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ORIGINAL RESEARCH ARTICLE

# Gateway and journey of patients with cardiac amyloidosis

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## Abstract

**Aims** Advances have been made over the last decade in the management of cardiac amyloidosis (CA), but a delayed diagnosis is still common. The aim of this study was to describe the journey to CA diagnosis from initial clinical and to analyse time to diagnosis.

**Methods and results** Between January 2001 and May 2019, 270 consecutive patients with CA diagnosed at Toulouse University Hospital were retrospectively included in this cross-sectional study: 111 (41%) light chain amyloidosis, 122 (45%) wild-type transthyretin amyloidosis, and 37 (14%) hereditary transthyretin amyloidosis.

CA onset occurred mostly with dyspnoea (50%) or systematic follow-up (10%). The cardiologist was the first line specialist in 68% of patients, followed by the nephrologist (9%) and neurologist (8%). Patients encountered a median (minimum–maximum) number of two (1–7) physician specialists and performed a median (minimum–maximum) number of three (1–8) tests before diagnosis. Median delay between symptom onset and CA diagnosis was 8 [IQR 5–14], 10 [IQR 3–34], and 18 [IQR 4–49] months, respectively, in light chain amyloidosis, wild-type transthyretin amyloidosis, and hereditary transthyretin amyloidosis subgroups ($P$ = .060). Having performed electromyography or spirometry was associated with a longer delay in diagnosis in the overall population: odds ratio = 1.13; 95% confidence interval 1.02 to 1.24; and odds ratio = 1.13; 1.03 to 1.24, respectively, probably due to non-specific initial symptoms.

**Conclusions** CA is a protean disease with various first line specialists causing a diagnostic wandering despite increasing medical community awareness. It requires a multidisciplinary specialist care networks to educate and manage symptoms and therapies.

**Keywords** Cardiac amyloidosis; Diagnostic delay; Journey of patient; First line specialist

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## Introduction

Cardiac amyloidosis (CA) is defined as the deposition of insoluble misfolded protein aggregates within the myocardium causing a dysfunction.[1] Approximately 60 heterogeneous amyloidogenic proteins have been identified, 27 of these associated with known human disease with immunoglobulin light chains the most common involved proteins followed by transthyretin.

The incidence and prevalence of CA have increased since the last decades.[2–4] Light chain amyloidosis (AL) affects approximately 8 to 12 new individuals per million person years.[5] Heart involvement occurs in 50% to 75% of AL patients.[6] Prognosis is poor with a median survival in the untreated AL patient of 6 months from the onset of congestive heart failure.[7] Median survival in untreated patients is reported to be 2.5 years after diagnosis for hereditary transthyretin

amyloidosis (ATTRv; v for variant) and 3.6 years for wild-type transthyretin amyloidosis (ATTRwt).[8,9]

Advances have been made over the last decade in diagnosis,[10,11] amyloid typing,[12,13] and treatment of CA.[14,15]

Early detection and therapy can halt cardiac damage, but delayed diagnosis is frequent and can require visits to multiple physicians after initial symptoms.[16]

The aim of this study was to describe the journey to CA diagnosis from initial clinical presentation and analyse time to diagnosis.

# Methods

## Study population

Between January 2001 and May 2019, consecutive patients with CA diagnosed at Toulouse University Hospital were retrospectively enrolled in this cross-sectional study.

Patient's medical records were reviewed to establish clinical history, physical examination, blood chemistry parameters, and journey to diagnosis.

The investigation conforms with the principles outlined in the Declaration of Helsinki. According to French law on ethics, patients were informed that their codified data will be used for the study. According to the French ethics and regulatory law (public health code), retrospective studies based on the exploitation of usual care data should not be submitted at an ethics committee, but they have to be declared or covered by reference methodology of the French National Commission for Informatics and Liberties (CNIL). A collection and computer processing of personal and medical data was implemented to analyse the results of the research. Toulouse University Hospital signed a commitment of compliance to the reference methodology MR-004 of the French National CNIL. After evaluation and validation by the data protection officer and according to the General Data Protection Regulation, this study, completing all the criteria, is registered in the register of retrospective study of the Toulouse University Hospital and cover by the MR-004 (CNIL number: 2206723v0). This study was approved by Toulouse University Hospital and confirms that ethic requirements were totally respected in the above report.

## Diagnosis of cardiac amyloidosis

Diagnosis of CA was defined if either an endomyocardial biopsy demonstrates amyloidosis or echocardiographically in presence of systemic amyloidosis proven by extra-cardiac biopsy. Echocardiographic criteria was an end-diastolic thickness of the interventricular septum $>12$ mm in the absence of hypertension or other potential causes of left ventricular hypertrophy.[17] In case echocardiography was not able to confirm CA diagnosis, cardiac magnetic resonance definition was used. Cardiac magnetic resonance was considered as suggestive of CA when it was impossible to cancel the myocardial signal on a delayed contrast enhancement look-Locker sequence with inversion time $>$ 300 ms[18] or when late gadolinium enhancement was present in a circumferential pattern involving the entire subendocardium, extending to adjacent myocardium.[19]

For transthyretin amyloidosis (ATTR), diagnosis of CA was defined according to Perugini score 2 or 3 cardiac uptake on a $^{99m}$Tc-hydroxymethylene-diphosphonate ($^{99m}$Tc-HMDP) scintigraphy and AL exclusion by absence of a detectable monoclonal protein.[20]

Systemic amyloidosis was defined by histological documentation of Congo Red staining and apple-green birefringence under cross-polarized light in at least one organ.[21] Amyloid typing relied on immunofluorescence on frozen sections by staining with polyclonal antibodies against light chains (kappa or lambda) and TTR[22] or mass spectrometric-based proteomic analysis after laser dissection of paraffin embedded samples when required.[12]

All patients diagnosed for ATTR underwent DNA analysis with sequencing of the transthyretin gene.

## Time to diagnosis

Diagnostic delay was defined as months from patient's first symptoms onset to diagnosis of CA confirmed and amyloid typing. Typing time was included in time to diagnosis.

For patients with ATTRv, time of diagnosis was retained at the time of ATTR identification because pathogenic transthyretin gene mutation identification by DNA analysis may be of varying duration.

To investigate whether diagnostic delay has decreased in recent years, patients were divided into groups according to the year CA was first suspected. Quartiles were used as groups boundaries.

## Journey to diagnosis

Date of first symptoms reported, numbers of various physician specialists encountered, dates and numbers of non-invasive, and invasive tests performed were collected from the history section of the patient's medical records. Monoclonal proteins tests and echocardiography were not included as there were performed for all the patients. Several biopsies were considered as a single test. The first line specialist was defined as the physician specialist who first suspected and mentioned CA.

## Statistical analysis

Continuous variables were tested for normal distribution using the Kolmogorov–Smirnov test and expressed as mean ± standard deviation. Results of values not normally distributed were presented as medians with interquartile ranges (IQRs). Nominal values were expressed as numbers and percentages. Association between the mean values of continuous variables was compared using the Mann–Whitney rank sum test. Nominal variables were investigated by the Pearson $\chi^2$ test or the Fisher exact test when appropriate. Group comparisons were made using ANOVA test or the Kruskal–Wallis test when appropriate for continuous variables and $\chi^2$ test for categorical variables, using the Kruskal–Wallis test and the Fisher exact test, respectively, for multiple comparisons. The effect of non-invasive and invasive testing on diagnostic delay was assessed using generalized linear models with a log link for statistically significant associations in univariate analysis. All the tests significantly associated with a delay diagnosis in univariate analysis were entered in the multivariate analysis for the overall population and for each group. Diagnostic delay was not normally distributed and was log transformed. Likelihood ratio tests were used to select predictors in the model. Differences were considered statistically significant for $P$ values of <0.05 unless otherwise stated. All analyses were performed using standard statistical software, SPSS version 25 (SPSS Inc., Chicago, Illinois, USA).

# Results

## Baseline characteristics

Three hundred and fifty patients with systemic amyloidosis were retrospectively screened during the period of inclusion. Among them, 306 (87%) had CA. One and four patients with Apolipoprotein A2 and AA amyloidosis, respectively, were excluded of the study. Twenty-three patients had incomplete medical records and were excluded. Eight patients could not be typed and were excluded. Finally, 270 patients with CA were retrospectively included in the study: 111 (41%) AL, 122 (45%) ATTRwt, and 37 (14%) ATTRv.

Baseline characteristics and treatment of patients at the first evaluation according to type of amyloidosis are presented in *Table 1*.

Among patient with AL, organ involvement was proved by endomyocardial biopsy in 23 (21%) patients and by salivary gland, kidney, and hepatic biopsies in 39 (35%), 31 (28%), and 5 (5%), respectively. Eighty-two (74%) and 29 (26%) patients had lambda and kappa light chains isotype, respectively.

Among patient with ATTR, organ involvement was proved by endomyocardial, salivary gland, neuromuscular, and hepatic biopsies in 9 (6%), 16 (10%), 4 (3%), and 1 (1%) patients, respectively. All other patients had grade 2 or 3 $^{99m}$Tc-HMDP scintigraphy without detectable monoclonal protein.

Male sex dominated in the overall population. Age at symptom onset and at CA diagnosis was significantly higher in ATTRwt subgroup. Thereby, CA patients with ATTRwt were more likely to have history of previous atrial fibrillation. Patients with AL had a lower blood pressure, a higher heart rate, and were less likely to have history of carpal tunnel syndrome or pacemaker. Biologically, creatinine level was significantly higher in ATTRwt group leading to a worse estimated glomerular filtration rate, although amyloidosis renal involvement was higher in AL group.

Concerning cardiac involvement severity, patients with ATTRv had a trend to have lower natriuretic peptides concentrations and better global longitudinal strain in comparison with other groups. Left ventricular ejection fraction was lower in ATTRwt group.

Concerning medications at first evaluation, CA patients with ATTRwt were more treated by beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers. CA patients with ATTRv were less treated by mineralocorticoid receptor antagonist and furosemide.

## Symptoms

Amyloidosis first symptoms are illustrated in *Figure 1*. Among the 270 patients included in the study, main symptom was dyspnoea (50%). Second, amyloidosis onset was through systematic follow-up for a cardiac or extra-cardiac condition in 26 (10%) patients. Patients were asymptomatic, and a systematic follow-up was performed for a previous chronic condition as hypertension, renal failure, monoclonal gammopathy finding, a family cascade screening, or cancer extension work-up. The third most common symptom was asthenia in 21 (8%) patients.

For patients with AL, main symptoms were also dyspnoea, asthenia, and oedema in, respectively, 43%, 14%, and 12% of the cases.

Seventy-nine (65%) patients with ATTRwt experienced dyspnoea. For 13 (11%) patients, amyloidosis was an incidental finding during systematic follow-up for another chronic condition.

For patients with ATTRv, the most common symptom was dysesthesia occurring in 10 (27%) patients followed by dyspnoea (19%) and systematic follow-up (19%).

**Table 1** Baseline characteristics and treatment of patients at the first evaluation according to type of amyloidosis

| | Overall | AL (1) | ATTRwt (2) | ATTRv (3) | | Post-hoc analysis | | |
|---|---|---|---|---|---|---|---|---|
| | *n* = 270 | *n* = 111 | *n* = 122 | *n* = 37 | *P* value | 1 vs. 2 | 2 vs. 3 | 3 vs. 1 |
| Age at symptom onset, years | 71 ± 11 | 66 ± 10 | 79 ± 8 | 65 ± 10 | <0.001 | <0.001 | <0.001 | 0.697 |
| Age at diagnosis, years | 73 ± 11 | 67 ± 10 | 81 ± 7 | 67 ± 10 | <0.001 | <0.001 | <0.001 | 0.820 |
| Male, *n* (%) | 195 (72) | 62 (56) | 102 (84) | 31 (84) | <0.001 | <0.001 | 0.983 | 0.001 |
| Weight, kg | 72 ± 12 | 70 ± 13 | 74 ± 12 | 73 ± 12 | 0.087 | | | |
| Height, cm | 169 ± 8 | 168 ± 9 | 169 ± 8 | 171 ± 7 | 0.089 | | | |
| Body mass index, kg/m$^2$ | 25 ± 4 | 25 ± 4 | 26 ± 4 | 25 ± 4 | 0.113 | | | |
| NYHA stage, *n* (%) | | | | | 0.003 | 0.108 | 0.001 | 0.032 |
| I | 78 (29) | 36 (32) | 23 (19) | 19 (51) | | | | |
| II | 122 (45) | 44 (40) | 66 (54) | 12 (32) | | | | |
| III | 61 (23) | 31 (28) | 24 (20) | 6 (16) | | | | |
| IV | 9 (3) | 0 (0) | 9 (7) | 0 (0) | | | | |
| Systolic blood pressure, mmHg | 126 ± 20 | 119 ± 20 | 130 ± 19 | 130 ± 21 | <0.001 | <0.001 | 0.728 | 0.008 |
| Diastolic blood pressure, mmHg | 74 ± 12 | 71 ± 12 | 75 ± 11 | 78 ± 11 | 0.002 | 0.014 | 0.125 | 0.001 |
| Renal involvement, *n* (%) | 80 (30) | 71 (64) | 6 (5) | 3 (8) | <0.001 | <0.001 | 0.710 | <0.001 |
| Medical history | | | | | | | | |
| Hypertension, *n* (%) | 129 (48) | 52 (47) | 64 (52) | 13 (35) | 0.181 | | | |
| Diabetes mellitus, *n* (%) | 39 (14) | 15 (14) | 21 (17) | 3 (8) | 0.366 | | | |
| Hyperlipidemia, *n* (%) | 88 (33) | 30 (27) | 46 (38) | 12 (32) | 0.229 | | | |
| Current/previous smoking, *n* (%) | 92 (34) | 39 (35) | 40 (33) | 13 (35) | 0.922 | | | |
| Coronary artery disease, *n* (%) | 59 (22) | 16 (14) | 37 (30) | 6 (16) | 0.009 | 0.003 | 0.069 | 0.819 |
| Carpal tunnel syndrome, *n* (%) | 69 (26) | 14 (13) | 42 (34) | 13 (35) | <0.001 | <0.001 | 0.931 | 0.007 |
| Atrial fibrillation, *n* (%) | 142 (53) | 38 (34) | 87 (71) | 17 (46) | <0.001 | <0.001 | 0.007 | 0.217 |
| Pacemaker, *n* (%) | 53 (20) | 10 (9) | 32 (26) | 11 (30) | 0.001 | <0.001 | 0.661 | 0.006 |
| ECG | | | | | | | | |
| Heart rate, beats per min | 76 ± 15 | 81 ± 15 | 73 ± 14 | 72 ± 13 | <0.001 | <0.001 | 0.879 | 0.003 |
| PR interval, ms | 199 ± 46 | 189 ± 42 | 214 ± 49 | 195 ± 43 | 0.005 | 0.001 | 0.069 | 0.533 |
| Right bundle branch block, *n* (%) | 40 (49) | 8 (44) | 28 (54) | 4 (36) | 0.492 | | | |
| Left bundle branch block, *n* (%) | 23 (28) | 6 (33) | 15 (29) | 2 (18) | 0.718 | | | |
| Low QRS voltage, *n* (%) | 50 (19) | 32 (29) | 13 (11) | 5 (14) | 0.001 | <0.001 | 0.696 | 0.038 |
| Biology | | | | | | | | |
| Creatinine, μmol/L | 123 ± 70 | 122 ± 82 | 129 ± 64 | 104 ± 35 | 0.002 | 0.002 | 0.007 | 0.562 |
| Glomerular filtration rate, mL/min | 58 ± 24 | 62 ± 28 | 51 ± 19 | 67 ± 19 | <0.001 | 0.001 | <0.001 | 0.171 |
| BNP, pg/mL | 440 [224–792] | 561 [216–940] | 437 [326–773] | 211 [137–314] | 0.029 | 0.666 | 0.017 | 0.013 |
| NT-proBNP, pg/mL | 3,092 [1,522–6,958] | 3,177 [1,503–9,138] | 3,257 [1808–6,873] | 2,136 [621–4,112] | 0.039 | 0.847 | 0.017 | 0.016 |
| Troponin T us, ng/mL | 0.2 [0.1–0.4] | 0.1 [0.1–0.4] | 0.2 [0.1–0.3] | 0.3 [0.1–0.6] | 0.680 | | | |
| Troponin T hs, ng/mL | 72 [41–117] | 84 [38–140] | 72 [43–111] | 54 [35–76] | 0.111 | | | |
| Echocardiography | | | | | | | | |
| Left ventricular ejection fraction, % | 53 ± 12 | 56 ± 11 | 49 ± 11 | 54 ± 15 | <0.001 | <0.001 | 0.003 | 0.817 |
| Global longitudinal strain, % | −11 ± 4 | −11 ± 4 | −10 ± 3 | −13 ± 4 | 0.019 | 0.240 | 0.005 | 0.052 |
| Diastolic LV septum thickness, mm | 16 ± 5 | 15 ± 3 | 17 ± 5 | 18 ± 10 | <0.001 | <0.001 | 0.628 | 0.019 |
| Diastolic LV posterior thickness, mm | 15 ± 3 | 14 ± 3 | 15 ± 3 | 14 ± 2 | 0.168 | | | |
| LVEDD, mm | 43 ± 7 | 42 ± 7 | 45 ± 8 | 43 ± 6 | 0.014 | 0.009 | 0.190 | 0.596 |
| LV mass (Penn), g/m$^2$ | 187 ± 99 | 162 ± 54 | 201 ± 73 | 208 ± 204 | <0.001 | <0.001 | 0.114 | 0.214 |
| Transmitral flow peak E velocity, cm/s | 88 ± 27 | 92 ± 28 | 86 ± 26 | 86 ± 25 | 0.308 | | | |
| E/A ratio | 2 ± 1 | 2 ± 1 | 2 ± 1 | 2 ± 1 | 0.859 | | | |
| Mitral annulus lateral Ea, cm/s | 6 ± 3 | 6 ± 3 | 6 ± 2 | 7 ± 4 | 0.141 | | | |
| E/Ea ratio | 16 ± 7 | 16 ± 7 | 16 ± 7 | 14 ± 8 | 0.269 | | | |
| Medications at first evaluation | | | | | | | | |
| Beta-blockers, *n* (%) | 94 (35) | 33 (30) | 56 (46) | 5 (14) | <0.001 | 0.010 | <0.001 | 0.073 |
| Calcium channel blockers, *n* (%) | 39 (14) | 17 (15) | 20 (16) | 2 (5) | 0.240 | | | |
| ACEI/ARB, *n* (%) | 104 (39) | 36 (32) | 60 (49) | 8 (22) | 0.002 | 0.009 | 0.003 | 0.243 |

(*Continues*)

**Table 1** (continued)

| | Overall | AL (1) | ATTRwt (2) | ATTRv (3) | | Post-hoc analysis | | |
|---|---|---|---|---|---|---|---|---|
| | *n* = 270 | *n* = 111 | *n* = 122 | *n* = 37 | *P* value | 1 vs. 2 | 2 vs. 3 | 3 vs. 1 |
| MRA, *n* (%) | 43 (16) | 20 (18) | 23 (19) | 0 (0) | 0.019 | 0.862 | 0.006 | 0.010 |
| Thiazide, *n* (%) | 19 (7) | 5 (5) | 11 (9) | 3 (8) | 0.383 | | | |
| Furosemide, *n* (%) | 150 (56) | 59 (53) | 82 (67) | 9 (24) | <0.001 | 0.031 | <0.001 | 0.002 |
| Posology (mg/day) | 40 [0–80] | 20 [0–80] | 40 [0–80] | 0 [0–0] | <0.001 | 0.023 | <0.001 | 0.006 |

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BNP, b-type natriuretic peptide; LV, left ventricular; LVEDD, LV end-diastolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-BNP; NYHA, New York Heart Association.
Bonferroni adjusted significance level for post-hoc analysis = 0.0167.

## First line specialist

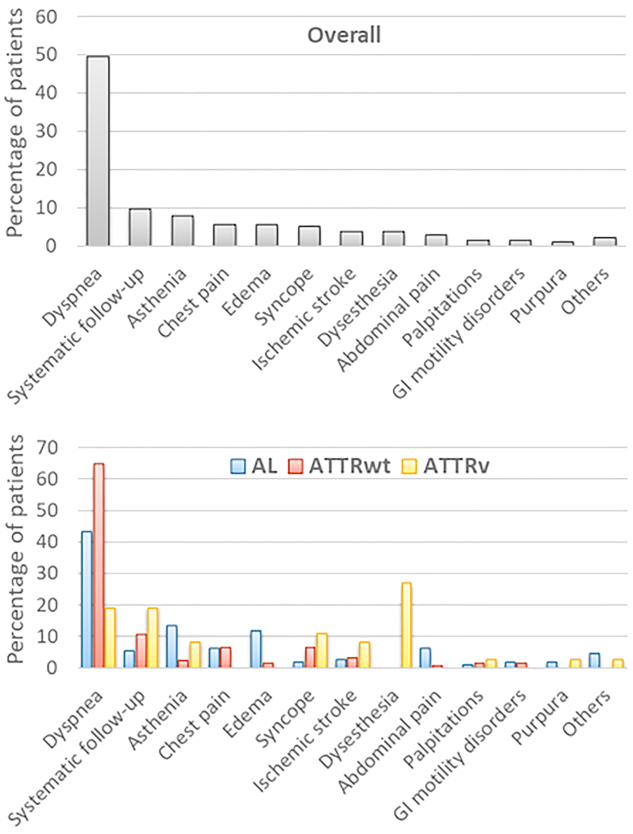
Physician specialists who first suspected CA are summarized in *Table 2*.

Cardiologist was most of the time the first physician specialist encountered by the patient in 92%, 49%, and 46% of patients with ATTRwt, AL, and ATTRv, respectively (*Figure 2*). Typical clinical presentations were heart failure, left ventricular hypertrophy, or atrial fibrillation findings (*Figure 3*). In half the AL patients, CA suspicion was set by another specialty.

Nephrologists were the first specialists to suspect CA exclusively for patient with AL and were the second most common first specialist encountered in this group with 22% of the cases ($P < .001$). Patients presented most of the time nephrotic syndrome, one patient had an acute tubular necrosis, two patients were monitored for myeloma, and one for non-CA.

Neurologists were the third most commonly encountered physician specialist, especially in ATTRv, in 41%, 4%, and 2% of the cases, respectively, for ATTRv, AL, and ATTRwt groups ($P < .001$). Clinical presentations were ischaemic stroke, neuropathy, or family cascade screening.

**Figure 1** Amyloidosis first symptoms. Prevalence of initial symptoms among the whole cohort (top). Prevalence of initial symptoms according to type of amyloidosis (bottom). GI: gastrointestinal; others: jaundice, low back pain, erectile dysfunction, skin sclerosis, macroglossia, cutaneous bleeding.




## Physician specialists and tests

Among the 270 patients included in the study, the median (minimum–maximum) number of physician specialists seen before diagnosis was 2 (1–7) (*Figure 4*). The median (minimum–maximum) number was 3 (1–7), 1 (1–6), and 2 (1–5), respectively, in AL, ATTRwt, and ATTRv groups ($P < .001$).

The median (minimum–maximum) number of tests in the overall population was 3 (1–8). The median (minimum–maximum) number was 4 (1–8), 2 (1–7), and 3 (1–7), respectively, in AL, ATTRwt, and ATTRv groups ($P < .001$).

## Time delay from symptom to diagnosis

Median delay between symptom onset and CA diagnosis was 10 months [IQR 4–26] in the overall population. It was 8 [IQR 5–14], 10 [IQR 3–34], and 18 [IQR 4–49] months, respectively, in AL, ATTRwt, and ATTRv subgroups with no significant difference ($P = .060$).

Forty (36%), 45 (37%), and 12 (32%) patients, respectively, in AL, ATTRwt, and ATTRv groups were diagnosed within the first 6 months (*Figure 5*).

**Table 2** First line specialist

| | Overall $n = 270$ | AL (1) $n = 111$ | ATTRwt (2) $n = 122$ | ATTRv (3) $n = 37$ | $P$ value | Post-hoc analysis 1 vs. 2 | 2 vs. 3 | 3 vs. 1 |
|---|---|---|---|---|---|---|---|---|
| Cardiologist, *n* (%) | 183 (68) | 54 (49) | 112 (92) | 17 (46) | <0.001 | <0.001 | <0.001 | 0.761 |
| Nephrologist, *n* (%) | 24 (9) | 24 (22) | 0 (0) | 0 (0) | <0.001 | <0.001 | 1.000 | <0.001 |
| Neurologist, *n* (%) | 21 (8) | 4 (4) | 2 (2) | 15 (41) | <0.001 | 0.577 | <0.001 | <0.001 |
| Gastroenterologist, *n* (%) | 11 (4) | 10 (9) | 0 (0) | 1 (3) | <0.001 | <0.001 | 0.467 | 0.093 |
| Geriatrician, *n* (%) | 5 (2) | 1 (1) | 3 (2) | 1 (3) | 0.557 | | | |
| Haematologist, *n* (%) | 5 (2) | 5 (5) | 0 (0) | 0 (0) | 0.031 | 0.011 | 1.000 | 0.079 |
| Internist, *n* (%) | 5 (2) | 5 (5) | 0 (0) | 0 (0) | 0.031 | 0.011 | 1.000 | 0.079 |
| Anaesthesiologist and intensivist, *n* (%) | 5 (2) | 4 (4) | 0 (0) | 1 (3) | 0.098 | | | |
| Orthopaedist, *n* (%) | 3 (1) | 0 (0) | 3 (2) | 0 (0) | 0.363 | | | |
| Rheumatologist, *n* (%) | 3 (1) | 1 (1) | 1 (1) | 1 (3) | 0.518 | | | |
| Pulmonologist, *n* (%) | 2 (1) | 2 (2) | 0 (0) | 0 (0) | 0.424 | | | |
| Urologist, *n* (%) | 2 (1) | 0 (0) | 1 (1) | 1 (3) | 0.256 | | | |
| Dermatologist, *n* (%) | 1 (0) | 1 (1) | 0 (0) | 0 (0) | 0.548 | | | |

Bonferroni adjusted significance level for post-hoc analysis = 0.0167.

The patient with the longest diagnostic delay (16 years) was 82 years old at CA diagnosis time, had no history of hypertension, was followed for a chronic coronary artery disease, and a left ventricular hypertrophy. A $^{99m}$Tc-HMDP scintigraphy was performed throughout a coronary reassessment confirming ATTRwt CA.

There was no significant difference between subgroups in delay between symptom onset and CA diagnosis according to type of first symptoms. Median diagnostic delay was the longest with dysesthesia (49 months [IQR 35–66]) in the overall population and in ATTRv subgroup. Shortest median delay occurred in the overall population in case of oedema as first symptom (4 months [IQR 1–8]).

Average numbers of tests according to diagnostic delay are illustrated in *Figure 6*. Patient with AL amyloidosis with diagnostic delay from 7 to 8 years had an average number of seven tests and encountered an average number of seven physician specialists.

Diagnostic delays according to type of test performed are summarized in *Table 3*.

TAmong the overall population, median diagnostic delay was 27 months [IQR 8–47] when other tissue biopsy (bronchopulmonary, ganglion, tongue, skin, neuromuscular, bone, and bladder) was performed vs. 9 months [IQR 4–22] when it was not performed ($P$ = .002 in univariate analysis). Diagnostic delay was also longer when electromyography (EMG) was performed (18 months [IQR 7–50] vs. 8 months [IQR 3–19]; $P$ < .001) and when spirometry was performed (15 months [IQR 7–46] vs. 8 months [IQR 3–23]; $P$ = .002).

**Figure 2** First line specialist. Type of physician specialist who first suspected cardiac amyloidosis on a decimal logarithmic scale in the overall population; in patients with AL; in patients with ATTRwt; in patients with ATTRv. Others: orthopaedist, rheumatologist, pulmonologist, urologist, dermatologist.

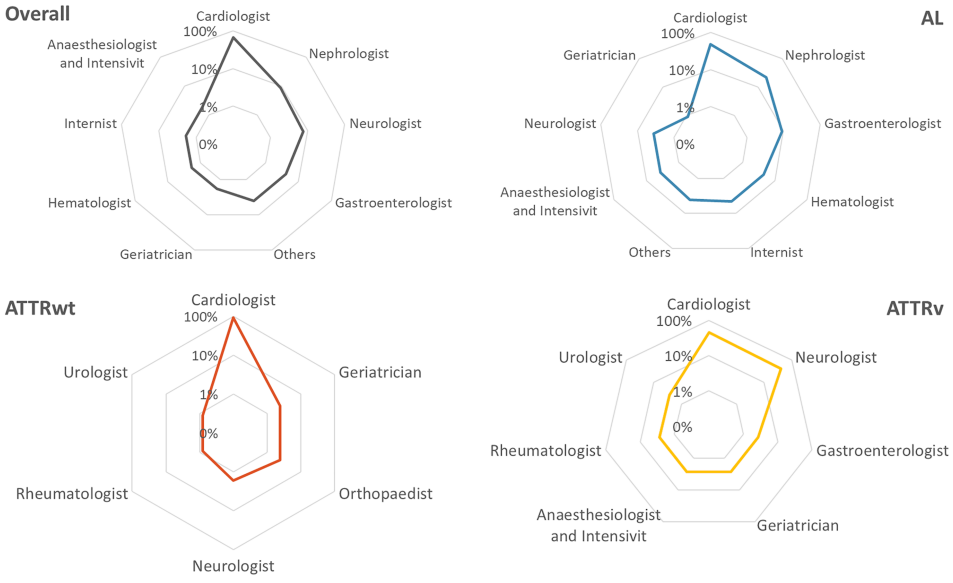




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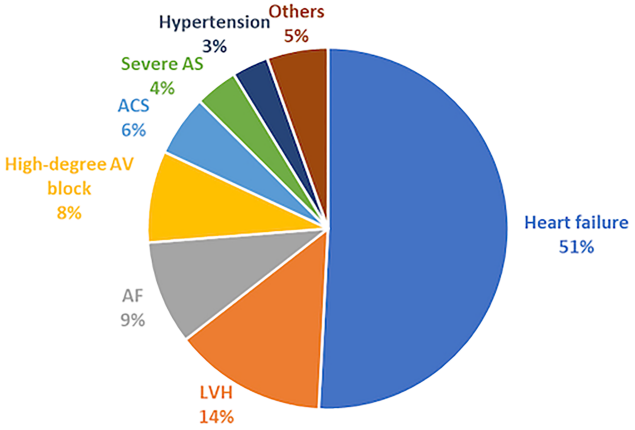
**Figure 3** Clinical presentations in case of cardiologist as first line specialist. ACS: acute coronary syndrome; AF: atrial fibrillation; AS: aortic stenosis; AV: atrioventricular; LVH: left ventricular hypertrophy. Others: 3 positive stress tests, 3 coronary artery diseases, 2 pulmonary embolisms, 2 ventricular tachycardias.




Patients with AL had longer diagnostic delay when bone marrow aspiration was performed (10 months [IQR 6–19] vs. 6 months [IQR 3–11] when it was not performed; *P* = .002) and when EMG was performed (13 months [IQR 6–33] vs. 7 months [IQR 4–14] when it was not performed; *P* = .012).

The median diagnostic delay was 17 months [IQR 8–49] when salivary gland biopsy was performed in patients with ATTRwt vs. 8 months [IQR 3–32] when biopsy was not (*P* = .015). Likewise, diagnostic delay was superior when endomyocardial biopsy was performed (49 months [IQR 14–66] vs. 9 months [IQR 3–32]; *P* = .009), when gastric biopsy or digestive endoscopy was performed (63 months [IQR 42–93] vs. 10 months [IQR 3–32]; *P* < .001), when abdominal subcutaneous fat pad aspiration was performed (46 [IQR 12–84] vs. 9 months [IQR 3–32]; *P* = .009), and when other tissue biopsy was performed (55 months [IQR 21–67] vs. 10 [IQR 3–32]; *P* = .024). ATTRwt diagnostic delay was also longer when spirometry was performed (15 months [IQR 10–57] vs. 8 [IQR 3–33]; *P* = .024).

Among patients with ATTRv, the delay was longer when EMG was performed (40 months [IQR 32–62] vs. 14 [IQR 4–49]; P = .011).

In multivariate analysis, having performed an EMG [odds ratio (OR) = 1.13; 95% confidence interval 1.02 to 1.24] and having performed a spirometry (OR = 1.13; 1.03 to 1.24) were still associated with a longer delay in diagnosis in the overall population. Among patients with AL, having performed a bone marrow aspiration (OR = 1.12; 1.02 to 1.22) was associated with a longer delay. In the ATTRwt group, none of the previous described variables were significantly associated with longer delay. Among patient with ATTRv, having performed an EMG remained

**Figure 4** Number of physician specialists and number of tests in the overall population and according to type of amyloidosis. (A) Mean and maximum number of physician specialists encountered before CA diagnosis. (B) Median and IQR number of physician specialists encountered before CA diagnosis. (C) Mean and maximum number of tests performed before CA diagnosis. (D) Median and IQR number of tests performed before CA diagnosis. $^{*}P < .05$, $^{**}P < .001$, † non-significant.

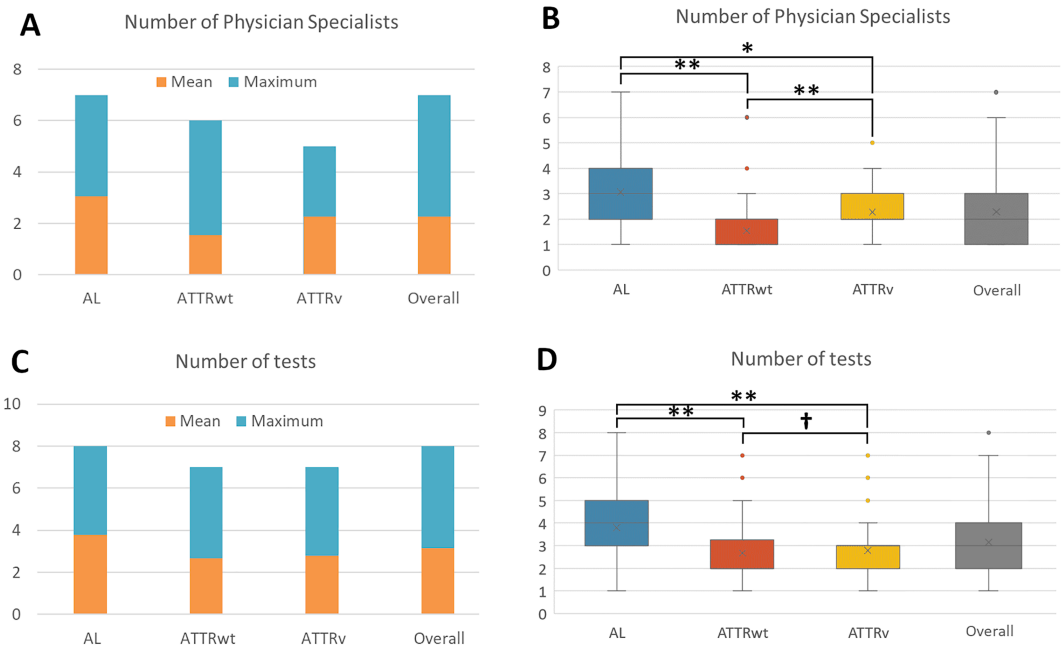
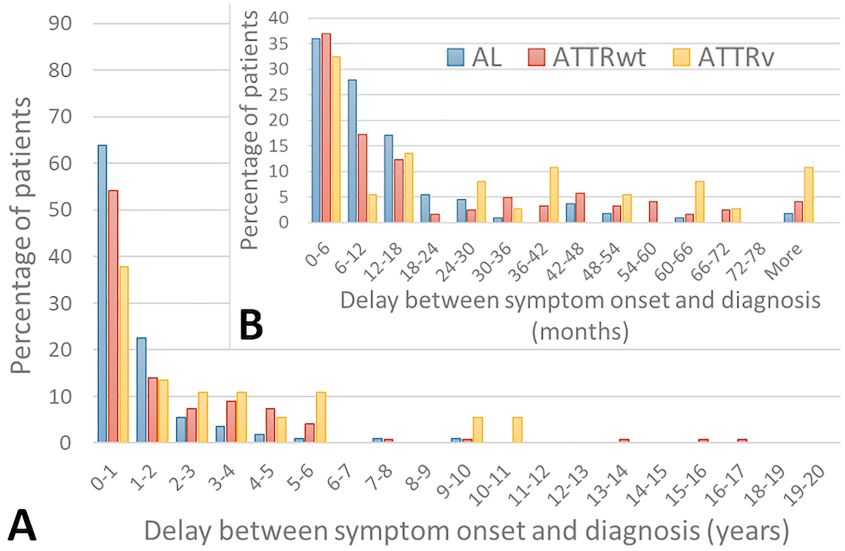


**Figure 5** Delay between symptom onset and CA diagnosis according to type of amyloidosis. (A) in years; (B) in months.




associated with greater diagnostic delay (OR = 1.24; 1.05 to 1.46).

Diagnostic delays according to year of CA was first suspected are presented in *Table 4*.

Delays between symptom onset and CA diagnosis were significantly shorter after 2012 especially for ATTRwt.

## Comparison of the last 5 years

This study extended through a long period of almost 20 years during which the diagnostic tools had evolved. Thus, we focused on the last 5 years, 2015 being the median year of our study. Results are presented in Supporting Information.

In 2001–2014 and in 2015–2019 periods, dyspnoea was still the main symptom (Figure *S1*), and cardiologist remained the first line specialist (Figure *S2*). Cardiac clinical presentations were the same in both periods (Figure *S3*). For patients with ATTRwt, first line specialists were less diverse in the recent era focusing on cardiologists. For patients with ATTRv, specialists who first suspected CA were more various in 2015–2019 era than in 2001–2014 era, showing an evolution towards a multidisciplinary care network. There had been no major change in the number of physician specialists-encountered profile and in the number of tests performed profile (Figure *S4* and *S6*). Concerning delay between symptom onset and diagnosis, there was a fewer percentage of patients with long delay in the last 5 years (Figure *S5*).

**Figure 6** Average numbers of tests according to diagnostic delay in the three subgroups.

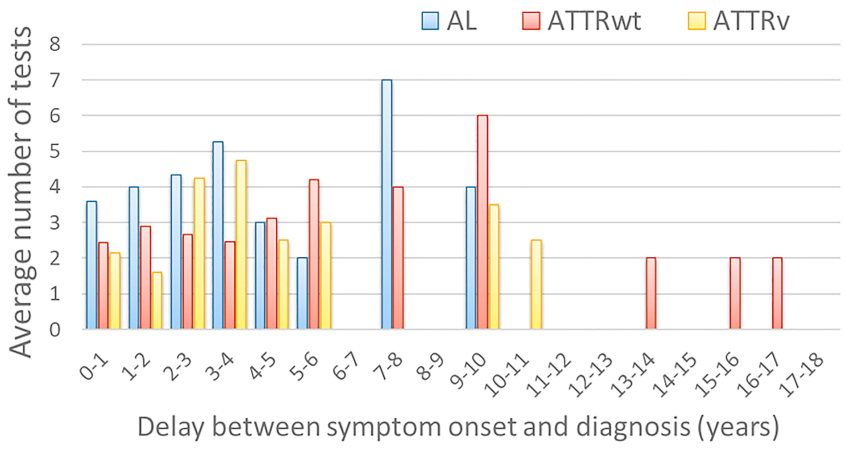




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**Table 3** Diagnostic delays in months according to type of test performed

| | Overall | | | AL | | | ATTRwt | | | ATTRv | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Not performed | Performed | *P* value | Not performed | Performed | *P* value | Not performed | Performed | *P* value | Not performed | Performed | *P* value |
| Labial salivary gland biopsy | 8 [3–27] | 12 [5–25] | 0.152 | 8 [4–19] | 7 [5–14] | 0.664 | 8 [3–32] | 17 [8–49] | 0.015 | 13 [4–45] | 37 [5–62] | 0.19 |
| Renal biopsy | 10 [4–28] | 9 [4–17] | 0.745 | 7 [5–14] | 9 [4–15] | 0.716 | 10 [3–33] | [a] | 0.361 | 18 [4–49] | [b] | [b] |
| Endomyocardial biopsy | 10 [4–26] | 10 [5–26] | 0.707 | 8 [4–14] | 7 [5–12] | 0.606 | 9 [3–32] | 49 [14–66] | 0.009 | 22 [4–49] | [a] | 0.703 |

$^{99m}$Tc-HMDP, $^{99m}$Tc-hydroxymethylene-diphosphonate; ASFA, abdominal subcutaneous fat pad aspiration; CMR, cardiac magnetic resonance; CT scan, computed tomography Scan; EGD, esophagogastroduodenoscopy; PET-CT, positron emission tomography–computed tomography.
[a]Subgroup containing only one patient.
[b]Not performed because one subgroup is empty.

# Discussion

In this retrospective study involving 270 patients, we describe the gateway and the journey to diagnosis of CA patients seen in our institution from 2001 to 2019. There are five major findings: (i) CA onset occurs mostly with dyspnoea or systematic follow-up, especially in ATTRwt; (ii) as expected, cardiologist are most of the time the first line specialist, followed by nephrologist especially in AL and neurologist especially in ATTRv; (iii) patients encountered a median number of 2 physician specialists and performed a median number of 3 tests before diagnosis; (iv) median delay between symptom onset and CA diagnosis was 10 months without significant difference between type of amyloidosis; (v) and finally, the higher the number of tests performed, the greater the diagnostic delay, which shows that the diagnostic challenge of the disease is a source of diagnostic wandering.

Our data are consistent with those reported in AL and other cardiac amyloidosis, although heterogeneous for ATTR CA diagnostic delay,[2,23–25] reporting a median (IQR) delay from 6 (1–21) months to 39 (8–78) months. In the THAOS registry, mainly composed of ATTRv, median disease duration was up to 4.0 [0.8–12.1] and 3.1 [0.6–11.9] years, respectively, in patients with ATTRv and ATTRwt.[26]

As well, in these studies, most of patients have seen three[27] or more than three[16] different physicians with various specialties before amyloidosis diagnosis was made. To explore this delayed diagnosis, Bishop *et al*. looked at patient clinical characteristics and showed that ATTR type, having carpal tunnel syndrome, having a pacemaker, being younger at symptom onset, having a presenting symptom of neuropathy, having chronic obstructive pulmonary disease, and having chronic kidney disease were significantly associated with a longer delay in diagnosis.[25] However, most of these clinical signs should now be considered as 'red flags' of the disease and reduce diagnostic delays.[28]

## Protean disease

Initial symptoms and clinical presentations of ATTRwt CA are quite homogeneous but are protean regarding the others type of amyloidosis. Clinical manifestations are consequence of advanced organ damage, mimicking other more common condition of the elderly. Patient may associate these symptoms with the ageing process or attribute them to other more prevalent chronic conditions.[27] These non-specific symptoms may not raise immediate concern for patients contributing to delays in seeking medical attention. Even in the presence of distinctive, but uncommon symptom, as purpura,[29] proper diagnosis of amyloidosis may be missed showing how difficult CA diagnosis could be.[30]

The protean clinical features of AL reflect its systemic nature that may affect kidney, heart, liver, nerve system, or gastro-intestinal tract. Even in ATTRwt, wandering may be long as clinical phenotype of wall thickening, and heart failure may be attributed to other common diseases such as hypertensive heart disease, aortic stenosis, or hypertrophic cardiomyopathy as illustrated by our longest diagnostic delay in our

**Table 4** Diagnostic delays in months according to year of cardiac amyloidosis was first suspected

| | 2001–2012 1 | 2013–2014 2 | 2015–2016 3 | 2017–2019 4 | *P* value | Post-hoc analysis 1 vs. 2 | 2 vs. 3 | 3 vs. 4 | 4 vs. 2 | 3 vs. 1 |
|---|---|---|---|---|---|---|---|---|---|---|
| Overall | *n* = 75 26 [7–57] | *n* = 55 9 [2–18] | *n* = 68 10 [4–26] | *n* = 72 6 [3–11] | <.0001 | <.0001 | 0.423 | 0.020 | <.0001 | 0.163 | <.0001 |
| AL | *n* = 37 10 [5–25] | *n* = 31 7 [2–14] | *n* = 22 9 [4–16] | *n* = 21 7 [5–13] | 0.198 | | | | | | |
| ATTRwt | *n* = 25 56 [44–71] | *n* = 17 12 [2–25] | *n* = 38 10 [3–19] | *n* = 42 5 [1–9] | <.0001 | <.0001 | 0.991 | 0.025 | <.0001 | 0.079 | <.0001 |
| ATTRv | *n* = 13 25 [6–64] | *n* = 7 18 [2–39] | *n* = 8 28 [4–59] | *n* = 9 7 [3–79] | 0.895 | | | | | | |

Bonferroni adjusted significance level for post-hoc analysis = 0.0083.

study up to 16 years. However, several coexisting cardiac conditions over time cannot be excluded in this case. In addition to that, there was for a long time a perceived rarity of ATTR CA related to confusion with the AL type, and the disease was believed to be untreatable.

### Tests and delay

Our results show that there is not a single test that leads to the CA diagnosis. The more non-specific tests are performed, the longer the time to diagnosis is. In ATTR, extra-cardiac biopsies (salivary gland or fat pad) are often negative[31,32] causing diagnostic delay or erroneously exclude diagnosis. Difficulties to prove systemic amyloidosis may lead to endomyocardial biopsy and may explain longer time to diagnosis. Unusual biopsy sites are related to more challenging diagnosis causing delay.

On the other hand, EMG or spirometry is associated with diagnostic delay probably due to non-specific initial symptoms and non-specific test results. Indeed, in our study, EMG was performed in 6% of ATTRwt, 22% of AL, and 43% of ATTRv ($P < .001$) (Data *S1*), showing the link between the final diagnosis and the tests carried out due to a different semiology according to the type of amyloidosis. Finally, bone marrow aspiration is related with delay in AL because this test is not performed to directly diagnose amyloidosis.

### Various first line specialists

ATTRwt gateway is almost exclusively cardiac while patient with AL and ATTRv CA encounter various first line specialist. Lousada *et al*. have already outlined that patients were often referred by their primary care physician to a cardiologist.[16] Atrial fibrillation is common in ATTRwt because of atrial infiltration with amyloid, increased left atrial pressure, and the advanced age of the patient.[33]

Nephrologist appears to be the first line specialist exclusively in AL as kidneys in ATTR are usually free of amyloid.[34] Although it does exist, renal involvement in ATTR is rare.[35] Neurologist is common at the front line in case of ATTRv as neuropathy represents the second main clinical manifestation of this disease.[36] Except for these three specialties, first line physician may be heterogeneous reflecting the protean clinical features of CA.

### Specialist care networks

All these findings justify the establishment of multidisciplinary specialist care networks to educate physicians and manage disease. Indeed as suggested in the guidelines on the management of AL,[37] patients with amyloidosis should be mostly treated in designated centres that have on-site availability of multidisciplinary care with interest and experience in managing patients with amyloidosis. Patients with CA should follow the same pathway. Such organizations in the field of infective endocarditis, for example, have shown to significantly reduce the mortality,[38] and this multidisciplinary approach is strongly recommended.[39] Network organization and improvement of diagnostic techniques, especially for ATTRwt, appear to reduce diagnostic delays.

CA is a diagnostic challenge. Systematic follow-up being the second most common onset of ATTwt CA shows that amyloidosis is insidious for a long time, requesting an early diagnosis. On the other hand, it means there is scope for actions to shorten diagnostic delay. The aim is identifying pre-symptomatic patients with initial, possibly reversible, organ involvement. Thus, diagnosis scores have been proposed[40,41] integrating simple clinical, biological, electrocardiographic, and echocardiographic features to optimize delay in CA diagnosis thanks to simple and accessible parameters.

### Limitations

This study shares all limitations and bias associated with retrospective and single-site studies.

Time to diagnosis depends on date of first symptom, which accuracy may be varying in patient medical records as symptoms are not very specific. However, a questionnaire-based survey may suffer more from recall bias.

Strength of the study was that while other studies have investigated the diagnosing physician showing patients usually received the correct diagnosis from a haematologist/oncologist,[16] but to our knowledge, there was no study evaluating the first line physician specialist.

Finally, we cannot exclude that there may be a referral bias with a strong cardiology and amyloidosis program in our hospital and an increased awareness of amyloidosis causing changes in the patient's journey.

## Conclusions

CA is a protean disease with various first line specialists causing a diagnostic wandering despite increasing medical community awareness, requiring the establishment of multidisciplinary specialist care networks to educate physicians and manage disease.

Further studies looking at impact of delayed diagnosis on mortality might be interesting.

## Conflict of interest

None declared.

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## Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

**Data S1.** Number of patients who underwent each test

***Figure S1.*** *Amyloidosis first symptoms. Prevalence of initial symptoms among the whole cohort for the period 2001 to 2014 (in the top left corner). Prevalence of initial symptoms according to type of amyloidosis for the period 2001 to 2014 (in the bottom left corner). Prevalence of initial symptoms among the whole cohort for the period 2015 to 2019 (in the top right corner). Prevalence of initial symptoms according to type of amyloidosis for the period 2015 to 2019 (in the bottom right corner). GI: gastrointestinal; Others: jaundice, low back pain, erectile dysfunction, skin sclerosis, macroglossia, cutaneous bleeding*

***Figure S2.*** *First line specialist. Type of physician specialist who first suspected cardiac amyloidosis on a decimal logarithmic scale in the overall population; in patients with AL; in patients with ATTRWt; in patients with ATTRv for the period 2001 to 2014 (left) and for the period 2015 to 2019 (right). Others: orthopaedist, rheumatologist, pulmonologist, urologist, dermatologist*

***Figure S3.*** *Clinical presentations in case of cardiologist as first line specialist for the period 2001 to 2014 (left) and for the period 2015 to 2019 (right). ACS: acute coronary syndrome; AF: atrial fibrillation; AS: aortic stenosis; AV: atrioventricular; LVH: left ventricular hypertrophy. Others: 3 positive stress tests, 3 coronary artery diseases, 2 pulmonary embolisms, 2 ventricular tachycardias.*

***Figure S4.*** *Number of Physician specialists and number of tests in the overall population and according to type of amyloidosis. A. Mean and maximum number of Physician specialists encountered before CA diagnosis for the period 2001 to 2014. B. Median and IQR number of Physician specialists encountered before CA diagnosis for the period 2001 to 2014. C. Mean and maximum number of tests performed before CA diagnosis for the period 2001 to 2014. D. Median and IQR number of tests performed before CA diagnosis for the period 2001 to 2014. E. Mean and maximum number of Physician specialists encountered before CA diagnosis for the period 2015 to 2019. F. Median and IQR number of Physician specialists encountered before CA diagnosis for the period 2015 to 2019. G. Mean and maximum number of tests performed before CA diagnosis for the period 2015 to 2019. H. Median and IQR number of tests performed before CA diagnosis for the period 2015 to 2019. * $P < .05$, ** $P < .001$, † non-significant*

***Figure S5.*** *Delay between symptom onset and CA diagnosis according to type of amyloidosis. A. in years for the period 2001 to 2014, B. in months for the period 2001 to 2014. C. in years for the period 2015 to 2019. D. in months for the period 2015 to 2019*

***Figure S6.*** *Average numbers of tests according to diagnostic delay in the three subgroups for the period 2001 to 2014 (left) and for the period 2015 to 2019 (right)*

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