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CONTEMPORARY REVIEW

Value of Artificial Intelligence for Enhancing Suspicion of Cardiac Amyloidosis Using Electrocardiography and Echocardiography: A Narrative Review

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ABSTRACT: Nonspecific symptoms and other diagnostic challenges lead to underdiagnosis of cardiac amyloidosis (CA). Artificial intelligence (AI) could help address these challenges, but a summary of the performance of these tools is lacking. This narrative review of published literature describes the performance of AI tools that use data from ECGs and echocardiography to improve identification of CA and challenges that hinder adoption of these tools. Thirteen studies met inclusion criteria with sample sizes ranging from 50 to 2451 patients. Four studies used ECG data, 8 used echocardiography data, and 1 used both. The CA gold standard was typically defined as a CA diagnosis in an institutional or other database but the requirements for these diagnoses were heterogenous across studies, and many did not distinguish among CA subtypes. AI model development varied considerably, and only 4 studies included external validation. The ability of models to predict CA ranged from 0.71 to 1.00, sensitivity ranged from 16% to 100%, and specificity from 75% to 100%. Only 1 study reported model performance across strata of sex, age, race, and CA type. Persistent challenges to AI adoption include usability, cost, value added, electronic health record/information technology interoperability, patient-related factors, regulation, and privacy and liability. Published studies on AI for improved identification of CA show favorable performance measures but numerous methodologic and other challenges must be addressed before these tools are more widely adopted.

Key Words: artificial intelligence ■ cardiac amyloidosis ■ echocardiography ■ electrocardiography

Amyloidosis is a rare disorder in which misfolded proteins accumulate in tissues and organs as insoluble fibrils, ultimately causing progressive organ failure.[1] At least 36 proteins cause amyloidosis, and these amyloids can affect virtually any organ, including the heart, kidneys, liver, spleen, nervous system, and digestive tract.[2] Amyloidosis syndromes are categorized according to the fibril-forming protein that is implicated in tissue damage, with the most common forms being immunoglobulin light-chain (AL) and transthyretin (ATTR) amyloidosis. In AL amyloidosis misfolded immunoglobulin light chain proteins produced from abnormal plasma cells in the bone marrow aggregate to form amyloid fibrils. ATTR amyloidosis is caused by the accumulation of misfolded transthyretin produced by the liver. ATTR amyloidosis may occur due to inherited variants (ATTR-v) or due to wild-type forms in which a pathogenic variant is not present. Among patients with AL, ATTR-v, and ATTR-wild type amyloidosis, cardiac involvement is common and is the most important determinant of prognosis.[3,4] Untreated AL amyloidosis is a medical urgency, with one retrospective study demonstrating that sudden death occurred in 29% of all AL deaths.[5] Cardiac amyloidosis

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Nonstandard Abbreviations and Acronyms

AL	light chain amyloidosis
ATTR	transthyretin amyloidosis
CA	cardiac amyloidosis

(CA) and heart failure (HF) are closely linked. A recent multicenter study involving 453 patients demonstrated that CA was the cause of HF in 20% of cases, underscoring the need for screening in older patients with HF and myocardial thickening, regardless of sex and left ventricular ejection fraction.[6] Claims data suggest that there were approximately 12 000 patients diagnosed with AL in the United States in 2015, and extrapolated autopsy data from patients with HF suggest there are at least 155 000 people with ATTR in the United States.[4,7,8]

DIAGNOSTIC DILEMMAS

CA is underdiagnosed because of the nonspecificity of amyloidosis symptoms and multiple diagnostic challenges.[9,10] The similarity between CA and other conditions that are characterized by left ventricular hypertrophy (LVH) is a persistent challenge for clinicians. Diagnostic delays average 6.1 years for ATTR-wild type and 5.7 years for ATTR-v, and misdiagnosis occurs in as many as 50% of these patients.[11] Median delay between symptom onset and diagnosis of AL amyloidosis is 2.7 years, with half of patients seeing 5 or more types of physicians before diagnosis.[12] There are significant disparities in CA diagnosis, with Black patients and those living far from large academic medical centers less likely to be diagnosed.[13] CA is therefore often diagnosed when the disease is advanced, with unfavorable impacts on patients and the health care system.[14,15] In the year after diagnosis, patients with ATTR amyloid cardiomyopathy have twice as many outpatient visits and 50% more hospitalizations than patients with HF without ATTR, and patients with CA lose an average of 13 years of life with two thirds dying of cardiovascular disease.[16–18]

ARTIFICIAL INTELLIGENCE IN CARDIAC AMYLOIDOSIS DIAGNOSIS

To improve outcomes for patients with CA, diagnostic gaps must be addressed in a manner that is convenient for patients and providers and cost effective for health systems and payers. Because patients with undiagnosed CA often present with an array of cardiovascular complaints that trigger cardiovascular diagnostic testing, optimizing use of these data to increase suspicion of CA among high-risk patients has the potential to address a stubborn diagnostic gap by identifying the need for further assessments. Improving the rate, time to and accuracy of diagnosis is a longstanding priority among CA stakeholders.[19,20] There is growing interest in how artificial intelligence (AI) tools could address persistent challenges by supplementing the clinician's toolbox for patients who present with cardiac abnormalities that are consistent with CA. These include recognizing subtle, but potentially relevant patterns in large data sets. A growing body of research is focused on how AI models can leverage data from ECG and echocardiography to improve identification of patients with CA in high-risk patient populations. This narrative review summarizes published research on these models, how well they perform, and barriers that hinder widespread adoption of these tools in routine cardiology care.

THE AMYLOIDOSIS STAKEHOLDER PARTNERSHIPS FOR IMPACT, REACH AND EQUITY INITIATIVE

Established in 2021 under the auspices of the Amyloidosis Research Consortium, ASPIRE (Amyloidosis Stakeholder Partnerships for Impact, Reach and Equity) is a collaboration among biotech and pharmaceutical companies that are committed to advancing solutions, improving diagnosis and systems of care, and addressing obstacles to health equity on behalf of patients with amyloidosis. Amyloidosis Research Consortium established ASPIRE as a strategic initiative to drive evidence-based programs that shape the rapidly evolving amyloidosis landscape for the benefit of patients. Channeling AI to improve timely, accurate, and equitable diagnosis of amyloidosis is among ASPIRE's priority areas.[21,22]

ASPIRE's Artificial Intelligence Working Group identified the need to (1) compile, review, and synthesize published research on how AI can be used to increase suspicion of CA using ECG and echocardiography data; (2) identify opportunities and current limitations for broader implementation of AI tools for patients with CA; and (3) inform best practices on broad implementation of AI tools for CA. Although less commonly used imaging methodologies like cardiac magnetic resonance and positron emission tomography have been targeted for AI development, the ASPIRE AI Working Group focused on ECG and echocardiography because almost all patients receive these tests during early cardiac assessment. The group opted for a narrative review because of the lack of clinical trials and heterogeneity of data inputs and outputs among

observational studies, as well as its interest in qualitative issues that hinder uptake of these technologies into routine practice. Meta-analysis was therefore not pursued.

A structured literature review [("machine learning"[tw] OR "artificial intelligence"[tw] OR Algorithms [mesh]) AND (amyloidosis[tw] or amyloidosis[mesh])] covering the period 2018 to 2023 was conducted to identify published reports describing use of AI/machine learning tools (subsequently referred to as AI) to raise suspicion of CA using ECG or echocardiography data. From these reports, selected study characteristics were collected, including demographic information, whether ECG or echocardiography data were used to develop the models, the number of CA cases that were used for model development, how CA cases were identified (clinic, database, etc.) and defined (sometimes called the "truth standard"), whether models were validated internally (using data from the same institution or data set used for testing) or externally (using data from a different institution), and whether controls were specified by the investigators or derived from real-world samples. We used the terminology "validation" or "test" as reported in the included papers. The authors may have employed varied definitions, and to fully understand the methodology, one must refer to the specific methods section of each paper. We also collected model performance characteristics, whether 1 or multiple sites contributed data to model development, whether the model was meant to identify CA subtypes or not, and what data extraction method was used. The latter were defined as raw, tabular, image based or segmented. Some papers used more than 1 method. Studies were categorized according to the type of prediction model used: classical machine learning or neural networks (sometimes referred to as deep learning).

ASPIRE's Artificial Intelligence Working Group also sought improved understanding of factors that affect the ability of AI tools to be incorporated into workflows of patients with CA. To inform on these issues, review articles, relevant material from advocacy organizations, and information from interviews with 3 AI tool developers that are active in the CA space were reviewed to gather relevant information.

The technical and nontechnical challenges that hinder the adoption of these AI tools were identified through both the review of article and the ASPIRE work, which involved input from a diverse group of stakeholders including amyloidosis physicians, cardiologists experienced in amyloidosis, cardiac imaging experts, AI software developers, amyloidosis drug sponsors, and the Amyloidosis Research Consortium. These challenges were compiled through in-depth expert panel discussions.

CURRENT EVIDENCE

Research Settings and Data Sources

We identified 13 published studies on AI-driven tools that leveraged ECG or echocardiography data to identify CA in research settings. Nine studies used a neural network model (sometimes referred to as deep learning) and 4 studies used a classical machine learning model (Table 1). ECG data served as the model input in 4 studies, echocardiography data in 8 studies, and both ECG and echocardiography data were used together in 1 study (Table 1).[23–35] These were based at or affiliated with academic medical centers in Austria, China, South Korea, Japan, the United Kingdom, and the United States. Most included data from patients with CA and other LVH-related conditions such as hypertrophic cardiomyopathy, end-stage renal disease, hypertension, and aortic stenosis or patients who had undergone ECG or echocardiography during routine care. Studies identified patients with CA from medical records, amyloidosis registries, outpatient clinics, and echocardiography databases. Four relied on ECG data for AI model development and training,[26–28,31] 8 used echocardiography data,[23,24,29,30,32–35] and 1 used both.[25] Nine studies used data from institution[23,26,28,30–35] and the remaining 4 used data from multiple sites.[24,25,27,29] Image-based extraction was the most common method of data extraction (used in 11 of 13 studies) and 8 studies[23,24,27,30–34] used more than 1 extraction method. All studies were retrospective.

Sample Sizes and Patient Demographics

The number of patients with CA whose data were used to develop the AI models ranged from 50 to 2451 individuals (Table 1). Among these patients, most were men over the age of 60 years, and in some studies, men accounted for more than 75% of patients with CA. In studies conducted outside of Asia, most patients were White, and across all studies, most patients were men over the age of 60 years. One study reported model performance characteristics across strata of age, sex, and race,[28] and the other 12 reported results for the study sample as a whole.

Definition of the Gold Standard

The performance of AI tools was assessed against a CA gold standard that was typically defined as the presence of an amyloidosis diagnosis in an institutional or other database. The underlying requirements for these diagnoses were heterogenous, typically defined by positive findings for determinations such as tissue biopsies from cardiac or other tissue, nuclear medicine scans, or genetic testing, as appropriate for AL or ATTR at the institution where the research was conducted

Table 1. Characteristics of Studies Describing AI Tools for Detection of Cardiac Amyloidosis

Author, year, location	No. Amyloidosis cases	Data source	Age, y Sex Race	Prediction model	Model input data	No. sites	Data allocation and validation	Real-world controls	Extraction method
Cotella, 2023 (United States)[23]	Total: 51 AL:11 ATTR+ATTR-wt:36 Undefined: 4	Confirmed CA cases with echocardiography data before and at diagnosis	Age: 80.2±10 Male: 52.9% Black:88.2% White:11.8%	ML	Echocardiography	Single	Blind comparison of commercially available AI algorithms compared with conventional measures from certified echocardiography techs. No validation	N/A	Segmented, I
Duffy, 2022 (United States)[24]	Total:1187 CA type unspecified	Physician-curated cohorts from 2 academic medical centers and data from Unity Imaging Collaborative	Full study sample: Age: 61.6±17.4 Male: 45.8% White: 42.3% Black: 4.0%	NN	Echocardiography	Multi	Training, external validation, test	No	Segmented, I
Goto, 2021 (United States)[25]	ECG cohort: 480 echocardiography cohort: 609 ATTR: 433 AL:159 Other: 17 Analyses pooled all cases	Five academic medical centers	Age: 69.2–75.6* Male: 68.7–89.2%	ML	ECG Echocardiography	Multi	Derivation, external validation, test	Yes	I
Grogan, 2021 (United States)[26†]	2541 AL and ATTR cases	Institutional amyloid database	Age>60: 68.1%–73.0% Male: 68.3%–73.6% White: 91.7%–93.5%	NN	ECG	Single	Training, internal validation, test	No	Raw
Haimovich, 2023 (United States)[27†]	Total: 304 CA type unspecified	Patients with ECGs performed during routine medical care at academic medical center	Age: 62.7–63.2±15.0–15.3 Male: 55.6%–60.2% White: 80.9%–87.2% Black: 3.3%–7.5%	NN	ECG	Multi	Derivation and external validation samples	Yes	Raw, Tabular, I
Harmon, 2023 (United States)[28]	Total: 440 AL: 219 ATTR-wt: 201 ATTR-variants: 20	Institutional amyloid database	Total CA cases: Age: 70.4±10.3 Male: 75.0% White: 89.1% Black: 5.9% Other: 3.2% Hispanic: 1.8%	NN	ECG	Single	Postdevelopment performance and internal validation against 15:1 age/sex matched controls with echocardiography+ECG and ECG	No	Raw
Hwang, 2022 (South Korea)[29]	AL CA: 81	Subjects identified from echocardiography database of 2 university hospitals	Age: Median 68±11.2 Male: 53.1%	NN	Echocardiography	Multi	Training, internal validation, and test data sets	No	I
Li, 2023 (United States)[30]	244 CA cases CA type unspecified	Patients with established diagnoses identified from provider records	Age: 69.3±11.2 Male: 80.3% White: 87.7% Black: 4.9%	NN	Echocardiography	Single	Training, internal validation, and test data sets	No	Segmented, I
Schrutka, 2022 (Austria)[31]	50 AL and ATTR CA cases	Amyloidosis outpatient clinic	Group 1 (n=20) Age: 76 (70–79) Male: 80%	ML	ECG	Single	Training and 2 external validation methods	No	Segmented, I
Wu, 2023 (China)[32]	74 AL CA cases	Patients referred from university teaching hospital	Age: 60.9±9.7 Male: 60.8%	ML	Echocardiography	Single	Training and internal validation data sets	No	Segmented, I
Yu, 2021 (China)[33]	58 CA cases; CA type unspecified	Echocardiography database of university hospital	Age: 61.0±8.4 Male: 77.5%	NN	Echocardiography	Single	Training, internal validation, and test sets	No	Segmented, I
Zhang, 2018 (United States)[34*]	81 ATTR CA cases	Echocardiography database of university hospital and probands from familial cardiomyopathy clinic	Age: 65±11 Male: 78.0%	NN	Echocardiography	Single	Training and test sets; internal validation	?????	Raw, Segmented, I
Zhang, 2023 (China)[35]	50 CA cases; CA type unspecified	Cases identified from academic medical center	Age: 58.8±6.7 Male: 74.0%	NN	Echocardiography	Single	Training, test sets; no validation reported	No	I

AI indicates artificial intelligence; AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; CA, cardiac amyloidosis; I, image based; ML, machine learning; NN, neural network;and wt, wild type.
*Data reported as ranges of institution-specific means and percents for the echocardiography cohort.
†Data reported as ranges of training, test, and validation data sets.

Table 2. Cardiac Amyloidosis Case Definitions in 12 Studies Assessing the Value of AI for Enhancing Suspicion of Cardiac Amyloidosis Using Electrocardiography and Echocardiography

Author, year, location	No. CA type(s) included in study	CA case definition(s)
Cotella, 2023 (United States)[23]	AL, ATTR+ATTR-wt, undefined	Confirmed CA according to cited guideline[45]
Duffy, 2022 (United States)[24]	CA type unspecified	No case definition reported
Goto, 2021 (United States)[25]	ATTR, AL, other	Amyloidosis patients were first identified based on diagnostic codes or echocardiography reports and then manually confirmed by chart review. Patients with ATTR CA were required to have confirmation of amyloid disease by tissue biopsy, nuclear medicine scan, cardiac magnetic resonance imaging, or genetic testing (transthyretin variant). For AL amyloid, biopsy confirmation was required as well as some evidence of cardiac involvement, whether by cardiac magnetic resonance or echocardiography. The method and date of diagnosis were also identified by chart review. A positive result for myocardial biopsy, cardiac MRI or pyrophosphate scan was considered diagnostic, and the date of whichever study came first defined as the diagnosis date.
Grogan, 2021 (United States)[26]	AL, ATTR	AL: cardiac or noncardiac biopsy with positive staining; ATTR: tissue diagnosis or abnormality on scintigraphy
Haimovich, 2023 (United States)[27]	CA type unspecified	Potential patients identified by screening pathology (myocardial biopsy, fat pad biopsy, and cardiac explants), cardiac MRI, and 99mtechnetium pyrophosphate scintigraphy reports for the terms “Congo red” and “amyloid.” A single study author (J.S.H.) unblinded to the screening results then manually reviewed each report. A patient was determined to carry a diagnosis of cardiac amyloidosis based on: - Myocardial biopsy or cardiac explant positive for amyloid - Fat pad biopsy positive for amyloid and an average interventricular septal and posterior wall thickness >12 cm on echocardiogram - Cardiac MRI diagnostic or strongly suggestive of cardiac amyloidosis (per radiology report) - 99mtechnetium pyrophosphate scintigraphy diagnostic of cardiac amyloidosis
Harmon, 2023 (United States)[28]	AL, ATTR-wt, ATTR-variant	Diagnosis confirmation with cardiac or noncardiac biopsy for AL and biopsy or positive technetium Tc 99m pyrophosphate scintigraphy for ATTR
Hwang, 2022 (South Korea)[29]	AL	AL CA on echocardiography was suggested when the left ventricular wall thickness max was >12 mm.[21] Other typical features on echocardiography, such as (1) symmetrical LV thickening; (2) right ventricular free wall thickening; (3) small pericardial effusion; (4) thickening of the atrioventricular valves and interatrial septum; (5) abnormal myocardial texture characterized as a speckled appearance; (6) voltage mass discrepancy; (7) base-to-apex strain gradient or relative apical sparing of longitudinal strain; and (8) typical findings on CMR (patchy, subendocardial circumferential, or diffuse fuzzy late gadolinium enhancement of the LV), were used for clinical suspicion and detection of AL CA. Definite evidence of amyloid involvement on EMB was required.
Li, 2023 (United States)[30]	CA type unspecified	Diagnosis was confirmed by technetium Tc99m pyrophosphate scanning or endomyocardial biopsy.
Schrutka, 2022 (Austria)[31]	AL, ATTR	Amyloidosis outpatient clinic; significant myocardial tracer uptake (Perugini grade ≥ 2) on bone scintigraphy and absence of paraprotein detected by serum immunofixation, urine immunofixation, and serum assay for free light chains. After 2016, the collection of endomyocardial biopsies for the diagnosis of ATTR became necessary only when noninvasive test results were ambiguous or unclear. If cardiac ATTR was diagnosed, patients were offered sequencing of the TTR gene. Cardiac light-chain amyloidosis was diagnosed, if myocardial or extramyocardial biopsy samples stained positive for Congo red, showed apple green birefringence under polarized light and reacted with light-chain antibodies during immunohistochemical staining.
Wu, 2023 (China)[32]	AL	Endomyocardial biopsy or noncardiac biopsy+cardiac MRI
Yu, 2021 (China)[33]	CA type unspecified	Confirmed CA by tissue biopsy, or confirmed by late gadolinium enhancement CMR imaging
Zhang, 2018 (United States)[34]	ATTR	Echocardiography evidence of LVH or echocardiography suspicion of CA and confirmation of amyloid disease by biopsy, nuclear medicine scan, CMRI, or genetic testing (transthyretin variant)
Zhang, 2023 (China)[35]	CA type unspecified	Myocardial intimal biopsy showing amyloid deposition after Congo red staining

AI indicates artificial intelligence; AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; MRI, magnetic resonance imaging; and wt, wild type.

(Table 2). In some studies, AL and ATTR cases were distinguished from one another[23,25,28,31]; in others, these distinctions were not specified,[24,26,27,30,33,35] and in still others, only data on AL cases were reported.[29,32]

AI Models to Identify CA in Research Settings

The reports in this review described models with a variety of input data types, notably ECG waveforms and echocardiogram videos. Structured data were often described as the input for random forest, support vector machine, and logistic regression models, whereas ECG and echocardiography data were often the input for convolutional neural networks.

Statistical Models and Performance Metrics

After training, model performance was assessed on validation or test data sets to quantify their ability to distinguish patients with CA from other patients, most often those with other LVH-related conditions. Data were often split randomly for training and internal validation,[26,28–30,32–34] with only a few models validated on external data (Table 1).[24,25,27,31] Two studies did not report validation.[23,35] Standard measures were used to quantify model performance, including sensitivity, specificity, positive and negative predictive values (PPV, NPV), and area under the receiver operator curve. In some studies, the models' ability to identify patients with CA was compared with experienced cardiologists or echocardiography technicians (Table 3).[23–25,29,31,33]

Assessment of model performance relied on data from patients with a wide array of disease states. Although all studies reported various aspects of model performance, only 2 reported findings for different CA types.[25,28] (Table 3). Some studies assessed model performance using a single control group with, for example, patients with cardiomyopathy or HF with preserved ejection fraction, whereas others reported data from multiple control groups. The latter studies included data from patients with hypertensive heart disease, aortic stenosis, "other LVH," normal patients, and patients without CA who had suitable ECG or echocardiography data (data not shown).

Performance of AI Tools for Identifying Cardiac Amyloidosis

Among the 12 studies that reported area under the receiver operator curve for predicting CA, this measure ranged from 0.71 to 1.00. Of the 9 studies that reported sensitivity and the 8 that reported specificity for correctly identifying and ruling out CA, these measures ranged from 16% to 100% and 75% to 100%, respectively. The 4 studies that reported predictive values showed PPVs ranging from 30.9% to 86% and NPVs ranging from 84% to 99.3%. Although performance measures for most studies reflected the models' ability to predict CA for entire study samples, 1 focused on postdevelopment validation of an existing model on patients with CA stratified by CA type, sex, age, and race.[28] That study showed similar algorithm performance between AL and ATTR-w, between men and women, and among Blacks, Whites, and people of other races or ethnicities. However, it showed lower or uncertain performance in patients with ATTR-v and Hispanic patients with CA. In analyses stratified by both age and sex, model performance was less favorable or more uncertain among men aged <30 years, 30 to 39 years, and 40 to 49 years.

Grogan et al. (2021)[26] demonstrated that their AI model successfully predicted the presence of CA more than 6 months before clinical diagnosis in 59% of cases. Cotella et al. (2021)[23] demonstrated that both manual and automated AI tools are highly accurate and allow sensitive and specific detection of abnormalities, which are crucial for CA early diagnosis. There were no significant differences between manually detected and AI detected abnormalities. Additionally, there was no significant difference in the time to detect abnormalities between the 2 methods when comparing pre-CA measurements to the time of diagnosis.

Barriers to Implementation: Data, Algorithms, and Study Design

Our review identified research design barriers that may hinder widespread adoption into clinical practice of AI-driven tools to improve identification of CA (Table 4).[25,36,37] Among the most important observations was that the definition of the CA gold standard against which models were trained varied across studies. The generally accepted gold standard defined by Congo red staining on cardiac biopsy was not a required element in all studies (Table 2). Additional design challenges involved model specifications that were unique to each study, thereby hindering comparisons across studies and institutions; use of highly curated data rather than more generalizable data sources; lack of real-world controls in many studies; uncertainty about whether algorithms can handle real-world input; the lack of distinction between ATTR and AL in model performance; small numbers of ATTR patients; "overmatching" patients in case–control designs by applying strict eligibility criteria to select controls, which enhances performance measures but does not reflect real-world practice; and the absence of data on early-stage CA in most studies. A limitation that warrants emphasis is the relatively small sample sizes that were used to train the models. In several studies, the number of CA cases used for training was limited to approximately 50 patients. Other important considerations

Table 3. Performance Characteristics of AI-Enhanced Electrocardiogram and AI-Enhanced Echocardiography for Early Detection of Cardiac Amyloidosis

Author, year	AUC for CA	Sensitivity, specificity, positive predictive value, negative predictive value	Model performance for identifying CA relative to experienced clinicians
Cotella, 2023 (United States)[23]		Abnormal LVEF pre-CA diagnosis: Sensitivity: 83% Specificity: 86% Abnormal LVEF at CA diagnosis: Sensitivity: 70% Specificity: 79% Abnormal GLS pre-CA diagnosis: Sensitivity: 82% Specificity: 86% Abnormal GLS at CA diagnosis: Sensitivity: 100% Specificity: 67%	No difference between AI and manual measures
Duffy, 2022 (United States)[24]	0.83: hold-out test set 0.79: external test set	NR	Deep learning algorithm compared with 2 level 3 echocardiography-certified cardiologists
Goto (United States), 2021[25]	Overall ECG: 0.83–0.91 ATTR: 0.87–0.97 AL: 0.78–0.92 Overall echocardiography: 0.80–1.00 ATTR:0.94–1.0 AL: 0.84–0.95		Model outperformed cardiologists/expert echocardiography readers
Grogan, 2021 (United States)[26]	0.91	Sensitivity: 84% Specificity: 85% PPV: 86%* NPV: 84%*	396 patients with ECG 5 y to 6 mos before diagnosis; 59% identified by AI model.
Haimovich, 2023 (United States)[27†]	0.95	Sensitivity: 54.8% Specificity: 99.0% PPV: 58.1% NPV: 98.9%	
Harmon, 2023 (United States)[28]	Overall CA: 0.84 AL: 0.85 ATTR-wild type: 0.84 ATTR-variant: 0.76	Overall sensitivity: 64.3% Overall specificity: 90.4% Overall PPV: 30.9% Overall NPV: 97.4%	
Hwang, 2022 (South Korea)[29]	0.95	Sensitivity: 92.9% Specificity: 95.7% PPV: 68.4% NPV: 99.3%	echocardiography expert: Sensitivity: 50.0% Specificity: 96.1% PPV: 56.0% NPV: 95.1%
Li, 2023 (United States)[30]	0.90	Sensitivity: 75%	
Schrutka, 2022 (Austria)[31]	0.97	Sensitivity: 89% Specificity: 96%	Model used to train cardiologists whose AUC was 0.69 before model training and 0.97 after training. Sensitivity and specificity of cardiologists before training: 32% and 80%, respectively
Wu, 2023[32]	0.95–0.98	Sensitivity: 88%–96% Specificity: 95%–100%	PPV: 0.93–1.0 NPV: 0.91–0.94 Three machine learning models: support vector machine, random forest, gradient boosting; results did not differ from traditional logistic regression
Yu, 2021 (China)[33]	0.93–0.94	Sensitivity: 88%–100% Specificity: 75%–93%	Three models: raw images, auto-segmented images, manually segmented images; models outperformed experienced echocardiographers on LVH cause: 75.7% vs 55.2%
Zhang, 2018 (United States)[34]	0.87		
Zhang, 2023 (China)[35]	CA vs non-CA: 0.71–0.81 for the 4 models	Overall population, CA vs non-CA: Sensitivity: 16%–25%‡ Specificity: 94%–100%	Four models: logistic regression, random forest, support vector machine, gradient decision-making lifting tree

*In a prevalence setting defined by 1:1 matching.

†Sensitivity, PPV, NPV results based on a set specificity of 99%.

‡Subgroup analyses for CA vs other groups showed better sensitivity.

AI indicates artificial intelligence; AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; AUC, area under the receiver operator curve; CA, cardiac amyloidosis; GLS, global longitudinal strain; LVEF, left ventricular ejection fraction; NPV, negative predictive value; NR, not reported; and PPV, positive predictive value.

Table 4. Technical Challenges and Limitations That May Hinder Adoption of AI Tools for Identifying and Diagnosing Cardiac Amyloidosis*

Challenge or limitation	Solutions
Training data sets do not reflect real-world experience	Ensure that data used to train and test models reflects information that would be used in routine clinical settings
Models can be over fit	External validation and prospective clinical trials.
Technical specs for identifying abnormalities to feed models often highly specific within study	Develop models with specifications that reflect practice guidelines or other widely-accepted definitions
Algorithms need to handle real-world input	Ensure models can handle varying quality, missing data, different approaches to data storage and export
Training data should not be used for testing models	Use independent samples for training and testing
Models need to be robust to intracardiac leads, wall thickness, and other variables that affect performance	Appropriate selection of control patients during model training rather than simply age/sex matched controls.
Models need to distinguish CA from other conditions with cardiac hypertrophy	Use a wide array of control data from diverse patient populations with left ventricular hypertrophy
Most studies do not have validation data sets outside their institutions	Develop collaborations that facilitate access to validation and testing data from institutions other than the one supplying training data
Most studies do not address distinction between transthyretin amyloidosis and light chain amyloidosis; CA can have many patterns that need to be detected	Train models using heterogenous samples of patients with CA
Some studies based on 2-dimensional echocardiography; future work could use more ultrasonic sections [Wu]	Ensure training data uses a variety of ultrasound systems.
Studies not conducted using the gold standard of cardiac biopsy. Truth standards differs across studies, and standard changed within some studies	Move toward agreement on a single gold standard or conduct sensitivity analyses to understand implications for model performance of different gold standards
Some performance measures depend on prevalence of CA in test populations	Promote understanding of the impact of prevalence of predictive values and the importance of applying AI models in populations that are enriched for potential amyloidosis cases
Some studies based on small samples in single centers.	Promote collaborations that yield larger numbers of amyloidosis patients that can be used for model development and refinement
Thresholds on reporting of performance measures differ	Move toward broad agreement on thresholds for reporting various performance measures
Definition of control patients differed across studies	Mostly patients with HF, but heterogenous across studies: HF with preserved EF or HF with reduced EF, hypertrophic cardiomyopathy, valvular heart disease, cardiac sarcoidosis, and hypertrophic cardiomyopathy with or without left ventricular outflow tract obstruction, as well as other rare HF conditions.
Studies that "overmatch" patients enhance performance measures but do not reflect real-world inputs	Discourage use of case–control designs in favor of optimizing consecutive patient panels or other selection strategies that avoid overmatching.
Studies use different approaches to identifying the final model	Move toward agreement on model specifications, thresholds, and reporting protocols.
Performance measures based on different comparisons and patient populations	Promote uniformity in reporting and encourage inclusion of heterogenous comparison groups
Most data do not inform on model utility in early stage CA	Encourage retrospective use of serial ECG and echocardiography data when available and apply models to historical data
Studies that compared models and experts did not mimic real-world circumstances	Research that aims to show superiority of AI-driven models over expert cardiologists, should endeavor to mimic real-world settings for cardiologists with regard to patient histories, clinical data, etc.

*Data derived from Nicolosi et al., 2023,[36] Goto et al., 2021,[25] Wu et al., 2023,[32] Agibetov et al., 2020.[37] AI indicates artificial intelligence; CA, cardiac amyloidosis; EF, ejection fraction; and HF, heart failure.

in research design involved the relative homogeneity of input data by sex and age that were used for model development. Similarly, in most studies, models were trained and validated on data sets from the same institution, and performance was often assessed in relation to a single comparison group of patients with LVH-related conditions.

Barriers to Widespread Adoption and Implementation

The results reveal key challenges to adopting AI tools, based on in-depth expert panel discussions. An array of adoption- and implementation-related issues hinder AI uptake in cardiology practice settings (Table 5). These challenges include clinicians' limited understanding of AI, lack of trust in AI in clinical practice, concerns about usability at the point of care, justifying the cost of AI, determining its value in specific institutional settings, how well these tools integrate into existing electronic health records systems, and the applicability in real-world settings of research that was tailored to a single or a few institutions.[36,38,39]

Table 5. Nontechnical Barriers That May Hinder Adoption and Implementation of AI in Cardiovascular Medicine*

Barrier	Detail	Potential Solutions
Knowledge	Limited understanding of which EHR-based and digital tools in clinical practices/systems use AI algorithms	Improve clinician education about current and potential AI use in patient care
Trust	Lack of trust in human–AI collaboration. Concerns about use of AI to dictate clinical decisions, validity of data, and data privacy. Lack of trust in tools developed by third-party vendors, who IT administrators perceive fail to deliver on promises of prescriptive AI	Work with professional societies to create and disseminate targeted education to mitigate clinician concerns about AI dictating decision-making
Usability	Concern about usability and integration of cardiovascular-focused AI tools into clinical workflows.	Promote research to drive and facilitate integration of AI tools into existing workflows
Cost	Hospitals and large clinical practices have constrained AI budgets regardless of potential benefits. Stakeholders (cardiologists and IT administrators) must justify cost to procurement and value assessment committees.	Promote research that informs on various aspects of return on investment of AI tools
Value added	Value of AI may be greater for smaller institutions with fewer resources	Ensure that return on investment research is tailored to the concerns of large and small hospitals and outpatient practices
EHR/IT Interoperability	Integration of AI tools into existing IT (Ex: EPID, Cerner, Allscripts) EHRs can be challenging and tools from different vendors are often incompatible with each other.	Identify and facilitate access to collaborative pathways between AI developers and EHR vendors
Research conducted in isolation	Studies with results that are tailored to a single institution or workflow may have limited potential for widespread application	Promote collaboration across institutions to optimize generalizability of clinical data and applicability of results
Patient-related factors	AI research has not addressed patient preferences, fears, or cultural factors that may affect acceptance of these technologies	Promote research that addresses patient perceptions about AI in cardiovascular care
Regulation	Some AI products may be regulated as medical devices; there is a trend toward increasing Food and Drug Administration oversight	Improved evidence is needed for reimbursement and approval for marketing
Privacy and liability	Ambiguity concerning privacy and legal responsibilities	On premise AI models would limit data transfer outside of health care system
Product design		Developers need to identify who needs solutions
Workflow	Products that are not tailored to organization-specific workflow and culture present challenges for adoption	Products need to support the right workflow sequencing for the right provider
Strategic partnerships	Niche products that are not viewed as foundational to organizational operations are unlikely to be adopted	Developers must be able to communicate that AI tools are integrated into, and run throughout the hospital or system in which they are implemented

*Data derived from Schepart et al., 2023,[38] Koulaouzidis et al., 2022,[39] Nicolosi et al., 2023.[36] AI indicates artificial intelligence; EHR, electronic health record; and IT, information technology.

In addition to factors at the provider and institutional levels, patient-level factors can also affect AI uptake in cardiology. These include limited consideration of patients' concerns and preferences among AI developers and researchers and the social environment in which these tools are deployed. Privacy and legal considerations are also important, especially those related to liability if AI tools do not meet patients' or clinicians' expectations. Finally, because some AI products may be regulated as medical devices, regulatory requirements may impose challenges for product developers and added cost for customers, thereby affect incentives for both development and adoption of these tools.

METHODOLOGICAL CHALLENGES AND FUTURE DIRECTIONS

This narrative review of AI-driven tools that use ECG or echocardiography data to improve identification of CA demonstrates that these tools have excellent sensitivity and specificity for distinguishing CA from other LVH-related cardiac conditions. Some studies showed that models perform similarly to cardiologists in identifying CA, whereas others showed they perform better and could identify CA years before typical diagnosis. Against the backdrop of persistent challenges that characterize CA diagnosis, these observations suggest substantial potential for AI to optimize existing ECG and

echocardiography data to benefit patients with CA and the clinicians who care for them. If they are developed beyond research settings and widely adopted in routine practice, AI tools could help raise suspicion of CA, help clinicians identify patients who could be triaged for additional assessments, and ultimately increase CA diagnosis early in the disease course. Despite this promise, our review also highlighted the lack of prospective studies and only 2 ongoing clinical trials.[40–42]

We also identified an array of technical and other challenges that hinder widespread adoption of AI as a tool to raise suspicion of CA. Among these challenges are factors related to data, study design, training methods, and validation approaches as well as nontechnical barriers such as the need for more real-world evidence including how AI would be incorporated into routine workflows, how these products would be incorporated into institutional electronic health records, how patient preferences should be assessed and incorporated into these technologies, and how to make a compelling value proposition to hospitals and large clinical practices. Our review showed that there is much work to be done before the potential benefits of AI can be realized for patients with CA and their care teams.

Despite these challenges, a growing body of research on AI tools for CA suggests the potential to address the persistent diagnostic lags and downstream consequences that characterize this condition.[11,12] Longstanding, undiagnosed CA cases result in greatly reduced life expectancy at the point of diagnosis as well as increased costs associated with treating patients with advanced disease.[16,17] The potential benefits of AI to address these challenges is reflected in their ability to discriminate between CA and other LVH-related conditions and to identify CA cases as much as 5 years before a typical diagnosis.[26]

There is a paucity of CA data relative to other cardiovascular conditions, and this has presented meaningful challenges to developing reliable, scalable, and generalizable AI-based models for use in CA assessment.[43] However, methods such as transfer learning and especially federated learning—an approach that capitalizes on sharing of data sets from multiple institutions without sharing raw data—has been effective in developing highly generalizable, AI-driven tools to improve detection of hypertrophic cardiomyopathy, and these approaches may offer a pathway to develop similar tools for CA.[44] In addition to the convenience of using readily available ECG and echocardiography input data, using AI to improve CA screening fits into the existing list of cardiac-level red flags that should increase suspicion of CA without the need for advanced imaging modalities.[31,45] However, there is a dearth of implementation studies testing the effect of an AI-based tool on workflows. For example, there is no work on the potential impacts of implementing tests with low positive predictive value that could potentially lead to orders for many unnecessary confirmatory tests.

The use of AI to optimize ECG and echocardiography data in cardiac care is not new. The US Food and Drug Administration has granted de novo approval and breakthrough status for AI-driven technologies for both HF with preserved ejection fraction and hypertrophic cardiomyopathy, and these technologies are currently used to triage patients for diagnosis and further evaluation.[46,47] The drive to incorporate AI into patient care is unambiguous: As of January, 2023, more than 500 market-cleared AI algorithms were available in the United States, with the vast majority linked to medical imaging.[48] However, the Food and Drug Administration recognizes that the adaptive and iterative nature of AI-based technologies does not fit its traditional paradigm of medical device regulation.[49] Responding to the novel impacts of AI on regulatory oversight, stakeholder input, and the need to encourage ongoing innovation while protecting patient safety, the Food and Drug Administration identified an action plan to address AI/machine learning.[50] These approaches apply to the technologies that were reviewed in this report, requiring developers and other stakeholders to monitor the evolving regulatory environment, including evolving Food and Drug Administration requirements for postapproval updates of existing algorithms.

The promise of AI for increasing clinicians' suspicion of CA and ultimately improving diagnosis through additional testing must be tempered by the need to address key barriers that hinder implementation of these technologies. Among these is variability in the gold standard on which model performance characteristics are based. The gold standard for diagnosing CA is Congo red staining of cardiac biopsy tissue. However, in practice, patients are commonly diagnosed with other measures that are becoming more common, such as bone scintigraphy for ATTR. As researchers and developers continue to move this field forward, it will be important to consider the implications of developing high-performing models that are based on cardiac biopsy input data if these data are not universally available.

Another methodological consideration is how sample selection methods affect model performance characteristics. Studies reporting PPV and NPV must be interpreted in the context of the prevalence of CA in the samples that drive the statistics because prevalence impacts both PPV and NPV. As prevalence increases, PPV increases and NPV decreases, and as prevalence decreases PPV decreases and NPV increases. In highly curated study samples or those that were enriched for CA cases and used matched controls, the prevalence of CA is higher than it would be in routine practice, and in settings with very few CA cases as a share of all study subjects, prevalence is low. Both

scenarios impact PPV and NPV and should be considered against the prevailing makeup of clinical settings in which AI tools for CA would be deployed.

LIMITATIONS OF THE CURRENT EVIDENCE

A limitation of most research reviewed in this report was the absence of information on model performance across categories of potentially confounding variables like age, race, sex, and CA type. One study that examined these issues by validating a previously developed model found that the tool performed well across most demographic categories with relatively large CA sample sizes[28]; model performance was less favorable as case numbers diminished, including among patients with ATTR-v. These findings demonstrate the robustness of AI models in the setting of adequate CA sample sizes and emphasize the need for more CA training data from specific groups like younger men, people of Hispanic origin, and those with ATTR-v.

There was a general lack of standardization across studies, resulting in nongeneralizability as a limitation. The major differences between studies were so pronounced that subtle distinctions have not been captured.

A limitation of our review is that we relied on the validation and test criteria reported by the authors of the referenced studies. This introduces variability, as each study may have used different definitions and criteria for validation and testing. Due to the retrospective nature of our project, we had to accept these varying definitions as provided by the authors of the included publications. To improve the reliability and comparability of future research, there needs to be more consistency across the board in these definitions. Additionally, future reviews using a more rigorous Delphi process would further help evaluate the performance of AI tools and the challenges that hinder their adoption through structured process that involves multiple rounds of surveys to gather opinions from experts, with the goal of achieving a consensus on a specific topic.

CONCLUSIONS

This narrative review demonstrated that an array of AI models had excellent performance characteristics for identifying CA. However, the persistent lack of prospective studies, methodologic heterogeneity in existing research, as well as a dearth of data on real-world implementation pose meaningful challenges that hinder uptake of these technologies into practice. These research gaps and implementation barriers need to be addressed before patients with CA and their care teams can realize the full potential of these technologies.

ARTICLE INFORMATION

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