ESC European Society of Cardiology

European Heart Journal - Digital Health (2023) **4**, 302–315
https://doi.org/10.1093/ehjdh/ztad031

ORIGINAL ARTICLE

Artificial intelligence modelling to assess the risk of cardiovascular disease in oncology patients

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Received 10 October 2022; revised 11 April 2023; accepted 4 May 2023; online publish-ahead-of-print 8 May 2023

Aims There are no comprehensive machine learning (ML) tools used by oncologists to assist with risk identification and referrals to cardio-oncology. This study applies ML algorithms to identify oncology patients at risk for cardiovascular disease for referrals to cardio-oncology and to generate risk scores to support quality of care.

Methods and results De-identified patient data were obtained from Vanderbilt University Medical Center. Patients with breast, kidney, and B-cell lymphoma cancers were targeted. Additionally, the study included patients who received immunotherapy drugs for treatment of melanoma, lung cancer, or kidney cancer. Random forest (RF) and artificial neural network (ANN) ML models were applied to analyse each cohort: A total of 20 023 records were analysed (breast cancer, 6299; B-cell lymphoma, 9227; kidney cancer, 2047; and immunotherapy for three covered cancers, 2450). Data were divided randomly into training (80%) and test (20%) data sets. Random forest and ANN performed over 90% for accuracy and area under the curve (AUC). All ANN models performed better than RF models and produced accurate referrals.

Conclusion Predictive models are ready for translation into oncology practice to identify and care for patients who are at risk of cardiovascular disease. The models are being integrated with electronic health record application as a report of patients who should be referred to cardio-oncology for monitoring and/or tailored treatments. Models operationally support cardio-oncology practice. Limited validation identified 86% of the lymphoma and 58% of the kidney cancer patients with major risk for cardiotoxicity who were not referred to cardio-oncology.

Lay Summary Cancer survival rates continue to improve due to advancements in medical science. While new treatments increase survival, they can lead to side effects due to the toxicity of cancer therapies. Cardiotoxicity, harm caused to the heart from medication or treatment, impacts heart health of cancer survivors and is rated as the second leading cause of death after a cancer diagnosis. Cardio-oncology is a new and growing field that focuses on improving heart health in cancer patients and cancer survivors. As a new field, the identification of who to refer to cardio-oncologists remains spotty. Using machine learning (ML) approach and structured input from physicians specialized in cardio-oncology, oncology, and family medicine, we created and validated predictive models that help identify and refer eligible patients with cardiovascular issues to cardio-oncology specialists.

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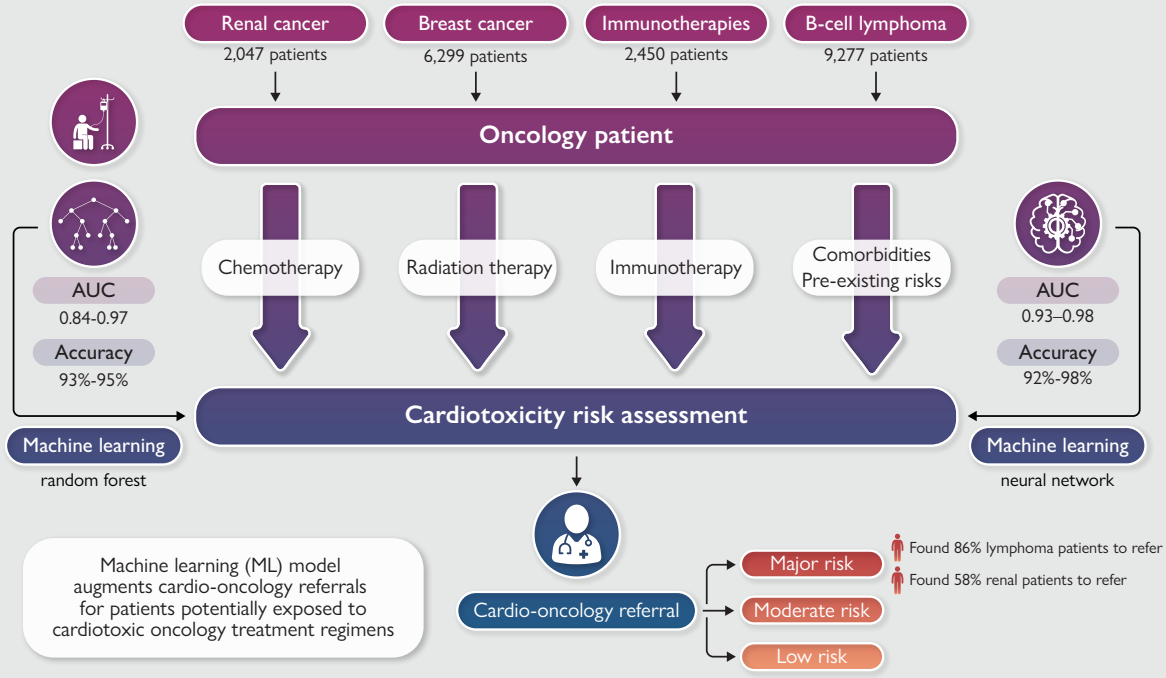
This research demonstrates the ability of predictive ML models to identify individuals at risk for cardiovascular problems during cancer treatment. These models, when integrated in electronic health record (EHR) systems, may alert physicians of cancer patients about the potential risk and promote a standardized and timely referral to cardio-oncology. Implementation of ML algorithms in medical practice has implications for future cardiotoxicity research. By establishing foundation for specialized real-world evidence (RWE) patient data sets combined with other information such as genetics, proteomics, electrocardiogram (ECG), new biomarkers, and unstructured clinical notes, computer models can help scientists answer research questions about cardiotoxicity through insights derived from data.

Graphical Abstract



Keywords Medical artificial intelligence • Cardio-oncology • Machine learning • Cardiotoxicity • Cardiovascular risk assessment • Cardiovascular disease

Introduction

Cardiotoxicity is defined by the US National Cancer Institute as any 'toxicity that affects the heart'.[1] More specific clinical definitions of cardiotoxicity include changes in the left ventricular ejection fraction (LVEF), such as a decline of 10% points to a LVEF below 53%.[2] There is a wide range of medications that can affect the heart, but this area is predominated by oncologic therapies including chemotherapy, radiotherapy, targeted therapy, and immunotherapy. More than 30% of cardiovascular disease (CVD) in cancer patients is attributed to toxicity caused by anticancer therapies.[3] Many of these events are acute or subacute, but some therapies cause cardiotoxic events decades after the completion of a cancer treatment.

Historically, patients are referred to cardiologists by their oncologists when cardiovascular complications are observed. However, general cardiologists may not be sufficiently knowledgeable in the various cardiac toxicities of historic and novel cancer treatments.[4] Particularly, with the increased development of new oncologic therapies, many cardiologists may not be familiar with the class of therapy their patient is receiving. Thus, over the last decade, the field of cardio-oncology has grown and matured to address this knowledge gap.

Cardio-oncology is an emerging field focused on the prevention and treatment of CVD developing among cancer patients and survivors. Great progress has been made in research and clinical applications, as well as improving awareness, but standardized recommendations and structured workflow among oncologists and cardio-oncologists are still limited.[5] This is due in part to the lack of integrated workflow technology that could facilitate and support partnership between oncology and cardio-oncology practices to improve coordination. Recently, a risk score stratification was developed by the European Society of Cardiology (ESC), aiming to identify patients at risk for cardiotoxicity

development, prior to the initiation of cancer therapy, who should be referred for cardio-oncology assessment.[2,6,7] However, it included multiple clinical parameters, making its use challenging for the oncologist. Therefore, there is an urge for a simpler, automated risk assessment strategy to accurately recognize patients at risk for cardiotoxicity and facilitate coordination between an oncologist and a cardio-oncology practice, resulting in early diagnosis to help improve the patient prognosis.

Aside from limited developments focused on a single element of cardiovascular care, there is little comprehensive analytical support for cardio-oncology despite opportunities for automated identification of potential referrals and proper risk assessment given vast amounts of information contained (but not summarized) in medical records. A machine learning (ML) model capable of identifying patients regardless of their demographics and access to care would constitute a breakthrough that has so far relied on organic growth with sporadic patient access to care. Particularly, this model is necessary to undertake the task of producing accurate and timely patient referrals according to the risk of developing cardiovascular complications and based on assessments derived from patient information stored in medical records—the primary goal of this ML model development study.

Integrating ML models applied in cancer patients' electronic health record (EHR) workflow will improve patient care. This is accomplished by using the predictive models for the stratification of CVD risk scores. Operational reports can be generated to flag patients with high risk. Likewise, alerts can be triggered when a patient chart is under review. Finally, the application of ML into EHR system introduces electronic guidelines applied across the board for eligible patient populations and ensures appropriate patient referrals, as well as equity in access to cardio-oncology care as an inconspicuous benefit. The models automate referrals based on clinical data and reduce reliance on human factors that could leave some patient populations at a disadvantage depending on their access to quality care. Machine learning serves as an equalizer of opportunities as it only utilizes those factors that are built into the algorithms and bypasses human factors in the decision-making process. Machine learning also serves in an implementation role ensuring that the latest clinical cardiotoxicity guidelines are converted into predictive models in EHR to accommodate the dynamic nature of cardio-oncology as an evolving medical specialty.

Machine learning technology is a discipline of artificial intelligence (AI) and computer science that utilizes algorithms to find patterns in data. Supervised ML algorithms involves training algorithms using empirical data.[8] This type of learning utilizes input data to create models that can predict future events. Random forest (RF) and artificial neural network (ANN) algorithms were utilized in this study to create cardiotoxicity predictive risk score models. Treatment of cancer patients compels the need for the development of a model for identifying patients who are at risk of developing CVD. The risk of CVD is determined by several factors including demographics, medical history of cardiac risk factors, genetic attributes, cardiac biomarkers, and numerous observations from laboratory, imaging studies, and other diagnostic tests that are accounted for in the overall complexity of estimating the potential impact of cardiotoxicity.[6,9–14] These factors were accounted for in the ML model, targeting the primary goal of developing a referral tool that assesses the overall risk of CVD in cancer patients.

Methods

In this retrospective study, ML models were created for referring eligible patients to cardio-oncologists based on predicted risk of developing CVD in cancer patients. Supervised ML models were trained on de-identified data sets, which were comprised of four patient cohorts: breast cancer, kidney cancer, B-cell lymphoma, and patients treated with immunotherapy drugs for melanoma, lung cancer, or kidney cancer. Cohorts were formed by a selection of the applicable International Classification of Diseases 9th and 10th Editions-Clinical Modification (ICD-9-CM and ICD-10) diagnosis codes directly related to the above cancers. For patient records dated prior to 1 October 2015, when ICD-10 entered circulation in clinical documentation in the USA, the corresponding ICD-9-CM codes were utilized in the model. *Table 1* lists ICD-10 codes and the corresponding diagnoses incorporated into the model.

The data were obtained from Vanderbilt University Medical Center (VUMC) Department of Biomedical Informatics Synthetic Derivative (SD) Database.[29] The SD database contains de-identified data derived from the VUMC EHR system as a stand-alone research resource. It contains ICD-9 and ICD-10 billable codes, current procedure terminology (CPT) codes, medications, lab results, and demographic data. A non-human subject Institutional Review Board (IRB) application was approved to conduct this study.

A startup funding totalling about $2000 was internally approved by VUMC to extract data sets for each cohort using code and medication qualifiers. *Table 2* lists medications probed for each cohort, with finer details provided in the data supplement (Supplementary data online, *Tables F–I*).

A team of cardio-oncology specialists devised the risk factors as inputs into the ML model, shown in *Table 3*, for calculating the risk scores. The risk factors are comprised of the cancer therapies, medications, patient test results, medical conditions, or individualized patient attributes. Using the Delphi methodology, the subject area clinical experts arrived at four different risk scores: *major*, *moderate*, *low*, and *potential*. These risk factors are corroborated by clinical literature.[6,9–14] The clinical experts also recommended oncology use cases selected for the retrospective study based on prevalence of cardiotoxicity within these use cases. These use case selections were also made based on sufficiency of the available patient data to support training of the ML models. In total, there are 21 risk factors for breast cancer and B-cell lymphoma and 20 factors for kidney and immunotherapy cohorts since chest radiation therapy was not a risk factor for those. Cancer therapy dosages, while known to affect the cardiotoxic risk mainly related to anthracyclines, were de-prioritized based on the main premise of the project to refer patients exposed to cardiotoxic treatments and research showing that even smaller doses of therapies such as anthracyclines warrant appropriate follow-up with a cardiologist.[30]

The clinical risk estimation model was developed wholistically, taking assessment of the entire patient history available in EHR into consideration, which includes pre-existing conditions and those conditions developed at the time of exposure to oncology regimens. The model keeps track of the timespan and is capable of reporting on medical conditions prior and after exposure. The reason for this wholistic focus on the entire patient record is purpose of the project—to refer eligible patients when appropriate by assigning a risk score, rather than to conduct pre-/post-exposure experiments, or attempting to predict an outcome of cardiotoxic exposure.

Using Python programming language, a script was developed to assemble the risk factors for each patient. For each cohort, a data set containing patients' risk factors was created for ML training and testing. Each risk factor was coded as 0 or 1 representing absence or presence of the risk, respectively. The outcome is a data set containing a snapshot of each patient risk factors overtime as he/she ages. Risk factor snapshots were taken at yearly increments over the span of patient care history and as the patient aged. *Table 1* lists the clinical risk factors identified for this study. Lastly, to obtain a complete supervised training data set, a risk score variable was added as formulated by the clinical experts. The risk score calculation is described in *Table 3*. The risk score is a number between 0 and 3 representing *potential*, *low*, *moderate*, and *major* risks, respectively. Calculations utilize any and all data available for a patient, thus enabling us to deal with missing data by simply utilizing what we do know about the patient. A certain number of risk factors under one risk level may upgrade the risk and warrant migration of risk status into a higher category, as outlined in *Table 3*.

A supervised ML algorithm will try to find the best function that maps between the input (risk factors) and the output (risk score) using the constructed supervised data set. A supervised model is the best controlled method of ensuring that it incorporates feedback from clinicians, inputs from continued release of the updated clinical guidelines,[7] and allows for maintenance as a 'living' model. Mathematically, this algorithm can be described more formally as a function:

$$y_n = f(x_n) \text{ for } n = 1, 2, 3, \ldots, n$$

where y_n represents the risk score, x_n represents the risk factors, and n represents the row number in the data set.

Table 1 Diagnoses and risk factors

Attribute	Description	Source
Breast Cancer	Breast cancer diagnosis	ICD: C50[a]
B-Cell Lymphoma	B-cell lymphoma diagnosis	ICD: C83.0[a], C83.0[a], C85.1[a], C85.2[a], C88.0
Kidney Cancer	Kidney cancer diagnosis	ICD: C65.1, C65.9 C68.0, C68.1, C68.8, C68.9, C79.0[a]
Immunotherapy-Specific Cancers	Melanoma, lung cancer, or kidney cancer diagnoses	ICD: C34[a], C46[a], C64[a], C78.0[a], C78.2[a], C79[a]
OVER_65[6,15]	Patient over 65 years old	Patient demographic
AF_AM[16]	African American race	Patient demographics
Radiation[6]	Radiation therapy	CPT
SYSTOLIC[17]	Systolic heart failure	ICD: I50.20, I50.21, I50.22, I50.23, I50.40, I50.41, I50.42, I50.43
ISCHAEMIC[18,19]	Ischaemic cardiomyopathy	ICD: I25.5
CORONARY_ARTERY_DISEASE[20,21]	Coronary artery disease	ICD: I25.70[a], I25.71[a], I25.72[a], I25.73[a], I25.75[a], I25.76[a], I25.79[a], I25.8[a]
DIASTOLIC[21]	Diastolic heart failure	ICD: I50.30, I50.31, I50.32, I50.33
HYPERTENSION[6,22]	Hypertension	ICD: I10
DIABETES[6,21]	Type I or type II diabetes	ICD: E10[a], E11[a]
HYPERLIPIDAEMIA[11,23]	Hyperlipidaemia	ICD: E78[a]
XANTHOMA[11,23]	Xanthoma	ICD: H02.60, K13.4 E75.5, E78.2
ATRIAL_FIBRILLATION[24]	Atrial fibrillation	ICD: I48[a]
LDL_GE_190[11,23]	LDL ≥ 190	Lab result
LDL_160_189[11,23]	LDL between 160 and 189	Lab result
HDL_LE_40[23]	HDL ≤ 40	Lab result
HDL_41_59[11,23]	HDL between 41 and 59	Lab result
EF_LE_50[6,22]	EF ≤ 50%	Lab result
EF_51_54[6,22]	EF between 51% and 54%	Lab result
BMI_GT_35[9,25]	BMI > 35	Measure
A1C_GT_9[26]	A1C > 100	Lab result
BNP_GT_100[27]	BNP > 100	Lab result
CURRENT_SMOKER[10,11,20,23]	Current smoker	Patient history
FORMER_SMOKER[10,11,20,23]	Former smoker	Patient history
TRPI_GT_02[28]	TRPI > 02	Lab result
SEVERE_AORTIC_STENOSIS[6]	Severe aortic stenosis	Echocardiogram
SEVERE_MITRAL_REGURGITATION[6]	Severe mitral regurgitation	Echocardiogram
BP_GE_140_90[6,22]	Systolic BP ≥ 140 and diastolic BP ≥ 90	Measure
RVSP_GE_60[17]	RVSP ≥ 60	Echocardiogram

A1C, haemoglobin HbA1c test; BMI, body max index; BNP, brain natriuretic peptide test; EF, ejection fraction; TRPI, troponin test; ICD, international classification of disease; CPT, current procedure code.
Present attributes are converted to binary values. If a condition is present based on ICD codes, then the attribute is marked as 1 otherwise 0. This is a necessary format to use for machine learning algorithms as numerical data are required.
[a]Indicates a group code and there are multiple codes that contain a greater level of detail.

To create and assess a ML model, the supervised data set is split into training data set, 80%, and test data set, 20%. The test data set is used to evaluate the model performance. *Figure 1* shows the entire system process flow at a high level.

Two different ML multiclass algorithms were used for creating predictive models, RF and ANN. Multiclass classifier algorithms make predictions into three or more classes. This was necessitated as our function y_n or prediction score is composed of four different classes or risk score outcomes. Python Spark ML libraries for RF classifier[31] and ANN multilayer perceptron classifier[32] (MLPC) were chosen to train these models. The RF classifier is an ensemble of many decision tree classifiers.[33] To classify an input vector x_n, each decision tree is used to give a classification output y_n. This is normally referred to as the decision tree 'vote'. The chosen prediction is the classification with the most 'votes'.

The RF can be described as an algorithm of applying wisdom of the majority. Using a tree ensemble approach improves accuracy and reduces the risk of overfitting. Artificial neural network is a computing model fashioned after the brain neural network which consists of neurons and synapses. Each node represents a function, and every connection between two nodes represents a weight used by the node function.[34] An input vector x_n is fed into the network through the input layer which is evaluated throughout the network via one or more hidden layers producing a prediction outcome y_n represented by the output layer. Multilayer perceptron classifier is a supervised learning multilayer perception algorithm with backward propagation. *Figure 2* outlines the key components of an ANN.

Model validation was performed on a limited data set collected by medical fellows looking through patient charts for B-cell lymphoma and kidney cancer patients. Validation was approved by the IRB office under the terms

Table 2 Medications by cohort

Cohort	Medication	Number of Medication Administrations per Medication Group
Breast Cancer	**Bevacizumab** (**Avastin**, Mvasi, Zirabev)	732
	Daunorubicin (Vyxeos)	18
	Doxorubicin (**Adriamycin**)	2484
	Idarubicin (Idamycin)	29
	Epirubicin (Ellence)	41
	Hyaluronidase and Pertuzumab (Perjeta, Phesgo)	111
	Lapatinib (**Tykerb**)	345
	Neratinib (Nerlynx)	
	Ramucirumab (Cyramza)	
	Trastuzumab (Enhertu, **Herceptin**, Herzuma, Hylecta, Kadcyla, Kanjinti, Ogivri, Ontruzant, Phesgo, Trazimera)	2219
	Tucatinib (Tukysa)	
B-cell Lymphoma	**Acalabrutinib** (**Calquence**)	25
	Bendamustine (Belrapzo, Bendeka, Treanda)	
	Bortezomib (Velcade)	995
	Cisplatin (**Platinol**)	392
	Cyclophosphamide	3145
	Doxorubicin (**Adriamycin**)	2918
	Etoposide (**Etopophos**, Toposar, Vepesid)	1846
	Everolimus (Afinitor, Zortress)	21
	Ibritumomab (Zevalin)	
	Ibrutinib (**Imbruvica**)	524
	Lenalidomide (**Revlimid**)	1015
	Obinutuzumab (Gazyva)	
	Pembrolizumab (**Keytruda**)	51
	Rituximab (Riabni, **Rituxan**, Ruxience, Truxima)	4928
	Venetoclax (Venclexta)	
	Vincristine (Marqibo, Oncovin, Vincasar)	2288
Kidney Cancer	Axitinib (Inlyta)	
	Bevacizumab (**Avastin**, Mvasi, Zirabev)	625
	Cabozantinib (Cabometyx, Cometriq)	
	Everolimus (Afinitor, Zortress)	245
	Lenvatinib (Lenvima)	
	Pazopanib (Votrient)	
	Regorafenib (Stivarga)	
	Sorafenib (**Nexavar**)	327
	Sunitinib (**Sutent**)	774
	Temsirolimus (**Torisel**)	326
	Tivozanib (Fotivda)	
	Vandetanib (Caprelsa)	
Immunotherapy	**Nivolumab** (**Opdivo**)	1488
	Pembrolizumab (**Keytruda**)	1176
	Ipilimumab (**Yervoy**)	1210
	Durvalumab (Imfinzi)	102
	Atezolizumab (**Tecentriq**)	185
	Avelumab (**Bavencio**)	25

Bolded medication names indicate that the medication was used for at least one of the patients in that cohort, and non-bolded medications indicate that none of the cancer patients in that cohort was prescribed that medication.

Any totals for drug administrations per patient cohort may differ from the total number of patients found in each cohort, due to several factors including administration of more than one drug, multiple administrations of drugs for several cancer recurrences over medical history, treatment was not administered for medical reasons, and other causes.

Table 3 Risk score calculation and the resulting clinical risk model

Risk Score	Risk Factors
Potential	Any patient in any of the cohorts on medications listed in medication *Table 2*
Low	Hyperlipidaemia
One or more of these risk factors	HDL between 41 and 59
	LDL between 160 and 189
	Former smoker
Moderate	Essential hypertension
Two to four of these risk factors	HDL ≤ 40
	Diabetes mellitus
	Age over 65
	African American race
	LDL ≥ 190 and/or xanthoma
	BMI > 35
	Current smoker
	EF 51–54%
	Blood pressure ≥ 140/90
	Pro-BNP ≥ 400
	BNP > 100
Major	Radiation
One or more of these risk factors.	Systolic heart failure
Five or more of the *moderate risk factors*. Also two or more of the *immunotherapy drugs*.	Ischaemic cardiomyopathy and other cardiomyopathy
	Coronary artery disease
	Diastolic heart failure
	Severe aortic stenosis
	Severe mitral regurgitation
	Atrial fibrillation
	EF ≤ 50%
	Severe pulmonary hypertension (RVSP > 60)
	Troponin > 0.02
	A1C > 9

Risk scores depend on the presence and quantity of risk factors. Some risk factors weigh more than others in calculating the risk score.

and methods described in the following sentences. Data collected contained risk factors for each patient and an indicator flag denoting referral to a cardiologist. Medical fellows filled out structured spreadsheets with columns representing discrete data types accessed by ML models and rows representing each patient record. A 'dummy' patient number was recorded and tracked to ensure that patient records were properly matched yet revealing no identification of the patient and thus maintaining the de-identified nature of the ML data access. The data from spreadsheets was entered into ML models to produce referral recommendations and risk scores, subsequently discussed with practicing oncologists and cardio-oncologists on the clinical team to verify clinical validity of the output.

Machine learning was a strategic choice for this research project: as algorithms are enhanced from this prototype with more variables and data types such as genetic and proteomic data, computer models will be ready to accept greater data challenges that require ML, including natural language processing (NLP), to analyse patient charts in search of the early pre-treatment intervention opportunities. This issue can be better understood when considering the important trend of the growing use of immune therapies and, even more so, the use of new types of combined oncologic therapies such as immune checkpoint inhibitor (ICI) + ICI or ICI and chemotherapy. When implemented as a prospective study and a service to medical practice, the program will inevitably face larger volumes of data and must be ready for growth in the face of such volumes. Rule-based methods of data analysis can be effective with small(er) amounts of retrospective data, but not for training and prospective studies analysing large amounts of patient data in real time.

Results

A total of 20 023 records were analysed (breast cancer, 6299; B-cell lymphoma, 9227; kidney cancer, 2047; and immunotherapy for patients with melanoma, lung cancer, or kidney cancer, 2450). Data supplement (see Supplementary data online, *Tables A–D*) contains demographic and clinical details about each cohort of patients. Data were randomly divided into training (80%) and test (20%) data sets. Random forest and ANN performed over 92% for accuracy and performed over 82% for area under the curve (AUC) with 95% confidence interval (CI), except for RF immunotherapy cohort where CI was <95%. Per results outlined in *Table 4*, all ANN models performed better than RF models on accuracy and AUC metrics. *Figures 3–6* show top and bottom AUC comparisons of RF vs. ANN for all cohorts. While other potential metrices could be produced and reported to show performance of the ML models, accuracy and AUC metrics are good statistical representations of the ML model performance, for programmed algorithms implementing dynamic data mining and analysis functions.

The data sets which included the risk factors for each patient were run against the corresponding B-cell lymphoma and kidney cancer ML models calculating cardiotoxicity score for each patient. As shown in *Table 5*, out of 43 B-cell lymphoma patients who are not under the care of a cardiologist, 14 were considered major risk, 22 moderate risk, 3 low risk, and 4 potential risk. Twelve out of 14 (86%) patients with major risk were not referred to a cardiologist. Similarly for kidney cancer patients, out of 43 patients who are not under the care of a cardiologist, 19 were considered major risk, 21 moderate risk, and 3 potential risk. Eleven out of 19 (58%) of patients with major risk were not referred to a cardiologist. A complete breakdown of patient risk assessments is presented in the data supplement (Supplementary data online, *Table E*).

Discussion

This research is among early novel studies to apply ML to design and validate predictive risk models for CVD, adding to a small but growing number of efforts to quantify the risk of cardiovascular injury following exposure to oncology treatments.[35–37] This study was restricted to patients diagnosed with four types of cancer and to patients treated with specific anti-cancer therapies and medications. Validation effort with a subset of patients in the B-cell lymphoma and kidney cancer cohorts revealed the potential of ML models to effectively identify patients at risk for CVD, quantify this risk via prediction techniques, and assist clinicians and care coordinators with the creation of more consistent and reliable business processes to correctly refer cancer patients and expand access to quality cardiovascular care. The reported variations in the numbers and ratios of patients with major and moderate risks referred/not referred to a cardiologist, between lymphoma and kidney cancer patient cohorts, can be explained by variations in business practices rather than clinical factors or variances in the ML model performance.

Despite the relatively small validation data set, the predictive models have demonstrated that the majority of major risk cancer patients is not being appropriately referred to a cardiologist to mitigate the threat of

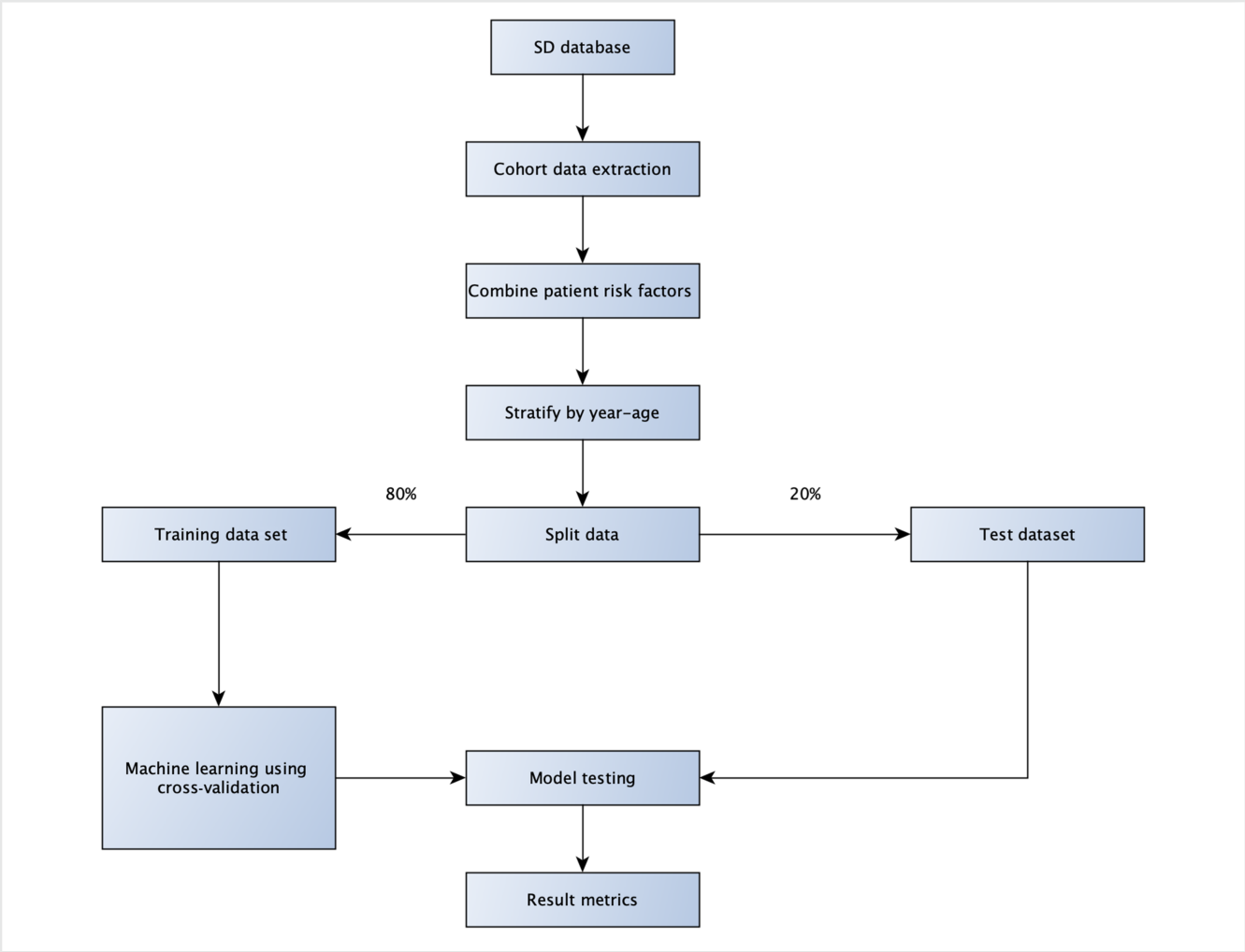


Figure 1 Method process flow. SD, synthetic derivative; ETL, extract; transform, and load; RF, random forest; ANN, artificial neural network; ML, machine learning. Data from VUMC SD database were extracted for each cohort. An ETL program written in Python was used to combine patient risk factors and stratify records by year–age making a suitable machine learning data set. Each data set was then split into training set (80%) and test set (20%). RF and ANN ML algorithms were trained using cross-validation to develop the models. The developed models were validated using the test data sets, and the statistical metrics were computed to measure model performances.

CVD. Undoubtedly, knowing the risks and pre-empting CVD development is a major concern for preventing comorbidity in patient care and ensuring better quality of life for cancer survivors post treatment through timely follow-up. Unlike human care coordinators, who would still be in charge of reviewing the output from computer models, ML algorithms can work around the clock and for years following exposure to cardiotoxic oncology treatments. Algorithms will then reliably mine available patient data and flag those who should be seen to prevent or address cardiovascular complications. Ultimately, all independent variables summarized in *Table 3* are available to the clinician in EHR yet require time, effort, and analysis to derive summative CVD assessment score. Medical providers operating in modern high-volume patient care settings have limited time to perform such assessment and reliably flag patients in need of cardiovascular care. Machine learning model serves as a reliable mechanism of ensuring that every oncology patient receives CVD assessment, every time. This study has potential to extend into other cancer types and therapies, but further research is necessary.

Study limitations

As any research project involving the application of computer algorithms in medicine, there are gaps to be noted. First, the study was approved as a retrospective research project with de-identified patient data, which did not allow researchers to test the entire output from computer models against full lists of patients referred to cardio-oncology. We relied on medical fellows to perform validation based on random sample of patients whose charts were reviewed in accordance with criteria set for the algorithms and without sharing identifiable patient information. Second, there are opportunities for enhancing the models with more variables as we continue the research and tap into new data sources. Third, there are no current ML approaches to risk modelling for cardio-oncology, so models were created with a combination of input from practicing clinicians and published medical literature. Our computer code is modular and can be updated to incorporate clinical risk modelling changes with relative ease as cardio-oncology field evolves.

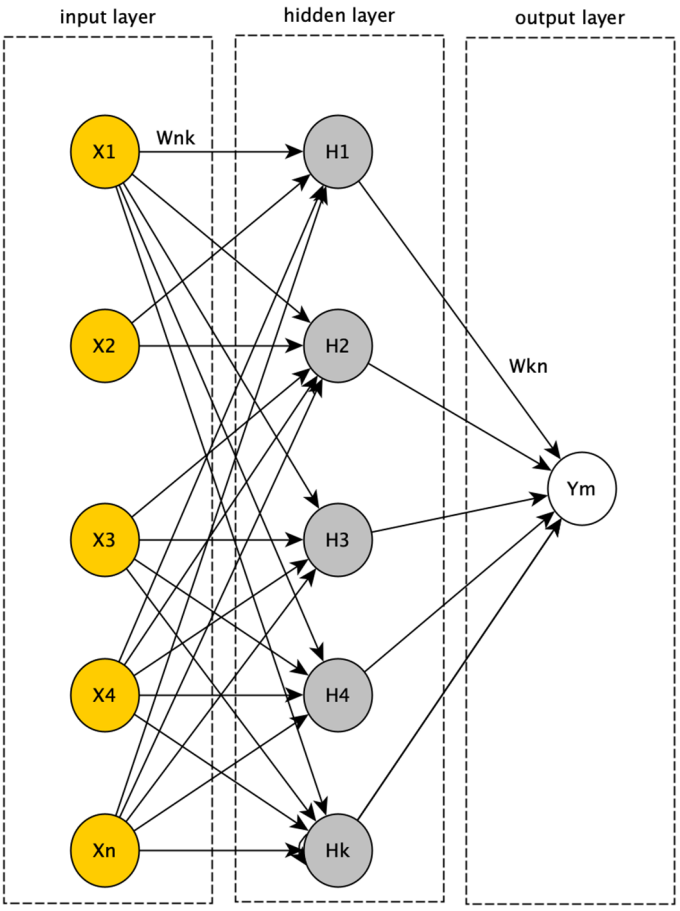


Figure 2 Artificial neural network architecture. In a supervised learning ANN algorithm, the weights *W* are adjusted repeatedly by comparing the prediction at the output layer with labels (true outcomes) to devise the best representative mathematical function.

Table 4 Statistical outcomes from random forest and artificial neural network cardiotoxicity risk predictions

Data set	Accuracy	Weighted Precision	Weighted Recall	AUC	AUC CI	Algorithm
B-cell lymphoma	0.929	0.931	0.929	0.909	0.853–0.965	RF
B-cell lymphoma	0.978	0.978	0.978	0.963	0.926–1.0	ANN
Breast cancer	0.926	0.929	0.926	0.904	0.846–0.962	RF
Breast cancer	0.974	0.974	0.974	0.984	0.959–1.0	ANN
Immunotherapy	0.944	0.946	0.944	0.968	0.934–1.0	RF
Immunotherapy	0.992	0.993	0.992	0.996	0.984–1.0	ANN
Kidney cancer	0.924	0.917	0.924	0.835	0.762–0.908	RF
Kidney cancer	0.986	0.986	0.986	0.931	0.881–0.981	ANN

AUC, area under the receiver operating curve; CI, confidence interval; RF, random forest; ANN, artificial neural network.

Fourth, we are still in the process of translating this research into medical practice as a prospective study with live identified patient data and cannot report on implementation strategies and outcomes. Yet, translation analysis has been completed and the models are built against real patient data in full volumes, on industry standard infrastructure and utilizing production quality development tools, so we are fully confident in our ability to deliver real value to patients and providers. Fifth, as any other business or clinical process at a healthcare organization, we rely on

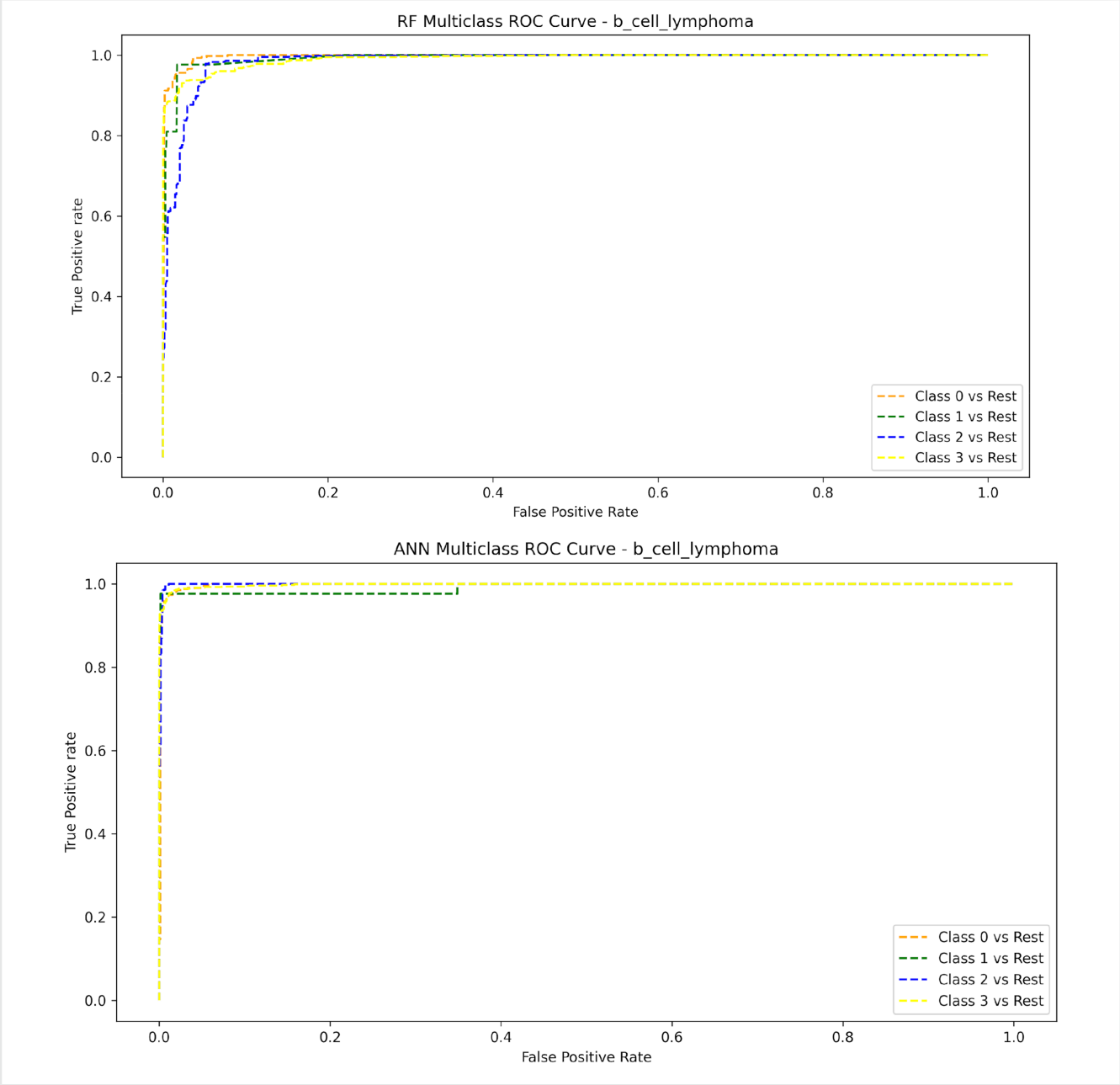


Figure 3 Operating characteristic area under the curve (AUC) plots for the B-cell lymphoma cohort. RF, random forest; ANN, artificial neural network; class: 0, potential; 1, low; 2, moderate; 3, major. Comparing the two plots shows that ANN model performed better in classification as its areas under the curves are slightly bigger.

EHR to serve as the accurate 'master record' for all patient history, after performing technical validation of the extracted data. By ingesting 'big data' into the ML model, we improve its accuracy by training it, yet must live with the potential inaccuracies of the source systems.

Translational outlook

There is a shortage of cardio-oncology practitioners at most institutions of care, and it would be up to each medical practice to determine their own strategies for employing output of the models to assist with referrals, i.e. only refer patients with the most critical needs and/or address needs of those patients who received specific cardiotoxic treatments of the utmost concern. In order to achieve this business objective and operational flexibility, justification for flagging patients with risks of cardiotoxicity can be provided as additional information to clinicians, as part of the output from computer algorithms. These business considerations would fold under the umbrella of a new translational project to migrate cardio-oncology ML models into medical practice. We are aware of the patient volume and staffing concerns and designed algorithms to be flexible and provide the maximum amount of relevant information to allow care coordinators to make informed decisions within the framework of real-world medical practices. In order to serve this

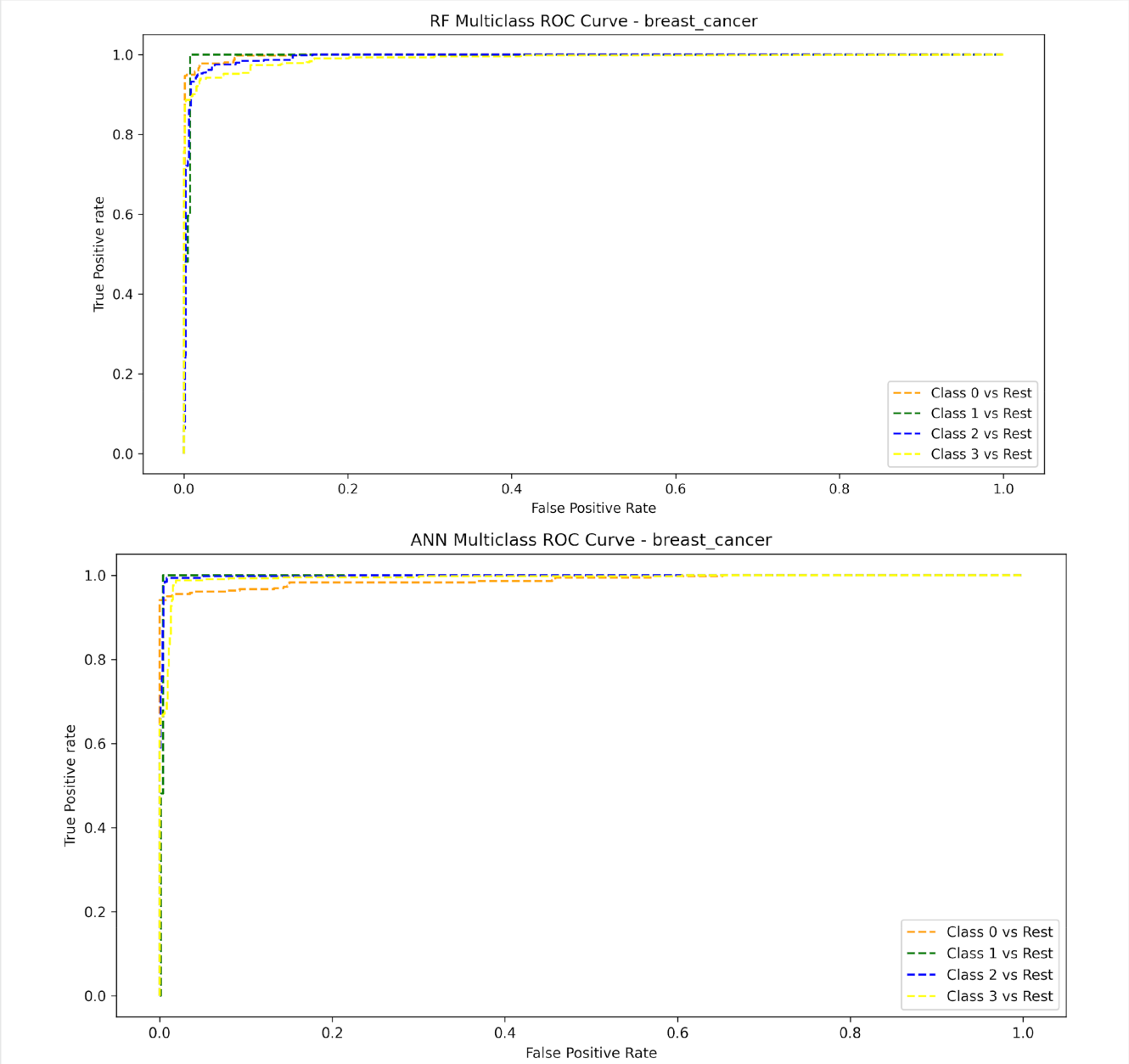


Figure 4 Operating characteristic area under the curve (AUC) plots for the breast cancer cohort. RF, random forest; ANN, artificial neural network; class: 0, potential; 1, low; 2, moderate; 3, major. Comparing the two plots shows that ANN model performed better in classification as its areas under the curves are slightly bigger.

need and aid the job of clinicians, explainable AI (XAI) elements would be added to the output, revealing top contributing factors that played major roles in the referral and risk classification.

In addition to care coordination, our clinical experts identified a potential opportunity to partner with primary care physicians (PCP) to share knowledge, information, and referral opportunities. Our study identified numerous patients with CVD risks, who had no regular contact with general cardiology specialists, which is a missed opportunity that could be partially fulfilled by PCP looped into the cancer care process.

A few other retrospective studies have outlined the potential for ML to improve upon human processes for identifying and highlighting cardiotoxicity risk.[35–37] These studies took unique approaches to building clinical risk models for predicting cardiovascular complications in oncology patients. Many of the clinical and cardiac imaging inputs are similar, yet categorization and grouping of the factors differ. We built our models with expected implementation for medical practice in mind and Python code in modular ways, separating each oncology use case into its own model for ease of modification and alteration as medical practice needs change and new data types get added. Our four simple risk 'buckets' are designed for simplicity and easy adoption into the workflows of busy oncology and cardio-oncology medical practices. New clinical risk models can be spawned on the basis of these

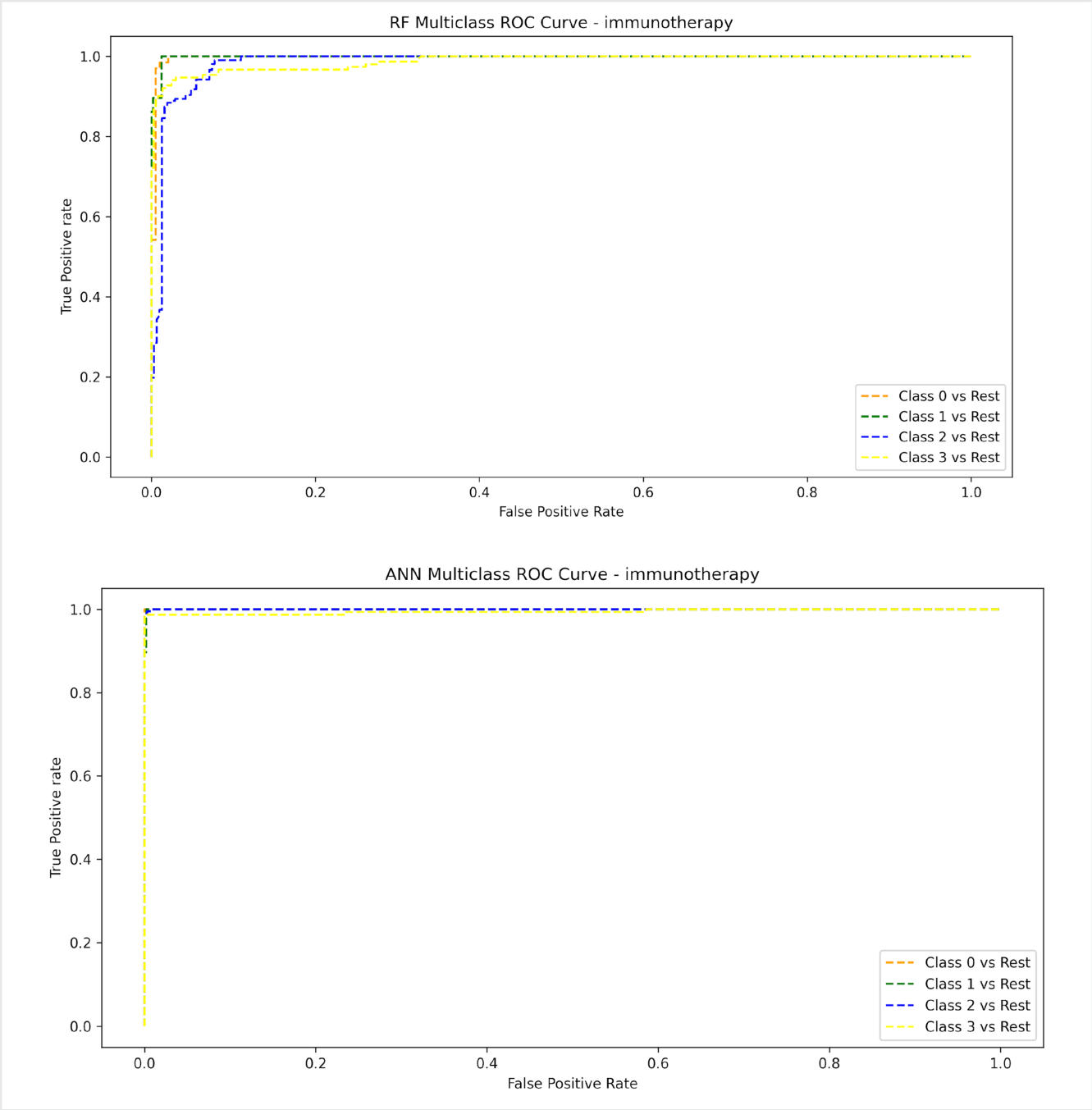


Figure 5 Operating characteristic area under the curve (AUC) plots for the immunotherapy cohort. RF, random forest; ANN, artificial neural network; class: 0, potential; 1, low; 2, moderate; 3, major. Comparing the two plots shows that ANN model performed better in classification as its areas under the curves are slightly bigger.

existing models, in collaboration with clinicians specializing in the corresponding types of cancer. The research team is in the process of implementing a prospective study in partnership with a kidney cancer specialist.

Conclusion

This study demonstrates a capability of AI to support cardio-oncology medical practice and displays the potential for computer-based automation to provide oncology patients with an equitable opportunity to access the latest advances in cardiovascular care. Identification of patients at risk for CVD from their cancer treatments is essential to improving clinical care, and this model offers a novel and effective method to ensure appropriate triage. Artificial intelligence offers providers a reliable mechanism for improving business practices and quality of care by tracking CVD risk continuously throughout the cycle of patient care. Building enriched cardio-oncology data sets with eligible patient populations mined using sophisticated computer algorithms opens far-reaching research potential for discovering cardiotoxicity

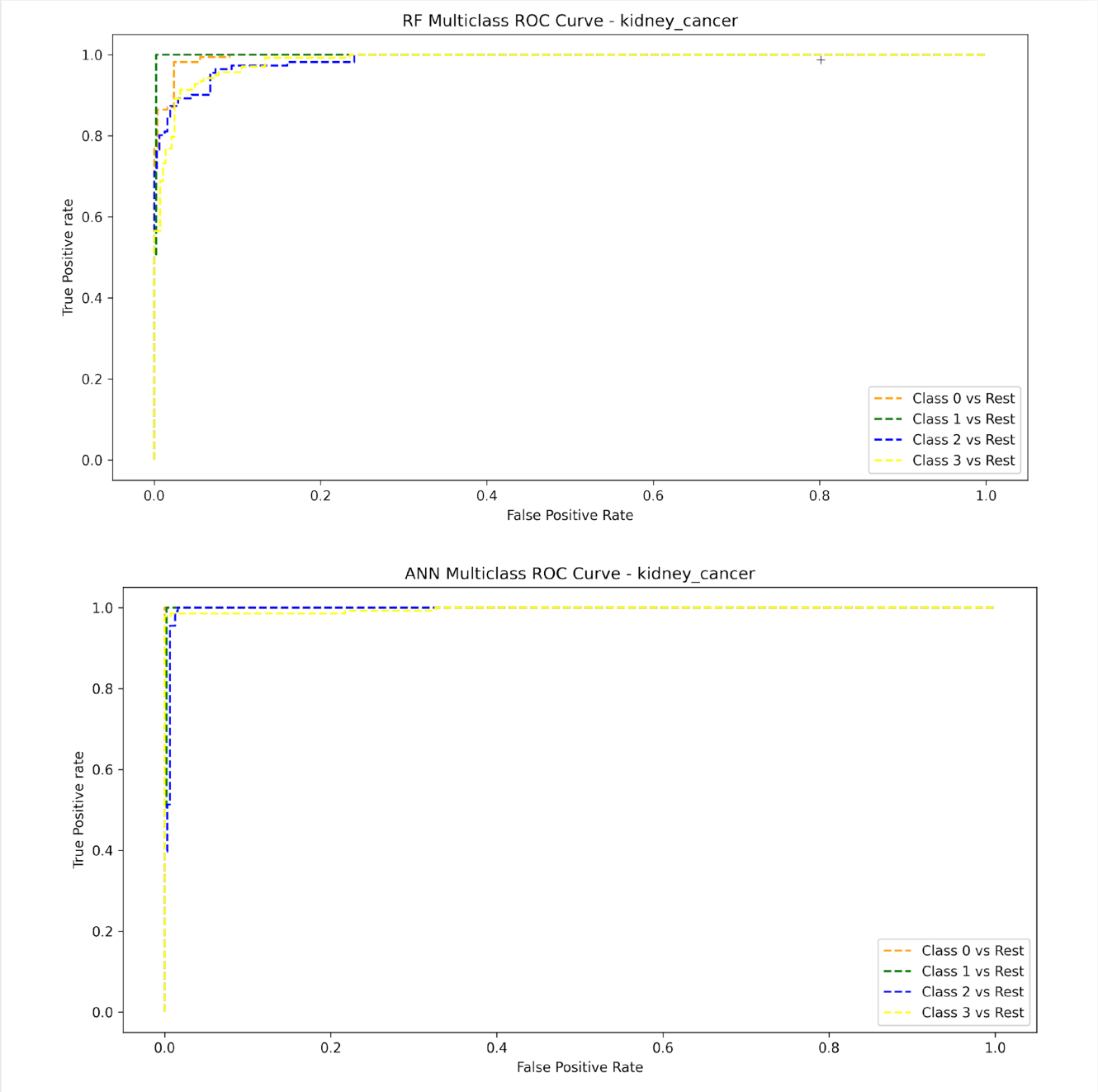


Figure 6 Operating characteristic area under the curve plots for kidney cancer cohort. RF, random forest; ANN, artificial neural network; class: 0, potential; 1, low; 2, moderate; 3, major. Comparing the two plots shows that ANN model performed better in classification as its areas under the curves are slightly bigger.

using real-world evidence (RWE) and data mining techniques. Using de-identified patient data also enables collaboration among multiple institutions to combine their small(er) data sets to grow available data, with the aim to strengthen queries addressing some of the most pressing, and unanswered, questions about cardiotoxicity including the role of specific oncology regimens in impacting cardiovascular health of the patients.

There is also the potential to bring more clinical data into the clinical risk models beyond the initial set of discrete variables implemented through ML algorithms. These variables include genomic, proteomic, and cardiac rehab data. Natural language processing would also enable scientists to tap into unstructured clinical data and to intervene in the care process at its earliest stages, potentially prior to administration of cardiotoxic regimens.

Table 5 Risk score predictions and referral summary for B-cell lymphoma and kidney cancer patients

Cancer Type	Risk Score	Referred to Cardio-Oncology	Count
B-Cell	Major	No	12
Lymphoma	Major	Yes	2
	Total major		14
	Moderate	No	19
	Moderate	Yes	3
	Total moderate		22
	Low	No	3
	Total low		3
	Potential	No	2
	Potential	Yes	2
	Total potential		4
	Total scores		43
Kidney	Major	No	11
Cancer	Major	Yes	8
	Total major		19
	Moderate	No	15
	Moderate	Yes	6
	Total moderate		21
	Potential	No	2
	Potential	Yes	1
	Total potential		3
	Total scores		43

RF, random forest; ANN, artificial neural network.
Summary count of risk score model predictions by referrals for B-cell lymphoma using validation data. The numbers show that patients with *major risk and not referred to cardio-oncology* are about 86% (12/14). Both RF and ANN models produced the same predictions.
Summary count of risk score model predictions by referrals for kidney cancer using validation data. The numbers show that patients with *major risk and not referred to cardio-oncology* are about 58% (11/19). Both RF and ANN models produced the same predictions.

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Supplementary material

Supplementary material is available at *European Heart Journal – Digital Health*.

Acknowledgements

The authors would like to acknowledge VUMC support from Dr Michael Savona for recruiting medical fellows to help with AI model validation, Dr Kerry Schaffer for contributing ideas to translate this research into medical practice, and Peter Shave and Chris Grabiel for business leadership in translating this research into medical practice. Work was performed at VUMC, Nashville, Tennessee, USA.

Funding

Funding was provided by the Vanderbilt Institute for Clinical and Translation Research through a voucher grant to pay for the cost of extracting de-identified cancer patient data from the synthetic derivative database.

Conflict of interest: None declared.

Data availability

All de-identified patient data extracted from EHR and research database, along with outputs from ML models, for this study have been summarized in the manuscript and detailed at the aggregate level in the data supplement document. Access to row-level patient data is subject to Protected Health Information (PHI) privacy regulations and would require review by and a data sharing agreement with VUMC. Interested parties may contact the corresponding author with requests for details.

References

1. Definition of cardiotoxicity - NCI Dictionary of Cancer Terms - National Cancer Institute [Internet]. 2011 [cited 2022 Mar 21]. Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/cardiotoxicity.
2. Čelutkienė J, Pudil R, López-Fernández T, Grapsa J, Nihoyannopoulos P, Bergler-Klein J, *et al.* Role of cardiovascular imaging in cancer patients receiving cardiotoxic therapies: a position statement on behalf of the Heart Failure Association (HFA), the European Association of Cardiovascular Imaging (EACVI) and the Cardio-Oncology Council of the European Society of Cardiology (ESC). *Eur J Heart Fail* 2020;**22**:1504–1524.
3. Fradley MG, Brown AC, Shields B, Viganego F, Damrongwatanasuk R, Patel AA, *et al.* Developing a comprehensive cardio-oncology program at a cancer institute: the Moffitt Cancer Center experience. *Oncol Rev* 2017;**11**:340.
4. Sulpher J, Mathur S, Graham N, Crawley F, Turek M, Johnson C, *et al.* Clinical experience of patients referred to a multidisciplinary cardiac oncology clinic: an observational study. *J Oncol* 2015;**2015**:671232.
5. Michel L, Rassaf T. Cardio-oncology: need for novel structures. *Eur J Med Res* 2019;**24**:1.
6. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, *et al.* Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail* 2020;**22**:1945–1960.
7. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, *et al.* 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J* 2022;**43**:4229–4361.
8. Bhardwaj R, Nambiar AR, Dutta D. A study of machine learning in healthcare. In: *2017 IEEE 41st Annual Computer Software and Applications Conference (COMPSAC)*; 2017. p236–241. IEEE.
9. Hershman DL, Till C, Shen S, Wright JD, Ramsey SD, Barlow WE, *et al.* Association of cardiovascular risk factors with cardiac events and survival outcomes among patients with breast cancer enrolled in SWOG clinical trials. *J Clin Oncol* 2018;**36**:2710–2717.

10. López-Sendón J, Álvarez-Ortega C, Zamora Auñon P, Buño Soto A, Lyon AR, Farmakis D, *et al.* Classification, prevalence, and outcomes of anticancer therapy-induced cardiotoxicity: the CARDIOTOX registry. *Eur Heart J* 2020;**41**:1720–1172.
11. Cueva JF, Antolín S, Calvo L, Fernández I, Ramos M, de Paz L, *et al.* Galician consensus on management of cardiotoxicity in breast cancer: risk factors, prevention, and early intervention. *Clin Transl Oncol* 2017;**19**:1067–1078.
12. Kamphuis JAM, Linschoten M, Cramer MJ, Alsemgeest F, van Kessel DJW, Urgel K, *et al.* ONCOR: design of the Dutch cardio-oncology registry. *Neth Heart J* 2021;**29**:288–294.
13. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, *et al.* Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;**368**:987–998.
14. Gunaldi M, Duman BB, Afsar CU, Paydas S, Erkisi M, Kara IO, *et al.* Risk factors for developing cardiotoxicity of trastuzumab in breast cancer patients: an observational single-centre study. *J Oncol Pharm Pract* 2016;**22**:242–247.
15. Hershman DL, Wright JD, Lim E, Buono DL, Tsai WY, Neugut AI. Contraindicated use of bevacizumab and toxicity in elderly patients with cancer. *J Clin Oncol* 2013;**31**: 3592–3599.
16. Hasan S, Dinh K, Lombardo F, Kark J. Doxorubicin cardiotoxicity in African Americans. *J Natl Med Assoc* 2004;**96**:196–199.
17. Alexandre J, Cautela J, Ederhy S, Damaj GL, Salem JE, Barlesi F, *et al.* Cardiovascular toxicity related to cancer treatment: a pragmatic approach to the American and European Cardio-Oncology Guidelines. *J Am Heart Assoc* 2020;**9**:e018403.
18. Giza DE, Iliescu G, Hassan S, Marmagkiolis K, Iliescu C. Cancer as a risk factor for cardiovascular disease. *Curr Oncol Rep* 2017;**19**:39.
19. Serrano C, Cortés J, De Mattos-Arruda L, Bellet M, Gómez P, Saura C, *et al.* Trastuzumab-related cardiotoxicity in the elderly: a role for cardiovascular risk factors. *Ann Oncol* 2019;**30**:1178.
20. Shah CP, Moreb JS. Cardiotoxicity due to targeted anticancer agents: a growing challenge. *Ther Adv Cardiovasc Dis* 2019;**13**:1753944719843435.
21. Cochet A, Quilichini G, Dygai-Cochet I, Touzery C, Toubeau M, Berriolo-Riedinger A, *et al.* Baseline diastolic dysfunction as a predictive factor of trastuzumab-mediated cardiotoxicity after adjuvant anthracycline therapy in breast cancer. *Breast Cancer Res Treat* 2011;**130**:845–854.
22. Tajiri K, Aonuma K, Sekine I. Cardio-oncology: a multidisciplinary approach for detection, prevention and management of cardiac dysfunction in cancer patients. *Jpn J Clin Oncol* 2017;**47**:678–682.
23. Martín García A, Mitroi C, Mazón Ramos P, García Sanz R, Virizuela JA, Arenas M, *et al.* Stratification and management of cardiovascular risk in cancer patients. A consensus document of the SEC, FEC, SEOM, SEOR, SEHH, SEMG, AEEMT, AEEC, and AECC. *Rev Esp Cardiol* 2021;**74**:438–448.
24. Yang X, Li X, Yuan M, Tian C, Yang Y, Wang X, *et al.* Anticancer therapy-induced atrial fibrillation: electrophysiology and related mechanisms. *Front Pharmacol* 2018;**9**:1058.
25. Simões R, Silva LM, de Oliveira AN, Alves MT, Pestana RMC, de Souza IDP, *et al.* Identification of clinical and laboratory variables associated with cardiotoxicity events due to doxorubicin in breast cancer patients: a 1-year follow-up study. *Cardiovasc Toxicol* 2021;**21**:106–114.
26. Foglietta J, Inno A, de Iuliis F, Sini V, Duranti S, Turazza M, *et al.* Cardiotoxicity of aromatase inhibitors in breast cancer patients. *Clin Breast Cancer* 2017;**17**:11–17.
27. Schlitt A, Jordan K, Vordermark D, Schwamborn J, Langer T, Thomssen C. Cardiotoxicity and oncological treatments. *Dtsch Arztebl Int* 2014;**111**:161–168.
28. Volkova M, Russell R. Anthracycline cardiotoxicity: prevalence, pathogenesis and treatment. *Curr Cardiol Rev* 2011;**7**:214–220.
29. Synthetic derivative | Department of Biomedical Informatics [Internet]. [cited 2022 Mar 21]. https://www.vumc.org/dbmi/synthetic-derivative.
30. Armenian SH, Lacchetti C, Barac A, Carver J, Constine LS, Denduluri N, *et al.* Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. *J Clin Oncol* 2017;**35**:893–911.
31. Classification and regression - Spark 3.0.0 Documentation - Random forest classifier [Internet]. [cited 2022 Mar 21]. https://spark.apache.org/docs/3.0.0/ml-classification-regression.html#random-forest-classifier.
32. Classification and regression - Spark 3.0.0 Documentation - Multilayer perceptron classifier [Internet]. [cited 2022 Mar 21]. https://spark.apache.org/docs/3.0.0/ml-classification-regression.html#multilayer-perceptron-classifier.
33. Fawagreh K, Gaber MM, Elyan E. Random forests: from early developments to recent advancements. *Syst Sci Control Eng* 2014;**2**:602–609.
34. Amato F, López A, Peña-Méndez EM, Vaňhara P, Hampl A, Havel J. Artificial neural networks in medical diagnosis. *J Appl Biomed* 2013;**11**:47–58.
35. Zhou Y, Hou Y, Hussain M, Brown SA, Budd T, Tang WHW, *et al.* Machine learning-based risk assessment for cancer therapy-related cardiac dysfunction in 4300 longitudinal oncology patients. *J Am Heart Assoc* 2020;**9**:e019628.
36. Hou Y, Zhou Y, Hussain M, Budd GT, Tang WHW, Abraham J, *et al.* Cardiac risk stratification in cancer patients: a longitudinal patient-patient network analysis. *PLoS Med* 2021;**18**:e1003736.
37. PhD SAB MD. Patient similarity for decision-making in prevention of cardiovascular toxicity: a feasibility study [Internet]. clinicaltrials.gov; 2022 May [cited 2022 Jul 14]. Report No.: NCT05377320. https://clinicaltrials.gov/ct2/show/NCT05377320.