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ORIGINAL ARTICLE

Prevalence of Cardiac Amyloidosis in Elderly Patients With Aortic Stenosis

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Abstract

Background: Aortic Stenosis (AS) is one of the most common valvular heart diseases in adults, especially the elderly. The persistence of heart failure symptoms and worse outcomes despite valve replacement treatment may be associated with the coexistence of Cardiac Amyloidosis (CA).

Objective: To determine the prevalence of CA in patients with calcific AS.

Methods: This was a cross-sectional study. Elderly patients with moderate to severe AS underwent cardiac scintigraphy with bone radiotracer for diagnosis of CA. Patients diagnosed with Transthyretin (TTR) amyloidosis by scintigraphy underwent genetic studies. Groups with altered and unaltered scintigraphy results for continuous variables were compared using an independent t-test for normally distributed variables and a Mann-Whitney test for those with asymmetric distribution. Statistical significance was set at p-value < 0.05

Results: Forty-one patients with AS underwent pyrophosphate scintigraphy. The mean age of the cases was 79 ± 6 years, 23 (56%) were female, 23 (56%) had classic severe AS pattern, and 8 (19.5%) had low-flow low-gradient AS with reduced Ejection Fraction (EF). Carpal tunnel syndrome was present in 2 (4%) patients, 8 (19%) had polyneuropathy. A RAISE score ≥ 2 was found in 4 patients (9%). Four patients were diagnosed with TTR amyloidosis, one of whom had a Val122I genetic mutation. Three (75%) of the patients diagnosed with AE/AI were male. There were no statistically significant differences between the isolated AS and AS/CA groups.

Conclusion: The prevalence of CA in patients with moderate to severe AS of probable calcified etiology in our sample was 10%.

Keywords: Aortic Valve Stenosis; Amyloidosis; Radionuclide Imaging; Prealbumin.

Introduction

Aortic Stenosis (AS) is one of the most common valvular diseases, affecting approximately 5% of adults over 75 years old.[1,2] Cardiac Amyloidosis (CA) is a rare disease primarily affecting the elderly, characterized by the extracellular deposition of insoluble fibrils of low molecular weight proteins.[3] Early diagnosis of CA can influence its progression.[4,5]

AS and CA are two entities that, despite having distinct etiologies, share pathophysiological similarities, as both can lead to myocardial hypertrophy and comparable hemodynamic repercussions, mainly associated with heart failure (HF).[6-8]

The exact prevalence of CA in the general population, as well as in those with AS, is underestimated, as systematic screening is not yet in place.[6]

Recent studies suggest that the coexistence of AS and CA is more common than previously thought, reaching approximately 16%. The potential coexistence of CA and AS may impact the clinical course of elderly patients with these conditions. [6,8,9]

This study aimed to estimate the prevalence of CA in elderly patients with moderate to severe AS.

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Central Illustration: **Prevalence of Cardiac Amyloidosis in Elderly Patients With Aortic Stenosis**

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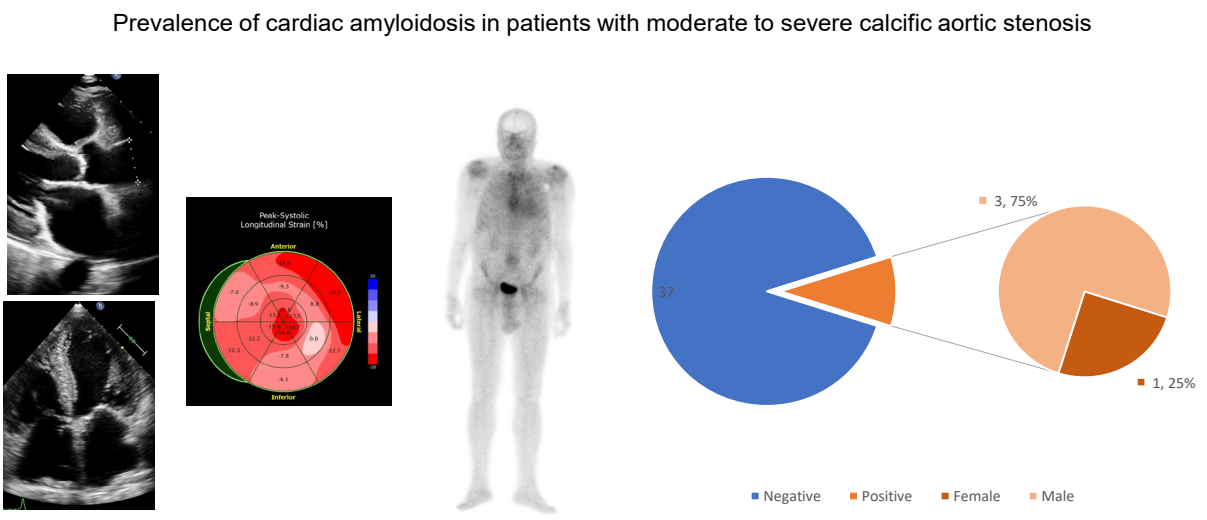

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Methods

Study Design

This cross-sectional study was conducted on patients diagnosed with moderate to severe AS of probable calcific etiology, treated at Santa Izabel Hospital - Santa Casa de Misericórdia da Bahia in the city of Salvador, identified through an active search in electronic medical records from August 2021 to November 2023.

This study was approved by the Research Ethics Committee of Santa Izabel Hospital. All patients provided written informed consent under Resolution 466/2012 to participate in the study. Data were kept confidential, and only investigators had access to the project database.

Criteria and eligibility

The inclusion criteria were elderly individuals aged 65 years and above, diagnosed with moderate or severe AS of probable calcific etiology, regardless of whether they had undergone valve intervention. The exclusion criteria were patients with AS of probable congenital or rheumatic etiology, and those unable to undergo scintigraphy.

Study protocol

Demographic, clinical, laboratory, resting electrocardiogram, echocardiogram with color Doppler, cardiac catheterization, and coronary CT angiography data were collected. Preoperative risk scores including EuroScore, Society of Thoracic Surgeons (STS) score, and TAVR (Transcatheter Aortic Valve Replacement) score were calculated, as well as the Edmonton Frailty Score. A cognitive assessment was conducted using the Mini-Mental State Examination.

A strain echocardiogram was performed by a single researcher at the echocardiography department of Santa Izabel Hospital using Phillips Affinity 70 or Epiq machines.

The RAISE score, as proposed by Nitsche et al., was computed, which correlates ventricular hypertrophy and diastolic dysfunction (R: remodeling), age (A: age), troponin levels (I: injury), presence of carpal tunnel syndrome (S: systemic), and right bundle branch block or reduced voltage (E: electric) to determine the likelihood of concomitant CA. A score equal to or greater than 2 would prompt further investigation for the disease.[9]

Following the diagnosis of moderate or severe AS, patients underwent bone scintigraphy with technetium-99m pyrophosphate at Santa Izabel Hospital. No detection of monoclonal protein associated with radionuclide uptake at grades 2 and 3 indicated a high probability for transthyretin

cardiac amyloidosis (ATTR) rather than amyloid light chain (AL) amyloidosis. In cases of AL amyloidosis diagnosis, patients were referred for a hematological consultation.

Patients with abnormal scintigraphy findings and diagnosis of ATTR underwent genetic testing for mutations in the transthyretin (TTR) gene to identify the subtype of hereditary ATTR. Genetic mutation testing was performed by the researcher using oral swabs, and samples were sent to Mendelics, a partner laboratory. In the case of positive genetic testing, the patients and their families were referred for genetic counseling.

Statistical analysis

Statistical Package for Social Sciences (SPSS Inc., Chicago, IL, USA), version 18.0 for Windows, was used for data analysis. Normality was assessed using the Shapiro-Wilk test. Categorical variables were presented as absolute and relative frequencies. Continuous variables with normal distribution were described through mean ± standard deviation and those without normal distribution were described through median and interquartile range

Groups with altered and unaltered scintigraphy results for continuous variables were compared using an independent t-test for normally distributed variables and a Mann-Whitney test for those with asymmetric distribution. The Chi-square test was applied for comparison between groups and categorical variables, while Fisher's exact test was utilized when the distribution comprised fewer than five individuals in each category.

A p-value < 0.05 was considered statistically significant.

Sample size estimation was based on previous studies investigating the presence of occult CA in patients with AS undergoing surgical valve replacement or percutaneous aortic valve implantation. These studies reported a prevalence between 5-25%.[9-13] For sample size calculation, the Winpepi software was used. An expected proportion of 16% was defined based on the study by Castano et al. assessing the coexistence of AS and CA in patients undergoing percutaneous aortic valve implantation.[10] With a significance level (α) of 5% and power of 95%, the sample size was estimated at 52 patients.

Results

Forty-one elderly patients with moderate or severe AS were evaluated. The mean age of the cases was 79 ± 6 years, 23 (56%) were female, 22 (53%) exhibited some degree of frailty according to the Edmonton Frail Scale, and eight (23%) had cognitive impairment. Thirty-eight (92%) patients had symptomatic AS, with six (15%) patients classified as New York Heart Association (NYHA) functional Class III. Dyspnea was the most commonly reported symptom, with 33 (80%) patients reporting this complaint. (see Table 1).

There was a predominance of patients with classic severe AS pattern with elevated gradient and preserved Ejection Fraction (EF) (56%). Ten patients (24%) had low-flow low-gradient pattern. (see Table 1).

A RAISE score ≥ 2 was found in four patients (9%).

Regarding the assessment of surgical risk scores, 28 (68%) had an STS score of less than four, indicating low surgical risk (see Table 2).

Carpal tunnel syndrome was present in two (4%) patients, and eight (19%) had polyneuropathy.

Table 3 outlines the main electrocardiographic characteristics and cardiac marker levels.

Regarding echocardiographic data, the mean EF was 59.2% ± 15.3%, with 11 (26%) patients having ventricular dysfunction with EF less than 50%. (see Table 4).

The distribution of scintigraphy findings according to Perugini classification was as follows: 8 (19%) patients with no uptake, 24 (58%) with grade 1 uptake, and nine (22%) with grade 2/3 uptake.

Four patients were found to have scintigraphy highly suggestive of ATTR (high uptake in both quantitative and qualitative assessments), with one of them having a genetic mutation of Val122Ile, classified as Variant Transthyretin Amyloidosis (ATTRv). Thus, three patients were classified as Wild-type Amyloidosis (ATTRwt).

A comparison was made between patients with AS diagnosed with CA (scintigraphy with high quantitative and qualitative uptake) and those without CA on scintigraphy. There was no statistically significant difference between the groups for the variables evaluated (see Table 5).

In the group diagnosed with amyloidosis, three (75%) patients were male. NT-proBNP and troponin levels were higher in those with amyloidosis on scintigraphy but with non-significant p-values.

A RAISE score ≥ 2 was found in one patient with amyloidosis and three patients without amyloidosis.

The calcium score was higher in those without CA compared to those with CA, but with non-significant p-values.

Table 1 – Clinical and Demographic Characteristics of the Total Population

Variables	Total N = 41
Age*	79.6 ± 6,6 years
Gender (%)	
Female	23 (56.1)
Ethnicity (%)	
Black	3 (7.3)
Pardo	23 (56.1)
White	15 (36.6)
Body Mass Index kg/m²	26.7 ± 4.4 kg/m²
Mini-Mental † (%)	
≤ 24	8 (22.9)
Edmonton Scale **(%)**	
No frailty	7 (17.0)
Vulnerable	12 (29.3)
Mild frailty	10 (24.4)
Moderate frailty	8 (19.5)
Severe frailty	4 (9.8)
AS Pattern (%)	
Moderate AS	4 (9.8)
Classic severe AS	23 (56)
Low-flow, low-gradient severe AS with reduced EF	8 (19.5)
Low-gradient severe AS with reduced EF	2 (4.8)
Low-gradient normal flow with preserved EF	4 (9.8)
Symptoms (%)	38 (92.7)
Angina	16 (39.0)
Syncope	7 (17.1)
Dyspnea	33 (80)

† Mini Mental < 24 indicates some degree of cognitive impairment. AS: Aortic Stenosis; EF: Ejection Fraction.

Discussion

AS and CA represent two distinct yet pathophysiologically intertwined conditions, both capable of inducing myocardial hypertrophy and hemodynamic alterations, particularly associated with Heart Failure with Preserved Ejection Fraction (HFpEF).[12,13]

This study, conducted at a leading referral center specializing in percutaneous aortic valve implantation, elucidated several noteworthy findings. The majority of patients exhibited classic severe AS, characterized by elevated systolic gradients and preserved EF. Notably, the literature often portrays a different pattern in AS/CA coexistence, frequently presenting as paradoxical low-flow, low-gradient AS with preserved EF.[14]

The increased prevalence of low-flow status in CA patients may be attributed to pronounced left ventricular concentric remodeling, worsened

Table 2 – Clinical and Demographic Characteristics of the Total Population - Continued

Comorbidity (%)	N = 41
Hypertension	37 (90.2)
Diabetes Mellitus	22 (53.7)
Stroke	35 (85.4)
Coronary Artery Disease	29 (70.7)
Smoking	23 (56.1)
Chronic Obstructive Pulmonary Disease	3 (7.3)
Previous Myocardial Infarction	13 (31.7)
Dyslipidemia	40 (97.6)
STS score † (%)	2.3(1.8-4.7)
High	6 (14.6)
Intermediate	7 (17.1)
Low	28 (68.3)

STS: Society of Thoracic Surgeons.

Table 3 – Electrocardiogram and Laboratory

Electrocardiogram and Laboratory	N = 41
ECG	
Sinus Rhythm	37 (90.2)
Pacemaker	3 (7.3)
Atrial Fibrillation or Flutter	1 (2.4)
Right Bundle Branch Block	2 (4.9)
Left Bundle Branch Block	11 (26.8)
First-degree Atrioventricular Block	12 (30.8)
Left Atrial Overload	17 (41.5)
Left ventricular overload	15 (36.6)
Low voltage	1 (2.4)
Renal Dysfunction (eGFR < 60ml/m²)	27 (65.9)
Troponin (ng/l)	0.01 (0.001-0.78)
NT-proBNP (pg/m)	450 (114-1109)

ECG: electrocardiogram; eGFR: estimated glomerular filtration rate.

ventricular filling, left atrial dysfunction and remodeling, significant longitudinal strain reduction (greater than or equal to -12%), and right ventricular remodeling and dysfunction.[14-16]

Remarkably, our study revealed only a small proportion of patients with moderate AS, with one individual demonstrating high tracer uptake on scintigraphy and a diagnosis of wild-type ATTR. This

Table 4 – Description of echocardiographic and cardiac tomography data

Echocardiographic Data	N = 41
LVEF*	59.2 ± 15.3
Pulmonary Hypertension (sPAP > 35)	3 (7.5)
Longitudinal Left Ventricular Strain	14.3 ± 3.7
Right Ventricular Hypertrophy	4 (9.8)
Right Ventricular Strain	21.2 ± 5.9
Left Atrial Strain	22.6 ± 9.3
Left Atrium Enlargement	40 (97.6)
Calcium score (n = 30) Agatston	2337 (1604-4589)

**LVEF: Left Ventricular Ejection Fraction; sPAP: systolic pulmonary artery pressure.*

underscores the importance of closely monitoring patients with moderate AS for potential amyloid deposition and its impact on valve disease progression.[11,17,18]

In terms of cardiac biomarkers (BNP and troponin), our data indicated persistently elevated levels, indicative of silent myocardial injury despite preserved EF, consistent with the existing literature.[13]

While many studies rely solely on the Perugini score for scintigraphy interpretation, we opted for a comprehensive approach, considering both qualitative and quantitative criteria. This approach allowed us to identify a subset of patients with concomitant AS and CA, shedding light on a potentially underrecognized cohort.[19-21]

Although Perugini grade 1 uptake was prevalent among AS patients in our cohort, indicating subclinical amyloid deposition, its clinical significance and progression to CA remain elusive.[22] Nonetheless, the existing literature suggests worse outcomes in patients with such findings, emphasizing the need for further investigation.[1,23]

Furthermore, our study uncovered a case of hereditary ATTR with the Val122I mutation, a variant commonly associated with cardiomyopathy, particularly among African American populations.[24]

The concept of occult amyloidosis first emerged in 2016 among patients referred for percutaneous aortic valve implantation, sparking subsequent research endeavors aimed at detecting ATTR. However, the systematic screening of AS patients for amyloidosis using cardiac scintigraphy with bone tracers remains impractical in most cardiology centers.[25,26]

The RAISE score offers a valuable tool for integrating various clinical parameters to guide further investigation, such as scintigraphy. While our study did not identify a significant association between the RAISE score and amyloidosis diagnosis, its role in risk stratification warrants further exploration.[9]

Hussain et al. described a sub-cohort of patients with CA who may develop severe AS in the absence of significant calcification (with calcium scores that, according to conventional guidelines, would make the diagnosis of significant AS unlikely). This finding suggests that aortic valve calcium scores may be less applicable in a subset of patients with CA for assessing the severity of AS.[27] This study also noted a potential trend of lower calcium scores in patients with high radiotracer uptake on scintigraphy, although the p-value was not significant. This could be attributed to the small sample size, which may increase the risk of overestimating the magnitude of the effects or associations observed.

The primary limitation of this study was the small sample size (41 patients). The sample size estimation was based on a previous study that expected a 16% coexistence rate of AS and CA, estimating a sample size of 52 patients. It is essential to interpret the 10% prevalence found for the coexistence of AS/CA within the context of the study's sample size. In this scenario, a lower statistical power is insufficient to detect a significant difference between the estimated and actual prevalence. A larger sample size would be particularly important for making more meaningful comparisons between patients with positive and negative scintigraphy results in terms of sociodemographic and clinical characteristics.

Table 5 – Comparison of positive or negative scintigraphy results with sociodemographic and clinical characteristics

	Not altered (n = 37)	Altered (n = 4)	P-value
Gender			0.303 †
Female	22 (59.5)	1 (25.0)	
Male	15 (40.5)	3 (75.0)	
Ethnicity			0.681*
White	14 (37.8)	1 (25.0)	
Brown	20 (54.1)	3 (75.0)	
Black	3 (8.1)	0	
Left ventricular disfunction	9 (25.0)	2 (50.0)	0.300 †
Pulmonary hypertension (sPAP > 35)	2 (5.6)	1 (25.0)	0.277 †
BMI > 30	7 (18.9)	2 (50.0)	0.204 †
NT-proBNP (pg/ml)	391 (121-1022)	1109 (596-2094)	0.490 ‡
Calcium score Agatston	2509 (1654-3014)	944 (917-1311)	0.061 ‡
RAISE Score			0.255*
0	22 (59.5)	3 (75.0)	
1	12 (32.4)	0	
2	1 (2.7)	1 (25.0)	
3	1 (2.7)	0	
6	1 (2.7)	0	
Left ventricular strain (%)	14.1 ± 3.8	15.5 ± 3.4	0.500 §
Apical sparing	0	1 (25.0)	0.098 †
Troponin (ug/L)	0.0010 (0.0010-0.605)	1.15 (0.0010-3.26)	0.610 ‡
Right Ventricular Hypertrophy	3 (8.1)	1 (25.0)	0.348 †
Right ventricular Strain (%)	21.2 ± 6.0	19.1 ± 4.9	0.549 §
Left Atrium Strain (%)	22.1 ± 9.6	20.0 ± 6,6	0.623 §

***Chi-square test; † Fischer's exact test; ‡ Mann-Whitney test; § Independent t-test**
BMI: body mass index; sPAP: systolic pulmonary artery pressure.

Therefore, we have taken care to report this limitation and acknowledge that these data are preliminary, serving as precursors for future research.

Our study was conducted at a single referral center, limiting the generalizability of our findings. Additionally, the true prevalence of AS/CA coexistence remains uncertain, necessitating further investigation in diverse populations and settings.[26,28]

The bone radiotracer used in the scintigraphy for diagnosing TTR amyloidosis was technetium-99m pyrophosphate. At the beginning of the study, there was a period in 2021 when this material was unavailable, which affected the inclusion of a larger number of patients.

Despite the small sample size of this study, a 10% prevalence of AS/CA coexistence was found, a value consistent with that reported in other cohorts.[9,13]

This study aimed to evaluate the prevalence of amyloidosis, primarily of the TTR type, in the context of AS. The inclusion criteria focused on patients with high radiotracer uptake on both qualitative and quantitative scintigraphy evaluations, excluding those with grade

1 uptake indicative of subclinical amyloidosis. This approach ensured a more accurate assessment of clinically relevant amyloidosis cases associated with AS.

Despite these limitations, our study provides valuable insights into the prevalence and clinical implications of AS/CA coexistence, laying the groundwork for future research endeavors in this rapidly evolving area of investigation.

Conclusion

The prevalence of CA in patients with moderate to severe calcific AS in our sample was 9%. Due to the low prevalence of the condition, the sample size was insufficient to characterize clinical and echocardiographic differences between patients with or without amyloidosis.

This study was pioneering in attempting to diagnose CA in patients with moderate and severe AS in our population, confirming the coexistence, which may have clinical and prognostic implications.

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Author Contributions

Conception and design of the research: Key NK, Melo AS, Sena JP, Dourado AD, Brito JCR, Feitosa G, Feitosa-Filho GS; acquisition of data: Key NK, Melo AS, Sena JP, Dourado AD, Perez JM, Brito JCR; analysis and interpretation of the data: Key NK, Melo AS, Feitosa G, Feitosa-Filho GS; statistical analysis: Key NK; obtaining financing: Key NK, Melo AS, Brito JCR; writing of the manuscript: Key NK, Melo AS, Feitosa-Filho GS; critical revision of the manuscript for intellectual content: Key NK, Melo AS, Sena JP, Dourado AD, Perez JM, Brito JCR, Feitosa G, Feitosa-Filho GS.

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 study was approved by the Ethics Committee of the Hospital Santa Izabel under the protocol number 40888820.9.0000.5520. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

References

1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP 3rd, Gentile F, et al. 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol. 2021;77(4):25-197. doi: 10.1016/j.jacc.2020.11.018.
2. Tastet L, Tribouilloy C, Maréchaux S, Vollema EM, Delgado V, Salaun E, et al. Staging Cardiac Damage in Patients with Asymptomatic Aortic Valve Stenosis. J Am Coll Cardiol. 2019;74(4):550-63. doi: 10.1016/j.jacc.2019.04.065.
3. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-art Review. J Am Coll Cardiol. 2019;73(22):2872-91. doi: 10.1016/j.jacc.2019.04.003.
4. 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. doi: 10.1161/CIRCULATIONAHA.116.021612.
5. Simões MV, Fernandes F, Marcondes-Braga FG, Scheinberg P, Correia EB, Rohde LEP, et al. Position Statement on Diagnosis and Treatment of Cardiac Amyloidosis - 2021. Arq Bras Cardiol. 2021;117(3):561-98. doi: 10.36660/abc.20210718.
6. Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, et al. Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. Circ Cardiovasc Imaging. 2016;9(8):e005066. doi: 10.1161/CIRCIMAGING.116.005066.
7. Peskó G, Jenei Z, Varga G, Apor A, Vágó H, Czibor S, et al. Coexistence of Aortic Valve Stenosis and Cardiac Amyloidosis: Echocardiographic and Clinical Significance. Cardiovasc Ultrasound. 2019;17(1):32. doi: 10.1186/s12947-019-0182-y.
8. Scully PR, Treibel TA, Fontana M, Lloyd G, Mullen M, Pugliese F, et al. Prevalence of Cardiac Amyloidosis in Patients Referred for Transcatheter Aortic Valve Replacement. J Am Coll Cardiol. 2018;71(4):463-4. doi: 10.1016/j.jacc.2017.11.037.

9. Nitsche C, Scully PR, Patel KP, Kammerlander AA, Koschutnik M, Dona C, et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol. 2021;77(2):128-39. doi: 10.1016/j.jacc.2020.11.006.

10. Pibarot P, Lancellotti P, Narula J. Concomitant Cardiac Amyloidosis in Severe Aortic Stenosis: The Trojan Horse? J Am Coll Cardiol. 2021;77(2):140-3. doi: 10.1016/j.jacc.2020.11.007.

11. Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, et al. Aortic Stenosis and Cardiac Amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol. 2019;74(21):2638-51. doi: 10.1016/j.jacc.2019.09.056.

12. Longhi S, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, et al. Coexistence of Degenerative Aortic Stenosis and Wild-type Transthyretin-related Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2016;9(3):325-7. doi: 10.1016/j.jcmg.2015.04.012.

13. Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, et al. Cardiac Amyloidosis is Prevalent in Older Patients with Aortic Stenosis and Carries Worse Prognosis. J Cardiovasc Magn Reson. 2017;19(1):98. doi: 10.1186/s12968-017-0415-x.

14. Chadha G, Bohbot Y, Rusinaru D, Maréchaux S, Tribouilloy C. Outcome of Normal-flow Low-gradient Severe Aortic Stenosis with Preserved Left Ventricular Ejection Fraction: A Propensity-matched Study. J Am Heart Assoc. 2019;8(19):e012301. doi: 10.1161/JAHA.119.012301.

15. Senior R, Khattar RS. Assessment of Aortic Stenosis: Time to go with the Flow. J Am Coll Cardiol. 2020;75(15):1770-1. doi: 10.1016/j.jacc.2020.02.042.

16. Alkhalil M. Staging Cardiac Damage in Aortic Stenosis. J Am Coll Cardiol. 2019;74(22):2824-5. doi: 10.1016/j.jacc.2019.08.1067.

17. Jaiswal V, Agrawal V, Khulbe Y, Hanif M, Huang H, Hameed M, et al. Cardiac Amyloidosis and Aortic Stenosis: A State-of-the-art Review. Eur Heart J Open. 2023;3(6):oead106. doi: 10.1093/ehjopen/oead106.

18. Mohty D, Damy T, Cosnay P, Echahidi N, Casset-Senon D, Virot P, et al. Cardiac Amyloidosis: Updates in Diagnosis and Management. Arch Cardiovasc Dis. 2013;106(10):528-40. doi: 10.1016/j.acvd.2013.06.051.

19. Dobson LE, Prendergast BD. Heart Valve Disease: A Journey of Discovery. Heart. 2022;108(10):774-9. doi: 10.1136/heartjnl-2021-320146.

20. Kang DH, Park SJ, Lee SA, Lee S, Kim DH, Kim HK, et al. Early Surgery or Conservative Care for Asymptomatic Aortic Stenosis. N Engl J Med. 2020;382(2):111-9. doi: 10.1056/NEJMoa1912846.

21. Bonelli A, Paris S, Nardi M, Henein MY, Agricola E, Troise G, et al. Aortic Valve Stenosis and Cardiac Amyloidosis: A Misleading Association. J Clin Med. 2021;10(18):4234. doi: 10.3390/jcm10184234.

22. Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, et al. Screening for Transthyretin Amyloid Cardiomyopathy in Everyday Practice. JACC Heart Fail. 2019;7(8):709-16. doi: 10.1016/j.jchf.2019.04.010.

23. Brandão SCS, Quagliato PC, Lopes RW, Matushita CS, Amorin BJ, Mesquita CT. Guideline de Cintilografia com Marcadores Ósseos para Pesquisa de Amiloidose Cardíaca por Transtirretina. São Paulo: Sociedade Brasileira de Medicina Nuclear; 2019.

24. Grodin JL, Maurer MS. The Truth is Unfolding About Transthyretin Cardiac Amyloidosis. Circulation. 2019;140(1):27-30. doi: 10.1161/CIRCULATIONAHA.119.041015.

25. Salinger T, Hu K, Liu D, Herrmann S, Lorenz K, Ertl G, et al. Cardiac Amyloidosis Mimicking Severe Aortic Valve Stenosis - A Case Report Demonstrating Diagnostic Pitfalls and Role of Dobutamine Stress Echocardiography. BMC Cardiovasc Disord. 2017;17(1):86. doi: 10.1186/s12872-017-0519-0.

26. Galat A, Guellich A, Bodez D, Slama M, Dijos M, Zeitoun DM, et al. Aortic Stenosis and Transthyretin Cardiac Amyloidosis: The Chicken or the Egg? Eur Heart J. 2016;37(47):3525-31. doi: 10.1093/eurheartj/ehw033.

27. Hussain M, Hanna M, Rodriguez L, Griffin B, Watson C, Phelan D, et al. Subthreshold Aortic Valve Calcium Scores in Severe Aortic Stenosis and Transthyretin Cardiac Amyloidosis. JACC Case Rep. 2020;2(14):2205-9. doi: 10.1016/j.jaccas.2020.10.002.

28. Peterzan M. Screening for Cardiac Amyloidosis in Aortic Stenosis. London: British Cardiovascular Society; 2020.