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Posted Date: 29 April 2026

doi: 10.20944/preprints202603.1420.v2

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Clinical, Genetic and Phenotypic Characterization of Hereditary Transthyretin Amyloidosis (ATTRv) in Peruvian Population: Real-World Data from a Case Series—IMPAC-FE Study

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Abstract

Background: Hereditary transthyretin amyloidosis (ATTRv) is a rare multisystemic disease with variable phenotypic expression. No published data exist on the clinical characteristics of ATTRv in the Peruvian population. **Objective:** To describe the demographic, genetic, and clinical characteristics of patients with ATTRv in Peru, and to determine the distribution of clinical phenotypes according to internationally validated criteria. **Methods:** Descriptive, observational, retrospective case series of patients with ATTRv confirmed by molecular genetic testing, evaluated in Lima, Peru, between 2021 and December 2025 (IMPAC-FE study). Demographic, genetic, neurological (NIS, Norfolk QOL-DN, PND), autonomic (COMPASS-31, SUDOSCAN), and cardiovascular variables (echocardiography, septal thickness, E/e', apical sparing pattern, Tc99m-pyrophosphate scintigraphy, NT-proBNP, troponin) were assessed. Phenotypes were classified according to AHA/ACC criteria and the THAOS registry. **Results:** Twenty-three patients were included (69.6% male, median age 60 years, IQR 45–70). The identified variants were Val142Ile (13/23, 56.5%), Ala65Val (8/23, 34.8%), and Val50Met (2/23, 8.7%). Overall phenotypic distribution: preclinical 8/23 (34.8%), mixed 9/23 (39.1%), cardiac 5/23 (21.7%), and neurological 1/23 (4.3%). Norfolk QOL-DN (n=18): median 6.0. COMPASS-31 (n=18): median 6.0. NIS Total (n=15): median 0.0. LVEF (n=16): mean 60.5%. LV mass (n=12): mean 102.9 g. Troponin T (n=9): median 47 ng/L. Tc99m-PYP scintigraphy (n=9): Perugini grade 3 in 7 (77.8%). **Conclusions:** This first case series of ATTRv in a Peruvian population shows clinical and genetic heterogeneity, with a predominance of the Val142Ile and Ala65Val variants, and a phenotypic distribution consistent with international registries. The high proportion of preclinical patients and the extended cardiovascular evaluation reinforce the need for early diagnosis and timely initiation of disease-modifying therapies.

Keywords: transthyretin amyloidosis; ATTRv; familial amyloid polyneuropathy; cardiomyopathy; Peru; rare diseases; genetic variants

Introduction

Hereditary transthyretin amyloidosis (ATTRv, formerly designated ATTRm) is an autosomal dominant disease caused by mutations in the TTR gene that lead to systemic deposition of amyloid fibrils derived from misfolded transthyretin. More than 140 pathogenic variants of the TTR gene have

 doi:10.20944/preprints202603.1420.v2

been described [1,2], with variable phenotypic expression that includes progressive sensorimotor polyneuropathy, infiltrative cardiomyopathy, autonomic dysfunction, and ocular and leptomeningeal involvement [1].

Historically considered an endemic disease of specific regions such as Portugal, Sweden, and Japan [2,3], ATTRv is now recognized as a condition of worldwide distribution, although with significant differences in the frequency of genetic variants and phenotypic expression among populations [1,2]. The THAOS registry (Transthyretin Amyloidosis Outcomes Survey), the largest worldwide with more than 3,000 patients, has shown that approximately one third of patients present a mixed phenotype (cardiac and neurological), while pure cardiac or neurological phenotypes each account for approximately one third of cases [4].

In Latin America, information on ATTRv is limited. Recent studies from Brazil [5], Argentina [6], and Mexico [7] have begun to characterize local populations, identifying important differences in the distribution of genetic variants and clinical presentation compared with classical European cohorts. Nevertheless, there are no published data on the characteristics of ATTRv in the Peruvian population.

Early diagnosis of ATTRv is crucial given the advent of disease-modifying therapies, including transthyretin stabilizers (tafamidis) [8], gene silencers (patisiran [9], inotersen [10]), and, more recently, gene-editing therapies (NTLA-2001) [11]. Early initiation of treatment, ideally in preclinical stages or in mild disease, is associated with better clinical outcomes [8–10].

The aim of this study was to characterize the clinical, genetic, and phenotypic profile of patients with confirmed ATTRv evaluated in Lima, Peru, within the framework of the IMPAC-FE study, with emphasis on: (a) the distribution of genetic variants and their phenotypic correlation; (b) the proportion of patients in preclinical stages as an indicator of early diagnosis; (c) the degree of subclinical cardiovascular involvement assessed by extended echocardiographic parameters and technetium pyrophosphate scintigraphy; and (d) the yield of family screening as a diagnostic strategy. This first case series seeks to contribute to the knowledge of this orphan disease in Latin America, where information is limited [5–7].

Methods

Study Design

This was a descriptive, observational, retrospective case series of patients with confirmed hereditary transthyretin amyloidosis (ATTRv) evaluated in Lima, Peru, between 2021 and December 2025. The study was conducted within the IMPAC-FE project (Clinical and Economic Impact in Amyloidosis – Pharmacoeconomics), developed by the Amiloidosis Perú research group, the Hospital Nacional Cayetano Heredia, the Faculty of Human Medicine of the Universidad de San Martín de Porres, and the Fundación Esperantra.

Inclusion criteria: patients aged 18 years or older with a diagnosis of ATTRv confirmed by molecular genetic testing (pathogenic or likely pathogenic variant in the TTR gene).

Exclusion criteria: age younger than 18 years and absence of a confirmed genetic diagnosis.

Variables Assessed

Clinical data were retrospectively collected from three sources: (1) clinical interviews conducted directly by the investigators with the patients, (2) clinical studies and medical documentation provided by the patients themselves, and (3) medical records from the referring institutions. Demographic variables, genetic variant, neurological assessment, autonomic assessment, cardiovascular assessment, quality-of-life scales, and clinical outcomes were collected.

Owing to the retrospective nature of the study, not all patients had complete evaluations across all clinical domains.

Demographic and genetic variables: age, sex, identified TTR genetic variant, and anthropometric data (weight, height, body mass index).

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Neurological assessment: the Neuropathy Impairment Score (NIS) [1] was used to quantify objective neurological deficit (range 0–244, higher scores indicating greater impairment), evaluating muscle weakness, reflexes, and sensation. Neuropathy-related quality of life was assessed with the Norfolk Quality of Life-Diabetic Neuropathy questionnaire (Norfolk QOL-DN, range 0–136, higher scores indicating worse quality of life). Neuropathic pain was quantified with the Neuropathic Pain Scale (NPS, range 0–100). Functional staging was performed using the Coutinho Polyneuropathy Disability (PND) scale. Functional tests included the Timed Up and Go, the 5-repetition Sit-to-Stand, and the single-leg balance test.

Autonomic assessment: autonomic symptoms were evaluated with the Composite Autonomic Symptom Score-31 (COMPASS-31 [12], range 0–100, higher scores indicating greater dysfunction). Sudomotor function was objectively assessed with SUDOSCAN [13] (Impeto Medical, Paris), measuring electrochemical skin conductance in hands and feet (normal values: feet >60 μS, hands >40 μS).

Cardiovascular assessment: transthoracic echocardiography was performed, evaluating left ventricular ejection fraction (LVEF), left ventricular mass, TAPSE (Tricuspid Annular Plane Systolic Excursion), and diastolic function pattern. High-sensitivity troponin T was measured as a biomarker of myocardial damage.

The extended cardiovascular assessment additionally included: interventricular septum and posterior wall thickness, the E/e' ratio as a marker of filling pressures, presence of the cherry-on-top sign [14] (apical sparing on longitudinal strain), bilateral atrial size, presence of pericardial and pleural effusion, right ventricular hypertrophy, and pulmonary artery systolic pressure. In selected patients, cardiac scintigraphy with sodium Tc99m-pyrophosphate was performed, classifying uptake according to the Perugini score (grade 0: no uptake; grade 1: less than bone; grade 2: equal to bone; grade 3: greater than bone). NT-proBNP was measured as an additional biomarker of myocardial stress.

Genetic characterization included variant type (missense, nonsense), zygosity (homozygous/heterozygous), clinical significance (pathogenic/likely pathogenic), and the type of sample used for genetic analysis. Age at diagnosis and the relationship of the case to the family index case were recorded.

Additional Clinical Variables

Relevant medical history was recorded, including arterial hypertension, diabetes mellitus, kidney disease, dyslipidemia, hypothyroidism, cerebrovascular disease, smoking, clinical dysautonomia, carpal tunnel syndrome, macroglossia, and palpebral purpura. Cardiac quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). The origin and referring hospital of each patient were recorded.

Classification of Clinical Phenotypes

Clinical phenotypes were classified according to criteria derived from the AHA/ACC guidelines [15] and the THAOS registry [4]:

Cardiac involvement (hATTR-CM): defined by at least one of the following criteria: left ventricular mass >150 g, troponin T >14 ng/L, or restrictive/monophasic diastolic pattern.

Neurological involvement (hATTR-PN): defined by at least one of the following criteria: NIS >0 (any objective deficit), Norfolk QOL-DN ≥20 points, or PND stage ≥I (presence of sensorimotor symptoms).

Mixed phenotype: defined when criteria for both cardiac AND neurological involvement coexist.

Carrier/Preclinical: defined in carriers of the genetic variant without objective evidence of significant cardiac or neurological organ involvement.

Statistical Analysis

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Continuous variables were described using median and interquartile range (IQR), given the limited sample size and the expected non-normal distribution. Categorical variables were expressed as absolute frequencies and percentages. The number of patients with available data is reported for each variable (available n / total n). Analysis was performed with Python 3.11 using the pandas and numpy libraries.

Missing data were handled by available-case analysis. Each variable was analyzed using all available observations, reporting the specific sample size for each evaluation. Imputation methods were not applied, given the descriptive nature and the limited sample size of the study.

Ethical Considerations

The study was conducted under the academic framework of the Universidad de San Martín de Porres and was approved by the Institutional Research Ethics Committee of the Faculty of Human Medicine (approval number E10012025057, approved on 6 October 2025). All patients came from different healthcare institutions and provided written informed consent for the use of their clinical data for research purposes. Data were anonymized prior to analysis, and confidentiality of the information was guaranteed.

Results

Demographic and Genetic Characteristics

Twenty-three patients with confirmed ATTRv were included. The median age was 60 years (IQR 45–70), with male predominance (69.6%, n=16). The genetic variants identified were Val142Ile in 13 patients (56.5%), Ala65Val in 8 (34.8%), and Val50Met in 2 (8.7%) (Table 1, Figure 1).

Table 1. Demographic, genetic, and anthropometric characteristics.

Variable	Total (n=23)	Val142Ile (n=13)	Ala65Val (n=8)	Val50Met (n=2)
Age, years – median (IQR)	60 (45–70)	65 (41–76)	51 (46–66)	64 (60–68)
Male sex, n (%)	16 (69.6%)	8 (61.5%)	7 (87.5%)	1 (50.0%)
Height, cm – mean (n=17)	168.1	171.0 (n=8)	172.8 (n=4)	158.5 (n=2)
Weight, kg – mean (n=17)	70.8	72.9 (n=8)	67.5 (n=4)	58.0 (n=2)
BMI – mean (n=6)	28.3	24.0 (n=2)	31.0 (n=1)	N/A
Zygosity – Heterozygous, n/total (%)	16/16 (100%)	8/8 (100%)	5/5 (100%)	2/2 (100%)
Pathogenic	13/16 (81.3%)	8/8 (100%)	2/5 (40.0%)	2/2 (100%)
Likely pathogenic	3/16 (18.7%)	0/8 (0%)	3/5 (60.0%)	0/2 (0%)
Age at diagnosis, years – mean	57.4	63.8 (n=9)	42.0 (n=5)	62.5 (n=2)
Age at diagnosis, years – median	66.0	67.0	40.0	62.5
Index case, n/total (%)	10/21 (47.6%)	5/12 (41.7%)	3/7 (42.9%)	2/2 (100%)
Family screening, n/total (%)	11/21 (52.4%)	7/12 (58.3%)	4/7 (57.1%)	0/2 (0%)

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EsSalud, n (%)	14/21 (66.7%)	8/12 (66.7%)	5/7 (71.4%)	1/2 (50.0%)
MINSA, n (%)	5/21 (23.8%)	2/12 (16.7%)	2/7 (28.6%)	1/2 (50.0%)
Private, n (%)	2/21 (9.5%)	2/12 (16.7%)	0/7 (0%)	0/2 (0%)
Number of hospitals	8	4	4	2
Mortality, n (%)	1/23 (4.3%)	1 (7.7%)	0 (0%)	0 (0%)

Values are expressed as median (IQR) for continuous variables and n (%) for categorical variables. Anthropometric data were available in a subgroup of patients (n indicated by variable). Classification of clinical significance follows the ACMG criteria. EsSalud: Peruvian Social Security; MINSA: Ministry of Health.

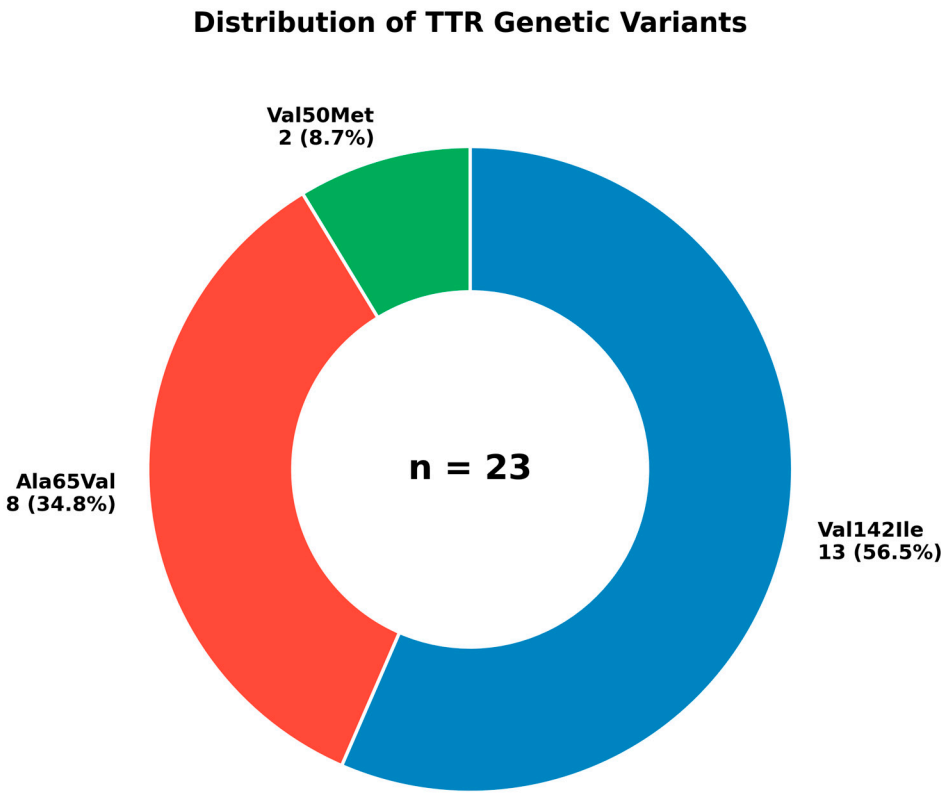

Figure 1. Distribution of genetic variants (n=23). The Val142Ile variant was the most frequent (56.5%), followed by Ala65Val (34.8%) and Val50Met (8.7%). All included patients had confirmatory genetic testing.

Anthropometric data were available in 6 patients, with a median BMI of 29.5 kg/m² (IQR 25.8–31.0). Nutritional distribution showed no underweight (0%), with 16.7% in the normal range, 33.3% with overweight, and 50% with obesity (Table 1).

The median age at diagnosis was 66 years (IQR 48–68, n=9), suggesting a diagnostic delay relative to the age of clinical presentation. All patients in whom molecular genetic characterization was completed (n=16) carried missense variants in heterozygous state. Classification of clinical significance showed 81.2% pathogenic variants (13/16) and 18.8% likely pathogenic (3/16). The sample used for genetic diagnosis was peripheral blood in 88.9% and buccal swab in 11.1%.

Kinship analysis (n=21) revealed that 47.6% of patients were index cases, while 52.4% were identified through family screening (siblings 18.2%, daughters 18.2%, sons 9.1%, sisters 9.1%).

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Patients were referred from 8 different hospitals, with predominance of EsSalud (66.7%) over MINSA (23.8%) and private clinics (9.5%).

Neurological Assessment

NIS evaluation was available in 15 patients. The median total NIS was 0.0 (IQR 0.0–10.0), indicating that most patients had no quantifiable neurological deficit. Of these, 73.3% (n=11) had no deficit (NIS=0), while 26.7% had neuropathy of variable grade.

Quality of life as assessed by the Norfolk QOL-DN (n=18) showed a median of 6.0 points (IQR 0.0–34.2). Of the patients, 55.6% had minimal functional impact (<20 points), while 22.2% had mild impact (20–39) and 22.2% had moderate-to-severe impact (≥40 points) (Table 2, Figure 4).

Table 2. Neurological assessment.

Variable	n	Value
NIS Total, median (range)	15	0.0 (0–137)
NIS = 0, n (%)	15	11 (73.3%)
NIS > 0, n (%)	15	4 (26.7%)
Norfolk QOL-DN, median	18	6.0
Norfolk <20 (minimal), n (%)	18	10 (55.6%)
Norfolk 20–39 (mild), n (%)	18	4 (22.2%)
Norfolk ≥40 (moderate–severe), n (%)	18	4 (22.2%)

NIS: Neuropathy Impairment Score (range 0–244, higher score indicates greater impairment). Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire (range 0–136). Cutoffs: <20 minimal impact, 20–39 mild, ≥40 moderate–severe. PND: Polyneuropathy Disability score; NPS: Neuropathic Pain Scale.

PND staging was available in 8 patients: 12.5% asymptomatic, 62.5% in stage I (mild sensory symptoms without gait limitation), 12.5% in stage II, and 12.5% in stage IIIb.

Regarding neuropathic pain (NPS, n=17), the median was 12.0 (IQR 0.0–35.0), with 47.1% of patients without pain, 17.6% with mild pain, 23.5% moderate, and 11.8% severe.

Functional tests showed: Timed Up and Go with a median of 10.6 seconds (IQR 9.1–14.8), with 29.4% of patients having a time >12 seconds, indicative of an increased risk of falls; 5-repetition Sit-to-Stand with a median of 10.0 seconds (IQR 8.0–17.2).

Autonomic Assessment

COMPASS-31 (n=18) showed a median of 6.0 points (IQR 0.0–11.2), indicating mild autonomic symptoms in most patients. Of the patients, 70.6% had no significant dysautonomia (<10 points), 23.5% had mild dysautonomia (10–19), and 5.9% moderate dysautonomia (20–39). No patient had severe dysautonomia (Table 3).

Table 3. Autonomic dysfunction.

Variable	n	Value
COMPASS-31, median	18	6.0

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SUDOSCAN feet, µS	6	Data available
SUDOSCAN hands, µS	6	Data available
Dysautonomia, n (%)	13	3 (23.1%)

COMPASS-31: Composite Autonomic Symptom Score (range 0–100, higher score indicates greater autonomic dysfunction). SUDOSCAN: objective evaluation of sudomotor function via electrochemical skin conductance (µS). Reduced values: <60 µS in feet, <40 µS in hands.

Objective evaluation with SUDOSCAN (n=6) showed foot conductance with a median of 66.0 µS (IQR 63.2–74.0), with 16.7% showing reduced values (<60 µS). In the hands, the median was 58.5 µS (IQR 43.0–64.2), with 33.3% showing reduced conductance (<40 µS). The cardiac autonomic neuropathy (CNA) risk score had a median of 29.0 (IQR 20.0–37.2), with 50% at low risk and 50% at moderate risk.

Cardiovascular Assessment

Complete cardiovascular evaluation was available in 16 patients (69.6% of the cohort). Mean LVEF was 60.5% (median 63.0%), with 81.2% having preserved systolic function (≥50%), 12.5% mildly reduced (40–49%), and 6.2% reduced (<40%) (Table 4, Figure 5).

Table 4. Cardiovascular assessment.

Variable	n	Value	Abnormal %
LVEF %, mean (median)	16	60.5% (63.0%)	—
LVEF <50%	16	3/16 (18.8%)	18.8%
GLS %, mean	15	15.5%	—
LV mass, g – mean (median)	12	102.9 (84.5)	—
LV mass >150 g	13	2/12 (16.7%)	16.7%
TAPSE, mm – mean	15	18.8	—
Septal thickness, mm – mean (median)	15	14.1 (15.0)	—
Posterior wall, mm – mean	15	12.9	—
E/e′ ratio – mean (median)	15	15.0 (13.8)	—
Cherry-on-top (apical sparing)	16	9/16 (56.2%)	56.2%
Troponin T, ng/L – median	9	47.0	—
Troponin T >14 ng/L	9	8/9 (88.9%)	88.9%
NT-proBNP, pg/mL – median (range)	9	834.5 (85.9–5096.0)	—
Tc99m-PYP Perugini grade 3	9	7/9 (77.8%)	77.8%
Tc99m-PYP Perugini grade 0	9	2/9 (22.2%)	22.2%

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ECG sinus rhythm	12	10/12 (83.3%)	83.3%
ECG atrial fibrillation	12	1/12 (8.3%)	8.3%
ECG flutter	12	1/12 (8.3%)	8.3%
Low-voltage ECG	12	7/12 (58.3%)	58.3%
Pacemaker	11	1/11 (9.1%)	9.1%

LVEF: left ventricular ejection fraction; LV mass: left ventricular mass; GLS: global longitudinal strain; TAPSE: tricuspid annular plane systolic excursion; E/e′: ratio of diastolic filling velocities; Cherry-on-top: apical sparing pattern on longitudinal strain. Tc99m-PYP scintigraphy classified by the Perugini scale (0–3). ECG: electrocardiogram.

Left ventricular mass (n=12) had a mean of 102.9 g (median 84.5 g), with 16.7% showing increased values (>150 g). Median TAPSE was 18 mm (n=15), with 6.7% showing reduced values (<17 mm).

The diastolic function pattern showed significant alterations: 55.6% had a monophasic/restrictive pattern, 11.1% grade III dysfunction, 22.2% impaired relaxation (grade I), and 11.1% normal or non-evaluable pattern.

Troponin T (n=9) showed a median of 47.0 ng/L, with 88.9% having elevated values (>14 ng/L).

The extended echocardiographic evaluation (n=16 patients with detailed cardiac assessment) revealed additional relevant findings: mean septal thickness of 14.2 mm (median 15.5 mm), with 75.0% of patients above the 12 mm cutoff for ventricular hypertrophy. Posterior wall thickness was consistently elevated. Mean E/e′ ratio was 15.0 (median 13.8), with 66.7% of patients having values >14, indicative of elevated filling pressures. The cherry-on-top sign (apical sparing on longitudinal strain) was positive in 50.0% of evaluated patients (n=16), a finding highly specific for cardiac amyloidosis. Right ventricular hypertrophy was observed in 75% (3/4) and pericardial effusion in 20% (1/5). The mean pulmonary artery systolic pressure was 21.0 mmHg.

Cardiac scintigraphy with Tc99m-pyrophosphate was performed in 9 patients, being positive in 7 (77.8%) with Perugini grade 3 score (uptake greater than bone) and negative in 2 (22.2%, Perugini 0), confirming significant cardiac amyloid deposition in most of those evaluated (Table 4, Figure 6).

NT-proBNP was available in 9 patients, with a median of 834.5 pg/mL (range 85.9–5096.0). One patient was identified with a severely elevated NT-proBNP (5096 pg/mL), consistent with a profile of severe cardiac involvement. The remaining evaluated patients had normal to mildly elevated values. Overall, most evaluated patients showed evidence of cardiac involvement according to the predefined criteria.

Electrocardiogram and Medical History

ECG (n=12) showed sinus rhythm in 83.3% of patients and low voltage in 58.3%. One case of mortality was recorded (4.3%, 1/23) during follow-up, in a 67-year-old male patient carrying the Val142Ile variant.

Medical history was available in a subgroup of patients (n=13–14 depending on variable). Arterial hypertension was the most frequent comorbidity, present in 50% of those evaluated. Carpal tunnel syndrome was reported in 23.1%, clinical dysautonomia in 23.1%, and arrhythmia in 23.1%. Diabetes mellitus was identified in 1 patient (7.7%), chronic kidney disease in 2 (15.4%), and cerebrovascular disease in 1 (7.7%). No cases of dyslipidemia were recorded (Table 7).

Distribution of Clinical Phenotypes

 doi:10.20944/preprints202603.1420.v2

Applying the phenotypic classification criteria, the distribution was: preclinical 8/23 (34.8%), mixed phenotype 9/23 (39.1%), cardiac 5/23 (21.7%), and pure neurological 1/23 (4.3%) (Table 5, Figure 2).

Table 5. Phenotype distribution.

Phenotype	Total n=23 (%)	Val142Ile (n=13)	Ala65Val (n=8)	Val50Met (n=2)
Preclinical	8 (34.8%)	7 (53.8%)	1 (12.5%)	0
Mixed	9 (39.1%)	3 (23.1%)	4 (50.0%)	2 (100%)
Cardiac	5 (21.7%)	3 (23.1%)	2 (25.0%)	0
Neurological	1 (4.3%)	0	1 (12.5%)	0

Phenotypic classification according to criteria derived from the AHA/ACC 2025 guidelines and the THAOS registry. Cardiac: LV mass >150 g, troponin T >14 ng/L, or restrictive diastolic pattern. Neurological: NIS >0, Norfolk QOL-DN ≥20, or PND ≥I. Mixed: cardiac and neurological criteria. Preclinical: carrier without criteria for organ involvement.

Analysis by genetic variant showed differential patterns: the Val142Ile variant (n=13) was associated with a preclinical phenotype in 53.8%, cardiac in 23.1%, and mixed in 23.1%. The Ala65Val variant (n=8) showed a mixed phenotype in 50.0%, cardiac in 25.0%, preclinical in 12.5%, and neurological in 12.5%, with 75.0% having global cardiovascular involvement. The Val50Met variant (n=2) was associated with a mixed phenotype in 100% of cases (Figure 3).

Median age varied by phenotype: carriers/preclinical 53 years, cardiac 48 years, neurological 76 years, and mixed 58 years.

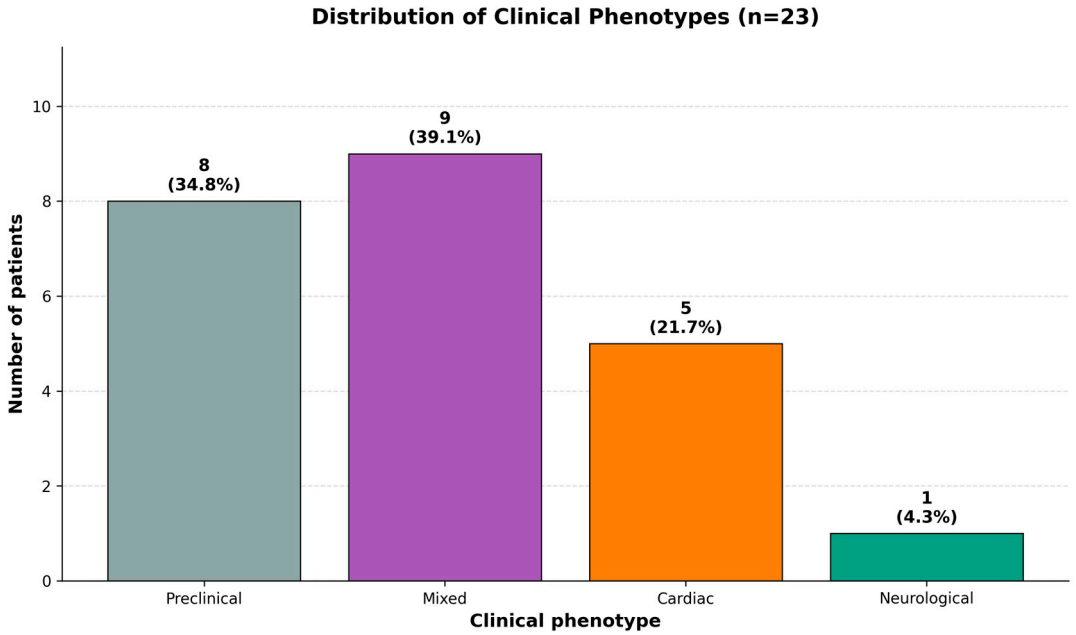

Figure 2. Distribution of clinical phenotypes (n=23). The mixed phenotype was the most prevalent (39.1%), followed by preclinical (34.8%), cardiac (21.7%), and pure neurological (4.3%). Classification according to AHA/ACC 2025 criteria and the THAOS registry.

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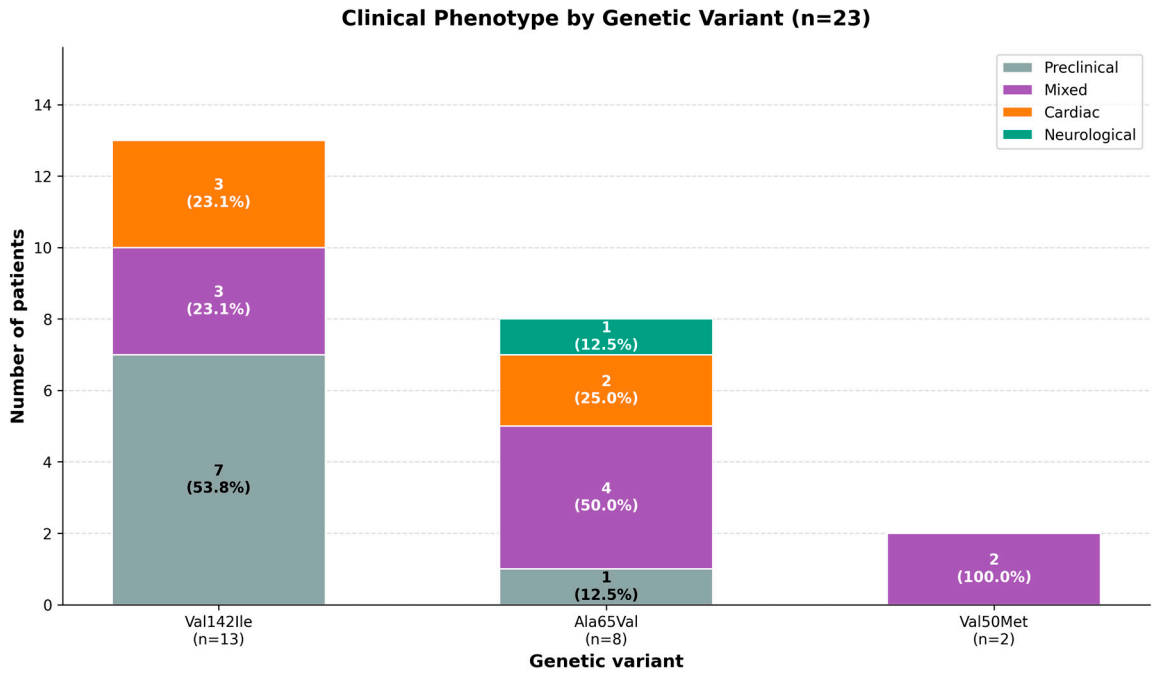

Figure 3. Clinical phenotype by genetic variant (n=23). Val142Ile showed a preclinical predominance (53.8%); Ala65Val showed a higher proportion of mixed phenotype (50.0%) and overall cardiovascular involvement (75.0%); Val50Met was associated exclusively with mixed phenotype (100%).

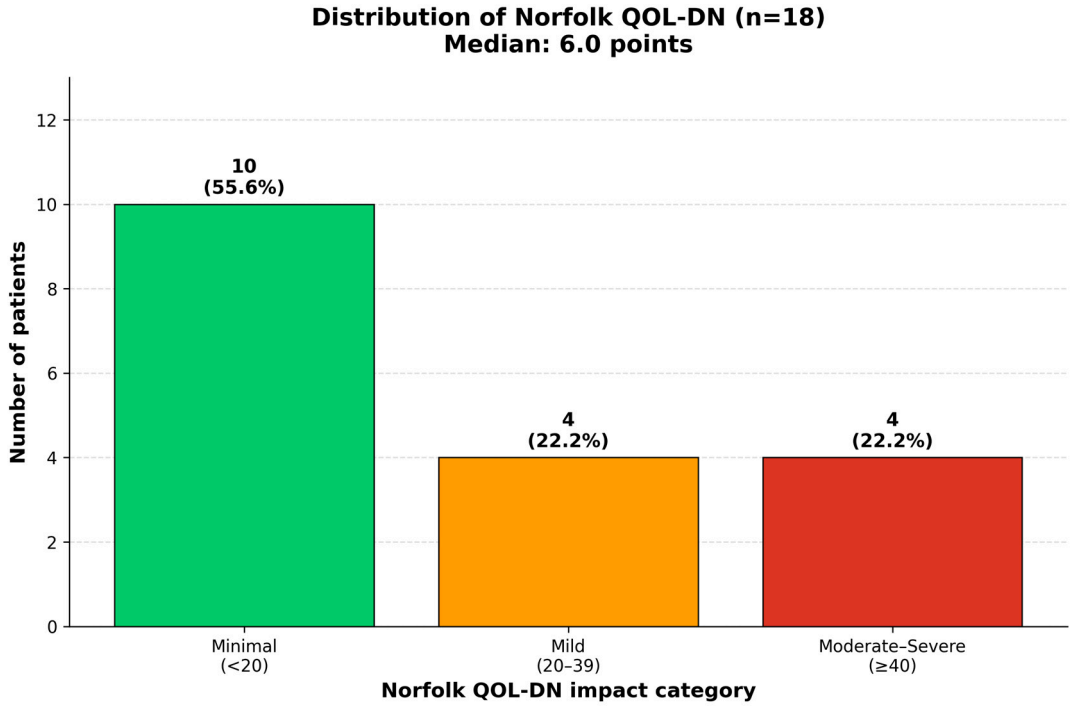

Figure 4. Distribution of Norfolk QOL-DN (n=18). Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy questionnaire. Most patients had minimal impact (<20 points, 55.6%), followed by mild (20–39, 22.2%) and moderate–severe (≥40, 22.2%). Median: 6.0 points.

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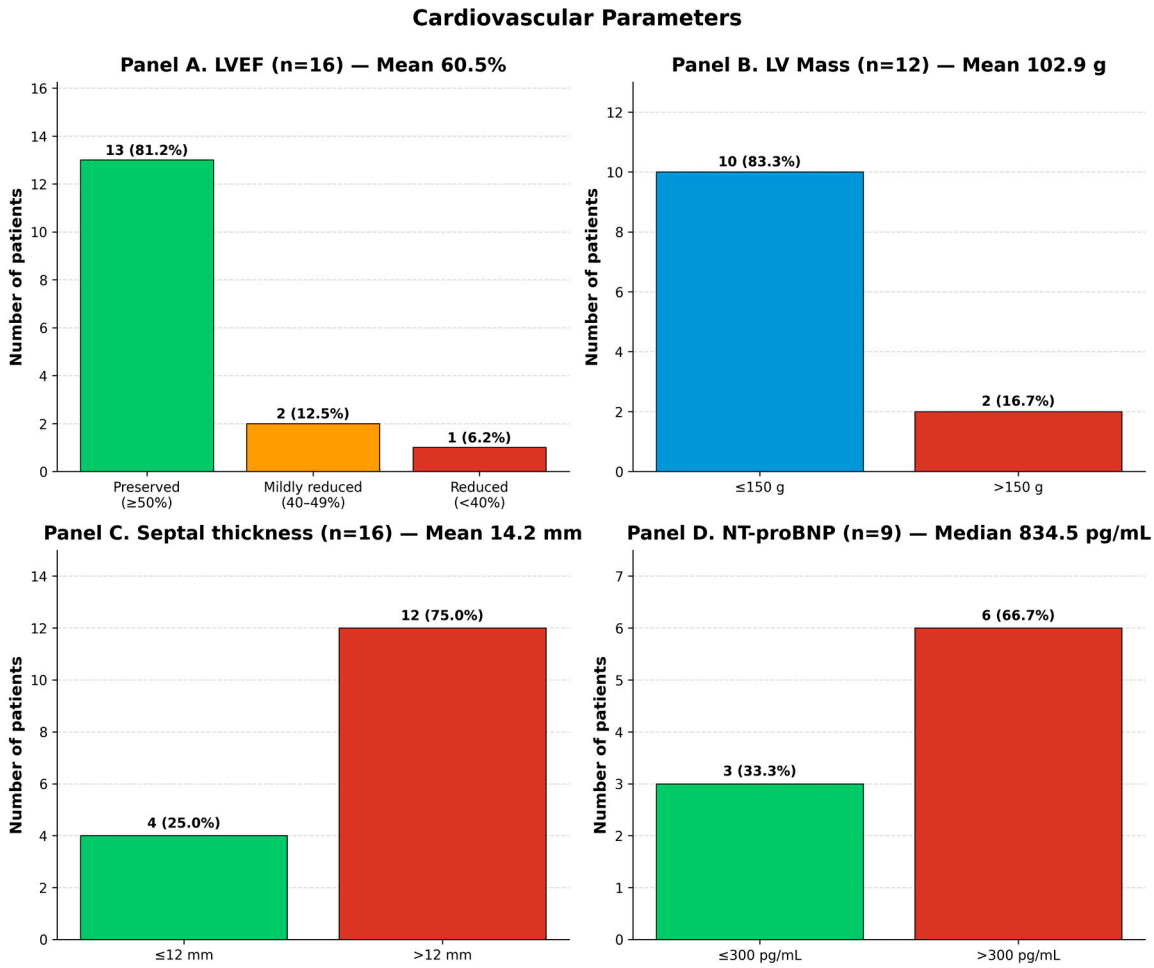
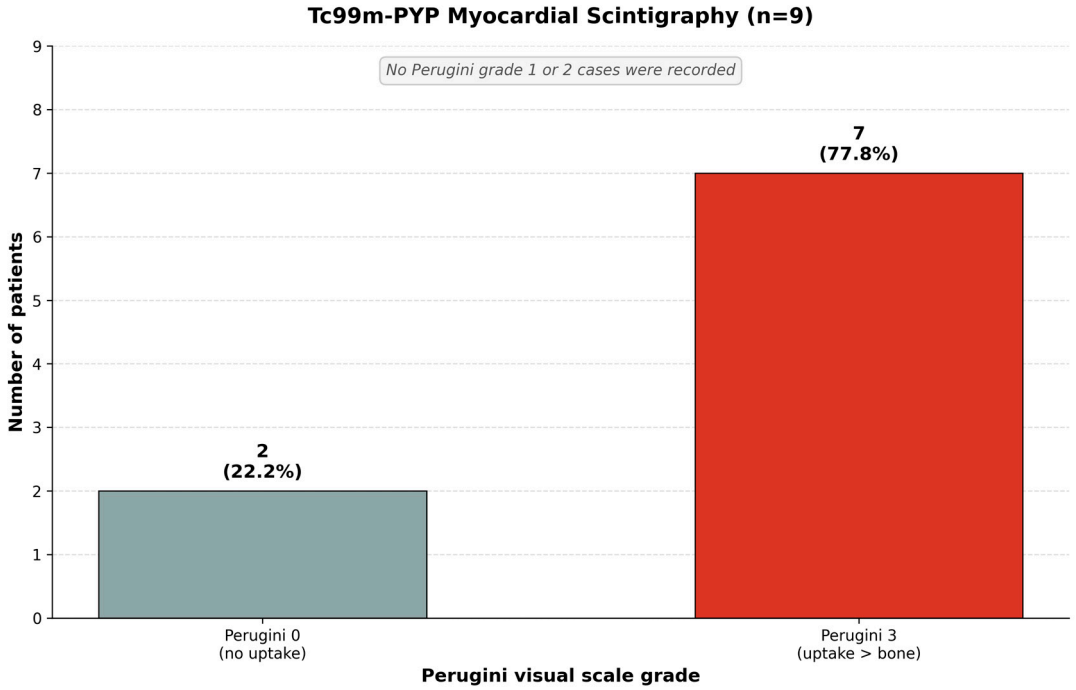


Figure 5. Cardiovascular parameters. Panel A: LVEF (n=16, mean 60.5%, <50% in 18.8%). Panel B: Left ventricular mass (n=12, mean 102.9 g, >150 g in 16.7%). Panel C: Septal thickness (n=16, mean 14.2 mm, >12 mm in 75.0%). Panel D: NT-proBNP (n=9, median 834.5 pg/mL, >300 in 66.7%). Red dashed lines: abnormality cutoffs; green lines: cohort mean/median.



 doi:10.20944/preprints202603.1420.v2

Figure 6. Tc99m-PYP scintigraphy results (n=9). Myocardial uptake classified by the Perugini visual scale. Grade 3 (uptake greater than bone) in 77.8% (7/9) and grade 0 (no uptake) in 22.2% (2/9). No Perugini grade 1 or grade 2 cases were recorded.

Discussion

This study represents the first systematic characterization of patients with ATTRv in the Peruvian population, contributing to the knowledge of this orphan disease in Latin America. Our findings reveal a phenotypic distribution consistent with international registries [4], although with particularities in the distribution of genetic variants and the degree of subclinical cardiovascular involvement that warrant discussion.

The distribution of genetic variants in our cohort differs notably from classical European series [1,2] and from other Latin American cohorts [5–7]. The Val142Ile variant, predominant in our series (56.5%), is characteristic of populations of African descent, with an estimated prevalence of 3–4% in African Americans [16], and is typically associated with late-onset cardiomyopathy [17,18]. Its high frequency in our Peruvian cohort may reflect the genetic admixture characteristic of the Latin American population and warrants further investigation through population studies. Notably, in our series, most carriers of Val142Ile (53.8%) were in a preclinical stage, consistent with the incomplete penetrance and late expression described for this variant [17,18].

The Ala65Val variant, second in frequency in our cohort (34.8%), suggests a tendency toward greater cardiovascular involvement, with 75.0% of patients showing cardiac involvement. Various amino-acid substitutions at TTR position 65 (p.Ala65Ser, p.Ala65Thr, p.Ala65Gly) have been associated with isolated cardiomyopathy, while p.Ala65Val has been linked with a mixed cardiac and neuropathic phenotype [19]. Notably, Saez et al. [6], in the first epidemiological report from a reference center in Argentina (n=576), did not identify this variant among the eight detected mutations, suggesting that the presence of p.Ala65Val in our Peruvian cohort may represent a distinctive regional finding. Likewise, the REACT-SP registry in Brazil (n=644) reported a predominance of Val50Met (47.5%) and Val142Ile (39.2%), with no mention of Ala65Val [5], reinforcing the singularity of this finding.

The Val50Met variant (formerly Val30Met), the most frequent worldwide and characteristic of the endemic foci of Portugal and Japan [2,3], represented only 8.7% of our cohort. Both patients with this variant had neurological involvement, consistent with the classical familial amyloid polyneuropathy phenotype originally described by Andrade [3].

The proportion of mixed phenotype in our cohort (39.1%) is consistent with that reported in the THAOS registry (33.5%) [4], the largest global ATTRv registry. However, we observed a lower proportion of pure neurological phenotype (4.3%) compared with European series in which the Val50Met variant predominates [2]. The observed phenotypic distribution validates the applicability of the classification criteria derived from the AHA guidelines [15] and the THAOS registry [4] in our population, and is consistent with the profile described in European series with predominantly cardiac phenotype [20].

The high proportion of patients in a preclinical stage (34.8%) has favorable clinical implications. Early initiation of treatment, particularly in preclinical stages or in mild disease, is associated with better outcomes according to the extension data of the tafamidis [8], patisiran [9], and inotersen [10] clinical trials. The quality-of-life findings reinforce this notion: the median Norfolk QOL-DN [21] of 6.0 points and the predominant proportion of patients with minimal impact (<20 points, 55.6%) suggest diagnosis at early stages. However, the 17.6% of patients with moderate-to-severe impact (≥40 points) represents a subgroup with significant functional involvement that requires priority therapeutic intervention (Table 6). Nevertheless, this high preclinical proportion may partly reflect a detection bias, since active genetic screening of relatives of index cases preferentially identifies asymptomatic carriers who would not otherwise seek medical attention.

 doi:10.20944/preprints202603.1420.v2

Table 6. Quality of life.

Variable	n	Value
Norfolk QOL-DN	18	—
<20 (minimal)	18	10 (55.6%)
20–39 (mild)	18	4 (22.2%)
≥40 (moderate–severe)	18	4 (22.2%)
KCCQ – Positive	6	5 (83.3%)
KCCQ – Negative	6	1 (16.7%)

Norfolk QOL-DN: Norfolk Quality of Life-Diabetic Neuropathy (range 0–136). KCCQ: Kansas City Cardiomyopathy Questionnaire; a positive result indicates preserved quality of life. Norfolk values were stratified by impact: <20 minimal, 20–39 mild, ≥40 moderate–severe.

Table 7. Medical history and extracardiac manifestations.

Variable	n evaluated	Positive n (%)
Hypertension	14	7 (50.0%)
Diabetes	13	1 (7.7%)
Arrhythmia	13	3 (23.1%)
Renal disease	13	2 (15.4%)
Dyslipidemia	13	0 (0%)
Hypothyroidism	13	0 (0%)
Stroke	13	1 (7.7%)
Smoking	13	0 (0%)
Carpal tunnel syndrome	13	3 (23.1%)
Macroglossia	13	1 (7.7%)
Purpura	13	0 (0%)

Data available in a subgroup of evaluated patients (n indicated by variable). Carpal tunnel syndrome and macroglossia are more commonly associated with AL (light-chain) amyloidosis than with ATTRv; their presence should prompt consideration of alternative or concurrent etiologies.

Autonomic evaluation by COMPASS-31 [12] showed a predominance of mild symptoms, although objective evaluation with SUDOSCAN [13] revealed subclinical dysfunction in the hands (33.3% with reduced conductance) in a higher proportion than suggested by symptoms. This discrepancy between symptoms and objective findings underscores the importance of multimodal evaluation in ATTRv [22].

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The findings of the extended echocardiographic evaluation reinforce the usefulness of complementary parameters in characterizing cardiac involvement in ATTRv. Elevated septal thickness (mean 14.2 mm, median 15.5 mm), the prevalence of the cherry-on-top sign (50.0%) [14], and the elevated E/e' ratio complement the phenotypic classification criteria and may be useful for risk stratification. Notably, the 9 patients evaluated with Tc99m-pyrophosphate scintigraphy showed Perugini [23] grade 3 uptake in 77.8% (7/9) and grade 0 in 22.2% (2/9), confirming that this diagnostic tool allows non-invasive identification of cardiac amyloidosis with high specificity [24]. The absence of grade 1 or 2 uptake in our series suggests a bimodal distribution (severe involvement vs. absence) that may be related to the timing of evaluation in the natural history of the disease.

The finding that 100% of patients with molecular characterization were heterozygous is consistent with the autosomal dominant inheritance pattern of ATTRv [1,2]. The fact that 52.4% of patients were identified through family screening underscores the importance of screening programs in first-degree relatives [25], a strategy that probably contributes to the high proportion of preclinical patients in our cohort. This finding is consistent with international recommendations for genetic counseling and presymptomatic evaluation in relatives of carriers of pathogenic TTR variants [25].

The patients included in this series came from various institutions of the Peruvian healthcare system, including EsSalud (66.7%), MINSA (23.8%), and private institutions (9.5%), reflecting the institutional dispersion characteristic of an orphan disease.

One case of mortality was recorded (4.3%, 1/23) during the follow-up period, in a 67-year-old male patient carrying the Val142Ile variant. This finding, although limited by the small sample size, highlights the importance of close clinical follow-up and timely evaluation for the initiation of disease-modifying therapies [8–10].

This study has limitations inherent to its design. The sample size (n=23) reflects the rarity of ATTRv diagnosed in Peru and the challenges in identifying patients with this orphan disease. The cross-sectional design precludes evaluation of disease progression and natural history. Not all patients had complete evaluations across all domains (for example, only 69.6% had a complete cardiac evaluation), which introduces a possible selection bias in domain-specific analyses. Recruitment from tertiary referral centers may overrepresent more severe phenotypes, limiting generalizability. The lack of longitudinal follow-up data limits the ability to assess treatment response and disease trajectory.

Despite these limitations, this study contributes valuable information to the Peruvian and Latin American medical community. Recognition of ATTRv as a cause of polyneuropathy and cardiomyopathy, together with the availability of diagnostic tools (including cardiac scintigraphy with technetium pyrophosphate [23,24]) and disease-modifying therapies [8–11], makes early diagnosis imperative. Identification of red-flag symptom clusters [22] and systematic family screening [25] are key strategies. Our data may serve as a reference for future studies and for the planning of healthcare services targeted at this population.

Conclusions

In this first case series of hereditary transthyretin amyloidosis (ATTRv) in the Peruvian population, important clinical and genetic heterogeneity was observed, with a predominance of patients in preclinical stages or with mild disease, and a phenotypic distribution consistent with international registries. The Val142Ile and Ala65Val variants were the most frequent, with differentiated phenotypic patterns that have implications for clinical follow-up.

The extended cardiovascular evaluation data, including septal thickness, apical sparing, and pyrophosphate scintigraphy, suggest the severity of cardiac involvement in patients with cardiac or mixed phenotypes and reinforce the need for systematic multimodal evaluation.

Early identification of carriers and patients with incipient disease represents an opportunity for the timely initiation of disease-modifying therapies, with potential favorable impact on clinical outcomes. Multicenter prospective studies are needed to better characterize the natural history of ATTRv in the Peruvian population and to evaluate response to available therapies.

 doi:10.20944/preprints202603.1420.v2

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