Original Article

Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review

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Abstract

Background: **Hereditary transthyretin amyloidosis (ATTRv) is a genetic disorder caused by extracellular deposition of amyloid fibrils derived from plasma transthyretin in tissues following loss of its tetrameric structure, affecting the heart and nervous system.**

Objective: **This study aimed to assess left atrial function in ATTRv and to discuss its relevance as a tool for early detection of cardiac involvement, as well as its prognostic value.**

Methods: **This systematic literature review was conducted in accordance with PRISMA guidelines and registered in PROSPERO (CRD42051116316). The following databases were searched: Embase, PubMed, Scopus, and LILACS, including studies published between January 2010 and August 2025. MeSH terms used included "cardiac amyloidosis," "transthyretin amyloidosis," "ATTR," "echocardiography," "strain," and "left atrium."**

Results: **Nine studies were included, comprising a total of 1,290 patients with amyloidosis. Assessment of left atrial function demonstrated a progressive reduction in left atrial strain, particularly reservoir strain, measured by peak atrial longitudinal strain (PALS), across the clinical spectrum of ATTRv, as follows: unaffected carriers (PALS 23%–30%), neuropathic phenotype (PALS 20%–25%), and amyloid cardiomyopathy (PALS 8%–15%).**

Conclusion: **This systematic review demonstrates that left atrial strain dysfunction is a consistent finding in patients with ATTRv, including carriers and individuals with isolated polyneuropathy. Reduced PALS and increased atrial stiffness emerge as promising parameters for early detection of cardiac involvement, with potential prognostic value. These findings should be interpreted with caution due to the observational design of the included studies. Further studies with larger sample sizes are needed.**

Keywords: **Amyloidosis; Left Atrial Function; Familial Amyloid Neuropathies.**

Introduction

Amyloidosis is a disease characterized by abnormal deposition of amyloid fibrils, mainly affecting the heart and nervous system. It may result from immunoglobulin light chains, variant transthyretin, or wild-type transthyretin.[1-4] In hereditary transthyretin amyloidosis (ATTRv), the mutant transthyretin protein, which has a tetrameric structure, loses its stability and misfolds, forming fibrillar aggregates that deposit in several organs, particularly in the peripheral and autonomic nervous systems (polyneuropathy phenotype), cardiac chambers (cardiomyopathy phenotype), or presenting a mixed phenotype.[3,5,6] The diagnosis and treatment of this potentially severe and underdiagnosed disease have significantly advanced in recent years, highlighting the need for early identification of cardiac involvement in individuals carrying pathogenic variants.[2,7,8]

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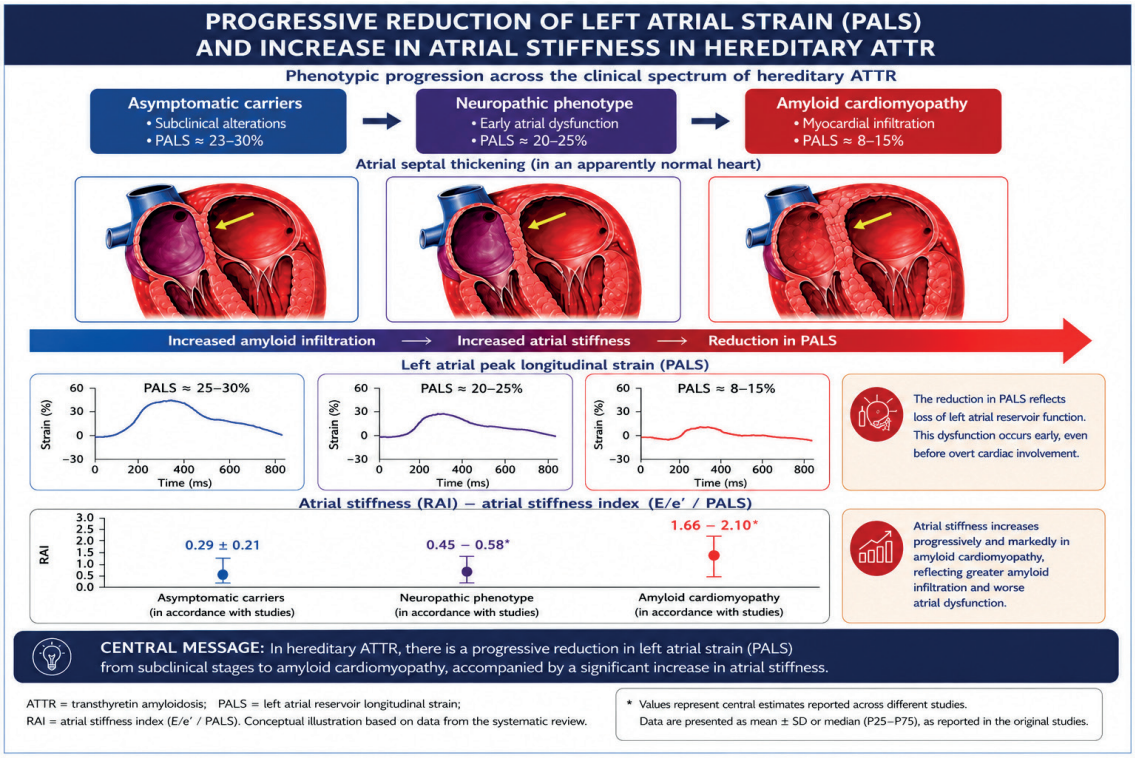
Speckle-tracking echocardiography has demonstrated an important role in the diagnosis of cardiac amyloidosis through the assessment of myocardial deformation (strain), particularly by identifying the apical sparing pattern, characterized by preserved contractility of the apical segment and greater impairment of basal segments of the left ventricle.[9-11] The assessment of atrial function using speckle-tracking has emerged as an early diagnostic tool in hereditary amyloidosis.[12]

The left atrium performs three fundamental functions: it acts as a reservoir, serves as a conduit, and has a contractile (pump) role.[12] Bandera et al. defined reservoir strain, or peak atrial longitudinal strain (PALS), as the ability of the atrium to expand during ventricular systole, with its peak value occurring at the beginning of left ventricular filling. Contraction strain (pump function) represents atrial shortening, with peak value at the onset of atrial contraction (in individuals in sinus rhythm), whereas conduit strain reflects early diastolic emptying and is calculated as the difference between reservoir and contraction strain.[13,14] Left atrial stiffness is calculated as the ratio between E/e′ and reservoir strain.[13,15,16] According to Pathan et al. (2016), normal reference values for reservoir, conduit, and contraction strain are 39.4% (95% confidence interval [CI]: 38.0%–40.8%), 23.0% (95% CI: 20.7%–25.2%),

Central Illustration: Left Atrial Strain Assessment in Hereditary Amyloidosis: A Systematic Review



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Progressive reduction in left atrial strain (PALS) and increase in atrial stiffness across the clinical spectrum of hereditary ATTR. Conceptual illustration based on findings from the systematic review. ATTR: transthyretin amyloidosis; PALS: peak atrial longitudinal strain; RAI: atrial stiffness index (E/e' divided by PALS).

and 17.4% (95% CI: 16.0%–19.0%), respectively.[12] Normal atrial stiffness values have a mean of 0.21 ± 0.1.[17]

This review aimed to identify alterations in left atrial strain assessed by speckle-tracking echocardiography in patients with ATTRv and to discuss its relevance for early detection of cardiac involvement and prognostic value (Central Illustration).

Methods

A systematic review was conducted according to a prespecified protocol registered in PROSPERO and reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (Figure 1).

Selection criteria

Inclusion criteria

We included original observational studies (cross-sectional, case-control, and cohort) evaluating left atrial function in individuals with ATTRv. The search was restricted to studies published in Portuguese and English.

Exclusion criteria

We excluded duplicate studies, case reports, and case series with fewer than 10 patients. Additionally, studies published in other languages, those focusing on immunoglobulin light-chain amyloidosis, and those evaluating left atrial strain in cardiopathies unrelated to ATTRv were excluded.

Search strategy

A comprehensive and systematic search was conducted in the electronic databases Embase, PubMed, Scopus, and LILACS, covering the period from January 2010 to August 2025. The search strategies (i.e., specific keywords and MeSH terms used) are detailed in the Supplementary Material.

Study analysis

Two authors independently reviewed titles and abstracts of articles and selected the studies compatible with the inclusion criteria. Afterwards, final eligibility was determined through full-text review. Any disagreement was resolved by consulting a third author.

Data from the included articles were extracted using a data collection form, including study design, year of publication,

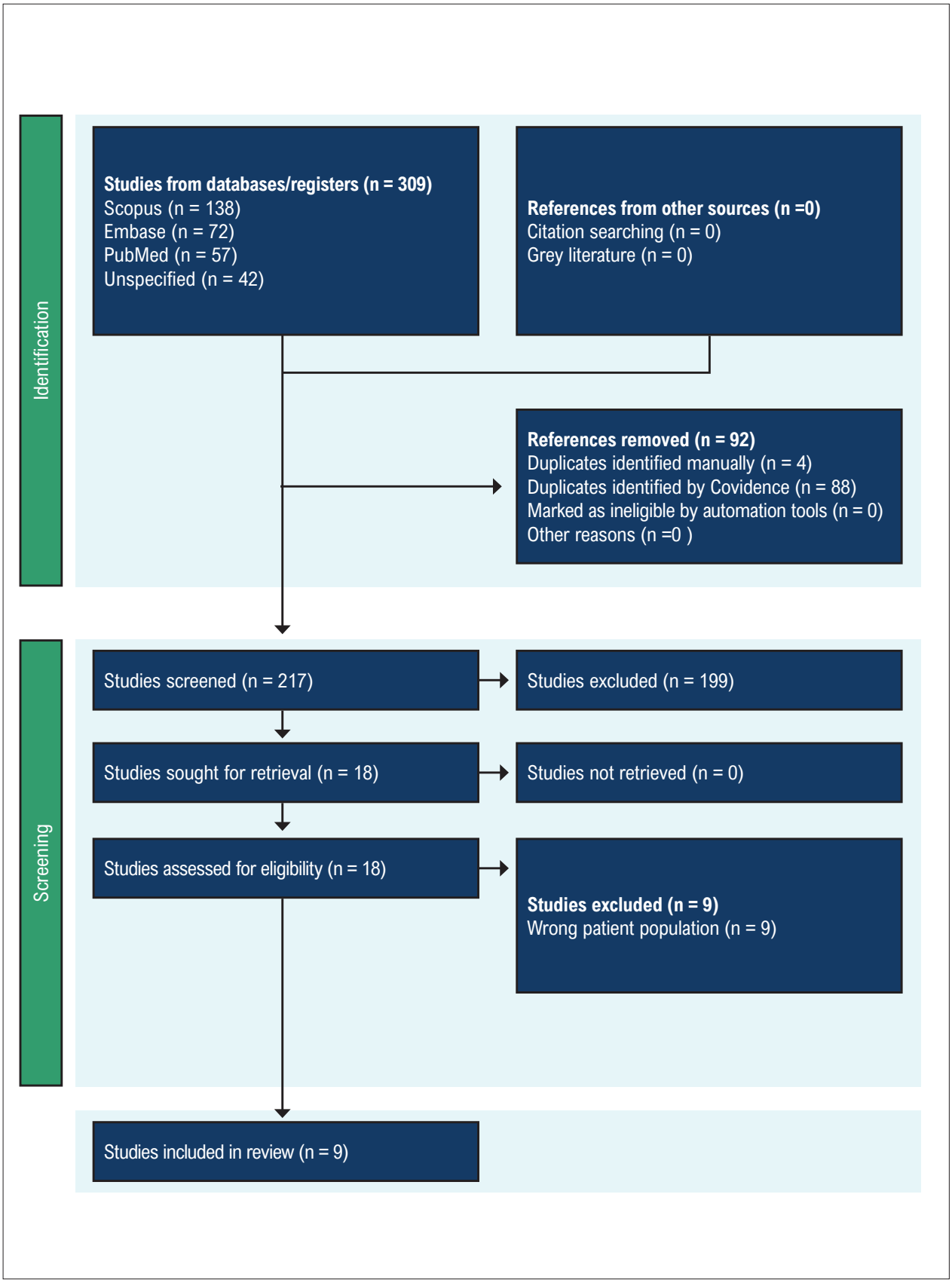

Figure 1 – *Systematic literature review flowchart.*

methodology, demographic characteristics, sample size, and clinical outcomes. In studies with heterogeneous populations, only data related to patients with ATTRv were extracted. PALS, also referred to as reservoir strain, was analyzed in all studies. Conduit strain, contraction strain, and left atrial stiffness were also assessed when available.

Assessment of risk of bias and statistical analysis

The methodological quality of the included studies was independently assessed by two reviewers using the Newcastle–Ottawa Scale (NOS), adapted for application to observational studies with different designs, including cohort, case-control, and cross-sectional studies. Although widely used, it is recognized that the NOS has limitations when evaluating studies without a control group.

The scale is structured into three main domains: selection of participants, comparability of groups, and assessment of outcomes. A total score was calculated for each study, allowing classification of methodological quality (risk of bias) as low, moderate, or high. Disagreements between reviewers were resolved by consensus.

Results

The search strategy identified 309 potentially relevant studies. After removal of duplicates, 217 studies remained and were screened by title and abstract; subsequently, relevant articles were selected for full-text review. A total of 18 articles were assessed in full, of which 9 were excluded based on the predefined criteria. Consequently, 9 studies were included in the systematic review.

A total of 1,290 individuals with amyloidosis were included in the analysis. The search was completed in August 2025. The included studies were conducted in Italy (n = 5), England (n = 1), Mexico (n = 1), the United States (n = 1), and Sweden (n = 1) and were published between 2016 and 2024. The analyzed studies included patients with hereditary amyloidosis categorized into three groups: unaffected carriers, patients with polyneuropathy, and patients with cardiac amyloidosis. Sample sizes ranged from 21 to 241 individuals with the genetic mutation.

All studies used ultrasound equipment (GE; Esaote; Philips Medical) with dedicated software for left atrial assessment using speckle-tracking echocardiography. Most studies reported data collection for at least one of the three functional phases of the left atrium (PALS, conduit, and contraction), as well as atrial stiffness when available (Table 1).

Outcomes were reported as mean and standard deviation or median and interquartile range for strain parameters (PALS, conduit, contraction, atrial stiffness), rather than as proportions of individuals classified as having abnormal values based on validated cutoff points.

Across all included studies, a reduction in left atrial strain was observed, with varying magnitudes according to clinical phenotype (Figure 2). This alteration was present not only in patients with cardiac amyloidosis but also in carriers and in patients with polyneuropathy without overt cardiac involvement. Although the high frequency of this finding suggests that atrial dysfunction is common in ATTRv, it was not possible to estimate its prevalence, as the included studies primarily reported mean values or between-group differences rather than proportions of affected individuals.

Unaffected carriers

The results showed that unaffected carriers had mildly reduced PALS values,[18-20] consistent with the findings of Aceves Velazquez et al.,[21] who studied 30 individuals (PALS 30%, p = 0.03). In 2023, Di Lisi et al.[15] published a study to identify early signs of cardiac involvement across different groups of hereditary amyloidosis. In group C of Di Lisi et al.[15] (carriers), PALS values were reduced in 11 individuals (23.64% ± 10.06%), while mean atrial stiffness was above the normal range (0.29 ± 0.21).

Patients with isolated polyneuropathy

In patients with polyneuropathy, the results showed a significant reduction in left atrial function even in the absence of overt cardiac involvement. Group B of Di Lisi et al.[15] (only polyneuropathy) demonstrated reduced PALS values (23.63% ± 11.2%, p = 0.005; group A vs. group B) and increased atrial stiffness (0.58 ± 0.2). In 2024, Di Lisi et al.[16] published a study evaluating the effects of patisiran on cardiac function. At baseline (T0), the neuropathy group (n = 14) showed reduced PALS (24.65% ± 11.35%) and elevated atrial stiffness (0.45 ± 0.43).[22] In the study by Di Bella et al.,[23] 28 patients were evaluated using both echocardiography and cardiac magnetic resonance imaging (MRI). Late gadolinium enhancement (LGE) on MRI was used to assess atrial amyloid deposition, while echocardiographic strain was used to quantify left atrial deformation. PALS values were significantly lower in the group with atrial LGE (n = 14) compared with the group without LGE (n = 14) (22.8% ± 13% vs. 59.6% ± 33.1%; p = 0.002 and p = 0.001, respectively).

The other phases of atrial function were also more impaired in the LGE group than in the non-LGE group. Conduit strain was significantly lower in the LGE group compared with the non-LGE group (10.2% ± 6.2% vs. 30.2% ± 22.4%; p = 0.01 and p < 0.0001, respectively). Similarly, contraction strain (global pre-A strain) was reduced in the LGE group compared with the non-LGE group (12.6% ± 7.8% vs. 26.2% ± 15%; p = 0.001 and p = 0.01, respectively). Overall, left atrial function was significantly lower in patients with atrial LGE than in those without LGE.

Cardiac amyloidosis

Patients with overt cardiac amyloidosis exhibited the most pronounced reductions in PALS. In the study by Bandera et al.,[13] individuals with the V122I mutation had lower PALS values (8.0% [5.3%–10.9%]) compared with those carrying the T60A mutation (11.4% [7.0%–15.7%]; p < 0.05). Other parameters of atrial function were also consistently reduced. Conduit strain was 7.0% (4.7%–10.0%) in T60A and 6.1% (4.2%–8.2%) in V122I (p = NS), while contraction strain was 5.0% (2.8%–8.4%) in T60A and 3.1% (1.6%–5.0%) in V122I (p < 0.05). In addition, atrial stiffness was significantly higher (2.12 vs. 1.67; p < 0.001).

Table 1 – Summary of study design, results, and conclusions

Study	Method	Outcome	Results	Conclusions
Aceves Velazquez et al., 2020[21]	Cross-sectional within a cohort. Objective: To determine whether strain is a good predictor of cardiac involvement suggestive of amyloid deposition in the heart. Population: 30 participants with ATTRv without known cardiac involvement.	PALS	PALS decreased from 34% to 30% (p = 0.03).	Echocardiographic strain may detect early abnormalities in patients with cardiac involvement due to ATTRv, suggesting potential prognostic value.
Bandera et al., 2022[13]	Cross-sectional. Objective: To assess LA stiffness and mechanics using speckle-tracking echocardiography and to analyze the association between atrial functional parameters and clinical outcomes. Population: Patients with ATTR-CA. N = 906 participants (551 ATTRwt; 355 ATTRv – 241 V122I; 93 T60A and 21 others).	PALS, conduit strain, contraction strain, atrial stiffness	PALS (%): T60A 11.4% (7.0%–15.7%); V122I 8.0% (5.3%–10.9%), p < 0.05 (T60A vs. V122I). Conduit strain (%): T60A 7.0% (4.7%–10.0%); V122I 6.1% (4.2%–8.2%), p = NS. Contraction strain (%): T60A 5.0% (2.8%–8.4%); V122I 3.1% (1.6%–5.0%), p < 0.05. Atrial stiffness: T60A 1.67 (0.87–2.70); V122I 2.12 (1.34–3.29), p < 0.001.	Lower PALS in V122I compared to ATTRwt and T60A; higher LA stiffness in V122I; both associated with worse prognosis.
de Gregorio et al., 2016[22]	Cross-sectional. Objective: To evaluate and compare distinctive characteristics of LA size and function in patients with ATTR-CA and HCM. Population: 32 patients (16 with ATTR-CA and 16 with HCM) and 15 healthy controls.	PALS and contraction strain	PALS (%): 14.1 ± 4.7, p < 0.001 (comparison between ATTR-CA, HCM, and controls). Contraction strain (%): 0.92 ± 0.56, p < 0.01.	PALS significantly impaired in ATTR-CA vs. HCM and controls; also lower in HCM vs. controls. PALS < 19% in 94% of ATTR-CA vs. 31% of HCM and none of controls (p < 0.001). ROC suggested cutoff PALS ≤ 19% and contraction ≤ 1.1%.
Di Bella et al., 2016[23]	Case-control study. Objective: To analyze atrial function in patients with and without atrial amyloid deposition. Population: Patients with familial amyloid polyneuropathy (TTR-related) without cardiac disease. 50 participants: 28 patients and 22 controls.	PALS, conduit strain, contraction strain	PALS: LGE-atrial group (n = 14) 22.8% ± 13%, p = 0.002; non-LGE (n = 14) 59.6% ± 33.1%, p = 0.001; controls 47.4% ± 16.4%. Conduit strain: LGE 10.2% ± 6.2%, p = 0.01; non-LGE 30.2% ± 22.4%, p < 0.0001; controls 26.3% ± 11.9%. Contraction strain: LGE 12.6% ± 7.8%, p = 0.001; non-LGE 26.2% ± 15%, p = 0.01.	Cutoff PALS ≤ 40.9%: sensitivity 100%, specificity 71.6% (AUC 0.91). LA remodeling and dysfunction present; useful for clinical and prognostic stratification.
Di Lisi et al., 2023[15]	Cross-sectional. Objective: To analyze echocardiographic and speckle-tracking differences among carriers, neuropathic patients, and CA patients. Population: 31 patients with TTR mutation.	PALS and atrial stiffness	PALS: group A 9.8% ± 3; group B 23.63% ± 11.2 (p = 0.005); group C 23.64% ± 10.06. Atrial stiffness: group A 1.6 ± 0.30; group B 0.58 ± 0.2; group C 0.29 ± 0.21.	Monitoring PALS and stiffness may help identify disease progression.

Di Lisi et al., 2024[16]	Non-randomized experimental study. Objective: To evaluate patisiran effects on cardiac function using speckle-tracking. Population: ATTRv patients (group A n = 7; group B n = 14).	PALS and atrial stiffness	PALS: group A 12% ± 6%; group B 24.65% ± 11.35%. Stiffness: group A 2 ± 1; group B 0.45 ± 0.43.	Speckle-tracking useful for early diagnosis and monitoring; larger studies needed.
Henein et al., 2018[19]	Cross-sectional. Objective: Evaluate LA function in ATTRv and compare with HCM and controls.	Reservoir, conduit, contraction strain	PALS: 24 ± 7 vs. 29 ± 10 (controls), p = 0.015. Conduit: 1.0 ± 0.6 vs. 1.4 ± 0.6, p = 0.005. Contraction: 1.4 ± 0.5 vs. 1.7 ± 0.6, p = 0.025.	LA function reduced regardless of left ventricular thickness; useful for early screening and arrhythmic risk prediction.
Nochioka et al., 2017[18]	Cross-sectional. Objective: Characterize LA function in CA and determine mechanisms.	PALS, conduit, contraction strain	PALS 20.1 ± 13.9; multiple strain parameters impaired; no significant p differences.	Reduced LA function associated with worse survival; ATTRwt worst prognosis.
Trimarchi et al., 2023[24]	Cross-sectional. Objective: Compare ATTRwt-CA vs. ATTRv-CA.	PALS, conduit, contraction strain	PALS: 9.7 ± 3.7 vs. 17.6 ± 7.5 (p = 0.004). Conduit: 7.6 ± 2.3 vs. 8 ± 3.5 (p = 0.8). Contraction: 2.5 ± 3.1 vs. 10 ± 4.7 (p < 0.0001).	Advanced echocardiography differentiates atrial and ventricular involvement between subtypes.

ATTR-CA: transthyretin cardiac amyloidosis; ATTRv: hereditary transthyretin amyloidosis; ATTRwt: wild-type transthyretin amyloidosis; AUC: area under the receiver operating characteristic curve; CA: cardiac amyloidosis; HCM: hypertrophic cardiomyopathy; LA: left atrial; LGE: late gadolinium enhancement; NS: not significant; PALS: peak atrial longitudinal strain; ROC: receiver operating characteristic curve; TTR: transthyretin.

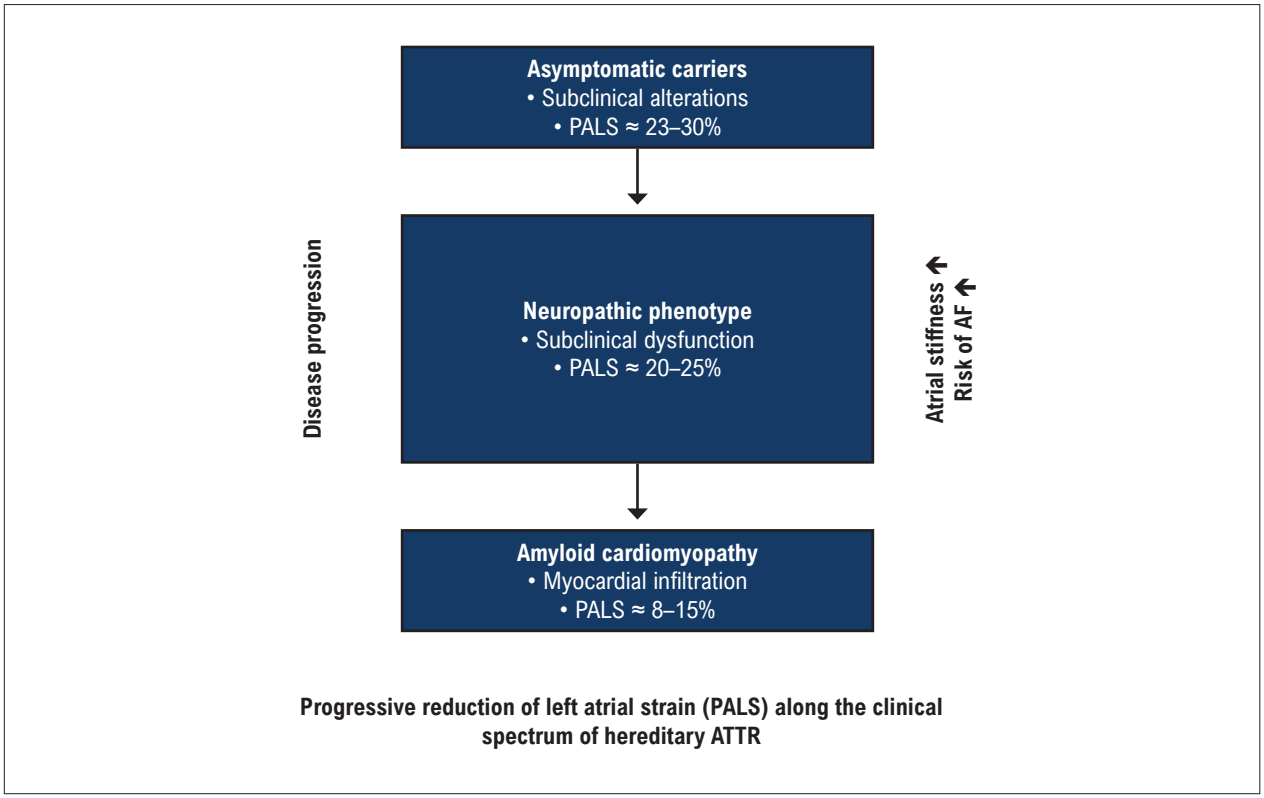

Figure 2 – *Progression of atrial dysfunction in ATTRv. AF: atrial fibrillation; ATTR: transthyretin amyloidosis; PALS: peak atrial longitudinal strain.*

Similarly, group A (cardiac involvement) in Di Lisi et al.[15] showed reduced PALS (9.8% ± 3%) and increased atrial stiffness (1.6 ± 0.30) in 7 individuals. Comparable findings were reported in the cardiac amyloidosis group at baseline (T0, n = 7) in Di Lisi et al.,[16] with PALS of 12% ± 6% and atrial stiffness of 2 ± 1.

Henein et al.[19] evaluated 46 patients with ATTRv confirmed by abdominal biopsy and genetic testing (predominantly V30M). Among them, 32 had left ventricular wall thickness > 12 mm (classified as "amyloid hypertrophy") and 14 had wall thickness ≤ 12 mm. The mean PALS value was 24% ± 7% (p = 0.015). Additionally, parameters derived from conduit and contraction strain were also reduced compared with healthy controls. Conduit strain (LASRe) was −1.0 ± 0.6 in the ATTR group versus −1.4 ± 0.6 in controls (p = 0.005), and contraction strain (LASRa) was −1.4 ± 0.5 versus −1.7 ± 0.6 (p = 0.025), respectively.

Nochioka et al.[18] demonstrated that all parameters derived from speckle-tracking assessment of left atrial function were markedly impaired in 29 patients with cardiac amyloidosis. PALS was 20.1% ± 13.9% (p = 0.47), peak longitudinal strain rate (LSR) was 0.88 ± 0.54 (p = 0.12), and total emptying fraction was 45.7% ± 16.8% (p = 0.73). Conduit function parameters included early LSR of −0.81 ± 0.53 (p = 0.13) and passive emptying fraction of 23.6% ± 11.3% (p = 0.16). Contraction function parameters included late LSR of −0.95 ± 0.91 (p = 0.28) and active emptying fraction of 31.8% ± 16.9% (p = 0.16).

Trimarchi et al.[24] reported reductions across all three phases of atrial function in 20 patients with cardiac amyloidosis: PALS 17.6% ± 7.5% (p = 0.004), conduit strain −8 ± 3.5 (p = 0.8), and contraction strain −10 ± 4.7 (p < 0.0001).

In the study by de Gregorio et al.,[22] which evaluated left atrial size and function in 16 patients with transthyretin cardiac amyloidosis, 16 with hypertrophic cardiomyopathy (HCM), and 15 controls, mean PALS was significantly reduced in patients with transthyretin cardiac amyloidosis (14.1% ± 4.7%) compared with HCM (19%–20%) and controls (39%–40%) (p < 0.001), demonstrating good diagnostic performance for differentiating these conditions (cutoff PALS ≤ 19%). Similarly, contraction strain was also reduced (−0.92 ± 0.56; p < 0.01).

Atrial stiffness emerged as an important prognostic marker. Bandera et al.[13] identified it as an independent predictor of mortality (hazard ratio 1.23; 95% CI 1.03–1.49; p = 0.029). Other studies confirmed its association with the degree of atrial involvement and with impairment of reservoir, conduit, and contractile functions.

Lower PALS values and higher atrial stiffness were consistently associated with worse survival, greater atrial dilation, and increased risk of atrial arrhythmias. Furthermore, longitudinal data suggest that these alterations may precede clinical manifestations of heart failure, supporting their role as early screening tools.

Although multiple studies evaluating atrial strain in ATTRv were identified, a formal meta-analysis was not performed due to substantial clinical (different phenotypes), methodological (different software and acquisition protocols), and statistical heterogeneity (I^2 > 90% in exploratory analyses). In addition, variability in data reporting (mean ± standard deviation vs. median and interquartile range or proportions based on cutoffs) limited direct comparability. Therefore, a narrative and tabular synthesis was performed, highlighting consistent trends, particularly the progressive reduction in PALS and increase in atrial stiffness across the disease spectrum.

Risk of bias analysis

According to the methodology described, the risk of bias was assessed using the NOS (Figure 3). Only two of the nine included studies were classified as having high methodological quality, characterized by larger sample sizes and robust multivariate analysis (Bandera et al.[13] and Nochioka et al.[18]), while the remaining studies were classified as having moderate quality.

The main limitations were related to small sample sizes (Trimarchi et al.,[24] Henein et al.,[19] de Gregorio et al.,[22] Di Lisi et al.,[15] and Di Bella et al.[23]), lack of adjustment for potential confounding factors (Henein et al.,[19] Di Bella et al.,[23] and Trimarchi et al.[24]), and methodological heterogeneity.

These findings highlight the need for prospective studies with greater methodological rigor to consolidate the prognostic role of atrial strain in ATTRv. A detailed description of the methodological quality assessment of the included studies, including individual NOS domain scores, is provided in the Supplementary Material.

Discussion

In this systematic review, left atrial dysfunction was consistently observed across different stages of ATTRv, including asymptomatic carriers, patients with isolated polyneuropathy, and those with overt cardiomyopathy. In all analyzed studies, PALS was reduced compared with reference values described in healthy individuals, and this alteration was associated with worse prognosis, increased atrial stiffness, and progressive left atrial dilation.

Amyloid fibril deposition in the atria and ventricles has been increasingly studied, and it is believed that deterioration of atrial function may occur early due to impairment of atrial mechanics secondary to fibril deposition, rather than solely as a consequence of ventricular dysfunction and diastolic impairment.

Cardiac amyloidosis is histologically characterized by extensive amyloid infiltration of the atria, leading to loss of normal architecture, vascular remodeling, and increased subendocardial collagen deposition, which translates into a significant increase in atrial stiffness. This abnormal stiffness is associated with reduced reservoir and contractile functions. Approximately one third of patients may present with absence of atrial contraction despite sinus rhythm on electrocardiography, a phenomenon known as atrial electromechanical dissociation. This finding, described by Bandera et al.,[13] is associated with a thromboembolic risk similar to that observed in patients with atrial fibrillation, suggesting that atrial strain assessment may play a key role in cardioembolic risk stratification and may even support the indication for anticoagulation in patients without sustained atrial fibrillation.

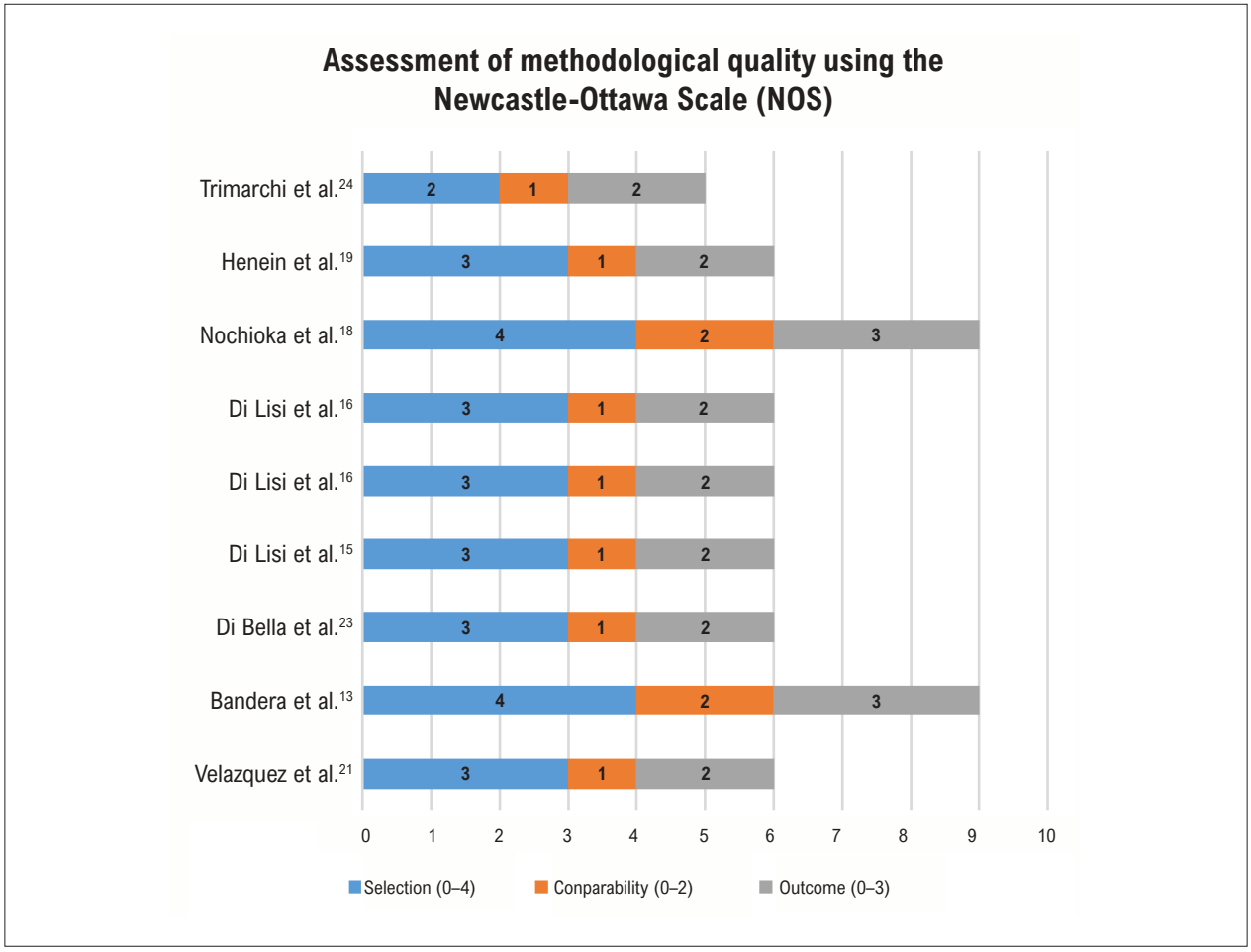

Figure 3 – *Assessment of the methodological quality of the included studies using the Newcastle–Ottawa Scale (NOS), considering the domains of selection, comparability, and outcome. Most studies demonstrated moderate methodological quality, with two studies classified as high quality.*

Another important finding of this review is the prognostic role of atrial strain. Akintoye et al.[20] demonstrated that progressive reductions in PALS and atrial contraction function are associated with a higher risk of mortality and heart failure hospitalization. Consistently, Bandera et al.[13] identified atrial stiffness as an independent predictor of mortality, even after adjustment for biomarkers and clinical variables, reinforcing the role of atrial strain as a robust prognostic tool.

The complexity of cardiac amyloidosis remains a challenge in cardiology. It is a genetic condition that leads to restrictive cardiomyopathy, involving mutations in the transthyretin gene located on chromosome 18q12.1, with multiple variants, different degrees of penetrance, variable expressivity, and environmental factors that interact in disease expression. Some mutations are predominantly associated with polyneuropathy, such as V30M, whereas others, such as V122I, are more frequently associated with cardiomyopathy or mixed phenotypes.

With the increasing availability of genetic testing, the natural history of asymptomatic TTR mutation carriers has changed, with greater emphasis on detecting subclinical cardiac involvement using imaging modalities such as cardiac MRI, bone scintigraphy with pyrophosphate, and speckle-tracking echocardiography. The study by Aceves Velázquez et al.[21] demonstrated that even asymptomatic carriers may show reduced PALS and progressive increases in atrial stiffness over time, even in the absence of ventricular dysfunction, supporting the role of atrial strain as an early marker of amyloid infiltration.

De Gregorio et al.[22] reported reduced PALS and contraction strain in patients with cardiac amyloidosis compared with controls and individuals with HCM, independent of left atrial volume and ventricular ejection fraction. These findings are consistent with those of Nochioka et al.,[18] who demonstrated impairment of conduit and contraction components across different etiologies of cardiac amyloidosis. Thus, atrial dysfunction in ATTRv reflects not only increased filling pressures and restrictive ventricular physiology but also intrinsic atrial failure related to amyloid infiltration.

In the study by Di Lisi et al.,[15] a progressive worsening of atrial dysfunction (PALS and stiffness) was observed from

asymptomatic carriers to patients with polyneuropathy and cardiomyopathy, reinforcing the importance of early assessment in these groups. The authors suggest that carriers should be monitored by echocardiography up to 10 years before the expected age of clinical manifestation in order to detect early changes. Notably, Di Bella et al.[23] proposed a PALS cutoff ≤ 40.9% for the diagnosis of atrial amyloidosis, with 100% sensitivity and 71.6% specificity (AUC 0.91), suggesting additional diagnostic value for this parameter.

More recently, beyond its diagnostic role, atrial strain has also been investigated as a parameter for therapeutic monitoring. Di Lisi et al.[16] reported significant improvement in atrial deformation parameters in patients treated with patisiran, supporting its role in assessing response to disease-modifying therapies.

Finally, the study by Henein et al.[19] showed that patients with ATTRv, increased septal thickness, and fragmented fibrils have a higher risk of arrhythmias, suggesting that atrial function assessment may contribute not only to early detection and prognosis but also to arrhythmic risk stratification and to defining the optimal timing for initiation of antiarrhythmic therapy.

Limitations

Some limitations inherent to this systematic review should be considered. First, the predominance of observational studies, often single-center and with small sample sizes, limits the generalizability of the findings.

Second, significant methodological heterogeneity was identified among the included studies, including differences in echocardiographic acquisition protocols, frame rates, speckle-tracking software, and definitions of atrial strain parameters.

Additionally, the inclusion of populations across different stages of the disease spectrum — from asymptomatic carriers and predominantly neuropathic phenotypes to patients with established cardiac amyloidosis — provided a comprehensive overview but precluded the performance of a formal quantitative meta-analysis.

Conclusion

This systematic review demonstrates that left atrial dysfunction, as assessed by speckle-tracking echocardiography, is a consistent finding in patients with ATTRv. The available evidence suggests that left atrial strain is useful not only in patients with established cardiac amyloidosis but also in carriers and individuals with isolated amyloid polyneuropathy, enabling early detection of subclinical cardiac involvement.

Atrial stiffness, associated with impairment of reservoir, conduit, and contractile functions, emerges as an independent prognostic marker in this population. Therefore, the integration of left atrial strain into routine clinical follow-up may facilitate timely diagnosis of cardiac involvement and allow earlier implementation of therapeutic strategies that have significantly improved clinical outcomes and prognosis in hereditary amyloidosis.

Author Contributions

Conception and design of the research: Cardoso LAA, Hatem MAB, Aras R; acquisition of data: Cardoso LAA, Silva RO; analysis and interpretation of the data: Cardoso LAA, Hatem MAB, Cardoso RO, Silva RO; statistical analysis: Cardoso LAA, Cardoso RO, Silva RO; writing of the manuscript: Cardoso LAA, Hatem MAB, Cardoso RO, Aras R; critical revision of the manuscript for intellectual content: Hatem MAB, Aras R.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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Ethics Approval and Consent to Participate

This article does not contain any studies with human participants or animals performed by any of the authors.

Use of Artificial Intelligence

During the preparation of this work, the author(s) used ChatGPT to assist with translation, figure creation, and grammar correction. After using this tool/service, the author(s) reviewed and edited the content as needed and take full responsibility for the content of the published article.

Availability of Research Data

The underlying content of the research text is contained within the manuscript.

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***Supplemental Materials**

For additional information, please click here.