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Artificial intelligence-driven electrocardiography: Innovations in hypertrophic cardiomyopathy management

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A B S T R A C T

Hypertrophic Cardiomyopathy (HCM) presents a complex diagnostic and prognostic challenge due to its heterogeneous phenotype and clinical course. Artificial Intelligence (AI) and Machine Learning (ML) techniques hold promise in transforming the role of Electrocardiography (ECG) in HCM diagnosis, prognosis, and management.

AI, including Deep Learning (DL), enables computers to learn patterns from data, allowing for the development of models capable of analyzing ECG signals. DL models, such as convolutional neural networks, have shown promise in accurately identifying HCM-related abnormalities in ECGs, surpassing traditional diagnostic methods.

In diagnosing HCM, ML models have demonstrated high accuracy in distinguishing between HCM and other cardiac conditions, even in cases with normal ECG findings. Additionally, AI models have enhanced risk assessment by predicting arrhythmic events leading to sudden cardiac death and identifying patients at risk for atrial fibrillation and heart failure. These models incorporate clinical and imaging data, offering a comprehensive evaluation of patient risk profiles. Challenges remain, including the need for larger and more diverse datasets to improve model generalizability and address imbalances inherent in rare event prediction. Nevertheless, AI-driven approaches have the potential to revolutionize HCM management by providing timely and accurate diagnoses, prognoses, and personalized treatment strategies based on individual patient risk profiles.

This review explores the current landscape of AI applications in ECG analysis for HCM, focusing on advancements in AI methodologies and their specific implementation in HCM care.

Introduction

Artificial Intelligence (AI) holds immense potential in medical applications, particularly in diagnosing complex diseases like hypertrophic cardiomyopathy (HCM), the most common heritable cardiovascular disorder. Characterized by left ventricular hypertrophy (LVH) and a high risk of arrhythmia, sudden cardiac death, and stroke, HCM presents a heterogeneous phenotype with increased mortality compared to the general population [1,2]. The electrocardiogram (ECG) is crucial in HCM management but insufficient alone for diagnosis or prognosis [1,2]. AI can revolutionize ECG's role in diagnosing, differentiating, assessing arrhythmic risk, and managing HCM. This review explores AI's application in HCM, focusing on its use in ECG for diagnosis, prognosis, and treatment, while addressing its limitations.

Artificial intelligence, machine learning, and deep learning and electrocardiography

Artificial Intelligence (AI) is a technology-creating hardware and software system capable of mimicking human traits, such as image recognition, and decision-making [3]. Machine Learning (ML), a subset of AI, employs algorithms to learn from data, improving performance over time. Deep Learning (DL), a branch of ML, uses artificial neural networks and excels in processing extensive datasets to identify complex patterns [3] (Fig. 1).

With ML systems, an algorithm is learned from the data, allowing the system to build a model linking input and output. In ML projects, datasets are typically divided into training, validation, and testing subsets to refine models. ML approaches include supervised, unsupervised, and reinforcement learning. Supervised learning uses labeled data to predict outcomes with algorithms such as linear regression and decision trees, while unsupervised learning uncovers hidden patterns in unlabeled data through clustering techniques [4,5] (Fig. 1). Reinforcement learning, less common in medicine, adjusts actions based on feedback to maximize rewards [3].

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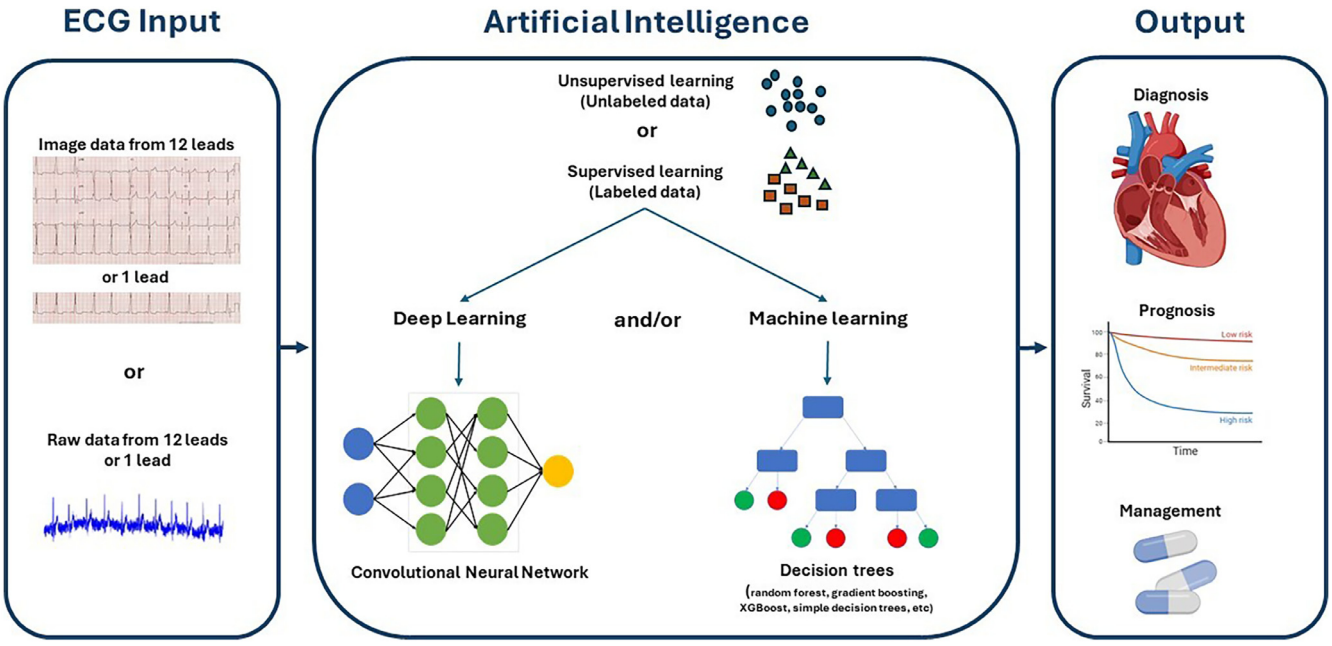

Fig. 1. Left panel: The ECG input could be in the form of a 12-lead ECG or 1-lead ECG as image data or raw data. Central panel: AI analyzes ECG input using DL or ML methods, employing supervised learning with labeled data or unsupervised learning with unlabeled data. Right panel: The output of AI-ECG models could be the diagnosis, prognosis, or management of diseases.

DL models are structured similarly to the human brain, using layers of nodes or neurons with the first layer receiving input data and the subsequent hidden layers acting as regression functions, processing the data until the final output layer is generated, allowing the identification of patterns within large datasets. This is especially effective in analyzing visual data, like ECGs (Fig. 2)[3,6]. Convolutional Neural Networks (CNNs), a DL technique, excel in ECG analysis by extracting complex patterns, aiding in diagnosis and management [3,6,7].

ECG data are converted into matrices for DL analysis, with the first dimension representing spatial data, while the second dimension represents temporal data [3,8,9]. In most cases of applying DL to ECG, raw input data directly acquired from digital ECG storage is used. The raw data are represented as a vector of voltages recorded in a time series for each lead, allowing for signal analysis with minimal preprocessing. Challenges arise from digitizing older, printed ECG records, prompting research into using ECG images for DL applications [10]. Sangha et al. created a convolutional neural network to identify rhythm and conduction disorders using 2,228,236 12-lead ECG images. The model performed well on a separate test set and outperformed signal-based models [11]. Single-lead ECG models, endorsed for detecting conditions like atrial fibrillation (AF), enhance continuous patient monitoring via wearable devices [12,13]. AI-ECG models increasingly use larger, privately curated datasets to enhance accuracy and performance metrics like the area under the receiver operating characteristic curve (AUC-ROC)[6].

AI and ECG in HCM

For the present analysis, we included a total of 19 original research papers exploring AI's applications in ECG for HCM (Table 1). The process started with a PubMed query for the terms: (electrocardiogram OR ecg OR ekg OR electrocardiograph) AND (deep learning) OR (machine learning OR artificial intelligence) AND (hypertrophic cardiomyopathy).

Diagnosis of HCM

According to the most recent European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines, a 12-lead ECG is recommended for the initial evaluation and periodic follow-up (every 1 to 2 years) of patients with HCM [1,2]. ECG abnormalities, such as prominent Q waves, ST-T segment abnormalities, giant negative T waves, QTc prolongation, or signs of LVH, are common but not specific to HCM and can be seen in other conditions as well [1,2]. AI has the potential to revolutionize ECG as a diagnostic tool, aiding in differential diagnosis and serving as a powerful screening tool, especially for young athletes.

Detection and screening tool

In 1998, Ouyang et al. conducted one of the earliest AI-ECG studies on HCM, using 40 measurements from 79 ECGs to train and test supervised ML for diagnosing the hypertrophic portions of HCM [14]. However, with the current widespread use of echocardiograms, this approach is less relevant today. Recently, AI applications in ECG have surged, particularly using DL methods like convolutional neural networks (CNNs).

Tison et al. developed an AI model combining ML and DL to analyze 36,186 raw ECG recordings, aiming to detect conditions such as HCM, pulmonary arterial hypertension, cardiac amyloidosis, and mitral valve prolapse, and to estimate cardiac structure parameters like LVH and left atrial volume. Their model used a multilayered neural network with a hidden Markov model for ECG segmentation, followed by a gradient-boosted machine for disease detection. The model demonstrated strong performance, with an AUC-ROC of 0.91 for HCM detection [9] (Fig. 3).

In 2020, the Mayo Clinic developed another AI-ECG model for HCM detection. Using raw ECG data from 3060 HCM patients and 63,941 controls, they trained a CNN model, achieving an AUC of 0.95 [15]. This model was evaluated as a screening tool in a pediatric population, achieving an AUC of 0.98 with a sensitivity of 92 % and specificity of 95 % [16]. However, the same model showed a high false-positive rate in subjects over 40 years old, with the ac-

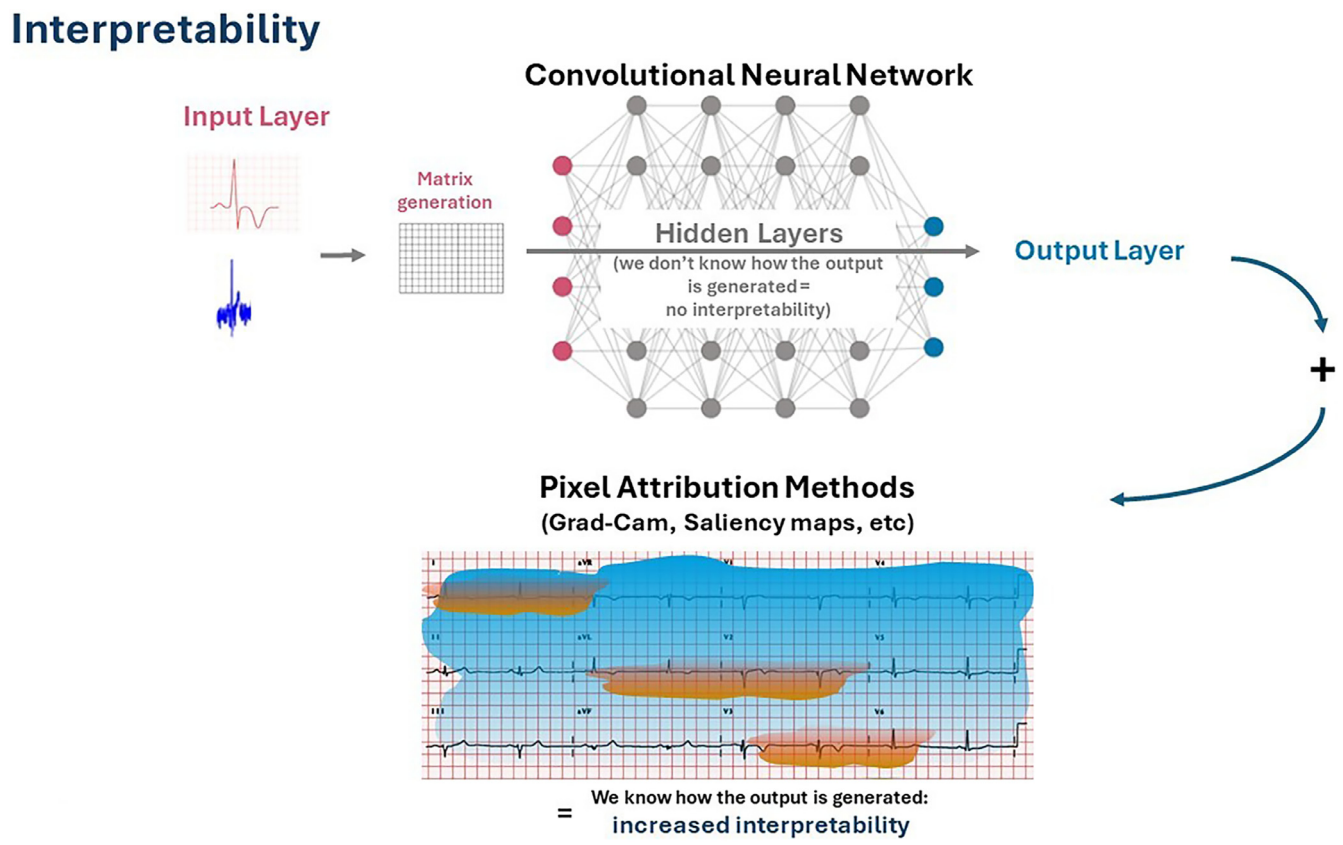

Fig. 2. The convolutional neural network is the most commonly used DL method for analyzing ECGs. It is characterized by a lack of interpretability due to its hidden layers. However, the use of pixel attribution methods such as Grad-Cam or Saliency maps could reveal the portions of ECGs that contributed to generating the output, thus increasing interpretability.

AI-ECG models for detecting HCM

	Tison GH, et al. Circ Cardiovasc Qual Outcomes. 2019	Ko WY, et al. J Am Coll Cardiol., 2020	Goto S, et al. Circulation, 2022	Sangha V, et al. medRxiv, 2023	Siontis KC, et al. J Electrocardio, 2023
Population	36186 ECGs from UCSF	3060 HCM 63941 Controls	12396 HCM 61980 Controls	12680 HCM 111873 Controls	3047 HCM 63926 Controls
Input Data	Raw Data 12-leads ECG	Raw Data 12-leads ECG	Raw Data 12-leads ECG	Image Data 12-leads ECG	Raw Data Single-lead ECG
AI Method	CNN + ML	CNN	CNN	CNN	CNN
AUC	0.91	0.96	0.96	0.96	0.90
Strength	Good interpretability	Wide HCM population; Good performance even in normal ECG	Wide HCM population; Federated learning = good generalizability; Grad Cam to improve interpretability	Wide HCM population; Use of ECG images; Grad Cam to improve interpretability	Wide HCM population; Use of Single-Lead ECG; Saliency maps to improve interpretability
Limitation	Single center = low generalizability	Low interpretability; High false positives; Single center = low generalizability	Original data can be extracted by reverse engineering;	High false positives; Single center = low generalizability	Single center = low generalizability

Fig. 3. Description of the main AI-ECG models created to detect HCM.

Table 1
Summary of reviewed studies on AI applied to ECG in HCM, including their performance and characteristics.

Model Outcome	Cases ECG tested	ECG Input	Description of Controls	AI Method	AUC	Reference
Detection of the hypertrophic portion of HCM	79	Measurement extracted from 12-lead ECG	–	Neural Network	–	Ouyang et al. [14]
Detection of diseases: HCM, PAH, CA, MVP. Detection of cardiac structure parameters: LVH, LAV, medial e′.	36,186	12-leads ECG (Raw data)	1:5 matched by age, sex, year of study, and race	CNN Supervised ML (Hidden Markov Model Gradient Boosted Machine)	0.94 (PAH) 0.91 (HCM) 0.86 (CA) 0.77 (MVP) 0.87 (LVH) 0.84 (medial e′) 0.62 (LAV)	Tison et al. [9]
Detection of HCM	3060	12-leads ECG (Raw data)	63,941 sex- and age-matched	CNN	0.96	Ko et al. [15]
Detection of HCM in children and adolescents	300	12-leads ECG (Raw data)	18,439 sex- and age-matched	CNN	0.98	Siontis et al. [16]
Detection of HCM and dilated HCM	140	8-leads ECG, Single lead, Double leads, Triple leads. (Raw data)	19,030	CNN	0.85 (8-lead HCM) 0.86 (one-lead HCM) 0.92 (8-lead dHCM) 0.95 (one-lead dHCM)	Hirota et al. [17]
Detection of HCM	20,677 15,147	12-leads ECG (Raw data)	–	CNN Supervised ML (logistic regression)	0.81	Maanja et al. [18]
Detection of HCM	3047	Single-lead ECG (L1) (Raw data)	63,926 sex- and age-matched	CNN Pixel attribution method (Saliency maps)	0.90	Siontis et al. [35]
Detection of HCM	12,396	12-leads ECG (Raw data)	61,980 sex- and age-matched	CNN in federated learning Pixel attribution method (Grad-Cam)	0.96	Goto et al. [19]
Detection of HCM	12,680	12-leads ECG (Standard Image data)	111,873 sex- and age-matched	CNN Pixel attribution method (Grad-Cam)	0.96	Sangha et al. [10]
Differential diagnosis of LVH	50,709 with or without LVH	12-leads ECG and single-lead ECG (L1-L2) (Raw data)	–	CNN	0.95 (CA) 0.92 (HCM) 0.90 (AS) 0.76 (HTN) 0.69 (other LVH)	Haimovich et al. [20]
Differential diagnosis of LVH	15,761 with LVH	12-leads ECG (Raw data)	–	CNN	0.87 (HCM using ECG) 0.92 (HCM using ECG and Echo)	Soto et al. [21]
Predictive Genotypes	178	12-leads ECG (Raw data)	–	CNN	0.89	Chen et al. [25]
High Arrhythmic Risk imaging features	1930	12-leads ECG (Raw data)	–	CNN	0.72 (systolic dysfunction) 0.83 (massive hypertrophy) 0.93 (apical aneurysm) 0.76 (extensive LGE)	Carrick et al. [27]
Arrhythmic Risk phenotype	85	12-leads Holter ECGs (Raw data)	35	Unsupervised ML (Clustering)	–	Lyon et al. [28]
Heart Failure Risk	218	12-leads ECG ECGs (Raw data)	245	CNN	0.71 (mild HF) 0.71 (moderate HF) 0.80 (severe HF)	Togo et al. [29]
Heart Failure Risk	54	8-leads ECG (L1, L2, V1-V6). Single lead. Double leads (L1-L2). (Raw data)	17,324	CNN	0.92 (8-lead) 0.95 (Single lead V5) 0.89 (Double lead L1-L2).	Hirota et al. [30]

(continued on next page)

Table 1 (*continued*)

Model Outcome	Cases ECG tested	ECG Input	Description of Controls	AI Method	AUC	Reference
Therapeutic Response with Mavacamten	216	12-leads ECG (Raw data)	–	CNN	0.67 vs 0.38 (pre- vs post-treatment UCSF algorithm) 0.85 vs 0.37 (pre- vs post-treatment Mayo algorithm)	Tison et al. [31]
Therapeutic Response with Mavacamten	216	12-leads ECG (Raw data)	2600 sex- and age-matched	CNN	0.70 vs 0.35 (pre- vs post-treatment UCSF algorithm) 0.80 vs 0.45 (pre- vs post-treatment Mayo algorithm)	Siontis et al. [32]
Therapeutic Response with Mavacamten and SRT	315 (SRT) 36 (Mavacamten)	12-leads ECG (Standard Image data)	–	CNN	0.41 vs 0.28 (pre-and post-Mavacamten) 0.55 vs 0.59 (pre- and post-SRT)	Dhingra et al. [33]

AS= aortic stenosis; CA=cardiac amyloidosis; CNN=convolutional neural network; dHCM=dilated hypertrophic cardiomyopathy; HCM= hypertrophic cardiomyopathy; HTN=hypertension; LAV=left atrial volume; LGE= left gadolinium enhancement; LVH: left ventricular hypertrophy; MVP= mitral valve prolapse; PAH=Pulmonary artery hypertension; SRT=septal reduction therapy.

curacy improved only when combined with other ML methods [17] (Fig. 3). Maanja et al. enhanced the Mayo Clinic model by combining it with an univariable logistic regression algorithm to analyze clinical features. This combined approach improved HCM detection with an AUC of 0.84, reducing false positives and enhancing interpretability [18]. Nevertheless, the current data do not support the use of AI-ECG as a screening tool for detecting HCM. The high false positive rate of existing models raises concerns about the potential costs to the healthcare system associated with identifying HCM patients

ECG images as input

While raw ECG data are commonly used in AI-ECG models, Sangha et al. proposed using ECG images. Their model, based on 12-lead ECG images, distinguished HCM from other conditions using MRI criteria, achieving an AUROC of 0.96. They used GRAD-CAM for interpretability, identifying leads V4 and V5 as key regions [10] (Fig. 3).

Differential diagnosis in LVH

AI-ECG can effectively distinguish HCM from other conditions presenting with LVH, such as cardiac amyloidosis, aortic stenosis, and hypertension [9,19]. Haimovich et al. developed an AI-ECG model using raw ECG data from 50,709 patients with LVH, demonstrating high performance in detecting cardiac amyloidosis, HCM, aortic stenosis, and hypertensive LVH [20]. Soto et al. created a multimodal DL model combining ECG and echocardiogram data from 2728 patients, which accurately distinguished HCM from hypertension [21].

Predictive genotype

HCM is a heritable cardiovascular disorder with variable expressivity and age-related penetrance. Genetic testing is essential for the diagnosis, prognosis, and screening of at-risk family members. However, the specific mutation remains unidentified in up to 50 % of HCM patients [1,22]. Despite advancements, variants of unknown significance complicate clinical interpretation. Traditional scoring systems, like the Toronto and Mayo HCM genotype scores, predict genetic testing outcomes [23]. Recently, AI has improved predictions [24,25]; a DL model using raw ECG data from 178 HCM patients achieved an AUC of 0.89, outperforming both the Mayo and Toronto scores [25]. No AI-ECG models currently predict phenotype development, but exploring these could enhance understanding and follow-up in mutation carriers.

Prognosis of HCM

HCM patients are at risk of developing sudden cardiac death (SCD), AF, stroke, and heart failure. Risk assessment is crucial to promptly implement specific therapeutic measures that can reduce morbidity and mortality.

Arrhythmia and SCD

Current risk stratification models for arrhythmia and SCD in HCM patients rely on multiple clinical parameters, including electrocardiographic and echocardiographic data, analyzed using traditional statistical methods. The ESC risk assessment employs the 2014 HCM Risk-SCD calculator, which provides a quantitative 5-year SCD risk score, incorporating new risk factors such as apical aneurysm, extensive late gadolinium enhancement (LGE) >15 %, and ejection fraction <50 % in the 2023 guidelines [1]. The 2020 ACC/AHA guidelines and the most recent 2024 update, include additional risk factors like family history of SCD, unexplained syncope, maximal wall thickness of 30 mm, and left ventricular (LV) end-stage remodeling [2]. The 2020 ACC/AHA guidelines showed a sensitivity of 95 % and a specificity of 78 %, while the 2014 ESC criteria had a sensitivity of 58 % and a specificity of 81 % [26]. Carrick et al. developed a DL ECG model to identify high arrhythmic risk features per the 2020 ACC/AHA guidelines. This model, trained on ECG data from 1930 HCM patients, demonstrated a sensitivity of 97 % when combined with echocardiography, reducing the need

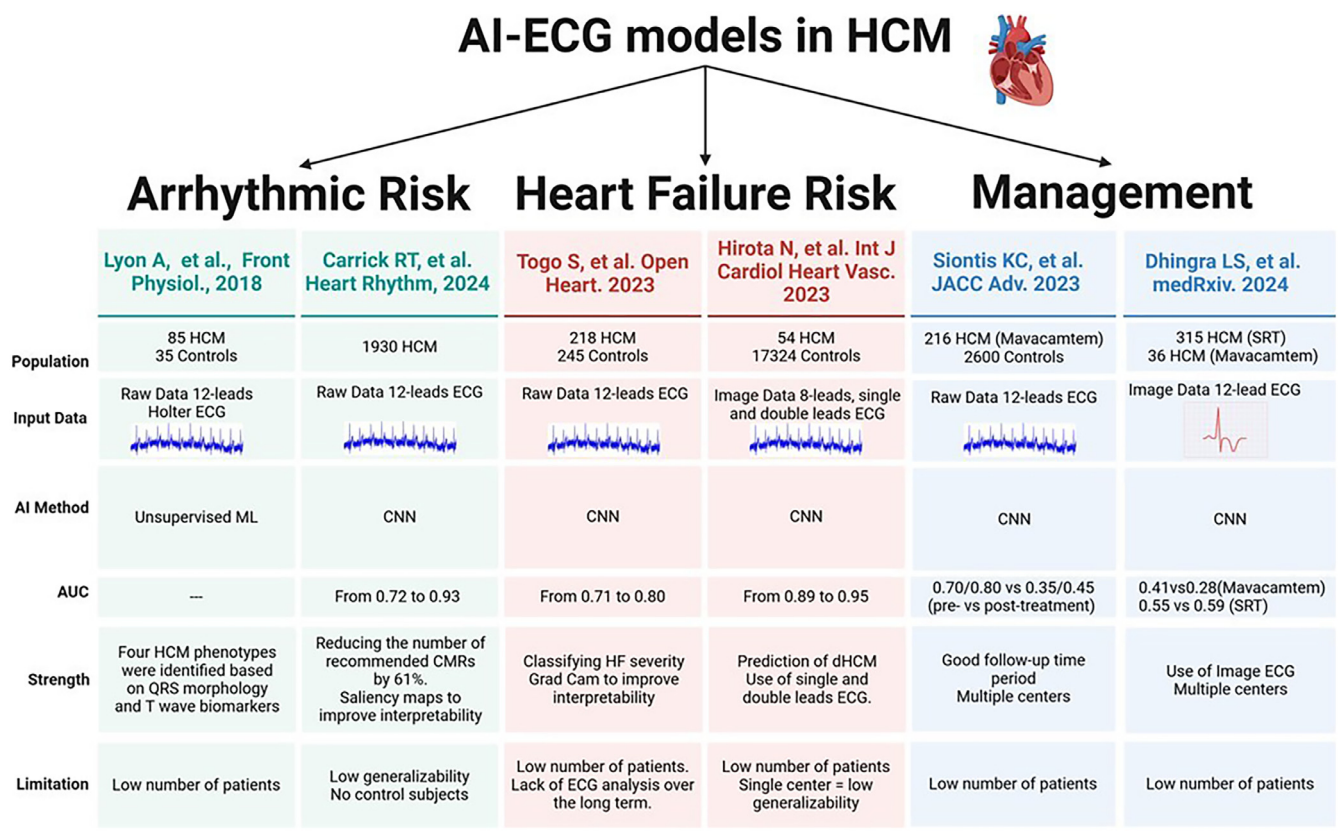

Fig. 4. Description of the main AI-ECG models created to assess arrhythmic risk, heart failure risk, and the management of HCM patients.

for cardiac magnetic resonance imaging (CMR) by 61 % [27] (Fig. 4). AI models can also enhance risk assessment by analyzing extensive datasets to determine primary prevention ICD implantation. Lyon et al. used an unsupervised ML model to identify four HCM subgroups based on QRS and T wave biomarkers, finding that primary T-wave inversion correlated with higher arrhythmic risk [28] (Fig. 4).

Atrial fibrillation

AF occurs in about 20 % of HCM patients, leading to worsened quality of life and a high risk of embolic stroke, requiring anticoagulation therapy regardless of the CHA2DS2-VASc score. Early identification of AF is crucial as it is often asymptomatic, and stroke can be its first manifestation [1,2]. However, to date there are no studies addressing the prediction of AF by using AI-ECG.

Heart failure

Aside from arrhythmia and SCD, advanced heart failure (HF) affects 35–50 % of HCM patients, with left ventricular outflow tract obstruction (LVOTO) (gradient >30 mmHg) linked to a higher risk [1,2]. DL methods can also identify HF severity by extracting specific ECG features, providing additional tools alongside the New York Heart Association (NYHA) classification or the Kansas City Cardiomyopathy Questionnaire (KCCQ). Togo et al. developed a DL ECG model associating QRS complex features with mild to moderate HF and ST-T wave features with severe cases [29] (Fig. 4). DL models also showed good diagnostic performance in identifying the dilated phase of HCM using various ECG leads, despite data imbalance leading to higher false positives [30] (Fig. 4).

Evaluation of therapeutic response

Managing HCM involves addressing complications like arrhythmic sudden death, AF, and progressive heart failure. AI has the potential to identify ECG features associated with disease progression and therapeutic response; however, there are no valid studies to date indicating that the tool can help physicians in this field. Two papers analyzed 216 ECGs from the phase 2 PIONEER-OLE trial of Mavacamten. The ECG changes during treatment, did not make the model more capable of identifying HCM [31,32] (Fig. 4). The ECG changes observed in these studies probably were linked to the reduction of LVOTO; however, in another study analyzing patients with invasive reduction of LVOTO, these phenomena were not observed, probably suggesting that invasive reduction, eliciting local reaction, like inflammation and fibrosis, does not change ECG even in presence of LVOTO reduction [33] (Fig. 4).

Limitations and challenges of AI-ECG

The adoption of AI-ECG technologies presents several limitations and challenges that must be addressed to transition these models from hypothesis-generating research projects to tools with clinical utility.

Lack of transparency and explainability

One major limitation of CNN models is their “black box” nature, where the decision-making process is not transparent. This lack of transparency makes it difficult for clinicians to trust and understand AI-driven diagnostics fully. Explainability methods, such as saliency maps and gradient-weighted class activation mapping (Grad-CAM), have been developed to address this issue. These methods improve the interpretability of AI models by highlighting parts of the input important for the model’s decision, providing insights into how the model makes predictions [34,35] (Fig. 2). For instance, Siontis et al. used saliency maps to identify ECG segments influencing CNN detection of HCM, revealing the ST-T segment as fundamental for detection [35] (Fig. 3). These techniques are cru-

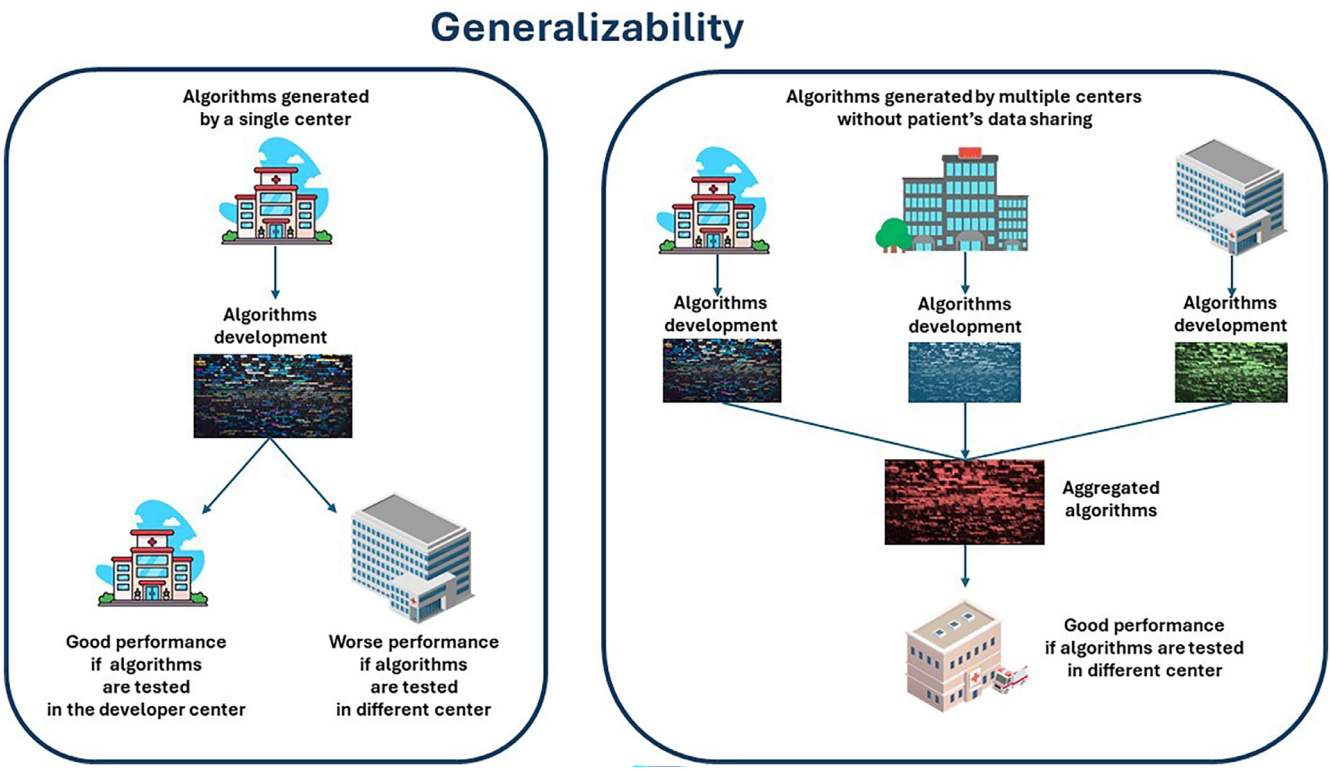

Fig. 5. Left panel: Deep learning models often show low generalizability and poor performance when faced with new and unseen data, particularly when trained in a single center, resulting in overfitting. Right panel: To improve generalizability, federated learning can be utilized to create a model based on data from multiple centers without sharing private data.

cial for building trust and ensuring that the models are not only accurate but also understandable.

Overfitting and data limitations

Another significant challenge is overfitting, where models perform well on training data but poorly on unseen data. This issue is particularly relevant in ECG analysis due to the variability in data quality and patient demographics. Overfitting can lead to models that are not generalizable, reducing their effectiveness in clinical practice. Additionally, the lack of large, digitized clinical datasets is a barrier for AI development in ECG analysis. The variability in ECG data, influenced by factors such as patient age, comorbidities, and the equipment used for ECG recording, makes it challenging to create robust models that perform well across different populations.

Data privacy and federated learning

The scarcity of large-scale datasets is compounded by concerns about patient privacy, which limits data sharing between institutions. Federated learning is a promising approach to address this issue. It allows institutions to collaboratively train models on their private data without sharing the data itself, thus preserving patient privacy [19] (Fig. 5). For example, Goto et al. used multinational federated learning to develop an AI-ECG model with data from four medical centers. This approach improved model performance across different datasets [19] (Fig. 3). Federated learning enables the use of distributed data while maintaining patient privacy, which is crucial for developing more accurate and generalizable AI models.

However, the current environment of AI model development is often fragmented, with limited sharing of models and data between researchers. This lack of transparency and availability prohibits investigators from building off each other's work and limits the ability to compare the performance of different models in various HCM cohorts. The inability to validate and improve upon existing models prevents the advancement of the field. Greater transparency and collaboration are essential to overcome these barriers. By sharing models, datasets, and methodologies, researchers can validate findings, replicate studies, and refine algorithms, leading to more robust and clinically useful AI-ECG tools.

Regulatory challenges

The regulatory landscape for AI in healthcare is still evolving. The absence of clear regulations for AI use in healthcare poses a significant challenge. Regulatory bodies need to establish guidelines that ensure the safety, reliability, and accountability of AI-driven tools. This includes defining standards for model validation, performance benchmarks, and protocols for managing digital errors. Establishing guidelines for accountability in case of digital errors will increase confidence in AI tools among healthcare providers and patients. Clear regulations will also facilitate the integration of AI models into clinical workflows, ensuring they meet the necessary safety and efficacy standards [4,6,8,13].

Call for transparency and collaboration

To move AI-ECG models from research to clinical practice, the field must prioritize transparency and collaboration. Researchers should be encouraged to share their models and data openly, favoring an environment of innovation and continuous improvement. Collaborative efforts can lead to the development of standardized benchmarks and datasets, enabling balanced comparisons between different AI models. This collective approach is critical for advancing the field and ensuring that AI-ECG models can be effectively integrated into clinical practice, ultimately improving patient outcomes. Despite these challenges, AI and ML continue reshaping healthcare by enhancing diagnostic precision and personalized medicine through improved ECG analysis [3,13]. It is imperative for the community to advocate for more transparency, collabora-

tion, and regulatory clarity to fully realize the potential of AI-ECG in clinical practice.

Conclusion

AI is transforming the use of ECG in diagnosing and managing HCM, showing high accuracy and potential for clinical application, and enabling more precise and personalized care. However, it is necessary to improve research to develop an accurate AI-ECG model that also considers interpretability and generalizability. Additionally, clinical trials will be necessary to use these models widely. Continued development and integration of AI in clinical practice promise to revolutionize cardiovascular diagnostics and treatment, improving risk assessment and reducing morbidity and mortality in HCM patients**.**

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Declaration of competing interest

None.

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Leopoldo Ordine: Writing – original draft, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Grazia Canciello:** Supervision, Software, Project administration, Methodology, Investigation, Data curation. **Felice Borrelli:** Visualization, Software, Methodology, Investigation. **Raffaella Lombardi:** Supervision, Methodology, Investigation, Formal analysis. **Salvatore Di Napoli:** Software, Methodology, Investigation, Formal analysis, Data curation. **Roberto Polizzi:** Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation. **Cristina Falcone:** Resources, Methodology, Investigation. **Brigida Napolitano:** Resources, Methodology, Investigation, Formal analysis, Data curation. **Lorenzo Moscano:** Supervision, Methodology, Investigation, Data curation. **Alessandra Spinelli:** Supervision, Resources, Funding acquisition. **Elio Masciari:** Validation, Supervision, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Giovanni Esposito:** Writing – review & editing, Supervision. **Maria-Angela Losi:** Writing – review & editing, Validation, Supervision, Resources, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

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