Title

Evaluating the Additive Value of Machine Learning in Clinical Risk Prediction: A Comparative Study Across Three Patient Cohorts

ISBN

9798293830213

Author

Hutchins, Elizabeth Jean

Publication Date

2025-09-10

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA

Los Angeles

Evaluating the Additive Value of Machine Learning in Clinical Risk Prediction: A Comparative Study Across Three Patient Cohorts

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy in Medical Informatics

by

Elizabeth Jean Hutchins

2025

ABSTRACT OF THE DISSERTATION

Evaluating the Additive Value of Machine Learning in Clinical Risk Prediction: A Comparative Study Across Three Patient Cohorts

by

Elizabeth Jean Hutchins
Doctor of Philosophy in Medical Informatics
University of California, Los Angeles, 2025
Professor Alex A.T. Bui, Chair

This dissertation evaluates when and how machine learning (ML) adds value beyond traditional statistical methods for cardiovascular risk prediction across three electronic health record (EHR)-derived cohorts. It consists of three projects. Project 1 examined major adverse cardiovascular events (MACE) in 5,766 patients treated with immune checkpoint inhibitors (ICIs). MACE occurred in 19.6% of patients and was associated with traditional risk factors, cancer exposures, and treatment intensity. ML (XGBoost, AUROC 0.71) identified non-cardiovascular immune-related adverse events requiring prednisone as a novel, high-impact predictor. Project 2 investigated new-onset left ventricular systolic dysfunction (LVSD) after orthotopic liver transplantation in 956 patients. LVSD developed in approximately 7% of patients, typically early in the post-transplant course, and was often reversible. Risk markers included mineralocorticoid receptor antagonist use, lower pre-operative hemoglobin,

intraoperative dialysis, and diastolic/pulmonary hemodynamic features; ML (XGBoost, AUROC 0.73) revealed important non-linear interactions among echocardiographic variables. Project 3 analyzed predictors of successful decannulation in veno-arterial extracorporeal membrane oxygenation (VA-ECMO). Among 199 patients, successful decannulation occurred in 48.5%. ML (random forest, AUROC 0.94) and regression converged on higher mixed venous oxygen saturation as the dominant predictor.

Across these three projects, ML complemented logistic regression by uncovering novel predictors in Project 1, capturing complex interactions in Project 2, and isolating a single dominant predictor in Project 3. Together, the combined use of traditional statistical methods and ML enhanced risk stratification across diverse cohorts and provides a framework for future applications in cardiovascular prediction.

The dissertation of Elizabeth Jean Hutchins is approved.

Linda L. Demer

Tzung Hsiai

William Hsu

Alex A. T. Bui, Committee Chair

University of California, Los Angeles

2025

DEDICATION

This work is dedicated to my family and my mentors

for their incredible support throughout the years.

And to the cancer, liver transplant, ECMO patients of UCLA for the ability to study these

conditions to help improve future outcomes

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF SUPPLEMENTAL TABLES

PREFACE

Chapter 2. A version of this manuscript is published as a chapter in a textbook: Hutchins E, Stein-Merlob AF, Yang EH, Eljalby M, Zaha VG. Role of informatics in cardio-oncology. In: Brown S-A, ed. *Innovations in Cardio-Oncology*. San Diego, CA: Academic Press; 2025:355-378.

Chapter 3. A version of this manuscript has been submitted to *JACC: Cardio-Oncology* and is under review for publication. Co-authors on this publication are: Jeffrey Feng, Eric Yang, Zehua Feng, Melissa G. Lechner, Alexandra Drakaki, Jeffrey Xia, David Madnick, Eric H. Yang, Alex A. T. Bui, and Ashley F. Stein-Merlob

Chapter 4. A version of this manuscript is under preparation for publication. Co-authors are: Martine Webb, Jeffrey Feng, Andrew Melehy, Samuel Daneshvar, Megan Kamath, Vatche Agopian, Alex A.T. Bui, Ashley F. Stein-Merlob

Chapter 1, 5, 6. These manuscripts are not intended for publication.

This work was supported by the National Institutes of Health through the NHLBI Cardiovascular Scientist Training Program (T32 HL007895) awarded to the Division of Cardiology, University of California, Los Angeles

VITA

EDUCATION

2016	M.D. Columbia College of Physicians and Surgeons	Columbia University New York, NY
2010	M.S. Clinical and Molecular Nutrition. Institute of Human Nutrition	Columbia University New York, NY
2008	B.A. Neuroscience and Behavior, Mathematics. Columbia College	Columbia University New York, NY

POST-GRADUATE CLINICAL TRAINING

2023 - 2024	Chief Fellow	Cardiovascular Medicine	University of California, Los Angeles Los Angeles, CA
2020 - 2025	Fellow, STAR Track	Cardiovascular Medicine	University of California, Los Angeles Los Angeles, CA
2016 - 2019	Intern and Resident	Internal Medicine	Harbor-UCLA Medical Center Torrance, CA

PEER REVIEWED PUBLICATIONS

1. **Hutchins E,** Yang EH, Stein-Merlob AF. Inflammation in Chemotherapy-Induced Cardiotoxicity. *Curr Cardiol Rep.* 2024 Oct 8.
2. **Hutchins E,** Bokhoor P. A Rare Cause of Angina: Scimitar Syndrome Case Report. *Eur Heart J Case Rep*. 2023 Jul 20;7(8):ytad327.
3. Bowman CA, **Hutchins E**, Burgermaster M, Sant V, Seres DS. Nasal Feeding Tubes Are Associated with Fewer Adverse Events than Feeding via Ostomy in Hospitalized Patients Receiving Enteral Nutrition. *Am J Med*. 2022 Jan;135(1):97-102.
4. **Hutchins E,** Shaikh K, Kinninger A et al**.** Aged Garlic Extract May Reduce Left Ventricular Myocardial Mass in Patients with Diabetes: Results from Prospective Randomized Controlled Double-Blind Study. *Experimental and Therapeutic Medicine*. 2020 Feb;19(2):1468-1471.
5. **Hutchins E**, Wang R, Rahmani S, Nakanishi R, Witt M, Kingsley L, Haberlen S, Jacobson L, Palella F, Budoff M, Post W. HIV Infection is Associated with Increased Left Ventricular Mass in the Multi-Center AIDS Cohort Study (MACS). *AIDS Research and Human Retroviruses*. 2019 Aug;35(8):755-761.
6. Ochner CN, Stice E, **Hutchins E**, Afifi L, Geliebter A, Hirsch J, Teixiera J. Relation between changes in neural responsivity and reductions in desire to eat high-calorie foods following gastric bypass surgery. *Neuroscience*. 2012 May;209:128-35.

BOOK CHAPTERS

1. **Hutchins E,** Stein-Merlob AF, Yang EH, Eljalby M, Zaha VG. Role of informatics in cardio-oncology. In: Brown S-A, ed. *Innovations in Cardio-Oncology*. San Diego, CA: Academic Press; 2025:355-378.
2. Bui A, **Hutchins E**, Rahrooh A, Yadav A, Hsu W, "Chapter 21: Imaging Informatics." *Health Informatics: Practical Guide, 8th Edition,* edited by Willian Hersh, Lulu Press, 2022, pp. 401-412.

ABSTRACT & ORAL PRESENTATION

1. **Hutchins E**, Rahrooh A, Feng J, Chandra N, Hsu J, Bui A. Predicting Successful ECMO Decannulation: A Novel Machine Learning Approach. Oral Presentation at: Northwestern Cardiovascular Young Investigators Forum; September 2023; Chicago, IL.
2. **Hutchins E**, Ellenberg S, Snyder P, Budoff M. Testosterone Gel Increases Left Ventricular Mass in Older Men: Results from the Testosterone Trial. Oral presentation at: American Heart Association Scientific Sessions; November 2019; Philadelphia, PA.
3. **Hutchins E**, Wang R, Rahmani S, Nakanishi R, Witt M, Kingsley L, Haberlen S, Jacobson L, Palella F, Budoff M, Post W. HIV Infection is Associated with Increased Left Ventricular Mass in the Multi-Center AIDS Cohort Study (MACS). Oral presentation at: Solomon Scholars; June 2018; Los Angeles, CA.
4. **Hutchins E**, Wang R, Rahmani S, Nakanishi R, Witt M, Kingsley L, Haberlen S, Jacobson L, Palella F, Budoff M, Post W. The Heart in the Era of HAART: Data from the Multi-Center AIDS Cohort Study (MACS). Oral presentation at Harbor-UCLA Research Day; May 2018; Torrance, CA.
5. **Hutchins E**, Miller J. Resting State fMRI in Patients Undergoing Cognitive Behavioral Therapy for Major Depressive Disorder. Oral presentation at: NIH Summer Scholars Research Symposium; August 2013; New York, NY.

SELECTED ABSTRACT & POSTER PRESENTATION

1. **Hutchins E**, Feng J, Yang EH, Lechner M, Brakaki A, Arega E, Yang E, Bui A, Madnick D, Stein-Merlob AF. Cancer Type and Baseline Cardiometabolic Risk Factors Predict Major Adverse Cardiac Events in Patients Receiving Immune Checkpoint Inhibitor Therapy. Poster session presented at: America Heart Association Scientific Sessions; November 2024
2. **Hutchins E**, Rahrooh A, Feng J, Chandra N, Hsu J, Bui A. Predicting Successful ECMO Decannulation: A Novel Machine Learning Approach. Poster session presented at: America Heart Association Scientific Sessions; November 2023
3. **Hutchins E**, Burgermaster M, Seres D. Nasal Feeding Tubes Associated with Fewer Adverse Events than Feeding Ostomies in Hospitalized Patients Receiving Enteral Nutrition. Poster session presented at: Harbor-UCLA Resident Research Day; May 2019; Torrance, CA
4. **Hutchins E**, Joo E, Darabian S, Budoff M. High Sensitivity Cardiac Troponin is Associated with Elevated Coronary Artery Calcium Score on CT Coronary Angiogram. Poster session presented at: Southern California ACP Conference; October 2018; Huntington Beach, CA.
5. **Hutchins E**, Wang R, Rahmani S, Nakanishi R, Witt M, Kingsley L, Haberlen S, Jacobson L, Palella F, Budoff M, Post W. The Heart in the Era of HAART: Data from the Multi-Center AIDS Cohort Study (MACS). Poster session presented at: Solomon Scholars; June 2018; Los Angeles, CA.

Chapter 1

Introduction

The goals of this dissertation are twofold: clinical and technical. Clinically, the aim is to identify risk factors for adverse cardiovascular outcomes across three electronic health record (EHR)-derived cohorts using both traditional statistical techniques and modern machine-learning (ML) approaches. Technically, the aim is to specify the ways in which ML can provide *additive value* beyond traditional statistical methods in these concrete clinical settings.

Traditional statistical techniques (e.g., logistic regression) and ML differ in their assumptions, interpretability, and flexibility. Logistic regression (LR), a generalized linear model, has been the mainstay for prediction of binary outcomes in clinical medicine. It relies on strong assumptions, namely linear relationships on the log-odds scale, additivity of effects, and usually requires exclusion of highly collinear predictors. Investigators must often manually specify interaction terms or nonlinear transformations *a priori*. These constraints can limit logistic regression's ability to fit complex patterns in data, especially in high-dimensional EHR datasets with numerous clinical variables. In contrast, machine learning models can automatically model nonlinearities and interactions: for instance, tree-based methods partition the data based on predictor cut-points (capturing threshold effects), and ensemble methods like random forests and XGBoost aggregate many decision trees to model intricate relationships. ML models can thus handle high-dimensional inputs and capture subtle variable interactions without explicit specification. This flexibility comes at the cost of interpretability: complex ML models are often considered "black boxes" by clinicians. It can be challenging to understand how an ML algorithm weights each predictor or to extract simple risk

equations, whereas LR provides clear coefficients and odds ratios. The reduced transparency of ML has implications for clinical implementation and trust.

Several studies have compared machine learning with logistic regression, but most have emphasized their different abilities with regard to discrimination – typically by comparing the area under the receiver operating characteristic curve (AUROC) of both methods [1-3]. Little work has systematically quantified the *additive value* of ML to logistic regression across multiple cohorts.

Accordingly, this dissertation evaluates the combined value of LR and ML in three distinct patient datasets. These datasets are EHR-derived, providing granular clinical information (laboratory values, imaging results, diagnoses, and longitudinal follow-up) and enabling targeted manual chart abstraction. Because these cohorts are EHR-derived, data quality, missingness, and temporal drift receive explicit treatment through prespecified preprocessing and robustness checks.

The datasets will be labeled Projects 1-3. **Project 1 ("Immunotox")** includes all patients treated with immune checkpoint inhibitors for solid organ malignancies between 1/1/2015 and 12/31/2023. **Project 2 ("Liver Transplant")** identifies liver transplant recipients using United Network for Organ Sharing (UNOS) data linked to institutional records, with variables abstracted by chart review and echocardiogram interpretation. **Project 3 ("ECMO")** comprises extracorporeal membrane oxygenation (ECMO) patients identified via the UCLA cardiovascular surgery service, with detailed variables collected by manual chart abstraction. Each dataset is used to determine risk factors for adverse cardiovascular outcomes in these settings with both traditional statistics and

ML. For each project, the specific additive value of ML is evaluated and synthesized and reported in the corresponding chapter as well as in this dissertation's conclusion.

The overarching contribution of this dissertation is not merely to report model performance, but to provide decision-relevant guidance about when and how ML meaningfully augments traditional statistics in cardiovascular risk prediction. As a background to these analyses, a chapter discussing the role of informatics in cardio-oncology, relevant in clinical content to Project 1, but to the methodology of all Projects in this dissertation, is first presented.

Chapter 2

Background

The Role of Informatics in Cardio-Oncology Research

CURRENT APPLICATIONS/PRACTICE:

Cardio-oncology is a multidisciplinary field that requires the integration of immense amounts of data, and health informatics is critical for the advancement of this field. Health Informatics sits at the intersection of clinical medicine, healthcare enterprises and information science and technology (See **Figure 1**, adapted from [4]). *It is the practice of using technology to convert health data into actionable knowledge used for both clinical applications and research purposes*. This field encompasses the acquisition, transfer and utilization of health data, aiming to enhance decision-making, problem-solving, and communication within the healthcare domain. It is crucial to the operations of cardio-oncology specialists.

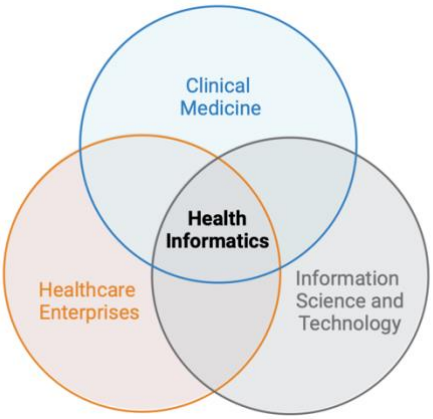

Figure 1: Domains of Health Informatics Informatics sits at the intersection of the domains of clinical medicine, healthcare enterprises, and information science and technology. Adapted from (1)

Data Collection and Integration:

Informatics, at its core, is the study of information, or data. There are many different sources of data collected in cardio-oncology practice and research which are reviewed here. Depending on the purpose and methods of collection, data span from high-resolution individual, clinical data to large, deidentified databases.

Individual patient data: In the field of cardio-oncology, a patient will have a diverse range of data gathered both as part of their treatment and through their involvement in registries or research trials. Data can be grouped as: phenotype-specific data, or phenomics, and comprehensive biological data, or multi-omics data. The integration of these data types provides a complete picture of a cardio-oncology patient, as summarized in **Figure 2**.

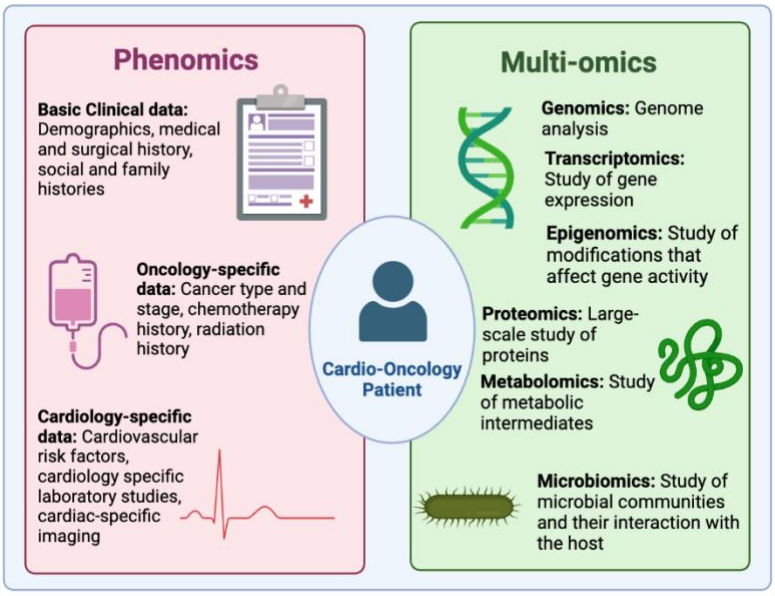

Figure 2: Individual patient data: The comprehensive care of the cardio-oncology patient involves integration of both phenomics and multi-omics data

1. **Phenomoics:** Phenomics includes basic clinical data, cardiology-specific data, and oncology-specific data. Basic clinical data include demographics (e.g., age, biological sex, gender identity, address, ethnicity, socioeconomic status), medical and surgical history and social and family histories. Cardiology specific data includes information gathered specifically about a patient's cardiovascular health. This includes cardiovascular risk factors, cardiac-specific laboratory studies (notably, troponin and B-type naturetic peptide), and cardiac imaging (ECG, echocardiogram, MRI, CT, PET). Oncology-specific data includes data about a patient's oncologic risk factors, data about their cancer (type and stage, tumor pathology, tumor biomarkers), cancer-related imaging (such as full-body PET-CT), as well as chemotherapy and radiation history.

2. **Multi-omics:** Multi-Omics data refer to the comprehensive data that characterize a biological system, i.e., a patient. These include: genome analysis, or genomics; the complete set of RNA transcripts, or transcriptomics; the study of epigenetic modifications that affect gene activity without altering the DNA, or epigenomics; the large-scale study of proteins, or proteomics; the study of small molecule metabolic intermediates and products, or metabolomics; the collective study of microorganisms that live on and in the human body, or microbiomics. Genomics, or genome analysis, involves the sequencing and analysis of a patient's complete set of DNA, exploring the genetic makeup. It can identify genetic variations that may predispose to certain cancers or cardiovascular diseases or even treatment responses. For instance, genomics might reveal a mutation in the BRCA1 gene, suggesting a higher risk for certain cancers and influencing the choice of prevention strategies or treatments. Additionally, there is a growing field of clonal hematopoiesis of indeterminate potential (CHIP) whereby somatic mutations that are associated with hematologic malignancies also portend an increased risk of cardiovascular disease [5]. *Transcriptomics* involves the study of RNA transcripts to understand gene expression. In cardio-oncology it can help elucidate the molecular mechanisms underlying cardiotoxicity from cancer treatments For example, transcriptomic profiling has revealed the p53 protein as a key regulator of transcriptomic changes induced by doxorubicin which lead to cardiotoxicity [6]. *Epigenomics* involves the study of reversible modifications of cellular DNA or histones that influence the gene expression without modification of the DNA sequence. It can help in understanding the cardiotoxicity induced by cancer therapies; for example anthracyclines (e.g., doxorubicin), can induce DNA methylation changes in cardiac cells, leading to mitochondrial dysfunction and altered metabolic pathways [7]. *Proteomics* is the study of

the comprehensive expression of proteins in tissues or plasma, including the location, quantification, structure, function, and interactions of different proteins. As currently clinically used, specific proteins, like prostate specific antigen (PSA) or CA125, are used as biomarkers for cancer diagnosis, prognosis and treatment response. However, broader studies of proteomics have identified novel markers of cardiotoxicity in the population of patients with cancer [8]. *Metabolomics* refers to the study of metabolites, which are small molecules generated as intermediates or products of metabolism. Changes in the levels of certain metabolites can signal alterations in both cancer progression and cardiovascular health. Elevated levels of lactate, for example, could indicate tumor growth, while changes in carnitine levels might reflect disruptions in cardiovascular mitochondrial function. *Microbiomics* is the study of microbial communities and their interactions with the host. This is applicable to cardio-oncology as cancer treatments can disrupt the balance of the gut microbiome (dysbiosis), Dysbiosis may lead to cardiovascular disease in cancer patients by promoting inflammatory pathways and affecting metabolic functions critical to heart health [9].

All of the above data integrates into the electronic health record (EHR) and is used in clinical care and research in cardio-oncology. Individual data within the EHR provides highly detailed patient specific data that is frequently used in daily clinical care or in small scale research studies. However, this type of individual level data is often difficult to translate into large scale research due to various obstacles, including patient privacy laws, data storage, and variations in data collection techniques.

Large Databases in cardio-oncology: To advance the field of cardio-oncology, individual data must be collected into large data repositories or databases, which can take on various forms. These data repositories are often referred to as 'big data' (see preceding chapter). Types of big data include national registries and claim databases, aggregate EHR data warehouses, multicenter institutional registries, and biobanks. National registries and claims warehouses are most often coordinated by government agencies and collect data on individuals residing within a particular country or other geographic area. In the United States, one notable national registry is the Surveillance, Epidemiology, and End Results (SEER)-Medicare Program which is a population-based database that provides detailed information about Medicare beneficiaries with cancer [10]. Many Scandinavian countries with national health systems, such as Demark, have also national healthcare registries, with a unique identifier for each individual. Aggregate electronic health record (EHR) data warehouses consolidate deidentified patient information from EHR systems across multiple institutions; one example is the Kaiser system which has a warehouse storing information across multiple practice locations [11]. Another is CancerLinQ – a longitudinal, aggregate EHR warehouse derived from more than 60 oncology practices across the United States [12]. Multicenter Institutional registries

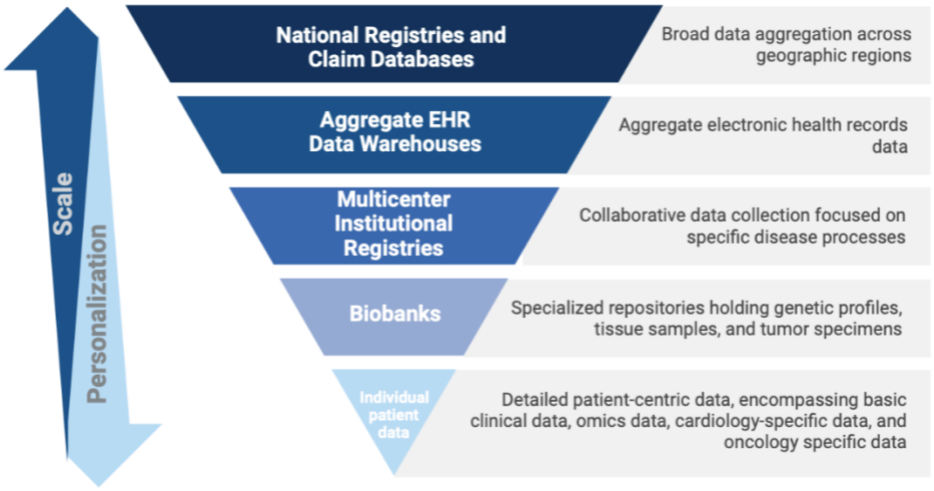

Figure 3: Spectrum of Data Types in Cardio-Oncology: Depicting the spectrum of data types in cardio-oncology, this figure shows gradation from highly personalized individual patient data at the bottom to broadly aggregated national registries and claim databases at the top.

gather patient data from multiple institutions to investigate specific disease processes which require active participation by local site investigators to identify patients and submit predetermined types of patient data. Examples include the International ICI Myocarditis Registry, which is a retrospective multicenter registry including 49 institutions and 11 countries built using a Research Electronic Data Capture web-based platform to study immune checkpoint inhibitor related myocarditis [13] and Global Cardio-Oncology Registry (G-COR) which is a multinational, multicenter prospective registry which studies prevalence of anti-cancer therapy-related cardiovascular toxicity in different risk groups, practice settings, and geographic locations [14]. To allow deeper biological studies, biobanks store biological material and associated data. They may contain plasma samples for biomarker analysis, genetic profiles, tumor specimens for cancer genomics, and heart tissue samples for research into cardiotoxic effects of anti-cancer treatments. These can either be institutional or government run, as in the UK Biobank and the National Heart, Lung, and Blood Institute's Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC) in the United States. Note that as a trend, as the scale, or number of patients, increases in a database the amount of information and quality of information, or personalization, of the data decreases. National registries and claim databases contain the most patients with often the least amount of data about each patient without the option for further data collection, whereas biobanks tend to contain less patients, but much more comprehensive and higher quality information about each patient (see **Figure 3**). With regard to big data sources, cardio-oncology is unique in that it blends two specialties, and so there are databases that have often been established within each specialty that can be used.

Pharmacovigilance Databases: Within the field of cardio-oncology, pharmacovigilance most often refers to monitoring the cardiac safety profile of anti-cancer therapies. Pharmacovigilance is defined by the World Health Organization (WHO) as "*the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine/vaccine related problem" [15].* These registries are particularly useful in cardio-oncology, as cardiotoxicity associated with a specific cancer therapy can be rare and manifest clinically long after a treatment is started or ended. Therefore, safety of certain cancer therapies is often not adequately captured in clinical trials, and the safety profile of a drug is more adequately profiled by pharmacovigilance registries. One such registry is Vigibase, which is managed by the Uppsala Monitoring Centre (UMC, Uppsala, Sweden) and contains 19 million reports submitted by national pharmacovigilance centers since 1967. Several studies have resulted from analysis of the Vigibase registry. One report showed the association of immune checkpoint inhibitors with life-threatening ventricular arrhythmias [16]. Another study found that the odds of developing heart failure with different metastatic breast cancer regimens were highest with a combination of trastuzumab, pertuzumab and docetaxel and lowest with lapatinib and capecitabine [17]. Another example of a pharmacovigilance database is the FDA adverse event reporting system (FAERS) which is a national reporting system run by the FDA in the United States. Note that pharmacovigilance databases face several challenges such as inconsistent reporting of adverse events by patients and healthcare providers, under-reporting of such events, and difficulties in determining the causality between a drug and an adverse event [18].

Challenges to Developing Large Databases:

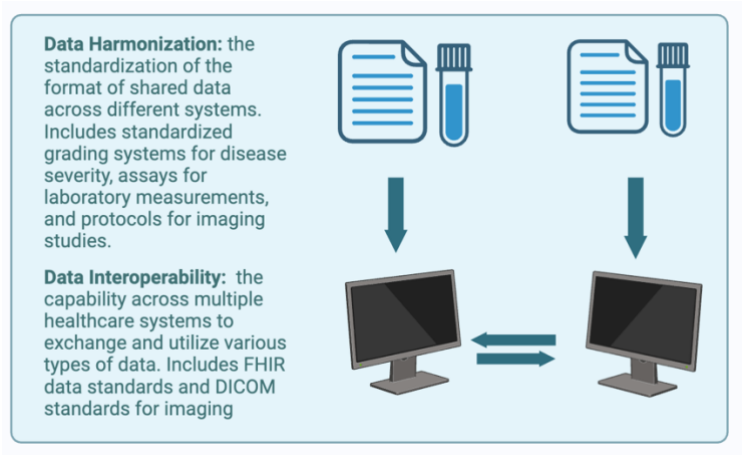

Figure 4: Data Interoperability and Harmonization in Cardio-Oncology: This figure illustrates the concepts of data harmonization and interoperability within the context of cardio-oncology.

Data Interoperability: refers to the capability to exchange and utilize various types of data across multiple healthcare systems. Interoperability is ensured via data standards, the most prevalent of which are the Fast Healthcare Interoperability Resources (FHIR) standards. These are international standards the ensure that information is formatted in standard way regardless of what EHR is used. Within cancer care, the mCODE, or minimum Common Oncology Data Elements, initiative is a set of data standards that adhere to FHIR and ensure interoperability of cancer data [19]. For imaging data interoperability, the Digital Imaging and Communications in Medicine (DICOM) standard protocol is most used. The DICOM standardized file format is providing interoperability for managing, storing, transmitting and viewing medical imaging data and related metadata including technical and patient information encoded in a single file. The format is device and manufacturer-independent and can be universally viewed.

Data harmonization is the standardization of the format of shared data across different systems (**Figure 4**). Harmonization refers to the process of bringing together data with varying naming conventions, file formats and sizes, and transforming them into one cohesive data set with a common data format. For example, this includes using uniform grading systems for disease severity, units for laboratory measurements, and protocols for imaging studies.

For an example of interoperability and harmonization in action, consider multicenter research surrounding immune checkpoint inhibitor myocarditis. Interoperability would ensure that sites adhere to the same data standards in storing patient data, such as DICOM files, that can be easily shared and used by multiple sites. Harmonization would require each site to use consistent grading systems for myocarditis severity, measurement units for assays such as troponin and sequence protocols for cardiac MRI. Both data interoperability and harmonization are required to allow data to be shared among different centers for both patient care and research.

Data protection and privacy: When handling any patient data, it is of paramount importance that the data be protected and patient privacy ensured. Encryption ensures that patient data, whether in transit over networks or at rest in storage systems, is securely encoded, making it inaccessible to unauthorized parties. Compliance with the Health Insurance Portability and Accountability Act (HIPAA) is also critical. HIPAA establishes national standards to protect sensitive patient health information from being disclosed without the patient's consent or knowledge. However, instituted in 1996, HIPAA faces contemporary challenges in the digital age [20]. The scope of data now used in healthcare and healthcare research is broader than it was in the inception of HIPAA. For example, the use of large sets of individual-derived aggregate data (i.e., multi-omics data), very limited limited in the 1990s, now offers a distinct ability to identify a unique pattern specific to a patient, raising the risk of privacy breach through reverse engineering from data to individuals, such as DNA in an attribute disclosure attack [21] [22]. In addition, wearable devices and mobile health applications collect a substantial amount of personal health information that is not covered by HIPAA [20, 23]. Policy updates are ongoing

and must be continually reviewed to maintain adequate patient privacy in cardio-oncology care and research.

Electronic Health Record (EHR) Informatics Tools: EHR is the digital tool that stores individual patients' health record, including all demographics, physician notes, laboratory values, imaging tests and more, that is used for clinical care, billing, and administrative purposes. Over time, the EHR has grown to include an immense amount of individual data. Therefore, to harness this information there has been a proliferation of informatics tools that can be utilized for the management of cardio-oncology patients. Examples of informatics tools are discussed here, with basic to complex functionalities. **Figure 5** depicts how EHR tools can be applied to the management of anthracycline-induced cardiomyopathy.

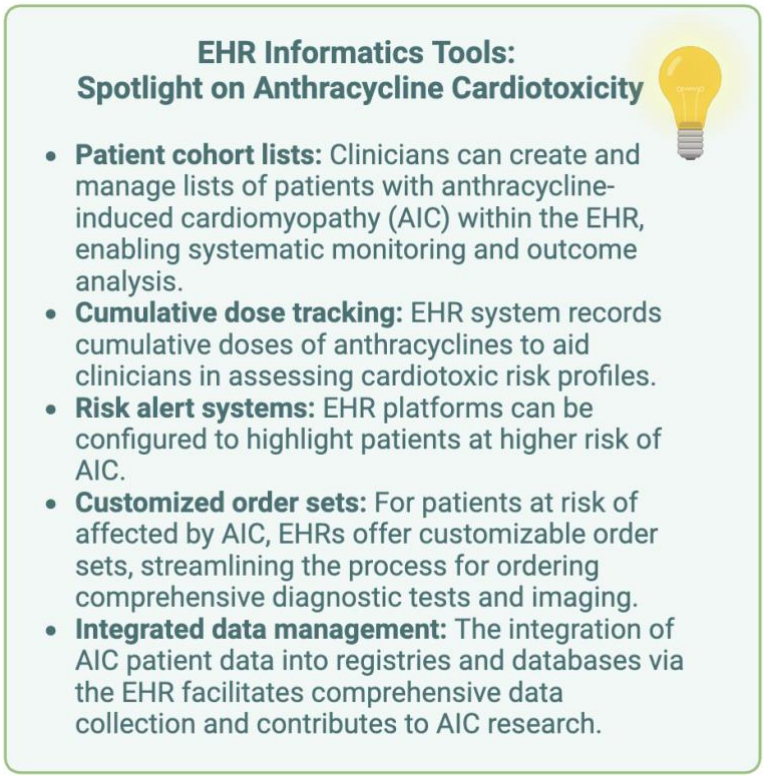

Figure 5: EHR Informatics Tools: Focus on Anthracycline Cardiotoxicity: This figure highlights various electronic health record (EHR) informatics tools in the context of managing anthracycline cardiotoxicity.

Patient lists – cohort tracking: Providers can create patient lists within the EHR that are shareable amongst providers. Such lists keep track of patients with similar disease processes for clinical management, research, and referral to clinical trials.

Cumulative dose tracking: The EHR can track cumulative doses of administered chemotherapies and display these in an organized fashion.

Risk alert systems: Using the EHR, patients with particular cardio-oncologic diagnoses can be identified and brought to the attention of a cardio-oncology team. For example, EHR tools can identify patients with toxicity from immune check-point inhibitors and alert specialized providers to these patients [24] [25]. Care must be made to avoid 'alert fatigue,' which refers to physicians disregarding best practice advisories (BPA) due to their increasing prevalence. Attention must be paid to quality, over quantity, of alerts to avoid such burnout.

Customized order sets: For an identified cardio-oncology patient, or for an oncology patient at risk of cardio-toxicity, the EHR has the capability of customized order sets of commonly used laboratory tests or imaging studies that the provider may use to quickly and thoroughly assess and care for the patient.

Telehealth and Remote Monitoring Tools: With the increasing prevalence of telehealth, cardio-oncologists can monitor patients remotely, especially useful for managing chronic conditions or assessing treatment-related cardiotoxicity for patients in remote areas. Wearable devices and remote monitoring tools, such as watch data, can track vital signs, heart rhythms, and other relevant health metrics and integrate these into the EHR.

Patient Portal Systems: These allow for enhanced patient engagement and communication. Patients can access their health information, communicate with their healthcare providers, and manage appointments, which is vital for the often complex and multi-faceted care involved in cardio-oncology.

Clinical decision support systems (CDSS): These are advanced tools that assist healthcare professionals in making informed decisions by providing evidence-based recommendations and insights. They integrate patient data and use algorithms to provide evidence-based recommendations, alerts for potential drug interactions (especially important for patients receiving both oncology and cardiology medications), and reminders for patient follow-up and screening.

Care gap identification: These tools can be used to identify care gaps and encourage physicians to adhere to guide-line directed therapies [26].

Registry and Database Integration: These are tools that facilitate the integration of EHR data with specialized registries (like cancer or cardiac registries) and databases. This integration helps in tracking long-term outcomes and understanding the interplay between cardiac and anti-cancer treatments.

Data Analytics in Cardio-Oncology Research

Benefits of an informatics approach to cardio-oncology research: The utilization of advanced analytics in cardio-oncology research is increasingly recognized as a valuable alternative to traditional clinical trials for several reasons. First, the substantial volume of patient data in both cardiology and oncology allows significant insights to be derived from observational data. Second, using an informatics approach to analyze big sources of data provides a better reflection of 'real-world' patient profiles. This is particularly relevant as cardiology patients are often excluded from oncology trials, and vice versa. Moreover, oncology trials typically include only about 5% of patients with cancer [27]. Furthermore, health informatics is instrumental in capturing data on underserved populations, who are often underrepresented in large clinical trials [28] [29]. By integrating these data, informatics ensures a more inclusive and

comprehensive understanding of patients across various populations, addressing disparities in healthcare and advancing the cardio-oncology field towards more equitable and effective patient care.

Interdisciplinary approach to cardio-oncology research: Effective cardio-oncology informatics research requires a team that brings together cardiologists, oncologists, informatics specialists, and data scientists. These multidisciplinary teams are increasingly common worldwide [30]. Efforts in data science, facilitated by such collaborations, are essential for the application of multi-omics in both research and clinical care of cardio-oncology patients. The National Institutes of Health has recently awarded a significant grant to support these initiatives [31]. Moreover, productive collaborations include not just different professional types but also a variety of institutional types. Partnerships among technology companies, industrial entities, academic institutions, and private practices are crucial for advancing the field [32].

Data science methods and their use in cardio-oncology: **Table 1** summarizes key data analytic processes and includes examples of their utility in the field of cardio-oncology.

Table 1: Data Analysis Methods in Cardio-Oncology Informatics

	Data Analysis Type	Brief Description	Example
Classical statistical methods	Descriptive statistics	Tools that summarize current and historical data to identify trends and patterns.	Evaluating the incidence of cardiotoxicity in breast cancer patients treated with anthracyclines.
	Hypothesis testing	Techniques for analyzing data that describe relationships and test hypotheses about variables.	Comparing cardiotoxicity rates between different patient populations treated with anthracyclines.
AI-enhanced data analytics	Machine learning	Algorithms that allow computers to uncover insights from data.	Developing predictive models for risk of chemotherapy-induced cardiomyopathy.
	Natural Language Processing	A branch of AI that enables computers to understand, interpret, and generate human language.	Mining large volumes of physician notes to identify cardiac risk factors in oncology patients.

	Deep learning	A subset of machine learning that uses neural networks with many layers to learn data representations.	Imaging analysis for detecting early signs of cardiac dysfunction in cancer patients.

Descriptive statistics: Descriptive statistics involves the calculation of various statistical measures-such as frequencies, averages, variations, and percentiles-that summarize and describe the characteristics of a large volume of data in a manageable form. In cardio-oncology, large registries can be queried to determine prevalence of cardiotoxic side effects of anti-cancer therapies [16, 17] and prescribing behaviors of oncologists [33].

Hypothesis testing: Hypothesis testing is an established statistical technique that evaluate relationships between variables and test hypotheses within datasets. In this type of data analytics, two or more populations can be compared. These techniques can compare anti-cancer treatment protocols to determine which protocol places patients at higher risk of cardio-toxicity [34] [35].

Machine learning: Machine learning, as it applies to data analytics, encompasses a spectrum of algorithms that enables computers to identify trends and make predictions based on data analysis without being explicitly programmed, in particular they have the ability to learn from a data set and adapt. Machine learning can be used to create sophisticated risk models for anti-cancer therapy related cardiac dysfunction [36]. It can also analyze genetic and pharmacogenetic data to predict genetic risk for drug induced cardiotoxicity [37] [38]. As early detection of cardiotoxicity can improve cardiac outcomes, these risk models provide valuable insight for the provider caring for the cancer patient.

Natural language processing: Natural language processing (NLP) is a branch of artificial intelligence that enables computers to understand, interpret, and generate human language. This enables faster processing of language-based research in cardio-oncology. NLP models can identify the presence of cardiovascular comorbidities in free-text health records of cancer patients [39]. Studies have shown success with leveraging natural language processing (NLP) and speech recognition technologies to 'listen' to patient-provider interactions and chart symptoms [40]. This functionality promises to enhance the accuracy of medical records and free up valuable time for healthcare professionals.

Deep learning: Deep learning, a subset of machine learning, uses convolutional neural networks which consists of multiple layers that enable computers to comprehend complex data representations, closely emulating the neural network patterns of the human brain. This advanced capability opens a new frontier in cardio-oncology applications. Deep-learning enabled algorithms can accurately analyze ECGs and assess patients at risk for drug-induced QT prolongation [41], which is crucial for cardio-oncologists as many anti-cancer therapies can cause QT prolongation. Additionally, deep-learning algorithms can be applied to ECGs to detect drop in ejection fraction, which could help a cardio-oncologist more easily and quickly screen for anthracycline-induced cardiomyopathy [42]. Deep-learning image analysis

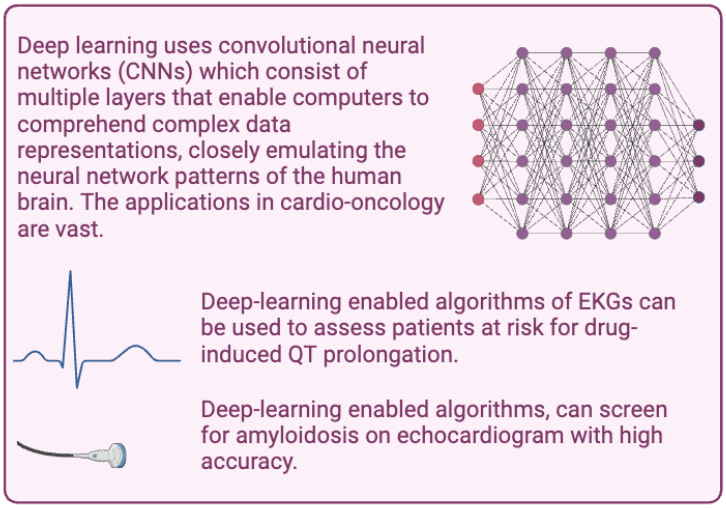

Figure 6: Deep Learning in Cardio-Oncology: Applications of deep learning, specifically convolutional neural networks (CNNs), in cardio-oncology.

can be used to detect cardiac amyloidosis [43] enabling expanded detection of this often missed cardio-oncologic diagnosis. **Figure 6** summarizes applications of deep learning in cardio-oncology.

FUTURE PREDICTIONS/DIRECTIONS

The field of informatics is undergoing rapid development and there are many developments which will soon change the way the field of cardio-oncology is practiced and studied. The following are predictions in how the role of informatics in cardio-oncology will continue to advance (**Figure 7**).

Expanded data sources: In cardio-oncology, an increase in patient numbers and data types will boost data volume and variety. Increased data volume is expected because both number of patients living with cancer and cardiovascular conditions will rise and also because increased integration of EHR data into health registries is anticipated [26]. Data variety will also increase to include more mobile health and wearable technologies (mHealth, see separate chapter) as well as more comprehensive omics profiles. This will facilitate the development of advanced analytical tools for better disease understanding and management.

Increased computing power: The increase data volume and variety demands advanced computing resources for effective storage, retrieval, and examination of cardio-oncology data [22]. Various advanced computing methods such as cloud computing, high performance computing, tensor processing units (TPUs) and quantum computing, are being develop to address these needs. Quantum computing is a revolutionary technology that operates on the principles of quantum mechanics. Unlike traditional computers, which use bits as the smallest unit of data, quantum computers use quantum bits, or qubits. This allows quantum computers to process a vast number of possibilities at once [44]. Advanced computers, such as quantum computers, will allow for handling of larger cardio-oncology datasets and more complex data analysis while providing more data security through enhanced data encryption methods.

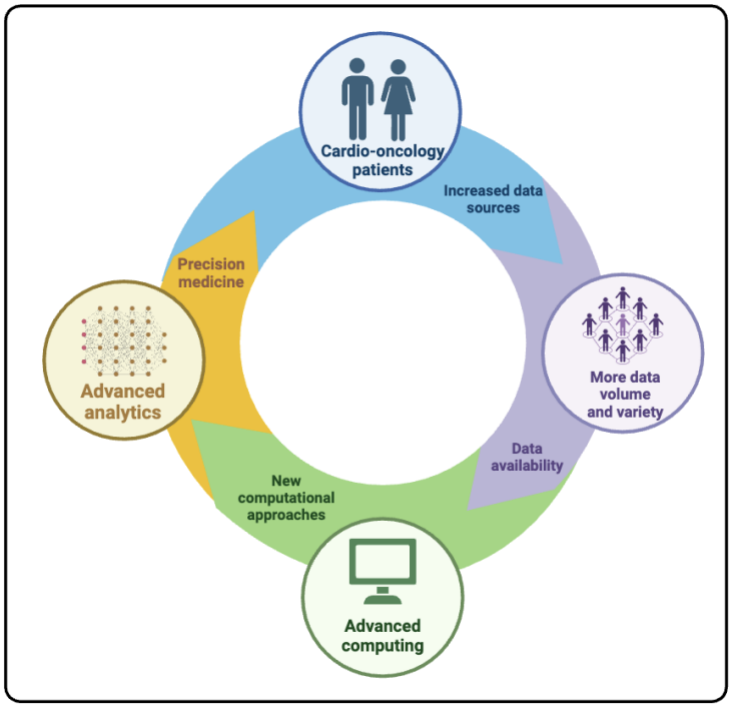

Figure 7: Future of Cardio-Oncology Informatics: As the population of cardio-oncology grows, so will their incorporation into registries and databases. This will lead to more data volume and variety which will be handled by more powerful computers. With use of more advanced computing, AI-tools, advanced analytics will generate novel insights to allow precision medicine that can be used to better care for the growing cardio-oncology patient population.

Advanced analytic tools: Artificial intelligence (AI), including machine learning, deep learning and large language models (LLM), will play an integral role in interpreting complex data patterns

and creating advanced analytic tools for use in cardio-oncology clinical care and research. These analytic tools will aid in creating more sophisticated clinical decision support algorithms. In the realm of imaging, AI tools will progress to allow earlier detection of cardiotoxicity and more precise imaging diagnoses (see separate AI-imaging chapters). LLM, which uses deep learning techniques on massively large language datasets to understand, manipulate and generate human language, has vast potential in the field of cardio-oncology. For providers, LLMs can process vast amounts of medical literature to support clinical decision-making. For patients, these models will create personalized educational material, explaining complex medical conditions and treatments in an accessible manner. The various potential uses of large language models in cardio-oncology are detailed in **Table 2**.

Table 2: Large Language Model Use Cases in Cardio-Oncology

Large language model (LLM) use	Brief Description
Patient education	LLMs can generate patient-friendly explanations of complex medical conditions, treatments, and research findings.
Patient interaction	Chatbots powered by LLMs can be deployed to answer patient inquiries, provide guidance on managing symptoms, and offer support for medication adherence and lifestyle changes
Coding and billing optimization	LLMs can accurately translating clinical procedures and diagnoses into the appropriate billing codes, which can save provider's time and optimize reimbursement.
Data mining from EHRs	LLMs, through NLP capabilities, can extract relevant information from electronic health records, for use in research and clinical care
Synthesizing research	LLMs can digest and summarize vast amounts of scientific literature, helping to identify gaps in knowledge, potential areas for investigation, and recent advances in the field of cardio-oncology.

Increased interdisciplinary collaboration: The interdisciplinary nature of cardio-oncology will further solidify, with collaboration between clinicians, data scientists, patient advocates, and policy makers becoming more integral. These collaborations will drive innovation, from the development of new informatics tools to the formulation of policies that promote the use of these tools in clinical practice [32].

Expanded access to care: Informatics can expand access to quality cardio-oncology care for underserved populations. Telehealth and wearable devices facilitate remote consultations and monitoring, overcoming barriers for geographically isolated or transportation-limited patients [45]. Machine learning algorithms can analyze vast datasets to identify early signs of decompensation, enabling targeted interventions that enhance resource allocation and equitable access to specialized care [46] [47] [48]. Patient-centered platforms may improve communication with healthcare providers and disseminate culturally appropriate educational materials, empowering patients to actively participate in their health care [48]. However, careful consideration ought to be made to avoid exacerbating healthcare disparities through informatics. Limited digital literacy or access to internet connectivity can exacerbate the "digital divide" affecting underserved communities [49]. Similarly, machine learning algorithms trained on biased data can perpetuate existing disparities in healthcare access and outcomes [50, 51]. Concerted efforts to study the barriers faced by underserved communities and means to overcome them are hence warranted [52, 53].

Policy and Ethical Considerations: As informatics becomes more embedded in cardio-oncology, there will be a greater need for policies that govern the ethical use of data. Issues such as patient consent, data privacy, and security will be at the forefront. Additionally, policies will need to ensure that advancements in informatics do not increase health inequities but instead contribute to more equitable health outcomes. The future of cardio-oncology informatics is marked by rapid advancements in data collection, management, and analysis. The integration of these developments will not only enhance our understanding of cardio-oncology but also significantly improve patient care and outcomes. As we embrace these changes, the field is

poised for a transformative shift that will redefine the boundaries of patient treatment and research in cardio-oncology, making quality care more accessible and equitable for all.

SUMMARY/CONCLUSIONS: In summary, the current chapter has explored the multifaceted realm of health informatics within the context of cardio-oncology. This chapter has discussed the variety of different data types collected for individual cardio-oncology patients, including phenotype data, or phenomics, such as basic clinical data, oncology- and cardiology-specific data, and comprehensive biological data, or multi-omics data. It has discussed integration of this data into 'big-data' databases including biobanks, multi-institutional registries, aggregated EHR data warehouses and national and claims-based registries. It detailed the considerations necessary when using big-data, namely data interoperability, harmonization, privacy and security. Informatics tools in the EHR are discussed within the context of their role in the practice of cardio-oncology, including cohort tracking, cumulative dose tracking, clinical decision support systems, and risk alerts. Data analytic methods including both classical statistical methods, as well as artificial intelligence enhanced methods are detailed. Finally, future predictions and directions highlight the expected expansion in data sources, advancements in computing, and the development of new analytic tools with the goal of more improved care of the cardio-oncology patient.

Chapter 3

Project 1

Major Adverse Cardiovascular Events Following Immune Checkpoint Inhibitor Therapy: Clinical Predictors and Associated Mortality

Abstract:

Background: Immune checkpoint inhibitors (ICIs) have revolutionized cancer therapy, but growing evidence links them to increased risk of major adverse cardiovascular events (MACE). Risk factors for MACE in ICI-treated patients remain poorly defined.

Objectives: To assess the incidence, predictors, and mortality impact of MACE in patients receiving ICI therapy.

Methods: We retrospectively analyzed 5,766 patients treated with ICIs from 2015 to 2024 at a single center. The primary outcome of this study was MACE, defined as new-onset atherosclerotic cardiovascular disease, arrhythmia, or heart failure. Predictors of MACE were identified using multivariable logistic regression and machine learning (XGBoost with SHAP feature importance). ICI-related myocarditis and pericarditis were analyzed separately.

Results: MACE occurred in 1,130 patients (19.6%) with a mean time to event of 336.7 days. MACE was more likely to occur on ICI therapy than after ICI therapy (60.3% versus 39.7%, $p<0.001$). Patients with MACE had higher cumulative ICI exposure (18.6 versus 11.8 ICI doses, $p <0.001$; 383.8 versus 219.6 days on therapy, $p<0.001$). MACE was associated with several traditional cardiovascular risk factors. Lung and genitourinary cancers were associated with higher MACE risk, (OR 1.12, 95% CI: 1.02–1.23; and OR 1.14, 95% CI: 1.05–1.24, respectively). In melanoma, exposure to multiple ICI types was associated with increased risk (OR 1.37, 95% CI: 1.14–1.66); in genitourinary cancers, VEGF inhibitor use was predictive (OR 1.32, 95% CI: 1.10–1.59). Machine learning analysis (AUROC of 0.706 (95% CI, 0.669–0.742)) identified non-cardiovascular immune related adverse events (irAEs) requiring prednisone as a

top predictor of MACE. Patients with MACE had higher peak measures of inflammation. MACE was associated with higher all-cause mortality (59.8 versus 52.6%, p<0.001) but a longer time to death (536.4 versus 330.7 days, p< 0.001). Myocarditis or pericarditis occurred in 0.5% of patients; Black race was associated with increased risk (OR 1.40, 95% CI 1.40–1.79).

Conclusions: MACE is common in ICI-treated patients and linked to increased mortality. Risk is linked to traditional cardiovascular risk factors, cancer-specific exposures, irAEs, inflammation, and cumulative ICI exposure. These findings identify vulnerable populations who may benefit from cardiovascular risk factor modification during ICI therapy.

Introduction

Immune checkpoint inhibitors (ICIs) have emerged as a transformative class of immunotherapeutic agents in oncology, fundamentally altering the treatment landscape for numerous malignancies [54-56]. Tumor cells evade the immune system by expressing immune checkpoint proteins that effectively suppress the native T-cell response. ICIs are monoclonal antibodies targeting specific checkpoints, including programmed cell death 1 (PD-1), programmed cell death-ligand 1 (PD-L1) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), which reactivate the antitumor response of T-cells [57]. As this mechanism is agnostic of cancer type, these therapies are used for a wide variety of malignancies, even at advanced stages. Indeed, recent studies estimate that over 50% of patients with cancer may be eligible for these therapies [58]. Early investigations into ICI-related cardiotoxicity primarily focused on myocarditis [59-61], a rare but highly fatal early complication of ICI therapy. However, due to the incredible survival benefits of these therapies, attention to the long-term cardiovascular (CV) effects is critical.

Long-term cardiovascular risks are often underreported in clinical trials due to several factors including short follow-up, selection bias such as exclusion of patients with pre-existing CV disease [62], and lack of formal CV event adjudication and endpoints [63]. Preclinical and clinical data suggest a link between ICI use and accelerated atherosclerosis. Atherosclerosis is a chronic inflammatory condition, and preclinical studies have shown that the PD1 pathway is critical for T cell exhaustion within atherosclerotic plaques, indicating a mechanistic etiology for ICI-induced atherosclerosis [64-66]. Emerging clinical and imaging evidence has indicated increased atherosclerotic plaque progression in patients receiving ICIs [67, 68]. Beyond plaque progression, an increased risk of overall major adverse cardiovascular events (MACE) has been

recently identified in limited cohorts and meta-analyses [69, 70]. However, an understanding of which patients are most at risk for MACE remains incompletely understood.

Our study seeks to address this knowledge gap by analyzing a large, real-world cohort of patients undergoing ICI treatment for solid organ malignancies at a single center. Herein we describe the risk factors for development of MACE on ICI and evaluate associated mortality using traditional statistical methods as well as machine learning analysis.

Methods

Study Design and Outcome Definition: We retrospectively identified all patients treated with FDA approved ICIs for solid organ malignancies at UCLA-Jonsson Comprehensive Cancer Center (JCCC) between January 1, 2015, and January 19, 2024. The UCLA-JCCC is an academic tertiary referral cancer center with community clinics. Patients were included if they received at least one dose of a CTLA-4, PD-1, and/or a PDL-1 inhibitor, as defined by the drugs ipilimumab, atezolizumab, durvalumab, pembrolizumab, nivolumab, cemiplimab, or avelumab. The primary outcome was defined as MACE, which was identified using International Classification of Diseases (ICD)-9 and ICD-10 codes, given as a composite endpoint of new-onset atherosclerotic cardiovascular disease (ASCVD) (including acute coronary syndrome (ACS), coronary artery disease (CAD), ischemic stroke, cardiac arrest), new-onset heart failure, and new-onset arrhythmia. Patients who developed myocarditis or pericarditis attributed to ICI therapy were identified via first screening for ICD codes and prednisone prescriptions and then manually adjudicated with chart review. These patients were removed from the cohort that was included in the MACE analysis and analyzed separately (**Figure 1)**. The protocol was approved by the Institutional Review Board of University of California, Los Angeles (IRB #20-0857).

Patient Characteristics: Patient demographics were extracted from the electronic health record (EHR) and cardiovascular risk factors identified using ICD codes where applicable. Baseline laboratory values were defined as the most recent measurements within six months prior to initiation of ICI therapy and within seven days post-ICI initiation. Peak labs were defined as the highest values recorded during ICI therapy. Cardiovascular medication use was captured as active prescriptions during ICI treatment and prior to MACE, if MACE occurred. Exposure to potentially cardiotoxic anti-cancer medications was documented if administered before a MACE event occurred. For each patient, detailed information on ICI therapy, including specific drug exposure, number of doses, and total duration of treatment, was collected. Non-cardiovascular (CV) immune-related adverse events (irAEs) requiring prednisone were identified by first screening patients prescribed prednisone during immune checkpoint inhibitor (ICI) therapy, followed by manual chart review to determine prednisone indication. The cancer type for each patient was identified based on the cancer ICD code recorded closest to the initiation date of ICI therapy. In cases where multiple cancer types were identified, cancer type was adjudicated by manual case review to determine the primary malignancy for which ICI was prescribed. Cancer types representing more than 5% of the study population were reported individually, while those with less than 5% prevalence were grouped together as “other cancer types.” Finally, mortality status and time to death were analyzed for all patients in the cohort.

Statistical Analyses: Descriptive statistics summarized patient characteristics, with continuous variables presented as mean ± standard deviation (SD) or median ± interquartile range (IQR) and categorical variables as counts with percentages. Continuous variables were compared using two-sample t tests or Mann-Whitney U tests as appropriate, while categorical variables were compared using chi-squared or Fisher’s exact tests. Several multivariable logistic

regression models were constructed to assess overall risk of MACE, counting only the first MACE event. Kaplan-Meier analyses were constructed for survival analyses and time to MACE. All analyses were performed using Python 3.9.19 with scikit-learn v1.5.0, scipy v1.13.1, and lifelines v0.28.0.

Machine Learning Analysis: All identified variables as reported in Table 1 were included in an XGBoost model [71] with the task of predicting MACE. An 80/20 stratified split of the data was used to train and evaluate the model. The 80% training data was further divided into five stratified folds for hyperparameter tuning and cross validation. For each fold, models were trained and tuned over a grid-search of hyperparameters, including the fitting of standardization and imputation parameters. The optimal configuration across the five folds was retrained on the full train set and evaluated on the 20% holdout set. Performance on the holdout was measured using area under the receiver operating characteristic (AUROC), accuracy, precision, and recall. Confidence intervals were obtained using 2,000 bootstrap iterations of the holdout set. SHapley Additive exPlanations (SHAP) values were calculated to quantify the impact of each predictor on the model's output for MACE risk.

Results

MACE Outcome and Patient Characteristics: A total of 5,766 patients undergoing ICI were identified, of which 1,130 (19.6%) were identified as having MACE after the start of ICI therapy, with a total of 1,800 events. **Figure 8** shows the patient selection process as well as the breakdown of the primary outcome of MACE, using first MACE as the classifier; there were 550 (48.7%) with ASCVD, 366 (32.4%) with arrhythmia, and 214 (18.9%) with heart failure. MACE events occurred more frequently while on ICI treatment compared to after ICI treatment (60.3%

versus 39.7%, p<0.001, **Supplemental Table 1**). The average time to development of first MACE event was 336.7 ± 450.6 days. The time to development and cumulative incidence of each MACE type varied significantly (Gray's test p<0.001, **Figure 9**).

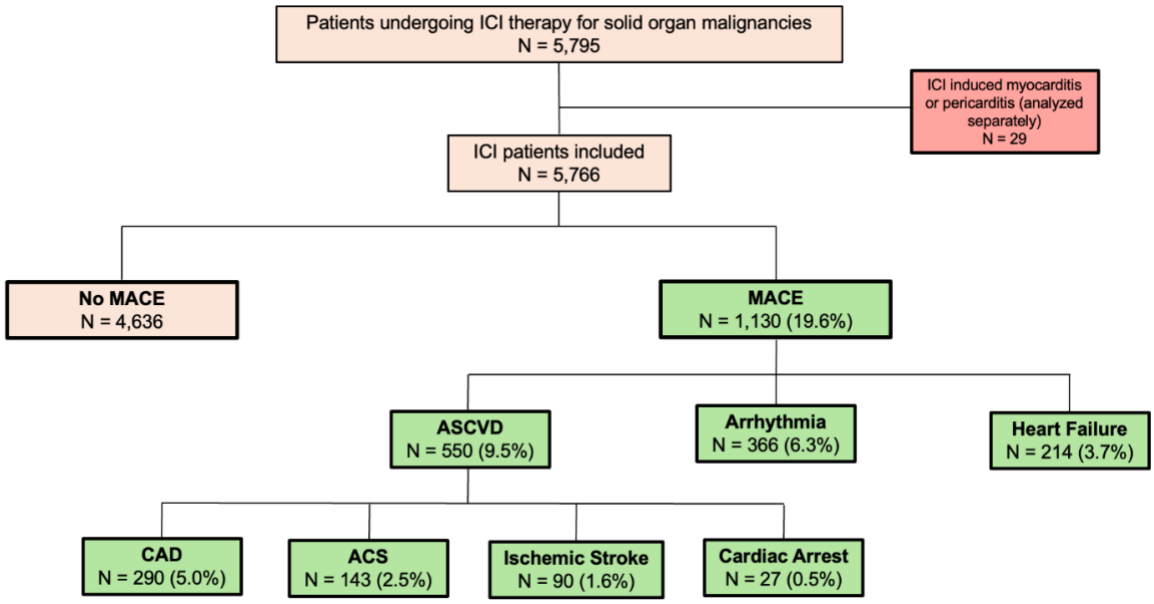

Figure 8: Patient Selection and Outcome Breakdown. Flow diagram of patient selection (orange) and subsequent breakdown of the components of the primary outcome, major adverse cardiovascular events (green). Patients with ICI induced myocarditis and pericarditis were not included in the MACE cohort and were analyzed separately (red). ICI = immune checkpoint inhibitor; MACE major adverse cardiovascular events; ASCVD = atherosclerotic cardiovascular disease; CAD = coronary artery disease; ACS = acute coronary syndrome

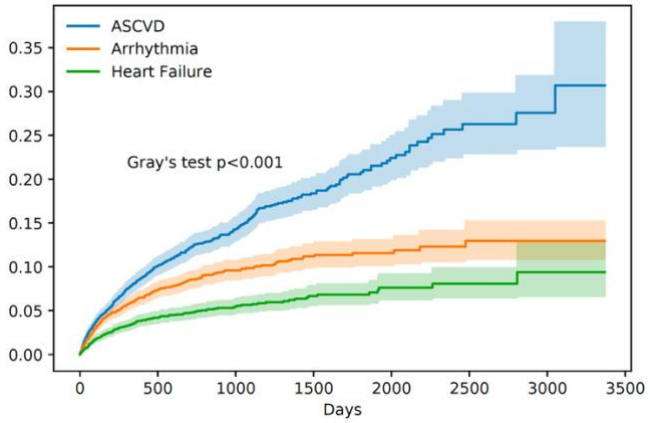

Figure 9: Cumulative Incidence Curve: Cumulative incidence of each component of MACE. ASCVD = atherosclerotic cardiovascular disease

Patient characteristics are shown in **Table 3**. Demographics and baseline cardiovascular risk factors differed significantly between the two groups. Exposure to potentially cardiotoxic chemotherapies were analyzed and there was no difference in exposure to these chemotherapies between groups. Prednisone use for non-CV irAEs was more likely in patients who developed MACE versus those who did not (21.1% versus 11.3% p<0.001). Patients with MACE were more likely to have been exposed to multiple ICI medications during the study period (21.3 versus 14.3%, p<0.001) and were more likely to have received dual ICI therapy (14.2 versus 10.8%, p=0.002). Total ICI doses and days on ICI were higher in the group that developed MACE versus the group that did not (18.6 versus 11.8 doses, p<0.001; 383.8 versus 219.6 days, p<0.001, respectively).

Patient Characteristic	Overall (n = 5766)	No MACE (n = 4636)	MACE (n = 1130)	p-value
Patient Demographics				
Age at first ICI, years, mean (SD)	66.3 (14.5)	65.4 (14.7)	70.0 (12.9)	<0.001
Sex, male, n (%)	3057 (53.0)	2351 (50.7)	706 (62.5)	<0.001
Self-reported race, n (%)				0.132
Asian	674 (11.7)	554 (12.0)	120 (10.6)	
Black	184 (3.2)	140 (3.0)	44 (3.9)	
White	2986 (51.8)	2417 (52.2)	569 (50.4)	
Other	1917 (33.3)	1520 (32.8)	397 (35.1)	
Ethnicity, n (%)				0.308
Hispanic or Latino	581 (11.1)	474 (11.4)	107 (10.2)	
Not Hispanic or Latino	4638 (88.9)	3696 (88.6)	942 (89.8)	
ADI National Rank, mean (SD)	10.0 (11.3)	10.1 (11.4)	9.3 (11.2)	0.065
ADI State Rank, mean (SD)	3.5 (2.2)	3.5 (2.2)	3.2 (2.3)	0.004
Body mass index, kg/m^2, mean (SD)	25.6 (5.5)	25.4 (5.4)	26.4 (5.5)	<0.001
Cardiovascular Risk Factors				
Hypertension, n (%)	2147 (37.2)	1546 (33.3)	601 (53.2)	<0.001
Type II diabetes mellitus, n (%)	827 (14.3)	589 (12.7)	238 (21.1)	<0.001
Hyperlipidemia, n (%)	1748 (30.3)	1227 (26.5)	521 (46.1)	<0.001
History of MACE, n (%)	1344 (23.3)	855 (18.4)	489 (43.3)	<0.001
Coronary artery disease	594 (44.2)	389 (45.5)	205 (41.9)	
Acute coronary syndrome	79 (5.9)	53 (6.2)	26 (5.3)	
Cardiac arrest	8 (0.6)	5 (0.6)	3 (0.6)	
Ischemic stroke	106 (7.9)	68 (8.0)	38 (7.8)	
Heart failure	120 (8.9)	74 (8.7)	46 (9.4)	
Arrhythmia	437 (32.5)	266 (31.1)	171 (35.0)	
Smoker, current or previous, n (%)	2744 (48.3)	2120 (46.6)	624 (55.4)	<0.001
Baseline Laboratory Values				
GFR < 60 mL/min/1.73 m^2, n (%)	586 (22.8)	371 (19.6)	215 (31.7)	<0.001
Creatinine, mg/dL, mean (SD)	1.0 (0.7)	0.9 (0.6)	1.1 (0.9)	<0.001
Total Cholesterol, mg/dL, mean (SD)	182.4 (46.6)	184.6 (47.8)	177.6 (43.6)	0.029
HDL, mg/dL, mean (SD)	51.5 (18.0)	52.3 (18.3)	49.5 (17.2)	0.331
LDL, mg/dL, mean (SD)	95.2 (39.7)	97.3 (40.7)	90.0 (36.7)	<0.001
Triglycerides, mg/dL, mean (SD)	122.9 (110.8)	124.4 (124.8)	119.2 (63.1)	0.248

Hemoglobin A1c, %, mean (SD)	6.0 (1.0)	6.0 (0.9)	6.3 (1.3)	0.023
Erythrocyte sedimentation rate, mm/hr, mean (SD)	32.4 (28.2)	31.7 (28.8)	34.3 (26.7)	0.210
C-reactive protein, mg/dL, mean (SD)	3.3 (5.1)	3.2 (5.0)	3.6 (5.4)	0.420
Uric acid, mg/dL, mean (SD)	5.3 (2.0)	5.2 (1.9)	5.5 (2.0)	0.009
Medications				
Beta blockers, n (%)	780 (13.5)	535 (11.5)	245 (21.7)	<0.001
ACEi or ARB, n (%)	938 (16.3)	717 (15.5)	221 (19.6)	0.001
Mineralocorticoid receptor antagonist, n (%)	208 (3.6)	170 (3.7)	38 (3.4)	0.687
SGLT2i, n (%)	97 (1.7)	80 (1.7)	17 (1.5)	0.697
Sacubitril-valsartan, n (%)	15 (0.3)	6 (0.1)	9 (0.8)	0.001
Statin, n (%)	982 (17.0)	724 (15.6)	258 (22.8)	<0.001
Prednisone for non-CV irAE, n (%)	762 (13.2)	524 (11.3)	238 (21.1)	<0.001
Cancer Types				
Lung cancer, n (%)	1356 (23.5)	1049 (22.6)	307 (27.2)	0.001
Melanoma, n (%)	813 (14.1)	655 (14.1)	158 (14.0)	0.941
Genitourinary cancer, n (%)	718 (12.5)	539 (11.6)	179 (15.8)	<0.001
Hepatobiliary cancer, n (%)	465 (8.1)	372 (8.0)	93 (8.2)	0.864
Head and neck cancer, n (%)	448 (7.8)	371 (8.0)	77 (6.8)	0.203
Gynecologic cancer, n (%)	431 (7.5)	362 (7.8)	69 (6.1)	0.060
Breast cancer, n (%)	363 (6.3)	330 (7.1)	33 (2.9)	<0.001
Upper gastrointestinal cancer, n (%)	304 (5.3)	248 (5.3)	56 (5.0)	0.650
Other cancer types, n (%)	868 (15.0)	710 (15.3)	158 (14.0)	<0.001
Potentially Cardiotoxic Anti-Cancer Medications (previous or concurrent)				
5-Fluorouricil, n (%)	257 (4.5)	206 (4.4)	51 (4.5)	0.983
Anthracyclines, n (%)	141 (2.4)	116 (2.5)	25 (2.2)	0.647
VEGF inhibitor all, n (%)	710 (12.3)	551 (11.9)	159 (14.1)	0.051
Non-VEGF tyrosine kinase inhibitor, n (%)	54 (0.9)	41 (0.9)	13 (1.2)	0.509
HER-2 targeted therapies, n (%)	34 (0.6)	26 (0.6)	8 (0.7)	0.717
Immune Checkpoint Inhibitor (ICI) Use				
ICI Type, n (%)				
Pembrolizumab	3186 (55.3)	2568 (55.4)	618 (54.7)	0.695
Nivolumab	2055 (35.6)	1622 (35.0)	433 (38.3)	0.039
Atezolizumab	491 (8.5)	400 (8.6)	91 (8.1)	0.574
Ipilimumab	741 (12.9)	561 (12.1)	180 (15.9)	0.001
Durvalumab	221 (3.8)	154 (3.3)	67 (5.9)	<0.001
Cemiplimab	82 (1.4)	63 (1.4)	19 (1.7)	0.496
Avelumab	33 (0.6)	26 (0.6)	7 (0.6)	0.988
Exposure to multiple ICIs, n (%)	902 (15.6)	661 (14.3)	241 (21.3)	<0.001
Dual ICI therapy, n (%)	664 (11.5)	503 (10.8)	161 (14.2)	0.002
Total days on ICI, mean (SD)	251.8 (390.3)	219.6 (346.1)	383.8 (514.5)	<0.001
Total ICI doses, mean (SD)	13.1 (19.6)	11.8 (18.1)	18.6 (24.0)	<0.001
ICI doses prior MACE, mean (SD)		N/A	11.8 (17.1)	
Days on ICI prior to MACE, mean (SD)		N/A	336.7 (450.6)	
Days on ICI prior to ASCVD, mean (SD)		N/A	396.2 (504.1)	
Days on ICI prior to arrhythmia, mean (SD)		N/A	266.8 (355.8)	
Days on ICI prior to heart failure, mean (SD)		N/A	303.5 (431.2)	
Total follow-up time, days, mean (SD)	564.0 (626.3)	511.8 (588.4)	777.9 (724.4)	<0.001
Mortality				
All-cause mortality, n (%)	3115 (54.0)	2439 (52.6)	676 (59.8)	<0.001
Time to death, days, mean (SD)	375.2 (432.7)	330.6 (383.7)	536.4 (546.7)	<0.001

Table 3: Patient Characteristics. MACE = major adverse cardiovascular event; ICI = immune checkpoint inhibitor; SD = standard deviation; n = number of patients; ADI = area deprivation index; VEGF = vascular endothelial growth factor; GFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; SGLT2i = sodium-glucose co-transporter 2 inhibitor; CV = cardiovascular; irAE = immune related adverse event; VEGF = vascular endothelial growth factor; HER2 = human epidermal growth factor receptor 2

Traditional Cardiovascular Risk Factors: In a multivariate linear regression of selected demographics and cardiovascular risk factors, the following variables were associated with significantly higher likelihood of MACE with following odds ratios (OR) and 95% confidence intervals (CI): age (OR 1.19, 95% CI 1.1-1.3), male sex (OR 1.16, 95% CI 1.08-1.24), history of hypertension (OR 1.11, 95% CI 1.02-1.20), history of hyperlipidemia (OR 1.13, 95% CI 1.05-1.22), estimated GFR < 60 mL/min/1.73 m^2 (OR 1.14, 95% CI 1.04-1.25) were associated with the development of the primary outcome of MACE (**Figure 10** for Forest Plot, **Supplemental Table 2** for full ORs and 95% CIs of the model).

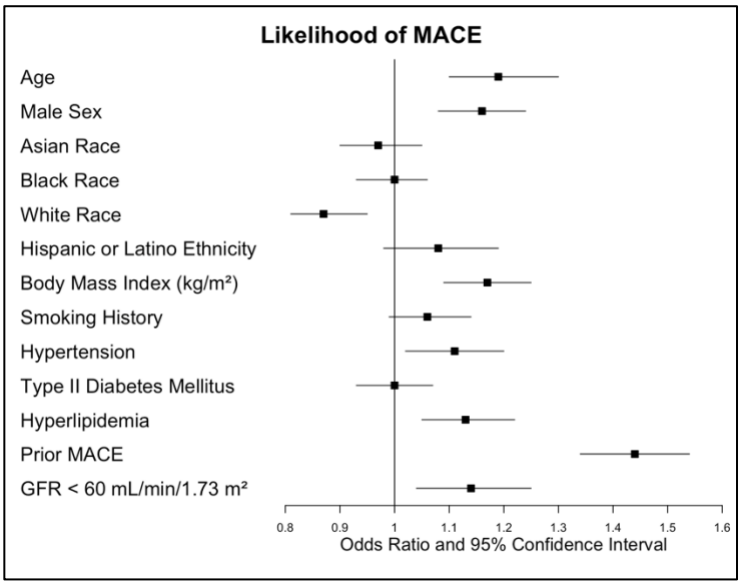

Figure 10: Multivariable Logistic Regression Model of the Likelihood of MACE by Demographics and Cardiovascular Risk Factors. MACE = major adverse cardiovascular event; GFR = estimated glomerular filtration rate.

Cancer Types: In the multivariate logistic regression of MACE likelihood by cancer type, lung and genitourinary cancers were associated with higher MACE risk, with OR of 1.12 (95% CI: 1.02-1.23) and 1.14 (95% CI: 1.05-1.24), respectively (**Figure 11; Supplemental Table 3** for full OR and CIs).

Multivariable logistic regressions were used to examine demographic, cardiovascular risk factors, and cancer variables associated with MACE for the three most prevalent cancer types in the cohort: lung cancer, melanoma, and genitourinary cancer (**Table 4**). Notably, a history of previous MACE was a strong predictor of new MACE development across all three cancer types (for lung cancer: OR 1.57, 95% CI 1.36-1.80; for melanoma: OR 1.64, 95% CI 1.33-1.98; for genitourinary cancer: OR 1.35, 95% CI 1.10-1.63). Additionally, exposure to multiple ICI types was linked to increased MACE risk in melanoma (OR 1.37, 95% CI 1.14-1.66), while prior exposure to VEGF inhibitors was associated with elevated MACE risk in patients with genitourinary cancer (OR 1.32, 95% CI 1.10-1.59). **Supplemental Table 4** provides a numerical breakdown of events by cancer type.

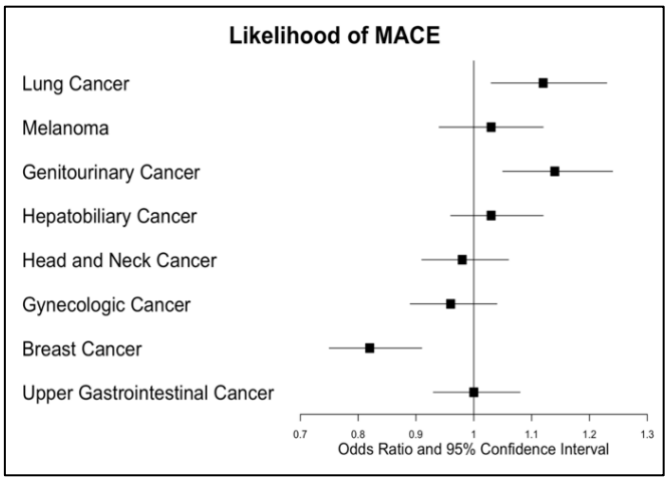

Figure 11: Multivariate Logistic Regression of Likelihood of Major Adverse Cardiovascular Events (MACE) by Cancer Types.

	Lung Cancer			Melanoma			Genitourinary Cancer		
Risk Factor	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**	**OR**	**95% CI**	**p-value**
Age	0.98	0.84-1.13	0.793	1.62	1.29-2.06	<0.001*	1.17	0.95-1.44	0.175
Hypertension	1.17	0.99-1.36	0.055	1.40	1.12-1.74	0.004*	1.03	0.81-1.31	0.849
Type II Diabetes	0.96	0.84-1.09	0.591	1.06	0.88-1.24	0.202	1.10	0.90-1.32	0.314
Hyperlipidemia	1.07	0.91-1.25	0.418	0.86	0.69-1.06	0.254	1.29	1.02-1.59	0.033*
GFR < 60 mL/min/1.73 m^2	1.09	0.89-1.32	0.437	1.24	0.88-1.70	0.254	1.15	0.87-1.49	0.357
Prior MACE	1.57	1.36-1.80	<0.001*	1.64	1.33-1.98	<0.001*	1.35	1.10-1.63	0.004*
Body Mass Index (kg/m^2)	1.16	1.02-1.32	0.028*	1.06	0.87-1.27	0.580	0.95	0.78-1.13	0.546
Smoking History	1.11	0.96-1.29	0.196	1.06	0.87-1.28	0.577	1.01	0.84-1.22	0.940
Treatment with Multiple ICI Types	1.11	0.98-1.25	0.086	1.38	1.14-1.67	0.002*	1.21	0.99-1.45	0.064
Treatment with VEGFi	1.01	0.86-1.16	0.810	0.93	0.71-1.10	0.984	1.33	1.10-1.59	0.003*

Table 4: Multivariate Logistic Regression of Likelihood of MACE by Cancer Type: Results of multivariate logistic regression models of selected risk factors in the three most prevalent cancer types in the cohort: lung cancer, melanoma, and genitourinary cancer. *Denotes statistical significance. OR = odds ratio; CI = confidence interval; GFR = estimated glomerular filtration rate; MACE = Major adverse cardiovascular event; ICI = immune checkpoint inhibitor; VEGFi = vascular endothelial growth factor inhibitor.

Machine Learning Analysis: An XGBoost model incorporating all variables from Table 1 achieved an AUROC of 0.706 (95% CI, 0.669-0.742), with curve plotted in **Figure 12A**. Model accuracy was 0.730 (95% CI, 0.703-0.757), precision was 0.382 (95% CI 0.330-0.431), recall was 0.564 (95% CI 0.500-0.627) and the Brier score was 0.145 (95% CI, 0.132-0.158). SHAP feature importance analysis identified prior MACE and use of prednisone for immune-related adverse events (irAEs) as the two most influential variables in the model (**Figure 12B**).

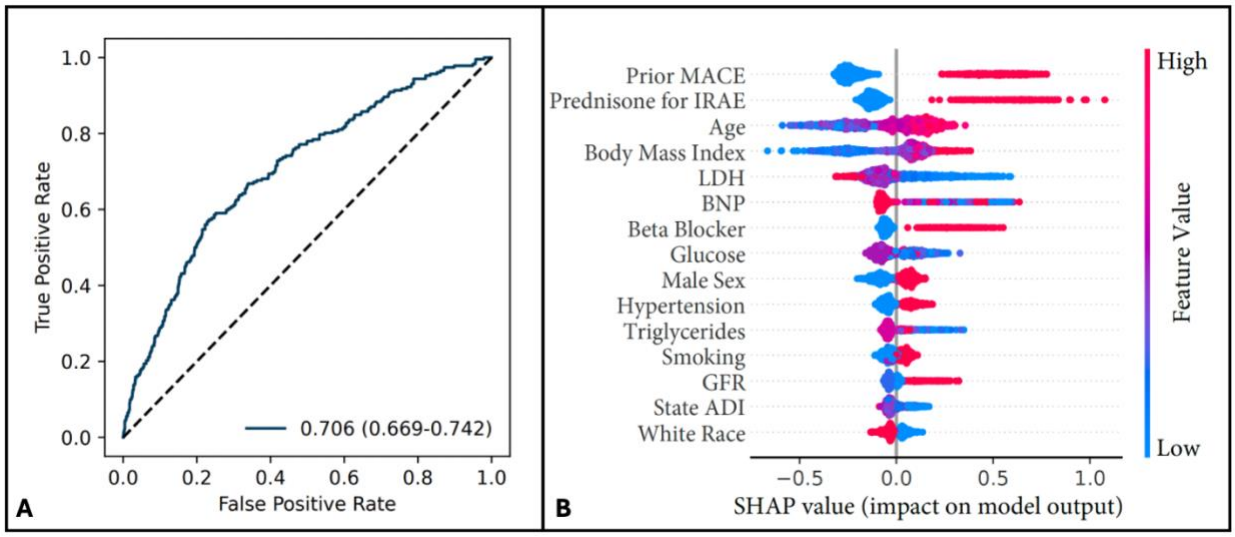

Figure 12: XGBoost Model Predicting Likelihood of MACE. A. Receiver operating characteristic (ROC) curve for the XGBoost model. **B.** SHAP (SHapley Additive exPlanations) summary plot showing feature importance. Abbreviations: MACE = major adverse cardiovascular event; irAE = immune related adverse event; LDH = lactate dehydrogenase; BNP = B-type naturetic peptide; GFR = estimated glomerular filtration rate; ADI = area deprivation index

Non-Cardiovascular Immune-Related Adverse Events and Inflammatory Markers as Risk Factors for MACE: Given the importance of prednisone-treated irAEs in the XGBoost model, further analyses were performed to explore the relationship between irAEs, inflammation, and MACE. Kaplan-Meier curves (**Figure 13A**) demonstrated that patients who developed non-CV irAEs requiring prednisone experienced shorter times to MACE than those who did not (log-rank test $p<0.001$). In multivariable logistic regression evaluating the association between specific non-CV irAE types and MACE, pulmonary irAEs were significantly associated with increased

MACE risk (OR 1.34, 95% CI, 1.05-1.70, p<0.018), while other irAE types were not (**Figure 13B; Supplemental Table 5 for ORs and CIs**). Markers of inflammation were also examined. Patients who developed MACE had significantly higher peak erythrocyte sedimentation rates (45.1 versus 38.2 mm/hr, p = 0.015) and peak uric acid levels (5.93 versus 5.59 mg/dL, p=0.014) during ICI therapy. Peak C-reactive protein levels did not differ significantly between groups (4.77 versus 4.53 mg/dL, p=0.14) (**Figure 14**).

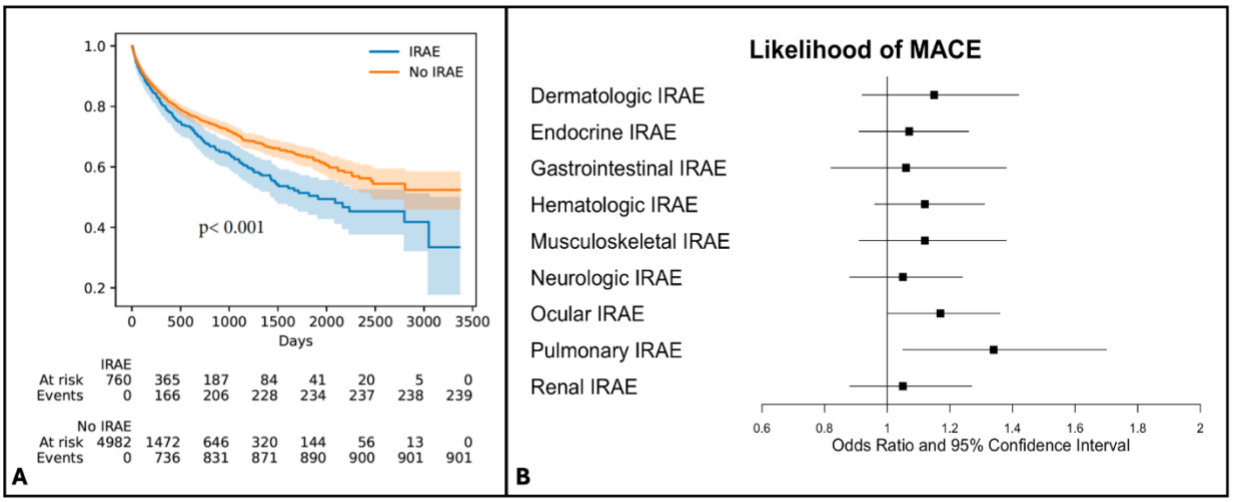

Figure 13: Non-CV Immune Related Adverse Events as Risk Factor for MACE. **A.** Kaplan-Meier curves depict time to major adverse cardiovascular events (MACE) stratified by the presence or absence of immune-related adverse events (irAEs). Time is shown in days from immune checkpoint inhibitor initiation. **B.** Forest plot displaying results of multivariate logistic regression of likelihood of MACE by irAE type.

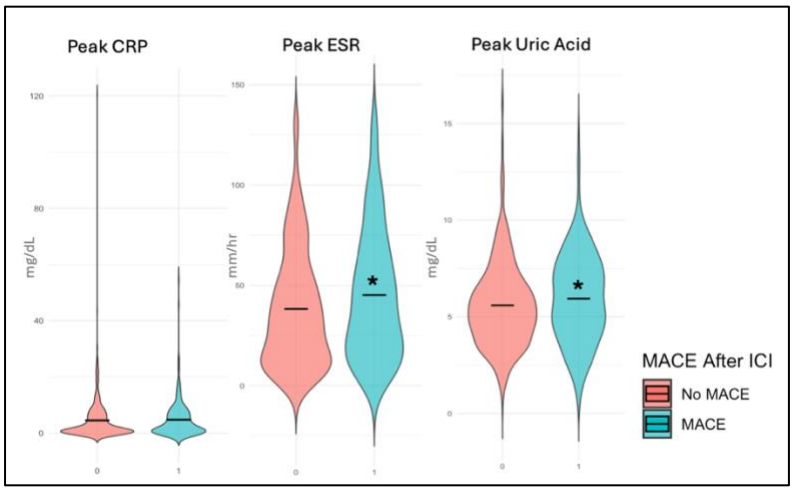

Figure 14: Inflammatory Markers in ICI-Treated Patients With and Without MACE. Violin plots show peak levels of inflammatory markers—C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and uric acid—stratified by occurrence of major adverse cardiovascular events (MACE). Asterisks (*) indicate statistically significant differences. MACE = major adverse cardiovascular event; ICI = immune checkpoint inhibitor

Myocarditis and Pericarditis due to ICI: In this cohort, 29 patients (0.5%) developed ICI-related myocarditis or pericarditis. **Supplementary Table 6** summarizes the characteristics of these patients. Notably, race differed significantly among them (p=0.005). In the multivariable logistic regression model assessing the likelihood of developing ICI-related myocarditis or pericarditis, Black race was associated with an increased risk (OR 1.40, 95% CI 1.40-1.79) (**Figure 15**).

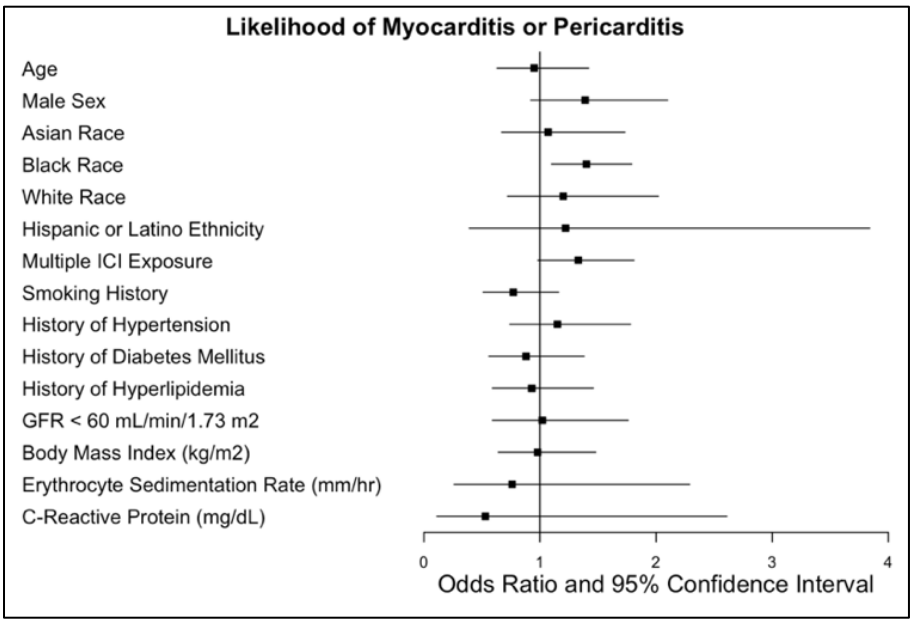

Figure 15: Multivariable Logistic Regression Model of the Likelihood of ICI related Myocarditis and Pericarditis MACE: Major Adverse Cardiovascular Event; GFR: estimated glomerular filtration rate; ICI: immune checkpoint inhibitor.

Survival Analyses: Compared to patients without MACE, patients who experienced MACE had a higher mortality rate (59.8% compared to 52.6%) but a longer average time to death (536.4 days versus 330.7 days, p<0.001) (**Table 3)**; the increased mortality for patients with MACE occurred around 2250 days (~6 years) on the Kaplan-Meier curve (multiple direction log rank test p <0.001; **Figure 16A**). Mortality rates and time to death for patients with myocarditis or pericarditis were not significantly different from those without this outcome (59.3% versus 54.0%, p=0.725; 570.9 days versus 375.3 days, p=0.186, respectively) (**Supplemental Table 6, Figure 16B**).

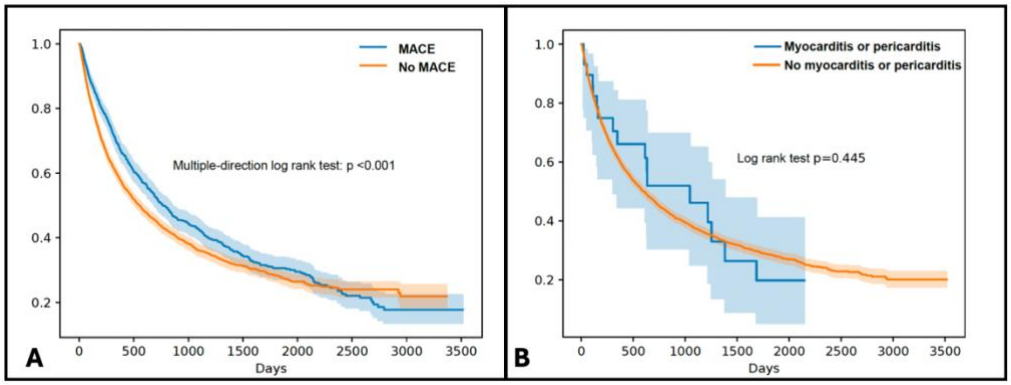

Figure 16: Survival Analysis Curves. A. Kaplan Meier curves of time to death for patients with and without MACE. **B.** Kaplan Meier curves showing time to death for patients with and without myocarditis or pericarditis.

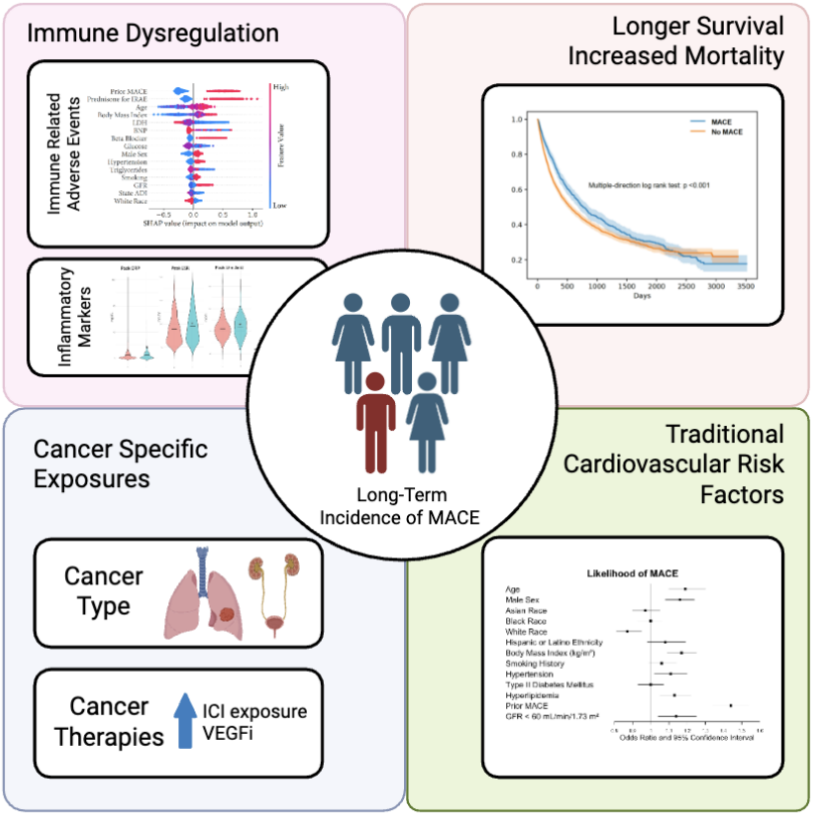

Figure 17: Central Illustration. Major adverse cardiovascular events (MACE) occurred in 19.6% of patients receiving immune checkpoint inhibitor (ICI) therapy. This study highlights the multifactorial contributors to MACE in this population. Immune dysregulation – including non-cardiovascular immune-related adverse events (irAEs) and elevated inflammatory markers – emerged as novel risk factors. Cancer-specific exposures, such as increased ICI exposure, VEGF inhibitor therapies, and certain cancer types (lung and genitourinary), were also associated with higher risk. Traditional cardiovascular risk factors remained important predictors. Longer survival following ICI therapy both increased ICI exposure and extended the window for MACE development and was associated with increased long-term mortality. These findings underscore the

importance of integrated cardiovascular risk assessment and surveillance in patients undergoing ICI therapy.

Discussion

As ICIs continue to extend survival and transform cancer into a chronic disease state [55, 56], cardiovascular health becomes an increasingly relevant concern, especially given cancer and cardiovascular disease share many risk factors [72]. In the present study, we found that 19.6% of patients receiving ICI therapy developed a major adverse cardiovascular event (MACE) after ICI initiation. Using both traditional statistical and machine learning approaches, our analysis identified key predictors of MACE: increased ICI exposure, non-cardiovascular (non-CV) immune related adverse events (irAEs), elevated inflammatory markers while on ICI therapy, traditional cardiovascular risk factors, cancer-specific exposures, and longer survival time. Finally, we find that development of MACE on ICI therapy is associated with a higher mortality.

Prior studies support an elevated cardiovascular risk among patients receiving ICIs. Drobni *et al*. reported a fourfold increase in atherosclerotic events, defined as myocardial infarction, coronary revascularization, and ischemic stroke, in 2,842 ICI-treated patients compared to matched controls, with an overall event incidence of 4.2% [67]. Similarly, Laenens *et al*. found a 10.3% incidence of MACE (defined as ACS, heart failure, stroke, and TIA) in 681 ICI-treated patients, with significantly lower event rates in a matched comparator group (HR 0.61) [69]. The higher incidence observed in our cohort likely reflects both a broader definition of MACE and a longer follow-up duration. While these and other studies [68, 73] have effectively established a link between ICI exposure and MACE, there remains an opportunity to explore in more depth the risk factors for development of MACE on ICI therapy. The present study is uniquely poised to do so, with one of the largest single center cohort of patients, with robust EHR level data, and a long duration of follow-up.

One of the most novel risk factors identified in our study was non-cardiovascular (non-CV) immune related adverse events (irAEs). irAEs reflect systemic immune activation that can lead to off-target attacks by the immune system on native tissue, and occur in up to 70% of treated patients [74]. In our analysis, non-CV irAEs requiring prednisone were nearly twice as prevalent in patients who developed MACE than those who did not (21.1% versus 11.3%). In a machine learning model (XGBoost with SHAP interpretation), the occurrence of a non-CV irAE was among the top predictors of MACE, surpassing many traditional risk factors in importance and nearly matching prior MACE in predictive importance. Given our careful exclusion of prednisone use unrelated to irAEs, the association is likely attributable directly to the irAE rather than corticosteroid treatment, a critical distinction as corticosteroids have shown beneficial effects on plaque stabilization in ICI-treated patients [67] and have been associated with decreased risk of MACE [75].

Non-CV irAEs may contribute to the risk of MACE through several interrelated mechanisms. Prior research has demonstrated that irAEs signal an effective anti-tumor response and are associated with improved survival rates [76, 77]; thus, the increased survival duration allows more opportunity for cardiovascular events to develop. Additionally, irAEs may signal a state of heightened immune activation and inflammation, which are known to contribute to adverse cardiovascular outcomes [78-80]. Supporting this inflammatory hypothesis, patients who developed MACE in our study had higher peak ESR and uric acid levels, established markers of inflammation, during ICI therapy. These findings suggest that systemic inflammation and immune-mediated tissue injury contribute to atherosclerosis, arrhythmogenesis, and myocardial dysfunction in this population, mechanisms supported by preclinical and translational studies [81-83]. Finally, a regression analysis pinpointed pulmonary irAEs as the most predictive among all irAEs for the development of MACE. This may be due to close cardiopulmonary

interactions such as induction of pulmonary hypertension, however this novel interaction between a new autoimmune pulmonary process and cardiovascular injury warrants further investigation.

Our study highlights the importance of traditional cardiovascular risk factors on the development of MACE. In the present study, many traditional cardiovascular risk factors were predictive of the development of MACE, namely, older age, male sex, higher BMI, history of hypertension and hyperlipidemia, prior MACE events, and reduced renal function (eGFR <60 mL/min/1.72m^2). These findings are consistent with prior studies: older age and male sex [70, 73], hypertension [67, 70], hyperlipidemia [70], and history of cardiovascular disease [68] have all been shown to increase MACE risk in patients receiving ICI therapy, though definitions of MACE vary slightly amongst these studies.

Cancer-specific exposures also conferred increased susceptibility to MACE. Increased ICI exposure, namely longer treatment duration, higher cumulative doses, use of multiple ICI agents, and dual ICI therapy, was significantly associated with MACE. Lung and genitourinary cancers were associated with higher MACE risk, which has been shown in general cancer populations [84, 85]. Additionally, Kwan *et al.* found that lung cancer was a risk factor for the development of MACE in ICI treated population [70]. In melanoma, exposure to multiple ICI types was linked to MACE risk, notable given dual-ICI therapy is often the first-line treatment for melanoma. Dual ICI therapy has been associated with MACE among all cancer types previously [70], however, our findings highlight the increased susceptibility specifically in the melanoma population. In genitourinary cancers, VEGF inhibitor use was significantly associated with MACE. VEGF inhibitors are well-documented for inducing hypertension, vascular dysfunction, and arterial ischemic events [86-88]. A study of VEGF inhibitor TKIs in patients with renal cell carcinoma found nearly double the MACE incidence compared to those receiving cytokine

therapies [89]. Furthermore, Chitturi *et al.* studied the influence of ICI on the development of MACE in patients with lung cancer, and found that combination therapy with ICI and VEGF or TKI was associated with higher MACE risk [90]. These findings emphasize the importance of cardiovascular surveillance and risk modification strategies in patients receiving dual ICI for melanoma and VEGF-targeted therapies for genitourinary cancer.

The above findings highlight the complex interplay between cardiovascular, oncologic and inflammatory processes that all contribute to the onset of MACE. To account for this multifactorial risk, we utilized a machine learning model for prediction of MACE to incorporate all potential risk factors. The overall model characteristics demonstrate a prediction model with AUROC of 0.7 and model accuracy of 0.73. To our knowledge, this is the most accurate reported machine learning model [75] in the literature and the only one using structured EHR-based data. The model offers a data-driven, unbiased approach for identifying novel risk factors. Importantly, the use of EHR data *confirmed* with manual chart review is particularly important in understanding the contributions of more clinically complex disease processes, such as irAEs, which are not well captured with ICD codes alone. Given the inherent complex nature of cardio-oncology, machine learning is a promising tool for identifying patients at highest risk for MACE.

In the present study, MACE was associated with an overall higher mortality rate. Kaplan-Meier analysis demonstrated that although patients who developed MACE had initially improved survival, survival curves diverged around six years (~2,250 days) indicating the increasing impact of cardiovascular disease over extended survivorship. This finding highlights an important strength of this study in following the long-term outcomes of patients receiving ICI therapy, compared to prior studies which have shorter follow up times [67, 68, 90]. Based on the findings of this study, we propose that longer treatment duration and more intense treatment regimens are associated with cardiovascular risk by both increasing ICI related cardiotoxicity

(through direct effects on atherosclerosis progression and an increased inflammatory state from off-target irAEs) and extending survival time, allowing cardiovascular disease to develop.

Our findings underscore the critical importance of early identification and management of modifiable cardiovascular risk factors in this population. MACE occurred in our study early into treatment course (average time 336.7 days) with most events occurring while still on ICI therapy. In this cohort, however, we observed suboptimal management of such risk factors: only 22.8% of patients who developed MACE were on a statin, despite 46.1% having pre-existing hyperlipidemia. This is of particular importance as statins have been shown to attenuate the risk of accelerated atherosclerosis with ICI use [67]. Similarly, while 23.3% of patients had prior MACE, cardioprotective medication use was comparatively low (beta-blockers: 13.5%; ACEi/ARBs: 16.3%). These findings highlight a critical need for optimized cardiovascular risk mitigation strategies, consistent with cardio-oncology guidelines that emphasize the initiation of preventive measures prior to anticancer therapy [91].

Myocarditis and Pericarditis Substudy:

To isolate broader cardiovascular risk beyond ICI myocarditis or pericarditis, patients with these diagnoses were excluded from the MACE analysis and examined separately. With regard to ICI myocarditis or pericarditis, we found that 0.5% of the nearly 6,000 patients analyzed experienced these complications, a rate slightly lower than previous estimates (e.g., for myocarditis alone: 0.72% in a 2023 meta-analysis [92] and 1.14% in registry analysis [60]). The lower incidence on our cohort may be due to historical under-recognition of these conditions as ICI-related side effects in the early period of ICI use. Additionally, this institution does not routinely monitor troponin levels outside of clinical trials for ICI patients, potentially

missing subclinical cases. Notably, Black race was most associated with the development of ICI-related myocarditis or pericarditis, a novel finding that warrants further investigation.

Limitations and Future Directions:

This study has several limitations. Conducted at a single tertiary referral cancer center, its generalizability may be limited. Although the population was diverse with 47% female patients, Black patient representation was low (3.2% of the cohort). Additionally, the retrospective design introduces selection bias and may skew results toward individuals with better healthcare access. Reliance on ICD codes for identifying MACE events and baseline diagnoses, rather than a standardized prospective data collection approach, could lead to inaccuracies due to physician misreporting or omission during billing. irAEs were identified using prednisone prescriptions followed by manual adjudication, this does not capture irAEs not treated with prednisone or lower grade irAEs. Mortality analyses were limited to all-cause mortality. Newer agents, including LAG-3 inhibitors (e.g., relatlimab), were not included in this analysis. Future directions include matched cohort studies comparing ICI-treated and non-ICI-treated cancer patients to more explicitly quantify the impact of ICI on the development of MACE, which could not br done in this analysis due to the absence of a comparator group. Our finding that non-cardiovascular irAEs requiring prednisone are predictive of MACE warrants further investigation to validate this association and to elucidate potential mechanisms linking specific irAEs, systemic inflammation, and adverse cardiovascular outcomes.

Conclusions

In this study of a large, real-world cancer population receiving immune checkpoint inhibitors (ICIs), we observed a high incidence of major adverse cardiovascular events (MACE), which

were significantly associated with increased overall mortality. In addition to established cardiovascular risk factors, we identified several cancer-related predictors of MACE, including non-cardiovascular immune-related adverse events (irAEs), elevated inflammatory markers, specific cancer types, prolonged ICI exposure, and additional cancer-directed therapies. As ICIs continue to improve cancer survival, the need for early cardiovascular risk stratification becomes increasingly important. Incorporating advanced tools such as machine learning, alongside proactive management of traditional risk factors and targeted surveillance in high-risk patients, will be critical for mitigating cardiovascular morbidity and mortality. These strategies offer a path toward optimizing long-term outcomes in the growing population of cancer survivors.

Supplemental Tables

MACE Type	Total (n = 1800)	On ICI Treatment (n = 1085)	After ICI Treatment (n = 715)
ASCVD, n (% total events)	4826 (45.9)	501 (27.8)	325 (18.1)
Coronary artery disease	416 (23.1)	266 (14.8)	150 (8.3)
Acute coronary syndrome	199 (11.1)	114 (6.3)	85 (4.7)
Ischemic Stroke	159 (8.8)	95 (5.3)	64 (3.6)
Cardiac Arrest	52 (1.8)	26 (1.4)	26 (1.4)
Arrhythmia, n (% total events)	564 (31.3)	351 (19.5)	213 (10.9)
Heart Failure, n (% total events)	410 (22.8)	233 (12.9)	177 (9.8)

Supplemental Table 1: Major Adverse Cardiovascular Events (MACE) at Event Level. This table displays the number of MACE events, stratified by event type and timing in relation to ICI therapy (total, during ICI treatment, and after ICI treatment). MACE events were significantly more likely to occur during ICI treatment than after treatment (60.2% versus 39.7%; chi-squared test, $p < 0.001$). Data are presented at the event level, not the patient level.

Variable	OR	95% CI	p-value
Age	1.19	1.10-1.30	<0.001*
Male Sex	1.16	1.08-1.24	<0.001*
Asian Race	0.97	0.90-1.05	0.440
Black Race	1.00	0.93-1.06	0.960
White Race	0.87	0.81-0.95	0.010*
Hispanic or Latino Ethnicity	1.08	0.98-1.19	0.190
Body Mass Index (kg/m^2)	1.17	1.09-1.25	<0.001*
Smoking History	1.06	0.99-1.14	0.040*
Hypertension	1.11	1.02-1.20	0.010*
Type II Diabetes Mellitus	1.00	0.93-1.07	0.970
Hyperlipidemia	1.13	1.05-1.22	0.002*
Prior MACE	1.44	1.34-1.54	<0.001*
GFR < 60 mL/min/$1.73m^2$	1.14	1.04-1.25	0.004*

Supplemental Table 2: Odds Ratios and 95% Confidence Interval Values for Multivariable Logistic Regression Model of the Likelihood of MACE.

MACE = major adverse cardiovascular events, GFR = estimated glomerular filtration rate. *denotes statistical significance

Cancer Type	OR	95% CI	p-value
Lung	1.12	1.03-1.23	0.012
Melanoma	1.03	0.94-1.12	0.519
Genitourinary	1.14	1.05-1.24	0.001
Hepatobiliary	1.03	0.96-1.12	0.425
Head and neck	0.98	0.91-1.06	0.649
Gynecologic	0.96	0.88-1.04	0.328
Breast	0.82	0.75-0.91	<0.001
Upper gastrointestinal	1.00	0.93-1.08	0.933

Supplemental Table 3: Odds Ratios and 95% Confidence Interval Values for Multivariate Logistic Regression Model of the Likelihood of MACE by Cancer Type

	ASCVD (n = 550)	Arrhythmia (n = 366)	Heart Failure (n = 214)	Myocarditis and Pericarditis (n = 29)
Lung cancer	146	108	53	10
Melanoma	75	55	28	8
Genitourinary cancer	96	46	37	1
Hepatobiliary cancer	50	29	14	2
Head and neck cancer	41	20	16	1
Gynecologic cancer	31	25	13	2
Breast cancer	15	12	6	0
Upper gastrointestinal cancer	27	21	8	1
Other cancer types	125	82	61	5

Supplemental Table 4: MACE Type by Cancer Type. ASCVD = atherosclerotic cardiovascular disease

irAE Type	OR	95% CI	p-value
Dermatologic	1.15	0.92-1.42	0.219
Endocrine	1.07	0.91-1.26	0.403
Gastrointestinal	1.06	0.82-1.38	0.641
Hematologic	1.12	0.96-1.31	0.139
Musculoskeletal	1.12	0.91-1.38	0.289
Neurologic	1.05	0.88-1.24	0.598
Ocular	1.17	1.00-1.36	0.047*
Pulmonary	1.34	1.05-1.70	0.018
Renal	1.05	0.88-1.27	0.576

Supplemental Table 5: Odds ratios and 95% Confidence Intervals for Multivariate Logistic Regression of Likelihood of MACE by irAE Type. *denotes statistical significance. irAE = immune related adverse event; OR = odds ratio; CI = confidence interval

Patient Characteristic		No ICI Myocarditis or Pericarditis (n = 5766)	ICI Myocarditis or Pericarditis (n = 29)	p-value
Patient Demographics				
Age at first ICI, years, median (IQR)		68.0 (17.7)	68.2 (20.3)	0.934
Sex, male, n (%)		3057 (53.0)	19 (65.5)	0.246
Self-reported race, n (%)				0.006
	Asian	674 (11.7)	4 (13.8)	
	Black	184 (3.2)	4 (13.8)	
	White	2986 (51.8)	16 (55.2)	
	Other	1917 (33.3)	5 (17.2)	

Ethnicity, n (%)			0.365
Hispanic or Latino	581 (11.1)	1 (3.4)	
Not Hispanic or Latino	4638 (88.9)	28 (96.6)	
ADI National Rank, median (IQR)	6.0 (9.0)	9.0 (16.0)	0.218
ADI State Rank, median (IQR)	3.0 (3.0)	4.0 (5.0)	0.193
Body mass index, kg/m^2, median (IQR)	24.8 (6.5)	26.1 (8.5)	0.619
Cardiovascular Risk Factors			
Hypertension, n (%)	2147 (37.2)	123 (44.8)	0.515
Type II diabetes mellitus, n (%)	827 (14.3)	0 (0.0)	1.000
Hyperlipidemia, n (%)	1748 (30.3)	9 (31.0)	1.000
History of MACE, n (%)	1344 (23.3)	11 (37.9)	0.102
Coronary artery disease	594 (44.2)	4 (36.4)	
Acute coronary syndrome	79 (5.9)	0 (0)	
Cardiac arrest	8 (0.6)	1 (9.1)	
Ischemic stroke	106 (7.9)	1 (9.1)	
Heart failure/cardiomyopathy	120 (8.9)	2 (18.2)	
Arrhythmia	437 (32.5)	3 (27.3)	
Smoker, current or previous, n (%)	2744 (48.3)	11 (37.9)	0.352
Baseline Laboratory Values			
GFR < 60 mL/min/1.73 m^2, n (%)	586 (22.8)	3 (25.0)	0.741
Creatinine, mg/dL, median (IQR)	0.8 (0.4)	0.9 (0.3)	0.657
Total Cholesterol, mg/dL, median (IQR)	177.0 (57.4)	170 (41.0)	0.226
HDL, mg/dL, median (IQR)	49.0 (22.0)	52.3 (6.6)	0.772
LDL, mg/dL, median (IQR)	90.0 (49.2)	95.0 (34.0)	0.798
Triglycerides, mg/dL, median (IQR)	103.0 (68.0)	80.0 (84.0)	0.275
Hemoglobin A1c, %, median (IQR)	5.8 (0.8)	6.4 (1.1)	0.826
Erythrocyte sedimentation rate, mm/hr, median (IQR)	34.0 (37.0)	10.5 (13.0)	0.385
C-reactive protein, mg/dL, median (IQR)	0.9 (3.2)	0.3 (0.3)	0.138
Uric acid, mg/dL, median (IQR)	5.0 (2.4)	5.5 (1.8)	0.779
Cardiovascular Medications			
Beta blockers, n (%)	780 (13.5)	6 (20.7)	0.272
ACEi or ARB, n (%)	938 (16.3)	4 (13.8)	1.000
Mineralocorticoid receptor antagonist, n (%)	208 (3.6)	0 (0.0)	0.625
SGLT2i, n (%)	97 (1.7)	1 (3.4)	0.391
Entresto, n (%)	15 (0.3)	1 (3.4)	0.077
Statin, n (%)	982 (17.0)	8 (27.6)	0.138
Cancer Types			
Lung cancer, n (%)	1356 (23.5)	10 (34.5)	0.243
Melanoma, n (%)	813 (14.1)	8 (27.6)	0.070
Genitourinary cancer, n (%)	718 (12.5)	1 (3.4)	0.250
Hepatobiliary cancer, n (%)	465 (8.1)	2 (6.9)	1.0
Head and neck cancer, n (%)	448 (7.8)	1 (3.4)	0.723
Gynecologic cancer, n (%)	431 (7.5)	2 (6.9)	1.0
Breast cancer, n (%)	363 (6.3)	0 (0.0)	0.257
Upper gastrointestinal cancer, n (%)	304 (5.3)	0 (0.0)	0.402
Other cancer types, n (%)	868 (15.1)	5 (17.2)	0.946
Anti-Cancer Medications (previous or concurrent)			
5-Fluorouricil, n (%)	257 (4.5)	1 (3.7)	1
Anthracyclines, n (%)	141 (2.4)	0 (0)	1
VEGF inhibitor, n (%)	710 (12.3)	4 (14.8)	0.567
Non-VEGF tyrosine kinase inhibitor, n (%)	54 (0.9)	0 (0)	1
HER-2 targeted therapies, n (%)	34 (0.6)	0 (0)	1
Immune Checkpoint Inhibitor (ICI) Use			
ICI Type, n (%)			
Pembrolizumab	3187 (55.3)	10 (34.5)	0.040
Nivolumab	2055 (35.6)	14 (48.3)	0.22
Atezolizumab	492 (8.5)	3 (11.1)	0.499
Ipilimumab	741 (12.9)	6 (20.7)	0.258
Durvalumab	221 (3.8)	3 (10.3)	0.100
Cemiplimab	82 (1.4)	1 (3.4)	0.343
Avelumab	33 (0.6)	0 (0)	1.000
Exposure to multiple ICIs, n (%)	902 (15.6)	8 (27.6)	0.118

Dual ICI therapy, n (%)	664 (11.5)	5 (17.2)	0.374
Total days on ICI, median (IQR)	110.0 (288.0)	84.0 (322.0)	0.743
Total ICI doses, median (IQR)	7.0 (12.0)	4.0 (13.0)	0.405
ICI doses prior myocarditis or pericarditis, median (IQR)	N/A	3.0 [2.0,10.0]	
Days on ICI prior to myocarditis or pericarditis, median (IQR)	N/A	79.0 (41.0-290.0)	
Follow-up time, days, median (IQR))	329.0 (640)	556.0 (941.0)	0.335
Mortality			
All-cause mortality, n (%)	3115 (54.0)	17 (58.6)	0.758
Time to death, days, median (IQR)	221.0 (405.5)	346.0 (931.0)	0.176

Supplemental Table 6: Patient Characteristics: Myocarditis or Pericarditis versus No Myocarditis or Pericarditis. MACE = major adverse cardiovascular event; ICI = immune checkpoint inhibitor; SD = standard deviation; n = number of patients; IQR = interquartile range; ADI = area deprivation index; VEGF = vascular endothelial growth factor; GFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; LDL = low-density lipoprotein; ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; SGLT2i = sodium-glucose co-transporter 2 inhibitor; VEGF = vascular endothelial growth factor; HER2 = human epidermal growth factor receptor 2

Chapter 4

Project 2

Predictors, Recovery and Mortality Associated with Left Ventricular Systolic Dysfunction Following Orthotopic Liver Transplantation: A Propensity-Matched Case-Control Study

Abstract:

Background: New onset left ventricular systolic dysfunction (LVSD) after orthotopic liver transplantation (OLT) contributes to postoperative morbidity, yet predictors, recovery, and outcomes remain incompletely defined.

Methods: We performed a single-center retrospective, propensity-matched case-control study of adults undergoing OLT from 2015–2022. Cases were defined as a ≥10% decline in LVEF to ≤50% within one year. Controls were matched 1:1 on age, sex, MELD, cirrhosis etiology, and pre-transplant LVEF with a caliper 0.2. Clinical, perioperative, and echocardiographic variables were evaluated with stepwise and multivariable logistic regression; survival used Kaplan–Meier. An XGBoost model with SHAP explanations and partial dependence plots (PDPs) assessed variable importance and interactions.

Results: Among 956 OLT recipients, 66 (6.9%) developed LVSD and were matched to 66 controls. LVSD occurred early (median 6.5 days [IQR 2.25–62.5]); 62.1% by 30 days and 72.4% by 60 days. ICU length of stay was longer with LVSD (56.2 ± 53.7 vs. 33.1 ± 25.3 days; p=0.002). EF recovered to ≥50% in 53/66 (80.3%) with median recovery 18 days (IQR 7–136.8). Mortality was similar between groups (33.3% vs. 28.8%; p=0.71). Mineralocorticoid receptor antagonist (MRA) use predicted LVSD (OR 2.67, 95% CI 1.28–5.73; p=0.01), while higher pre-operative hemoglobin was protective (OR 0.70, 95% CI 0.49–0.94; p=0.03). Among peri-operative variables, intraoperative dialysis was independently associated with LVSD (OR 2.94, 95% CI 1.14–8.00; p=0.03). Among echocardiographic variables larger left ventricular size (OR 3.40, 95% CI 1.22–11.40, p=0.03), left atrial size (OR 1.65, 95% CI 1.05–2.67, p=0.04), higher mitral annular e′ (OR 1.18, 95% CI 1.03–1.37, p=0.02), and higher pulmonary artery systolic pressure (OR 1.11, 95% CI 0.04–1.01, p=0.04) were associated with LVSD, while increased

right ventricular basal diameter was protective (OR 0.56, 95% CI 0.32–0.94, p=0.03). The ML model achieved AUROC 0.734 and many of the top features were related to diastolic function; PDPs demonstrated non-linear interactions among these top predictors.

Conclusions: Post-OLT LVSD occurs in approximately 7% of recipients and is typically manifests early in the post-operative course, is often reversible, and associated with longer ICU stay without excess mortality. MRA use, lower hemoglobin, and intraoperative dialysis identify higher-risk patients. Echocardiographic features, SHAP results, and PDP-defined interactions highlight diastolic and pulmonary hemodynamics as key contributors, informing perioperative risk stratification.

Introduction:

Liver cirrhosis remains a major global health burden, accounting for approximately two million deaths per year [93]. Orthotopic liver transplantation (OLT) is the definitive treatment for end-stage liver disease, and its utilization has grown steadily, with nearly 34,700 liver transplants performed worldwide in 2021[94]. As post-transplant survival has improved, cardiovascular complications have emerged as the leading cause of non-graft mortality in liver recipients [95]. Among these, new-onset left ventricular systolic dysfunction (LVSD), defined as a reduction of left ventricular ejection fraction (LVEF) in patients with previously normal LVEF, is increasingly recognized after OLT [96].

The cause of post-OLT LVSD is not known but may arise from cirrhotic cardiomyopathy or stress cardiomyopathy. Cirrhotic cardiomyopathy refers to the chronic cardiac dysfunction in patients with advanced liver disease, characterized by blunted contractile reserve and diastolic dysfunction that is often masked by the hyperdynamic circulation and systemic vasodilation of advanced liver disease [97, 98]. Stress-induced cardiomyopathy is an acute, typically reversible, form of non-ischemic cardiomyopathy triggered by intense physical stress and catecholamine surge and has been increasingly implicated in the early postoperative course of OLT [99, 100]. Postoperative LVSD has been reported in 6–14% of OLT recipients [101-103] and has been shown to be associated with excess mortality [102].

Despite the frequency of this complication, risk factors for left ventricular systolic dysfunction (LVSD) after OLT remain incompletely defined. Moreover, significant gaps persist in the understanding of the natural history of post-transplant LVSD, including the likelihood of recovery and its long-term impact on survival. To address these gaps, we conducted a single-center study to evaluate the incidence, risk factors, recovery, and mortality associated with post-OLT LVSD using both traditional statistical approaches and machine learning techniques.

Methods:

Study Design and Patient Selection: We identified all patients undergoing orthotopic liver transplantation (OLT), or dual OLT and kidney transplant, from 2015 to 2022 at an academic, tertiary care center. Cases were defined as patients who experienced a reduction in left ventricular ejection fraction (LVEF) of at least 10% from baseline and a post-OLT LVEF of ≤50% within one year. For patients with multiple OLTs during the study period, only the first event was included. Patients without a pre-OLT transthoracic echocardiogram (TTE), those undergoing simultaneous heart-liver transplantation, or those with less than one year of follow-up were excluded. Controls were identified using 1:1 propensity matching on age, sex, pre-OLT Model for End-Stage Liver Disease (MELD) score, cirrhosis etiology, and pre-transplant LVEF, using a caliper of 0.2 (**Figure 18**). This study was approved by the institutional review board (IRB-11-0489).

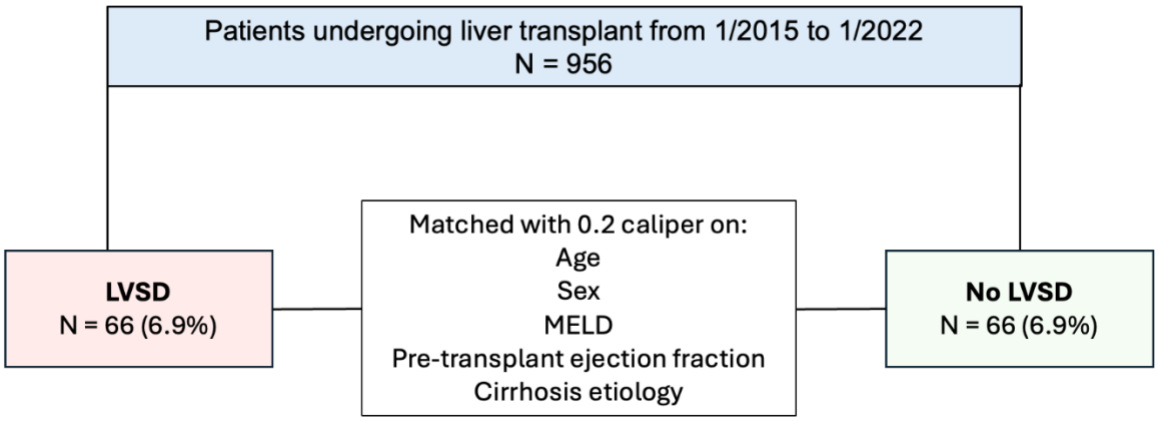

Figure 18: Patient Selection

Patient characteristics: Baseline demographic and clinical variables were collected from the transplant database and through manual chart review. These included age, sex, ethnicity, race, body mass index (BMI), hospital length of stay, intensive care unit (ICU) length of stay, hypertension, diabetes mellitus type 2 (DM2), coronary artery disease (as determined by

angiogram), hyperlipidemia, obstructive sleep apnea, chronic obstructive pulmonary disease (COPD), chronic kidney disease (stage 3 or greater), dialysis during the transplant admission, and prior smoking history. Pre-transplant medications collected included beta blockers, ACE inhibitors, ARBs, statins, and mineralocorticoid receptor antagonists (MRAs). Laboratory values were obtained from the most recent pre-operative labs. Right heart catheterization data were included if performed within one year prior to transplant.

Perioperative variables included total fluids administered (blood products, crystalloid, and albumin), intraoperative dialysis, cold ischemia time, deferred biliary reconstruction, and use of intraoperative venous-venous bypass. Cardiac risk stratification modality was recorded (nuclear perfusion scan, stress echocardiogram, or coronary angiogram) and whether revascularization was performed via percutaneous coronary intervention (PCI) pre-transplant or via surgical coronary artery bypass graft (CABG) at time of transplant. Echocardiographic data were abstracted from clinical reports and direct review of images, including atrial and ventricular chamber sizes, right ventricular basal diameter, tricuspid annular plane systolic excursion (TAPSE), left ventricular posterior wall thickness (LVPWd), interventricular septal thickness (IVSd), left ventricular internal diameter at end diastole (LVIDd), E and A wave velocities, mitral annular e′, diastolic dysfunction, right atrial pressure, right ventricular systolic pressure (RVSP), pulmonary artery systolic pressure (PASP), tricuspid regurgitant jet velocity, left ventricular outflow tract (LVOT) VTI, LVOT peak velocity, LVOT diameter, stroke volume, cardiac output, and systemic vascular resistance. Time to development of LVSD was calculated as the interval from OLT to the first recorded LVEF ≤50%. Heart rate and blood pressure at the time of echocardiography were recorded. All-cause mortality and time to death was also determined for each patient.

Statistical analysis: Continuous variables are presented as mean ± standard deviation (SD) or median ± interquartile range (IQR); categorical variables as counts and percentages. Continuous variables were compared using two-sample t-tests, Mann-Whitney U tests, or Kruskal-Wallis tests as appropriate. Categorical variables were compared with chi-squared or Fisher's exact tests. Bidirectional stepwise regression models were used to identify predictors of post-OLT LVSD among demographic and echocardiographic variables. Perioperative predictors were evaluated using multivariate logistic regression. Survival analyses were performed with Kaplan-Meier curves. Analyses were conducted in R version 2024.04.1+748.

Machine Learning Analysis: We developed an XGBoost model to predict LVSD, including all demographic, clinical, laboratory, perioperative, and echocardiographic variables. Data were split into training (80%) and validation (20%) sets with stratified random sampling. Hyperparameter tuning used grid search and five-fold cross-validation. Model performance was assessed by AUROC, accuracy, sensitivity, specificity, and Brier score in the validation set. SHapley Additive exPlanations (SHAP) were used for variable importance. Partial dependency plots were created to determine interactions amongst the variables. Analyses were conducted in R version 2024.04.1+748.

Results:

Matching variables and outcome timing: Between 2015 and 2022, 956 patients underwent OLT, and 66 (6.9%) developed LVSD within one year. Propensity score matching yielded 69 controls. The most common liver failure etiology was alcoholic cirrhosis (**Supplemental Table 7** for all matching variables). The median time to LVSD was 6.5 days (IQR 2.25–62.5), mean 44.8 ± 68.7 days; 62.1% developed LVSD by 30 days and 72.4% by 60 days post-transplant (**Figure 19).**

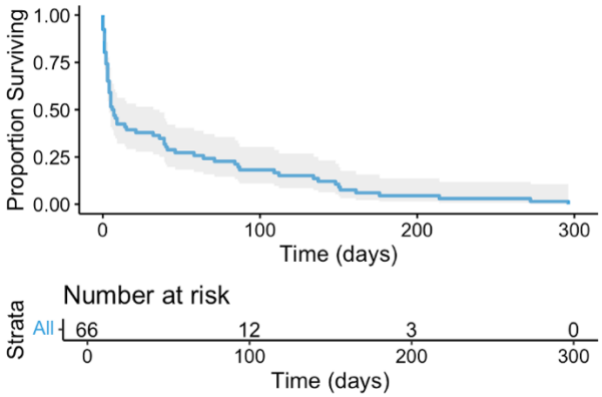

Figure 19: Time to Development of Outcome

Ejection Fraction: The mean pre-OLT EF was 64.0% ± 6.3% in the no LVSD group and 63.5% ± 6.3% in the LVSD group. The mean post-OLT EF for those with LVSD was 36.9% ± 9.7%, compared with 63.0% ± 6.8% in those without LVSD. Among the 66 patients with LVSD, 53 (80.3%) recovered their EF to ≥50% (**Figure 20**), with a median recovery time of 18 days (IQR: 7–136.8 days) and a mean recovery time of 183.9 ± 404.2 days. Lack of EF recovery was not associated with increased mortality (6/13 [46.2%] without recovery died vs. 16/53 [30.2%] with recovery died; Fisher's exact test, p = 0.33).

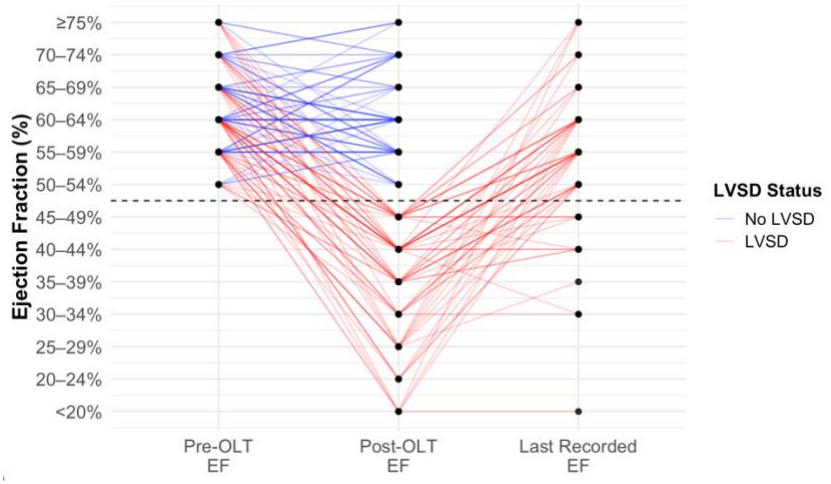

Figure 20: Ejection Fraction Pre-OLT, Post-OLT and Last Recorded. Abbreviations: OLT = orthotropic liver transplantation; EF = ejection fraction; LVSD = left ventricular systolic dysfunction.

Demographics, cardiovascular risk factors, laboratory variables, and medications: **Table 5** summarizes patient characteristics. Mean hospital length of stay did not differ between groups (79 ± 60.3 vs. 62.6 ± 44.9 days, p=0.08) however patients with LVSD had a significantly longer ICU stay (56.2 ± 53.7 vs. 33.1 ± 25.3 days, p=0.002). All demographics, cardiovascular risk factors, and laboratory studies collected were similar between groups. Beta blocker, angiotensin-converting enzyme inhibitor (ACEi)/angiotensin II receptor blocker (ARB), and statin use were similar. MRA use was higher in those with LVSD (65.2% vs. 40.9%, p=0.009).

Predictor variable	No LVSD (n = 66)	LVSD (n = 66)	p-value
Total LOS, mean, (SD)	62.64 (44.93)	79.00 (60.28)	0.079
ICU LOS, mean (SD)	33.05 (25.29)	56.21 (53.66)	0.002
BMI, mean (SD)	28.71 (7.07)	26.88 (6.87)	0.133
Smoking history, n (%)	19 (28.8)	24 (36.4)	0.458
Medical Histories			
HTN, n (%)	25 (37.9)	25 (37.9)	1
DM2, n (%)	28 (42.4)	18 (27.3)	0.1
CAD on angiogram, n (%)	9 (13.6)	14 (21.2)	0.359
CAD >50% on angiogram, n (%)	4 (6.1)	8 (12.1)	0.354
HLD, n (%)	11 (16.7)	10 (15.2)	1
OSA, n (%)	3 (4.5)	6 (9.1)	0.49
COPD, n (%)	1 (1.5)	7 (10.6)	0.068

CKD, n (%)	23 (34.8)	27 (40.9)	0.59
Dialysis during admission, n (%)	49 (74.2)	49 (74.2)	1
Pre-transplant labs			
Hgb, mean (SD)	8.66 (1.68)	8.23 (0.84)	0.062
Creatinine, mean (SD)	1.51 (1.16)	1.28 (1.06)	0.235
Albumin, mean (SD)	3.86 (0.95)	3.73 (0.81)	0.392
Sodium, mean (SD)	136.45 (4.42)	136.67 (4.35)	0.782
Medications			
Beta blocker, n (%)	16 (24.2)	15 (22.7)	1
ACEi/ARB, n (%)	4 (6.1)	3 (4.5)	1
Statin, n (%)	9 (13.6)	6 (9.1)	0.583
MRA, n (%)	27 (40.9)	43 (65.2)	0.009

Table 5: Patient Characteristics

In a bidirectional stepwise regression model, a use of mineralocorticoid receptor antagonists (MRA) was associated with the outcome of post-OLT LVSD (OR 2.67, 95% CI 1.28-5.73, p = 0.01) and higher preoperative hemoglobin was protective against the development of post-OLT LVSD (OR 0.70, CI = 0.49 - 0.94, p=0.03) **(Figure 21)**. The rest of the variables included in the stepwise analysis, namely body mass index, hypertension, type 2 diabetes mellitus, obstructive coronary artery disease, hyperlipidemia, chronic kidney disease, dialysis at admission, tobacco use, hemoglobin, serum creatinine, serum albumin and serum sodium were not predictive of the outcome.

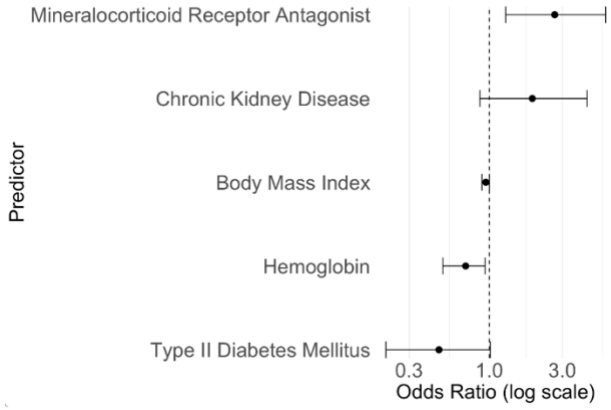

Figure 21: Patient Characteristics as Risk Factors for Left Ventricular Systolic Dysfunction (LVSD)

Perioperative Factors: Intraoperative dialysis was more frequent in LVSD cases (37.9% vs. 19.7%, p=0.034) and remained significant in multivariate analysis (OR 2.94, 95% CI 1.14–8.00, p=0.03). There was no difference in venous-venous bypass (53% vs. 43.9%, p=0.384), deferred

biliary reconstruction (40.9% vs. 34.8%, p=0.59), or total fluids transfused (16.4 vs. 16.5 liters, p=0.419) between groups. No differences were seen for individual transfused components. Ischemic time was similar (13.05 ± 31.0 vs. 8.58 ± 2.47 hours).

Echocardiographic Factors: No single echocardiographic variable differed between groups on univariate analysis (**Supplemental Table 8**). In stepwise analysis, larger left ventricular size (OR 3.40, 95% CI 1.22–11.40, p=0.03), left atrial size (OR 1.65, 95% CI 1.05–2.67, p=0.04), higher mitral annular e′ (OR 1.18, 95% CI 1.03–1.37, p=0.02), and higher PASP (OR 1.11, 95% CI 0.04–1.01, p=0.04) were associated with LVSD, while increased right ventricular basal diameter was protective (OR 0.56, 95% CI 0.32–0.94, p=0.03; **Figure 22**)

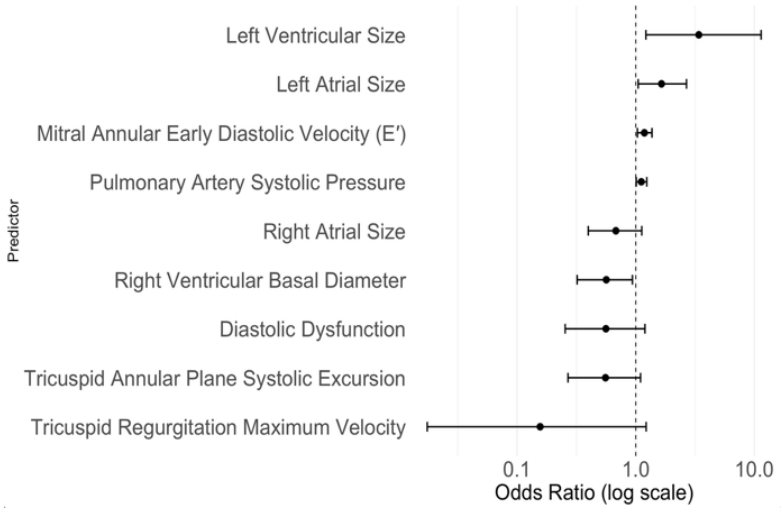

Figure 22: Bidirectional Stepwise Analysis of Echocardiographic Variables as Predictors of left ventricular systolic dysfunction (LVSD)

Preoperative Risk Stratification Analysis: Preoperative risk stratification was performed in 125 of 132 patients (94.7%) with either and coronary angiogram (CA), nuclear stress test or stress echocardiography. Patients with CA as the risk stratification modality were more likely to develop the outcome (65.2% versus 40.9%, p = 0.02). Seven patients who underwent coronary artery revascularization developed LVSD (10.6%), while none of the patients in the group without LVSD were revascularized (p = 0.02). Patients with any coronary artery disease on

angiogram had a significantly longer time to HF compared with those without disease (median [IQR]: 65 [14.2–151.0] vs. 5 [1.75–39.0] days; Wilcoxon rank-sum test, p = 0.0012). The use of nuclear medicine stress testing for preoperative risk stratification was similar between the group who developed LVSD versus the group who did not (39.4% versus 51.5%, p = 0.89). There was one patient in the group who developed LVSD that was found to have an abnormal nuclear medicine stress test and subsequently underwent CA.

Mortality Analysis:

Mortality was similar between the two groups (33.3% in the group with LVSD versus 28.8% in the group without LVSD, p = 0.71). Length of time to death was not significantly different between those with and those without LVSD, but there was a trend towards shorter time to death in the group with LVSD (722.4 ± 729.0 days versus 1123.5 ± 714.6 days, Welch's t-test p = 0.084). Kaplan Meier curve with log-rank p value of 0.41 is shown in **Figure 23.**

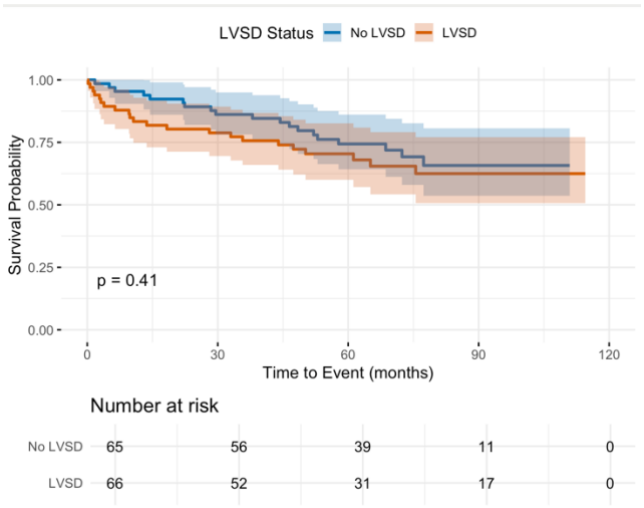

Figure 23: Kaplan Meier Curve of Mortality by Outcome of left ventricular systolic dysfunction (LVSD)

Machine Learning Analysis: The XGBoost model incorporating all variables achieved an area under the receiver operating characteristic curve (AUROC) of 0.734 (**Figure 24A**), with an accuracy of 0.65, precision of 0.62, and recall of 0.67. SHAP feature importance analysis identified peak early diastolic transmitral flow velocity (E), peak late diastolic (atrial) transmitral

flow velocity (A), heart rate at the time of echocardiography, mitral annular early diastolic velocity (e′), and tricuspid regurgitation maximum velocity (TR Vmax) as the five most important predictive features (**Figure 24B**). Since all top predictors were echocardiographic parameters, partial dependence plots were constructed to evaluate interactions between E and A, E and heart rate, A and heart rate, A and e′, and A and TR Vmax. These plots demonstrated significant interaction effects among these variables (**Figure 25**).

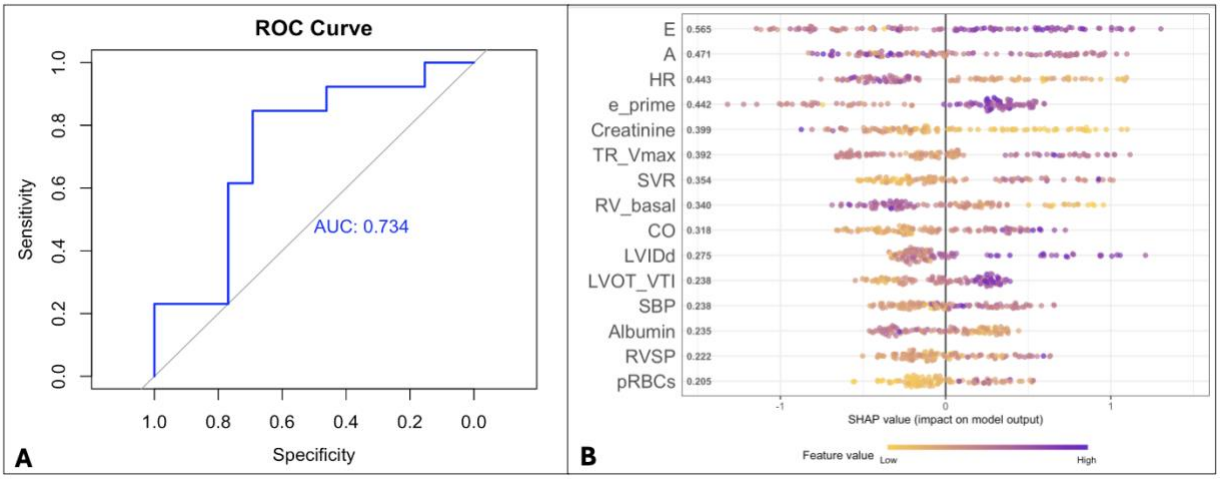

Figure 24: XGBoost Analysis. A. AUROC Curve for XGBoost. **B**. SHAP feature importance for to 15 most important predictors. Abbreviations: AUROC = area under the receiver operating curve. SHAP = SHapley Additive exPlanations

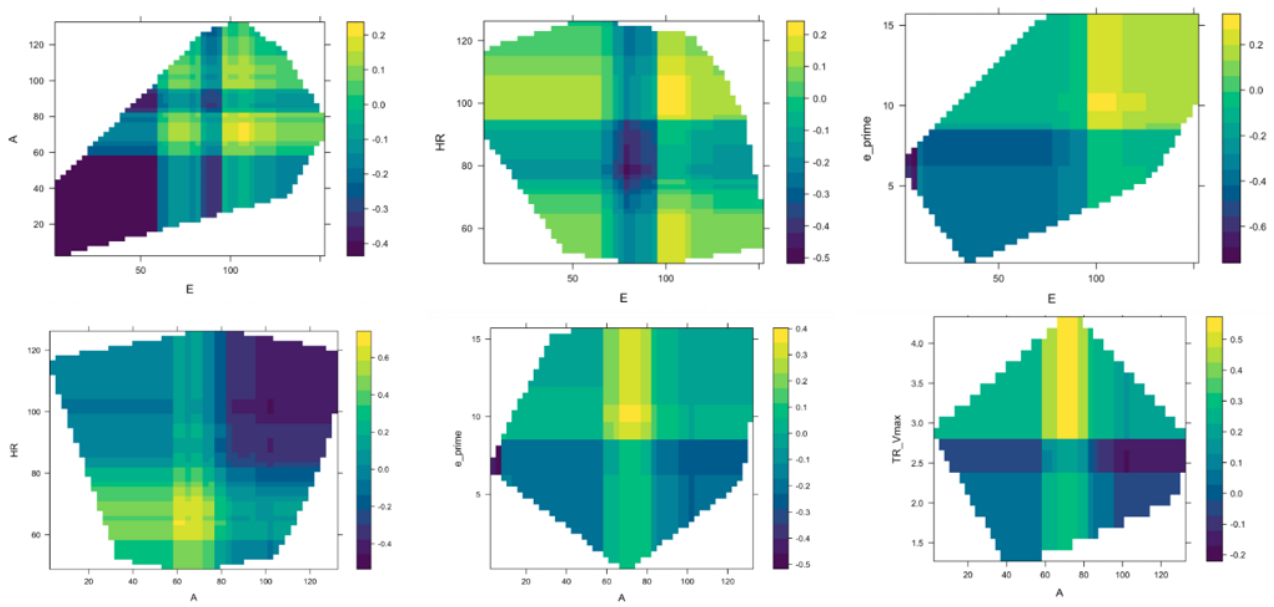

Figure 25: Partial Dependency Plots for Most Important SHAP Predictors. Abbreviations: HR = heart rate; A = late (atrial) transmitral inflow velocity; E = early transmitral inflow velocity; e' = mitral annular early diastolic velocity; TR Vmax = peak tricuspid regurgitant jet velocity

Discussion:

As the global burden of liver disease continues to rise, orthotopic liver transplantation (OLT) remains a critical therapy for end-stage liver disease, reflected by the steadily increasing number of OLT procedures performed annually in the United States [104]. In this single center study spanning from 2015 to 2022, we found that approximately 7% of orthotopic liver transplant (OLT) recipients developed new-onset left ventricular systolic dysfunction (LVSD) within one year, typically manifesting in the early postoperative period (median ~6.5 days post-OLT). In this propensity matched case-control study, key predictors of post-transplant LVSD included pre-transplant use of mineralocorticoid receptor antagonists (MRAs) and lower baseline hemoglobin, as well as the need for intraoperative renal replacement therapy (dialysis). Patients who developed LVSD had larger left atrial and ventricular dimensions, higher mitral annular e′ velocities, and higher estimated pulmonary artery systolic pressures on baseline

echocardiogram prior to transplant, despite preserved pre-OLT ejection fractions in all cases. Notably, although LVSD was associated with significantly longer intensive care unit stays, we observed no statistically significant difference mortality between the LVSD group and matched controls.

The observed incidence of post-OLT systolic heart failure in our study (6.9%) is in line with prior reports, which have ranged from roughly 6% to 14% depending on the patient population and definitions used [102, 105]. For example, Eimer *et al.* reported an incidence of severe acute heart failure of ~7% in a series liver transplant patients [105], while Sakr *et al*. noted a higher incidence (~14%) of acute HFrEF in their single-center cohort [102]. Our finding that most LVSD events occurred early (over 60% within 30 days post-OLT) is consistent with the timing reported in other studies [101]. Souki *et al.* recently documented a 6% incidence of new-onset systolic HF in the first year after transplant, with the majority of cases occurring in the immediate postoperative period (median onset 9 days) [101]. Given most cases happened quite soon after surgery, this may indicate that peri-transplant cardiovascular stress often unmasks latent cardiac dysfunction.

Importantly, LVSD in our cohort was largely reversible. Among the 66 patients with LVSD, 53 (80.3%) recovered their EF to ≥50%, with a median time to recovery of 18 days (IQR: 7–136.8 days) and a mean of 183.9 ± 404.2 days. Lack of EF recovery was not associated with increased mortality. These findings align with prior work by Souki et al. [3] which showed 70% recovery of LVSD. This may be indicative of the fact that LVSD after OLT is stress-related myocardial dysfunction which recovers well with supportive care.

Our analysis also provides insight into risk factors for post-OLT LVSD and how they compare to prior literature. Pre-transplant mineralocorticoid use (MRA) use emerged as a significant predictor of postoperative LVSD, which has not been previously reported. MRA

(spironolactone) is commonly used in cirrhosis for refractory ascites, and its use may be a marker of more advanced liver disease-related circulatory dysfunction [106]. Preoperative anemia was also identified as a possibly modifiable risk factor: higher hemoglobin was protective against LVSD. This finding is consistent with Sakr *et al.*, who found that a pre-transplant hemoglobin >8.5 g/dL was associated with significantly lower odds of post-OLT HFrEF [102]. In addition, Souki *et al,* found that patients with hemoglobin <7.2 g/dL had a higher incidence of post-transplant HF if they did not receive adequate transfusion support [101]. These observations suggest that optimizing hemoglobin levels pre-OLT could improve cardiac resilience during the transplant.

Likewise, we found that patients requiring intraoperative dialysis had nearly a three-fold higher risk of LVSD, which many underscore the interplay between renal dysfunction, metabolic derangements, fluid management, and cardiac outcomes. Interestingly, in our study, fluid administration during surgery was not associated with the adverse outcome, though this has been shown previously. Sakr *et al* [102] reported that transfusion of >11 units of packed red cells during OLT was associated with increased HFrEF incidence [102]. However, the finding of intra-operative dialysis being associated with the outcome of LVSD helps identify patients at risk for development of adverse cardiac outcomes after liver transplant surgery.

This study shows that pre-transplant echocardiography parameters are associated with development of LVSD, but this association is complex. Simple univariate analyses did not identify any predictors of LVSD, but using bidirectional stepwise analysis and a machine learning model it is clear that interaction between these parameters is key. Notably, a larger left atrium, larger left ventricular size, higher PASP, and a higher mitral annular e′ velocity were associated with post-OLT LVSD in bidirectional stepwise analysis. Consistent with this, Eimer *et al.* similarly found that OLT patients who developed HF had significantly higher preoperative

pulmonary artery pressures (mean ~43 vs. 30 mmHg) despite similar EF and blood pressure [105]. In a prior single-center study, Eyvazian *et al.* reported that the presence of any wall-motion abnormality on pre-transplant echo was a strong predictor of post-OLT LVSD, even when baseline EF was preserved [107]. The present study did not look at wall motion as a predictor however our results taken together suggest that heightened awareness of subclinical cardiac dysfunction is crucial, as these patients may benefit from closer perioperative monitoring or preemptive therapeutic strategies.

To further probe the complex associations of pre-operative variables, we applied a machine learning (XGBoost) model. Although its performance was modest (AUROC ~0.73, accuracy ~65%), the model consistently prioritized echocardiographic and hemodynamic features. The top predictors-early and late transmitral velocities (E, A), mitral annular e′, tricuspid regurgitant velocity (TR Vmax), and heart rate-point to diastolic function and pulmonary vascular load as central drivers of LVSD risk. Prior studies have similarly implicated diastolic dysfunction as a risk factor for post-OLT LVSD [108]. Notably, partial dependency analyses revealed non-linear interactions among these parameters, reinforcing that no single measure adequately captures vulnerability. While not yet clinically applicable, our model provides proof-of-concept that combining multiple echo-derived indices with clinical data can enhance risk stratification. Future research leveraging larger, multi-center cohorts may refine these models, improving predictive accuracy and enabling more personalized perioperative care.

Another notable finding was the role of coronary artery disease (CAD) in post-transplant cardiac dysfunction. We observed that patients who underwent invasive coronary evaluation (and especially those who required intervention for CAD) were over-represented among those who developed LVSD, likely representing selection bias. In our LVSD cohort, 10.6% had undergone coronary revascularization (percutaneous or surgical) whereas none of the matched

controls had needed revascularization. This disparity suggests that underlying ischemic heart disease contributed to a subset of LVSD cases despite adequate revascularization. Souki *et al.* recently highlighted that a subset of LVSD cases after OLT are due to ischemic cardiomyopathy, reporting that about 23% of cases were ischemic HF while 77% were non-ischemic [101]. Alexander *et al* found that the presence of 3 or more cardiovascular disease risk factors increased the risk of major adverse cardiovascular events and death post-transplant [109]. Thus, while cirrhotic cardiomyopathy (a form of non-ischemic dysfunction) is often the primary focus, ischemic cardiomyopathy can occur and may be under-recognized in this population. Importantly, both our data and prior studies suggest that ischemic LVSD tends to occur later in the post-transplant course, whereas early postoperative LVSD is predominantly non-ischemic in nature [107, 108]. A balanced approach addressing both components, both optimizing any coronary disease and recognizing high-risk non-ischemic cardiac features, is likely to yield the best outcomes.

Despite the frequency of LVSD after OLT, its impact on survival in our study was less dire than reported in some prior studies. We found no significant difference in all-cause mortality between the LVSD group and matched controls (33.3% vs. 27.4%, $p = 0.71$). This result contrasts with earlier cohorts that noted higher mortality among patients who develop post-transplant heart failure. For instance, Sakr *et al.* and Eyvazian *et al*. reported worse survival in patients with LVSD after OLT [102, 107]. There are several possible explanations for the more neutral survival effect in our series. First, by using propensity-matched controls, we ensured that the comparison group had similar baseline risk profiles (age, severity of liver disease, etc.), which may have elevated the background mortality rate in the control group and narrowed the difference between groups. Second, many episodes of LVSD were recognized within the first month post-OLT and thus likely promptly treated. Third, advancements in critical care and heart

failure therapies in recent years may have improved survival for those who do develop acute HF after OLT. Our data collection spanned 2015–2022, during which there has been growing awareness and prompt treatment of post-transplant cardiac complications, potentially mitigating their lethality. Nonetheless, it would be premature to conclude that post-OLT LVSD is benign. The LVSD group in our study did show a shorter average time to death (approximately 1.7 years vs. 2.9 years in controls), even if this did not reach statistical significance. With a larger sample size or longer follow-up, a mortality difference might yet emerge.

This study has important limitations. It was a single-center retrospective analysis with a relatively small number of LVSD events (66 cases), which may limit generalizability and the power to detect more subtle risk factors. Although we used propensity score matching to create a balanced control group, this also means that certain known risk factors (e.g., older age, higher MELD score) were equivalent between groups by design and thus could not be evaluated in our analysis. Furthermore, our definition of cardiomyopathy missed isolated right ventricular failure which is a related and clinically significant predictor.

Despite these limitations, our study offers a comprehensive evaluation of demographic, clinical, perioperative, and echocardiographic factors in relation to post-OLT LV dysfunction, and it is one of the first to apply machine learning to this problem. We confirmed several previously identified risk factors, such as anemia, diastolic dysfunction, and pulmonary hypertension, identified new associations, including MRA use and intraoperative dialysis, and highlight the nonlinear associations of echocardiographic parameters that merit further investigation.

Supplemental Tables:

Matching variable	No LVSD (n = 66)	LVSD (n = 66)	P-value
Sex, Male, n (%)	38 (57.6)	35 (53.0)	0.726
Age, mean (SD)	52.02 (12.23)	54.27 (12.29)	0.292
MELD, mean (SD)	37.53 (5.62)	37.48 (4.02)	0.957
Pre-transplant EF, mean (SD)	64.03 (6.34)	63.49 (6.30)	0.626
Liver failure etiology, n (%)			1.000

Acute	2 (3.0)	2 (3.0)
Alcoholic Cirrhosis	33 (50.0)	28 (42.4)
Autoimmune	5 (7.6)	3 (4.5)
Graft Failure	2 (3.0)	2 (3.0)
Hepatitis B	1 (1.5)	2 (3.0)
Hepatitis C	8 (12.1)	8 (12.1)
MASH	8 (12.1)	10 (15.2)
Other	7 (10.6)	11 (16.7)

Supplemental Table 7: Matching variables

Echocardiographic variable	No LVSD (n = 66)	LVSD (n = 66)	P-value
HR, mean (SD)	80.48 (14.64)	80.28 (18.28)	0.944
SBP, mean (SD)	112.46 (19.53)	111.56 (16.70)	0.782
DBP, mean (SD)	59.84 (12.24)	60.56 (12.48)	0.747
RA Size, n (%)			0.997
Normal	52 (78.8)	47 (77.0)	
Mildly Enlarged	5 (7.6)	5 (8.2)	
Moderately Enlarged	3 (4.5)	3 (4.9)	
Severely Enlarged	6 (9.1)	6 (9.8)	
RV Size, n (%)			0.999
Normal	49 (75.4)	50 (75.8)	
Mildly Enlarged	12 (18.5)	12 (18.2)	
Moderately Enlarged	4 (6.2)	4 (6.1)	
RV basal, mean (SD)	4.25 (1.30)	4.02 (0.72)	0.319
TAPSE, mean (SD)	2.51 (0.61)	2.49 (0.55)	0.834
LA Size, n (%)			0.381
Normal	45 (72.6)	40 (63.5)	
Mildly Enlarged	8 (12.9)	6 (9.5)	
Moderately Enlarged	3 (4.8)	5 (7.9)	
Severely Enlarged	6 (9.7)	12 (19.0)	
LV Size, n (%)			0.169
Normal	61 (92.4)	54 (81.8)	
Mildly Enlarged	4 (6.1)	8 (12.1)	
Moderately Enlarged	1 (1.5)	4 (6.1)	
LVPWd, mean (SD)	1.00 (0.19)	0.98 (0.18)	0.42
IVSd, mean (SD)	1.08 (0.51)	1.03 (0.22)	0.438
LVIDd, mean (SD)	4.72 (0.71)	4.80 (0.73)	0.556
E, mean (SD)	88.67 (28.57)	92.00 (26.29)	0.504
A, mean (SD)	77.34 (28.23)	75.01 (24.16)	0.637
EA, mean (SD)	1.38 (0.76)	1.35 (0.61)	0.798
e prime, mean (SD)	9.31 (3.02)	10.19 (2.69)	0.099
E to e prime, mean (SD)	10.33 (3.63)	9.73 (3.14)	0.354
Diastolic dysfunction, mean (SD)	0.32 (0.57)	0.36 (0.62)	0.712
RA_Pressure, mean (SD)	7.09 (3.78)	7.45 (3.98)	0.598
RVSP, mean (SD)	31.71 (9.73)	33.57 (11.44)	0.367
PASP, mean (SD)	31.71 (9.73)	33.54 (11.44)	0.377
TR Vmax, mean (SD)	2.44 (0.45)	2.50 (0.50)	0.532
LVOT VTI, mean (SD)	0.23 (0.05)	0.22 (0.06)	0.68
LVOT Vmax, mean (SD)	1.10 (0.29)	1.07 (0.25)	0.572
LVOTd, mean (SD)	2.05 (0.23)	2.08 (0.23)	0.494
Stroke volume, mean (SD)	74.34 (21.29)	77.87 (29.93)	0.499
Cardiac Output, mean (SD)	5.89 (1.99)	6.06 (2.34)	0.705
SVR, mean (SD)	1081.09 (401.52)	1087.60 (581.18)	0.949

Supplemental Table 8: Echocardiographic Variables by Outcome. Abbreviations SD = standard deviation; n = number; HR = heart rate; SBP = systolic blood pressure; DBP = diastolic blood pressure; RA = right atrium; RV = right ventricle; RV basal = right ventricular basal diameter; TAPSE = tricuspid annular plane systolic excursion; LA = left atrium; LV = left ventricle; LVPWd = left ventricular posterior wall thickness in diastole; IVSd = interventricular septal thickness in diastole; LVIDd = left ventricular internal diameter in diastole; E = early (mitral) transmitral inflow velocity; A = late/atrial transmitral inflow velocity; E/A = ratio of early-to-late transmitral velocities; e′ = mitral annular early diastolic velocity; E/e′ = ratio of E to e′; RA pressure = estimated right atrial pressure; RVSP = right ventricular systolic pressure; PASP = pulmonary artery systolic pressure; TR Vmax = peak tricuspid regurgitation jet velocity; LVOT = left ventricular outflow tract; VTI = velocity–time integral; Vmax = maximal velocity; LVOTd = LVOT diameter; SV = stroke volume; CO = cardiac output; SVR = systemic vascular resistance.

Chapter 5

Project 3

Predictors of Successful VA-ECMO Decannulation in Cardiogenic Shock: A Single Center Cohort Analysis

Introduction:

Veno-arterial extracorporeal membrane oxygenation (VA-ECMO) is a critical rescue therapy for patients in severe cardiogenic shock or cardiac arrest, providing temporary circulatory support when the native heart cannot maintain adequate perfusion. Despite its life-saving potential, outcomes remain poor – in-hospital mortality for VA-ECMO patients ranges from 40% to 60% [110, 111]. Successful ECMO decannulation (weaning) – defined as removal of support with the patient surviving without need for new mechanical circulatory support or transplant for a period (commonly 30 days) is therefore a pivotal milestone. Premature or failed decannulation can precipitate hemodynamic collapse and organ injury, whereas prolonging ECMO support unnecessarily increases the risk of complications (e.g., bleeding, limb ischemia, infection) and may itself worsen mortality [112].

Making decannulation decisions is challenging because there are no universally accepted weaning criteria or predictive algorithms. Current practice relies heavily on clinical judgment, bedside hemodynamics, and echocardiographic assessment of cardiac recovery. Various hemodynamic and imaging parameters, such as blood pressure stability, improvement in left ventricular ejection fraction (LVEF), right ventricular function, lactate clearance, have been proposed or studied as markers of readiness [111, 112]. However, most evidence comes from small observational studies and heterogeneous protocols, yielding inconsistent criteria across centers. As a result, clinicians often perform trial off-flow weaning tests and use subjective judgment in deciding if a patient can be successfully decannulated. Given the high stakes and complexity, there is a pressing need for objective tools to assist in ECMO weaning decisions.

In this single center cohort study, we use traditional statistical techniques as well as machine learning (ML) techniques to determine factors that predict successful ECMO decannulation to help inform clinical decision-making regarding timing of ECMO decannulation.

Methods:

Study Design and Patients: We conducted a retrospective cohort study of adult patients who received VA-ECMO support for cardiogenic shock at our center between 2015 and 2021. From an initial ECMO registry of 330 cases, we included 213 patients after applying exclusion criteria (e.g., non-weaning scenarios, pediatric cases) (**Figure 26**). For each patient, we collected a comprehensive set of pre-decannulation variables including demographics and comorbidities, clinical status and hemodynamics (heart rate, arterial blood pressures, central venous pressure, use of vasoactive drips), laboratory values (arterial blood gases, lactate, end-organ function labs), and ECMO-related parameters (indication for ECMO, cannulation approach, flow rates, support duration, complications). In addition, transthoracic echocardiography data (within 72 hours prior to decannulation) were reviewed for systolic function (LVEF, right ventricular function grading) and filling pressures (e.g., pulmonary artery diastolic pressure). The outcome of interest was successful decannulation, defined as the patient being weaned off VA-ECMO and surviving at least 30 days post-decannulation without requiring reinstitution of mechanical circulatory support or cardiac transplant. Patients who died on ECMO, or who were initially weaned but then needed a new ECMO, durable LV assist device (LVAD), or transplant within 30 days, were considered decannulation failures.

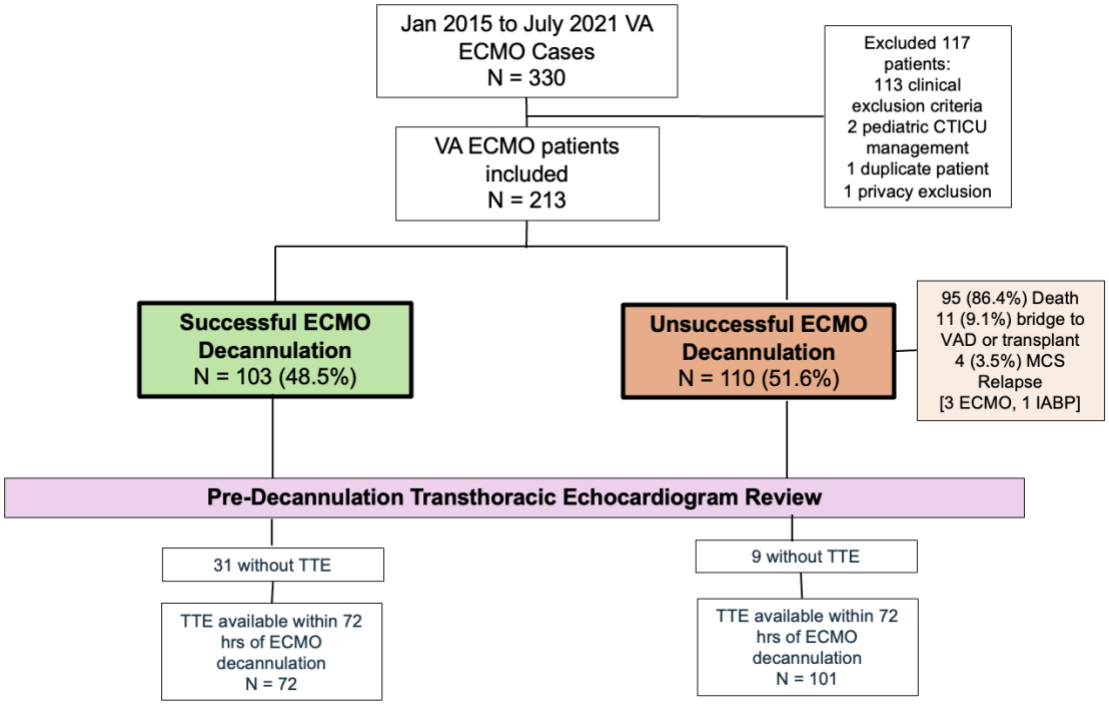

Figure 26: Patient Selection

Statistical Analysis: Descriptive statistics were done with t-test or Mann-U Whitney for continuous variables and categorical variables with Chi-square or Fisher's exact test. Multivariable logistic regression models were constructed to identify independent clinical predictors of successful weaning, using variables selected based on clinical relevance and significant univariate associations.

Machine learning: Three machine learning models, namely random forest (RF), support vector machine (SVM), and XGBoost, were constructed using all collected variables. Model development used an 80% training set and 20% holdout validation set; within training, we employed 5-fold cross-validation to tune hyperparameters and estimate performance stability. Model discrimination was evaluated by the area under the receiver-operating characteristic

curve (AUROC), accuracy, precision and recall. Feature importance was derived from the best performing model.

Results:

Cohort Characteristics and Decannulation Outcome: Among 213 VA-ECMO patients 103 (48.5%) achieved successful decannulation by the 30-day post-ECMO mark, while 110 (51.5%) were decannulation failures (**Figure 26**). **Table 6** provides patient characteristics by ECMO decannulation success. The group that was successfully decannulated was similar compared to the group that was not successfully decannulated with respect to age, sex, several past medical histories (namely, hypertension, diabetes, dyslipidemia, and chronic kidney disease). History of stroke was higher in the group that was unsuccessfully decannulated (10% versus 0%, p = 0.005). Cardiomyopathy type was similar between groups. The group that was successfully decannulated was more likely to have ventricular fibrillation at the time of ECMO cannulation (10% versus 2%, p = 0.03). Compared with those who failed decannulation, patients successfully weaned from VA-ECMO had higher systolic blood pressure (116.0 ± 21.6 vs. 93.4 ± 22.3 mmHg, p<0.001) and greater cardiac output (4.9 ± 1.7 vs. 3.6 ± 1.5 L/min, p<0.001), while diastolic blood pressure was slightly lower (61.1 ± 11.4 vs. 63.5 ± 13.5 mmHg, p=0.046). They demonstrated lower pulmonary artery pressures-systolic (29.2 ± 9.0 vs. 33.7 ± 12.8 mmHg, p=0.03), diastolic (15.5 ± 4.7 vs. 20.2 ± 7.1 mmHg, p<0.001), and mean (21.0 ± 5.9 vs. 25.0 ± 9.1 mmHg, p=0.007). Markers of perfusion also differed: lactate was markedly lower (15.2 ± 18.6 vs. 49.5 ± 58.3 mg/dL, p<0.001) and mixed venous O_2 was higher (85.0 ± 14.5 vs. 64.7 ± 34.7 mmHg, p<0.001) in the success group. Renal support was less common with success (dialysis 18% vs. 52%, p=0.03). Cardiac function favored success as well, with a higher LVEF (35.5 ± 17.4% vs. 25.9 ± 17.4%, p=0.05) and less frequent severe RV systolic dysfunction (9% vs. 27%, p=0.002).

Characteristic	Successful Decannulation (n = 103)	Unsuccessful Decannulation (n = 110)	p-value
Age at admission, years, mean (SD)	56.2 (14.6)	53.1 (16.2)	0.23
Sex, Female, n (%)	36 (35)	25 (26)	0.07
Non-cardiac past medical history, n (%)			
Hypertension	40 (39)	38 (40)	0.82
Diabetes	33 (32)	25 (26)	0.64
Dyslipidemia	27 (26)	20 (21)	0.45
Chronic kidney disease	13 (13)	12 (12)	0.86
Stroke*	0 (0)	10 (10)	0.005*
Cardiomyopathy type, n (%)			
Ischemic Cardiomyopathy	17 (17)	26 (27)	0.06
Non-ischemic cardiomyopathy	38 (37)	31 (32)	0.62
None	48 (47)	36 (38)	0.168
History of valve surgery, n (%)	5 (5)	7 (7)	0.42
Rhythm at time of ECMO cannulation, n (%)			
Normal sinus rhythm	67 (65)	62 (65)	1.00
Atrial fibrillation/Atrial flutter	16 (16)	21 (22)	0.50
Ventricular tachycardia	15 (15)	19 (20)	0.39
Ventricular fibrillation	10 (10)	2 (2)	0.03*
ECMO flow rate, L/min, mean (SD)	2.2 (1.1)	3.5 (1.2)	<0.001*
Additional Mechanical Circulatory Support, n (%)			
IABP	10 (10)	8 (8)	1.00
Impella	16 (16)	14 (15)	1.00
ECMO duration (hours), mean (SD)	108.3 (82.3)	127.5 (94.0)	0.05
ICU days, mean (SD)	28.3 (27.1)	21.4 (30.2)	0.03
Total hospital days, mean (SD)	36.8 (33.6)	24.7 (33.7)	0.02*
Heart rate, bpm, mean (SD)	91.6 (17.4)	91.0 (16.0)	1.00
Systolic blood pressure, mmHg, mean (SD)	116.0 (21.6)	93.4 (22.3)	<0.001*
Diastolic blood pressure, mmHg, mean (SD)	61.1 (11.4)	63.5 (13.5)	0.046*
Number of vasoactive agents, mean (SD)	1.7 (1.0)	1.9 (1.2)	0.29
Central venous pressure, mmHg, mean (SD)	9.9 (4.0)	10.7 (5.6)	0.98
PA Systolic Pressure, mmHg, mean (SD)	29.2 (9.0)	33.7 (12.8)	0.03*
PA Diastolic Pressure, mmHg, mean (SD)	15.5 (4.7)	20.2 (7.1)	<0.001*
Mean PA pressure, mmHg, mean (SD)	21.0 (5.9)	25.0 (9.1)	0.007*
Cardiac output, L/min, mean (SD)	4.9 (1.7)	3.6 (1.5)	<0.001*
Creatinine, mg/dL, mean (SD)	1.5 (0.9)	1.4 (1.1)	0.67
Dialysis, n (%), mean (SD)	19 (18)	50 (52)	0.03*
Lactate, mg/dL, mean (SD)	15.2 (18.6)	49.5 (58.3)	<0.001*

Mixed venous O2, mmHg, mean (SD)	85.0 (14.5)	64.7 (34.7)	<0.001*
LVEF by echocardiography, %, mean (SD)	35.5 (17.4)	25.9 (17.4)	0.05
RV systolic function by echo, n (%)			
Normal	30 (29)	15 (16)	0.05
Mildly reduced	8 (8)	13 (14)	0.18
Moderately reduced	13 (13)	20 (21)	0.15
Severely reduced	9 (9)	26 (27)	0.002*

Table 6: Patient Characteristics. Abbreviations: SD: standard deviation; n = number; ECMO = extra-corporeal membrane oxygenation; IABP = intra-aortic balloon pump; ICU = intensive care unit; PA = pulmonary artery; O2 = oxygen; LVEF = left ventricular ejection fraction; RV = right ventricular. * denotes statistical significance.

Multivariate logistic regression analysis: In a multivariable logistic regression of selected demographic and cardiovascular risk factors with successful decannulation as the outcome, end-stage renal disease (ESRD) was the only independent predictor, associated with markedly lower odds of success (OR 0.22**,** 95% CI 0.03–0.95). All other covariates were not significant: substance abuse OR 4.51 (0.54–94.79), obesity OR 3.32 (0.37–73.10), lung disease OR 2.46 (0.47–19.25), female sex OR 1.75 (0.94–3.31), diabetes OR 1.23 (0.64–2.38), hyperlipidemia OR 1.15 (0.51–2.60), CKD OR 1.09 (0.45–2.66), age per year OR 1.01 (0.99–1.04), hypertension OR 1.01 (0.48–2.14), and pulmonary hypertension OR 0.51 (0.04–5.19) (**Figure 27)**.

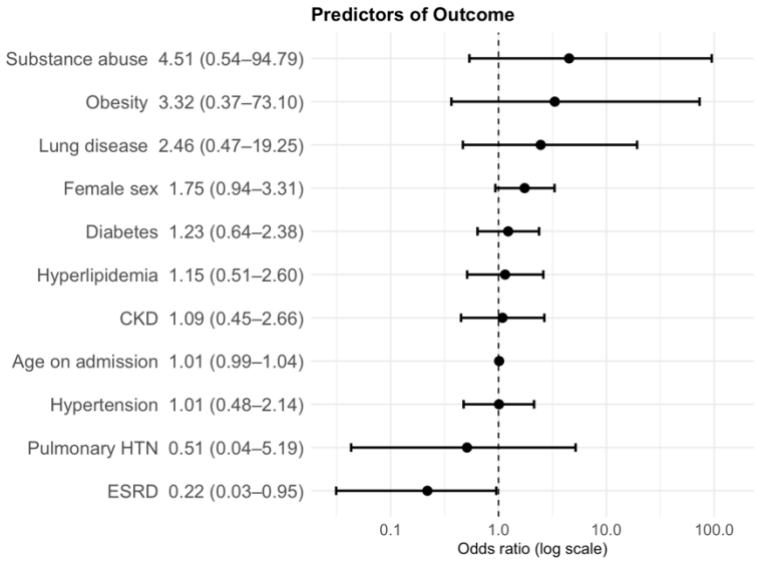

Figure 27: Multivariate logistic regression of selected demographic and cardiovascular risk factors predicting successful ECMO decannulation

In the multivariable model of ECMO characteristics for successful decannulation, two variables were independently associated with outcome. Peripheral cannulation was linked to higher odds of success (OR 5.44, 95% CI 1.19–29.40). In contrast, higher ECMO flow rate at the time of assessment was associated with lower odds of success (OR 0.36 per 1 L/min increase, 95% CI 0.25–0.49). All other covariates were not significant: heart transplant indication OR 6.05 (0.16–249.80), thrombosis complication OR 1.06 (0.30–4.06), ECMO duration OR 0.99 (0.99-1.00), additional MCS-Impella OR 0.86 (0.33-2.28), bleeding complication OR 0.70 (0.34-1.44), indication cardiogenic shock OR 0.63 (0.02-19.72), additional MCS-IABP OR 0.56 (0.14-2.21), indication cardiac arrest OR 0.50 (0.02-16.14), and infection complication OR 0.43 (0.10-1.69) (**Figure 28**).

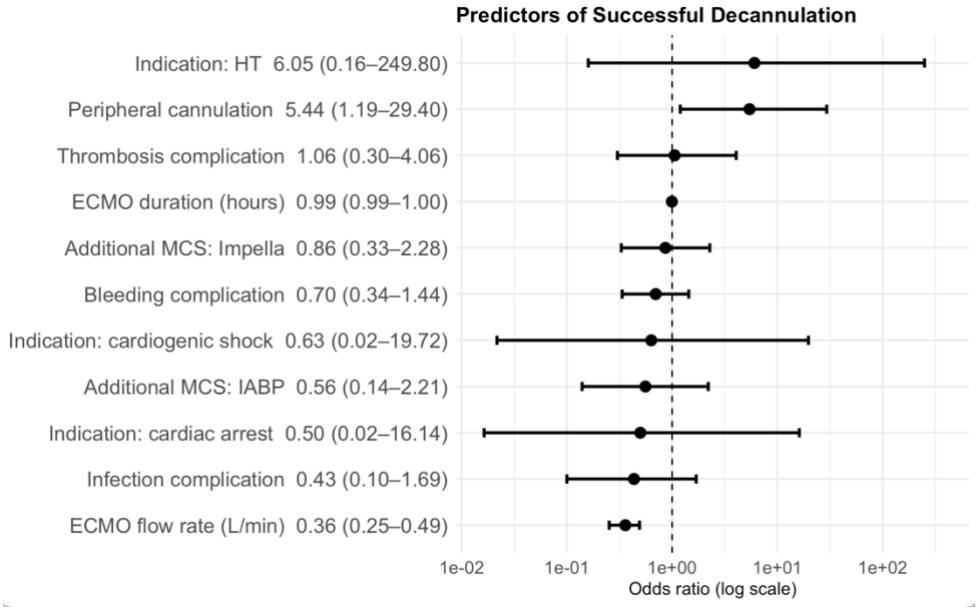

Figure 28: Multivariate logistic regression of ECMO variables predicting successful ECMO decannulation. Abbreviations: HT = heart transplant; ECMO = extra-corporeal membrane oxygenation; MCS = mechanical circulatory support; IABP = intra-aortic balloon pump

In a multivariable model of hemodynamic predictors, higher mixed venous O_2 independently predicted successful decannulation (OR 1.04, 95% CI 1.01-1.06), as did higher central venous pressure (OR 1.22, 95% CI 1.01-1.52). Higher pulmonary artery diastolic pressure was associated with lower odds of success (OR 0.67, 95% CI 0.48-0.87). Left ventricular EF showed a borderline positive association (OR 1.04, 95% CI 1.00-1.09). Cardiac output (OR 1.63, 95% CI 0.96-3.14) and pulmonary artery systolic pressure (OR 1.04, 95% CI 0.94-1.16) were not significant (**Figure 29**).

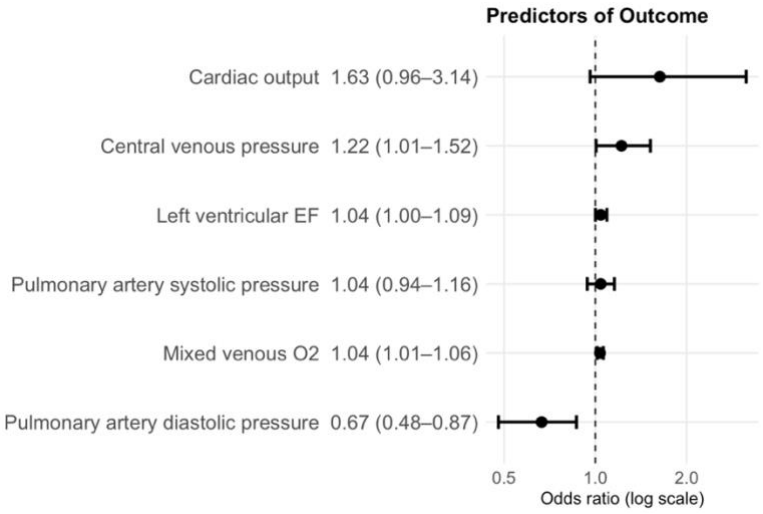

Figure 29: Multivariate logistic regression of hemodynamic variables predicting successful ECMO decannulation.

Machine learning analysis: The machine learning models overall achieved good discriminative ability for predicting decannulation outcome. In the validation set, the random forest performed best (accuracy 0.85, precision 0.90, recall 0.91, AUROC 0.94) (**Figure 30**). The support vector machine was similar but slightly inferior (accuracy 0.78, precision 0.81, recall 0.77, AUROC 0.88). XGBoost

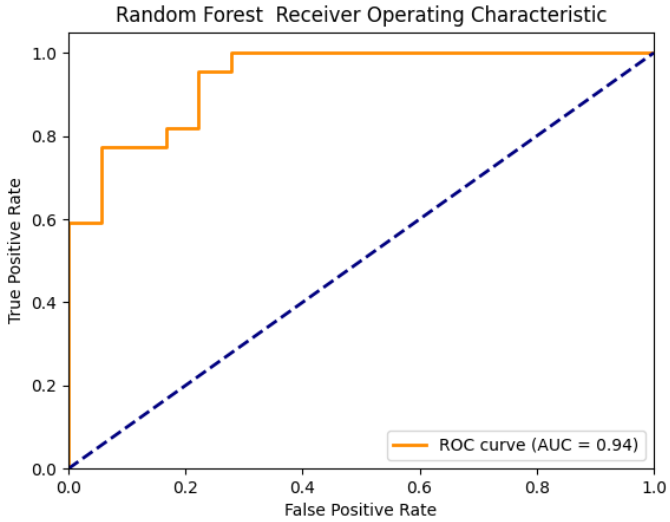

Figure 30: AUROC for Random Forest Model. Abbreviations: AUROC = area under the receiver operating characteristic.

showed similar threshold-level accuracy, precision, recall (0.85, 0.86, 0.86, respectively) but poor rank discrimination (AUROC 0.33) (**Table 7**). Accordingly, the random forest was selected for interpretation and reporting.

Model	Accuracy	Precision	Recall	AUROC
XGBoost	0.85	0.86	0.86	0.33
Support Vector Machine	0.78	0.81	0.77	0.88
Random Forest	0.85	0.9	0.91	0.94

Table 7: Model performance for machine learning models. Abbreviations: AUROC = area under the receiver operating characteristic.

In the best-performing model (random forest; AUROC 0.94), mixed venous oxygen saturation (MvO_2) was the dominant predictor of successful decannulation, clearly outranking all other variables. The next most informative features were systolic blood pressure, ECMO flow rate, and pulmonary artery diastolic pressure (**Figure 31**).

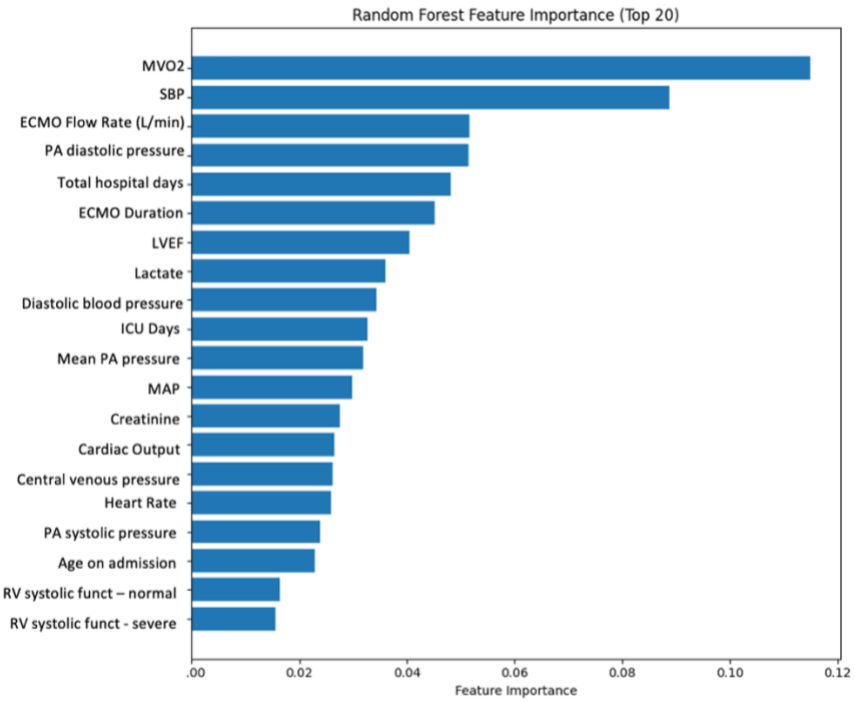

Figure 31: Random forest feature importance for predicting successful VA-ECMO decannulation. Abbreviations: MvO_2 = mixed venous oxygen saturation; SBP = systolic blood pressure; PA = pulmonary artery; MAP = mean arterial pressure = LVEF, left ventricular ejection fraction; RV = right ventricular.

Discussion

Despite its life-saving role, VA-ECMO is still associated with persistently high in-hospital mortality (~40-60%) [111, 112]. Therefore, in this single center retrospective study, we sought to develop objective, data-driven tools to identify which patients can safely be decannulated. Consistent with prior literature, in our study, ~52% of patients did not survive past 30 days after ECMO decannulation without death or relapse to MCS. We found several key factors that predict successful decannulation from ECMO, namely that patients do not require dialysis during ECMO, those with peripheral (versus central) cannulation, lower ECMO flow rates at weaning, higher mixed venous oxygen saturation (MvO_2), and lower pulmonary artery diastolic pressure (PADP) were significantly more likely to survive ECMO decannulation. The machine learning model incorporating these and other electronic health record (EHR) variables achieved high discriminative performance, exceeding that of traditional risk scores.

Our analysis identified several clinical risk factors for post-ECMO mortality that align with or add to predictors reported in previous studies. Consistent with prior work, the need for renal replacement therapy emerged as a strong predictor of mortality. Patients on ECMO who require dialysis have long been recognized as a high-risk subgroup, reflecting severe acute kidney injury and multi-organ failure; indeed, dialysis during ECMO has been associated with roughly a three-fold higher odds of mortality in prior series [110]. Similarly, the mode of ECMO cannulation was significant: patients cannulated centrally (e.g., direct cardiac cannulation) had worse outcomes compared to those with peripheral cannulation. This mirrors earlier findings that central cannulation (often used in post-cardiotomy or surgical ECMO) is associated with higher post-decannulation mortality [113]. Notably, lower ECMO flow at the time of weaning was associated with higher mortality. Although this finding may seem counterintuitive, it likely reflects instances in which flow was intentionally minimized for non-recovery reasons (e.g., impending

circuit removal or complication mitigation), rather than true physiologic readiness for decannulation.

High mixed venous oxygen saturation (MvO_2) at the time of weaning was associated with successful ECMO decannulation in a multivariate logistic regression. In addition, our machine-learning analysis ranked mixed venous oxygen saturation (MvO_2) as the dominant predictor of success. This aligns with physiology: a higher MvO_2 indicates that global oxygen delivery meets or exceeds metabolic demand, conditions under which separation from VA-ECMO is more likely to be tolerated. High MvO_2 at the time of weaning has indeed been associated with successful VA-ECMO decannulation in recent studies. For example, Hsu et al. observed that patients who survived after ECMO removal had significantly higher pre-weaning MvO_2 than those who died post-weaning [114]. In addition, Naruke *et al.* reported that patients with sustained $MvO_2 < 75\%$ during VA-ECMO had a higher rate of weaning success (88% vs. 47% $p < 0.01$) compared to patients that experienced periods of $MvO_2 > 75\%$ [115].

This study also used machine learning models to predict successful decannulation. Our ML models demonstrated improved performance compared to existing ECMO risk scores such as the SAVE and ECMO-ACCEPTS models. The SAVE score (Survival After Veno-arterial ECMO), derived from an international registry of ECMO cases, uses 11 pre-ECMO variables and had an AUROC of 0.68 [116]. The more recent ECMO-ACCEPTS score included 10 variables (e.g., age, diagnosis, organ failures) from a large national dataset and showed an AUROC of 0.64 [117]. The improved performance of our model likely represents the data fidelity and completeness inherent in EHR-level databases. Our dataset had minimal missing information and did not require surrogate coding due to manual chart abstraction of the variables. This data-driven advantage is reflected in the high performance of our model compared to those derived from registry data. Our model's recognition of MvO_2 as a critical

feature validates its clinical significance and suggests it could be a target for future monitoring protocols or even therapeutic intervention (e.g., optimizing flow or transfusion to ensure adequate oxygen utilization).

This study has several limitations. First, it is a single-center retrospective analysis, which may limit the generalizability of our findings. Practices surrounding patient selection, cannulation technique, management during ECMO, and weaning criteria can vary between centers; our model is inherently influenced by the protocols and patient population of our institution. External validation is needed to ensure the risk factors and model performance hold in different settings. Second, as a retrospective study, it is subject to bias in data recording and unmeasured confounders. Third, our cohort did not exclude palliative decannulations (withdrawal of ECMO for goals-of-care reasons). Accordingly, some patients were decannulated not because of physiologic recovery but as part of comfort-focused care. Inclusion of these non-survivable removals-where death is the anticipated outcome-likely inflates post-decannulation mortality estimates and may bias the model toward identifying end-of-life decisions rather than true readiness for separation. Prior studies have distinguished planned recovery weans from palliative withdrawals [118]; future analyses should adopt similar stratification to improve interpretability and generalizability.

In summary, we identified readily measurable predictors of successful VA-ECMO decannulation: absence of dialysis, peripheral rather than central cannulation, lower pump flow at weaning, higher MvO_2, and lower pulmonary artery diastolic pressure. In addition, we developed an EHR-based machine-learning model that outperformed established scores (SAVE, ECMO-ACCEPTS) and pinpointed MvO_2 as a dominant predictor of ECMO wean success. These findings support integrating physiology-anchored metrics and ML decision

support into decannulation workflows and warrant external validation and prospective testing across centers.

Chapter 6

Conclusion

This dissertation explored the integration of traditional statistical methods and machine learning (ML) techniques to enhance clinical prediction across three critical clinical scenarios: major adverse cardiovascular events (MACE) associated with immune checkpoint inhibitor (ICI) therapy (Project 1, “Immunotox”), new-onset left ventricular systolic dysfunction (LVSD) after orthotopic liver transplantation (Project 2, “Liver Transplant”), and successful decannulation from extracorporeal membrane oxygenation (Project 3, “ECMO”) (**Table 8**).

In Project 1 (“Immunotox”), our study identified key clinical predictors associated with incidence and mortality from MACE in patients undergoing ICI therapy. Importantly, the integration of an ML approach revealed a novel risk factor previously unrecognized by traditional statistical analysis. This novel predictor emerged as the most robust and distinctive finding of our analysis, underscoring the critical value ML methods can add in identifying previously overlooked clinical variables. This finding not only has implications for patient risk stratification but also sets a new direction for future research focused on targeted clinical management strategies in this patient population.

In Project 2 (“Liver Transplant”), evaluating LVSD after liver transplantation, we successfully identified multiple clinical risk factors predictive of post-transplant cardiac dysfunction. While traditional statistical methods effectively identified single-variable predictors, the application of ML unveiled complex interactions among echocardiographic variables. These multidimensional interactions, missed by conventional statistics, provided a deeper and more nuanced understanding of the conditions predisposing to LVSD. Consequently, ML facilitated a more sophisticated risk assessment, potentially enhancing preoperative screening and postoperative management protocols for liver transplant recipients.

In Project 3 (“ECMO”), the analysis of successful ECMO decannulation similarly benefitted significantly from the ML approach. Although traditional statistical analyses

highlighted several factors associated with successful decannulation, ML was uniquely capable of pinpointing a single dominant predictor with exceptional clarity. This singular variable, elevated by ML-driven feature importance analysis, provides clinicians with a streamlined focus for guiding clinical decision-making during ECMO management, ultimately optimizing patient outcomes.

Dataset	Clinical insight	Additive value of ML model
Project 1: Immunotox	Identified incidence of, risk factors for, and mortality associated with **major adverse cardiovascular events (MACE)** in patients undergoing **ICI therapy**	ML identified a **novel risk factor** that led to further analysis and became the strongest feature of the paper
Project 2: Liver Transplant	Identified incidence of, risk factors for and mortality associated with **left ventricular systolic dysfunction (LVSD)** after **liver transplant**	ML captured **complex interactions** across variables missed by traditional statistics
Project 3: ECMO	Identified factors that predict **successful decannulation** from **extracorporeal membrane oxygenation (ECMO)**	ML pinpointed **single dominant predictor**

Table 8: Conceptual Framework for Dissertation

In undertaking an informatics project of this scale, several lessons emerged. Data source critically influences accuracy: EHR-level, chart-verified data yielded high-fidelity variables with low missingness and likely contributed to the superior performance of our ECMO models. Most effort resided in data collection, cleaning, linkage, and precise variable definition, particularly in Project 1, where hundreds of variables were defined. Logistic regression performance degraded with low-incidence predictors and multicollinearity, necessitating variable removal in some analyses (e.g., chronic obstructive pulmonary disease and obstructive sleep apnea in the Liver Transplant project). Finally, ML and traditional statistics were complementary. ML added value by discovering novel predictors (Immunotox), elucidating complex interactions (Liver Transplant), and clarifying clinical priorities (ECMO), while statistical models provided transparent inference. Future work should externally validate these ML models, prospectively evaluate ML-informed workflows, and extend this *combined analytic strategy* to other complex

prediction problems. Strategically integrating interpretable ML with rigorous statistical baselines has the potential to advance precision medicine and improve patient outcomes.

Bibliography

1. Song X, L.X., Liu F, Wang C, *Comparison of machine learning and logistic regression models in predicting acute kidney injury: a systematic review and meta-analysis*. Int J Med Inform, 2021. **151**: p. 104484.
2. Khera R, H.J., Hurley NC, et al., *Use of Machine Learning Models to Predict Death After Acute Myocardial Infarction*. JAMA Cardiology, 2021. **6**(6): p. 633-641.
3. Wu H, L.B., Ji T, et al, *Comparison between traditional logistic regression and machine learning for predicting mortality in adult sepsis patients*. Front Med (Lausanne), 2024. **11**: p. 1496869.
4. Gardner RM, O.J., Steen EB, Munger BS, Holmes JH, Williamson JJ, Detmer DE; AMIA Board of Directors. , *Core content for the subspecialty of clinical informatics*. . J Am Med Inform Assoc, 2009. **16**(2): p. 153-7.
5. Nakao, T., Natarajan, P. , *Clonal hematopoiesis, multi-omics and coronary artery disease*. Nat Cardiovasc Res, 2022. **1**: p. 965-967.
6. McSweeney KM, B.W., Alterovitz WL, Zhang B., *Transcriptomic profiling reveals p53 as a key regulator of doxorubicin-induced cardiotoxicity*. Cell Death Discov., 2019 **5**(102).
7. Jin, N., George, T.L., Otterson, G.A. et al., *Advances in epigenetic therapeutics with focus on solid tumors*. Clin Epigenet, 2021. **13**(83).

8. Mörth, C., Sabaa, A.A., Freyhult, E. et al. , *Plasma proteome profiling of cardiotoxicity in patients with diffuse large B-cell lymphoma*. . Cardio-Oncology, 2021. **7**(6).

9. Paulsen JA, P.T., Carter SJ, Liu N, Kumar R, Hyndman L, et al, *ut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors*. Support Care Cancer, 2017. **25**: p. 1563-70.

10. *Surveillance, Epidemiology, and End Results (SEER) Program (www.seer.cancer.gov) SEER*Stat Database: Incidence - SEER Research Data, 8 Registries, Nov 2021 Sub (1975-2020) - Linked To County Attributes - Time Dependent (1990-2020) Income/Rurality, 1969-2020 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2023, based on the November 2022 submission*.

11. Chen W, X.F., Mccarthy DP, Reynolds KL, Lee M, Coleman KJ, Getahun D, Koebnick C, Jacobsen SJ. , *Research data warehouse: using electronic health records to conduct population-based observational studies*. . JAMIA Open., 2023. **6**(2).

12. Potter D, B.R., Kolacevski A, et al, *Development of CancerLinQ, a health information learning platform from multiple electronic health record systems to support improved quality of care*. JCO Clin Cancer Inform, 2020(4): p. 929-937.

13. Fenioux, C., Abbar, B., Boussouar, S. et al., *Thymus alterations and susceptibility to immune checkpoint inhibitor myocarditis*. Nat Med, 2023. **29**.

14. Arco J. Teske, R.M., Teresa López-Fernández, Ana Barac, Sherry Ann Brown, Anita Deswal, Tomas G. Neilan, Sarju Ganatra, Husam Abdel Qadir, Venu Menon, Aaron L. Sverdlov, Richard K. Cheng, Silvia Makhoul, Arjun K. Ghosh, Sebastian Szmit, Vlad Zaha, Daniel Addison, Lili Zhang, Joerg Herrmann, Jun H. Chong, Vivek Agarwala, Zaza Iakobishvili, Patricia Guerrero, Eric H. Yang, Monika Leja, Nausheen Akhter, Avirup Guha, Tochukwu M. Okwuosa, Carolina Carvalho Silva, Patrick Collier, Jeanne DeCara, Brenton Bauer, Carrie E. Lenneman and Diego Sadler, *Global Cardio Oncology Registry (G-COR): Registry Design, Primary Objectives, and Future Perspectives of a Multicenter Global Initiative*. Circulation: Cardiovascular Quality and Outcomes, 2023. **16**(10).

15. ; Available from: https://www.who.int/teams/regulation-prequalification/regulation-and-safety/pharmacovigilance.

16. Salem JE, N.L., Moslehi JJ, Ederhy S, Lebrun-Vignes B, Roden DM, Funck-Brentano C, Gougis P., *Anticancer drug-induced life-threatening ventricular arrhythmias: a World Health Organization pharmacovigilance study*. . Eur Heart J., 2021. **42**(38): p. 3915-3928.

17. Waliany S, C.-J.J., Riaz F, Myall N, Zhu H, Witteles R, Neal JW, *Pharmacovigilance Analysis of Heart Failure Associated With Anti-HER2 Monotherapies and Combination Regimens for Cancer*. J Am Coll Cardiol CardioOnc, 2023. **5**(1): p. 85-98.

18. Stergiopoulos S, B.C., Felix T, Grampp G, Getz KA., *A Survey of Adverse Event Reporting Practices Among US Healthcare Professionals*. . Drug Saf. , 2016. **39**(11): p. 1117-11127.

19. Osterman TJ, T.M., Miller RS, *mproving cancer data interoperability: The promise of the minimal common oncology data elements (mCODE) initiative*. JCO Clin Cancer Inform, 2020(4): p. 993-1001.

20. Theodos K, S.S., *Health Information Privacy Laws in the Digital Age: HIPAA Doesn't Apply*. Perspect Health Inf Manag, 2020. **18**(Winter): p. 1l.

21. Erlich Y , N.A., *Routes for breaching and protecting genetic privacy*. Nat Rev Genet 2014(15): p. 409-21.

22. Shawn M. Sweeney, H.K.H., Natalie Abrams, Stacey J. Adam, Sara Brenner, Dana E. Connors, Gerard J. Davis, Louis Fiore, Susan H. Gawel, Robert L. Grossman, Sean E. Hanlon, Karl Hsu, Gary J. Kelloff, Ilan R. Kirsch, Bill Louv, Deven McGraw, Frank Meng, Daniel Milgram, Robert S. Miller, Emily Morgan, Lata Mukundan, Thomas O'Brien, Paul Robbins, Eric H. Rubin, Wendy S. Rubinstein, Liz Salmi, Teilo Schaller, George Shi, Caroline C. Sigman, Sudhir Srivastava, *Challenges to Using Big Data in Cancer*. Cancer Res, 2023. **83**(8): p. 1175-1182.

23. Galvin HK, D.P., *Developments in Privacy and Data Ownership in Mobile Health Technologies, 2016-2019*. Yearb Med Inform, 2020. **29**: p. 32-43.

24. Zubiri L, M.G., Mooradian MJ, Cohen J, Durbin SM, Petrillo L, Boland GM, Juric D, Dougan M, Thomas MF, Faje AT, Rengarajan M, Guidon AC, Chen ST, Okin D, Medoff

BD, Nasrallah M, Kohler MJ, Schoenfeld SR, Karp-Leaf RS, Sise ME, Neilan TG, Zlotoff DA, Farmer JR, Bardia A, Sullivan RJ, Blum SM, Semenov YR, Villani AC, Reynolds KL., *Effect of a multidisciplinary Severe Immunotherapy Complications Service on outcomes for patients receiving immune checkpoint inhibitor therapy for cancer*. . J Immunother Cancer., 2021. **9**.

25. Abu-Shawer O, S.P., Yenulevich E, Brito A, Ni J, Abdulnour RE, Grover S, Manos M, Bowling P, LeBoeuf NR, Ott P, Stephen Hodi F, Jacobson J, Rahma O. , *Novel platform leveraging electronic medical record (EMR) to triage patients admitted with high-grade immune-related adverse events (irAEs) to the immune-toxicity (ITOX) service*. J Immunother Cancer., 2020. **8**(2).

26. Chandra A, P.S., Pandey A, Basit M, Kannan V, Sara EJ, Das SR, Lee SJC, Haley B, Willett DL, Zaha VG. , *Electronic Health Records-Based Cardio-Oncology Registry for Care Gap Identification and Pragmatic Research: Procedure and Observational Study*. . JMIR Cardio, 2021. **5**(1).

27. Agarwala V, K.S., Singal G, O'Connell C, Kuk D, Li G, et al., *Real-world evidence in support of precision medicine: clinico-genomic cancer data as a case study*. Health Affairs. , 2018(37): p. 765-72.

28. Prasad P, B., Mary, Asemota D, Elsayed R, Addison D, Brown S-A, *Cardio-oncology preventive care: racial and ethnic disparities*. . Curr Cardiovasc Risk Rep, 2020(14): p. 18.

29. Ohman RE, Y.E., Abel ML., *Inequity in Cardio-Oncology: Identifying Disparities in Cardiotoxicity and Links to Cardiac and Cancer Outcomes.* Am Heart Assoc. , 2021. **10**(24).

30. Brown SA, S.R., Osinski K, Zhang J, Blessing J, Cheng F, Hamid A, Berman G, Lee K, BagheriMohamadiPour M, Lal JC, Kothari AN, Caraballo P, Noseworthy P, Johnson RH, Hansen K, Sun LY, Crotty B, Cheng YC, Olson J, *Cardio-Oncology Artificial Intelligence Informatics & Precision (CAIP) Research Team Investigators*. *Establishing an interdisciplinary research team for cardio-oncology artificial intelligence informatics precision and health equity.* Am Heart J Plus, 2022: p. 100094.

31. Bates, S. *NIH awards $50.3 million for "multi-omics" research on human health and disease*. 2023; Available from: https://www.nih.gov/news-events/news-releases/nih-awards-503-million-multi-omics-research-human-health-disease#:~:text=Multi%2Domics%20refers%20to%20a,%2C%20transcriptomics%2C%20proteomics%20and%20metabolomics.

32. Brown SA, B.C., Martinez HR, Marshall CH, Olaye IM, Guha A, Cho D, Bailey A, Bergom C, Bansal N, Bauer B, Cheng RK., *Bridging the gap to advance the care of individuals with cancer: collaboration and partnership in the Cardiology Oncology Innovation Network (COIN).* . Cardiooncology, 2022. **8**(1): p. 2.

33. Upshaw JN, N.J., Rodday AM, et al., *Association of Preexisting Heart Failure With Outcomes in Older Patients With Diffuse Large B-Cell Lymphoma.* JAMA Cardiol., 2023. **8**(5): p. 453-461.

34. Greenlee, H., Iribarren, C., Rana, J. S., Cheng, R., Nguyen-Huynh, M., Rillamas-Sun, E., Shi, Z., Laurent, C. A., Lee, V. S., Roh, J. M., Santiago-Torres, M., Shen, H., Hershman, D. L., Kushi, L. H., Neugebauer, R., & Kwan, M. L. , *Risk of Cardiovascular Disease in Women With and Without Breast Cancer: The Pathways Heart Study.* . Journal of Clinical Oncology : Official Journal of the American Society of Clinical Oncology, 2022. **40**(15): p. 1647-1658.

35. Francis, S.A., Cheng, S., Arteaga, C. L., & Moslehi, J. , *Heart Failure and Breast Cancer Therapies: Moving Towards Personalized Risk Assessment.* Journal of the American Heart Association, 2014. **3**.

36. Zhou, Y., Hou, Y., Hussain, M., Brown, S.-A., Budd, T., Tang, W. H. Wilson, Abraham, J., Xu, B., Shah, C., Moudgil, R., Popovic, Z., Cho, L., Kanj, M., Watson, C., Griffin, B., Chung, M. K., Kapadia, S., Svensson, L., Collier, P., & Cheng, F. , *Machine Learning-Based Risk Assessment for Cancer Therapy-Related Cardiac Dysfunction in 4300 Longitudinal Oncology Patients.* Journal of the American Heart Association, 2020. **9**(23).

37. Chaix, M.A., Parmar, N., Kinnear, C., Lafreniere-Roula, M., Akinrinade, O., Yao, R., & Miron, A. , *Machine Learning Identifies Clinical and Genetic Factors Associated With*

Anthracycline Cardiotoxicity in Pediatric Cancer Survivors. J Am Coll Cardiol CardioOnc, 2020. **2**(5): p. 690-706.

38. Castrillon JA, E.C., Cheng F, *Pharmacogenomics for immunotherapy and immune-related cardiotoxicity*. Hum Mol Genet, 2020. **29**(R2): p. R186-R196.

39. Berman AN, B.D., Ginder C, Hulme OL, Marcusa D, Leiva O, Wu WY, Cardin N, Hainer J, Bhatt DL, Di Carli MF, Turchin A, Blankstein R. , *Natural language processing for the assessment of cardiovascular disease comorbidities: The cardio-Canary comorbidity project*. . Clin Cardiol., 2021. **44**(9): p. 1296-1304.

40. Rajkomar A, K.A., Chen K, et al., *Automatically Charting Symptoms From Patient-Physician Conversations Using Machine Learning*. JAMA Intern Med, 2019. **179**(6): p. 836-838.

41. Prifti E, F.A., Davogustto G, Pulini A, Denjoy I, Funck-Brentano C, et al., *Deep learning analysis of electrocardiogram for risk prediction of drug-induced arrhythmias and diagnosis of long QT syndrome*. Eur Heart J., 2021(42): p. 3948-61.

42. ao, X., Rushlow, D.R., Inselman, J.W. et al. , *Artificial intelligence-enabled electrocardiograms for identification of patients with low ejection fraction: a pragmatic, randomized clinical trial*. . Nat Med, 2021. **27**: p. 815-819.

43. Duffy G, C.P., Yuan N, He B, Kwan AC, Shun-Shin MJ, Alexander KM, Ebinger J, Lungren MP, Rader F, Liang DH, Schnittger I, Ashley EA, Zou JY, Patel J, Witteles R, Cheng S, Ouyang D., *High-Throughput Precision Phenotyping of Left Ventricular*

Hypertrophy With Cardiovascular Deep Learning. JAMA Cardiol., 2022. **7**(4): p. 386-395.

44. Solenov D, B.J., Scherrer JF., *The Potential of Quantum Computing and Machine Learning to Advance Clinical Research and Change the Practice of Medicine*. Mo Med, 2018. **115**(5): p. 463-467.

45. Haleem, A., Javaid, M., Singh, R.P., and Suman, R., *elemedicine for healthcare: Capabilities, features, barriers, and applications*. . Sens Int, 2021. **2**.

46. Yu, K.-H., Beam, A.L., and Kohane, I.S., *Artificial intelligence in healthcare*. Nat Biomed Eng, 2018. **2**: p. 719-731.

47. Ivanov, O., Wolf, L., Brecher, D., Lewis, E., Masek, K., Montgomery, K., Andrieiev, Y., McLaughlin, M., Liu, S., Dunne, R., et al. , *Improving ED Emergency Severity Index Acuity Assignment Using Machine Learning and Clinical Natural Language Processing*. J Emerg Nurs, 2021. **47**: p. 265-278.

48. Abernethy, A., Adams, L., Barrett, M., Bechtel, C., Brennan, P., Butte, A., Faulkner, J., Fontaine, E., Friedhoff, S., Halamka, J., et al. , *The Promise of Digital Health: Then, Now, and the Future*. NAM Perspect, 2022: p. 10.31478/202206e. 10.31478/202206e.

49. Saeed, S.A., and Masters, R.M., *Disparities in Health Care and the Digital Divide*. Curr Psychiatry Rep, 2021. **23**(61): p. 10.1007/s11920-021-01274-4.

50. Tanner, C., Gans, D., White, J., Nath, R., and Pohl, J. , *Electronic health records and patient safety: co-occurrence of early EHR implementation with patient safety practices in primary care settings.* Appl Clin Inform, 2015. **6**: p. 136-147.

51. Giordano, C., Brennan, M., Mohamed, B., Rashidi, P., Modave, F., and Tighe, P. , *Accessing Artificial Intelligence for Clinical Decision-Making.* Front Digit Health, 2021. **3**: p. 645232.

52. Chesser, A., Burke, A., Reyes, J., and Rohrberg, T. , *Navigating the digital divide: A systematic review of eHealth literacy in underserved populations in the United States.* Informatics for Health and Social Care, 2016. **41**: p. 1-19.

53. Chang, B.L., Bakken, S., Brown, S.S., Houston, T.K., Kreps, G.L., Kukafka, R., Safran, C., and Stavri, P.Z. , *Bridging the Digital Divide: Reaching Vulnerable Populations.* Journal of the American Medical Informatics Association, 2004. **11**: p. 448-457.

54. Wolchok, J.D., Chiarion-Sileni, V., Rutkowski, P., Cowey, C.L., Schadendorf, D., Wagstaff, J., Queirolo, P., Dummer, R., Butler, M.O., Hill, A.G., Postow, M.A., Gaudy-Marqueste, C., Medina, T., Lao, C.D., Walker, J., Márquez-Rodas, I., Haanen, J.B.A.G., Guidoboni, M., Maio, M., Schöffski, P., Carlino, M.S., Sandhu, S., Lebbé, C., Ascierto, P.A., Long, G.V., Ritchings, C., Nassar, A., Askelson, M., Benito, M.P., Wang, W., Hodi, F.S., Larkin, J., *Final, 10-Year Outcomes with Nivolumab plus Ipilimumab in Advanced Melanoma.* . New England Journal of Medicine, 2025. **392**: p. 11-22.

55. Reck M, R.-A.D., Robinson AG, Hui R, Csőszi T, Fülöp A, Gottfried M, Peled N, Tafreshi A, Cuffe S, O'Brien M, Rao S, Hotta K, Leiby MA, Lubiniecki GM, Shentu Y, Rangwala R, Brahmer JR; KEYNOTE-024 Investigators, *Pembrolizumab versus Chemotherapy for PD-L1-Positive Non-Small-Cell Lung Cancer*. N Engl J Med, 2016. **375**(19): p. 1823-1833.

56. Rini, B.I., Plimack, E.R., Stus, V., Gafanov, R., Hawkins, R., Nosov, D., Pouliot, F., Alekseev, B., Soulières, D., Melichar, B., Vynnychenko, I., Kryzhanivska, A., Bondarenko, I., Azevedo, S.J., Borchiellini, D., Szczylik, C., Markus, M., Mcdermott, R.S., Bedke, J., Tartas, S., Chang, Y.-H., Tamada, S., Shou, Q., Perini, R.F., Chen, M., Atkins, M.B., Powles, T., *Pembrolizumab plus Axitinib versus Sunitinib for Advanced Renal-Cell Carcinoma*. New England Journal of Medicine, 2019. **380**: p. 1116-1127.

57. He, X., Xu, C. , *Immune checkpoint signaling and cancer immunotherapy*. Cell Res, 2020. **30**: p. 660-669.

58. Haslam A, O.T., Prasad V. , *How many people in the US are eligible for and respond to checkpoint inhibitors: An empirical analysis*. Int J Cancer., 2025.

59. Johnson DB, B.J., Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, et al., *Fulminant myocarditis with combination immune checkpoint blockade*. N Engl J Med, 2016. **375**: p. 1749-1755.

60. Mahmood SS, F.M., Cohen JV, Nohria A, Reynolds KL, Heinzerling LM, Sullivan RJ, Damrongwatanasuk R, Chen CL, Gupta D, Kirchberger MC, Awadalla M, Hassan MZO, Moslehi JJ, Shah SP, Ganatra S, Thavendiranathan P, Lawrence DP, Groarke

JD, Neilan TG., *Myocarditis in Patients Treated With Immune Checkpoint Inhibitors*. J Am Coll Cardiol., 2018. **71**(16): p. 1755-1764.

61. Oren O, Y.E., Molina JR, Bailey KR, Blumenthal RS, Kopecky SL., *Cardiovascular Health and Outcomes in Cancer Patients Receiving Immune Checkpoint Inhibitors*. Am J Cardiol, 2020. **125**(12): p. 1920-1926.

62. Murthy VH, K.H., Gross CP, *Participation in cancer clinical trials: race-, sex-, and age-based disparities*. JAMA, 2004. **291**: p. 2720-2726.

63. Gujral D.M., C.S.J., Bhattacharyya S., *Cardiac safety evaluation in cancer clinical trials*. Eur J Cancer, 2018. **103**: p. 143-146.

64. Cochain C, C.S., Koch M, Wiendl H, Eckstein HH, Zernecke A., *Programmed cell death-1 deficiency exacerbates T cell activation and atherogenesis despite expansion of regulatory T cells in atherosclerosis-prone mice*. PLoS One, 2014. **9**: p. 1-10.

65. Bu DX, T.M., Maganto-Garcia E, et al., *Impairment of the programmed cell death-1 pathway increases atherosclerotic lesion development and inflammation*. Arterioscler. Thromb. Vasc. Biol, 2011. **31**: p. 1100-1107.

66. Gotsman I, G.N., Dacosta R, Sukhova G, Sharpe A, Lichtman AH, *Proatherogenic immune responses are regulated by the PD-1/PD-L pathway in mice*. J Clin. Invest, 2007. **117**: p. 2974-2982.

67. Drobni, Z.D., Alvi, R.M., Taron, J., Zafar, A., Murphy, S.P., Rambarat, P.K., Mosarla, R.C., Lee, C., Zlotoff, D.A., Raghu, V.K., Hartmann, S.E., Gilman, H.K., Gong, J.,

Zubiri, L., Sullivan, R.J., Reynolds, K.L., Mayrhofer, T., Zhang, L., Hoffmann, U., Neilan, T.G., *Association Between Immune Checkpoint Inhibitors With Cardiovascular Events and Atherosclerotic Plaque.* Circulation, 2020. **142**: p. 2299-2311.

68. Gong B, G.Y., Li Y, Wang J, Zhou G, Chen YH, Nie T, Yang M, Luo K, Zheng C, Pan F, Liang B, Yang L., *Immune checkpoint inhibitors in cancer: the increased risk of atherosclerotic cardiovascular disease events and progression of coronary artery calcium.* BMC Med, 2024. **22**(1): p. 44.

69. Laenens, D., Yu, Y., Santens, B., Jacobs, J., Beuselinck, B., Bechter, O., Wauters, E., Staessen, J., Janssens, S., Van Aelst, L., *Incidence of Cardiovascular Events in Patients Treated With Immune Checkpoint Inhibitors.* Journal of Clinical Oncology, 2022. **40**: p. 3430-3438.

70. Kwan JM, S.M., Akhlaghi N, Hu JR, Mora R, Cross JL, Jiang M, Mankbadi M, Wang P, Zaman S, Lee S, Im Y, Feher A, Liu YH, Ma SS, Tao W, Wei W, Baldassarre LA., *Adverse cardiovascular events and cardiac imaging findings in patients on immune checkpoint inhibitors.* PLoS One, 2024. **19**(12): p. e0314555.

71. Chen T, G.C., *XGBoost: A scalable tree boosting system.* Proceedings of the 22nd ACM SIGKDD International Conference on Knowledge Discovery and Data Mining, 2016: p. 785-794.

72. Koene, R.J., Prizment, A.E., Blaes, A., Konety, S.H., *Shared Risk Factors in Cardiovascular Disease and Cancer.* Circulation, 2016. **133**: p. 1104-1114.

73. Li H, Z.Y., Li B, Zhi Y, Chen M, Zeng J, et al., *Association among major adverse cardiovascular events with immune checkpoint inhibitors: A systematic review and meta-analysis*. J Intern Med, 2025. **297**: p. 36-46.

74. Jayathilaka, B., Mian, F., Franchini, F., Au-Yeung, G., Ijzerman, M., *Cancer and treatment specific incidence rates of immune-related adverse events induced by immune checkpoint inhibitors: a systematic review*. British Journal of Cancer, 2025. **132**: p. 51-57.

75. Heilbroner SP, F.R., Mueller J, Chalwa J, Charest F, Suryadevara S, Kratt C, Gomez-Caminero A, Dreyfus B, Neilan TG., *Predicting cardiac adverse events in patients receiving immune checkpoint inhibitors: a machine learning approach*. J Immunother Cancer., 2021. **9**(10): p. e002545.

76. Fan, Y., Xie, W., Huang, H., Wang, Y., Li, G., Geng, Y., Hao, Y., Zhang, Z.,, *Association of Immune Related Adverse Events With Efficacy of Immune Checkpoint Inhibitors and Overall Survival in Cancers: A Systemic Review and Meta-analysis*. . Frontiers in Oncology 2021. **11**.

77. Cook S, S.V., Meyers DE, et al. , *Immune-Related Adverse Events and Survival Among Patients With Metastatic NSCLC Treated With Immune Checkpoint Inhibitors*. JAMA Netw Open, 2024. **7**(1): p. e2352302.

78. Ajoolabady, A., Pratico, D., Lin, L. et al. , *Inflammation in atherosclerosis: pathophysiology and mechanisms*. Cell Death Dis, 2024. **15**: p. 817.

79. Ridker, P.M., Brendan M. Everett, Tom Thuren, Jean G. Macfadyen, William H. Chang, Christie Ballantyne, Francisco Fonseca, et al., *Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease*. N Engl J Med, 2017. **377**(12): p. 1119-31.

80. Ridker, P.M., Charles H. Hennekens, Julie E. Buring, and Nader Rifai., *C-reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women*. N Engl J Med, 2000. **342**(12): p. 836-43.

81. Vuong JT, S.-M.A., Nayeri A, Sallan T, Neilan TG, Yang EH, *Immune Checkpoint Therapies and Atherosclerosis: Mechanisms and Clinical Implications: JACC State-of-the-Art Review*. JACC, 2022. **79**(6): p. 577-593.

82. Li X, W.X., Chen X, Peng S, Chen S, Zhou G, Wei Y, Lu X, Zhou C, Ye Y, Li J, Liu S, Xu J., *Selective blockade of interleukin 6 trans-signaling depresses atrial fibrillation*. Heart Rhythm, 2023. **20**(12): p. 1759-1770.

83. Kubota T, M.C., Frye CS, Slawson SE, Lemster BH, Koretsky AP, Demetris AJ, Feldman AM., *Dilated cardiomyopathy in transgenic mice with cardiac-specific overexpression of tumor necrosis factor-alpha*. Circ Res, 1997. **81**(4): p. 627-35.

84. Mitchell JD, L.M., Xia Q, Dreyfus B, Jain N, Jain A, Lane D, Lenihan DJ, *Risk profiles and incidence of cardiovascular events across different cancer types*. ESMO Open, 2023. **6**: p. 101830.

85. Kraler S, L.L., Nopp S, et al, *Biomarker-enhanced cardiovascular risk prediction in patients with cancer: a prospective cohort study*. Journal of Thrombosis and Haemostasis, 2024. **22**(11): p. 3125-3136.

86. J.J., M., *Cardiovascular toxic effects of targeted cancer therapies*. New England Journal of Medicine, 2016. **375**: p. 1457-1467.

87. J., H., *Adverse cardiac effects of cancer therapies: cardiotoxicity and arrhythmia*. Nat Rev Cardiol, 2020. **17**: p. 474-502.

88. Kamba T., M.D.M., *Mechanisms of adverse effects of anti-VEGF therapy for cancer*. British Journal of Cancer, 2007. **96**: p. 1788-1795.

89. Chen, D.-Y., Liu, J.-R., Tseng, C.-N., Hsieh, M.-J., Chuang, C.-K., Pang, S.-T., Chen, S.-W., Hsieh, I.-C., Chu, P.-H., Chen, J.-S., Wen-Cheng Chang, J., Huang, W.-K., See, L.-C., *Major Adverse Cardiovascular Events in Patients With Renal Cell Carcinoma Treated With Targeted Therapies*. JACC: CardioOncology, 2022. **4**.

90. Chitturi KR, X.J., Araujo-Gutierrez R, Bhimaraj A, Guha A, Hussain I, Kassi M, Bernicker EH, Trachtenberg BH., *Checkpoint Inhibitor-Related Adverse Cardiovascular Events in Patients With Lung Cancer*. . JACC CardioOncol, 2019. **17**(2): p. 182-192.

91. A.R. Lyon, T.L.-F., L.S. Couch, R. Asteggiano, M.C. Aznar, J. Bergler-Klein, G. Boriani, D. Cardinale, R. Cordoba, B. Cosyns, D.J. Cutter, E. de Azambuja, R.A. de Boer, S.F. Dent, D. Farmakis, S.A. Gevaert, D.A. Gorog, J. Herrmann, D. Lenihan, J. Moslehi, 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**: p. 4229-4361.

92. Rubio-Infante N, R.F.Y., Castillo EC, Lozano O, García-Rivas G, Torre-Amione G., *Cardiotoxicity associated with immune checkpoint inhibitor therapy: a meta-analysis.* Eur J Heart Fail. , 2021. **23**: p. 1739-1747.

93. Devarbhavi H, A.S., Arab JP, Nartey YA, Pose E, Kamath PS. , *Global Burden of Liver Disease: 2023 Update.* . J Hepatol, 2023. **79**(2): p. 516-537.

94. Hashem M, M.M., Abdeltawab D, Makhlouf NA, *Expanding the liver donor pool worldwide with hepatitis C infected livers, is it the time?* World J Transplant, 2024. **14**(2): p. 90382.

95. M. Albeldawi, A.A., S. Madhwal, J. Cywinski, R. Lopez, B. Eghtesad, et al., *Cumulative risk of cardiovascular events after orthotopic liver transplantation.* Liver Transpl, 2012. **18**: p. 370-375.

96. Koshy AN, G.P., Han H-C, Teh AW, Jones R, Testro A, et al., *Cardiovascular Mortality following Liver Transplantation: Predictors and Temporal Trends over 30 years.* Eur Heart J Qual care Clin Outcomes, 2020. **6**(4): p. 243-253.

97. Liu H, N.J., Lin G, Lee SS, *Cardiomyopathy in cirrhosis: From pathophysiology to clinical care.* JHEP Reports, 2024. **6**(1): p. 100911.

98. Ridjab DA, I.I., Budiman F, Tenggara R., *Evaluation of subclinical ventricular systolic dysfunction assessed using global longitudinal strain in liver cirrhosis: A systematic review, meta-analysis, and meta-regression*. Plos One, 2022. **17**(6).

99. Rawashdeh B, Y.N., Sulieman D, Abuassi M, Cooper M, *Takotsubo cardiomyopathy after solid organ transplantation: a scoping review*. . Ann Med Surg (Lond), 2024. **86**(5): p. 2883-2891.

100. Souki FG, C.N., Fouda E, Nicolau-Raducu R, *Stress Cardiomyopathy Following Multivisceral Transplantation: A Case Report*. Cureus, 2025. **17**(2): p. e78851.

101. Souki FG, R.Y., Sancassani R, Livingstone J, Shatz V, Ashrafi B, Shuman M, Nicolau-Raducu R., *Characteristics, Risk Factors, and Outcome of New-onset Systolic Heart Failure After Liver Transplantation: A Single-center Cohort*. Transplant Direct, 2023. **9**: p. e1499.

102. Sakr AE, F.G., Doctorian TP, Kim HB, Narasimha D, Abudayyeh I, Hilliard AD, Shih W, de Vera ME, Baron PW, Volk ML, Stoletniy LN., *Predictors of Systolic Heart Failure and Mortality Following Orthotopic Liver Transplantation: a Single-Center Cohort*. . Transplant Proc, 2019. **51**(6): p. 1950-1055.

103. Kharawala A, S.I., Olayinka A, Hajra A, Seo J, Akunor H, Alhuarrat MAD, Thachil R., *Incidence, predictors and outcomes of new onset systolic heart failure following orthotopic liver transplant: A systematic review*. Transplant Rev (Orlando), 2023. **37**(2): p. 100758.

104. *US Department of Health and Human Services. Organ Procurement and Transplantation Network*. August 6, 2025]; Available from: https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#.

105. M.J. Eimer, J.M.W., E.C. Wang, L. Kulik, A. Blei, S. Flamm, et al., *Frequency and significance of acute heart failure following liver transplantation.* Am J Cardiol, 2008. **101**: p. 242-244.

106. Santos, J., Planas, R., Pardo, A et al, *Spironolactone alone or in combination with furosemide in the treatment of moderate ascites in nonazotemic cirrhosis. A randomized comparative study of efficacy and safety.* Journal of Hepatology, 2003. **39**(3): p. 336-342.

107. Eyvazian VA, G.J., Yang EH, Aksoy O, Honda HM, Busuttil RW, Agopian VG, Vorobiof G., *Incidence, Predictors, and Outcomes of New-Onset Left Ventricular Systolic Dysfunction After Orthotopic Liver Transplantation*. J Card Fail, 2019. **25**(3): p. 166-172.

108. Sonny A, G.S., Jaber WA, Cywinski JB, *Systolic heart failure after liver transplantation: incidence, predictors, and outcome.* Clin Transplant 2018. **32**(3): p. e13199.

109. Alexander S, T.M., Patel H, Chan EY, Doukky R., *The diagnostic and prognostic utility of risk factors defined by the AHA/ACCF on the evaluation of cardiac disease in liver transplantation candidates.* . BMC Cardiovasc Disord, 2019. **19**(1): p. 102.

110. Wang J, H.S., Feng K, Wu H, Shang L, Zhou Z, Liu Q, Chen J, Liang M, Chen G, Hou J, Wu Z., *Risk factors for mortality in patients receiving extracorporeal membrane oxygenation.* Ren Fail, 2024. **46**(2): p. 2395450.

111. Cusanno, A., Aissaoui, N., Minville, V. et al. , *Predictors of weaning failure in case of VA ECMO implantation*. Sci Rep, 2022. **12**: p. 13842.

112. Charbonneau F, C.K., Bebawi E, Lavigueur O, Lévesque É, Lamarche Y, Serri K, Albert M, Noly PE, Cournoyer A, Cavayas YA., *Parameters associated with successful weaning of veno-arterial extracorporeal membrane oxygenation: a systematic review.* Crit Care, 2022. **26**(1): p. 375.

113. Bjelic M, K.N., Gu Y, Chase K, Paic F, Gosev I., *Cause of In-Hospital Death After Weaning from Venoarterial-Extracorporeal Membrane Oxygenation*. J Intensive Care Med., 2022. **37**(12): p. 1545-1552.

114. J., H., *Clinical parameters for successful weaning from venous-arterial extracorporeal membrane oxygenation after cardiogenic shock.* J Am Coll Cardiol, 2012. **59**: p. E1022.

115. Naruke T, I.T., Kawaguchi T, et al., *Prognostic impact of dramatic alteration of mixed venous oxygen saturation on the hemodynamic recovery from veno-arterial extracorporeal membrane oxygenation.* Eur Heart J, 2012(33): p. 69.

116. Schmidt M, B.A., Roberts L, et al., *Predicting survival after ECMO for refractory cardiogenic shock: the survival after veno-arterial-ECMO (SAVE) score.* Eur Heart J, 2015. **36**(33): p. 2246-2256.

117. Becher PM, T.R., Schrage B, Schmack B, Sinning CR, Fluschnik N, Schwarzl M, Waldeyer C, Seiffert M, Clemmensen P, Neumann JT, Bernhardt AM, Zeymer U, Thiele H, Reichenspurner H, Blankenberg S, Westermann D. , *Risk prediction of in-hospital mortality in patients with venoarterial extracorporeal membrane oxygenation for cardiopulmonary support: The ECMO-ACCEPTS score.* J Crit Care, 2020. **56**: p. 100-105.

118. Jeong, J.H., Kook, H., Lee, S.H. et al. , *Predictors of in-hospital mortality after successful weaning of venoarterial extracorporeal membrane oxygenation in cardiogenic shock.* Sci Rep, 2023. **13**: p. 17529.