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Prospective Role of N-terminal Pro-type B Natriuretic Peptide and Troponins Biomarkers for Early Detection of Cardiotoxicity in Cancer Survivors

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Abstract
Cardiotoxicity remains a significant complication in cancer survivors receiving cardiotoxic therapies such as anthracyclines and HER2-targeted agents. Early detection of cardiac dysfunction is critical to prevent irreversible damage and optimize clinical outcomes. N-terminal pro-type B natriuretic peptide (NT-proBNP) and troponins, established cardiac biomarkers, have emerged as promising tools for the early identification of subclinical cardiotoxicity. This article reviews current evidence on the utility of NT-proBNP and troponins in prospective monitoring of cardiotoxic effects in cancer patients. Clinical trials, including the International Cardio-Oncology Society-one trial, highlight the prognostic value of these biomarkers in guiding preventive interventions such as enalapril therapy. Studies from registries like the Essen Cardio-Oncology Registry (ECoR) demonstrate the sensitivity and specificity of troponins and NT-proBNP for detecting early myocardial injury before symptomatic heart failure develops. Moreover, recent European Society of Cardiology (ESC) guidelines endorse the use of these biomarkers as part of comprehensive cardio-oncology risk assessment and management protocols. Despite some challenges in interpretation and variability, serial measurements of NT-proBNP and high-sensitivity troponins provide valuable, non-invasive insights into cardiac stress and injury related to chemotherapy. This review synthesizes findings from landmark studies and guidelines, supporting the integration of NT-proBNP and troponins into routine surveillance strategies to improve cardiovascular outcomes in cancer survivors. Further prospective research is warranted to refine biomarker thresholds and develop personalized monitoring algorithms for timely cardioprotective interventions

Keywords: N-Terminal Pro-Type B Natriuretic Peptide, Troponins, Cancer, Cardiotoxicity

Introduction
Advances in cancer therapy have greatly improved survival, but they have also revealed chronic complications such as cardiotoxicity, which is tighter and immediately balances benefit with risk. Emerging data indicate that cardiotoxicity may develop silently during or long after therapy, presenting as left ventricular dysfunction, heart failure, or asymptomatic myocardial injury [1]. The 2022 ESC Guidelines on cardio-oncology emphasize that predictive, preventive, and personalized monitoring tools for cancer survivors remain underdeveloped, particularly in the post-treatment phase [2]. This gap underscores the urgent need for accessible, biomarker-driven risk stratification strategies.

High-sensitivity troponin I (hs-TnI) and N-terminal pro-type B natriuretic peptide(NT-proBNP), are recognized for their

prognostic potential in cardio-oncology. hs-TnI are well-established markers of myocardial injury, while NT-proBNP reflects ventricular strain and fluid overload. Studies suggest that persistent elevation in cardiac hs-Tnl correlates with adverse cardiovascular outcomes in cancer patients receiving cardiotoxic regimens [3].

The clinical interpretation of these biomarkers in cancer patients is complex, as overlapping symptoms from tumor progression or therapy-related inflammation may confound results. As emphasized by Rassaf and Totzeck (2018), avoiding unnecessary treatment interruptions due to misinterpreted biomarker elevations is vital [4]. Therefore, establishing standardized thresholds and surveillance schedules is not only important but urgently needed. To address critical gaps in survivorship care, this proposal will develop a dual-biomarker (hs-troponin I + NT-proBNP) predictive model for anthracycline-exposed survivors, aligned with 2022 ESC priorities. By integrating serial measurements (0–24 months post-treatment) and regression, the aim to stratify patients into low-, moderate-, and high-risk trajectories, enabling personalized interventions (cardioprotective therapies, imaging frequency) before irreversible myocardial damage occurs. "Recent developments in Russia have added momentum to this conversation. Russian researchers, through a national precision medicine initiative, have begun implementing personalized cardio-oncology protocols, combining imaging with serial biomarker monitoring to predict cardiac risk profiles in cancer patients. Their pilot data support the use of longitudinal biomarker assessment as a cost-effective and non-invasive strategy for survivorship care. Given this backdrop, the present research will Integrate BNP and CRP (or NT-proBNP and troponins) into a predictive model, Target breast cancer and lymphoma survivors, two groups with high exposure to anthracyclines and HER2 inhibitors, with elevated risk for delayed cardiotoxicity. This defined focus enhances model specificity and clinical translatability, not just patients under active treatment, Focus on personalized, risk-based follow-up care, and support real-world implementation through clinically validated thresholds. By shifting focus from reactive treatment to proactive prevention, this work will contribute to improving quality of life and reducing cardiovascular morbidity among cancer survivors, a population expected to grow substantially in the coming decades.

Burden of Morbidity and Mortality in Survival

The long-term cardiovascular health of cancer survivors remains a critical and under-addressed issue. Cardiotoxicity caused by chemotherapeutic agents such as anthracyclines and HER2 inhibitors leads to a substantial burden of morbidity and mortality, often manifesting months to years after treatment completion. Current clinical monitoring during active treatment primarily focuses on acute cardiac events, leaving a significant gap in surveillance during the post-treatment survivorship phase.

Despite demonstrating potential during therapy, These biomarkers remain inconsistently applied in long-term follow-up of cancer survivors. Existing studies often isolate these biomarkers without integrating multiple markers or clinical variables into comprehensive predictive models tailored to survivors' unique risk profiles. This lack of standardized protocols and validated risk stratification tools contributes to inconsistent monitoring practices and missed opportunities for early intervention.

Given the increasing population of breast and lymphoma cancer survivors exposed to cardiotoxic regimens, there is a pressing need for reliable, non-invasive predictive models that incorporate serial biomarker assessment to identify individuals at highest risk for delayed cardiotoxicity. Without such tools, clinicians face challenges in balancing effective cancer treatment with cardiovascular safety, which may lead to suboptimal survivorship care and preventable cardiac complications.

The delayed manifestation of chemotherapy-induced cardiac dysfunction, often years after therapy demands proactive, biomarker-guided surveillance strategies. Breast cancer and lymphoma patients are disproportionately affected due to their high exposure to cardiotoxic regimens.

These markers are recognized for their diagnostic utility during treatment, their post-treatment prognostic role remains underutilized [5,6]. Recent findings from the ECoR Registry showed that troponins had a specificity of 95.47% but a sensitivity of just 13.64%, while NT-proBNP showed a specificity of 92.21% and sensitivity of 12.06% for detecting chemotherapy-related cardiotoxicity [7]. These values highlight their potential for confirming cardiac damage but also underscore the need for complementary, multivariable models to enhance early detection sensitivity especially before clinical symptoms manifest.

Furthermore, the interpretation of biomarker fluctuations in cancer survivors is complicated by overlapping non-cardiac conditions and the lack of standardized thresholds for intervention [8]. International protocols remain inconsistent, particularly in low- and middle-income countries, where post-treatment cardiac monitoring infrastructure is limited. This article is positioned to bridge this translational gap by outlining and discussion the potential roles of integrating these biomarkers, and key clinical-demographic variables to stratify survivors by their cardiotoxicity risk profile.

The article to predict the potential of these biomarkers becoming a predictive model that will not only quantify risk but will also be calibrated against clinically relevant thresholds, allowing seamless integration into follow-up workflows. Thus, It's output could guide echocardiography scheduling, cardiology referrals, and therapy adjustments, thus embedding it into routine survivorship care.

Chemotherapy-Induced Cardiotoxicity

Understanding the biological mechanisms underlying anthracycline cardiotoxicity is important to the development of successful strategies for its prevention, early detection, and personalized treatment. Anthracyclines such as doxorubicin are popularly used in oncology to treat cancer due to their efficacy against a broad range of malignancies. While anthracyclines significantly increase long-term cancer survival, this benefit often comes at the cost of substantial cardiovascular complications that can emerge long after therapy concludes. [2].

These late-onset effects, is called chemotherapy-induced cardiotoxicity; the structural or functional myocardial toxicity caused by anticancer agents, often presenting as asymptomatic left ventricular dysfunction, clinical heart failure, or arrhythmia [3].

Anthracycline cardiotoxicity risk is influenced by both treatment-related and patient-specific factors. Factors contributing to cardiotoxicity range from age and concurrent use of other cardiotoxic agents to genetic predispositions. Among the most critical is the cumulative dose of anthracyclines, as higher total exposure is consistently associated with a greater risk of irreversible myocardial injury for instance, the threshold for doxorubicin-induced heart failure is commonly cited at around 400–550 mg/m², beyond which risk increases steeply [9].

The spectrum of cardiotoxicity ranges from asymptomatic declines in ejection fraction to life-threatening heart failure. The Clinical manifestations of Cardiac dysfunction following chemotherapy is often delayed and insidious, with many patients developing left ventricular systolic dysfunction months or even years after completing treatment. Early subclinical myocardial injury may progress silently until the heart's compensatory capacity is overwhelmed, resulting in overt heart failure [9]. While Acute toxicity can occur within weeks of administration although relatively rare. The chronic form emerges within the first year, while late-onset cardiomyopathy may not appear until a decade post-therapy. This delayed presentation highlights the need for long-term cardiac surveillance in cancer survivors exposed to cardiotoxic agents.

Prospective Use of Predictive Models for Cardiotoxicity

Predictive models use statistical techniques such as logistic regression to combine variables such as biomarker trends, age, treatment history, and comorbidities into a tool that can estimate a patient's individual risk of developing cardiotoxicity. Current clinical risk models for chemotherapy-induced cardiotoxicity rely on conventional cardiovascular risk factors and imaging results, but these approaches tend to miss subclinical cardiac injury, especially after treatment ends [10]. A 2023 study published in Journal of America College of Cardiology: Cardio-oncology demonstrated that incorporating biomarkers such as NT-proBNP and hs-TnI into risk models significantly improves the early prediction of cardiotoxicity. This model, developed using logistic regression, showed strong predictive performance by integrating serial biomarker data rather than relying on baseline measurements alone. many existing tools have failed to include dynamic biomarker trends and individual treatment variations, limiting their sensitivity in post-treatment surveillance. In as much as the research indicates that predictive tools rarely account for differences in chemotherapy regimens or patient-specific susceptibility, which are critical to accurately estimating delayed cardiotoxicity risk. There's need for models that combine clinical factors with longitudinal biomarker monitoring to better identify patients at risk during survivorship.

Logistic Regression in Cardio-Oncology

Logistic regression remains a favored method in cardio-oncology predictive modeling due to its balance of accuracy and interpretability. In cardio-oncology, logistic regression models allow for the estimation of individualized risk probabilities, facilitating personalized monitoring strategies. These models can incorporate continuous biomarker levels and other variables to generate risk scores that guide clinical decision-making.

A comparative study published in Frontiers in Oncology (2024) evaluated logistic regression alongside advanced machine learning models, finding that while machine learning provided slight improvements in accuracy, logistic regression was preferred for its clinical transparency and ease of implementation. Their findings support the inclusion of NT-proBNP and hs-TnI as continuous predictors within logistic regression models to optimize early detection of myocardial injury. Another study in Pediatric Blood & Cancer focused on childhood cancer survivors demonstrated that logistic regression models incorporating serial NT-proBNP and hs-TnI levels substantially improved the prediction of late-onset cardiotoxicity compared to single time-point assessments. This study reinforces the importance of integrating biomarker trends over time into predictive algorithms to enhance risk stratification during long-term follow-up.

Logistic regression models still require robust datasets with comprehensive biomarker and clinical data for optimal performance. Integration of dynamic biomarker measurements over time into regression models remains an area of ongoing research to enhance predictive power and clinical utility.

Given the demonstrated predictive value of integrating NT-proBNP and hsTs with clinical variables, but recognizing the current gaps in incorporating dynamic biomarker data and individualized treatment factors, there is a clear opportunity to advance early cardiotoxicity detection through improved predictive modeling and that's why the proposed study aims to develop a logistic regression–based predictive model that leverages serial NT-proBNP and hs-TnI measurements specifically in cancer survivors during post-treatment surveillance. By focusing on this population, the model intends

to fill the critical gap in identifying subclinical cardiac injury before overt dysfunction emerges, enabling timely clinical interventions.

This model will prioritize the inclusion of longitudinal biomarker trends alongside relevant demographic, clinical, and treatment-related variables to enhance predictive accuracy and clinical applicability. This approach aligns with the emerging consensus that dynamic biomarker monitoring significantly improves risk stratification over static baseline assessments.

In contrast to many existing risk tools, this model's design centers on practical implementation in routine survivorship care, balancing statistical robustness with interpretability to facilitate adoption by clinicians. Ultimately, it seeks to contribute a validated, accessible tool that supports personalized cardiovascular monitoring, improves early detection, and reduces morbidity in cancer survivors exposed to cardiotoxic therapies.

Personalized Follow-Up

Translating Biomarker Risk into Care

Personalized follow-up for cancer survivors at risk of cardiotoxicity requires the integration of biomarker data with patient-specific factors such as age, comorbidities, cancer type, and cumulative treatment exposures. Studies have shown that both NT-proBNP and hs-TnI rise before symptomatic cardiac dysfunction becomes evident, highlighting their role in early detection. By combining these biomarkers with demographic and treatment histories, clinicians can create individualized risk profiles that better inform follow-up strategies. For instance, a prospective analysis demonstrated that serial elevations in NT-proBNP and hs-TnI correlated strongly with subclinical left ventricular dysfunction in breast and ovarian cancer patients treated with anthracyclines. This reinforces the value of routine biomarker surveillance beyond the treatment phase. High-risk survivors—those with elevated or upward-trending biomarkers can be triaged for advanced cardiac imaging, early pharmacological intervention (beta-blockers or ACE inhibitors), or referral to cardio-oncology services. On the other hand, those with stable profiles may benefit from simplified monitoring plans, reducing unnecessary testing and healthcare costs. Such risk-based pathways promote resource-efficient, proactive care tailored to each survivor's evolving cardiac risk.

Effective post-treatment management of cardiotoxicity hinges on integrating biomarker data with patients' demographic and treatment histories. Combining NT-proBNP and hs-TnI trends with factors such as age, sex, cumulative chemotherapy dose, and radiation exposure enhances the ability to stratify survivors by their individual cardiac risk profiles. This holistic approach allows clinicians to move beyond generic surveillance protocols toward personalized follow-up plans that target high-risk patients more intensively.

Translating biomarker risk into actionable care therefore requires a coordinated, multidisciplinary framework tailored to each survivor's risk category. This personalized strategy optimizes resource use by focusing advanced diagnostic and therapeutic efforts on those most likely to benefit, while minimizing unnecessary interventions in low-risk individuals.

Recent Development

Recent prospective and observational studies have examined the utility, timing, and integration of NT-proBNP and hs-TnI into clinical models.

Tanaka et al. (2023) conducted a prospective cohort study of 220 breast cancer survivors treated with anthracyclines, finding that serial NT-proBNP measurements were more predictive of cardiac dysfunction than single time-point values [10]. Similarly, observed in a longitudinal study of 154 HER2-positive patients that while baseline biomarkers correlated with LVEF decline (AUC = 0.77), the absence of post-treatment serial monitoring limited the model's utility.

In another prospective study, followed 130 breast and ovarian cancer patients and confirmed that both NT-proBNP and hs-TnI elevations were early indicators of cardiac risk. However, the study lacked model development or long-term follow-up. Yoon et al. (2023) provided further support for dynamic biomarkers in a cohort of 198 anthracycline-treated patients, where fluctuations in biomarker levels correlated with adverse outcomes, though the study did not propose a predictive tool.

From a practical standpoint, Moryoussef et al. (2021) and Adeyemi et al. (2022) explored NT-proBNP as a feasible, low-cost marker in resource-limited settings. While both found NT-proBNP useful, their observational nature and limited use of imaging reduced generalizability.

Advanced modeling approaches were taken by Rodriguez et al. (2023), who developed a risk score from a multicenter registry using a combination of NT-proBNP, troponins, age, and chemotherapy dose, achieving an AUC of 0.83. However, the model lacked external validation and did not account for serial biomarker dynamics.

Interventional work by Martinez et al. (2024) tested whether NT-proBNP-guided therapy could reduce heart failure incidence in high-risk lymphoma survivors. Results supported early cardioprotective treatment, although the sample was too small for subgroup analysis. Lastly, Kumar et al. (2023) tracked biomarker and echocardiographic data in 160

HER2-positive survivors and confirmed that NT-proBNP elevations often preceded changes in LVEF. Yet, they stopped short of developing a predictive model.

Together, these studies confirm the clinical value of NT-proBNP and hs-TnI, emphasize the advantages of serial monitoring over static thresholds, and highlight a key gap, the lack of simple, validated predictive models tailored to the survivorship period. This research article aimed to address these gaps by predicting the use and validating a logistic regression predictive model focused on cancer survivors during the post-treatment phase, using serial NT-proBNP and hs-TnI data combined with relevant clinical and demographic information. If this model will prioritize applicability in routine clinical practice, with the potential to be adapted and validated in diverse settings.

Conclusion

In the words of European Society of Cardiology, cancer survivors needs lifelong, risk-adapted monitoring by using variables and Cardiac biomarkers to mitigate Cardiac complications from chemotherapy induced cardiotoxicity [2]. Proactive surveillance and prediction of subclinical cardiac injury is potent and that is why within this framework, cardiac biomarkers could emerge as vital tools. There's need for locally validated, cost-effective predictive tools is urgent, especially in resource-limited settings where access to advanced imaging and frequent biomarker testing is constrained. Developing models that leverage widely available biomarkers such as NT-proBNP and troponins and are tailored to local patient demographics and treatment patterns can significantly improve early cardiotoxicity detection and patient outcomes. These biomarkers, when tracked longitudinally, offer a window into evolving cardiac risk often before symptoms manifest or echocardiographic abnormalities are detectable.

A prospective research on this will be grounded in this evolving paradigm: that the future of cancer survivorship lies not in waiting for heart failure to occur, but in using validated biomarkers to predict, stratify, and prevent. By targeting the under-monitored post-treatment period, and focusing on serial biomarker-based risk modeling, the study will directly address one of the most urgent challenges in cardio-oncology, personalized intervention before irreversible cardiac damage sets in [11-20].

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