Leveraging Machine Learning to Improve Cardio-Oncology Outcomes: A Cardiac Risk Stratification Model to Facilitate Cardiac Care Decisions for Cancer Patients

Executive Summary

Improvement in cancer therapies has led to an increase in the cancer survivor population.[1] However, cancer therapies often have cardiotoxic effects and are a leading cause of cardiovascular disease (CVD) in cancer patients.[2-5] The cardiotoxic nature of cancer therapies necessitates the incorporation of cardiac care into cancer management. However, a lack of cardiac risk assessment tools for identifying cancer patients at risk of CVD makes cardiac care decisions difficult for oncologists. This white paper focuses on a comprehensive cardiac risk stratification model developed by Cleveland Clinic[6] and discusses its potential role in improving cardiac care for cancer patients.

Introduction

Advances in cancer therapies have improved the survival probability of cancer patients. There are currently 18.1 million cancer survivors in the United States, and this number is projected to reach 22.5 million by 2032.[1] The upward trend in the survivor population is promising and indicates improved patient outcomes. However, cancer patients are at greater risk of cardiovascular disease (CVD)[7] partly attributed to the cardiotoxicity induced by cancer therapies, referred to as cancer therapy-related cardiac dysfunction (CTRCD).[2-5] The higher prevalence of CVD in cancer patients has led to the emergence of cardio-oncology—a multidisciplinary sub-specialty that incorporates cardiac care into cancer management.

Cardio-oncology involves collaboration among cardiologists and oncologists to assess and mitigate cardiovascular risks in cancer patients before, during, and after cancer treatment.[8]

Challenges in Cardio-oncology

Despite recognizing the need for cardiac care, oncologists inconsistently incorporate it into their clinical practice.[9] With limited guidelines, oncologists find it challenging to assess, prevent, and provide appropriate cardiac care to their patients.[10,11] Moreover, cardio-

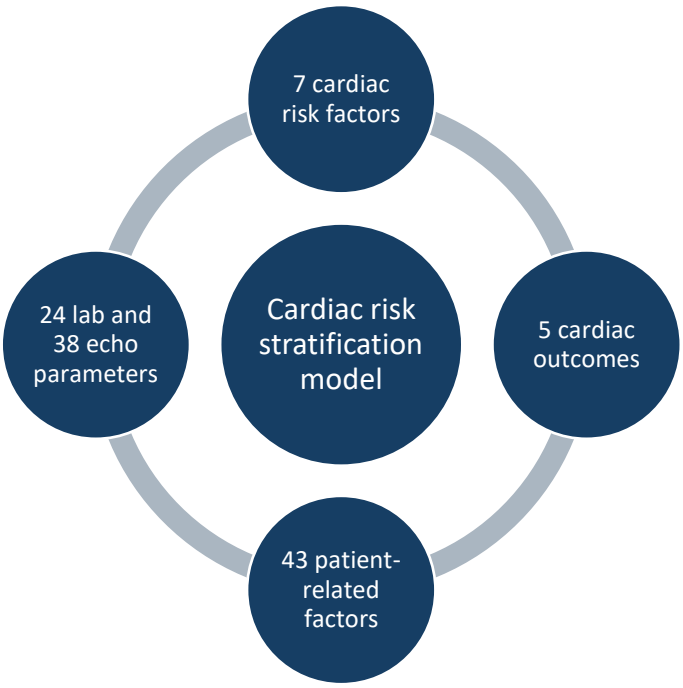
oncology is missing a cardiac risk stratification system, which further hinders guidelines development and complicates cardiac care decision for oncologists.

In recent years, prediction models have been developed for cardiac risk stratification in cancer patients.[12-16] These models identified cancer patients at risk for CTRCD and predicted the incidence of CTRCD with high specificity. However, the moderate sensitivity of these models, along with a small dataset, a limited number of risk factors and clinical parameters, inconsistent and short-term follow-ups, and lack of treatment variability, limit their applicability in the real-world. The limitations of these models emphasize the need for a comprehensive model that reliably captures the complexities of CVD, cancer, and CTRCD, along with patient heterogeneity. Nonetheless, developing such a model presents a unique challenge of analyzing and extracting patterns from large and complex electronic medical record (EMR) data.[17]

Machine learning tools for cardiac risk stratification

Machine learning (ML) offers powerful tools for developing a comprehensive cardiac risk stratification model. Appropriately, researchers at Cleveland Clinic leveraged the enormous data processing power of ML and created the risk stratification model that included every aspect of cardio-oncology.[5] We used longitudinal data from 4632 patients and collected 112 clinical parameters from each patient undergoing cancer treatments at Cleveland Clinic from 1997 to 2019 **(Fig.1)**. We included the following cardiac outcomes: atrial fibrillation (AF), heart failure (HF), coronary artery disease (CAD), myocardial infarction (MI), stroke, and de novo CTRCD. De novo CTRCD refers to cardiac events developed after initiating cancer therapy.

Fig. 1 Clinical parameters for cardiac risk stratification model



We employed ML tools to identify and group patients with similar clinical attributes into one cluster, thus creating a patient-patient similarity network. We also created a clinical variables network to identify clinically relevant biomarkers for the prognosis of cardiac events.

"Our hypothesis was that our unsupervised patient-patient similarity network-based risk assessment of CVD (psnCVD) can leverage heterogeneous patient data and generate interpretable models to visualize the decision boundary in cardiac risk stratification of cancer patients with CTRCD."

Key findings of network analysis

Our analysis revealed a few potential biomarkers for cardiac risk assessment. Notably, high Troponin T and NT-proB-type Natriuretic peptide (NT-proBNP), and creatinine levels were associated with the high incidence of de novo CTRCD and mortality rate. Further, we observed that high sodium and potassium levels were associated with a high mortality rate.

We identified 4 clinically relevant subgroups based on the number of patients diagnosed with de novo CTRCD, risk of developing de novo CTRCD, and clinically relevant variables **(Fig. 2)**.

Fig. 2 Key attributes of patient subgroups

Subgroup 1

- 51% of patients diagnosed with de novo CTRCD
- Highest risk of de novo CTRCD, with high cumulative hazard of de novo HF and AF
- Worst mortality rate
- Elevated serum levels of Troponin T, NT-proB-type Natriuretic peptide, and creatinine

Subgroup 2

- 46% of patients diagnosed with de novo CTRCD
- High risk of de novo CTRCD, with high cumulative hazard of de novo CAD

Subgroup 3

- 39% of patients diagnosed with de novo CTRCD
- Moderate risk of de novo CTRCD
- Worst survival probability and mortality rate
- Elevated serum levels of Troponin T, NT-proB-type Natriuretic peptide, sodium, and potassium

Subgroup 4

- 24% of patients diagnosed with de novo CTRCD
- Lowest risk of de novo CTRCD, with lowest cumulative hazard of de novo HF, AF, MI, and CAD
- Best survival probability
- Lowest serum levels of Troponin T and NT-proB- type Natriuretic peptide

CTRCD: Cancer therapy-related cardiac dysfunction, AF: atrial fibrillation, HF: heart failure, CAD: coronary artery disease, MI: myocardial infarction

To evaluate the generalizability of our model, we divided patients into training and test sets using time-split and random-split methodologies. In the test set, irrespective of the split methodology, all 4 subgroups were distinguishable for the risk of developing de novo CTRCD and survival probability.

Benefits of a cardiac risk stratification model

Cardiovascular care for cancer patients is complex and gets more challenging without knowing which patient will be at risk of CVD. Moreover, the majority of cardiovascular events are diagnosed within the first few years of initiating cancer therapy.[5] This highlights the need for a risk assessment tool that enables oncologists to identify patients at risk of developing CTRCD and intervene early with cardioprotective strategies. Additionally, identifying patients at risk of CVD before starting cancer therapy will allow oncologists to choose cancer treatment with less cardiotoxic effects. Further, such a tool can help develop clinical guidelines for cardiac care management in cancer patients.[18]

The Cleveland Clinic recognized the need for a risk stratification tool and developed a cardiac risk stratification model using longitudinal EMR data. The model appropriately stratified test set patients for the survival probability and risk of de novo CTRCD.

Call to action

Cleveland Clinic's comprehensive cardiac risk stratification model provides a useful tool to improve the clinical decision process in cardio-oncology. In addition to risk stratification, our analysis also revealed Troponin-T, NT-proBNP, and creatinine as potential predictors for the cardiovascular risk assessment. While our model demonstrated generalizability by appropriately stratifying test set patients, it needs to be evaluated in independent patient cohorts to validate its generalizability. Therefore, Cleveland Clinic encourages oncologists to use its model to validate its applicability in the real-world setting and further refine it for broader clinical use. To learn more about the model contact us at Cleveland Clinic.

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