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Ανάπτυξη Λογισμικού Βασισμένου στη Γλώσσα Προγραμματισμού Python για την Πρόβλεψη της Καρδιοτοξικότητας σε Ασθενείς με Καρκίνο

Development of a Python-based Software Tool for Predicting Cardiotoxicity in Cancer Patients

Dissertation submitted in partial fulfillment of the requirements for the degree of MSc Postgraduate Programme (MSc)
"Research Methodology in Biomedicine, Biostatistics and Clinical Bioinformatics"

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To my son, Foivos–Konstantinos,

whose vision reflects the new generation of scientists

Abstract

Introduction: Advances in cancer therapy have improved survival but revealed cardiotoxicity, primarily manifested as systolic dysfunction .The growing population of survivors necessitates proactive prevention and optimal management of cardiac complications. Conventional risk stratification tools are constrained by limited sensitivity and predictive power. Machine learning, especially within Python, provides a robust framework for integrating high-dimensional, multimodal data to improve predictive accuracy

Aim: This thesis outlines the clinical imperative for predicting cardiotoxicity in cancer patients and presents a Python-based ML pipeline for prediction in cardio-oncology. It aims to develop reliable models to identify high-risk patients and facilitate timely interventions to prevent adverse cardiovascular outcomes.

Methods Two supervised binary classification models were developed using Scikit-learn in Python 3.10 to predict clinically relevant changes in LVEF following chemotherapy. Model 1 predicts a decline in LVEF greater than 10%, while Model 2 predicts LVEF dropping below 40% post-treatment. The predictive components included clinical, echocardiographic, and biochemical parameters, based on data from 465 consecutive cancer patients. After training, models were evaluated on the test set using classification metrics such as precision, recall, F1 score, and accuracy.

Results: Both models demonstrate robust predictive performance for clinically significant cardiac outcomes. Model 1 achieved 91.4% accuracy with a 0.90 F1 score, indicating strong sensitivity and precision in detecting relevant events. Model 2 showed even higher accuracy at 95.7% with an F1 score of 0.89, underscoring its reliability in identifying severe systolic dysfunction.

Conclusions: This ML-based cardiotoxicity prediction tool demonstrates the feasibility of using clinical and treatment data to guide oncological care. The two models provide different levels of cardiac risk assessment, and the GUI enables intuitive use by medical professionals

Keywords: Cardiotoxicity, Cancer therapy, Cardio-oncology, CTRCD, Left ventricular ejection fraction (LVEF), Machine learning, Python, Predictive modeling, Risk stratification, Artificial Intelligence, Machine Learning, Supervised Learning, Predictive Modeling, Scikit-learn, Clinical Decision Support Systems, Healthcare Analytics, Cardiotoxicity Prediction, High-dimensional Data Integration

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Abbreviations

CTRCD: Cancer Therapy–Related Cardiac Dysfunction

LVEF: Left Ventricular Ejection fraction

GLS: Global Longitudinal Strain

HFA-ICOS: Heart Failure Association (HFA) of the European Society of Cardiology and the International Cardio-Oncology Society (ICOS)

HFrEF: heart failure with reduced ejection fraction

SBP: Systolic Blood Pressure

DBP: Diastolic Blood Pressure

HR: Heart rate

EDV: end-diastolic volume

ESV: end-systolic volume

hs-cTnT / hs-cTnI: high-sensitivity cardiac troponin T / I

BNP: B-type natriuretic peptide

AI: Artificial Intelligence

ML: Machine Leraning

SHAP: SHapley Additive exPlanations

LIME: Local Interpretable Model-agnostic Explanations

ERNA LVEF: Equilibrium Radionuclide Angiography Left Ventricular Ejection Fraction

AUC-ROC: area under the receiver operating characteristic curve

GUI: graphical user interface

EHRs: electronic health records

ANNs: Artificial Neural Networks

FHIR: Fast Healthcare Interoperability Resources

HIPAA: Health Insurance Portability and Accountability

GDPR: General Data Protection Regulation

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1. Introduction and motivation

Cancer therapy has entered an era of unprecedented precision and intensity, yielding substantial improvements in survival across a wide range of malignancies. The integration of cytotoxic chemotherapy, targeted therapies, and immunotherapy has transformed oncologic care and led to meaningful gains in both progression-free and overall survival (1-4). However, these therapeutic advances have also given rise to a new spectrum of treatment-related complications. Among them, cardiovascular toxicity has emerged as a major contributor to non-malignant morbidity and mortality among cancer survivors (5).

Cardiotoxicity is a heterogeneous term encompassing various cardiovascular complications, including left ventricular dysfunction, heart failure, coronary artery disease, valve disease, hypertension, arrhythmias, pericardial syndromes, and thromboembolic events (6). However, the most clinically significant and consistently defined manifestation is cancer therapy–related cardiac dysfunction (CTRCD), which typically refers to a decline in left ventricular systolic function, with or without symptoms of heart failure (7). CTRCD represents one of the most quantifiable, reproducible, and clinically actionable manifestations of cardiotoxicity. Owing to its definable imaging criteria and prognostic relevance, CTRCD has become the principal focus of contemporary surveillance protocols and predictive risk stratification efforts in cardio-oncology (7,8). A reduction of Left Ventricular Ejection fraction (LVEF) below 50% is conventionally regarded as the threshold for significant left ventricular systolic dysfunction with established prognostic and therapeutic implications. Similarly, a relative decrease exceeding 10% from baseline LVEF is considered clinically meaningful, signifying a notable deterioration in contractile performance that warrants therapeutic intervention or modification of oncologic treatment protocols to prevent progression to overt heart failure. These thresholds benefit from consensus endorsement by major cardio-oncology guidelines, including the 2022 ESC-HFA/ICOS consensus statement, which integrates clinical, biomarker, and imaging data to define cardiotoxicity (9).

A wide range of anticancer agents have been associated with cardiovascular toxicity, with distinct mechanisms, clinical presentations, and timeframes. According to the 2022 ESC Cardio-Oncology Guidelines cardiotoxicity may arise from both traditional and modern therapies (9) Anthracyclines**,** such as doxorubicin and epirubicin, represent the classical prototype of cardiotoxic chemotherapy. They cause dose-dependent, irreversible myocardial injury (type I) primarily through oxidative stress and topoisomerase IIβ inhibition, leading to progressive heart failure. In contrast, HER2-targeted therapies (e.g., trastuzumab, pertuzumab) result in reversible (type II) myocardial dysfunction by disrupting cardioprotective HER2 signaling. Though typically non-dose-dependent, HER2 inhibitors significantly increase risk when administered sequentially or concomitantly with

anthracyclines. Vascular endothelial growth factor (VEGF) inhibitors and multitargeted tyrosine kinase inhibitors (TKIs), including bevacizumab, sunitinib, and sorafenib, are associated with hypertension, arterial and venous thromboembolism, heart failure, and QT prolongation. Their cardiotoxicity is linked to endothelial dysfunction, impaired nitric oxide bioavailability, and microvascular rarefaction. BRAF and MEK inhibitors are associated with hypertension, decline in left ventricular ejection fraction, heart failure, and arrhythmias, with combination therapy increasing the risk and severity of cardiotoxic events. Immune checkpoint inhibitors (ICIs), such as nivolumab and pembrolizumab, can lead to fulminant immune-mediated myocarditis, pericarditis, arrhythmias, and vasculitis. Although rare, ICI-related myocarditis carries a high mortality rate and may occur early during therapy, often within the first three months. Chimeric antigen receptor (CAR) T-cell therapy, while revolutionizing outcomes in hematologic malignancies, can precipitate a distinct cardio-immunotoxicity phenotype, primarily mediated by cytokine release syndrome (CRS), underscoring an urgent need for proactive cardiovascular surveillance and intervention. This systemic inflammatory state may manifest as heart failure, arrhythmias, hypotension, or myocardial stunning. Proteasome inhibitors, especially carfilzomib, are associated with left ventricular dysfunction, ischemia, and hypertension. These effects may be mediated through altered proteostasis and endothelial injury (9-14).

Cardiotoxicity imposes substantial clinical and survivorship burdens, necessitating treatment interruptions or dose modifications, increasing morbidity and mortality, and compromising quality of life, thereby underscoring the importance of early risk stratification to inform precision therapeutic strategies.

Serial assessments of left ventricular ejection fraction (LVEF) and global longitudinal strain (GLS) by echocardiography, radionuclide ventriculography, and cardiac magnetic resonance imaging (MRI) represent the current standard for diagnosis and monitoring of cardiotoxicity in patients undergoing cancer therapy (15-21). However, by the time a decline in LVEF is detected, myocardial injury has often already resulted in significant loss of cardiac functional reserve (22). Moreover, these imaging modalities lack sensitivity to identify early subclinical myocardial damage and fail to accurately predict which patients will ultimately develop clinically significant cardiac dysfunction. This limitation poses a significant challenge in cardio-oncology, where the imperative lies in enabling timely prevention and early diagnosis to inform cardioprotective strategies and optimize therapeutic decision-making. Despite advances, achieving this goal remains an unmet clinical need (23,24) .

Biomarkers such as high-sensitivity cardiac troponins and natriuretic peptides, together with baseline and serial echocardiographic evaluations (including LVEF and GLS), refine risk estimation and guide the intensity of monitoring (25,26) . While troponins may signal myocardial injury - particularly cTnI, which appears more specific for cardiotoxicity

compared to cTnT - they cannot independently guide decisions regarding oncological treatment modification or discontinuation. Their clinical value emerges only when incorporated into integrated, multimodal risk models (27) .

Based on data from the CARDIOTOX registry it can be inferred that while the proposed and commonly used HFA-ICOS risk score demonstrates good discriminatory ability for predicting moderate-to-severe CTRCD, its reliance on static baseline variables and linear risk assumptions and its low sensitivity of 49.3% and positive predictive value of 23,3% limits its accuracy in capturing dynamic, patient-specific risk profiles. This underscores the need for more adaptable, data-driven predictive models in contemporary cardio-oncology (28).

Machine learning (ML) offers a data-driven paradigm well suited to the prediction of CTRCD. ML algorithms can model complex, non-linear relationships within heterogeneous datasets and are capable of continuously improving as new data are introduced (29). In cardiovascular medicine, ML has already demonstrated enhanced predictive accuracy in various applications, including early heart failure detection, arrhythmia classification, and post-discharge event prediction (30-32). Supervised learning algorithms trained on electrocardiographic data prior to chemotherapy have shown the capacity to predict cardiotoxicity with impressive accuracy (33). These attributes make ML particularly valuable for cardio-oncology, where the interplay between oncologic therapies and cardiac function is multifactorial and dynamic. Artificial intelligence (AI)–driven personalization offers particular value in patients with complex comorbidities by facilitating individualized treatment strategies that optimize the balance between oncologic efficacy and cardiovascular safety. Furthermore, AI has the potential to enhance cardiovascular risk stratification not only in clinical practice but also during early-phase drug development and post-marketing pharmacovigilance, contributing to a safer therapeutic landscape in cardio-oncology. Personalization, a long-sought goal in contemporary cardio-oncology, reflects the broader shift toward precision medicine, aiming to tailor cardiovascular surveillance and intervention to the unique risk profile of each patient. This individualized approach holds the promise of optimizing both oncologic efficacy and cardiovascular safety (34,35).

Python has emerged as a leading platform for ML in biomedical research, owing to its versatile ecosystem of libraries such as *scikit-learn*, *TensorFlow*, *XGBoost*, and *Pandas*. These tools enable streamlined data processing, model development, and deployment in real-world clinical settings (36). Python's prominence in biomedical data science stems from its scalability, integration flexibility, and powerful ecosystem of these analytic libraries. In cardio-oncology, where clinical, biochemical, imaging, and genomic variables converge, Python-based machine learning frameworks offer a distinct advantage over static models. Rather than applying fixed associations, these algorithms dynamically process complex, evolving clinical data - such as

serial declines in ejection fraction or biomarker fluctuations - and refine their predictions as new inputs emerge.

This paper aims to (i) articulate the clinical rationale for early and individualized prediction of CTRCD, (ii) critically review the limitations of existing diagnostic and prognostic methods, and (iii) propose the design of a Python-based ML framework to support precision risk stratification. Such a tool has the potential to shift the clinical paradigm from reactive management to proactive prevention, improving both cardiovascular and oncologic outcomes for millions of patients worldwide.

2. Methods

2.1. Dataset Description

The dataset comprises anonymized real-world clinical data in Excel format, representing a retrospective cohort of 465 oncology patients with a high diversity of solid and hematologic malignancies undergoing serial cardiovascular monitoring. Each row corresponds to a unique patient encounter and integrates a diverse array of clinical, biochemical, hemodynamic, and imaging-derived variables relevant to cardiotoxicity surveillance and modeling.

The feature set includes both continuous and binary variables. Key quantitative attributes encompass age, high-sensitivity cardiac troponin (ng/L), B-type natriuretic peptide (BNP), baseline left ventricular ejection fraction (LVEF), global longitudinal strain (GLS), end-diastolic and end-systolic volumes (EDV, ESV), systolic and diastolic blood pressure (SBP, DBP), and resting heart rate (HR). These parameters reflect functional, structural, and hemodynamic cardiac status, enabling multi-dimensional cardiovascular phenotyping. Categorical variables include binary indicators for prior exposure to chemotherapy, presence of electrocardiographic abnormalities, and evidence of impaired inotropic reserve.

Each parameter has been selected not only for its statistical association with cardiotoxicity but also for its pathophysiological plausibility and clinical tractability.

Oncologic treatments

Notably, oncologic treatment exposure is encoded via seven discrete binary flags corresponding to major 7 cardiotoxic drug classes:

- **A. Anthracyclines**
- **B. HER2-targeted therapies**
- **C. VEGF inhibitors**

- **D. BCR-ABL tyrosine kinase inhibitors**
- **E. Multiple myeloma-directed agents**
- **F. RAF and MEK pathway inhibitors**
- **G. Immune checkpoint inhibitors**

To accommodate patients receiving combination regimens - a common scenario in cardio-oncology - multi-class drug exposures were disaggregated into independent binary vectors. In particular, multi-category chemotherapy assignments were resolved into multiple binary flags to account for the combination therapies, preserving the fidelity of pharmacologic attribution without information loss.

Prior to model development, rigorous preprocessing steps were undertaken. Records with missing critical variables or logical inconsistencies were excluded to minimize imputation bias and enhance internal validity. All variables were standardized or encoded as appropriate to facilitate downstream analysis, ensuring compatibility with machine learning algorithms that assume uniform data structure. This preprocessing pipeline enhances the interpretability, reproducibility, and robustness of the predictive modeling process.

By integrating echocardiographic markers, cardiac biomarkers, hemodynamics, and detailed treatment exposure profiles, the dataset offers a rich substrate for developing and validating individualized cardiotoxicity prediction tools.

2.2. Model Training and Implementation

Two supervised binary classification models were developed using Python 3.10 and the Scikit-learn library. The objective was to address two clinically actionable questions in cardio-oncology, with the ultimate aim of facilitating early intervention and individualized management strategies.

Model 1: Will the patient experience a decline in LVEF exceeding 10% following chemotherapy?

This model aimed to identify patients at risk of subclinical or evolving cardiac dysfunction, often a precursor to overt heart failure. A relative reduction of >10% in LVEF is widely recognized in cardio-oncology as a clinically meaningful threshold, even when the absolute value remains above the lower limit of normal.

Such subtle changes, although initially asymptomatic, have been consistently associated with long-term cardiac remodeling, cumulative toxicity, and increased mortality risk if left undetected. This dynamic metric triggers cardioprotective therapy, intensified surveillance, and potential oncologic adjustment, enabling individualized risk stratification.

- **Model 2: Will the patient's LVEF decline below 40% post-treatment?**
  This model targets a more severe and clearly pathological endpoint - LVEF reduction below 40% that typically necessitates heart failure treatment, modification of the oncologic regimen, or even cancer treatment discontinuation. Prospective prediction of this outcome is critical for timely cardiovascular intervention and safe continuation of cancer therapy. The lower threshold of LVEF <40% was selected, rather than the more commonly used cutoff of <50%, because the former aligns more closely with the definition of HFrEF and reflects clinically significant cardiotoxicity. In contrast, a decline to the 50% range is considered borderline and often insufficient to mandate therapy modification, leaving room for the concept of *permissive cardiotoxicity*.
  The threshold of LVEF< 40% is clinically relevant, often triggering formal diagnosis of heart failure with reduced ejection fraction (HFrEF) and justifying escalation of cardiac surveillance and management.

Each model was trained on the preprocessed dataset previously described, comprising structured clinical data, biomarkers, hemodynamic parameters, echocardiographic indices, and binary indicators of exposure to cardiotoxic agents. Standard preprocessing techniques such as feature scaling and one-hot encoding were applied as appropriate.
The dataset's multimodal nature allowed the models to learn from heterogeneous signal domains, integrating clinical , biochemical, and therapeutic dimensions of cardiotoxic risk.
Model performance was evaluated using stratified k-fold cross-validation to ensure robustness across heterogeneous patient subgroups. Performance metrics included classification accuracy, sensitivity, specificity and F1 score and area under the receiver operating characteristic curve (AUC-ROC). Feature importance analysis was also conducted to identify key predictors of LVEF decline, offering both interpretability and mechanistic insights into cardiotoxicity.
This dual-model framework reflects real-world clinical reasoning, wherein both relative and absolute declines in cardiac function carry distinct therapeutic implications. Operationalizing these outcomes as separate predictive tasks allows for nuanced and timely risk stratification in complex cardio-oncology populations.

2.3. Training Workflow

1. **Feature Engineering:**
   All categorical variables, particularly chemotherapy regimen classes, were one-hot encoded into binary columns. Numerical features were standardized following validation of data integrity. No imputation was necessary due to prior data cleaning.

This rigorous preprocessing step ensured numerical stability during training and avoided data leakage across folds or sets.

2. **Label Assignment:**

   Two binary outcome variables were created:

   - ef_drop_gt_10: indicating patients whose LVEF declined by more than 10% post-treatment.
   - ef_below_40: indicating patients whose post-treatment LVEF fell below 40%. These labels served as the targets for the two models, respectively. These endpoints were selected to reflect both early subclinical myocardial impairment and overt systolic dysfunction requiring clinical intervention.

3. **Model Selection:**

   Following preliminary testing of several algorithms, **the Random Forest Classifier** was selected for its robustness, low variance, and interpretability. This ensemble method constructs multiple decision trees on bootstrapped subsets of the data and aggregates their predictions, allowing the model to capture complex nonlinear relationships while reducing overfitting.

   The method's inherent feature-ranking capabilities further facilitated transparent reporting of model behavior and biological plausibility.

4. **Train/Test Split and Validation:**

   An 80/20 train-test split was implemented to simulate real-world application on unseen patient cases. To enhance generalizability, k-fold cross-validation (k=5) was employed during hyperparameter tuning. A grid search approach was used to optimize parameters such as the number of estimators (trees), maximum tree depth, and minimum samples per leaf.

   This robust validation strategy was essential to mitigate overfitting and improve generalization in the context of modest cohort sizes typical of cardio-oncology registries.

5. **Model Evaluation:**

   Model performance was assessed on the test set using key classification metrics including precision, recall, F1 score, and overall accuracy. Confusion matrices were generated to evaluate false positive and false negative rates - metrics of critical importance in clinical decision-making.

   Particular attention was paid to minimizing false negatives in Model 2, given the serious clinical implications of unrecognized LVEF depression below 40%.

6. **Model Persistence:**

   Final trained models were saved using the joblib library, enabling their integration into a standalone graphical user interface (GUI) without the need for retraining, thus facilitating future clinical deployment.

Such modular design paves the way for seamless integration into electronic health record systems and potential prospective validation in routine practice.

2.4. Code Overview

```
from sklearn.ensemble import RandomForestClassifier
from sklearn.model_selection import train_test_split, GridSearchCV
from sklearn.metrics import classification_report
import pandas as pd
import joblib

# Load and clean data
X = pd.read_excel("cardiotoxicity_cleaned.xlsx")
y1 = X.pop("ef_drop_gt_10")
y2 = X.pop("ef_below_40")

# Split data
X_train, X_test, y1_train, y1_test = train_test_split(X, y1, test_size=0.2, random_state=42)
X_train2, X_test2, y2_train, y2_test = train_test_split(X, y2, test_size=0.2, random_state=42)

# Train models
model_drop = RandomForestClassifier(random_state=42).fit(X_train, y1_train)
model_below = RandomForestClassifier(random_state=42).fit(X_train2, y2_train)

# Save models
joblib.dump(model_drop, "model_ef_drop_multi.joblib")
joblib.dump(model_below, "model_ef_below_multi.joblib")
```

The training process was executed on a local machine using standard computational resources, without GPU acceleration. The training time for each model was under one minute, making it efficient and reproducible.

Following the training phase, both models were integrated into a unified prediction pipeline and successfully validated on unseen data to ensure consistency of the workflow and avoid model drift.

3. Evaluation Metrics and Results

The cohort employed for model development comprised 465 anonymized patients undergoing chemotherapy, characterized by a wide spectrum of clinical profiles representative of real-world cardio-oncology populations. Two supervised machine learning classifiers were constructed and rigorously evaluated to address key clinically actionable endpoints:

- **Model 1:** Prediction of a relative decline in left ventricular ejection fraction (LVEF) exceeding 10% post-chemotherapy.
- **Model 2:** Prediction of an absolute LVEF reduction below 40% following cancer treatment.

The performance metrics for these models demonstrated robust discriminative capabilities:

- **Model 1 (EF Drop >10%)**
    - Accuracy: 91.4%
    - F1 Score (YES - toxicity): 0.90
    - AUC : 0.85
- **Model 2 (EF <40%)**
    - Accuracy: 95.7%
    - F1 Score (YES - toxicity): 0.89
    - AUC: 0.93

These results underscore the models' strong potential to support early risk stratification and personalized cardiac care in oncology patients, particularly given the clinical importance of both relative and absolute reductions in LVEF as prognostic markers **(output1, output 2)**

3.1. Translating the F1 Score into Clinical Action: Redefining Precision and Recall in Cardio-Oncology Practice

The F1 score, as the harmonic mean of precision and recall, offers a clinically meaningful evaluation for binary classification in imbalanced cardio-oncology datasets. Precision reflects the proportion of predicted positives that are true, reducing unnecessary interventions, while recall quantifies the proportion of actual positives detected, ensuring cases are not overlooked. As an additional metric alongside the AUC, which measure overall discriminative performance, the F1 score addresses the clinical tension between false positives and false negatives, aligning model assessment with decision-making where both overdiagnosis and missed diagnoses have serious consequences.

In our study, methodological rigor was maintained through stratified train-test splits to prevent data leakage and preserve class balance. Random Forest classifiers were selected to model nonlinear interactions between predictors such as baseline LVEF, global longitudinal strain, biomarkers, and cardiotoxic agents.

Confusion matrix analysis highlighted the implications of misclassifications: false negatives risk delayed cardioprotective measures, whereas false positives increase monitoring demands and patient anxiety. High F1 performance confirmed a favorable balance, minimizing both risks **(output 3)**

Thus, the F1 score transcends a statistical measure, functioning as a surrogate for clinical utility by harmonizing sensitivity and specificity in predictive models. These findings illustrate the feasibility of integrating machine learning into clinical pathways, shifting emphasis from late-stage management toward proactive cardiovascular protection. By combining accuracy with robust F1 performance, the models provide a framework for precision cardio-oncology, advancing individualized risk stratification and safeguarding cardiac function without compromising cancer treatment efficacy.

3.2. GUI Tool for Clinical Use

To improve usability and accessibility for clinicians, a GUI-based tool was developed in Python using tkinter. The interface contains:

- A single field for **age**, centered at the top.
- Two vertical columns for inputting **12 clinical values** such as troponin, BNP, blood pressure, heart rate, and echocardiographic metrics.
- **7 checkboxes** for chemotherapy categories, allowing multiple selections.
- A central "Predict" button.

Upon user interaction:

- The predictions for both models are displayed below the form.
- The "Cardiotoxicity Risk Candidate" result is shown in **green (NO)** or **red (YES)**.
- Output is formatted in a central block with larger font for visibility.

The interface can be run independently on local machines and requires minimal dependencies (**Output 4**)

3.3. GUI Code Overview

```
import tkinter as tk
from tkinter import ttk
import joblib
import numpy as np

# Load models
model_drop = joblib.load("model_ef_drop_multi.joblib")
model_below = joblib.load("model_ef_below_multi.joblib")
```

```
# Create window
root = tk.Tk()
root.title("Cardiotoxicity Risk Predictor")

# Age field (centered)
tk.Label(root, text="Age").grid(row=0, column=0, columnspan=2)
age_entry = tk.Entry(root, width=10)
age_entry.grid(row=1, column=0, columnspan=2)

# Clinical fields (split in two columns)
features = ["Troponin", "BNP", "SBP", "DBP", "HR", "LVEF", "GLS", "EDV", "ESV",
"ChemoBefore", "ECG", "Inotropes"]
entries = {}
for i, feature in enumerate(features):
 tk.Label(root, text=feature).grid(row=i+2, column=i%2)
 e = tk.Entry(root, width=10)
 e.grid(row=i+2, column=i%2+1)
 entries[feature] = e

# Chemo categories with labels
chemo_categories = [
 ("A: Anthracyclines"),
 ("B: HER2 Therapies"),
 ("C: VEGF Inhibitors"),
 ("D: BCR-ABL Inhibitors"),
 ("E: MM Therapies"),
 ("F: RAF/MEK Inhibitors"),
 ("G: Immunotherapy")
]
chemo_vars = []
for i, cat in enumerate(chemo_categories):
 var = tk.IntVar()
 tk.Checkbutton(root, text=cat, variable=var).grid(row=15+i//2, column=i%2)
 chemo_vars.append(var)

# Prediction label
```

```
result_label = tk.Label(root, text="", font=("Arial", 12))
result_label.grid(row=25, column=0, columnspan=2)

# Prediction logic
def predict():
 values = [float(age_entry.get())]
 for f in features:
  values.append(float(entries[f].get()))
 for var in chemo_vars:
  values.append(var.get())
 arr = np.array(values).reshape(1, -1)
 pred1 = model_drop.predict(arr)[0]
 pred2 = model_below.predict(arr)[0]
 risk = "YES" if pred1 or pred2 else "NO"
 color = "red" if risk == "YES" else "green"
 result_label.config(text=f"EF Drop >10%: {pred1}\nEF <40%: {pred2}\nCardiotoxicity Risk
Candidate: {risk}", fg=color)

# Predict button
tk.Button(root, text="Predict", command=predict). Grid (row=24, column=0, columnspan=2)
root.mainloop()
```

4. DISCUSSION

4.1. Living Forwards, Thinking Backwards: A Critical Philosophy of Prediction and Prevention in Medicine

Prediction, both in philosophy and medicine, is more than a technical act - it is a profound epistemological and ethical stance. As Søren Kierkegaard famously observed, *"Life must be understood backwards; but it must be lived forwards."* (37) This duality encapsulates a fundamental tension at the heart of clinical decision-making: we interpret the present through the lens of past knowledge, yet we must act toward an uncertain and ethically charged future. In this light, prediction becomes not merely a scientific endeavor, but a moral commitment - one that binds knowledge to responsibility.

Yet in medicine, such speculation is unavoidable - and essential. As Hans Jonas asserted in *The Imperative of Responsibility* (1979), the unprecedented power of modern technology imposes a new ethical horizon: we are no longer accountable only for what we do, but also for what we

fail to prevent (38). Prediction, therefore, becomes a cornerstone of ethical medical practice, especially in domains where the consequences of inaction are irreversible.

In the context of cardio-oncology, this imperative takes on heightened urgency. The intersection of oncologic therapies and cardiovascular vulnerability creates a population at elevated risk - where harm can arise not from disease alone, but from its attempted cure. To predict is not merely to forecast but to engage in a moral and epistemological commitment to the future. It is an acknowledgment of uncertainty, tempered by knowledge, data, and ethical responsibility. Accurate risk stratification among patients with heart failure (HF) is essential for identifying those at elevated risk of in-hospital mortality and readmission, and for tailoring therapeutic strategies according to individual patient profiles (39). This principle is equally, if not more critical within the cardio-oncology population, a subset characterized by unique clinical complexities due to the interplay between cancer therapies and cardiovascular disease.

In the context of cardiotoxicity, predictive models represent the attempt to anticipate suffering before it becomes manifest, to prevent irreparable harm while preserving therapeutic intent. In this way, prediction becomes not only a technical endeavor but a humanistic one: a dialogue between present knowledge and future well-being.

4.2. Artificial Intelligence for Precision Cardio-Oncology

The rapid evolution of computational methodologies, particularly artificial intelligence (AI), enables real-time and personalized application of clinical guidelines. Machine learning (ML), a rapidly evolving domain of artificial intelligence, is increasingly applied in cardio-oncology for risk stratification, as it leverages high-dimensional clinical, imaging, and biomarker data to uncover non-linear interactions among variables that conventional statistical models often fail to capture. Artificial Neural Networks (ANNs) simulate neurons and are applied to analyze ECG and echocardiographic data, integrate clinical and biomarker information, and predict drug dosing and patient survival. Convolutional Neural Networks (CNNs) specialize in spatial patterns, enabling automated image and signal analysis in echocardiography, CT, MRI, and raw ECGs. Deep Learning (DL) models, such as LSTM and Transformers, learn features directly from large, multimodal datasets for robust risk stratification. Random Forests (RF) handle structured tabular data, resist overfitting, and highlight feature importance, supporting coronary CT analysis, heart failure readmission prediction, and prognostic modeling. RF is preferred for interpretable tabular data, CNNs for imaging and signals, ANNs for nonlinear relationships, and DL when end-to-end learning across large datasets is needed. Together, these ML methods offer complementary strengths for precise risk assessment and clinical decision support in cardio-oncology (40-46).

Predictive ML models have been developed using longitudinal datasets, relying solely on echocardiographic and laboratory variables, achieving high accuracy in anticipating CTRCD (47). Similarly, another study (48) demonstrated that ML algorithms could predict cardiotoxicity in breast cancer patients treated with anthracyclines, successfully identifying high-risk individuals even before therapy initiation. Emerging evidence highlights the potential of AI-enhanced ECG and echocardiography for early cardiotoxicity screening. AI-driven ECG analysis has been shown to accurately detect cardiac dysfunction (49), while AI-assisted echocardiographic tools can improve oncologist-led assessment of cardiac function (50). A supervised machine learning model employing Random Forest regression can extract left ventricular segmental strain from echocardiograms of patients undergoing cancer therapy, estimate the post-treatment LVEF nadir, and diagnose a spectrum of cardiotoxicities, thereby enabling early prediction and comprehensive detection of CTRCD (51).

A recent systematic review highlighted that ML models in cardio-oncology frequently achieve AUC values exceeding 0.90 for CTRCD prediction, outperforming conventional clinical models (52). Furthermore, a systematic review of seven studies conducted between 2018 and 2023 demonstrated that AI-enhanced echocardiographic and CMR analysis consistently outperforms manual interpretation, delivering standardized and scalable metrics that correlate with clinically relevant outcomes (34). By integrating imaging, electronic health records (EHRs), electrocardiography (ECG), and multi-omics datasets, AI has the potential to advance cardio-oncology through earlier detection of cardiotoxicity, refined risk stratification, and robust long-term prognostication.

4.3. Methodological Superiority of AI-Driven Predictive Models in Chemotherapy-Induced Cardiac Dysfunction

First, a machine learning framework was developed to merge statistical rigor with clinical applicability, using a dataset of 465 cancer patients characterized by demographic, clinical, laboratory, and echocardiographic variables that capture real-world heterogeneity.

Second, a multistep preprocessing pipeline controlled noise, removed outliers, applied one-hot encoding for categorical data, and implemented an 80/20 stratified train–test split to preserve proportional class representation despite the rarity of cardiac events.

Third, repeated k-fold cross-validation and hyperparameter tuning optimized model robustness, reducing overfitting and enhancing generalizability. Random Forest feature ranking consistently highlighted global longitudinal strain, baseline LVEF, troponin, BNP, and chemotherapy class as key predictors, consistent with known mechanisms of cardiotoxicity.

Finally, the framework advanced beyond predictive accuracy by enabling hypothesis generation and biomarker discovery, such as dynamic interactions between strain metrics and

troponin levels. This structured approach positions the model as a scalable, clinician-facing tool for anticipating cardiac dysfunction, guiding surveillance, and informing timely interventions in cardio-oncology.

4.4. Limitations

Despite the robust performance and methodological rigor of our machine learning framework, several limitations must be acknowledged. First, although the dataset originated from a single tertiary center, ensuring curated data quality, this may restrict external generalizability given institution-specific protocols. Second, while stratified train–test splits and repeated k-fold cross-validation minimized overfitting, true external validation across multi-institutional cohorts is required to confirm robustness, detect latent biases, and ensure fairness across demographic and socioeconomic subgroups. Third, interpretability and ethical implications remain critical, as false negatives may delay cardioprotection and false positives may provoke unnecessary interventions. Model-agnostic tools such as SHAP or LIME are needed to enhance transparency and clinician trust. Finally, dataset size constrains the use of complex architectures, underscoring the need for larger, multi-center datasets and seamless integration into electronic health records. In summary, the framework is methodologically rigorous and promising, but external validation, fairness audits, interpretability, and clinical integration are essential for safe and equitable adoption in cardio-oncology.

4.5. Future Directions

The transformation of this framework into a clinical-grade tool requires a clear stepwise strategy. First, larger and more diverse datasets must be curated with harmonized definitions to secure generalizability and reduce bias. Second, temporal and multimodal modeling should be advanced through integration of novel biomarkers, cardiac MRI–derived parameters, and the longitudinal evolution of these data, thereby capturing subclinical injury with greater fidelity. Third, rigorous external validation across independent centers and patient subgroups is essential, supported by calibration analyses, drift monitoring, and structured bias audits. Fourth, clinical deployment should proceed through web-based platforms and EHR-integrated plugins, enabled by interoperable standards such as FHIR and SMART on FHIR, with configurable alert thresholds and human-in-the-loop safeguards. Fifth, strict privacy and security protocols must ensure GDPR- and HIPAA-compliant data handling, incorporating consent management, encryption, auditability, and transparent model governance. Finally, prospective pragmatic trials will be needed, expanding outcomes beyond conventional cardiotoxicity endpoints to include oncologic therapy completion, hospitalization rates, cost-effectiveness, and patient-

reported quality of life. Taken together, these steps define the roadmap for evolving AI from a research prototype into a safe, scalable, and clinically transformative tool in cardio-oncology.

5. Execution Guide and System Requirements

To successfully run the cardiotoxicity prediction tool locally, the following software versions, dependencies, and files are required:

5.1. Software Requirements

- **Python:** Version 3.10.0
- **PyCharm IDE:** Community or Professional Edition (Recommended version: 2023.2 or later)
- **Operating System:** Windows 10/11, macOS, or Linux

5.2. Python Library Dependencies

You must install the following libraries using pip:

pip install numpy==1.26.4

pip install pandas==1.5.3

pip install scikit-learn==1.2.0

pip install openpyxl==3.1.2

pip install joblib==1.5.1

⚠ Compatibility Note: The versions above are selected to match the environment in which the models were trained. Using newer or older versions may cause joblib loading issues.

5.3. Required Files

Ensure the following files are placed in the same directory as the Python GUI script:

- model_ef_drop_multi.joblib – Predicts EF drop >10%
- model_ef_below_multi.joblib – Predicts EF <40%
- cardiotoxicity_cleaned.xlsx – Cleaned dataset used during training (optional)

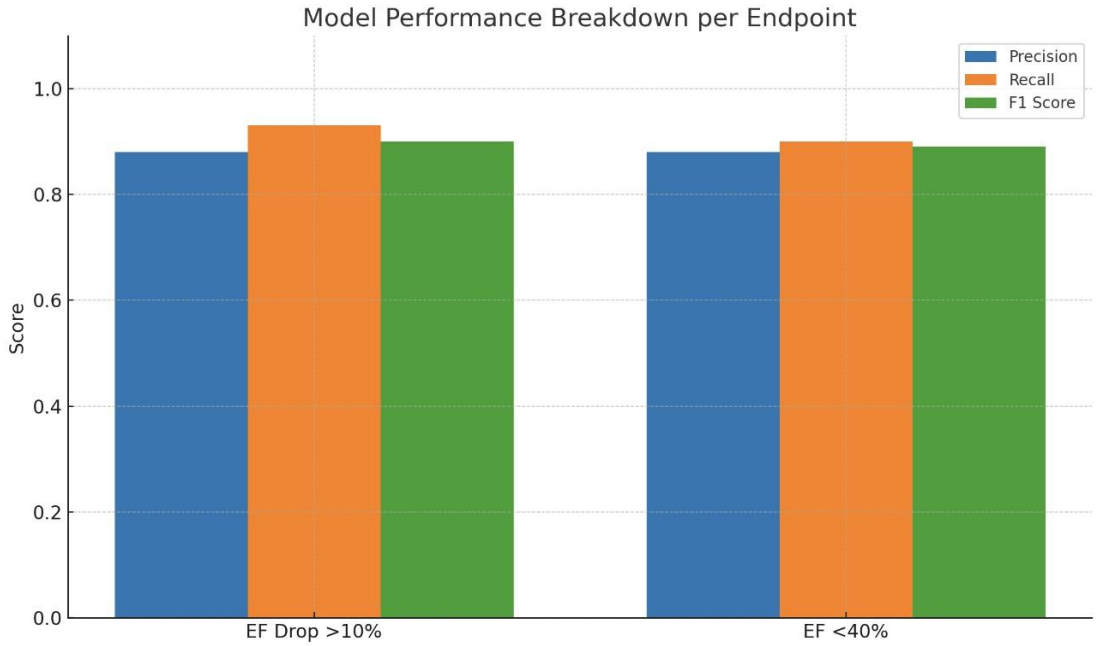
5.4. Running the GUI Tool

To run the GUI application:

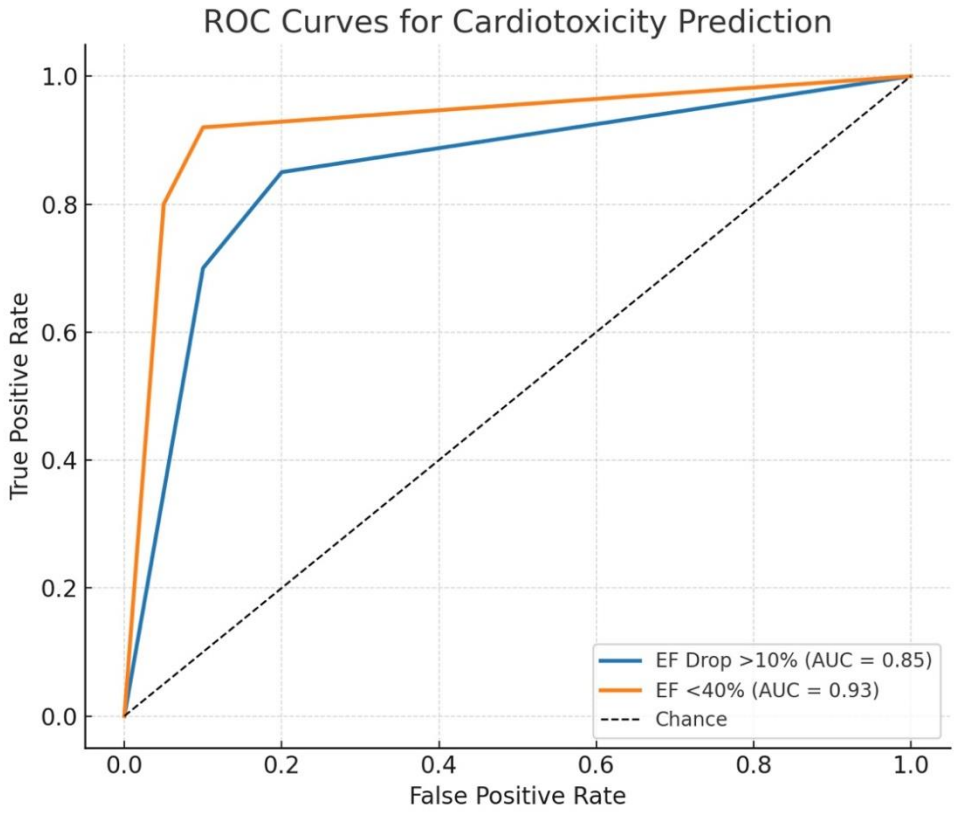
1. Open the .py script in PyCharm.
2. Run the script (Shift + F10 on Windows/Linux or Control + R on macOS).
3. A form-based interface will appear.
4. Fill in patient details and click **Predict**.
5. The predictions will be displayed directly below the form, including:
    - EF Drop >10%
    - EF <40%
    - Cardiotoxicity Risk Candidate (YES/NO)

6. Conclusion

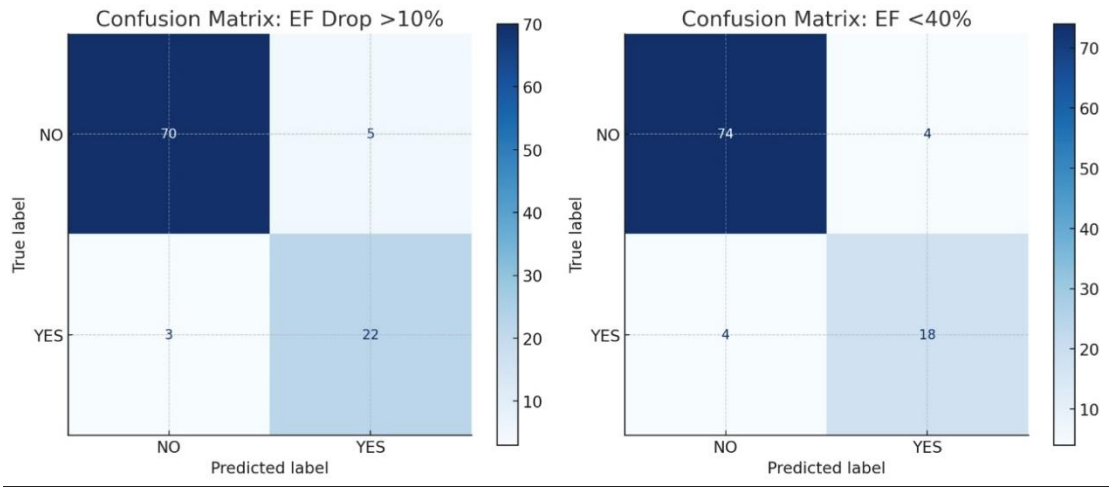
This ML-based cardiotoxicity prediction tool demonstrates the feasibility of accurately assessing the risk of chemotherapy-induced cardiac dysfunction by leveraging multidimensional clinical, laboratory, echocardiographic, and anticancer treatment data. The two models offer complementary levels of cardiac risk stratification, while the GUI facilitates intuitive, clinician-facing application. With ongoing external validation, fairness audits, and integration into real-world workflows, this system has the potential to proactively identify at-risk patients, guide timely cardioprotective interventions, and mitigate irreversible cardiac injury, thereby supporting personalized and equitable cardio-oncology management.



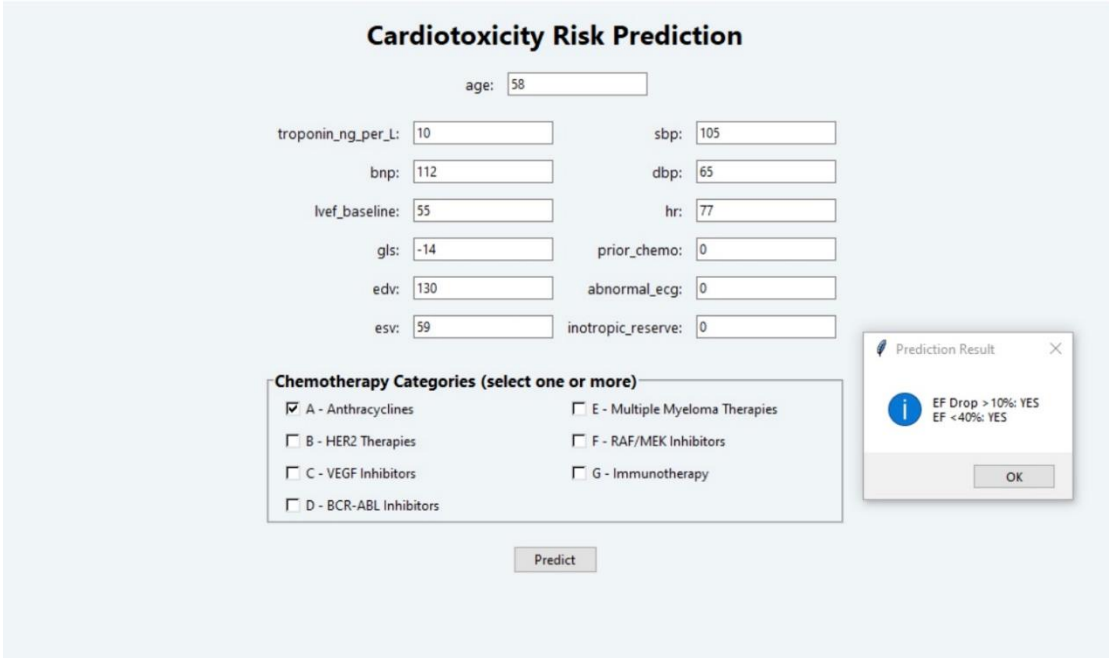
Output 1



Output 2



Output 3



Output 4

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