# Development and testing of Machine Learning Algorithms for early diagnosis of Amyloid Transthyretin Cardiomyopathy

U. Adiga

Dept. of Biochemistry, Apollo Institute of Medical Sciences and Research Chittoor, India.
*Corresponding author Email: ushachidu@yahoo.com

Journal of Livestock Science (ISSN online 2277-6214) 15: 292-299
Received on 30/7/24; Accepted on 30/8/24; Published on 16/9/24
doi. 10.33259/JLivestSci.2024.292-299

## Abstract

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a rare yet fatal condition characterized by the deposition of transthyretin amyloid fibrils in the heart. This review article synthesizes the findings of a proposed study aimed at comprehensively understanding ATTR-CM in the Indian population. The diagnosis of transthyretin amyloidosis (ATTR) cardiac disease faces several constraints that complicate early and accurate detection. One major challenge is the nonspecific nature of its clinical presentation, often mimicking other more common conditions like hypertensive heart disease or hypertrophic cardiomyopathy. This overlap can delay proper identification and lead to misdiagnoses. Additionally, the gold standard diagnostic tools, such as endomyocardial biopsy and advanced imaging techniques like cardiac MRI or scintigraphy with technetium-labeled compounds, are not always readily available, especially in resource-limited settings. Genetic testing, although essential for distinguishing hereditary from wild-type ATTR, may also be limited by access and cost. Furthermore, a lack of awareness and clinical suspicion among healthcare providers can result in underdiagnosis or late diagnosis, which significantly impacts patient outcomes.

The study intends to identify and analyze patients diagnosed with ATTR-CM in India to estimate its prevalence and describe patient characteristics, including gender differences and mortality rates. Moreover, it seeks to investigate the significance of early symptoms ("red flags") in identifying ATTR-CM and to develop and evaluate machine learning algorithms for its early diagnosis. Patients with ATTR-CM will be identified retrospectively using diagnosis codes and diagnostic algorithms, and compared with matched non-ATTR heart failure patients. Electronic records will be utilized for algorithm development and testing. Anticipated outcomes include providing the first statewide estimates of ATTR-CM prevalence and risk factors in India, emphasizing the disease's severity, and underlining the importance of early diagnosis, particularly among female patients, to facilitate effective treatment and disease progression prevention. Additionally, the study aims to demonstrate the utility of machine learning algorithms in early disease identification and detecting missed diagnoses. This review highlights the paucity of studies examining the prevalence of ATTR cardiomyopathy in India and underscores the need for machine learning algorithms for early detection, offering valuable insights into addressing this critical healthcare challenge.

**Key words:** Transthyretin amyloid cardiomyopathy; heart failure; machine learning

# Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) represents a rare and often fatal condition characterized by the deposition of transthyretin amyloid fibrils in the myocardium. It can manifest either through hereditary means, typically associated with variants in the transthyretin (TTR) gene (variant ATTR or ATTRv), or as a consequence of aging, particularly with a wild-type allelic constitution of the TTR gene (Rubin et al.,2020). Notably, Northern Sweden has been identified as an endemic area for ATTRv, notably linked to a V30M mutation, with a sizable population of late-onset cases demonstrating a higher propensity for developing cardiomyopathy compared to those with early-onset presentations (Holmgren et al.,1994; Suhr et al.,2006).

Despite increasing recognition, a significant proportion of ATTR-CM cases remain undiagnosed or suffer from delayed diagnosis, contributing to historically poor prognoses, with median survival post-diagnosis often falling below four years (Lane et al., 2019 ; Grogan et al.,2016,Ruberg et al.,2019;Pinney et al.,2013). Acknowledging the criticality of early detection, attention has been drawn to certain clinical findings or "red flags" associated with heightened risk of ATTR-CM development. While heart failure (HF) symptoms and arrhythmias are common presentations, the systemic nature of amyloidosis can lead to a spectrum of non-cardiac symptoms. These include but are not limited to carpal tunnel syndrome, spinal stenosis, intestinal disorders, ruptured distal biceps tendon, as well as heart-related conditions such as aortic stenosis, atrial fibrillation and flutter, or atrioventricular block (Ruberg et al., 2019;Pinney et al.,2013 ;Yanagisawa et al., 2015;Maurer et al.,2019; Geller et al., 2017; Castaño et al., 2017;Huang et al.,2015).

Despite the burgeoning research interest, significant gaps persist in understanding the epidemiology of ATTR-CM. Previous studies on patient characteristics, mortality, and potential red flags have often been limited to subgroup analyses over shorter time spans and have not directly compared with non-ATTR HF patients. In India, where studies on ATTR-CM are relatively scarce, notable efforts such as those by Mohan et al. and Agarwal et al. have shed light on the clinical landscape, albeit within single-center or retrospective frameworks (Bishay et al.,2023; Agarwal et al., 2021). These studies underscore the challenges in timely diagnosis and the need for heightened awareness among healthcare professionals, emphasizing the role of modern diagnostic techniques like advanced echocardiography and CMR.

International endeavors, such as those by Gracia et al., Agibetov et al., Martini et al., and Goto et al., highlight the potential of machine learning algorithms in enhancing diagnostic accuracy and prognostic assessment in ATTR-CM ( García-García et al., 2021; Agibetov et al., 2020; Martini et al., 2020;Schrutka et al.,2022; Goto et al.,2021). Leveraging data from clinical records, laboratory parameters, and imaging modalities, these studies demonstrate promising avenues for improving early detection and management. However, within the Indian context, there remains a notable dearth of comprehensive studies integrating clinical features, diagnostic markers, and imaging modalities into machine learning algorithms for ATTR-CM detection. Thus, our proposed study stands as a novel and pioneering effort in this domain within the Indian healthcare landscape, poised to advance early detection and intervention strategies for this debilitating condition.

# Need Assessment

Increased Attention to ATTR-CM: There has been a notable surge in interest among physicians and researchers regarding transthyretin amyloid cardiomyopathy (ATTR-CM) in recent years. This condition has gained recognition as a significant cause of heart failure (HF) and cardiomyopathy.

Advances in Treatment and Prognosis: Recent advancements in disease-modifying treatments have underscored the importance of recognizing ATTR-CM early. These treatments have the potential to improve both quality of life and mortality rates among patients who historically faced a poor prognosis.

Gaps in Epidemiological Knowledge: Despite the growing research focus, significant gaps persist in our understanding of the epidemiology of ATTR-CM. This lack of comprehensive knowledge hinders effective prevention, diagnosis, and management strategies.

Unclear Prevalence in India: The prevalence of ATTR-CM specifically within the Indian population remains uncertain. Limited data exists due to underdiagnosis and late presentation, posing challenges for healthcare professionals in addressing this condition effectively.

Sparse Data on Cardiac Amyloidosis in India: The available data on cardiac amyloidosis in India is scarce and primarily limited to isolated case reports and small case series. This dearth of information impedes comprehensive understanding and management of the condition within the Indian healthcare system.

Unique Challenges in India: India presents unique challenges in dealing with cardiac amyloidosis, including delayed diagnosis and advanced disease presentation. These challenges contribute to a uniformly poor prognosis, exacerbating the urgency for research and intervention strategies tailored to the Indian context.

Comparison with Non-ATTR HF Patients: Previous studies have often focused on specific subgroups or shorter time periods, failing to compare patient characteristics, mortality rates, and clinical findings of ATTR-CM with those of non-ATTR HF patients comprehensively. This lack of comparative data limits our understanding of the disease burden in India.

Undiagnosed or Misdiagnosed Cases: The global prevalence of heart disease is on the rise, leading to an increasing number of cases with symptoms overlapping with other heart diseases, potentially resulting in the underdiagnosis or misdiagnosis of ATTR-CM. Despite its increasing recognition, the true prevalence of ATTR-CM remains unknown, especially in developing countries like India.

Opportune Time for Clinical Diagnosis: With the development of therapeutics like tafamidis for transthyretin-associated cardiac amyloidosis, there is a pressing need to focus on clinical diagnosis efforts. The availability of effective treatments underscores the importance of early detection and intervention strategies.

Role of Machine Learning Algorithms: Machine learning algorithms offer promise in addressing the challenges associated with early identification of ATTR-CM. These algorithms can efficiently process large volumes of data and aid healthcare professionals in making accurate and timely diagnoses, bridging the gap between data complexity and human cognitive limitations.

In summary, the assessment highlights the growing importance of recognizing and addressing ATTR-CM, particularly within the Indian context, and underscores the role of advanced technologies like machine learning in improving diagnostic capabilities and patient outcomes.

## Patient inclusion criteria

1. Patient records of subjects older than 65 years
2. The total number of patients admitted to the hospital during the last twenty years with any pathology (In this way, possible undiagnosed cases would be susceptible to detection)
3. All the records, both structured and unstructured, will be included so as to analyze the primary diagnoses and comorbidities, detecting the weight that these could have had on identifying the patient with real ATTR CM.

## Patient exclusion criteria

1. Oncological patients with active treatment.
2. For each patient, a minimum of 10 years look-back period will be used to identify exclusion criteria, comorbidities and red flags.

## Data sources

Patient-level data will be extracted from the medical record departments of each tertiary care hospital, Prescription Drug Register and the Cause of Death Register, and will be linked together using unique personal identifiers. The medical record departments of tertiary care hospitals in Karnataka, India provide information on diagnoses according to the International Classification of Diseases version 10 (ICD-10), hospitalizations and outpatient specialist visits, as well as surgical and non-surgical procedures. The Prescription Drug Register contains data on all prescriptions filled at pharmacies, and the Cause of Death Register provides the confirmed dates of death and the registered cause of death.

## Patient identification

Patients will be identified retrospectively based on a combination of diagnosis codes as there is no specific ICD code for ATTR-CM. An algorithm developed to identify patients with ATTR-CM is as follows;

## Data extraction

Data extraction of all patients with an ICD-10 code for amyloidosis (AM) diagnoses (E85.0, E85.1, E85.2, E85.4, E85.8, E85.9), cardiomyopathy (CM) diagnoses (I42.0, I42.1, I42.2, I42.5, I42.8, I42.9, I43.1, I43.8) or HF diagnoses (I50) will be done. The study population will include all adult patients in tertiary care center with any of these diagnoses between 2001 and 2022(step 1).

### Identification of the ATTR-CM cohort

From the study population, patients with ATTR-CM will be identified. Patients with ATTR-CM will be defined as individuals diagnosed with HF or CM and AM between 2002 and 2022. It is required that the HF/CM diagnosis and the AM diagnosis be not more than 2 years apart.

**Table 1**: Key points on tools for diagnosis

| |
|---|
| Red flags, ECG and ECHO raise the suspicion of ATTR-CM and nuclear scintigraphy will be considered to confirm the diagnosis |
| Hematological tests done with ATTR-CM to rule out AL amyloidosis. |
| Nuclear scintigraphy performed on suspicion by patient history and ECHO/ECG. |
| **ECG**<br>**Pseudo infarct pattern: ECG showing old infarct pattern with low voltage. Commonly seen in** ATTRwt (63–65%) and ATTRv (18–69%)<br>Diagnostic yield of 60–65%<br>LVF without any infarction<br>HF with conduction disorders; left BBB, right BBB and first-degree AV blocks and other AV blocks<br>Goldberger triad (Low QRS voltage in limb leads, normal voltage in precordial leads, poor R wave progression (V1–V3)<br>RV dysfunction (R wave in aVR, positive T wave in aVR)<br>Isolated AF |
| **ECHO**<br>**Thick-walled LV, RV, RA**<br>**RCM or hypokinetic** nondilated CM<br>Markedly reduced GLS<br>LVEF/Longitudinal strain >4<br>'Bulls eye pattern' due to apical sparing<br>Apical strain/mid basal strain >3:1<br>Tissue doppler 5-5-5 sign |
| **CMR**<br>T-1> 1400msec<br>ECV >42% |
| Positive global subendocardial LGE<br>Thick-walled ventricle and atrium<br>Pleural effusion<br>DIR is a type of "black blood"<br>technique useful for visualizing the walls of the cardiac chambers and blood vessels (including the coronary arteries)<br>Abnormal gadolinium kinetics typical for amyloidosis, myocardial nulling prior to blood pool nulling |
| **Biochemical marker**<br>persistent increase in the levels of Troponin T > 0.05 ng/mL, NT-proBNP >3000 pg/mL |
| **Bone scintigraphy** |
| Semi-quantitative visual Grade of 2 or 3, target to background (LV myocardium to blood pool) ratio >1.5 and retention index >0.030/min.<br>If cardiac uptake is Grade 1, histological confirmation of amyloid deposits (could be extracardiac) is required as non-invasive diagnosis is not possible. |
| **Hematology** |
| Serum free kappa: lambda light chain ratio >3 and free light chain>18 mg/dL is suggestive to go for hematological testing; immunofixation electrophoresis of urine and serum |

Endomyocardial Biopsy (EMB) and proteomic assessment will not be mandated as essential criteria.

Several criteria will be used to exclude patients with light-chain (AL) amyloidosis from this cohort, in addition to exclusion based on the AL diagnosis code (ICD-10 code: E85.8A), will also be used. Based on the association of AL amyloidosis with multiple myeloma (MM), patients with MM diagnosis, patients with prescriptions of drugs commonly used in AL amyloidosis or MM treatment, and patients with hematopoietic stem cell transplant will also be excluded. Moreover, patients with more than two AM diagnoses from the hematology department will be defined as patients with AL amyloidosis will be excluded. In addition to patients with AL amyloidosis, individuals with a liver or heart transplant prior to diagnosis will also be excluded, as these are disease-modifying therapies.

The date of inclusion in the ATTR-CM cohort, the index date, will be the date of the CM/HF diagnosis used for identification. This date will be serving as proxy for the patient's first ATTR-CM diagnosis and is referred to as the time of ATTR-CM diagnosis throughout the text.

## HF comparison cohort

Patients with an HF diagnosis and not included in the ATTR-CM cohort will be matched to patients in the ATTR-CM cohort. Patients will be matched one-to-one, with replacement, on birth year, gender and the calendar

year of diagnosis. The diagnosis date for patients in the matched HF cohort will be the date of the first recorded HF diagnosis between 2001 and 2022.

## Patient characteristics

Gender and age of the patients will be measured at ATTR-CM diagnosis. Comorbidities will be measured during 3 years before diagnosis; the Elixhauser Comorbidity Index with 31 categories will be used to measure the burden of comorbidity. Moreover, all pharmacy-dispensed prescriptions of heart or cardiovascular medication will be recorded during 1 year before ATTR-CM diagnosis.

## Prevalence

To estimate the prevalence in a certain year, the number of patients with ATTR-CM (patients alive at the beginning of the year plus the new cases diagnosed during that year) will be taken in to consideration on 31$^{st}$ of December that year.

## Mortality

Kaplan-Meier estimates and Cox proportional hazards regression will be used to assess patients' survival after diagnosis compared with the matched control group.

## Red flags

A descriptive analysis of the history of red flags up to the time of diagnosis will be used to compare patients with ATTR-CM and the matched HF cohort. In addition, a multivariate logistic regression model will be used to estimate the importance of the same red flags in predicting a later diagnosis of ATTR-CM. Variables included in the regression will be the red flag diagnoses, as well as age, sex and comorbidity index at diagnosis.

## Data processing

Data analysis will be initiated by searching for diagnosed cases of ATTR-CM in extracted medical records. The data will be going through a preliminary preprocessing stage (step 2) before new fields are generated, and the transformation pipelines will be executed. The cleaning process will remove white spaces, special characters, null values and columns or rows with constant values. In addition, in order to join the data tables coming from different sources, a new episode primary key field will be created. Once the information is consolidated, new variables will be created manually following the clues provided by clinical practice (step 3).

In step 4, many fields with low-quality data will be discarded. The processing of each type of variable (text/categorical/numeric) will be carried out separately, treated in a particular way according to their nature (step 5). A generic dictionary will be elaborated to facilitate the reproducibility of encoded variables in the categorical pipeline (step 6), where all possible categories of each field were annotated for later dummy encoding.

All categorical data will be converted in to numerical data.

## Development of Algorithms for machine learning

**This phase will have two parts**

Following machine learning algorithms will be used to identify cardiac amyloidosis and to differentiate with non-amyloid heart failure cases using publicly available database of ATTR- CM and non-amyloid HF;

**Logistic Regression (LR):** Logistic regression which is a classification model, and it is often used in dichotomy. Logistic Regression is one of algorithms of ML to solving binary (0 or 1) problems, which is used to estimate the likelihood of some things.

**K Nearest Neighbour (kNN):** KNN is one of easiest algorithms in data analysis and it is a nonparametric statistical method for classification and regression.

**Naivers Bayes (NB):** Naive Bayes classifier is a series of simple probability classifier based on Bayes theorem under strong (naive) independence between assumed features. For example, Bayes' theorem is to solve the problem which often encountered in the real life.

**Decision Tree (DT):** Decision Tree is a tree structure which is binary or non-binary. Each non-leaf node represents a test on a feature attribute, each branch represents the output of this feature attribute on a range of values, and each leaf node stores a category.

**Linear SVM (SVM-Linear) and RBF SVM (SVM-RBF):** SVM is one of supervised learning methods, can be widely used in statistical classification and regression analysis. SVM belongs to generalized linear classifiers, which are characterized by their ability to minimize empirical error and maximize geometric edge region at the same time. Therefore, another name of SVM is maximum edge region classifier.

**Multi-Level Perceptron (MLP):** MLP is a kind of feed-forward neural network (ANN). The term MLP is vague, sometimes loosely applied to any feed-forward ANN, and sometimes strictly refers to a network consisting of multiple layers of perceptron.
**Ridge Classifier (RC):** In the least squares of ordinary linear regression, it is only valid when the matrix is nonsingular matrix, but in most cases the matrix is not rank, and ridge regression can be used to solve this problem.
**Random Forest (RF):** Random forest is a classifier which includes a lot decision trees, and its class of output is decided by mode of class of outputs of individual trees.
**Quadratic Disc. Analysis (QDA):** Quadratic Discriminant Analysis is improved on Linear Discriminant Analysis.
**AdaBoost (AdaBoost):** The Adaboost model is an iterative algorithm, whose core idea is to train different weak classifiers for the same training set, and then assemble these weak classifiers to form a strong classifier. Adaboost can handle classification and regression problems Gradient Boosting (GB).
**Linear Disc. Analysis (LDA):** LDA is a dimension reduction technique of supervised learning, that is to say, each sample of its data set is output by category.
**Extra Trees (ET):** Extra Trees is one of the most useful algorithms in Machine Learning. It is similar with Random Trees and it is generated by a lot decision trees.
**Extreme Gradient Boosting (XGBoost):** XGBoost is an open-source library, and it can provide an efficient and effective implementation of gradient enhancement algorithms.
**Light Gradient Boosting (LGB):** Light Gradient Boosting Machine is a framework to implement GBDT algorithm, which supports efficient parallel training, faster training speed, lower memory consumption, better accuracy, distributed support, and fast processing of massive data.
**CatBoost Classifier (CatBoost):** CatBoost is an open-source gradient enhancement library, and it is based on decision trees that provides off-the-shelf classification feature to support Python and R.
**Deep Forest (DF):** Deep Forest is an integration of the breadth and depth of the traditional forest. The purpose of integration in depth is to improve the classification capability. Purpose of integration in breadth is to reflect the difference of input data.
The data set will be divided, 10% of the dataset as the test dataset.90% of the entire dataset as the training dataset. The following situations will be compared: min-max normalization without SMOTE, min-max normalization with SMOTE, z-score normalization without SMOTE, z-score normalization with SMOTE. F1 score and accuracy as the evaluation metrics of different machine learning models.

**Statistical analyses**

All data management and statistical analyses will be performed using R V.4.0. The t-test and proportion t-test will be performed for continuous and binary outcomes, respectively. For time-to-event data log-rank tests will be used. Mood's median test will be performed for testing differences in median. The significant level used will be 5% and CI will be reported at the 95% level.
Sensitivity, specificity and accuracy are appropriate metrics to characterize the performance of the proposed training tests. To evaluate the model's learning ability in class imbalance scenarios, the area under the receiver operating characteristic curve (ROC) will be included.

## Expected Outcome/deliverables

To our knowledge, this study provides the first statewide estimates of ATTR-CM prevalence, mortality and risk factors.
1. We propose to combine multiple medical record registers to identify and study patients diagnosed with ATTR-CM.
2. India lacks in nationwide health registers, which give full healthcare coverage, and mandatory reporting of diagnosis codes from all inpatient and outpatient specialist visits. So it is inevitable to study individual Medical record departments of major tertiary care settings to identify ATTR-CM among patients
3. The study also proposes to evaluate the occurrence of red flags associated with increased risk of ATTR-CM development that can help to facilitate early diagnosis of ATTR-CM.
4. To our knowledge the proposed study may be an unique attempt compared with previous studies as we will be able to relate the prevalence of identified red flags in patients with ATTR-CM to patients with HF, and this will enable us to identify red flags that are unique to patients with ATTR-CM.
5. TTR amyloidosis has a low diagnostic rate, and the symptoms the patient displays are a treatable cause of heart failure. Only 13% of ATTR cases are detected in heart failure patients with preserved ejection fraction. Myocardial involvement is the most important driver of the prognosis of systemic amyloidosis. Medical diagnoses are generally based on patterns learned during clinical practice, based on individual experience about patients, losing the

advantage that technology offers by analyzing data according to latent knowledge and patterns present in the data recorded in electronic medical records. The starting point of personalized medicine must be an accurate diagnosis, which requires analysis beyond the data coded in the systems used in clinical practice. The introduction of machine learning algorithms may offer great potential for transforming the healthcare system. Artificial intelligence processing tools can close the gap between the large amount of data generated and the limited cognitive capacity of the human mind.

## Significance

Predictive algorithms can be used as a population screening system for a specific disease, in this case, cardiac amyloidosis, with the aim of diagnosing patients who suffer from the disease but do not have a correct diagnosis. In this way, clinical management could be optimized, improving the clinical, economic and social impact on the patient. The identification of red flags and keywords identified in the algorithm can be used in intelligent support systems in the electronic medical record, so that when the doctor or nurse write in the clinical evolutions, recommendations are made based on the appearance of any of those keywords in the text. These systems would support decision-making with a direct impact on clinical care. Machine learning can recognize numerical patterns that emerge from large volumes of health data and are not easily recognizable by humans.

Though machine learning algorithms cannot establish a cause–effect relationship, they can be synergistic to the physicians in clinical practice.

## AI in Clinical Data Analysis

**Electronic Health Records (EHRs)**

AI can extract valuable insights from electronic health records (EHRs), which contain vast amounts of patient data. Natural language processing (NLP) techniques are used to analyze unstructured text in EHRs, such as clinical notes and discharge summaries, to identify patterns and predict disease outcomes.

**Predictive Analytics**

Predictive analytics involves using AI to forecast disease progression and patient outcomes. For instance, AI models can predict the likelihood of hospital readmissions, enabling healthcare providers to implement preventive measures. Additionally, AI can identify patients at risk of developing chronic conditions like diabetes and hypertension, facilitating early intervention and management.

**Clinical Decision Support Systems (CDSS)**

AI-powered clinical decision support systems (CDSS) assist healthcare professionals in making informed decisions by providing evidence-based recommendations. These systems integrate patient data, clinical guidelines, and medical literature to offer diagnostic and treatment suggestions.

**Diagnostic Accuracy**

CDSS can improve diagnostic accuracy by cross-referencing symptoms, medical history, and test results with a vast database of medical knowledge. Studies have shown that AI-based CDSS can reduce diagnostic errors and enhance the quality of care.

**Personalized Medicine**

AI enables personalized medicine by tailoring treatment plans to individual patients based on their unique characteristics. For example, AI can recommend specific therapies based on a patient's genetic profile, lifestyle, and clinical data, optimizing treatment efficacy and minimizing side effects .

## Conclusion

The machine learning algorithm that is found to be sensitive, specific and accurate may be incorporated in regular screening of heart failure patients. Clinicians may be trained on the use of ML algorithms in the diagnosis of ATTR-CM.

# References

1). Agibetov, A., Seirer, B., Dachs, T.-M., Koschutnik, M., Dalos, D., Rettl, R., Duca, F., Schrutka, L., Agis, H., Kain, R., et al. 2020. Machine learning enables prediction of cardiac amyloidosis by routine laboratory parameters: a proof-of-concept study. Journal of Clinical Medicine, 9, 1334.

2). Agarwal, H., Ghosh, T., Arava, S., Ray, R., Seth, S. 2021. Cardiac amyloidosis in India: A clinicopathological study. Journal of Practical Cardiovascular Sciences, 7, 121–127.

3). Bishav, M., Singh, S., Tandon, R., et al. 2023. Clinical profile of patients with cardiac amyloidosis in India. Indian Heart Journal, 75(1), 73–76.

4). Castaño, A., Narotsky, D.L., Hamid, N., et al. 2017. Unveiling transthyretin cardiac amyloidosis and its

predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. European Heart Journal, 38, 2879–2887.

5). García-García, E., González-Romero, G.M., Martín-Pérez, E.M., Zapata Cornejo, E.D., Escobar-Aguilar, G., Cárdenas Bonnet, M.F. 2021. Real-world data and machine learning to predict cardiac amyloidosis. International Journal of Environmental Research and Public Health, 18(3), 908.

6). Geller, H.I., Singh, A., Alexander, K.M., et al. 2017. Association between ruptured distal biceps tendon and wild-type transthyretin cardiac amyloidosis. JAMA: The Journal of the American Medical Association, 318, 962–963.

7). Goto, S., Mahara, K., Beussink-Nelson, L., et al. 2021. Artificial intelligence-enabled fully automated detection of cardiac amyloidosis using electrocardiograms and echocardiograms. Nature Communications, 12, 2726.

8). Grogan, M., Scott, C.G., Kyle, R.A., et al. 2016. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. Journal of the American College of Cardiology, 68, 1014–1020.

9). Holmgren, G., Costa, P.M., Andersson, C., et al. 1994. Geographical distribution of TTR Met30 carriers in northern Sweden: discrepancy between carrier frequency and prevalence rate. Journal of Medical Genetics, 31, 351–354.

10). Huang, J., Zhao, S., Chen, Z., et al. 2015. Contribution of electrocardiogram in the differentiation of cardiac amyloidosis and nonobstructive hypertrophic cardiomyopathy. International Heart Journal, 56, 522–526.

11). Lane, T., Fontana, M., Martinez-Naharro, A., et al. 2019. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation, 140, 16–26.

12). Martini, N., Aimo, A., Barison, A., et al. 2020. Deep learning to diagnose cardiac amyloidosis from cardiovascular magnetic resonance. Journal of Cardiovascular Magnetic Resonance, 22(1), 84.

13). Maurer, M.S., Bokhari, S., Damy, T., et al. 2019. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circulation: Heart Failure, 12, e006075.

14). Mohan, B., Singh, S., Tandon, R., et al. 2023. Clinical profile of patients with cardiac amyloidosis in India. Indian Heart Journal, 75(1), 73–76.

15). Pinney, J.H., Whelan, C.J., Petrie, A., et al. 2013. Senile systemic amyloidosis: clinical features at presentation and outcome. Journal of the American Heart Association, 2, e000098.

16). Ruberg, F.L., Grogan, M., Hanna, M., et al. 2019. Transthyretin amyloid cardiomyopathy: JACC state-of-the-art review. Journal of the American College of Cardiology, 73, 2872–2891.

17). Rubin, J., & Maurer, M.S. 2020. Cardiac amyloidosis: overlooked, underappreciated, and treatable. Annual Review of Medicine, 71, 203–219.

18). Raut, N., Potdar, A., Sharma, S. 2019. Cardiac amyloidosis: A case series from India. The Journal of the Association of Physicians of India, 67(8), 35–38.

19). Schrutka, L., Anner, P., Agibetov, A., et al. 2022. Machine learning-derived electrocardiographic algorithm for the detection of cardiac amyloidosis. Heart, 108, 1137–1147.

20). Suhr, O.B., Lindqvist, P., Olofsson, B.-O., et al. 2006. Myocardial hypertrophy and function are related to age at onset in familial amyloidotic polyneuropathy. Amyloid, 13, 154–159.