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Clinical Research

Changes in amyloidosis phenotype over 11 years in a cardiac amyloidosis referral centre cohort in France

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ABSTRACT

Background: Early cardiac amyloidosis (CA) diagnosis enables patients to access effective treatments for better long-term outcomes, yet it remains under-recognised, misdiagnosed and inadequately managed.
Aim: To reduce diagnostic delays, we aimed to describe the epidemiological and clinical characteristics and changes over an 11-year period.
Methods: This was a retrospective, observational cohort study of all patients referred to the Henri-Mondor Hospital for suspected CA.
Results: Overall, 3194 patients were identified and 3022 were included and analysed. Our patients came from varied ethnic backgrounds, and more than half (55.2%) had confirmed CA. Over 11 years, referrals increased 4.4-fold, mostly from cardiologists. Notably, wild-type transthyretin amyloidosis (ATTRwt) became the predominant diagnosis, with referrals increasing 15-fold from 20 in 2010–2012 to 308 in 2019–2020. The number of amyloid light chain (AL) diagnoses increased, whilst

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variant transthyretin amyloidosis (ATTRv) numbers remained relatively stable. Concerning disease severity, AL patients presented more frequently with severe cardiac involvement whereas an increasing number of ATTRwt patients presented with National Amyloid Centre stage I (22.0% in 2013–2014 to 45.9% in 2019–2020). Lastly, among patients diagnosed with ATTRv in 2019–2020, 83.9% had ATTR Val122Ile cardiac phenotype.

Conclusions: This study shows that increasing cardiologist awareness and referrals have increased CA diagnoses. With improved awareness and non-invasive diagnostic techniques, more patients with ATTRwt with milder disease and more ATTRv Val122Ile mutations are being referred and diagnosed. Although more AL cases are being recognised, patients are diagnosed with severe cardiac involvement.

1. Abbreviations

AL	amyloid light chain
ATTR	transthyretin amyloidosis
ATTRv	variant transthyretin amyloidosis
ATTRwt	wild-type transthyretin amyloidosis
CA	cardiac amyloidosis
CARC	Cardiac Amyloidosis Referral Centre
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
ESC	European Society of Cardiology
GLS	global longitudinal strain
LVEF	left ventricular ejection fraction
NAC	National Amyloid Centre
NYHA	New York Heart Association
THAOS	Transthyretin Amyloidosis Outcomes Survey
TTR	transthyretin

2. Introduction

Cardiac amyloidosis (CA) is becoming a more acknowledged cause of heart failure or cardiomyopathy, yet remains underrecognised, misdiagnosed and inadequately managed [1]. The three most common CA subtypes are amyloid light chain (AL), variant transthyretin (ATTRv) and wild-type transthyretin (ATTRwt) amyloidosis [2], some of which can progress quickly with rapid myocardial wall thickening and congestive cardiac failure. Unfortunately, signs and symptoms of CA are nonspecific, heterogeneous and often appear once levels of organ amyloid fibril infiltration have become high. This means that diagnosis is delayed and commonly misrecognised as aging, hypertrophic cardiomyopathy, heart failure with preserved ejection fraction or hypertension [3–6].

Nevertheless, recent epidemiological and clinical research has identified hallmark warning signs and symptoms of systemic amyloidosis, which have enabled more accurate diagnosis. Warning signs include cardiac (dyspnoea, congestion, syncope and low voltage on electrocardiogram [ECG]) [7] and extracardiac (autonomic dysfunction, sensorimotor polyneuropathy and carpal tunnel syndrome) symptoms. These cardiac and extracardiac signs and symptoms appear to precede cardiac involvement and heart failure, providing a priceless window of opportunity for early intervention [3–6,8,9].

Although effective new treatments have become available in recent years for some forms of CA [10], there is a need to better understand the epidemiological and clinical characteristics of this group of diseases to define populations in clinical research protocols for new interventional therapies.

The Mondor Cardiology Department is a Cardiac Amyloidosis Referral Centre (CARC) with an onsite multidisciplinary team that collaborates with a 25-centre, national network (www.reseau-amylose.org) [11]. Over the last 10 years, an increasing number of patients with rare forms of cardiomyopathy have been referred for rapid diagnosis. This multidisciplinary collaboration has enabled the Mondor CARC to gain valuable experience in CA and build one of the largest patient populations in Europe. This makes the Mondor CARC well placed to investigate the epidemiological and clinical characteristics of the various CA subtypes.

This study aimed to describe and record changes in epidemiological and clinical characteristics among patients referred to and diagnosed at the CARC during 2010–2020.

3. Methods

This retrospective, observational, cohort study included patients referred to the Henri-Mondor Hospital for suspected CA. All patients registered in the hospital amyloidosis registry between 1 January 2010 and 31 December 2020 were included in the study population.

A prospectively formed database was created in 2009 and used to collect clinical data from each patient once included at the centre and from regular follow-up consultations or hospitalizations. Reports for patients monitored outside the Henri-Mondor Hospital were collected and imported into the database by physicians, department clinical research associates and secretaries from the CA heart failure departments as previously described [11].

3.1. Data collection

Once patients had been informed of the study and provided their consent to obtain their data, clinical data, laboratory results, imaging examinations (transthoracic echocardiogram, scintigraphy and magnetic resonance imaging) and pathology reports (endomyocardial and accessory salivary gland biopsies) and genetic testing were collected from the database. All patients provided consent to publish their data anonymously. This study was performed in accordance with the 1975 Helsinki Declaration. Data were recorded electronically in the Henri-Mondor Amyloidosis Network registry approved by the local ethics committee (Créteil) and by the National Committee for Data Protection (*Commission Nationale Informatique & Libertés* n° 1431858).

3.2. Data analysis

The 11 years of data were analysed in five periods of 3, 2, 2, 2 and 2 years. The first period contained 3 years of data as the multidisciplinary amyloidosis centre was newly created and patient numbers were lower. Period 1 was 1 January 2010 to 31 December 2012 and each period thereafter started on 1 January and ended on 31 December the following year until 2020.

3.3. Statistical analyses

The complete population data were analysed in terms of clinical parameters (New York Heart Association [NYHA] classification,

European Staging classification for AL [12,13] and National Amyloid Centre (NAC) transthyretin amyloidosis [ATTR] classification [8], laboratory results (estimated glomerular filtration rate [eGFR], creatinine, total bilirubin, N-terminal pro-B-type natriuretic peptide [NT-proBNP] and high-sensitivity troponin), ECG and echocardiography results.

The chi-squared test was used to analyse changes in these criteria over time. Differences between amyloidosis populations in each time period were analysed using the Kruskal-Wallis test. Graphs were created to visualise the changes and numbers are presented in tables. SPSS software was used for the statistical analyses. Significance threshold was set at $P < 0.05$.

4. Results

4.1. Study population

In total, 3194 patients were referred to the centre, 172 of whom were enrolled outside the defined study period and were therefore excluded. The remaining 3022 patients were included in the database (Fig. 1).

Patients seen at the centre are distributed throughout France. Most live in the Île de France region and as the distance increased from Paris, the number of patients decreased. Some patients came from Guadeloupe, the Reunion Islands, Martinique and French Guiana (Fig. A.1).

total of 3022 patients were treated at the centre, most of whom had CA ($n = 1668$; 55.2%), acquired cardiopathies ($n = 812$, 26.9%) and genetic cardiomyopathies ($n = 175$, 5.8%) other than ATTRv, and 367 (12.1%) were classified as "other", meaning that they had no diagnosis or were lost to follow-up during the diagnosis process or had conditions without associated cardiopathy (Fig. 2A and Table A.1). The numbers of cases enrolled increased throughout the 11-year period and CA remained the most common diagnosis (Fig. 2B).

The median age of patients with CA was 75 years and most were male (69.7%) (Table 1). In contrast, patients with acquired cardiopathies were younger (median 66 years), as were those with genetic cardiomyopathies other than ATTRv (median 57 years). Furthermore, patients with CA were more likely to present with severe cardiac involvement, higher NYHA classes, NT-proBNP and high-sensitivity troponin levels, lower left ventricular ejection fraction and worse global longitudinal strain (GLS) than those with genetic or acquired cardiopathies (Table 1).

4.2. Changes in CA subtype incidence

During the 2010–2012 period, ATTRv was the most common subtype, accounting for 46.8% ($n = 65$) of the CA population and the number of cases remained relatively stable over the study period, as did the numbers of patients with rare amyloidosis forms and asymptomatic transthyretin (TTR) mutations (Figs. 3 and 4). However, we observed that the number of AL patients increased over time, peaking in 2017–2018 with 132 patients and reducing slightly in 2019–2020 to 117 patients. Notably, ATTRwt numbers increased 15-fold from 20 people in 2010–2012 to 308 in 2019–2020, with this subtype becoming the predominant CA diagnosis in 2015–2016 and remaining this way since then (Figs. 3 and 4).

4.3. Characteristics of CA subtypes

Patient characteristics between the CA subtypes changed over the 11-year period and are presented in Table 2 for AL, Table 3 for ATTRv and Table 4 for ATTRwt. Fig. 5 shows the changes in European staging for AL and National Amyloid Centre staging for ATTRv and ATTRwt.

Although patient ages remained similar over time among patients with AL (Table 2) and ATTRwt (Table 4), the median age of patients with ATTRv increased from 60.3 years in 2010–2012 to 74.8 years in 2019–2020 (Table 3). Among patients with ATTRv, the proportion of male patients increased from 63.1% in 2010–2012 to 74.8% in 2019–2020 (Table 3).

Importantly, extracardiac symptoms appeared earlier than cardiac symptoms in all three subtypes (Tables 2–4). The times between the first extracardiac symptoms appearing and diagnosis were similar during all time periods in the three main CA subtypes, but were shortest in AL (approximately 10 months) and longest in ATTRwt (approximately 50 months) (Tables 2–4, Fig. A.2). Times from first cardiac symptoms to CA diagnosis reduced significantly over time in all CA subtypes from period 2 to 5, reducing in AL from 7 to 5 months, in ATTRv from to 17 to 10 and in ATTRwt from 27 to 12 months (Tables 2–4).

Disease severity differed during the study period for the three CA subtypes (Fig. 5). Among patients with AL, the proportion with severe cardiac involvement (European Staging 3a and 3b) remained stable at around 70% from 2013–2014 to 2019–2020 and GLS did not change significantly over time (Table 2, Fig. 5).

In contrast, among patients with ATTRv, the proportion with severe cardiac involvement (NAC stage 1 or 3) increased significantly ($P = 0.011$; Table 3 and Fig. 5). This coincided with the proportion with GLS < –14% increasing (Table 3). Interestingly, in 2019–2020, the mean NT-proBNP was lowered among ATTRv patients (Table 3). In 2010–2012, most patients with ATTRv had the neurologic phenotype ATTR Val30Met and few had the cardiac phenotype ATTR Val122Ile mutation (Fig. A.3). However, from 2013–2014 onwards, ATTR Val122Ile mutations overwhelmingly became the major mutation diagnosed by 2019–2020.

Among patients with ATTRwt, the proportion with NAC stage 1 increased significantly from 2013–2014 onwards ($P = 0.008$; Table 4, Fig. 5). This corresponded with significantly decreasing NT-proBNP levels (Table 4).

4.4. Genetic counselling activity for CA

Few asymptomatic ATTR carriers were present during 2010–2012 and 2013–2014 ($n = 12$ each) (Fig. A.4). During 2015–2016, two relatives without mutations were seen and this number increased to 30 during 2019–2020. Genetic counselling was recorded for the first time in 2017–2018, with four relatives, and this number increased dramatically to 26 patients in 2019–2020 (Fig. A.4).

4.5. Referrals for CA

During 2010–2012, few patients were referred to the centre by cardiologists (Fig. A.5). However, this increased steadily until 2015–2016, by which time they were referring the most patients and have continued to do so (Fig. A.5). Neurologists mainly refer patients with ATTRv to the CARC (Tables 2–4). Referral from nephrologists, internal medicine specialists and haematologists have remained largely consistent over time (Fig. A.5).

5. Discussion

This is one of the largest cohorts of patients with CA in Europe and our study clearly shows that marked changes have occurred in epidemiology and clinical characteristics over 11 years among patients with CA in this CARC. During the study period, the CARC activity more than tripled and more than half the patients referred were diagnosed with CA (55.2%). Also, ATTRwt became the predominant subtype, with patients increasing in number and proportion from 2015–2016 onwards. ATTRwt now accounts for 50.3% of all

Table 1
Baseline characteristics of patients presenting with Cardiac Amyloidosis (CA), acquired cardiopathies, genetic cardiopathies or other at the CARC.

	Cardiac Amyloidosis (n = 1668)	Acquired cardiopathies (n = 812)	Genetic cardiopathies (n = 175)	Other (n = 367)	P
Clinical characteristics					
Age (years)	75 (63–83)	66 (54–78)	57 (46–66)	73 (61–82)	< 0.001
Male	1162 (69.7)	515 (63.4)	111 (63.4)	224 (61.0)	< 0.001
NYHA class III or IV	557/1469 (37.9)	180/604 (29.8)	26/118 (22.0)	93/247 (33.9)	< 0.001
Systolic blood pressure (mmHg)	125 (110–140)	134 (120–153)	125 (115–139)	135 (120–149)	< 0.001
Atrial fibrillation or flutter	373/1468 (25.4)	100/641 (15.6)	15/134 (11.2)	50/282(17.7)	< 0.001
Extracardiac symptoms					
Carpal tunnel symptoms	818/1500 (54.5)	52/254(20.5)	6/56(10.7)	35/127 (27.6)	< 0.001
Carpal tunnel surgery	536 (32.1)	22 (2.7)	1 (0.6)	16 (4.4)	< 0.001
Hearing loss	595 (35.7)	55 (6.8)	15 (8.6)	25 (6.8)	< 0.001
Symptomatic dysautonomia (hypotension)	468 (28.1)	43 (5.3)	6 (3.4)	19 (5.2)	< 0.001
Laboratory variables					
NT-proBNP (pg/mL)	2813 (927–8331)	1212 (352–3116)	808 (219–1518)	911 (156–3168)	< 0.001
High-sensitivity troponin (ng/mL)	63 (34–105)	25 (13–37)	17 (11–36)	23 (11–47)	< 0.001
Creatinine (μmol/L)	108 (84–144)	100 (80–139)	85 (73–109)	101 (77–139)	< 0.001
eGFR (mL/min/1.73m^2)	57 (41–76)	63 (40–80)	78 (62–91)	63 (40–83)	< 0.001
Total bilirubin (μmol/L)	9 (6–15)	8 (5–12)	7 (5–9)	7 (5–11)	< 0.001
Echocardiographic characteristics					
Left ventricular ejection fraction (%)	53 (43–60)	55 (42–62)	59 (50–65)	56 (47–62.5)	< 0.001
LVST (mm)	16 (13–19)	13 (11–16)	16 (12–19)	12 (10–14)	< 0.001
GLS (%)	−10(−14 to −7)	−13 (−16 to −10)	−14.5 (−18 to −11)	−15 (−18 to −12)	< 0.001
Cardiac output (L/min)	4.3 (3.3–5.3)	4.8 (3.9–6.1)	5.2 (4.3–6.0)	5.0 (4.1–6.2)	< 0.001

Data are expressed as median (interquartile range), n (%) or n/N (%) in case of missing data. CA: cardiac amyloidosis; CARC: Cardiac Amyloidosis Referral Centre; eGFR: estimated glomerular filtration rate; GLS: global longitudinal strain; LVST: left ventricular septal thickness; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association.

Table 2
Changes in baseline clinical, electrocardiographic, echocardiographic and laboratory characteristics of patients with AL amyloidosis over time.

Time period	2010–2012[a] (*n* = 33)	2013–2014 (*n* = 52)	2015–2016 (*n* = 88)	2017–2018 (*n* = 132)	2019–2020 (*n* = 117)	*P*
Clinical characteristics						
Age (years)	64 (56–74)	67 (57–72)	68 (59–75)	67 (58–75)	67 (60–75)	0.201
Male	23 (69.7)	27 (51.9)	50 (56.8)	83 (62.9)	70 (59.8)	0.473
NYHA class						0.085
1	6 (18.2)	7 (13.5)	12 (13.6)	14 (10.6)	9 (7.7)	
2	10 (30.3)	9 (17.3)	26 (29.5)	47 (35.6)	46 (39.3)	
3	8 (24.2)	22 (42.3)	25 (28.4)	50 (37.9)	31 (26.5)	
4	4 (12.1)	5 (9.6)	15 (17.0)	8 (6.1)	10 (8.5)	
NA	5 (15.2)	9 (17.3)	10 (11.4)	13 (9.8)	21 (17.9)	
Systolic blood pressure (mmHg)	120 (105–133)	112 (97–126)	112 (100–128)	109 (101–127)	110 (97–125)	0.207
Specialty referring the patient						< 0.001
Cardiology	8 (24.2)	7 (13.5)	19 (21.6)	60 (45.5)	48 (41.0)	
Neurology	0 (0)	0 (0)	0 (0)	1 (0.8)	1 (0.9)	
Other specialties	25 (75.8)	45 (86.5)	69 (78.4)	71 (53.8)	68 (58.1)	
Diagnostic delay (months)						
Onset of first extracardiac symptoms to diagnosis	11 (3–48)	8 (2–16)	9 (3–26)	8 (4–27)	12 (3–30)	0.430
Onset of first cardiac symptoms to diagnosis	7 (2–12)	7 (2–12)	6 (2–13)	6 (3–20)	5 (2–19)	0.05
Laboratory variables						
European staging[b]	(*n* = 15)	(*n* = 38)	(*n* = 69)	(*n* = 109)	(*n* = 102)	0.264
I	3 (20.0)	2 (5.3)	5 (7.2)	7 (6.4)	5 (4.9)	
II	6 (40.0)	7 (18.4)	15 (21.7)	23 (21.1)	27 (26.5)	
IIIa	4 (26.7)	16 (42.1)	19 (27.5)	44 (40.4)	39 (38.2)	
IIIb	2 (13.3)	13 (34.2)	30 (43.5)	35 (32.1)	31 (30.4)	
NT-proBNP (ng/L)	2307 (249–5875)	3175 (1047–10,707)	5392 (1785–16,693)	4533 (1400–11,930)	4340 (2182–11,747)	0.364
Troponin (ng/L)	40 (11–85)	94 (50–169)	86 (46–189)	90 (43–140)	75 (42–129)	0.423
Creatinine (μmol/L)	96 (75–129)	119 (83–170)	105 (81–170)	111 (89–152)	111 (85–156)	0.260
Total bilirubin (μmol/L)	10.5 (6–16)	9 (5–14)	9 (5–15)	7 (5–12)	7 (5–13)	0.395
ALP (IU/L)	79 (57–99)	96 (74–125)	99 (66–177)	85 (65–119)	102 (65–147)	0.203
Kappa light chain (mg/L)	19 (7–50)	19 (8–47)	16 (9–61)	18 (11–46)	19 (12–42)	0.995
Lambda light chain (mg/L)	114 (11–269)	110 (33–345)	83 (30–358)	125 (36–249)	144 (35–314)	0.469
Kappa/lambda ratio	0.19 (0.02–5.24)	0.18 (0.05–1.49)	0.18 (0.04–0.99)	0.16 (0.06–0.78)	0.15 (0.05–0.76)	0.741
ECG						
PR interval (ms)	190 (154–212)	176 (148–198)	177 (160–200)	189 (160–200)	180 (154–200)	0.085
QRS duration (ms)	91 (81–104)	98 (80–120)	90 (80–105)	98 (85–120)	90 (80–120)	0.845
Echocardiography characteristics						
LVEDD (mm)	42 (39–48)	42 (38–46)	41 (37–47)	41 (37–46)	42 (39–49)	0.638
IVST (mm)	14 (13–17)	15 (13–19)	15 (13–17)	15 (14–17)	15 (13–17)	0.386
LVESD (mm)	30 (4–35)	28 (25–33)	28 (24–32)	27 (24–32)	30 (26–33)	0.051
LVEF	(*n* = 29)	(*n* = 43)	(*n* = 77)	(*n* = 115)	(*n* = 101)	0.052
> 50%	21 (72.4)	25 (58.1)	56 (72.7)	77 (67.0)	55 (54.5)	
40–49%	5 (17.2)	7 (16.3)	9 (11.7)	26 (22.6)	29 (28.7)	
< 40%	3 (10.3)	11 (25.6)	12 (15.6)	12 (10.4)	17 (16.8)	
GLS (%)	(*n* = 27)	(*n* = 45)	(*n* = 85)	(*n* = 117)	(*n* = 103)	0.083
< –17%	5 (18.5)	11 (24.4)	15 (18)	14 (12.0)	10 (9.7)	
–14% to –17%	6 (22.2)	6 (13.3)	9 (11)	9 (7.7)	14 (13.6)	
> –14%	16 (59.3)	28 (62.2)	61 (71)	94 (80.3)	79 (76.7)	
Cardiac output (L/min)	4.6 (3.1–6.1)	4.0 (3.2–5.1)	4.1 (3.4–5.1)	4.3 (3.5–5.2)	4.5 (3.2–5.7)	0.599

Data are expressed as *n* (%) or median and interquartile range. AL: amyloid light chain; ALP: alkaline phosphatase; CARC: Cardiac Amyloidosis Referral Centre; CI: confidence interval; ECG: electrocardiogram; GLS: global longitudinal strain; IVST: interventricular septal thickness; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; NA: not available; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

[a] Before the centre was classified as a CARC.

[b] Stage I: NT-proBNP ≤ 332 ng/L and high-sensitivity troponin T < 54 ng/L, stage II: NT-proBNP ≥ 332 ng/L or high-sensitivity troponin T ≥ 54 ng/L, Stage IIIa: NT-proBNP > 332 and < 8,500 ng/L and high-sensitivity troponin T ≥ 54 ng/L, stage IIIb: NT-proBNP ≥ 8500 ng/L and high-sensitivity troponin T 54 ≥ ng/L.

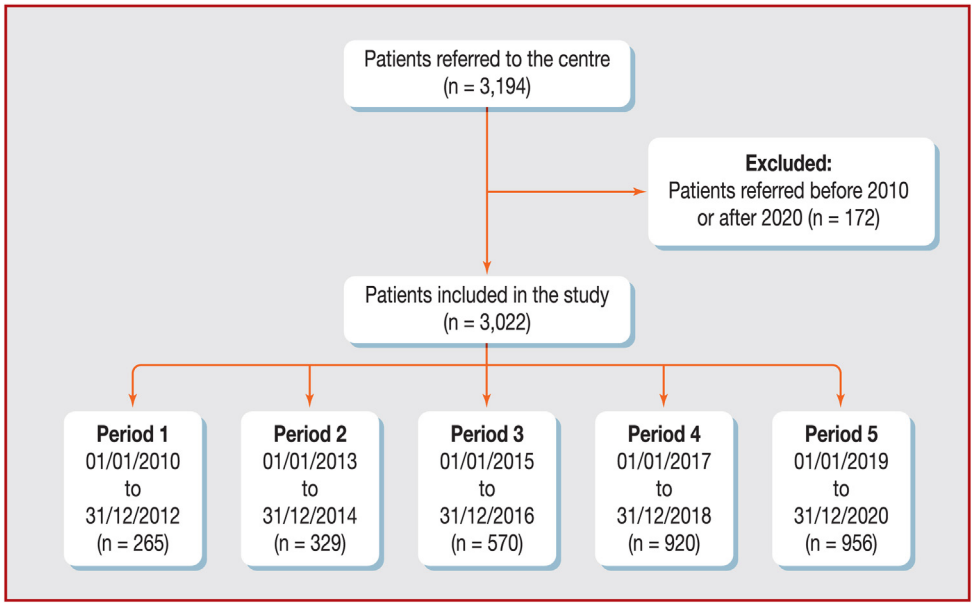


Fig. 1. Study flow chart.

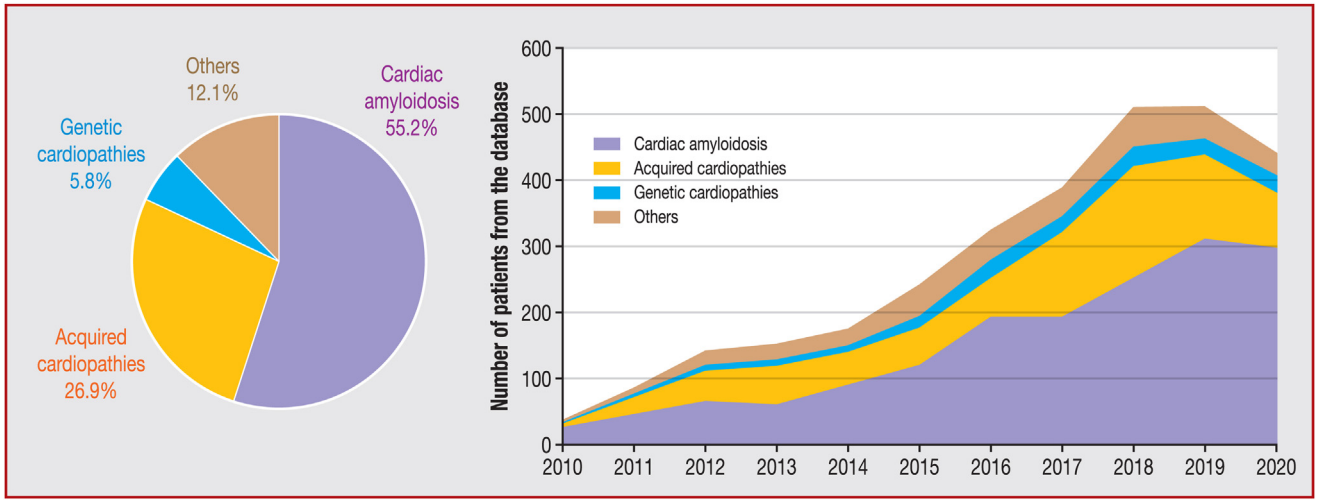


Fig. 2. A. Split of diagnoses. B. Increasing numbers of patients presenting with CA and other cardiopathies were referred to the CARC over the 11-year period. CA includes light chain amyloidosis, hereditary amyloidosis, wild-type amyloidosis, asymptomatic transthyretin mutation carrier, rare amyloidosis, amyloidosis assessment pending. Acquired cardiopathies includes hypertrophic cardiomyopathy, hypertensive cardiopathy, ischaemic cardiopathy, dilated cardiomyopathy, valvular cardiopathy, heart failure with preserved ejection fraction, and restrictive cardiomyopathy. Genetic cardiopathies includes sarcomeric cardiopathy, Fabry disease, sarcoidosis, left ventricular non-compaction and long QT syndrome. Other includes patients presenting with no diagnosis, lost to follow-up or conditions without associated cardiopathy. CA: cardiac amyloidosis; CARC: Cardiac Amyloidosis Referral Centre.

types of amyloidosis cases (Fig. 3). Furthermore, we observed that the ATTRv mutation type changed from a predominately ATTRv Val30Met mutation with neurological symptoms to predominately older patients with ATTR Val122Ile with cardiac phenotype. This differs markedly from the Transthyretin Amyloidosis Outcomes Survey (THAOS) study, the only other epidemiological reference currently available [14]. Lastly, the number of patients with AL increased gradually over time with increased severity.

5.1. Increased CARC activity

The increased activity observed is encouraging evidence of an increased awareness about CA among cardiologists and compares to reports that 5% of patients referred for hypertrophic cardiomyopathy or heart failure with preserved ejection fraction have CA [15,16]. Similarly, other major European reference centres have also reported increased activity. The other two main European centres, the Pavia reference centre in Italy [17] and the National Amyloidosis Centre in the UK [18] also reported an overall increase in the numbers of CA patients diagnosed.

5.2. Increased incidence over time

Numerous changes in recent times may have contributed to the increased numbers of patients with CA observed over time in France. Firstly, CA awareness has clearly improved in France. This most probably follows on from an increasing volume of national and international medical communication, congresses and published literature, which has helped physicians to better understand CA and promote research [19]. Particularly, local collaborative efforts with cardiologists from the Amylose Network have been active in raising awareness about CA among cardiologists in France.

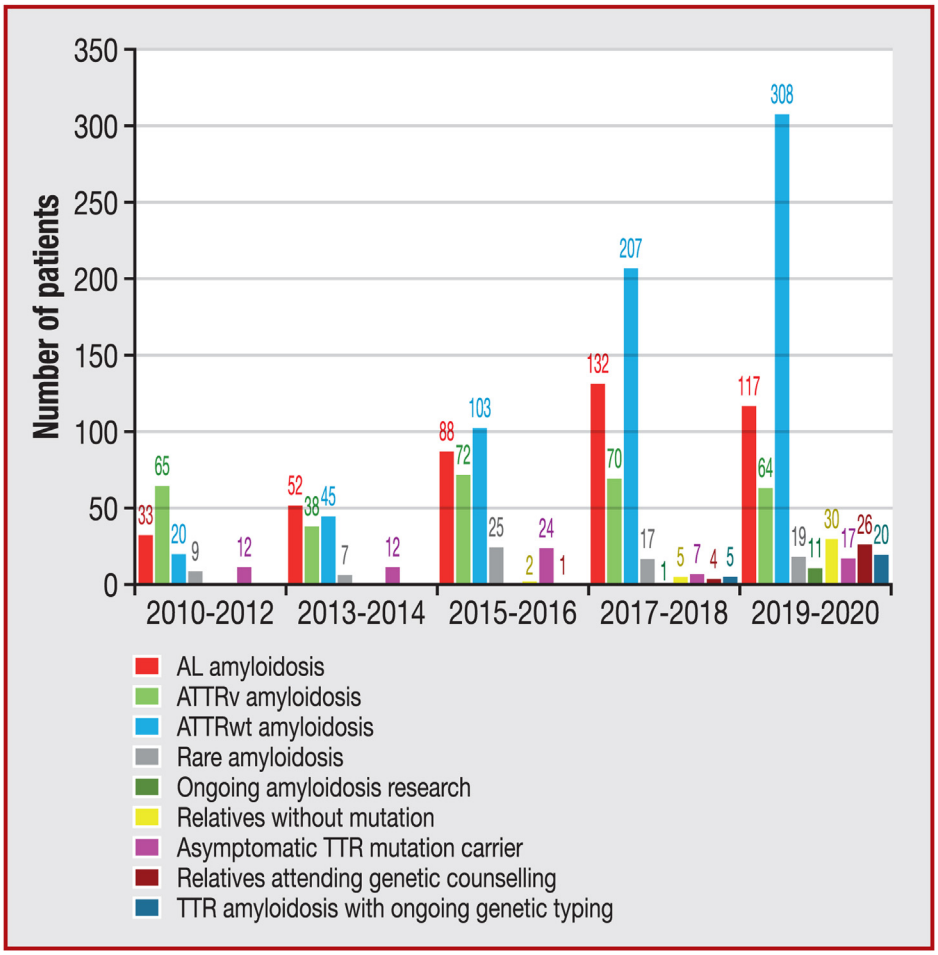


Fig. 3. Changes in the number of patients with different amyloidosis subtypes treated at the reference centre over the 11-year period. AL: amyloid light chain; ATTRv: variant transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; TTR: transthyretin.

The Network developed and disseminated information, presented at annual multidisciplinary conferences for multidisciplinary amyloidosis experts (Francophone Multidisciplinary Conference for Amyloidosis also called CFMA), for cardiologist experts in cardiomyopathy, (Cardiac Amyloidosis Masterclass called MAC) or private cardiologists (Cardiac Amyloidosis Conference Day called JACC), which are also available on dedicated websites (www.reseau-amylose.org; www.congres-amylose.fr). To improve current research dissemination, during bi-weekly webinars, two peer-reviewed publications are critiqued, discussed (in French) and recordings are available online (www.bibliose.org). Furthermore, a registry – Healthcare European Amyloidosis Research – has been created to collect data from more than 5000 patients with the suspicion of cardiac amyloidosis at 33 cardiology centres in 2023 (www.hearts-foundation.org). More than 4500 patients have been already included.

Furthermore, patient numbers have increased because diagnosing CA has become easier with progress made in genetic screening, cardiac imaging and disease-specific laboratory tests [20–22]. Previously, to diagnose CA, a positive endomyocardial biopsy or extracardiac biopsy combined with unexplained left ventricular wall thickness > 12 mm or characteristic cardiovascular magnetic resonance imaging features was required [3,22]. Now, other less invasive methods are accepted, namely laser microdissection and mass spectrometry-based proteomic assays [23–27], salivary gland biopsies [11,28,29], cardiac magnetic resonance [30–34], native myocardial T1-mapping and extracellular volume fraction measurements [35,36]. Lastly, our CARC uses myocardial radiotracer uptake on hydroxymethylene diphosphonate with early phase acquisition and/or late phase to diagnose CA [37,38]. This means that confirmatory endomyocardial biopsy is now often unnecessary [6]. Diagnosis has also been supported by the 2021 European Society of Cardiology (ESC) guidelines on amyloidosis and the Heart Failure ESC guidelines, in which the CA diagnostic pathway has been incorporated for the first time in this field. So, going forward, we can expect more patients will be diagnosed [22,39].

Additionally, having access to new, effective treatments such as tafamidis, patisiran and inotersen has encouraged more physicians to check for CA, which consequently increased CARC activity [10,18,40–44]. Furthermore, the CARC activity is supported by the holistic management we provide. Patients are referred to specialists onsite and have access to emergency consultations and clinical trials.

5.3. *Increased prevalence of ATTRwt*

Interestingly, the increased ATTRwt subtype prevalence observed has not been reported among other CARCs around the world. The Pavia CARC in Italy reported that 72% of their population with CA has AL [17], while the English CARC reported only 25% AL in 2016 but more recently, their website indicates that over half their population has AL [45,46], and Kumamoto in Japan reported 28.7% AL [47]. However, among patients with ATTR-CA, some centres have recently confirmed a trend towards an ATTRwt predominance [18,48,49], with one study revealing a significant increase in ATTRwt diagnosis between 2000 and 2012.

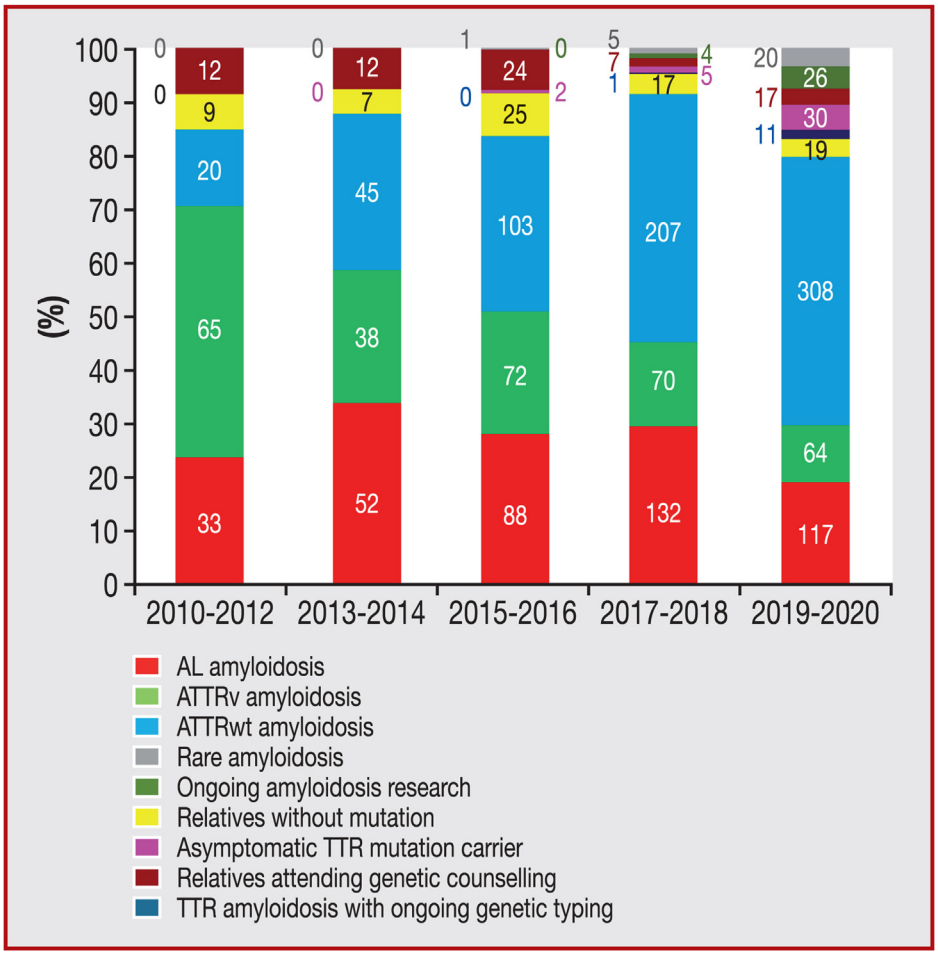


Fig. 4. The proportion of amyloidosis subtypes treated at the reference centre increased over the 11-year period. AL: amyloid light chain; ATTRv: variant transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; TTR: transthyretin.

Regarding the increased ATTRwt numbers specifically, our CARC works closely with geriatricians and geriatric departments within our network to raise awareness about ATTRwt, which has further contributed to increased patient referrals [50]. Also, with the increased use of bone scintigraphy (early phase acquisition) and treatment options, some older, severely ill patients are being considered for diagnosis [51]. This confers with recent literature that suggests that ATTRwt may account for up to 13% of heart failure with preserved ejection fraction cases in patients older than 65 years, meaning prevalence is higher than originally believed [16,52].

5.4. Reduced severity of cardiac involvement at diagnosis

Over time, the proportion of patients presenting with mild disease (NAC stage 1) has increased and the proportion of stage III patients has decreased. Nevertheless, the median delay between symptoms and diagnosis has been reported to be 92 (39–175) months when the extracardiac involvement [53], with diagnosis taking > 4 years for 42% of patients with ATTRwt [54]. A high level of suspicion is required, particularly when diagnostic red flags are identified. For example, carpal tunnel syndrome is a common extracardiac symptom of ATTR, but is not well recognised by cardiologists in clinical practice. These extracardiac symptoms can precede cardiac symptoms and ATTR diagnosis by means of 6.1 and 6.9 years, respectively [55].

This means that there is a continued need to improve CA awareness and develop tools and patient pathways to enhance early diagnosis [21]. To this end, we have instigated close collaboration with the French patient association (Association Française Contre l'Amylose) to further knowledge about CA and its burden from a patient perspective [21].

We also found that ATTRv patient characteristics changed over time, notably an increased proportion of Val122Ile mutation with cardiac phenotype. At the start of the study, neurologists mostly referred ATTRv patients with Val30Met mutation, early neurological phenotype, with few cardiac characteristics and better prognosis [56]. However, over the study period, cardiologists began referring more elderly patients with ATTR Val122Ile mutation with cardiac phenotype. This change differs markedly from the THAOS study published in 2019, which reported 44.7% Val30Met prevalence in France whereas our centre had only 23.6% in the same period. However, the THAOS data may not be representative of the CA population in France as the registry collects data from patients who present with neurological symptoms. In France, the ATTR Val122Ile mutation is the same as that found in the US following mutual involvement in the trade triangle between the 16th and 19th centuries and other colonial links with Sub-Saharan African countries. Although we found that ATTRv diagnostic delay improved, a median of 10 months is still long, and this persists according to the literature due to the heterogeneous presentation and overlapping clinical phenotypes, where most patients present with a mixed neurological and cardiological phenotype [5,57,58]. ATTRv disease awareness and its hallmark symptoms need to be raised further to reduce the diagnostic delay and ensure timely treatment is provided.

Table 3
Changes in baseline clinical, electrocardiographic, echocardiographic and laboratory characteristics of patients with ATTRv amyloidosis over time.

Time period	2010–2012[a] (*n* = 65)	2013–2014 (*n* = 38)	2015–2016 (*n* = 72)	2017–2018 (*n* = 70)	2019–2020 (*n* = 64)	*P*
Clinical characteristics						
Age (years)	60.3 (44.6–73.8)	69.1 (60.8–75.7)	69.2 (63.0–76.3)	70.7 (62.7–77.3)	74.8 (66.6–80.4)	0.003
Men	41 (63.1)	22 (57.9)	51 (70.8)	45 (64.3)	45 (70.3)	0.604
NYHA						0.001
1	23 (35.4)	10 (26.3)	14 (19.4)	10 (14.3)	9 (14.1)	
2	17 (26.2)	8 (21.1)	20 (27.8)	25 (35.7)	33 (51.6)	
3	7 (10.8)	12 (31.6)	29 (40.3)	22 (31.4)	16 (25.0)	
4	4 (6.2)	4 (10.5)	3 (4.2)	4 (5.7)	0 (0)	
NA	14 (21.5)	4 (10.5)	6 (12)	9 (7.7)	6 (9.3)	
Systolic blood pressure (mmHg)	127 (115–139)	118 (106–134)	121 (108–136)	123.5 (105–132)	125 (110–136)	0.541
Specialty referring the patient						0.001
Cardiology	8 (12.3)	15 (39.5)	34 (47.2)	52 (74.3)	42 (65.6)	
Neurology	26 (40.0)	5 (13.2)	8 (11.1)	4 (5.7)	1 (1.6)	
Other specialties	31 (47.7)	18 (47.4)	30 (41.7)	14 (20.0)	21 (32.8)	
Diagnostic delay (months)						
Onset of first extracardiac symptoms to diagnosis	51 (27–81)	39 (11–100)	44 (18–77)	59 (28–70)	43 (14–74)	0.230
Onset of first cardiac symptoms to diagnosis	26 (2–25)	17 (6–50)	15 (5–27)	13 (5–29)	10 (2–25)	0.002
Laboratory variables						
NAC staging[b]	(*n* = 57)	(*n* = 35)	(*n* = 67)	(*n* = 68)	(*n* = 61)	0.011
Stage 1	39 (68.4)	13 (37.1)	34 (50.7)	26 (38.2)	30 (49.2)	
Stage 2	14 (24.6)	13 (37.1)	17 (25.4)	21 (30.9)	22 (36.1)	
Stage 3	4 (7.0)	9 (25.7)	16 (23.9)	21 (30.9)	9 (14.8)	
NT-proBNP (ng/L)	488 (82–3141)	3026 (617–6336)	2028 (419–5419)	2602 (819–5149)	2015 (988–4360)	0.001
Troponin (ng/L)	15 (5–57)	56 (14–108)	64 (36–113)	61 (31–118)	64 (37–95)	0.004
Creatinine (μmol/L)	83 (68–102)	101 (80–138)	108 (73–150)	112 (81–157)	107 (76–132)	0.001
Total bilirubin (μmol/L)	8 (6–11)	10 (5–14)	12 (7–18)	10 (6–19)	12 (8–17)	0.025
ALP (IU/L)	67 (52–96)	91 (65–119)	86 (56–140)	83 (64–130)	88 (63–116)	0.103
ECG						
PR interval (ms)	178 (156–200)	200 (165–217)	188 (160–209)	194 (150–220)	178 (163–204)	0.080
QRS duration (ms)	90 (80–131)	107 (89–148)	101 (88–139)	97 (82–119)	93 (85–120)	0.552
Echocardiography characteristics						
LVEDD (mm)	45 (41–48)	44.5 (40–50)	45 (42–49.3)	44 (38–48)	44 (40–49)	0.531
IVST (mm)	14 (10–18)	18 (15–20.3)	18 (13.3–20)	17 (15–20)	16 (14–18)	0.008
LVESD (mm)	28 (24–31)	32 (28–39)	33 (28–38)	33 (27–39.8)	34 (26–39)	0.1
LVEF	(*n* = 55)	(*n* = 35)	(*n* = 60)	(*n* = 62)	(*n* = 54)	0.004
> 50%	46 (83.6)	14 (40.0)	30 (50.0)	33 (53.2)	28 (51.9)	
40–49%	5 (9.1)	8 (22.9)	12 (20.0)	13 (21.0)	11 (20.4)	
< 40%	4 (7.3)	13 (37.1)	18 (30.0)	16 (25.8)	15 (27.8)	
GLS	(*n* = 53)	(*n* = 35)	(*n* = 62)	(*n* = 55)	(*n* = 54)	< 0.001
< −17%	22 (41.5)	6 (17.1)	11 (17.7)	4 (7.3)	3 (5.6)	
−14% to −17%	9 (17.0)	4 (11.4)	10 (16.1)	6 (10.9)	(11.1)	
> −14%	22 (41.5)	25 (71.4)	41 (66.1)	45 (81.8)	45 (83.3)	
Cardiac output (L/min)	4.7 (4.1–5.5)	3.6 (2.8–5.7)	4.3 (3.4–5.7)	3.7 (3.1–5)	4 (2.9–4.9)	0.010

Data are expressed as *n* (%) or median and interquartile range. ALP: alkaline phosphatase; ATTRv: variant transthyretin amyloidosis; CARC: Cardiac Amyloidosis Referral Centre; CI: confidence interval; ECT: electrocardiogram; eGFR: estimated glomerular filtration rate; GLS: global longitudinal strain; IVST: interventricular septal thickness; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; NA: not available; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

[a] Before the centre was classified as a CARC.

[b] NAC stage 1: NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 mL/min, stage 3: NT-proBNP > 3000 ng/L and eGFR < 45 mL/min, and the remainder were stage 2 [8].

Table 4
Changes in baseline clinical, electrocardiographic, echocardiographic and laboratory characteristics of patients with ATTRwt amyloidosis over time.

Time period	2010–2012[a] (*n* = 20)	2013–2014 (*n* = 45)	2015–2016 (*n* = 103)	2017–2018 (*n* = 208)	2019–2020 (*n* = 308)	*P*
Clinical characteristics						
Age (years)	81.1 (77.2–87.2)	81.6 (77.1–86.3)	82.5 (78.1–86.2)	80.7 (75–84.7)	83.5 (77.6–86.7)	0.004
Male	17 (85.0)	41 (91.1)	92 (89.3)	179 (86.1)	249 (80.8)	0.143
NYHA						< 0.001
1	2 (10.0)	2 (4.4)	10 (9.7)	31 (14.9)	27 (8.8)	
2	7 (35.0)	9 (20.0)	37 (35.9)	101 (48.6)	160 (51.9)	
3	10 (50.0)	23 (51.1)	37 (35.9)	49 (23.6)	90 (29.2)	
4	0 (0)	4 (8.9)	13 (12.6)	11 (5.3)	13 (4.2)	

Table 4 (*Continued*)

Time period	2010–2012[a] (*n* = 20)	2013–2014 (*n* = 45)	2015–2016 (*n* = 103)	2017–2018 (*n* = 208)	2019–2020 (*n* = 308)	*P*
NA	1 (5.0)	7 (15.65)	6 (5.8)	16 (7.7)	18 (5.8)	
Systolic blood pressure (mmHg)	130 (108–140)	122 (110–140)	126 (112–138)	128 (116–141)	134 (122–147)	0.004
Specialty referring the patient						< 0.001
Cardiology	5 (25.0)	14 (31.1)	40 (38.8)	155 (74.5)	245 (79.5)	
Neurology	0 (0)	0 (0)	0 (0)	1 (0.5)	0 (0)	
Other specialties	15 (75.0)	31 (68.9)	63 (61.2)	52 (25.0)	63 (20.5)	
Diagnostic delay (months)	20 (5–114)	62 (14–111)	72 (16–118)	52 (14–90)	48 (17–93)	0.300
Onset of first extracardiac symptoms to diagnosis	5 (2–21)	27 (9–51)	26 (9–47)	17 (3–53)	12 (4–7)	0.020
Onset of first cardiac symptoms to diagnosis						
Laboratory variables	(*n* = 18)	(*n* = 41)	(*n* = 99)	(*n* = 207)	(*n* = 303)	0.008
NAC staging[b]	10 (55.6)	9 (22.0)	30 (30.3)	81 (39.1)	139 (45.9)	
Stage 1	6 (33.3)	17 (41.5)	45 (45.5)	73 (35.3)	111 (36.6)	
Stage 2	2 (11.1)	15 (36.6)	24 (24.2)	53 (25.6)	53 (17.5)	
Stage 3						
NT-proBNP (ng/L)	2840 (2138–5262)	4730 (2555–8938)	4174(2123–6924)	3244 (1628–6342)	2639 (1117–5215)	< 0.001
Troponin (ng/L)	49 (31–72)	84 (54–130)	80 (51–114)	64 (42–100)	62 (39–95)	0.018
Creatinine (μmol/L)	103 (88–121)	130 (100–159)	111 (93–143)	114 (92–145)	106 (88–134)	0.005
Total bilirubin (μmol/L)	13 (7–15)	14 (10–20)	11 (8–17)	11.3 (8–19)	10 (7–17)	0.195
ALP (IU/L)	97 (61–113)	116 (93–174)	99 (73–123)	93 (70–139)	86 (68–113)	0.003
ECG						
PR interval (ms)	200 (158–241)	200 (172–235)	191 (179–240)	200 (177–230)	200 (180–240)	0.955
QRS duration (ms)	117 (91–135)	120 (98–170)	124 (100–156)	120 (96–150)	120 (96–150)	0.603
Echocardiography characteristics						
LVEDD (mm)	43 (41–51.5)	46 (41–49.8)	43 (38.8–48)	45 (40–51)	44.8 (40–50)	0.553
IVST (mm)	18 (16–20.8)	17.5 (16–20.9)	18 (16–21)	17.3 (15–20)	16 (14–19)	0.001
LVESD (mm)	33 (26–38)	24 (26.5–42)	32.9 (26–37)	34 (28–39)	32 (28–37)	0.553
LVEF	(*n* = 18)	(*n* = 42)	(*n* = 95)	(*n* = 174)	(*n* = 245)	0.003
> 50%	7 (38.9)	12 (28.6)	37 (38.9)	90 (51.7)	127 (51.8)	
40–49%	5 (27.8)	13 (31.0)	29 (30.5)	51 (29.3)	80 (32.7)	
< 40%	6 (33.3)	17 (40.5)	29 (30.5)	33 (19.0)	38 (15.5)	
GLS	(*n* = 18)	(*n* = 41)	(*n* = 85)	(*n* = 167)	(*n* = 274)	0.341
<−17%	1 (5.6)	1 (2.4)	1 (1.2)	6 (3.6)	2 (0.7)	
−14% to −17%	1 (5.6)	2 (4.9)	8 (9.4)	15 (9.0)	33 (12.0)	
>−14%	16 (88.9)	38 (92.7)	76 (89.4)	146 (87.4)	239 (87.2)	
Cardiac output (L/min)	4.0 (2.9–5.0)	3.6 (3.0–4.6)	3.9 (3.1–4.9)	4.1 (3.4–5.1)	4.3 (3.5–5.3)	0.184

Data are expressed as *n* (%) or median and interquartile range. ALP: alkaline phosphatase; ATTRwt: wild-type transthyretin amyloidosis; CARC: Cardiac Amyloidosis Referral Centre; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; GLS: global longitudinal strain; IVST: interventricular septal thickness; LVEDD: left ventricular end-diastolic diameter; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; NA: not available; NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

[a] Before the centre was classified as a CARC.

[b] Stage I: NT-proBNP ≤ 3000 ng/L and eGFR ≥ 45 mL/min, stage III was defined as NT-proBNP > 3000 ng/L and eGFR < 45 mL/min, and the remainder were stage II [8].

5.5. Genetic counselling in CA

Genetic counselling is offered when hereditary ATTRv is diagnosed. Initially, genetic counselling was performed outside the CARC but this moved in-house in 2015. This explains the appearance of patients undergoing genetic counselling and relatives without mutations at this time. Patients who underwent genetic counselling and were diagnosed with a condition in one of the groups defined at the start of the study are no longer counted in the counselling activity. This means that the genetic counselling activity is probably underestimated and artificially diminished.

When a patient is diagnosed with ATTRv, our centre supports patients to inform and educate their family so carriers can be identified with genetic testing and timely disease-delaying treatment

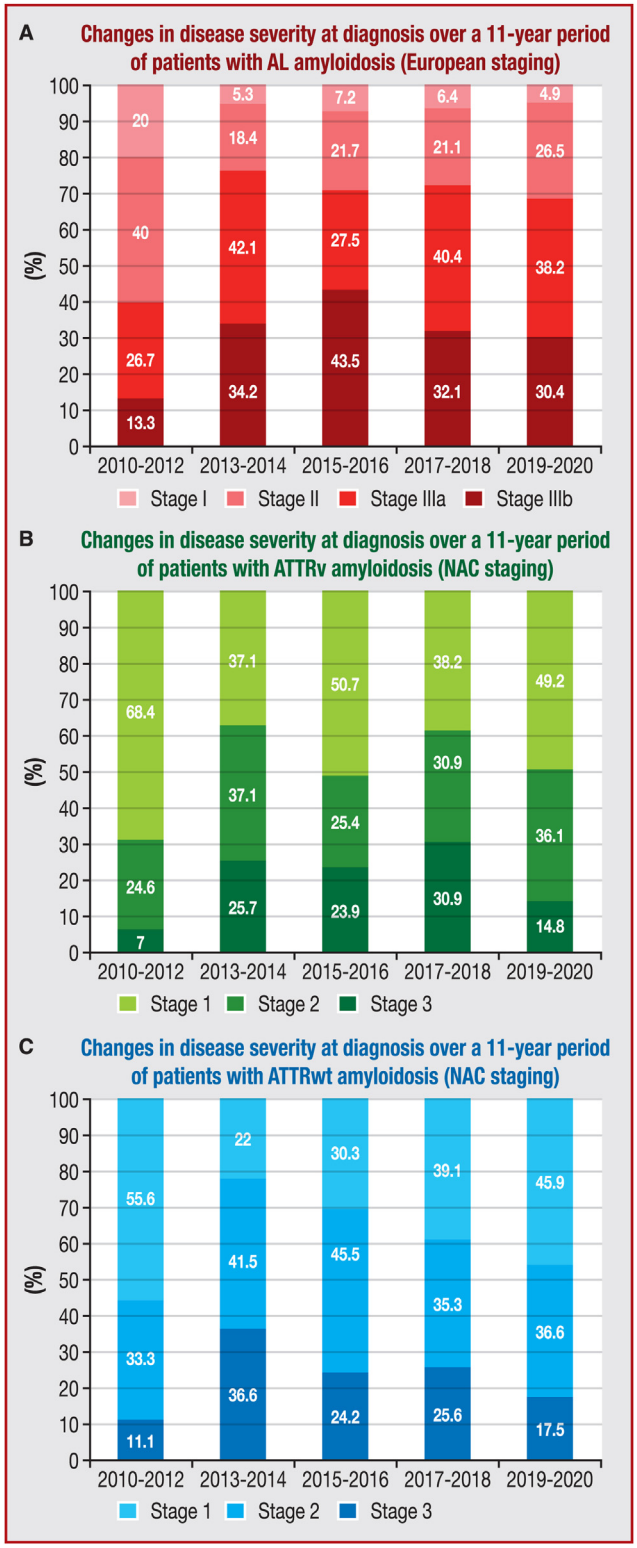


Fig. 5. Disease severity at diagnosis among patients with A. AL amyloidosis (European staging), B. ATTRv amyloidosis (NAC staging) and C. ATTRwt amyloidosis (NAC staging) over the 11-year period. AL: amyloid light chain; ATTRv: variant transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis.

can be provided [4,59,60]. However, family members do not always consult. This is probably due to fear of a diagnosis, lack of symptoms and little or no understanding about the disease. Furthermore, many Caribbean-African relatives of our patients live abroad, making it extremely difficult to screen relatives in our centre. Also, genetic counselling is time consuming, requiring several specialist consultations and genetic test results take several weeks to be returned. It can be hugely stressful for patients and requires specialised support. Our role is to promote this service to affected families, so subjects are diagnosed and carriers followed and "ignored" patients diagnosed and treated as early as possible while providing enough support to encourage them to go through the process.

5.6. Increased in AL CA diagnosis

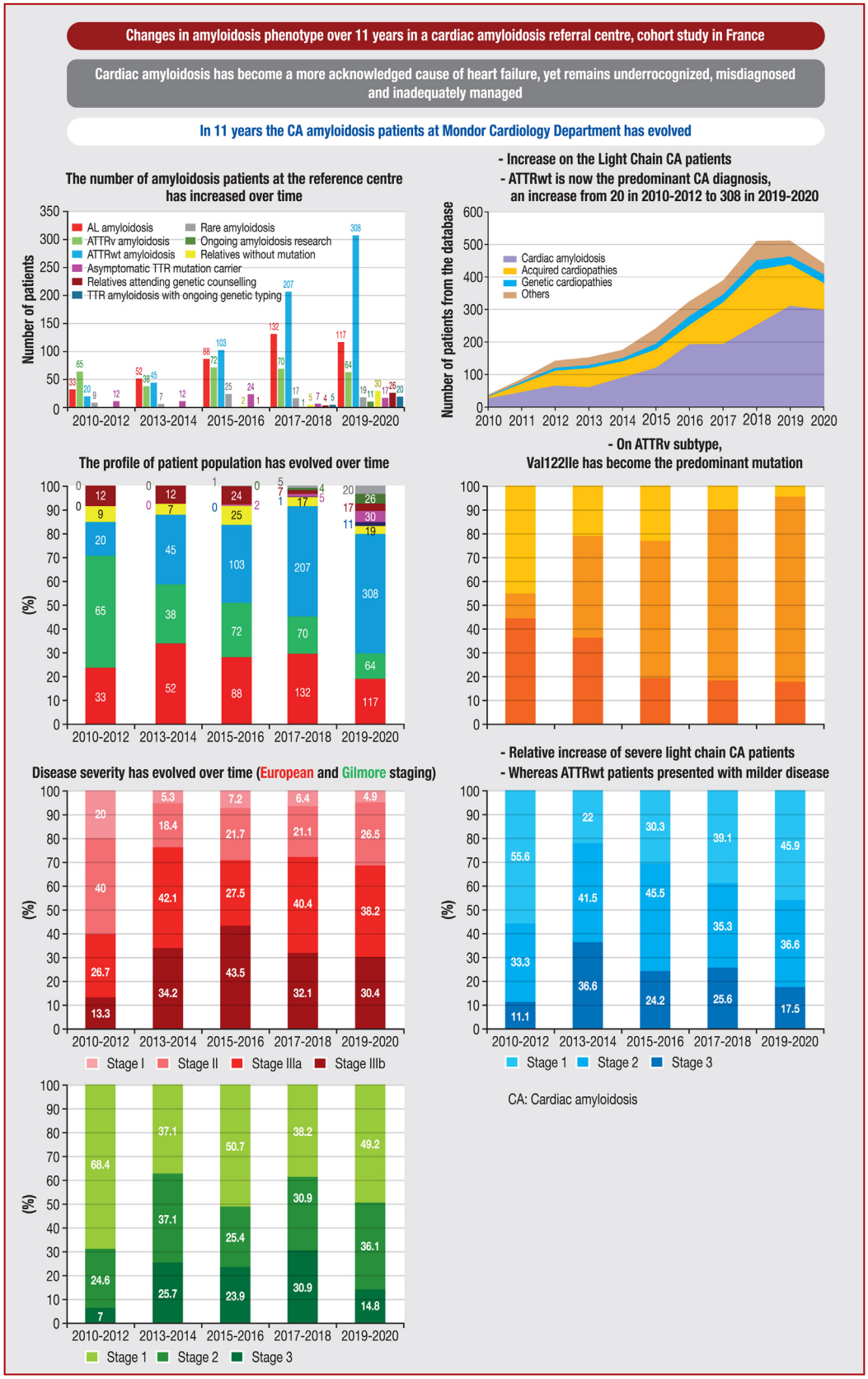
The numbers of patients with AL referred and diagnosed with cardiac involvement have also increased gradually over time at our CARC. This could be because cardiologists now diagnose AL more readily, whereas previously, many patients may have died without diagnosis. However, there has been little improvement in cardiac staging at diagnosis and early diagnosis is often challenging. Amyloid infiltrates rapidly and organ infiltration is high by the time patients recognise the symptoms. Although the numbers of patients with AL increased, the severity of AL cardiac involvement remained stable during the study. This contrasts with the Mayo clinic that reported less severe patients between 2000 and 2014 with less organ damage [61]. The severity of the patients with AL justifies continued improvements to the diagnostic pathway to reduce the diagnosis delay. The median (interquartile range) diagnostic time between first extra-cardiac symptoms and diagnosis in the last period of AL-CA was 12 (3–30) and between cardiac symptoms of 5 (2–19) months, which remains long for this disease that has a median survival time from the first symptoms of heart failure of < 6 months without treatment [62,63], which increases to 24 months with treatment [21,22].

5.7. Strengths and limitations

This is a retrospective analysis of activity in a tertiary referral centre for CA that consecutively included all patients in the database. Consequently, selection bias may have occurred, so the epidemiology may be less representative of the general patient population in France. Nevertheless, previous work performed using data from the French health system database indicates that the volume of CA patient has increased overall in France [64]. Also, we recognise that the recent COVID-19 pandemic with lockdowns and limited local and international movement may have affected the numbers of people being diagnosed and referred from France and abroad, which may explain the minor drop in patient numbers referred between 2019 and 2020. Also, we did not know which patients had received genetic counselling before being diagnosed, therefore properly evaluating this activity is difficult. In the ATTRwt subgroup, choosing a GLS threshold of –14% is probably too severe and indiscriminate for these patients. This population often has diastolic heart disease to which CA is added, so worsening these values. Choosing a lower threshold could have potentially highlighted more differences.

6. Conclusions

The considerable increase in CARC activity over the 11 years shows increasing cardiologist awareness, referrals and CA diagnoses. Notably, more ATTRwt patients with milder cardiac involvement and a change towards predominantly cardiological ATTR Val122Ile ATTRv mutations. Diagnostic delays still occur, particularly in CA AL patients, revealing the need to raise awareness among patients and particularly gastroenterologists, neurologists and internal medical specialists, and to provide physician training for those involved in the management of patients with heart failure or cardiomyopathy and continue research into new therapies (Central illustration).



Central illustration.

Sources of funding

None.

Author contributions

TD: conceptualization, methodology, supervision, original draft outline, reviewing and editing; AZ: conceptualization, writing original draft, supervision; MdeT: investigation, data curation, preparing and reviewing draft manuscript; MK: investigation, data curation, investigation, reviewing draft manuscript; RG, AG, SG, BF, EI, LR, VA, PF, VL, EP, KB, SM, GDSC, VP-B, TG, XC, SG, EB, SB, TF, FL, EA, DT, FC-P, J-PL, SS F-JA, SM, LH, J-PD, AB, SO: investigation, data curation, reviewing the draft manuscript; VM-F: investigation, data curation, reviewing and editing the draft manuscript; ET: supervision and reviewing the final manuscript.

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Disclosure of interest

The authors declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.acvd.2023.07.003.

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