SCIENTIFIC RESEARCH

99mTc-MDP MYOCARDIAL SCINTIGRAPHY IN DIAGNOSIS OF AMYLOID CARDIOMYOPATHY AT FV HOSPITAL, HCM CITY

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SUMMARY

Retrospective study of 99mTc-MDP myocardial scintigraphy for restrictive cardiomyopathy with suspicion of amyloidosis from Feb 2021-Nov 2021 at FV hospital.

Total 10 patients (7 male and 3 female patients) of age 37-85 years.

Injected dose 15-20 (555-740 MBq), Thorax planar and SPECT/low dose non contrast CT acquisition at 1 hour following tracer injection.

Qualitative analysis with Visual score and quantitative H/CL ratio

Positive scan is concluded in case of diffuse uptake in myocardium with Visual score 2-3 and H/CL ratio >1.5.

The procedure was performed safely with no side effect, no allergic to radiotracer recognized.

Results: Two male patients out of ten are positive for TTR-CA, at age 37 and 67. No myocardial biopsy is indicated for differential diagnosis between AL and TTR-CA. Eight patients are negative scintigraphically not specific for TTR-CA with H/CL <1.5 and Visual score 0.

Conclusion: 99mTc-MDP cardiac scintigraphy is a safe, reliable, non-invasive nuclear imaging applicated for early and differential diagnosis of cardiac amyloidosis replacing to myocardial biopsy. This approach contributes to reveal an undiagnosed disease at not so advanced cardiac involvement and with the progress of recent medical treatment, the survival is increasing. Other bone-avid tracers are encuraged for myocardial imaging depending on their availability.

Keywords: *Tc99m-MDP cardiac scintigraphy, cardiomyopathy amyloidosis, TTR-CA, AL, H/CL ratio, visual score.*

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I. PURPOSE

Amyloidoses are a group of rare diseases that usually go undiagnosed. Over 98% are caused by monoclonal immunoglobulin light chain (AL) or by extracellular deposition of transthyretin (TTR)-derived pathogenic insoluble fibrils in organs and tissues.

Cardiac amyloidosis caused by an acquired monoclonal light chain (AL) proteins secreted from abnormal plasma cells, frequency ~2500 new cases/year with cardiac evidences in about 50% of cases [5] . If left untreated, the prognosis is poor with a median survival of <1 year since it has been diagnosed with symptom of heart failure.

Transthyretin cardiac amyloidosis (TTR-CA) is related to transthyretin synthesized in the liver (TTR-related), which can be hereditary and acquired (wild-type Wt/in elderly patients over 60 years old), with slow progression, unknown clinical symptoms until serious cardiac complications occur. If early diagnosis and treatment is not made, the survival is within 10 years. Therefore, screening for cardiac injury is necessary in the management of patients with suspected TTR-CA.

The diagnosis of TTR-CA (previously based on invasive myocardial biopsy) that can be achieved with high sensitivity (95-100%) and near-perfect specificity (97-99%)[6], with exclusion of plasma cell dyscrasia by myocardial scintigraphy technique with bone-avid tracers[2] including PYP (pyrophosphate), DPD (3,3-diphosphono-1,2-propanodicarboxylic acid), HMDP (hydroxymethylene diphosphonate) and MDP (methylene diphosphonate) labeled with Tc99m radioactive isotopes is increasingly essential for the non-invasive diagnosis of TTR-CA, although the mechanism of binding to amyloid deposition remains unclear [1]. These tracers give similar results in the diagnosis of TTR-CA, but have no value in diagnosing the disease caused by the light chain (AL).

Conducting myocardial scintigraphy technique to contribute to the diagnosis of amyloid cardiomyopathy is a pioneering step in Vietnam because this is a hot topic in global cardiovascular nuclear medicine and molecular imaging. In addition, the 3 drugs recently approved by the US FDA for the treatment of TTR-CA are more necessary to further expand molecular imaging techniques in the diagnosis and management of amyloid cardiomyopathy.

II. SUBJECTS AND METHODS

1. Subjects

10 patients diagnosed with restrictive cardiomyopathy with suspected amyloidosis (some of them had biology, monoclonal protein tests, echocardiography, MRI, and no history of previous or recent myocardial infarction) were sent for myocardial scintigraphy from Feb 2021-Nov 2021 at FV hospital - Ho Chi Minh City.

2. Methods

Myocardial scintigraphy was conducted with MDP (Methylene diphosphonate from Isotope company) labeled with Tc99m as follows:

IV injection with 99mTc-MDP 15-20 mCi (555-740 MBq) was given.

After 1 hour[3]: The patient was placed in supine, and SIEMENS Symbia Intevo Excel Dual-head Gamma Camera System, with LEHR collimators was used.

- Static acquisition (Anterior, left oblique, left views), pause after 8 minutes or 750 Kcts, 512 x 512 matrix
- Chest SPECT/CT (low dose, no contrast) immediately after static acquisition. LEHR, detectors: 1 & 2, motion: non-circular, continuous, rotate 1800 counterclockwise, tomography. Energy: 140 keV, 15-20% window, 256 x 256 matrix, Zoom 1.45. CT scan: follow the Symbia Intevo Excel CT protocol: Rapid chest scan 08s
- Image processing: Draw region of interest (ROI) on heart region (H) and ROI mirrored on contralateral lung (CL)

Quantitative uptake is calculated as uptake ratio (H/CL ratio).

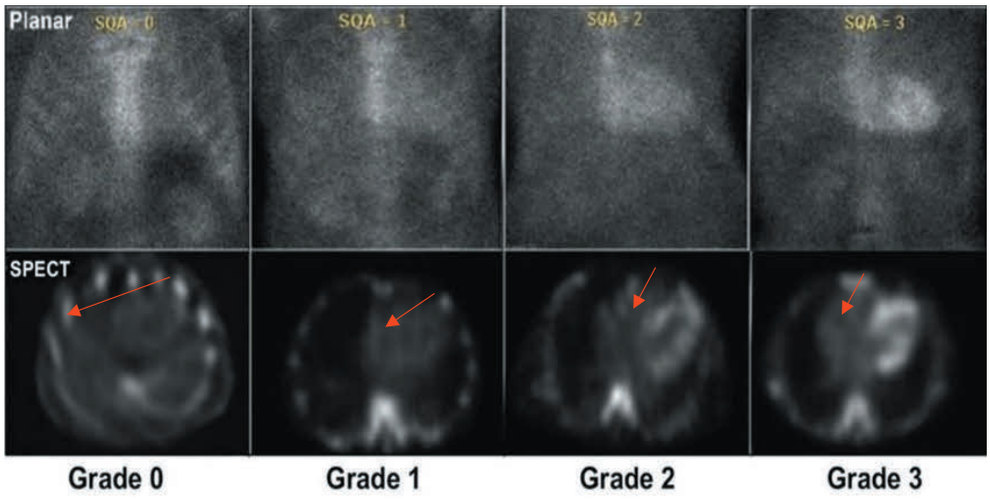
$$\text{H/CL ratio} = \frac{\text{Heart ROI Mean counts per pixel}}{\text{Contralateral ROI Mean counts per pixel}}$$

In which H (heart), CL (contralateral lung), Heart ROI Mean counts per pixel (average count per pixel on myocardium), Contralateral ROI Mean counts per pixel (average count per pixel on chest wall).

3. Interpretation of results

Assessment of qualitative uptake at myocardium on scintigraphy with the Perugini Visual Score: Grade 0:

Absent myocardial uptake, Grade 1: Myocardial uptake < bone, Grade 2: Myocardial uptake = bone, Grade 3: Myocardial uptake > bone (arrow, confirmed on SPECT images) and quantitative uptake [1].



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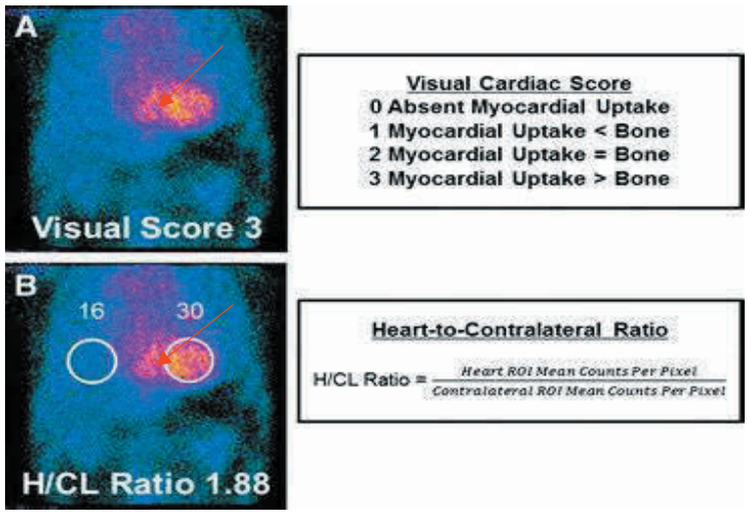

The scintigraphy is deemed positive in case of diffuse myocardial uptake, with H/CL ratio >1.5 plus grade 2-3 uptake and negative in case of H/CL ratio <1.5 plus grade 0-1 uptake [1].

III. RESULTS

1. By age

>60	6
<60	4
Total	10

The youngest age is 37y, the oldest age is 85y.

2. Gender: Male 7, Female 3

3. Assessment of myocardial uptake

> Bone H/CL >1.5	= Bone	< Bone and no uptake H/CL <1.5
2	0	8

There were no cases of adverse events or allergies after injection of radiopharmaceuticals.

4. Positive cases were assessed with both visual score and quantitative uptake. Two cases of positive myocardial uptake in a total of 10 patients (Figures 1 and 2).

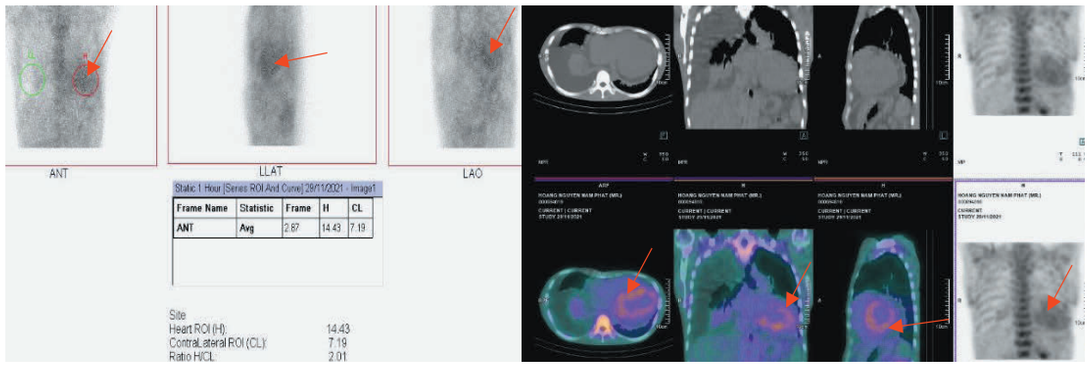

Figure 1. *A 37-year-old male patient, family history of mother and brother with hypertrophic cardiomyopathy, grade 2 heart failure. Echocardiography: restrictive cardiomyopathy, irregular rhythm, total wall thickness >22mm, diastolic dysfunction, small pericardial effusion, severe hypokinesia with EF 25%, regurgitation of heart valves, no pulmonary hypertension. ECG: AV block, incomplete right bundle branch block, ventricular premature beats, intraventricular conduction disturbance. Free light chain FLC (-), Monoclonal antibody (-). Cardiac MRI: delayed hyperintensity, increased left ventricular mass, asymmetric concentric hypertrophy of left ventricular wall with dominance of interventricular septum. Scintigraphy: total wall thickness, grade 3 homogeneous diffuse myocardial uptake (arrow), H/CL ratio 2.01.*

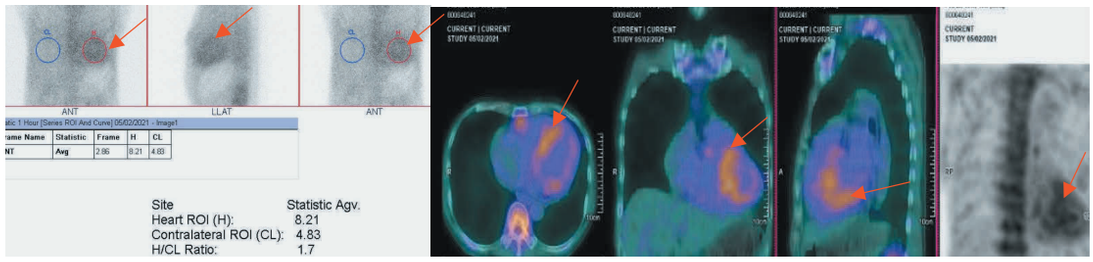

Figure 2. *A 67-year-old male patient, grade 2-3 heart failure from 1.5 years. Echocardiography: restrictive cardiomyopathy, wall thickness, EF 20%. Abdominal fat biopsy: amyloid deposition. Monoclonal protein (-). Scintigraphy: wall thickness, grade 3 diffuse myocardial uptake (arrow), H/CL ratio 1.7.*

5. The remaining cases with negative scintigraphy (Figure 3-6)

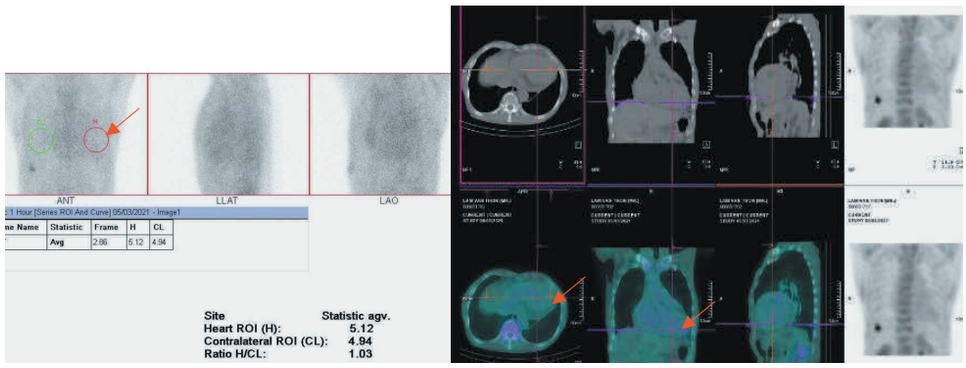

Figure 3. *A 85-year-old male patient, grade 3 heart failure, EF 45%, restrictive cardiomyopathy /multiple myeloma with suspected AL. No myocardial uptake (arrow), H/CL 1.03.*

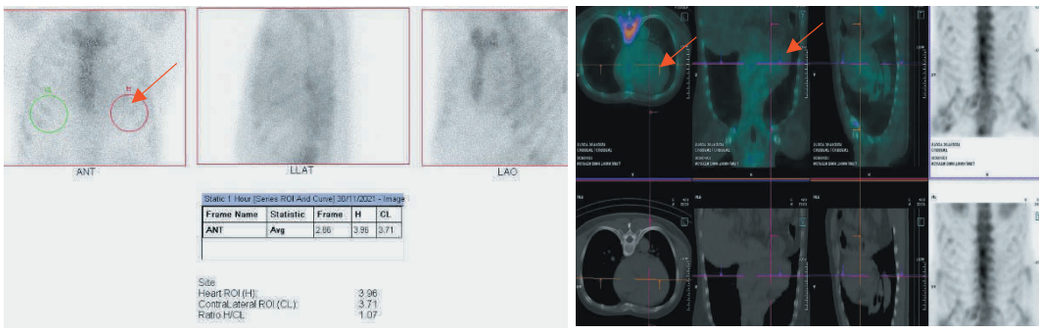

Figure 4. *A 56-year-old male patient. No myocardial uptake (arrow).*

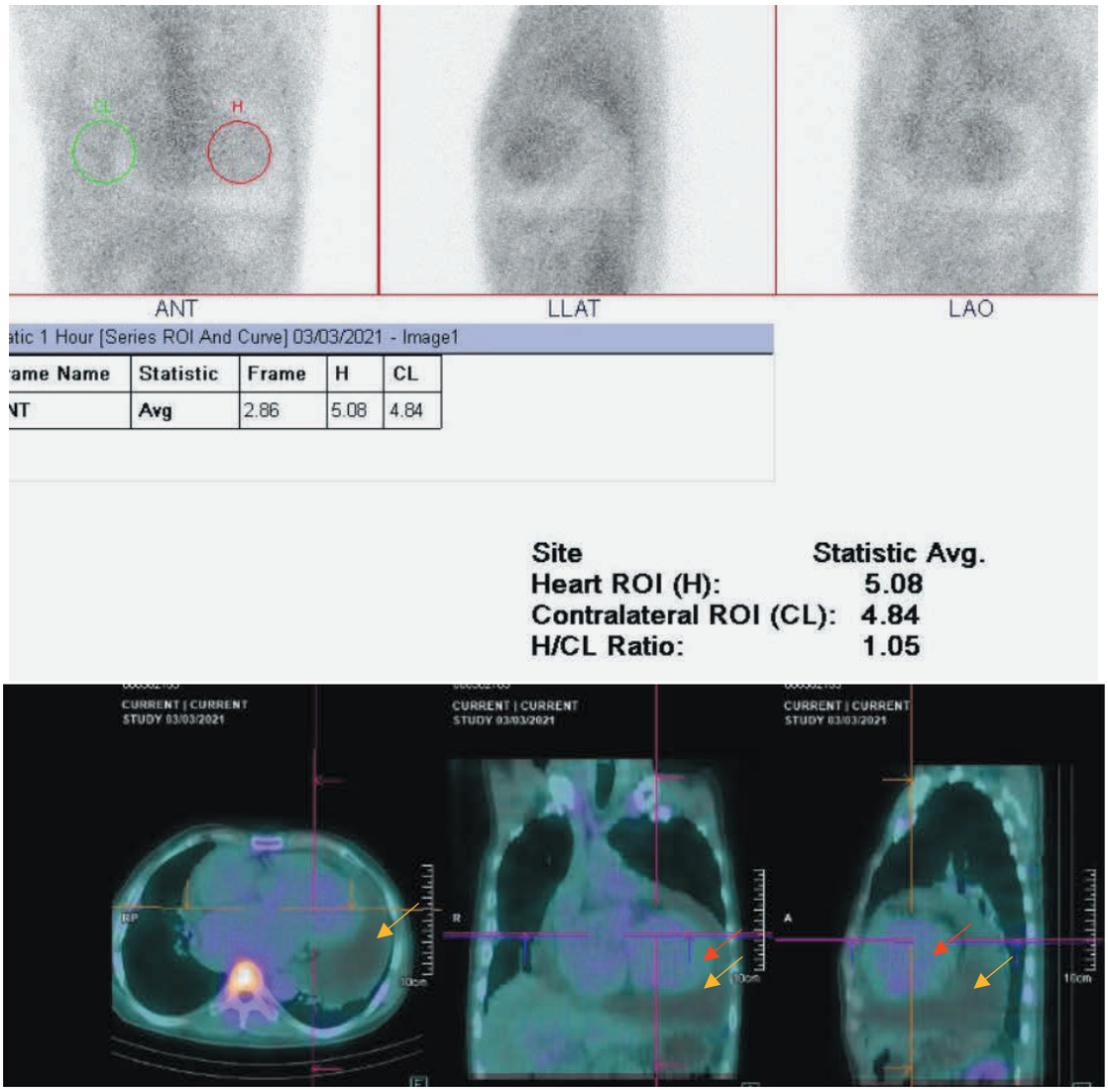

Figure 5. *A 60-year-old male patient, severe pericardial effusion (yellow arrow), no myocardial uptake (red arrow), blood pool (+).*

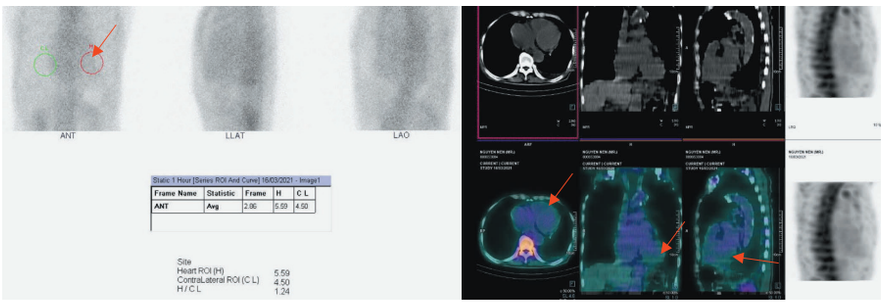

Figure 6. *A 85-year-old male patient, grade 2 heart failure, atrial fibrillation, increased Kappa, Lambda. H/CL ratio 1.24, no myocardial uptake, blood pool (+).*

IV. DISCUSSION

Some studies have shown that 99mTc-Methylene diphosphonate (MDP) has a low sensitivity in the diagnosis of TTR-CA, thus it is not recommended, although the mechanism by which bone-avid tracers bind to the myocardium is still not well understood. Results of this study indicated that there were 2 positive myocardial uptakes in a total of 10 patients (Figures 1 and 2) which is consistent with the 20% positive results of Joshua Dower et al. (55 cases (+)/273 myocardial scintigraphy with PYP at Tufts Medical Center, Boston-May, 2022) [3]. It has been hypothesized that these tracers bind to amyloid deposits with greater microcalcifications in ATTR than those in AL. However, microcalcification alone cannot completely account for the affinity of these tracers to TTR because patients with Phe64Leu mutation-related TTR-CA have low scintigraphy sensitivity with DPD and HMDP[8]. Further studies are needed as in contrast to scintigraphy tracers which bind to microcalcifications rather than directly to pathological fibrils (amyloid fibrils), there are at least 4 PET tracers which bind directly to amyloid fibrils, and have a higher affinity in AL than in TTR [2]. This indicates that the binding to tracers is determined by various mechanisms in CA disease.

Cardiac scintigraphy is interpreted with visual score and quantitative uptake indices. The most commonly used visual score is Perugini scale, which provide the comparison of cardiac to bone uptake (from 0 to 3); grades 2 and 3 are deemed positive for TTR-CA in the absence of monoclonal dyscrasia, while grade 0 is considered negative for TTR-CA. Grade 1 can be either AL or ATTR-CA. A multicenter study showed that patients with Perugini grade 2 or higher along with negative monoclonal gammopathy, a positive diagnosis of TTR-CA can be acceptable without confirmation of myocardial biopsy (positive predictive value and specificity > 98%). Quantitative indices, such as heart/contralateral lung (H/CL) ratio and heart/whole body (H/WB) ratio is validated for acquisition after 1 and 3 hours of injection to help improve the value of visual score. Furthermore, systematic reviews have confirmed interpretation of scintigraphy using either visual score or quantitative indices has > 90% sensitivity and specificity in the diagnosis of TTR-CA. Currently, scintigraphy with bone-avid tracers has dramatically changed the clinical diagnostic flowchart as an important non-invasive alternative to myocardial biopsy in the diagnosis of TTR-CA.

Myocardial uptake ratio (H/CL ratio) has diagnostic value but is not useful in the prognosis of ATTR-CA [7].

Diagnosis of CA according to the new European Society of Cardiology (ESC) guidelines aimed at determining the presence or absence of AL and TTR-CA cardiomyopathy: Assess monoclonal proteins (serum and urine electrophoresis with immunofixation, free light chain ratio) and perform scintigraphy with bone-avid tracers (completely specific for TTR-CA). Follow-up investigations with cardiac MRI and myocardial biopsy or extracardiac tissue biopsy is used when indicated. There are 4 possible scenarios:

- Monoclonal protein (-), scintigraphy scan (-): unlikely CA, consider cardiac MRI and biopsy if suspicion is still high.
- Monoclonal protein (-), scintigraphy scan (+): grade 2 or 3 uptake is adequate for diagnosis of TTR-CA and no myocardial biopsy is needed.
- Monoclonal protein (+), scintigraphy scan (-): possible AL and cardiac MRI is needed, if MRI (-), no cardiac injury, if MRI (+), biopsy is required.

- Monoclonal protein (+), scintigraphy scan (+): possible AL or TTR-CA or combined amyloidosis, myocardial biopsy is needed to confirm diagnosis.

For TTR-CA, genetic factors should be analyzed. This may contribute to prognosis, choice of treatment, and screening of the whole family.

V. CONCLUSION

Currently, myocardial scintigraphy with 99mTc-labeled bone-avid tracers is a hot topic and widely applied in patients with restrictive cardiomyopathy because it is a non-invasive nuclear medicine diagnostic method with high sensitivity (>95%) and high specificity (up to 99%) to differentiate TTR-CA from AL as a alternative method to myocardium biopsy which have potential risks (bleeding, hematoma, acute tamponade, arrhythmias, infection, etc.)[3] and especially that is not available at all healthcare facilities.

The definitive diagnosis of TTR-CA can contribute to early detection of heart injuries to help choose appropriate treatment and perform gene mutation investigation for family members, along with advances in treatment (newly approved by US FDA)[2]: Tafamidis is used as TTR stabilizer and Patisiran is used as TTR gene silencer, which prevent the synthesis of TTR, change the progression of the disease, and prolong the survival of patients.

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Received: 25/08/2022. Assessed: 29/08/2022. Accepted: 16/12/2023