Artificial intelligence opportunities in cardio-oncology: Overview with spotlight on electrocardiography

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1. Introduction

Cardiovascular disease (CVD) is a leading cause of death among cancer survivors, second only to cancer recurrence or development of new tumors. Cardio-oncology has therefore emerged as a relatively new subspecialty focused on prevention and management of cardiovascular consequences of cancer therapies. Challenges remain regarding precision and accuracy in predicting individuals at highest risk for cardiotoxicity. Barriers such as access to care also limit screening and early diagnosis to improve prognosis. Thus, developing innovative approaches for prediction and early detection of cardiovascular illness in this population is critical. In this review, we provide an overview of the present state of machine learning applications in cardio-oncology. We begin by outlining some factors that should be considered while utilizing machine learning algorithms. We then examine research in which machine learning has been applied to improve prediction of cardiac dysfunction in cancer survivors. We also highlight the use of artificial intelligence (AI) in conjunction with electrocardiograms (ECG) to predict cardiac malfunction and also discuss the potential role of wearables. Additionally, the article summarizes future prospects and critical takeaways for the application of machine learning in cardio-oncology. This study is the first in a series on artificial intelligence in cardio-oncology, and complements our manuscript on echocardiography and other forms of imaging relevant to cancer survivors cared for in cardiology clinical practice.
well as endocrine therapies, and targeted or immunotherapies can all cause cardiovascular toxicities [6–14], as can radiation therapy [15–17]. Cancer survivors are at increased risk for heart failure and cardiac mortality attributable to prior exposure to anthracycline chemotherapy and/or chest-directed radiation [18–20]. Early recognition of cardiomyopathy provides an opportunity for interventions that can potentially improve cardiac health and quality and length of survival [21,22]. Consequently, clinical practice guidelines recommend echocardiogram screening and early detection of asymptomatic cardiomyopathy, with the goal of reducing progression to symptomatic or fatal heart failure.

Guidelines from the American Society of Clinical Oncology (ASCO) and National Comprehensive Cancer Network (NCCN) recommend post-anthracycline echocardiography for patients with elevated cardiovascular risk [23–25]. However, these guidelines are inconsistently followed, and predicting anthracycline cardiotoxicity continues to be relatively evasive. Furthermore, variable definitions have been used for cardiovascular toxicity over time and some have been rather differential across studies. Parallel advancements in processing power, machine learning and timely interventions.

Cardiovascular toxicities associated with traditional chemotherapies. Table 1

| Cancer type | Class | Chemotherapeutic agents | Cardiovascular effects |
|-------------|-------|-------------------------|------------------------|
| Breast cancer, sarcoma, leukemia, and lymphomas | Anthracyclines | Doxorubicin, daunorubicin, idarubicin, epirubicin, and mitoxantrone | Increase clinical cardiotoxicity [36]. |
| Breast, head and neck, and gastrointestinal cancers | Fluoropyrimidines/antimetabolites | 5-Fluorouracil (5-FU) and capecitabine | Angina, myocardial infarction, arrhythmias, and infrequently acute pulmonary edema [37]. |
| Breast, head and neck, and gastrointestinal cancers | Microtubule-targeting agents | Paclitaxel and docetaxel | Abnormal conduction (e.g., bradycardia and heart block) [38,39]. |
| Breast cancers and lymphomas | Alkylating agents | Cyclophosphamide | Ventricular dysfunction and pericardial disease [40,41]. |
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2. Cardioxicities in cardio-oncology

2.1. Traditional chemotherapies

Anthracyclines are frequently used in the treatment of breast cancer, sarcoma, leukemia, and lymphomas. Anthracyclines are extremely effective against a variety of cancers but may cause cardiotoxicity [36] (Table 1). 5-fluorouracil (5-FU) and its metabolic precursor capecitabine are fluoropyrimidines or antimetabolites frequently used in multiple cancer treatments and typical associate with cardiotoxicity during the first cycle of chemotherapy [37]. Paclitaxel and docetaxel are microtubule-targeting agents typically used to treat breast, head and neck, and gastrointestinal cancers, and have been shown to cause abnormal conduction [38,39]. Cyclophosphamide is frequently used to treat breast cancers and lymphomas and also carries numerous cardiac adverse effects [40,41]. Cisplatin and busulfan have been linked to additional cardiovascular toxicities [42,43].

2.2. Targeted, endocrine, immune, and cell therapies

Trastuzumab is a monoclonal antibody to the human epidermal growth factor receptor 2 (HER2) receptors and is most frequently used to treat patients with HER2-positive breast cancer [44]. Concomitant use of anthracyclines and HER2 monoclonal antibodies is typically avoided, due to synergistic cardiotoxic effects (Table 2).

With excellent clinical outcomes, multitargeted TKIs such as bosutinib, dasatinib, ponatinib, and nilotinib have transformed the management of chronic myelogenous leukemia and acute lymphoblastic leukemia, and these drugs are also linked to cardiotoxicity. Bruton
### Table 2
Cardiovascular toxicities associated with targeted, endocrine, immune, and cell therapies.

| Cancer type                          | Class                        | Chemotherapeutic agents                                                                 | Cardiovascular effects                                                                 |
|--------------------------------------|------------------------------|----------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| Human epidermal growth factor receptor 2 (HER2)-positive breast cancer | Monoclonal antibodies        | Trastuzumab                                                                              | Synergistic toxic effects on cardiomyocytes with concomitant use of HER2 monoclonal antibodies and antracyclines [44]. |
| Chronic myelogenous leukemia and acute lymphocytic leukemia | Tyrosine kinase inhibitors (TKIs) | Bosutinib, dasatinib, ponatinib, and nilotinib                                           | QT prolongation, heart failure, myocardial infarction, and potentially fatal thrombosis [45]. |
| B-cell malignancies (chronic lymphocytic lymphoma and indolent lymphomas) | Bruton tyrosine kinase inhibitors | Ibrutinib                                                                               | Increase risk of atrial fibrillation or hypertension [45]. |
| Renal cell carcinoma                  | Angiogenesis inhibitors      | Sunitinib, axitinib, sorafenib, and pazopanib                                           | Hypertension, thrombosis, QT interval prolongation, or left ventricular dysfunction [46-48]. |
| Metastatic breast cancer              | Cyclin-dependent kinase inhibitors | Palbociclib, ribociclib, and abemaciclib                                                | Ribociclib has been shown to prolong the QTc interval [50]. |
| Multiple myeloma                     | Proteasome inhibitors        | Carfilzomib                                                                              | Heart failure, systemic and pulmonary hypertension, arrhythmias, and acute coronary syndrome [51,52]. |
| Hematological malignancies (lymphomas and multiple myeloma) | Histone deacetylase inhibitors | Vorinostat, romidepsin, and panobinostat                                                 | Cardiac ischemia, arrhythmias, and conduction abnormalities [53-56]. |
| Breast cancers                       | Aromatase inhibitors        | Anastrozole, letrozole, exemestane, and tamoxifen                                          | May increase the risk of ischemic heart disease [57-60]. |
| Breast cancer, head and neck, and lung cancers | Immune checkpoint inhibitors (monoclonal antibodies) | Anti-PD-1 and anti-PD-L1                                                               | Myocarditis [61]. |
| Recalcitrant hematological cancers    | Cellular therapy             | Chimeric antigen receptor (CAR)-T cell therapy                                          | Cardiovascular effects related to (CAR)-T cell therapy is primarily a result of cytokine release syndrome (CRS). Cardiovascular effects include sinus tachycardia, left ventricular systolic dysfunction, and hypotension [64]. |
| Multiple myeloma                     | Stem cell transplantation    | –                                                                                       | Increased risk for cardiovascular toxicity including cardiomyopathy [69]. |

**Note:**
- PD-1: Programmed death receptor-1; PD-L1: Programmed death receptor 1 ligand.
- Tyrosine kinase inhibitors have been used to manage B-cell malignancies, and have been shown to increase cardiotoxicity [45] (Table 2). Angiogenesis inhibitors may cause adverse effects such as hypertension, thrombosis, Q-T interval prolongation, or left ventricular dysfunction [46-48].
- Cyclin-dependent kinase inhibitors are used to treat metastatic breast cancer [49]. Ribociclib has been reported to prolong the QTc interval [50]. Proteasome inhibitors, such as carfilzomib, have resulted in unprecedented advances in the treatment of multiple myeloma [51,52]. Carfilzomib has been associated with cardiovascular adverse events such as heart failure, systemic and pulmonary hypertension, arrhythmias, and acute coronary syndrome. Histone deacetylase inhibitors, such as vorinostat, romidepsin, and panobinostat are used to treat hematological malignancies, and have been linked to cardiac ischemia, arrhythmias, and conduction abnormalities [53-56].
- There is some evidence that estrogen deprivation caused by aromatase inhibitors (e.g., anastrozole, letrozole, exemestane or tamoxifen) (an estrogen receptor selective modulator) used to treat early and advanced breast cancers may increase the risk of ischemic heart disease [57-60].
- Immune checkpoint inhibitors are monoclonal antibodies that activate T cells and initiate an adaptive immune response, enabling the immune system to launch an optimal immune response when exposed to cancerous cells, but this can associate with myocarditis [61].
- Cellular therapy, more precisely chimeric antigen receptor (CAR)-T cell therapy, has demonstrated early success in patients with relapsing hematological cancers [62,63]. Cardiovascular complications have been reported in this setting primarily as a result of cytokine release syndrome and complications [64]. The most common malignancy treated with autologous stem cell transplantation is multiple myeloma [65], which associates with cardiomyopathy and poor outcomes [55,66-69].

## 3. AI and cardio-oncology

Artificial intelligence (AI) advancements have gained traction in recent years, with the use of computer algorithms to simulate human intelligence [70,71]. In common practice, AI is already being used to a limited extent in the form of computer-generated electrocardiograms (ECGs) [70]. Machine Learning (ML) in particular, which employs advanced computer algorithms to learn complex patterns [71], has the potential to improve cancer survivor prediction, early diagnosis, and ultimately prevention. Over the last decade, the idea of applying machine learning to cardiology has generated considerable interest, with over 3000 papers published on the subject in the last five years alone [70,71].

Developing novel AI algorithms could provide an avenue for research to improve patient care for cancer patients and survivors at risk for cardiovascular disease related to cancer therapy. The term AI was first used in 1956 to refer to machines simulating human intelligence. AI comprises multiple techniques including Bayesian networks, ML, and hybrid intelligent systems that allow efficient data representations. AI processes and analyzes high-density data not otherwise feasible by hybrid intelligent systems that allow efficient data representations. AI differentiates itself from traditional parametric statistical methods by capturing high dimensional and hierarchical relationships, which makes AI more applicable to real-world problems.

In cardio-oncology, the use of machine learning to predict cardiac dysfunction (cardiomyopathy, left ventricular systolic dysfunction) in...
cancer survivors is of particular interest. Cardiac dysfunction is one of the most frequently reported long-term adverse effects of cancer therapy. This is especially true for some patients receiving anthracyclines, one of the most frequently prescribed classes of cancer medications [13].

In these patients, every doubling of the time required to detect and treat cardiac dysfunction can result in a fourfold reduction in the likelihood of complete recovery of cardiac function [72].

![Diagram of the human heart with ECG waveforms and annotations](image)

**Fig. 1.** The use of convolutional neural networks, a deep learning approach as a form of artificial intelligence, can be used to computationally predict cardiac dysfunction or atrial fibrillation in in silico experiments. Traditional multivariate discrimination approaches in statistics typically use known prespecified physiological parameters for analyses. In comparison, artificial intelligence methods can uncover and use subclinical unknown physiological parameters reflected in subtle changes on the ECG for improved prediction, early diagnosis, and prognosis of cardiac dysfunction and atrial fibrillation.

| Table 3 | Prediction of cardiovascular diseases in AI-ECG studies. |
|---------|----------------------------------------------------------|
| Number of patients | Predicted cardiovascular diseases | Predicted effect size | Cardiomyopathy study YES/NO | History of cancer YES/NO | Reference |
| 44,959 | Asymptomatic left ventricular dysfunction (ALVD), ejection fraction (EF) ≤35% | AUC of 0.93 | YES | NO | [100] |
| Subset of 16,056 | Left ventricular systolic dysfunction (LVSD), EF ≤35% | AUC of 0.918 (95% CI 0.902% - 0.934%) | YES | NO | [101] |
| 5680 | LVSD, EF ≤40% | AUC of 0.83 (95% CI 0.82-0.84) | YES | NO | [102] |
| 1606 | LVSD, EF ≤35% | AUC of 0.89 (95% CI 0.86-0.91) | YES | NO | [103] |
| 14,613 | LVSD, EF ≤50% | AUC of 0.85 (95% CI 0.83-0.88) | YES | NO | [104] |
| 22,641 | LVSD, EF ≤40% | AUC of 0.83 (95% CI 0.82-0.84) | YES | NO | [105] |
| Systematic review | LVSD, EF ≤35% | AUC of 0.89-0.93 and accuracy: 98% | NO | NO | [106] |
| Subset of 36,186 echocardiograms | Ischemic heart disease (eight reports) | AUC of 0.87 and accuracy: 87% | NO | NO | [107] |
| MIT-BIH arrhythmia database | Pulmonary arterial hypertension | AUROC of 0.94 (95% CI 0.93-0.95) | YES | NO | [108] |
| MIT-BIH arrhythmia database | Hypertrophic cardiomyopathy | AUROC of 0.91 (95% CI 0.90-0.92) | YES | NO | [109] |
| MIT-BIH arrhythmia database | Cardiac amyloid | AUROC of 0.86 (95% CI 0.82-0.89) | YES | NO | [110] |
| MIT-BIH arrhythmia database | Mitral valve prolapse | AUROC of 0.77 (95% CI, 0.76-0.78) | YES | NO | [111] |
| 1217 | Premature ventricular contraction (PVC) | Support vector machine (SVM): F1 score of 0.8193 | NO | NO | [112] |
| 52,870 | Cardiomyopathy | AUC of 0.87 (95% CI, 0.83 to 0.90) | YES | YES | [119] |
| | Non-Hispanic white (n = 44,524, AUC 0.931) | YES | YES | [110] |
| | Asian (n = 557, AUC 0.961) | YES | NO | [113] |
| | Black/African American (n = 651, AUC 0.937) | YES | YES | [114] |
| | Hispanic/Latino (n = 331, AUC 0.937) | YES | NO | [115] |
| | American Indian/Native Alaskan (n = 223, AUC 0.938) | YES | NO | [116] |

AI-ECG: artificial intelligence-enhanced electrocardiography; AUC: area under the curve; AUROC: area under the receiver operating characteristic curve; CI: confidence interval; EF: ejection fraction; F1: F-Score/F-Measure; LVSD: left ventricular systolic dysfunction; MIT-BIH: Massachusetts Institute of Technology-Beth Israel Hospital; OR: odds ratio.

* A combined measure representing algorithm precision and recall based on ability to predict true positive.

**In silico experiments**

**What features can the model recognize?**
4. AI opportunities for diagnosis, prognosis, and care delivery

The application of machine learning is contingent upon the ability of algorithms to process heterogeneous data within a learning dataset and to generate accurate and reliable predictions. After developing the algorithm, its performance must be validated against an alternate dataset to which the algorithm has never been exposed previously. The most frequently used validation parameters are those that assess the model’s ability to 1) discriminate between different outcomes, which is commonly expressed as an area under the curve (AUC) or a c-statistic, and 2) calibrate the model-derived risk estimate to observed outcomes [73,74]. Researchers evaluating machine learning algorithms work with a variety of datasets that are frequently consolidated retrospectively. The type of data collected varies between studies and may include baseline demographics, clinical characteristics, treatments, and outcome measures that may be adjudicated centrally. There is a dearth of data on the optimal type of machine learning algorithm to use or the parameters to set prior to initiating the learning process [75]. Nonetheless, some studies are demonstrating the utility of ML in cardiology.

4.1. AI techniques used in cardiology, oncology, and cardio-oncology

Various AI techniques have been applied in cardiology [32-34,71,76-83] and oncology [84,85] and are now also being used in cardio-oncology (Table 5). The most frequently used techniques in ML and DL generally fall within the two primary categories of ‘supervised learning’ and ‘unsupervised learning’. A recent publication has delineated advantages, disadvantages, and example uses cases of common algorithm subclasses within supervised or unsupervised learning [32]. In supervised learning, both input and output data are provided to algorithms, which then determine complex mathematical relationships between the input data and the expected output data [51]. In unsupervised learning, on the other hand, input data (without expected output data) are provided to the algorithm, which extracts insights from the data based only on its internal structure and statistics [31].

In supervised learning, the objectives are outcome prediction,
In unsupervised learning, the goals are discovery of hidden data structure, exploration of relationships between variables, and the tendency for features discovered by unsupervised learning often being available for incorporation into subsequent more explainable and interpretable supervised learning models [32]. Three common classes of algorithms in unsupervised learning are deep learning algorithms, tensor factorization, and topological data analysis [32]. Advantages of deep learning algorithms include the use of current state-of-the-art feature engineering techniques, and features are frequently then used as input to supervised learning models as described. Accordingly, the use of these algorithms is developing rapidly, with broad industry and academic interest. Disadvantages include computational cost to train the unsupervised algorithms, with large datasets needed to train the models, and interpretability of the model output can be challenging. An example application has been the unsupervised development of representative models predicting important patient characteristics using electronic health record data [95]. Advantages of tensor factorization include the ability to naturally incorporate both multidimensional and multimodal data. Disadvantages include small numbers of applications published in cardiovascular reports, and the factorization algorithm chosen is critical to the outcome. An example application has included evaluating subcategories of heart failure with preserved ejection fraction [96]. Advantages of topological data analysis include clustering and identification of variable relationships in an interpretable manner. Disadvantages include being less mature than other unsupervised learning methods, and the requirements for licensing agreements associated with frequently commercial algorithms. An example application has been determining subcategories of diabetes mellitus type 2 in data from electronic medical records [97].

4.2. Cardiac dysfunction in cancer survivors

ML has shown great promise in cardio-oncology research thus far. This is made possible in part by the availability of longitudinal clinical data, such as ECGs and cardiovascular imaging, which significantly improves performance when compared to static single timepoint data. Indeed, the robustness of the available data has an effect on the nature and quality of the algorithm that results [98]. In one such longitudinal study, researchers evaluated the use of machine learning algorithms to predict the risk of cardiac dysfunction (Table 3). In a longitudinal retrospective study of 4309 cancer patients, echocardiographic data were predictive of cardiac dysfunction, with laboratory data having limited additive value [94]. AUC of 0.85 was obtained from echocardiographic data alone, whereas AUC of 0.74 was obtained from laboratory data alone. Finally, the combined model incorporating both types of data demonstrated the best performance for diagnosing cardiac dysfunction (AUC 0.91). This analysis demonstrates the most robust cardio-oncology-specific risk estimates available in the published AI literature. After additional external validation, the algorithm will be made available in an online risk stratification tool.

In a subsequent study, this research group recently applied machine learning to large-scale institutional electronic medical records to predict which patients will have adverse cardiac outcomes [93]. They established a large longitudinal cardio-oncology cohort (with a maximum
follow-up of >20 years, from March 1997 to January 2019) of >4600 cancer patients at Cleveland Clinic who had one of five cardiac diagnoses: atrial fibrillation, coronary artery disease, heart failure, myocardial infarction, or stroke. The population as a whole was composed of 84% white Americans and 11% black Americans, with a median age of ~65 years. They used a topology-based K-means clustering approach to conduct unbiased patient–patient network analyses using data from general demographics, echocardiography (over 25,000), laboratory testing, and clinical factors. Hazard ratio (HR) and Kaplan–Meier analyses were used to identify clinically actionable variables. Cox regression models were used to eliminate all confounding variables. Random-split and time-split training-tests were used to validate the model. They identified four clinically significant subgroups of cancer survivors with four levels of cardiac events incidence and mortality. They demonstrated in this study that machine learning algorithms focused on analyzing similarity among patients over several years may facilitate the identification of cancer survivors at increased risk of cardiac dysfunction.

5. ECG for prediction and prognostication in cardio-oncology

Recent findings associating AI findings in ECGs with severe cardiac conditions represent a giant step forward in cardiology [99]. More precisely, using 12-lead ECGs AI algorithms can predict reduced left ventricular ejection fraction (LVEF <40%) and a patient’s predisposition to atrial fibrillation while in normal sinus rhythm (NSR) [99,100]. Deviations from NSR on ECG are being identified via AI technologies to automate diagnoses. AI-based predictive tools utilizing low-cost, accessible, and potentially remote applicable ECG data may become useful for screening and diagnosis in cardio-oncology. In this section, we describe various studies assessing the potential utility of ECG to define or predict cardiac pathology in the general population. We then outline how AI-ECG can be applied in cardio-oncology, with a focus on cardiomyopathy and atrial fibrillation and looking toward the future.

5.1. Cardiac pathology on ECG

This statement is supported by recent studies utilizing deep learning on 12-Lead ECG data in accurately estimating echocardiogram parameters representing left ventricular systolic dysfunction [101–103]. Further, there is also literature suggesting that deep learning applied to ECG alone can identify patients with no heart failure yet in risk for developing in 10 years (AUC of 0.76) with a similar accuracy to Framingham Heart Study’s risk calculator (AUC of 0.78) utilizing several clinical risk factors. Also, when AI-ECG results are combined with clinical risk factors, the accuracy was further increase (AUC of 0.83) confirming the added value of ECG in assessing cardiovascular risk [104]. Another study group determined whether AI-ECG could be used in a clinical decision support tool for early detection of cardiac dysfunction [105]. The study authors utilized a fast-paced low-cost pragmatic trial embedded in the electronic health record clinical workflow to generate real-world evidence in less than a two-year time period. They used existing and prospective real-time and longitudinal electronic health record data, incorporated with clinical decision support tools, throughout small and large hospital, academic, community, and rural practices. In the intervention arm, AI-ECG results were provided to 181 clinicians on 120 primary care teams from 45 clinics/hospitals; the control arm (standard care; 177 clinicians) did not receive the AI-ECG results. ECGs from >22,600 adults (n = 11,573 in the intervention group, n = 11,068 in the control group) without previously known left ventricular systolic dysfunction were obtained during routine visits. There was a greater number of subsequent early diagnoses of left ventricular systolic heart failure in the intervention group than the control group (2.1% vs. 1.6%, odds ratio (OR) 1.32, confidence interval (CI) 1.01–1.61, p = 0.007).

In another study, the authors evaluated the evidence for using DL to analyze resting electrocardiograms (ECG) in order to predict cardiac dysfunction, left ventricular hypertrophy, and coronary heart disease [106]. A systematic review was pursued, yielding 12 published reports on the application of DL algorithms to resting electrocardiogram signals. These algorithms were used for the detection of structural cardiac pathologies in the ambulatory setting, during stress testing, or from intracardiac/implantable devices; ECGs already clearly demonstrating arrhythmias were excluded. Three articles reported on the use of DL-ECG to detect cardiac systolic dysfunction, with an area under the curve (AUC) of 0.89–0.93 and a 98% accuracy. One study reported on the use of DL-ECG to detect ischemic heart disease and two articles reported on the use of DL-ECG to detect stable coronary heart disease (AUC 0.88–1.00, 83–99.9% accuracy). Algorithms for deep learning, particularly those based on convolutional neural networks, showed superior performance to rules-based and other ML algorithms. DL algorithms may provide promising methodologies for analyzing resting electrocardiogram signals to detect structural heart disease, including left ventricular dysfunction. This may have clinical utility for screening asymptomatic individuals and early diagnosis of symptomatic patients.

One group assessed >1 million raw 12-lead ECGs from >415,000 unique patients, paired with their clinical data, to predict the development of atrial fibrillation [107] (Table 4). Recordings were assigned to training, validation, and test sets, stratified by class, age, and gender. A random forest machine learning classifier was trained to estimate the risk of AF development within five years for a particular recording. Results indicated the highest accuracy of prediction with incorporation of heart rate variability, morphology of the ECG, and features derived from a variety of sources, including demographics, clinical data, designed features, and deep representation learning (AUR = 0.91). Another group applied a new combination of convolutional neural networks and hidden Markov models to >360 k 12-lead ECGs to diagnose pulmonary arterial hypertension, hypertrophic cardiomyopathy, cardiomyloid, and mitral valve prolapse (AUC 0.94, 0.91, 0.86, and 0.77, respectively) [108]. In recent years, investigators have sought to characterize the utility of AI-ECG as a predictor of future developing atrial fibrillation in more than 1900 participants, compared to the Cohorts for Aging and Research in Genomic Epidemiology–AF (CHARGE-AF) score [109]. They found improved C statistics for AI-ECG model output (0.69, 95% confidence interval (CI) 0.66–0.72) and CHARGE-AF (0.69, 95% CI 0.66–0.71) when the two features were combined (0.72, 95% CI 0.69–0.75). Several other authors have reported on the use of AI-ECG to predict cardiac pathology (see review [78]).

Although the studies mentioned above were not specifically on patients with a history of cancer, they demonstrate promise for application in cancer survivors. One advantage of AI is specifically DL algorithm. In these algorithms, learned information and patterns in pre-existing AI models can be utilized via transfer learning. This can be helpful for customizing models for cancer survivors. These models can be used to detect and predict a variety of forms of cardiotoxicity. Further, these models mainly use convolutional neural network architecture, which is a specific type of deep learning; yet there are other types of deep learning such as recurrent neural networks and long-short term memory networks that can also be implemented in the analysis of ECGs [110–115].

5.2. Cardiomyopathy

5.2.1. Children

In 2001, one of the first studies in this area evaluated ECG changes in children who developed a decline in cardiac function after receiving doses of various anthracyclines in the order of 198 to 737 mg/m<sup>2</sup> cumulative doxorubicin equivalents (CDEs) for various hematologic cancers and solid tumors [116] (Table 6). The ECGs of 16 children with cardiomyopathy (fractional shortening < 28%) were compared to ECGs
of 31 children without cardiomyopathy who also had received anthracycline therapy (CDE dose range 120–517 mg/m²). Age, body surface area, and time since anthracycline therapy were between the two groups. All ECGs were also compared to those of a second control group including 530 healthy children without cancer. A decrease in QRS duration was noted more frequently in children with cardiomyopathy compared to both control groups. In 2019, a study of 589 children treated with anthracyclines for various pediatric cancers demonstrated that a reduction of 0.6 mV in the sum of absolute QRS amplitude in the 6 limb leads (SQRS) and a 10 ms increase of QTc interval associated with a 17% (HR 1.174, p = 0.003) and 10% (HR 1.098, p < 0.006) increased risk of developing cardiomyopathy (defined as LVEF < 50%, fractional shortening < 26%, or left ventricular end-diastolic diameter z-score > 2.5), compared to those who did not develop cardiomyopathy (CDE median 236 mg/m² and range 153–329 mg/m² versus median 165 mg/m² and range 92–232 mg/m²) [117]. ECG changes were more pronounced for those who received higher doses of anthracyclines [117]. Neither of these studies in children with cardiomyopathy had yet evaluated the use of AI-ECG to predict cardiomyopathy. However, a recent study indicated that artificial intelligence algorithms trained on the ECGs of 1217 childhood cancer survivors (65% with lymphoma/leukemia and 77% received anthracyline therapy with median dose 169 mg/m² and range 35–734 mg/m²) can predict the development of late-onset cardiomyopathy (defined based on 2014 American Society for Echocardiography guidelines) compared to baseline in those at high risk among a test set of 244 individuals, with a sensitivity, specificity, and AUC of 76%, 79%, and 0.87 (95% CI 0.83–0.90), respectively [118,119].

5.2.2. Adults

In 1977, a study assessed factors associated with anthracycline-induced cardiomyopathy (based on published clinically actionable thresholds) in 53 adult cancer patients treated with doxorubicin for a variety of cancers [120]. The investigators found that a 30% decrease in QRS amplitude in the limb leads was significantly more frequently noted on the ECGs of 17 individuals who developed cardiomyopathy compared to the ECGs of 36 individuals who did not develop cardiomyopathy despite receipt of similar doses of anthracycline (median 510 mg/m², range 310–825 mg/m² versus median 510 mg/m², range 405–600 mg/m²). Subsequently, in 2009, a study revealed a 1 mV decrease in QRS amplitude and an approximately 15 ms increase in QTc as the two main ECG changes in 9 of 26 patients with leukemia who received anthracycline therapy (median 429 mg/m², range 240–715 mg/m²), with a statistically significant correlation between these electrical abnormalities and left ventricular systolic dysfunction (LVEF ≤55%) compared to baseline [121]. While both of these studies identified associations between changes in left ventricular conduction and systolic function, neither study pursued a prospective analysis nor the use of AI-ECG for prediction.

A recent AI study demonstrated that the 12-lead ECG can be used to identify patients in the general population (without a cancer history) with reduced ejection fraction with quite favorable test performance characteristics [100]. Since the 12-lead ECG is low-cost, widely available, and minimally invasive, it may serve as an ideal method to screen patients who remain at risk of low ejection fraction after receiving cardiotoxic chemotherapeutics. While it is currently unknown whether AI-ECG can be used to identify adult cancer patients or survivors at risk for cancer therapy-induced cardiomyopathy, this approach is currently being tested in the ongoing TACTIC trial (ClinicalTrials.gov Identifier: NCT03879629). The main objectives of this trial are to define the need, timing, and duration of cardioprotection with the beta-blocker carvedilol in individuals with breast cancer who are commenced on human epidermal growth factor receptor 2 (HER2)–targeted therapy. One of the subaims of the study is to assess how an AI-ECG algorithm developed to detect an LVEF < 35–40% in a community population performs in patients on HER2-directed therapies. In order to accomplish this aim, patients are asked to undergo serial ECGs in addition to troponins and echocardiography over a two-year period. Preliminary data are supportive of the concept, indicating a diagnostic performance of the AI-ECG algorithm for the detection of an LVEF < 40% that is similar to the general population. The hope is that, if confirmed, AI-ECG could be used as a gatekeeper to the currently recommended more costly serial imaging-based cardiac function studies. This aspect of cost-effectiveness is very pertinent, especially in times of challenging health care delivery scenarios such as viral pandemics.

5.3. Atrial fibrillation

No studies have been reported on using AI-ECG to predict atrial fibrillation or other arrhythmias in cancer patients or survivors. Yet, atrial fibrillation has become a common cardiovascular toxicity of antineoplastic therapy, including during irinotecan treatment for chronic lymphocytic leukemia (CLL), or after chest radiotherapy (which increases the risk of conduction abnormalities). Other contributors to atrial fibrillation in the cancer patients and survivors include underlying comorbidities, systemic inflammation or direct effect from the presence of the cancer itself, surgery, or pharmacologic cancer therapy [122]. The presence of AF in cancer patients and survivors confers an increased risk of CV complications, including a 3-fold risk of heart failure and a 5-fold risk of stroke, with prognostic implications [122]. AI-ECG could potentially identify cancer patients and survivors at high risk of atrial fibrillation and facilitate early individualized treatment choices or could inform shared decision-making.

5.4. Wearables and mobile devices

There has been an exponential increase in AI applications in medicine parallel to the technological advancements of the last decade. The integration of digitized medical data and electronic health records into daily living (e.g., wearables, smart phone apps) has produced massive data. These developments and their application hold promise for the transformation of medicine and are being increasingly available [123]. Recent technological advancements in biomedical engineering have enabled recording lead 1 of ECGs via smartwatches, conferring a tremendous opportunity for remote patient screening for detection and prediction of various cardiovascular risks facilitating earlier recognition and intervention. Moreover, recent literature shows that Lead 1 ECG collected via smartwatch is comparable to ECGs recorded via a Holter device or standard 12-Lead ECG in terms of known ECG characteristics including R peak location and P-wave amplitude [124–126].

Although current guidelines recommend serial echocardiography for patients who have received anthracyclines and other agents, clinical uptake of this practice is inconsistent, and many patients may not undergo surveillance due to the costs and cumbersome nature of screening. Therefore, the application of AI-ECG on convenient hand-held and mobile devices could improve screening rates without patients needing to present for in-person medical care. As part of the TACTIC study (Ongoing clinical trial, ClinicalTrials.gov Identifier: NCT03879629), ECGs from mobile devices (Kardia (AliveCor) and EKO device) are compared to in-clinic 12-lead ECGs and cardiac function parameters by echocardiography. Results will help us determine whether 12-lead
ECGs, or even 1-lead ECGs from mobile devices, can potentially serve as initial screening prior to echocardiography.

The idea of routine screening over time is interesting and particularly important in the setting of patients with current or prior treatment with cardiotoxic agents. AI-ECG has been shown to be effective in identifying patients at higher likelihood of low ejection fraction. This concept of using AI-ECG as a screening mechanism is being explicitly tested in the ongoing TACTIC trial (ClinicalTrials.gov Identifier: NCT03879629), which seeks to identify new systolic dysfunction among patients treated with chemotherapeutic agents for breast cancer. In this study, we are performing serial ECG and echocardiographic assessment of patients and we hope that some of these relationships will be clarified. Ongoing retrospective analyses of changes in model output over time are also ongoing and will help inform perspectives on the potential use of AI-ECG for screening in cancer patients and survivors. We will need to determine whether AI-ECG algorithms are useful for identifying changes in risk over time, rather than an isolated aggregate risk that remains relatively constant, while still important to identify.

In the general population, the detection of arrhythmias particularly atrial fibillation can be feasible and effective. This has been demonstrated by studies in which ambulatory automated handheld ECG-based apps can accurately monitor heart rhythm with 71% sensitivity and 99% specificity [127]. Wearables ECG-monitoring devices compared to ECG-based apps have also improved detection of atrial fibrillation, facilitating optimal anticoagulation. Translating the work that has been done in the general population on the development and validation of ECG-monitoring wearable (which depend on AI) in addition to AI-ECG algorithms that predict AF risk [99,127] to patients currently and previously treated for cancer is ongoing. Use of AI-ECG prior to treatment initiation to predict which of these patients will go on to develop an arrhythmia could facilitate targeted prevention and management strategies to improve outcomes.

6. AI in precision and translational cardio-oncology

6.1. Genomic and precision medicine using biologically relevant models

In a recent study, biologically relevant models capable of detecting drug-induced toxicity via phenotypic screening were developed [128]. Deep learning, high-content image analysis, and cardiomyocytes derived from induced pluripotent stem cells (iPSC-CMs) were used to rapidly screen for instigators of cardiotoxicity. Deep learning was used to determine a single-parameter score predicting cardiotoxicity induced by a library of ~1300 screened bioactive compounds. Compounds with potential cardiotoxic properties in iPSC-CMs were identified. DNA intercalators, epidermal growth factor receptor, cyclin-dependent kinase, and multi-kinase inhibitors were among the compounds that demonstrated cardiotoxicity in iPSC-CMs. Combining deep learning and iPSC technology in this way could be a powerful method for developing biologically relevant models for modeling cardiotoxicities from cancer therapies.

Another research group recently used machine learning algorithms to develop a clinical and genetic risk prediction model for anthracycline cardiotoxicity in survivors of childhood cancer [129]. The study authors sequenced the exomes of 289 childhood cancer survivors who had been exposed to anthracyclines for at least three years. 183 case patients with decreased left ventricular ejection fraction despite low-dose doxorubicin (<250 mg/m²) and 106 control patients with preserved left ventricular ejection fraction despite doxorubicin >250 mg/m² were chosen as extreme phenotypes in a nested case-control design. Rare/low-frequency variants were collapsed to identify genes that were differentially enriched for variants between case and control patients. The expression levels of five top-ranked genes were determined in cardiomyocytes derived from human induced pluripotent stem cells, and variant enrichment was confirmed in a replication cohort. A risk prediction model with genetic and clinical predictors was developed using random forest machine learning algorithms. Between case and control patients, 31 genes were significantly enriched for variants (p < 0.001). Only 42.6% of case patients and 89.6% of control patients had a variant in these genes (odds ratio: 0.09; 95% confidence interval: 0.04 to 0.17; p = 3.98 × 10⁻¹⁵). In comparison to a clinical-only model, a risk prediction model for cardiotoxicity that included clinical and genetic factors had a higher prediction accuracy and a lower misclassification rate. In vitro inhibition of gene-related pathways (PI3KR2, ZNF827) protected cardiomyocytes from cardiotoxicity. The study identified cardioprotective variants in cardiac injury pathway genes, aided in the development of a prediction model for delayed anthracycline cardiotoxicity, and identified novel targets in autophagy genes for the development of cardioprotective drugs.

Similar AI methods may potentially be applied to the study of electrophysiological parameters associated with adverse cardiovascular events from cancer therapy. The use of iPSC-CMs in cardio-oncology investigations is growing [130,131], and these include electrophysiology studies in cardio-oncology [132,133]. A translational study of acquired prolonged QT, or long QT syndrome (LQTS), and torsades de pointes (TdP) in iPSC-CM and in more than 6 million male patients from the United Kingdom Vigibase database investigated clinical features and underlying mechanisms of LQTS associated with androgen deprivation therapy (ADT) used to treat prostate cancer [132]. Particularly, enzalutamide (an androgen receptor antagonist) was associated with a higher rate of death compared to other ADT drugs used to treat prostate cancer (17% versus 8.1%, p < 0.0001). In this same translational study, enzalutamide was shown to prolong action potential durations and induced afterdepolarizations in iPSCs, via inhibition of the delayed rectifier potassium current and activation of the late sodium current; administration of the androgen dihydrotestosterone counteracted the effects of enzalutamide. It would be interesting to evaluate and determine the utility of applying machine learning or subset deep learning AI algorithms to electrophysiological changes in iPSCs in response to cancer therapies to predict (and ultimately prevent) adverse events in cardio-oncology.

7. Challenges and limitations

Despite early proof-of-concept publications in cardio-oncology, there is an unmet need for additional investigation of machine learning-based approaches in dedicated cardio-oncology cohorts. Prospective studies examining the impact of this technology on patient outcomes may shed additional light on the utility of AI utility for cardio-oncology patients. The widespread use of machine learning approaches is constrained by their heterogeneity and logistical challenges associated with their seamless integration into contemporary clinical practice [9]. Additionally, the validity and efficacy of such methods have not been established in well-designed prospective studies [39]. Current data challenges will need to be overcome through open access to algorithms and auto-population of research databases across multiple institutions to enable algorithms to be externally validated. Algorithms integrated as plugins into clinical systems may aid physicians by alerting them to subtle changes in their data interpretation that may require additional workup in high-risk patients.

We have discussed ECGs, echocardiograms, laboratory, and electronic health record data as input to algorithms. Additional publications on cardiac magnetic resonance, computed tomography, and nuclear imaging are also becoming available [6,29,40–42]. These cardio-oncology applications for patients at risk of coronary ischemia, myocarditis, hyperinflammatory response, and other conditions will almost certainly continue to benefit from ML research. Over the last decade, the use of AI applications in medicine has grown exponentially, particularly for remote monitoring and mobile and connected health, such as using smart devices (e.g., smartwatches) or smartphone apps to diagnose or manage various cardiac diseases [6,7]. Along with cardiomyopathy, the use of smartwatches to predict other cardiovascular
conditions such as atrial fibrillation is being studied and may become more prevalent in the future [6]. This has enormous potential for cardio-oncology patient monitoring.

Globally, significant advancements in cancer diagnosis and treatment have resulted in a continuous increase in the number of survivors. The application of machine learning to predict cardiac dysfunction (cardiomyopathy, left ventricular systolic dysfunction) in cancer survivors is of particular interest in cardio-oncology. Using machine learning to predict cardiac dysfunction in cancer survivors was more predictive than clinical laboratory data alone. However, combining both types of data resulted in the most precise prediction. In cardio-oncology, recent research indicates that machine learning can be used to analyze ECGs to detect subclinical cardiac dysfunction prior to major echocardiographic changes in patients receiving chemotherapy. Thus, machine learning algorithms have been used to detect subtle differences in cardiac mechanics in cancer survivors prior to the onset of overt cardiac dysfunction.

Additionally, efforts to apply AI in clinical practice must be directed toward overcoming rather than propagating health inequities and bias [43]. This is especially true in cardiology, oncology, and cardio-oncology, all of which are fields in which African Americans, for example, face a disproportionate risk of poor outcomes when compared to their Caucasian counterparts. For use in cardio-oncology, AI algorithms will need to be tested and validated in diverse populations, to ensure their appropriate and equitable use. Great care must be taken to ensure that AI models are generalizable to diverse populations, and that their implementation does not reflect or perpetuate healthcare disparities. The AI-ECG algorithms we have assessed in cardio-oncology so far show great promise for the detection of low ejection fraction across a range of ethnic and racial subgroups [134]. However, we must remain cognizant of the risk of AI models to reflect, perpetuate, and even promote bias in medicine.

Another challenge in developing and implementing AI-based clinical decision support tools on ECG is the infrastructural unpreparedness. The majority of AI-ECG models rely on using raw digital time-voltage ECG data. These raw data are typically not available through electronic health records and are typically underutilized/untouched in over 99% of institutions. Accessing these raw ECG data and integrating these data with clinical information requires technical knowledge and infrastructural investment. Further, in many cases, these raw ECG data are proprietary to vendors, making it more challenging to access ECG data for research purposes. These are not limitations specific to cancer survivors. However, studies involving cancer survivors often have small sample sizes. This compounds the limitations because large sample sizes are needed for training deep learning models.

We recognize that in general individual AI models can vary greatly depending on the architecture, data used to train, training methodology, and so on. Consequently, each model should be evaluated separately for generalizability and absence of propagation of bias. Additional challenges of AI-ECG include distinguishing signal data from noise (especially in wearables), recognizing and avoiding false positives or negatives, and optimizing the implementation of technologies to improve morbidity and mortality.

8. Conclusion

These studies add to the body of evidence demonstrating the utility of machine learning in predicting cardiac dysfunction in cancer survivors. As a result, AI has the potential to make a significant difference in predicting cardiac dysfunction in cancer survivors. In particular, over the course of half a century, ECG parameters have been evaluated and found to associate with (and perhaps predict) systolic dysfunction. With the dawn of the digital era, it will be prudent to advance our application of AI-ECG in cardio-oncology. Future studies should assess the ability of AI-ECG to predict the development of different cardiomyopathy phenotypes, AF, and other forms of cardiovascular toxicities in both children and adults, creating greater opportunity to pursue prophylactic and preventive cardioprotective measures, while facilitating cancer cure or palliation. One could imagine using AI-ECG to create an individualized profile of cardiotoxicity risk that could be used to tailor treatment choices and cardiovascular monitoring. Such applications are preco-

ors. As a result, AI has the potential to make a significant difference in cardio-oncology. Future studies should assess the ability of AI-ECG to predict the development of different cardiomyopathy phenotypes, AF, and other forms of cardiovascular toxicities in both children and adults, creating greater opportunity to pursue prophylactic and preventive cardioprotective measures, while facilitating cancer cure or palliation. One could imagine using AI-ECG to create an individualized profile of cardiotoxicity risk that could be used to tailor treatment choices and cardiovascular monitoring. Such applications are precocious at this point, but we anticipate that, with time, we will be able to leverage AI technologies to personalize care. This application of AI-ECG in cardio-oncology may be helpful to transform care in small and large hospital, academic, community, and rural practices, especially utilizing fast-paced low-cost pragmatic trial embedded in the electronic health records. Such incorporation of AI-ECG into cardio-oncology and other precision medicine programs may be beneficial to predict, preempt, and optimize cardiovascular health.

We did not obtain ethical/IRB approval for this literature review.

CRediT authorship contribution statement

Conception and design: SAB. Drafting of the manuscript: SAB, DLM. Interpretation of data: SAB, DLM, PN, OA, JH, KR, AH, RM, AS, RD, FG, JLJ. Critical revision: SAB, DLM, PN, OA, JH, KR, AH, RM, AS, RD, FG, JLJ, SAB. Final approval of manuscript: All authors.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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