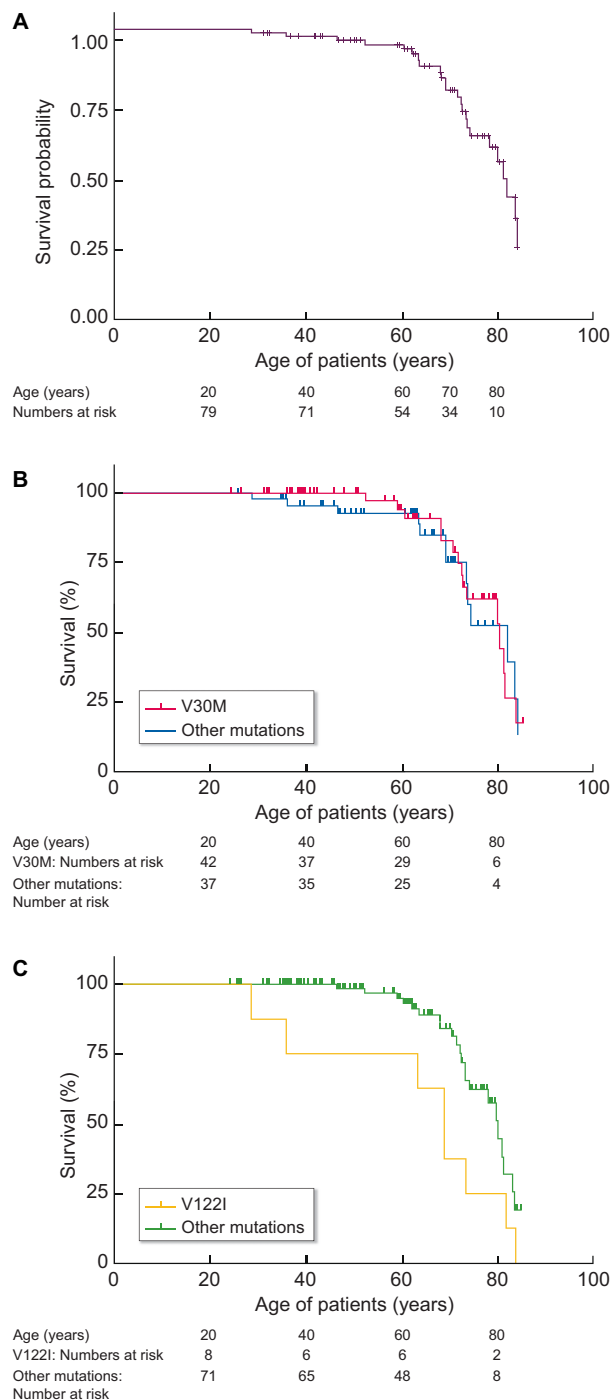
In this French cohort study, we showed a prevalence of CKD of 23% in all patients carrying a TTR mutation and of 30% among patients with symptomatic ATTRv. CKD was globally a late event in life (median CKD-free survival was estimated at 81 years) but could be encountered in young patients and could develop rapidly after the diagnosis of ATTRv. Not all TTR mutations were equal in terms of kidney involvement of ATTRv, and the V122I mutation seemed particularly at risk of CKD. We also describe here the first case of a young patient with a kidney-predominant involvement of ATTRv for whom treatment with TTR siRNA (patisiran) resulted in remission of the nephrotic syndrome.

Data on kidney function impairment in ATTRv are highly variable in the literature, with various definitions of CKD. The prevalence of CKD ranges from 10% to 50% of patients with symptomatic ATTRv in different cohorts [7, 16–19]. The three largest studies reporting kidney involvement in ATTRv are from Italy, the USA and Portugal. Ferraro et al. [13] reported a prevalence of CKD of 15% in a cohort of 46 patients with ATTRv (mostly with the F64L and V30M mutations). Gertz et al. [18] described 52 ATTRv patients from the Mayo Clinic carrying diverse mutations: 16% had CKD (without a precise definition of eGFR threshold) and 2% had ESKD. Lobato et al. [19] observed that among 403 symptomatic patients with the V30M mutation followed in three districts in Portugal, 36% had CKD (defined by a serum creatinine >106 µmol/L) and 11% had ESKD. Our study showed the same range of prevalence of CKD but a lower prevalence of ESKD than in Portugal. However, the phenotypic variability in ATTRv amyloidosis reflects the crucial role of genetic and environmental parameters.

Factors associated with CKD in the present study are both general, as described in the general population, and specific to ATTRv amyloidosis. The late onset of amyloid symptoms (>60 years of age) is strongly linked to CKD, as has been previously described by Lobato et al. [1]. Whether this association is coincidental, related to a survivorship bias (older patients being at higher risk of CKD), related to a peculiar susceptibility of older kidneys to amyloid deposition damage or related to a peculiar pattern of amyloid deposition in late-onset forms cannot be concluded here. As an age of symptom onset >60 years appears to be central to the assessment of CKD risk, we included this parameter in the multivariate analysis models. Severity of neuropathy was associated with CKD in univariate analysis, which has already been suggested in one study [17], as well as cardiac involvement. However, these parameters were no longer significantly associated with CKD after adjustment for age of symptom onset >60 years.

Importantly, this is the first study to suggest that the V122I mutation could be an important risk factor for CKD, as shown by multivariate and survival curve analyses. This mutation, which is encountered in 3.5% of African Americans, is associated with a cardiac predominant phenotype [20–22], which could be a confounding factor. Moreover, other risk factors for CKD among the V122I mutation carriers, such as sickle cell trait [23] or APOL1 gene variants [24], were not investigated and could be additional confounding factors.

The involvement of ATTRv per se in the development of CKD in this population remains to be determined. Proteinuria appears to be the first step in the natural history of ATTRv nephropathy. A prospective study of 52 patients, comprising 22 presymptomatic carriers, showed that the presence of microalbuminuria was associated with a risk ratio of 4.8 of developing neuropathy in presymptomatic carriers and with the risk of CKD



**FIGURE 2:** Survival without CKD (eGFR <60 mL/min/1.73 m<sup>2</sup>), from birth to the last assessment of kidney function: (A) in the 79 symptomatic patients from the present cohort, (B) V30M mutation versus other mutations and (C) V122I mutation versus other mutations (logrank test; *P* = .006).

in the overall cohort [25]. Similarly, a series of 62 patients with the V30M mutation on maintenance haemodialysis, which excluded liver transplant recipients, showed that 90% had proteinuria before ESKD [26]. In the present study, proteinuria was also strongly associated with CKD. The two patients who had a kidney biopsy displayed amyloid deposits in the glomeruli, vessels and tubulointerstitium. Nevertheless, proteinuria is not specific to renal amyloidosis and could be related to other kidney lesions.

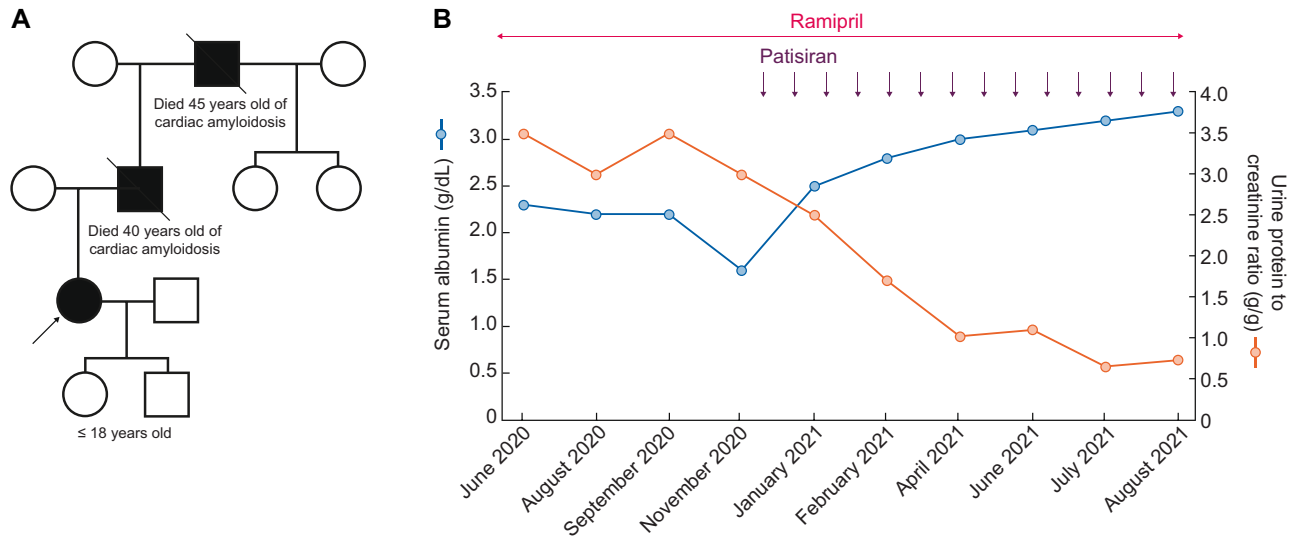


FIGURE 3: (A) Family history of the patient with predominant kidney involvement of ATTR. (B) Evolution of serum albumin and urine protein:creatinine ratio in the patient with predominant kidney involvement of ATTR.

A series of renal biopsies in the literature have shown the presence of amyloid deposits that can affect all compartments of the kidney, even in patients with CKD but without proteinuria [27–29].

However, amyloidosis does seem to be responsible for the renal damage in some patients; here we describe the case of a V30M patient with predominant kidney amyloidosis, with nephrotic syndrome and very mild neurological involvement, who was treated with patisiran with a remission of the nephrotic syndrome. This is a new dimension of siRNA, whose effectiveness has been established so far in the evolution of the neuropathy severity score [8]. Several case studies have shown a marked decrease in proteinuria with tafamidis, as well as a case of remission of a nephrotic syndrome within 1 year [30–32]. This suggests some degree of reversibility of ATTRv nephropathy when the process of amyloid fibrils deposition is blocked, which implies a dynamic turnover in the kidney with a clearance of deposits, as in abdominal fat [33].

Our study has several limitations beyond its retrospective design. A microalbuminuria assay was not available for all patients or presymptomatic carriers from the present cohort and proteinuria was measured in only 79% of patients. Thus the prevalence of microalbuminuria may have been underestimated. Factors associated with CKD were collected retrospectively. We did not study family aggregation of kidney involvement. But this study also has strengths. It is one of the largest cohorts evaluating kidney involvement in patients with ATTRv and comprises patients with various TTR mutations (only 54% of patients carried the V30M mutation). Because the exact timing of amyloid deposits is largely unknown, and the diagnosis of amyloidosis can be delayed, we decided to study CKD-free survival from birth and describe the factors associated with CKD in this population.

In conclusion, CKD affected almost one-third of patients with symptomatic ATTRv, with a mean age at CKD onset of 69 years, and could lead to ESKD. Proteinuria, late onset (>60 years) of amyloidosis symptoms and the V122I mutation were associated with CKD in this population. Predominant kidney ATTRv with nephrotic syndrome was observed in one patient who responded to gene silencing therapy. ATTRv is often diag-

nosed with delay in nonendemic regions such as France [34]. We recommend a more systematic screening of proteinuria and renal function in all ATTRv patients. We do not recommend performing a kidney biopsy systematically to document kidney involvement in ATTRv amyloidosis, but we believe that kidney biopsy can be valuable to rule out differential diagnoses in patients with nephrotic syndrome or rapidly decreasing kidney function. Greater awareness of nephrologists for this rare disease could allow earlier diagnosis and access to therapy for symptomatic patients.

## SUPPLEMENTARY DATA

Supplementary data are available at [ckj](https://ckj.oxfordjournals.org/) online.

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## CONFLICT OF INTEREST STATEMENT

None declared.

## REFERENCES

- Lobato L, Rocha A. Transthyretin amyloidosis and the kidney. *Clin J Am Soc Nephrol* 2012; 7: 1337–1346
- Schmidt M, Wiese S, Adak V et al. Cryo-EM structure of a transthyretin-derived amyloid fibril from a patient with hereditary ATTR amyloidosis. *Nat Commun* 2019; 10: 5008
- Conceição I, González-Duarte A, Obici L et al. “Red-flag” symptom clusters in transthyretin familial amyloid polyneuropathy. *J Peripher Nerv Syst* 2016; 21: 5–9



4. Parman Y, Adams D, Obici L et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. *Curr Opin Neurol* 2016; **29**: S3–S13
5. Gertz MA, Dispenzieri A. Systemic amyloidosis recognition, prognosis, and therapy: a systematic review. *JAMA* 2020; **324**: 79–89
6. Coelho T, Maia LF, Martins da Silva A et al. Tafamidis for transthyretin familial amyloid polyneuropathy. *Neurology* 2012; **79**: 785–792
7. Andersson R. Familial amyloidosis with polyneuropathy. A clinical study based on patients living in northern Sweden. *Acta Med Scand Suppl* 1976; **590**: 1–64
8. Adams D, Gonzalez-Duarte A, O’rordan WD et al. Patisiran, an RNAi therapeutic, for hereditary transthyretin amyloidosis. *N Engl J Med* 2018; **379**: 11–21
9. Benson MD, Waddington-Cruz M, Berk JL et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med* 2018; **379**: 22–31
10. Gillmore JD, Gane Ed, Taubel J et al. CRISPR-Cas9 in vivo gene editing for transthyretin amyloidosis. *N Engl J Med* 2021; **385**: 493–502
11. Mariani L-L, Lozeron P, Théaudin M et al. Genotype–phenotype correlation and course of transthyretin familial amyloid polyneuropathies in France. *Ann Neurol* 2015; **78**: 901–916
12. Coelho T, Maurer MS, Suhr OB. THAOS – the Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. *Curr Med Res Opin* 2013; **29**: 63–76
13. Ferraro PM, D’ambrosio V, Di Paolantonio A et al. Renal involvement in hereditary transthyretin amyloidosis: an Italian single-centre experience. *Brain Sci* 2021; **11**: 980
14. Gregg LP, Richardson PA, Akeroyd J et al. Effects of the 2021 CKD-EPI creatinine eGFR equation among a national US veteran cohort. *Clin J Am Soc Nephrol* 2022; **17**: 283–285
15. Hanewinkel R, Ikram MA, Van Doorn PA. Assessment scales for the diagnosis of polyneuropathy. *J Peripher Nerv Syst* 2016; **21**: 61–73
16. Steen L, Wahlin A, Bjerle P et al. Renal function in familial amyloidosis with polyneuropathy. *Acta Med Scand* 2009; **212**: 233–236
17. Ikeda S-I, Hanyu N, Hongo M et al. Hereditary generalized amyloidosis with polyneuropathy: clinicopathological study of 65 Japanese patients. *Brain* 1987; **110**: 315–337
18. Gertz MA, Kyle RA, Thibodeau SN. Familial amyloidosis: a study of 52 North American-born patients examined during a 30-year period. *Mayo Clin Proc* 1992; **67**: 428–440
19. Lobato L. A Nefropatia na Polineuropatia Amiloidotica Familiar de Tipo Portugues (TTR V30M). Porto: Instituto de Ciencias Biomedicas Abel Salazar, 2004
20. Maurer MS, Hanna M, Grogan M et al. Genotype and phenotype of transthyretin cardiac amyloidosis: THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol* 2016; **68**: 161–172
21. Buxbaum JN, Ruberg FL. Transthyretin V122I (pV142I)\* cardiac amyloidosis: an age-dependent autosomal dominant cardiomyopathy too common to be overlooked as a cause of significant heart disease in elderly African Americans. *Genet Med* 2017; **19**: 733–742
22. Jacobson DR, Alexander AA, Tagoe C et al. Prevalence of the amyloidogenic transthyretin (TTR) V122I allele in 14 333 African-Americans. *Amyloid* 2015; **22**: 171–174
23. Naik RP, Irvin MR, Judd S et al. Sickle cell trait and the risk of ESRD in Blacks. *J Am Soc Nephrol* 2017; **28**: 2180–2187
24. Freedman BI, Limou S, Ma L et al. APOL1-associated nephropathy: a key contributor to racial disparities in CKD. *Am J Kidney Dis* 2018; **72**: S8–S16
25. Lobato L, Beirão I, Silva M et al. Familial ATTR amyloidosis: microalbuminuria as a predictor of symptomatic disease and clinical nephropathy. *Nephrol Dial Transplant* 2003; **18**: 532–538
26. Lobato L, Beirão I, Silva M et al. End-stage renal disease and dialysis in hereditary amyloidosis TTR V30M: presentation, survival and prognostic factors. *Amyloid* 2004; **11**: 27–37
27. Lobato L, Beirão I, Guimaraes Sm et al. Familial amyloid polyneuropathy type I (Portuguese): distribution and characterization of renal amyloid deposits. *Am J Kidney Dis* 1998; **7**: 940–946
28. Snanoudj R, Durrbach A, Gauthier E et al. Changes in renal function in patients with familial amyloid polyneuropathy treated with orthotopic liver transplantation. *Nephrol Dial Transplant* 2004; **19**: 1779–1785
29. Oguchi K, Takei Yo-I, Ikeda S-I. Value of renal biopsy in the prognosis of liver transplantation in familial amyloid polyneuropathy ATTR Val30Met patients. *Amyloid* 2006; **13**: 99–107
30. Rocha A, Silva A, Cardoso M et al. Transthyretin (ATTR) amyloidosis nephropathy: lessons from a TTR stabilizer molecule. *Amyloid* 2017; **24**: 81–82
31. Ferrer-Nadal A, Ripoll T, Uson M et al. Significant reduction in proteinuria after treatment with tafamidis. *Amyloid* 2019; **26**: 67–68
32. Ikeda S-I, Hinenno A, Ichikawa T et al. Tafamidis dramatically improved severe proteinuria in a patient with TTR V30M hereditary ATTR amyloidosis. *Amyloid* 2019; **26**: 99–100
33. Tsuchiya A, Yazaki M, Kametani F et al. Marked regression of abdominal fat amyloid in patients with familial amyloid polyneuropathy during long-term follow-up after liver transplantation. *Liver Transpl* 2008; **14**: 563–570
34. Adams D, Lozeron P, Theaudin M et al. Regional difference and similarity of familial amyloidosis with polyneuropathy in France. *Amyloid* 2012; **19**: 61–64