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ORIGINAL ARTICLE

Change in prevalence of ATTR variants in Italy: results from a national survey

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Aims Hereditary transthyretin amyloidosis (ATTRv) is a rare, heterogeneous, inherited disorder caused by over 130 gene mutations. Its prevalence was estimated to 4.33/million in 2020 in Italy. Whether growing disease awareness and improved diagnostics may have increased national diagnoses in the last 4 years is unresolved.

Methods and results All alive ATTRv diagnoses from 2004 to 2024 from 16 Italian referral centres were retrospectively assessed and included in the analysis. As of March 2024, 373 ATTRv patients were in active follow-up, with an overall national prevalence increased from 2020 previous survey up to 6.33/million. The most prevalent mutations were Ile68Leu (25.1%), Phe64Leu (21.9%), Val30Met (19.3%), Glu89Gln (10.7%), and Val122Ile (6.7%). Ile68Leu, Val122Ile, and Val30Met were more common in

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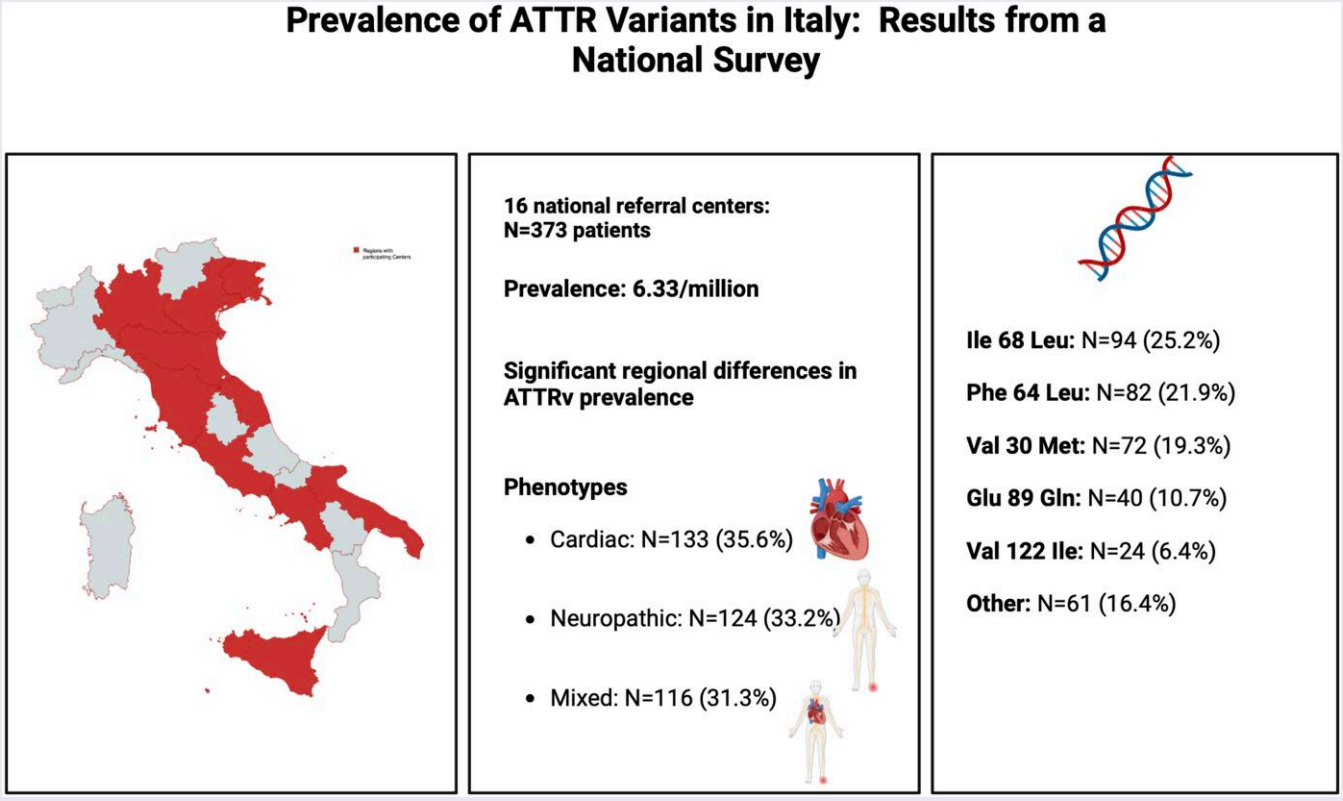
Northern and Central Italy, while Glu89Gln and Phe64Leu were prevalent in Southern Italy. Cardiovascular phenotype was the most common (35.6%), followed by neuropathic (33.2%) and mixed phenotypes (31.2%). Referral to disease-specific therapy mirrored the change in epidemiology.

Conclusion ATTRv prevalence in Italy has increased by 50% in a 4 years' time frame, with a shift towards milder disease stages and more mixed phenotypes. These changes may reflect improved disease awareness, enhanced genetic screening, and comprehensive care in specialized centres.

Graphical abstract



Keywords Transthyretin cardiac amyloidosis • Genotype • Screening • Epidemiology

Key Learning Points

What is already known:

- Hereditary transthyretin amyloidosis (ATTRv) is a rare autosomal dominant disease with variable genotype–phenotype expression, leading to cardiac and neurological involvement.
- The prevalence of ATTRv has historically been underestimated due to underdiagnosis and limited awareness, with significant regional differences in disease burden.
- Increased use of genetic cascade screening, non-invasive diagnostic tools, and disease-modifying therapies has improved early recognition and patient management.

What this study adds:

- Over a short 4-year period, there was a 50% increase in ATTRv prevalence in Italy, suggesting improved disease recognition rather than a true rise in incidence.
- The most prevalent genetic variants have shifted, with Ile68Leu and Phe64Leu surpassing Val30Met, and a corresponding increase in cardiovascular phenotypes at first presentation.
- A significant rise in mixed phenotypes suggests that more comprehensive cardiac and neurological evaluations are detecting previously overlooked disease manifestations, emphasizing the need for a multidisciplinary diagnostic approach.

Introduction

Hereditary transthyretin (TTR) amyloidosis (ATTRv) is a rare, autosomal dominant, progressive, life-threatening condition characterized by the systemic deposition of TTR-derived amyloid fibrils.[1] This deposition results in restrictive cardiomyopathy and progressive heart failure (HF), sensorimotor polyneuropathy, and autonomic manifestations. ATTRv is caused by over 130 mutations in the *TTR* gene, which exhibit variable prevalence worldwide.[1,2] Given the highly heterogeneous clinical manifestations of ATTRv, with some mutation carriers remaining asymptomatic for much of their lives and others developing severe cardiomyopathy and systemic involvement at a relatively young age, the current prevalence and penetrance of the disease are likely underestimated. Early diagnosis is crucial, as it allows for the initiation of disease-modifying treatments that can slow disease progression, improve quality of life, and extend survival.[3–5]

Cascade genetic screening in at-risk relatives emerges as a powerful tool when an ATTRv diagnosis is made.[6,7] This approach not only facilitates early intervention but also aids in accurately assessing the disease's penetrance. Despite its potential benefits, the implementation of cascade screening programmes for ATTRv faces several ethical, psychological, and logistical challenges.[8] In 2020, an Italian national registry assessed for the first time the prevalence of ATTRv across the country, with an estimated figure of 4.33/million.[9] Since then, a wider adoption of non-invasive diagnostic examinations and increased awareness of the disease, have led to a further expansion of ATTRv centres and improved care. Whether this has contributed to earlier diagnosis and increased recognition is yet unknown. As such, to better describe the current epidemiology of ATTRv in Italy, and highlight potential changes in regional practice, we conducted a survey involving referral centres located in Northern, Central, and Southern Italy to: (i) provide an updated estimate of the prevalence of clinical ATTRv and asymptomatic carrier and (ii) describe the phenotype in genotype-positive patients.

Methods

Study centres and patient population

A total of 16 national referral centres for ATTRv, expert in the diagnosis and management of the disease, participated to the present survey. Five were located in Northern Italy (Milan, Padova, Pavia, Trieste, and Udine), seven in Central Italy (Ancona, Bologna, Florence, Pisa, Rome Sant'Andrea Hospital, Rome Gemelli Hospital, and Rome Umberto I Hospital), and three in Southern Italy (Lecce, Messina, and Naples). All centres involved in the project are composed by a multidisciplinary team involving cardiologists, internal medicine specialists, neurologists, and clinical genetic specialists. Diagnosis of ATTRv and staging through the years was performed according to the evolving clinical practice and specific guidelines. Per centre local practice, patients receiving a diagnosis of ATTRv from 2004 to 2024 were offered genetic counselling and presymptomatic testing in at-risk relatives, with clinical follow-up evaluations scheduled every 6 or 12 months in mutation carriers to monitor disease onset.

The study was approved by the local Ethics Committees, and all participants gave written informed consent for their clinical data to be used for research purposes in accordance with the Declaration of Helsinki.

Data on demographic characteristics and instrumental evaluation at baseline clinical visit or first disease manifestation were retrospectively collected and included in the database. First line therapy was also recorded. To protect patient's privacy, each centre was allowed to review only their own data; the coordinating centre was able to collect global data anonymously. To avoid duplication among centres, upon inclusion in the study, individuals were assigned a unique study identifier by each participating referral centre which was made by Centre's initial letters, the first letter of the name and surname, and year of birth. In case of concordance of letters, mutation and year of birth the patient were discussed among involved centre to avoid duplication.

To determine the prevalence over the entire Italian population and by region, data on the latest census were accessed on the Italian National Statistics Institution.[10]

Only alive patients at database lock in March 2024 were considered for the present analysis.

Statistical analysis

For the present analysis, only data on clinical phenotype at disease diagnosis are described. For each patient, time from phenotype onset to last clinical evaluation was also determined. Continuous variables are expressed as median and interquartile (IQR) and were compared with non-parametric tests, while categorical variables are expressed as counts and percentages and were compare with χ^2 or Fisher's exact test, if the predicted count was <5. Patients' characteristics are presented by genotype status. Only patients with a confirmed pathogenic variant in the *TTR* gene and an overt clinical phenotype, and alive in March 2024, were included. Statistical analysis was performed with IBM SPSS 29.0 (Armonk, NY, USA).

Results

Baseline demographic characteristics

Overall, during the study period, a total of 772 subjects were recorded and alive at follow-up. Median time from phenotype diagnosis to last clinical follow-up was 3.0 [IQR 1.2–5.9] years. Among these, 373 (48.3%) had an overt clinical phenotype, while 399 were carriers therefore not included in this analysis.

Of 373 patients, 191 (51.2%) were diagnosed before 2019 while 182 (48.9%) cases were recorded from January 2019 to March 2024.

Distribution of genotypes and overall ATTRv prevalence by Italian regions is presented in *Figure 1*. Baseline clinical characteristics, as well as geographical distribution, are summarized in *Table 1*. Based to the Italian population,[10] the overall prevalence of ATTRv amyloidosis is 6.33/million inhabitants.

Among the 373 patients included in our study, 204 (54.7%) were index patients and 169 (45.3%) were diagnosed with cascade screening: 96 (25.7%) were diagnosed with overt ATTRv (genotype+/phenotype+) at initial presentation during a cascade family screening, while 73 (19.6%) were initially identified as carriers (G+/P–) and later developed overt disease (*Table 1*). Among these 73 patients, the transition to an overt phenotype was confirmed by neurologic testing in 42 cases (57.5%), cardiovascular imaging in 28 cases (38.4%), and biopsy in three cases (4.1%). Of those who converted, 43 (58.9%) exhibited a pure neuropathic phenotype, 28 (38.4%) a pure cardiac phenotype, and 2 (2.7%) a mixed phenotype. Of note, a total of 78/169 individuals reported a positive family history.

A total of 38 different mutations were identified. The most prevalent ATTRv genotype in affected patients was Ile68Leu ($n = 94$, 25.2%), followed by Phe64Leu ($n = 82$, 22.0%), Val30Met ($n = 72$, 19.3%), Glu89Gln ($n = 40$, 10.7%), and Val122Ile ($n = 24$, 6.7%). Other mutations accounted for 61 (16.4%) cases (single variants list is summarized in Supplementary material online, *Table S1*).

While Ile68Leu, Val122Ile, and Val30Met were the most prevalent variants in Northern and Central Italy, Glu89Gln and Phe64Leu were the most prevalent in Southern Italy (*Figure 1*).

The median age at diagnosis varied significantly among the different mutations (*Table 1*). Patients with the Ile68Leu and Val122Ile mutations were typically older at disease diagnosis (median ages 65 [50–75] and 65 [47–74], respectively) compared to those with the Glu89Gln and other mutations (median ages 49 [37–55] and 48 [38–64] years, respectively).

The male predominance was consistent across all mutations, similar across all variant groups ($P = 0.079$). The majority of patients were Caucasian, with very few Afro-Caribbean patients.

Baseline phenotype and management

The phenotypic presentation varied significantly among the different genetic variants. Overall, cardiac involvement was the most frequent

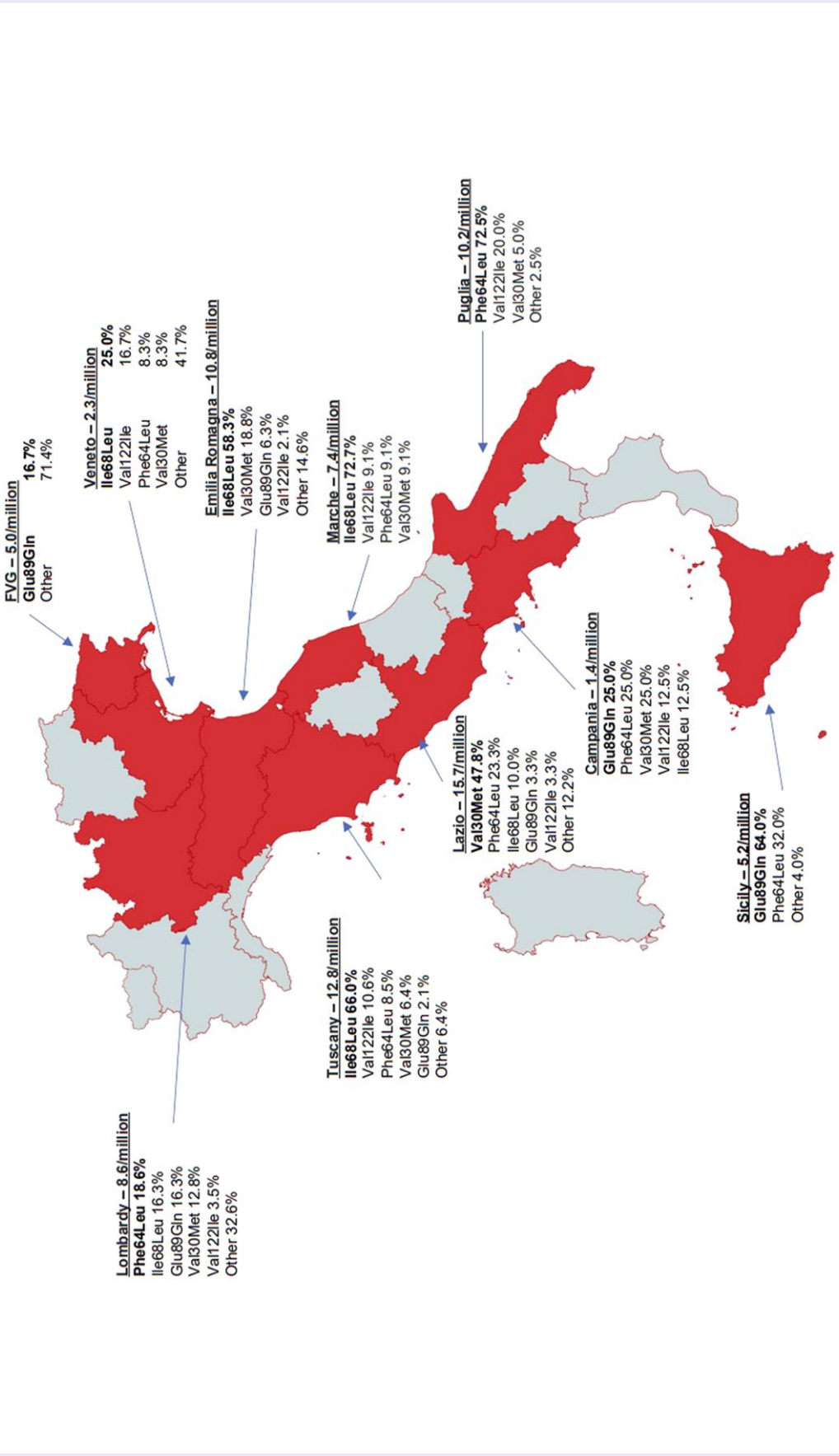


Figure 1 Distribution of genotypes and overall ATTRv prevalence by Italian regions.

Table 1 **Clinical and instrumental characteristics of patients diagnosed with vATTR and alive at survey closure**

	Overall population *N* = 373	Ile 68 Leu *N* = 94	Glu 89 Gln *N* = 40	Val 122 Ile *N* = 24	Phe 64 Leu *N* = 82	Val 30 Met *N* = 72	Other *N* = 61
Age at genetic test	67 [54–7]	65 [50–75]	49 [37–55]	65 [47–74]	62 [49–74]	61 [44–70]	48 [38–64]
Men, *N* (%)	255 (68.2)	67 (71.3)	24 (60.0)	19 (79.2)	57 (69.5)	55 (76.4)	33 (54.1)
Ethnicity, *N* (%)							
Caucasian, *N* (%)	371 (99.2)	94 (100.0)	40 (100.0)	24 (100.0)	82 (100.0)	71 (98.6)	60 (98.4)
Afro-Caribbean, *N* (%)	2 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.4)	1(1.6)
Diagnosed with cascade screening, *N* (%)	169 (45.3)	25 (26.6)	24 (60.0)	11 (45.8)	53 (64.6)	29 (40.3)	27 (44.3)
Carriers, *N* (%)	73 (19.6%)	11 (11.7)	16 (40.0)	2 (8.3)	18 (22.0)	11 (15.3)	15 (24.6)
Genotype +/Phenotype + (%)	96 (25.8)	14 (14.9)	8 (20.0)	9 (37.5)	35 (42.6)	18 (25.0)	12 (19.7)
Phenotype, *N* (%)							
Mixed	116 (31.3)	25 (26.6)	11 (27.5)	7 (29.2)	13 (15.9)	38 (52.7)	22 (36.7)
Cardiac	133 (35.6)	66 (70.2)	15 (37.5)	16 (66.7)	6 (7.3)	7 (9.7)	23 (38.3)
Neuropathic	124 (33.2)	3 (3.2)	14 (35.0)	1 (4.1)	63 (76.8)	27 (37.5)	16 (25.0)
Reason for referral, *N* (%)	280						
Heart failure	67 (24.2)	44 (49.4)	3 (10.3)	7 (29.2)	1 (2.5)	4 (6.3)	8 (18.2)
Arrhythmias	16 (5.7)	6 (6.7)	0 (0.0)	2 (8.3)	1 (2.5)	4 (6.3)	3 (6.8)
Neuropathy	88 (31.3)	4 (4.5)	10 (34.5)	0 (0.0)	23 (57.5)	36 (56.3)	15 (34.1)
Positive imaging	31 (11.0)	14 (15.7)	1 (3.4)	3 (12.5)	2 (5.0)	4 (6.3)	7 (15.9)
Family history	78 (27.8)	21 (23.6)	15 (51.7)	2 (8.3)	13 (32.5)	16 (25.0)	11 (25.0)
PND score, *N* (%)	256	85	24	14	34	57	42
Absent	96 (37.5)	60 (70.6)	8(33.3)	5 (35.7)	3 (8.8)	6 (10.5)	14 (33.3)
I	99 (38.7)	20 (23.5)	11 (45.8)	9 (64.3)	14 (41.2)	25 (43.9)	20 (47.6)
II	42 (16.4)	4 (4.7)	5 (20.8)	0 (0.0)	9 (26.5)	19 (33.3)	5 (11.9)
III A	12 (4.7)	1 (1.2)	0 (0.0)	0 (0.0)	7 (20.6)	4 (7.0)	0 (0.0)
III B	3 (1.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	2 (4.8)
IV	4 (1.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (2.9)	2 (3.5)	1 (2.4)
NYHA class, *N* (%)[a]	333						
Not applicable	51 (15.3)	2 (2.1)	9 (22.5)	1 (4.1)	14 (26.4)	8 (11.4)	17 (28.3)
I	140 (41.9)	26 (18.6)	20 (50.0)	3 (12.5)	31 (58.5)	36 (51.4)	24 (40.0)
II	123 (37.1)	57 (60.6)	10 (25.0)	10 (41.7)	7 (13.2)	23 (32.9)	16 (26.7)
III/IV	19 (5.7)	9 (9.6)	1 (2.5)	2 (8.3)	1 (1.9)	3 (4.3)	3 (5.0)
Abnormal ECG, *N* (%)	206 (55.0)	75 (79.8)	20 (50)	15 (62.5)	22 (26.5)	37 (52.1)	37 (60.7)
Atrial fibrillation, *N* (%)	57 (15.2)	32 (34.0)	1 (2.5)	6 (25.0)	4 (4.8)	6 (8.5)	8 (13.1)
Max LVWT, median [IQR]	14 [11–17]	16 [14–19]	12 [10–15]	17 [14–19]	12 [10–13]	14 [11–16]	14 [11–17]
EGFR, median [IQR]	78 [60–91]	70 [51–85]	92 [80–98]	57 [44–85]	90 [87–98]	86 [70–92]	87 [67–96]

Continued

Table 1 *Continued*

	Overall population N = 373	Ile 68 Leu N = 94	Glu 89 Gln N = 40	Val 122 Ile N = 24	Phe 64 Leu N = 82	Val 30 Met N = 72	Other N = 61
NT-proBNP, median [IQR]	1000 [314–2537]	1879 [898–3165]	621 [142–2058]	2536 [944–6640]	151 [78–386]	620 [298–1800]	957 [318–151]
Therapy, *N* (%)							
Tafamidis	183 (49.1)	46 (48.9)	16 (40.0)	15 (62.5)	35 (42.7)	34 (47.2)	37 (60.7)
20 mg	45 (24.5)	1 (2.2)	4 (25.0)	2 (8.3)	19 (54.3)	6 (17.5)	13 (35.1)
Patisiran	93 (24.9)	20 (21.3)	17 (42.5)	4 (16.7)	27 (32.9)	12 (16.7)	13 (21.3)
Inotersen	15 (4.0)	2 (2.1)	1 (2.5)	1 (4.2)	5 (6.1)	6 (8.3)	0
Diflunisal	8 (2.1)	2 (2.1)	3 (7.5)	0	1 (1.2)	0	2 (3.3)

[a]Hereditary transthyretin amyloidosis.

manifestation, occurring purely in 35.6% of individuals and as part of a mixed phenotype in 31.3%. Pure neuropathic involvement was observed in 33.2%. Among specific variants, the Ile68Leu mutation showed the highest rate of cardiac involvement (70.2%, $P < 0.001$), whereas Phe64Leu was predominantly neuropathic (76.8%, $P < 0.001$). Notably, mixed phenotypes exceeded 15% across all mutations analysed. Val30Met carriers presented with mixed involvement most often (52.7%), followed by Val122Ile (29.2%), Glu89Gln (27.5%), and Ile68Leu (26.6%). Even Phe64Leu—traditionally considered predominantly neuropathic—exhibited some degree of cardiac involvement, with a purely cardiac presentation in 7.3% of individuals and a mixed phenotype in 15.9%.

Parallel to phenotype at presentation, HF was the primary reason for referral for 67 (24.2%) of individuals, more common in patients with Ile68Leu (49.4%) and Val122Ile (53.3%) mutations ($P < 0.001$). Overall, among these patients, 51 (76.1%) received diuretics, 34 (50.7%) beta-blockers, 21 (31.4%) mineral corticoid receptor antagonists, 18 (26.9%) angiotensin-receptor blockers/angiotensin converting enzymes inhibitors, and 8 (11.9%) sodium-glucose transporter inhibitors.

In contrast, neuropathy was a common referral reason for those with Phe64Leu (57.5%) and Val30Met (56.3%) mutations with matching worse degrees of polyneuropathy, as expressed by the polyneuropathy disability staging system (PND).

Abnormal electrocardiogram (ECG) findings were most frequent in Ile68Leu (79.8%) and Val122Ile (62.5%) and patients ($P < 0.001$). Atrial fibrillation prevalence varied significantly, being highest in Ile68Leu (34%) and Val122Ile (25.0%) ($P < 0.001$). Maximal left ventricular wall thickness (Max LVWT) was highest in Val122Ile (17 [14–19] mm) and Ile68Leu (16 [14–19] mm).

The estimated glomerular filtration rate (eGFR) and NT-proBNP levels also differed significantly. Patients with the Val122Ile variant exhibited the most advanced disease profiles at diagnosis, with the lowest median eGFR at 57 [44–85] and the highest NT-proBNP levels at 2536 [944–6640]. Conversely, the Glu89Gln mutation was associated with the most favourable renal function (92 [80–98] mL/min/m^2).

In terms of first line therapy, Tafamidis was prescribed overall to 49.1% of patients (66.7% of Val122Ile, and 48.9% of Ile68Leu, 47.2% of Val30Met, 42.7% of Phe64Leu, and 40% of Glu89Gln). Tafamidis 20 mg was 24.5% of the entire prescriptions. Patients with Glu89Gln were most frequently referred to Patisiran as first line therapy. Other disease-modifying therapy was Inotersen in 4.0% of patients and Diflunisal in 2.1%.

Discussion

Our Italian collaborative research network showed that up until March 2024, there were 373 ATTRv patients in active follow-up, with an overall prevalence in the Italian population of 6.33/million. Our study confirms that Italy is a non-endemic country with a heterogeneous distribution of different variants, having a higher prevalence in the Lazio region (15.7/million) and a lower prevalence in the Campania region (1.4/million). While Ile68Leu, Val122Ile, and Val30Met were the most prevalent variants in Northern and Central Italy, Glu89Gln and Phe64Leu were the most prevalent in Southern regions.

The increased disease awareness, the availability of new therapeutic options, and the widespread use of effective diagnostic tools such as skin biopsy, cardiac magnetic resonance imaging (MRI), and pyrophosphate (PYP), 3,3-diphosphono-1,2-propanedicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP) tracer scintigraphy may explain the significant increase in ATTRv prevalence in respect to previous estimates.[5,11,12] Compared to a survey published in 2020, the overall national prevalence showed a 50% increase (from 4.33 to 6.33/million).[9] Remarkably, this increased prevalence was recorded

with a similar number of centres (16 in our report vs. 15 in the previous report): while an additional centre may have determined a change in the absolute number of individuals, it is also unlikely that it could have produced such a significant increase in the epidemiology at the national level.

Overall, the median interval between the clinical diagnosis of ATTRv and the end of follow-up was 3 years. Given that the follow-up ended in March 2024, this indicates that for half of the patients the diagnosis occurred after 2019.

Compared to the previous Italian report, the last 4 years were associated with dramatic changes in the genetic epidemiology of ATTRv, with a similar trend for local regions.[13] While in 2020, Val30Met was the most common variant, now Ile68Leu and Phe64Leu were the first and second most represented genotypes, accounting for almost half of the Italian cohort.[9]

Change in phenotype at first disease manifestation was also unexpected. Paralleling a trend reported for variant ATTR cardiomyopathy, where patients are diagnosed at progressively earlier stages of the disease and with milder phenotypes, the epidemiology of genotype/phenotype interactions of ATTRv has also changed. In 2020, the neuropathic phenotype was most predominant (47.7%), followed by cardiomyopathy-related symptoms (25.8%) and mixed phenotypes (15%).[9] By contrast, in 2024, the predominant phenotype was cardiovascular (35.4%), followed by neuropathic (33.2%) and mixed, which doubled within the timeframe, reaching an overall prevalence of 31.3%. While these differences can be explained by the change in variant prevalence, with an increase in cardiac-specific mutations, referral for HF symptoms was, on average, 22%, slightly lower than previously reported. Similar considerations apply to neuropathic symptoms, as expressed by the PND classes distribution among mutations with marked neurological involvement. These data suggest that the overall phenotype has shifted towards a milder spectrum.

The higher prevalence of mixed phenotypes across mutations previously considered polarized towards either a pure cardiac or neurological phenotype in line with a trend which has been recently highlighted[14–16] and confirms the importance of a multidisciplinary evaluation of patients and carriers. In fact, almost 30% of Ile 68 Leu and 36% of Val 122 Ile presented signs or symptoms of neurological involvement at diagnosis. Conversely, cardiac involvement was detected in 65% of Glu 89 Gln, 62% of Val 30 Met, and 23% of Phe 64 Leu. Therefore, a mixed phenotype accounted for a significant proportion of cases, mainly due to more in-depth and aggressive neurological and cardiac evaluations revealing mild disease manifestations that could have been previously overlooked.[3]

Limitations

The present analysis is a retrospective study of tertiary care centres specialized in ATTR amyloidosis. While the prevalence by region is inferred through the attending centre, it may be hypothesized that the origin of patients, who often travel across the country to seek specialized care, could play an important role. Thus, we cannot completely exclude that the prevalence of variants could be impacted by patients' journeys from their home region where referral centres are not present to proximal regions where ATTR specialized centres are present. Regional prevalence should be interpreted in this context. Furthermore, compared to a previous report published 4 years before, the present analysis was conducted with one additional centre which may have contributed to an increased disease prevalence, together with increased disease awareness. National prevalence, however, should be less influenced by these phenomena and may have only been underestimated by the voluntary nature of cascade screening. Further confirming this hypothesis, we acknowledge the presence of other referral centres which may not have been included in the present analysis, but still be following patients. Finally, data on systolic and diastolic function—as well as additional functional parameters—were not available for all participants, preventing us from including a more detailed echocardiographic analysis of potential differences between ATTRv subtypes.

Conclusions

Over a short timeframe of 4 years, a 50% increase in prevalence was recorded, with a significant shift to milder disease stages at diagnosis and an increase in the expression of mixed phenotypes. These epidemiological changes can be attributed to increased disease awareness, improved cascade family screening and carrier management, and the adoption of a comprehensive multidisciplinary approach to ATTRv in dedicated amyloidosis referral centres.

Supplementary material

Supplementary material is available at *European Heart Journal—Quality of Care and Clinical Outcomes* online.

Author contributions

C.F., S.L., L.O., G.L., F.P., and F.C.: conceptualization, investigation, data curation, methodology, formal analysis, writing, and editing. A.Ai., A.Ar., M.M., G.L., A.C., C.C., M.E., G.B., S.P., G.P., E.B., B.M., F.G., and G.S.: investigation, data curation, methodology, formal analysis, and editing. A.B., M.C., L.D.M., G.D.B., P.G., M.I., C.L., M.L., S.M., F.My., F.Mu., P.O., A.P., G.P., M.R., G.T., G.V., F.Va., F.Ve., G.G.V., and M.A.S.: data curation, methodology, and editing.

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Data availability

Data will be provided upon reasonable request.

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