# UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCHAREST
# DOCTORIAL SCHOOL
# FIELD OF MEDICINE

***The Contribution of Nuclear Medicine in the Diagnostic and Therapeutic Management of Cardiac Amyloidosis***

## SUMMARY OF THE DOCTORAL THESIS

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# SUMMARY

# General part

## Current state of knowledge

### Introduction

Amyloidoses represent a significant group of proteinopathies caused by systemic diseases, genetic mutations or aging, with outcomes dependent on the time of diagnosis. Fibrillar proteins deposited in the extracellular space lead to dysfunctional structures and multiorgan failure [1].

Cardiac amyloidosis involves biventricular dysfunction, driven by myocardial stiffness, and is the main cause of morbidity and mortality in multisystem amyloidosis. Most cases are due to the amyloid proteins AL (immunoglobulin light chain) and ATTR (transthyretin). AL amyloidosis results from uncontrolled proliferation of plasma cells, leading to organ infiltration by light chains with aggregation abnormalities. Untreated, it has a median survival of approximately 6 months [2,3].

ATTR amyloidosis, which has both hereditary (v) and age-related wild-type (wt) forms, manifests with neurological, cardiac and peripheral symptoms. ATTRwt amyloidosis affects the heart in all cases, with a median survival of 57 months, while ATTRv amyloidosis is localized to the heart in 30-100% of cases, with a median survival of 31 months, depending on the specific mutation [4].

### Diagnosis of Amyloidosis

### Clinical Manifestations

The heterogeneity of clinical manifestations usually delays diagnosis until functional exhaustion of the affected organs and tissues is reached [5]. Altered transthyretin induces a slowly progressive cardiomyopathy, while AL amyloidosis often associates a nephrotic-grade proteinuria. Neurological and peripheral autonomic system manifestations or digestive and musculoskeletal manifestations have variable penetrance [2]. CA-ATTR more often causes tenosynovial tissue manifestations, in the acquired form [6].

### Electrocardiography

QRS complex hypovoltage is seen in advanced stages of cardiac amyloidosis in 1/3 of patients and is accompanied by a low voltage-to-mass ratio, more characteristically due to amyloid infiltration rather than cardiomyocyte hypertrophy. Cardiac arrhythmias caused by fibrillar protein interference and signs such as inferior pseudoinfarction are alarm signs of CA. Although ECG changes are not specific, they raise clinical suspicion when combined with other warning signs [4,7,8].

### Echocardiography

Echocardiography is the imaging investigation of first choice in patients with heart failure, both for specifying the etiology and for following the evolution. With a high temporal resolution, well tolerated by patients, it identifies left ventricular hypertrophy in amyloid cardiomyopathy (CA) and other causes of it, such as aortic stenosis or hypertrophic cardiomyopathy. The main disadvantages of the method are the lack

of specificity for subtypes of amyloid cardiomyopathy, and changes in the early stages and the patient-dependent image quality [8].

**Cardiac magnetic resonance imaging (cMRI)**

The clinical value of cMRI is emphasized in two clinical scenarios: differentiating the LV substrate in CA from other cardiomyopathies and evaluating early cardiac infiltration in systemic amyloidosis. CMR can exclude cardiac amyloidosis and provide the etiological substrate in the presence of ultrasound-detected restrictive cardiomyopathy. However, cMRI cannot differentiate between ATTR and AL cardiomyopathy [9].

**Radionuclide imaging**

There are four categories of radiotracers for imaging amyloidosis: three for conventional nuclear imaging and one for PET. Serum amyloid P (SAP) scintigraphy, which has been used for over 30 years, is useful for diagnosing systemic amyloidosis but is less effective in cardiac cases. Cardiac denervation imaging uses the norepinephrine analogue metaiodobenzylguanidine (MIBG) to detect early changes in sympathetic transmission. PET imaging uses radiopharmaceuticals that target amyloidosis but cannot differentiate between ATTR and AL amyloidosis. Bisphosphonate scintigraphy is the preferred method for diagnosing transthyretin amyloidosis because of its high sensitivity and specificity in the nonbiological diagnosis of cardiac amyloidosis. A key advantage of radionuclide imaging is its ability to assess systemic disease, particularly by cardiac scanning [9,10].

**Serum biomarkers**

NT-proBNP is often elevated in cardiac amyloidosis, sometimes more than echocardiographic changes. It, together with troponin levels, helps identify risk in the Mayo staging systems [4].

A positive diagnosis of AL amyloidosis requires the discovery of abnormal plasma cells in the bone marrow. Serum and urine protein electrophoresis with immunofixation detects monoclonal proteins, while the Kappa/Lambda (K/L) light chain ratio identifies abnormal light chains [2,3].

**Diagnostic algorithm**

Clinical signs of tissue and organ involvement, together with ECG changes and imaging, raise the diagnostic suspicion of amyloidosis. Risk scores aid in classification, while noninvasive tests, such as SPECT with bisphosphonates and biomarkers of AL amyloidosis (serum and urinary FLC immunofixation and K/L ratio), aid in the diagnosis of amyloidosis, with transthyretin or light chains (Figure 1).

**Treatment of amyloidosis**

In AL amyloidosis, only 20% of patients are eligible for autologous stem cell transplantation. The combination chemotherapy regimen of cyclophosphamide, bortezomib, and dexamethasone (CyBorD) achieves hematologic response rates of up to 65% and complete response rates of up to 25%. Immunomodulatory agents have response rates of 40 to 60%. Daratumumab immunotherapy has shown superior outcomes to CyBorD in patients with relapsed or refractory disease [11,12,13].

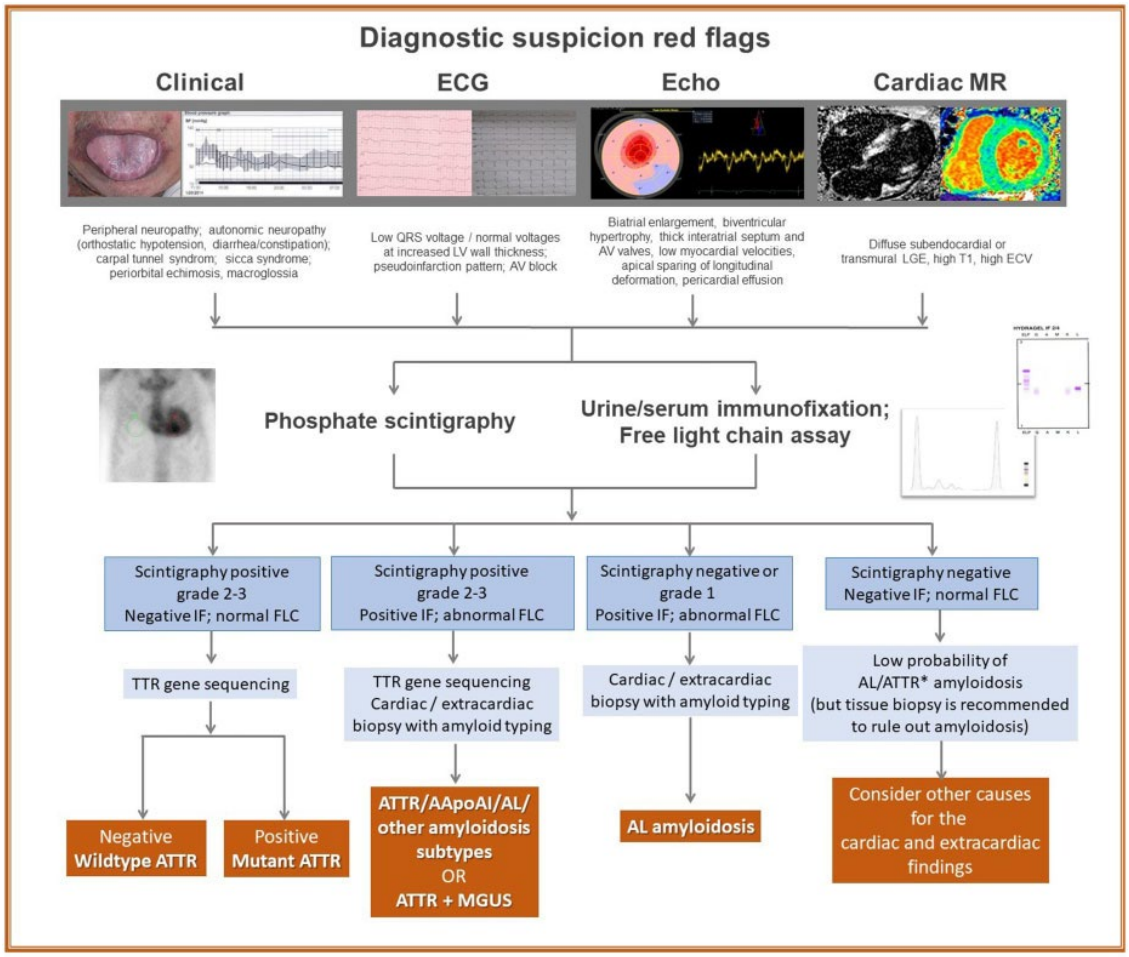


*Figure 1. Diagnostic algorithm in cardiac amyloidosis.*
** Exceptions are asymptomatic carriers discovered through family screening or rare forms of CA-ATTR with low avidity for bisphosphonate. FLC=free light chains, IF=immunofixation, MGUS=monoclonal gammopathy of uncertain significance, VEC=extracellular volume, LGE=late gadolinium uptake.*
*Images from the Expertise Center for Rare Genetic Cardiovascular Diseases, courtesy of Prof. Ruxandra Jurcut*

Currently, targeted therapy for ATTR cardiac amyloidosis includes TTR tetramer stabilizers. The first-line treatment for polyneuropathy, with or without cardiomyopathy, is small-molecule mRNA-interfering drugs and antisense oligonucleotides. Molecules that degrade ATTR fibrils, along with antifibril immunotherapy and gene therapies, create favorable prospects for the prognosis and complete remission rates in ATTR amyloidosis [14,15]. Currently, there is no specific therapy for heart failure in these patients. Diuretics are the mainstay of supportive therapy for symptom management. Disease progression leads to an increased thromboembolic risk, and anticoagulation in these patients, even in sinus rhythm, is protective [10].

# Original part - personal contributions.

## Awareness of nuclear medicine physicians in Romania in the diagnosis of cardiac amyloidosis - a survey-based study

### Introduction

Early diagnosis of cardiac amyloidosis is crucial for effective treatment, especially with the recent approval of transthyretin (TTR) stabilizers, which have been shown to reduce mortality and hospitalizations related to TTR amyloid cardiomyopathy (CA-ATTR). Our study used a questionnaire dedicated to nuclear medicine physicians (NMPs) in Romania to assess the knowledge of the diagnostic features of cardiac amyloidosis and its impact on their practice.

### Material and method

An online questionnaire was distributed to NMPs in the country between October 1, 2020 and January 31, 2021. It included 31 questions, focusing on general data on physician qualifications and diagnostic features of cardiac amyloidosis, especially acquisition and interpretation protocols. Out of approximately 65 NMPs in Romania, 35 (53%) participated, with responses being anonymous and voluntary. Ethics committee approval was not required, as participants were informed of the intention to publish the results. Data were collected and analyzed as percentages of total responses.

### Results

*Survey participants.*

Of the 35 survey participants, 85% practiced in the 3 largest university centers in Romania: 45% in Bucharest, 28% in Iași, and 11% in Cluj. The level of training of respondents in the specialty of nuclear medicine was: 62% primary care physicians, 22% specialists, and 14% residents.

*Experience in the diagnosis of cardiac amyloidosis*

74% of participants observed diffuse accumulation of bisphosphonates in the heart on bone scans. Myocardial uptake indicated: CA-AL in 3% and an uncertain aspect of CA in 9% of participants.

*CA Imaging Awareness*

5% of participants observed cardiac uptake on bone scan and did not classify it as CA-ATTR. 75% observed a CA-ATTR; of these, only 14% telephoned the referring physician.

*Cardiac Amyloidosis in the Nuclear Medicine Laboratory*

Only 69% perform SPECT acquisition, while only 88% use the Perugini visual score.

### Discussion

Involvement of NMPs in the “Amyloidosis Team”

Only 1/3 of participants are involved in the diagnosis of CA-ATTR, and of these, 44% perform between 2 and 4 bisphosphonate scans per month for this diagnosis.

*Incidentaloma of CA-ATTR on Bone Scan*

CA-ATTR is a rare disease, but often underestimated in prevalence, even by cardiologists [16]. Other specialties that refer patients for bone scintigraphy may miss the diagnosis of ATTR-CA.

*Significance of cardiac uptake and types of bisphosphonate radiopharmaceuticals*

The visual Perugini score for almost a third of participants is inaccurately assessed as cardiac uptake relative to the skeletal system rather than the costal arches. In addition, more than half of the participants were unaware that MDP is not recommended for the diagnosis of ATTR-CA due to its low sensitivity.

*Practical aspects in the Nuclear Medicine Laboratory*

The doses of radiotracer administered and the time interval until acquisition are not unanimously known. The mandatory SPECT procedure [9] is only performed by 64% of respondents. More than 1/3 of participants do not perform a complete qualitative and semiquantitative diagnosis (Perugini score) recommended by current guidelines (Figure 2).

*The value of SB compared to other investigations*

The advantage of SB is given by the availability of radiotracers recommended for the diagnosis of CA-ATTR in Romania, along with the ability of SB to contribute to the non-invasive diagnosis of cardiac amyloidosis.

**Study limitations**

Considering the small NMPs community in Romania, compared to other specialties, the addressability of the questionnaire was low. However, the study participants were from the three major university centers, and the number of respondents exceeded half of the NMPs community in Romania.

**Conclusions**

In Romania, nuclear medicine physicians are partially familiar with the diagnosis of CA by scintigraphy, with variable knowledge about its diagnostic potential, standardization, recommended radiotracers, acquisition times, and interpretation algorithms (Figure 2).

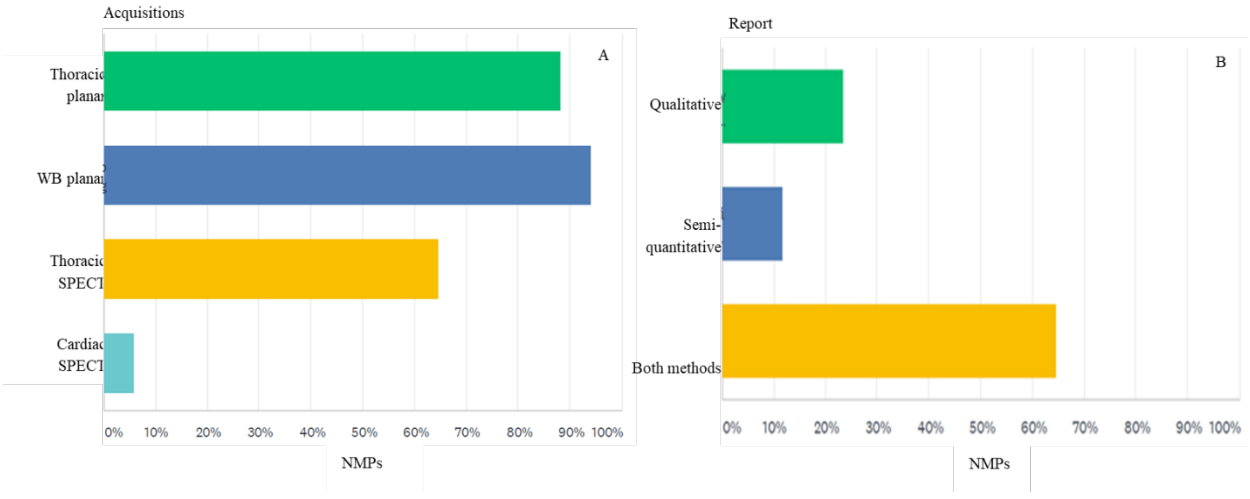

*Figure 2. Representative responses to the questionnaire (A) Image acquisition protocol in diagnosis CA-ATTR, WB = whole body, SPECT torace = single photon emission computer tomography (B) Reporting of 99mTc-bisphosphonate uptake in the myocardium.*

## Diagnostic accuracy of bisphosphonate scintigraphy in ATTRGlu54Gln cardiomyopathy

### Introduction

Technetium (99mTc)-labeled bisphosphonate scintigraphy has become a noninvasive diagnostic tool for CA-ATTR [4,7,9]. Although its diagnostic accuracy is well established for common variants, its efficacy in detecting certain variants, such as Ser97Tyr, Phe64Leu, has been suboptimal [7,17]. This study aimed to evaluate the diagnostic performance of bisphosphonate scintigraphy in CA-ATTR with the Glu54Gln mutation and to assess its correlation with clinical and imaging findings.

### Material and method

We conducted a descriptive, retrospective, multicenter study involving four centers in Romania and one in Florence, Italy, including 22 symptomatic patients with ATTR amyloidosis and 4 asymptomatic carriers with the Glu54Gln variant confirmed. We performed a comprehensive evaluation that included electrocardiography, echocardiography, bisphosphonate scintigraphy, and clinical biomarkers between February 2017 and January 2023, and asymptomatic carriers were subsequently excluded from the study.

### Results

All symptomatic patients (n = 22) with histologically confirmed CA-ATTR had positive results on bisphosphonate scintigraphy (BS) with a sensitivity of 100%. No false negative results were observed in asymptomatic carriers (n = 4). The Perugini visual score correlated with disease severity, with scores of grade 3 being associated with advanced cardiac involvement. We proposed a new parameter, the heart-to-liver uptake ratio (H/L), which demonstrated a strong positive correlation with both the heart-to-contralateral uptake ratio (H/CL) ($R2 = 0.768$, $p < 0.001$) and the interventricular septal thickness ($R2 = 0.584$, $p < 0.001$), as well as a weak correlation with the global longitudinal deformation of the left ventricle ($R2 = 0.212$, $p = 0.023$) (Figure 3).

### Discussion

*Prevalence of ATTR-Glu54Gln amyloidosis in Romania*

In Romania, the most frequent TTR mutation is Glu54Gln, identified by Coriu et al. in 2012, originating mainly from the northeast of the country, especially from Todirești, Suceava County [18]. The prevalence of ATTRv amyloidosis in Romania is 1.02 per million inhabitants (0.76 for the ATTR-Glu54Gln mutation), with 2.39 per 100,000 inhabitants in Suceava County [19].

*Diagnostic accuracy in detecting CA-ATTRGlu54Gln*

Our study showed that SB efficiently detects CA-ATTRGlu54Gln, with a Perugini score of G2/G3, providing 100% sensitivity for myocardial involvement. Negative scintigraphies reliably excluded cardiac amyloidosis in asymptomatic carriers. These results are in line with the literature data on the sensitivity of CA-ATTR detection for most TTR mutations [4,7,8,9] *(Figure 3)*.

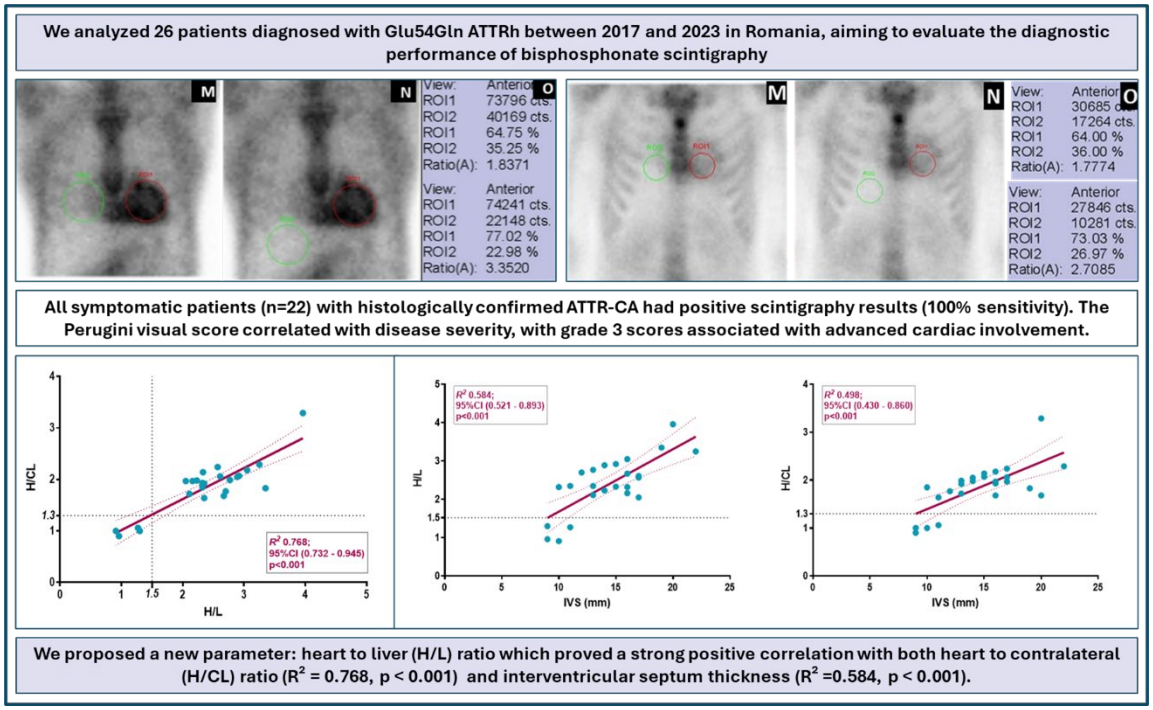


*Figure 3. Graphical abstract of bisphosphonate scintigraphy results and heart/liver ratio (H/L), correlated with heart/contralateral region (H/CL) score and interventricular septal thickness (IVS).*

*Conceptual differences between H/CL and H/L ratios*

The H/CL ratio can be influenced by factors such as right ventricular overlap, costal arch involvement, and increased right lung activity due to low eGFR or insufficient waiting time for scintigraphic data. Our study suggests that the H/L ratio may correlate more closely with Perugini grades and interventricular septal thickness than with the H/CL ratio. None of the parameters correlated with cardiac biomarkers, and their relationship with global longitudinal strain (GLS) was suboptimal.

**Study limitations**

Our study involved a small population, limiting statistical tests to the interpretation of trends rather than significance. The H/L ratio is promising but requires validation for reproducibility, diagnostic thresholds, and clinical relevance.

**Conclusions**

Bisphosphonate scintigraphy has 100% sensitivity in patients with symptomatic Glu54Gln ATTR amyloid cardiomyopathy and efficiently identifies mutation carriers, making it reliable for monitoring. Using the liver as a reference for the H/L ratio minimizes variability and artifacts, potentially increasing sensitivity for detecting myocardial injury.

## Segmental and global amyloid burden and myocardial mechanics: a multimodality imaging comparison

### Introduction

Bone scintigraphy with bisphosphonate tracers is a cornerstone of noninvasive diagnosis in transthyretin amyloid cardiomyopathy (ATTR-CM) [4,9]. However, methods for estimating the extent and regional distribution of myocardial amyloid burden using single-photon emission computed tomography (SPECT) remain insufficiently validated. In recent years, imaging quantification of amorphous material stored extracellularly at the cardiac level has replaced the need for cardiac biopsy [20]. The present study aimed to evaluate whether global and segmental radiotracer uptake assessed by cardiac SPECT correlates with myocardial amyloid infiltration measured by cMRI-derived ECV. In addition, we explored the relationship between these imaging parameters and myocardial mechanics assessed by longitudinal strain. We hypothesized that radiotracer uptake would demonstrate significant concordance with myocardial infiltration. The most important application of amyloid mapping could be the assessment of disease regression following therapy [21].

### Material and method

Twenty-seven patients with ATTR-CM who underwent multimodality imaging with bisphosphonate SPECT, cMRI, and transthoracic echocardiography (TTE) between 2017 and 2025 were retrospectively screened. Sixteen patients with complete segmental datasets across all imaging modalities were included in the final analysis. Segmental mixed-effects models were used to account for clustering of myocardial segments within patients.

### Results

Segmental extent of amyloid burden assessed by SPECT was significantly associated with segmental ECV ($\beta = 0.042$, SE = 0.010, $t = 4.22$), indicating higher radiotracer retention in segments with greater myocardial infiltration *(Figure 4)*. Segmental ECV demonstrated a strong association with impaired longitudinal strain ($\beta = 0.269$, SE = 0.043, $t = 6.22$) *(Figure 5)*. In contrast, the direct relationship between radiotracer uptake and longitudinal strain was weaker and not statistically significant ($\beta = 0.016$, SE = 0.010, $t = 1.60$). In combined models, ECV remained independently associated with strain ($\beta = 0.266$, SE = 0.045, $t = 5.96$), whereas radiotracer uptake lost significance ($\beta = 0.003$, SE = 0.010, $t = 0.29$). At the global level, global extent amyloid burden (GEAB) correlated significantly with ECV ($\beta = 0.435$, $p = 0.018$), while the association between GEAB and global longitudinal strain was weaker and nonsignificant ($\beta = 0.092$, $p = 0.10$) *(Figure 6)*.

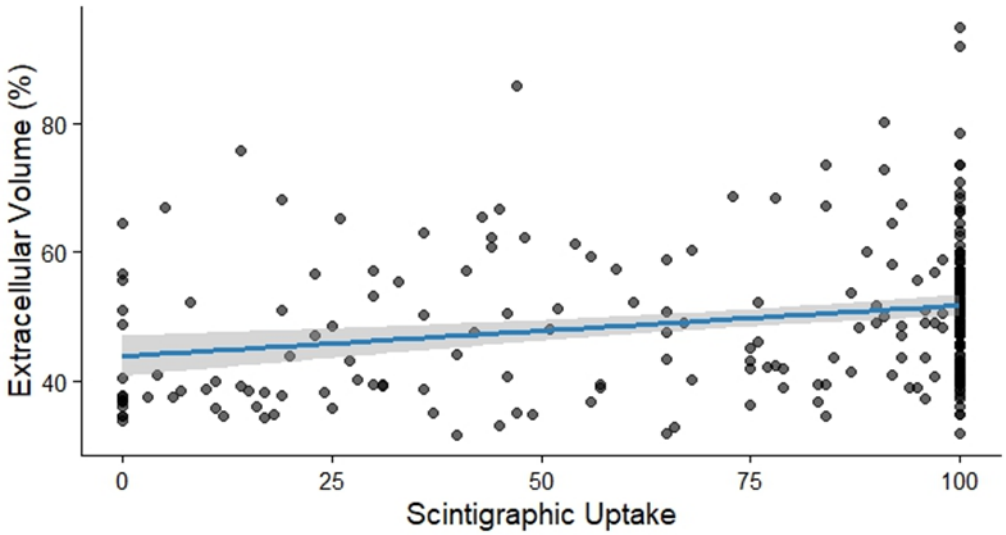


*Figure 4: Relationship between scintigraphic uptake and extracellular volume. A scatter plot illustrates the association between segmental scintigraphic uptake and extracellular volume. Increased tracer uptake was associated with higher myocardial ECV, indicating greater amyloid infiltration*

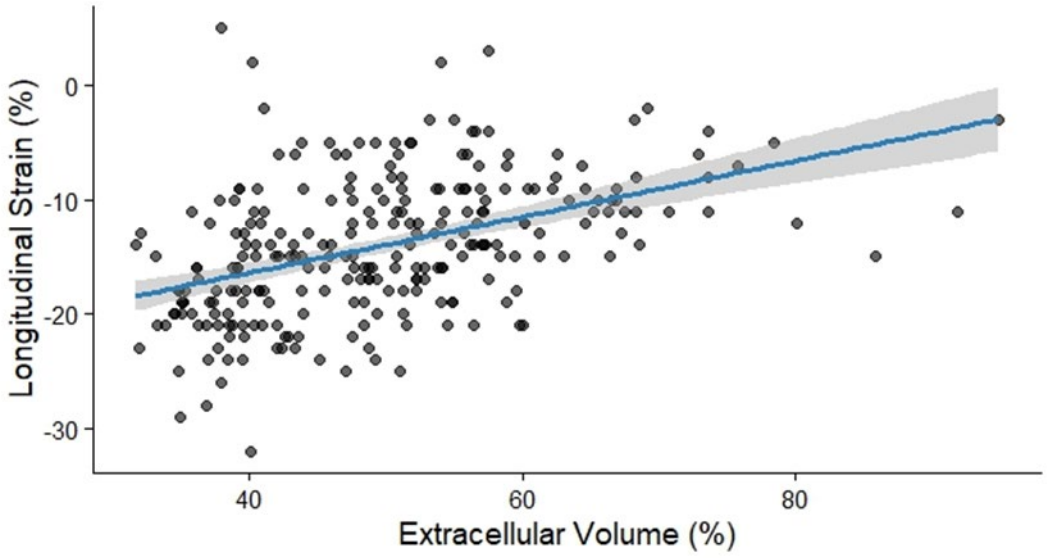


*Figure 5: Relationship between regional extracellular volume and longitudinal strain. A scatter plot shows the association between segmental extracellular volume (ECV) and longitudinal strain across all myocardial segments. The solid line represents linear regression with 95% confidence intervals. Higher ECV values were associated with more impaired longitudinal strain.*

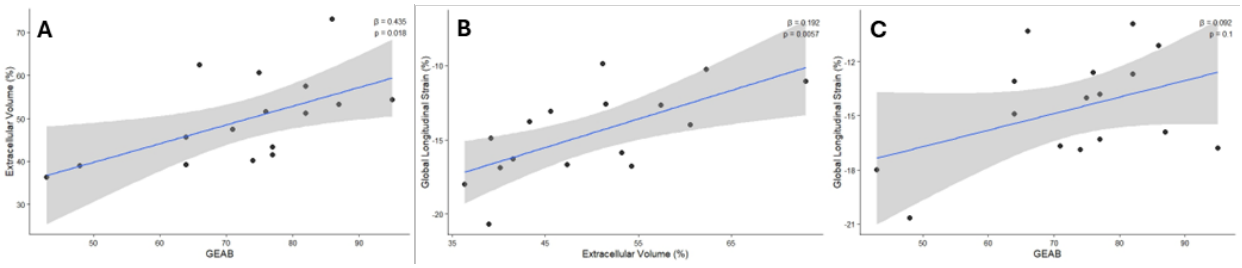


*Figure 6: Relationship between global extent amyloid burden (GEAB) on SPECT, extracellular volume (ECV), and longitudinal function (GLS). (A) GEAB is positively associated with ECV, reflecting higher radiotracer retention in patients with greater extracellular expansion. (B) ECV demonstrates a*

*significant association with GLS, with higher ECV values corresponding to impaired myocardial deformation. (C) GEAB shows a weaker, non-significant association with GLS. Collectively, these findings suggest that the relationship between radiotracer uptake and myocardial function is mediated by the degree of extracellular expansion rather than a direct effect of tracer uptake*

## Discussion

### *Main Findings*

This study evaluated the relationship between semiquantitative bisphosphonate SPECT uptake, cMRI-derived extracellular volume, and myocardial mechanics in patients with transthyretin cardiac amyloidosis. The principal findings are:

1. Semiquantitative scintigraphic uptake demonstrated significant concordance with cMRI-derived extracellular volume at both global and segmental levels.

2. Both radiotracer uptake and extracellular volume appear to reflect myocardial amyloid burden.

3. Extracellular volume demonstrated a closer association with myocardial mechanics than scintigraphic uptake.

4. Segmental SPECT analysis identified regional amyloid distribution patterns similar to those observed by cMRI, although with lower spatial precision.

Collectively, these findings support the concept that semiquantitative cardiac SPECT may provide clinically meaningful estimates of myocardial amyloid distribution.

### *Clinical Implications*

Our findings indicate that semiquantitative SPECT analysis can offer valuable insights into the extent and distribution of myocardial amyloid burden, surpassing conventional visual Perugini grading. Developing software for quantitative uptake measures in bisphosphonate scintigraphy with SPECT could enhance the diagnostic process and help predict extracellular volume (ECV) currently measured by cMRI. Potential applications include monitoring disease progression, evaluating responses to anti-amyloid therapies, and improving risk stratification. However, cMRI-derived ECV may be more closely linked to myocardial mechanics, better reflecting the structural basis of functional impairment.

## Limitations

This study has several limitations. First, the cohort size was small due to a limited number of patients receiving complete multimodality imaging with SPECT, cMRI, and echocardiography. Second, the retrospective design may introduce selection bias, but since each patient serves as their own control, this impact is minimized. Additionally, semiquantitative SPECT processing used software meant for myocardial perfusion imaging, which may affect uptake quantification due to factors like attenuation artifacts and normalization methods. These issues likely lead to lower segmental precision in SPECT compared to cMRI-derived extracellular volume mapping.

## Conclusions

Semiquantitative bisphosphonate SPECT shows significant alignment with cMRI-derived extracellular volume, effectively estimating myocardial amyloid burden distribution in transthyretin cardiac amyloidosis. While both methods reflect amyloid burden, ECV has a stronger association with myocardial mechanics due to direct quantification of remodeling and better spatial resolution. Further research is needed to standardize SPECT parameters for disease monitoring and treatment assessment in ATTR cardiomyopathy.

## Personal contributions

*Awareness of nuclear medicine physicians in Romania in the diagnosis of cardiac amyloidosis - a survey-based study*

Our study indicated that nuclear medicine physicians (NMPs) in Romania face significant challenges related to their knowledge of bisphosphonate scintigraphy for CA detection. We identified key areas where NMPs lack knowledge and believe it is crucial to organize conferences to enhance understanding of diagnostic guidelines in CA detection.

Raising awareness of the diagnostic accuracy of scintigraphy and its role in the diagnostic process, particularly in the exclusion of AL amyloidosis, is essential. It is vital to implement scintigraphy protocols in all medical centers specializing in cardiac amyloidosis.

Our study revealed several critical gaps that hinder accurate diagnosis, including issues with the administered doses, waiting times, acquisition methods, and the use of validated radiopharmaceuticals for CA. Additionally, it is important to adopt a comprehensive approach to interpreting scintigraphy that includes visual, qualitative, and semi-quantitative analyses—specifically, the Perugini visual score with uptake grading—following international recommendations.

Furthermore, our findings demonstrate that informing the referring physician about incidental diagnoses of CA-ATTR and recommending that the patient be referred to an amyloidosis expert center is vital for initiating appropriate treatment.

*Diagnostic accuracy of bisphosphonate scintigraphy in ATTRGlu54Gln cardiomyopathy*

Our study revealed that scintigraphy using a semi-quantitative approach (SB) demonstrates excellent diagnostic accuracy for identifying cardiac amyloidosis resulting from the CA-ATTR Glu54Gln mutation. A visual Perugini score of G2/G3 exhibited 100% sensitivity for detecting myocardial involvement, while negative scintigraphy results effectively excluded cardiac amyloidosis in asymptomatic carriers.

We observed a strong correlation between the Perugini score and disease severity; patients with a G3 score show more significant cardiac hypertrophy, elevated biomarkers, and decreased myocardial strain (GLS), reflecting advanced stages of the disease. The diagnostic sensitivity of SB for the Glu54Gln mutation was comparable to that of other prevalent TTR mutations. By integrating the semi-quantitative Perugini

G2/G3 score with the exclusion of monoclonal proteins, we achieved a specificity and positive predictive value of 100% in diagnosing CA-ATTR Glu54Gln.

SPECT analysis revealed diffuse right ventricular uptake in all 22 patients examined, indicating significant progression of transthyretin amyloidosis in individuals with the Glu54Gln mutation.

The findings from our study suggest that the H/L ratio may show a stronger correlation with Perugini grades and interventricular septal thickness than the H/CL ratio. Furthermore, the introduction of the proposed new semiquantitative parameter, the H/L ratio, may effectively address critical limitations associated with the H/CL ratio, potentially enhancing the method's sensitivity, particularly in equivocal results.

*Segmental and global amyloid burden and myocardial mechanics: a multimodality imaging comparison*

This study examined the relationship between semiquantitative SPECT uptake of bisphosphonates, cMRI-derived extracellular volume, and myocardial mechanics in patients with cardiac transthyretin amyloidosis. The main findings include:

1. Semiquantitative scintigraphic uptake exhibited significant agreement with cMRI-derived extracellular volume, both on a global and segmental level.

2. Both radiotracer uptake and extracellular volume appear to reflect the myocardial amyloid burden.

3. Extracellular volume showed a stronger association with myocardial mechanics compared to bisphosphonate scintigraphic uptake.

4. Segmental SPECT analysis revealed regional patterns of amyloid distribution that were similar to those observed with cMRI, although with less spatial precision.

Collectively, these findings support the notion that semiquantitative cSPECT can yield clinically meaningful estimates of myocardial amyloid distribution. Our results indicate that semiquantitative SPECT analysis can provide valuable insights into the extent and regional distribution of myocardial amyloid burden, surpassing the conventional Perugini grading system. Given that SPECT bisphosphonate scintigraphy is a critical component of the diagnostic process, the development of specialized software that offers a quantitative measure of uptake could serve as a tool for predicting extracellular volume, which is currently assessed solely through cMRI.

Potential applications of this research include monitoring disease progression, evaluating responses to anti-amyloid therapies, and enhancing multimodal risk stratification. However, it is important to note that cMRI-derived extracellular volume maintains a closer association with myocardial mechanics and may therefore more effectively reflect the structural underpinnings of functional impairment.

# Selective bibliography


1. Buxbaum JN, Eisenberg DS, Fändrich M, McPhail ED, Merlini G, Saraiva MJM, et al. Amyloid nomenclature 2024: update, novel proteins, and recommendations by the International Society of Amyloidosis (ISA) Nomenclature Committee. Amyloid. 2024 Sep 30;31(4):249–56.
2. Rajkumar SV. Multiple myeloma: 2022 update on diagnosis, risk stratification, and management. American Journal of Hematology. 2022 May 23;97(8).
3. Gustine JN, Staron A, Mendelson L, Joshi T, Gopal DM, Siddiqi OK, et al. Predictors of treatment response and survival outcomes in patients with advanced cardiac AL amyloidosis. Blood Advances. 2023 Aug 15;7(20):6080–91.
4. Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. European Heart Journal. 2021 Apr 7;42(16):1554–68.
5. Zampieri M, Nardi G, Monaco GD, Allinovi M, Gabriele M, Zocchi C, et al. Changes in the perceived epidemiology of amyloidosis: 20-year experience from a Tertiary Referral Centre in Tuscany. International Journal of Cardiology. 2021 Apr 16 ;335:123–7.
6. Castaño A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. European Heart Journal. 2017 Aug 1;38(38):2879–87.
7. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016;133(24):2404–12.
8. Bukhari S. Cardiac amyloidosis: state-of-the-art review. Journal of Geriatric Cardiology. 2023 May;20(5):361–75.
9. Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 1 of 2—Evidence Base and Standardized Methods of Imaging. Circulation: Cardiovascular Imaging. 2021 Jul;14(7).
10. Fontana M, Ioannou A, Cuddy S, Dorbala S, Masri A, Moon JC, et al. The Last Decade in Cardiac Amyloidosis: Advances in Understanding Pathophysiology, Diagnosis and Quantification, Prognosis, Treatment Strategies, and Monitoring Response. JACC Cardiovascular Imaging. 2025 Mar;S1936-878X(24)004583.
11. Al Hamed R, Bazarbachi AH, Bazarbachi A, Malard F, Harousseau JL, Mohty M. Comprehensive Review of AL amyloidosis: some practical recommendations. Blood Cancer Journal. 2021 May;11(5).
12. Wechalekar AD, Cibeira MT, Gibbs SD, Jaccard A, Kumar S, Merlini G, et al. Guidelines for non-transplant chemotherapy for treatment of systemic AL amyloidosis: EHA-ISA working group. Amyloid. 2022 Jul 15;1–15.
13. Sanchorawala V, Boccadoro M, Gertz M, Hegenbart U, Kastritis E, Landau H, et al. Guidelines for high dose chemotherapy and stem cell transplantation for systemic AL amyloidosis: EHA-ISA working group guidelines. Amyloid. 2021 Nov 16;29(1):1–7.
14. Maurer MS, Kale P, Fontana M, Berk JL, Grogan M, Gustafsson F, et al. Patisiran Treatment in Patients with Transthyretin Cardiac Amyloidosis. The New England Journal of Medicine. 2023 Oct 26;389(17):1553–65.
15. Griffin JM, Rosenthal JL, Grodin JL, Maurer MS, Grogan M, Cheng RK. ATTR Amyloidosis: Current and Emerging Management Strategies. JACC: CardioOncology. 2021 Oct 19;3(4):488–505.
16. Adam R, Neculae G, Stan C, Jurcut R. Current Challenges of Cardiac Amyloidosis Awareness among Romanian Cardiologists. Diagnostics (Basel, Switzerland). 2021 Jun;11(5):834.
17. Musumeci MB, Cappelli F, Russo D, Tini G, Canepa M, Milandri A, et al. Low Sensitivity of Bone Scintigraphy in Detecting Phe64Leu Mutation-Related Transthyretin Cardiac Amyloidosis. JACC: Cardiovascular Imaging. 2020 Jun;13(6):1314–21.
18. Hazenberg, B.P.C.; Bijzet, J. XIIIth International Symposium on Amyloidosis 2012 “From Misfolded Proteins to Well-Designed Treatment”. 2012. Available online: https://www.researchgate.net/publication/260086782_XIIIth_International_Symposium_on_Amyloidosis_2012_From_misfolded_proteins_to_well-designed_treatment

19. Andreea Jercan, Ene A, Ruxandra Jurcut, Mirela Draghici, Sorina Badelita, Dragomir M, et al. Clinical characteristics in patients with hereditary amyloidosis with Glu54Gln transthyretin identified in the Romanian population. Orphanet Journal of Rare Diseases. 2020 Jan 30;15(1).
20. Scully PR, Morris E, Patel KP, Treibel TA, Burniston M, Klotz E, et al. DPD Quantification in Cardiac Amyloidosis. JACC: Cardiovascular Imaging. 2020 Jun;13(6):1353–63.
21. Kessler L, Pedro Fragoso Costa, Kersting D, Jentzen W, Weber M, Lüdike P, et al. Quantitative 99mTc-DPD-SPECT/CT assessment of cardiac amyloidosis. Journal of Nuclear Cardiology. 2023 Feb 1;30(1):101–11.