“CAROL DAVILA” UNIVERSITY OF MEDICINE AND PHARMACY, BUCHAREST

FACULTY OF MEDICINE

THE PROGNOSTIC IMPACT OF CARDIAC BIOMARKERS IN PATIENTS WITH HEART FAILURE AND ASSOCIATED RENAL DYSFUNCTION

SUMMARY OF THE THESIS

Doctoral Supervisor:

PROFESSOR EMERITUS DR. DAN ANDREI-GHEORGHE

Doctoral student:

ANCA BREHA

2025

TABLE OF CONTENTS

LIST OF SCIENTIFIC WORKS PUBLISHED WITHIN THE DOCTORAL STUDIES

Scientific works list

1. **Anca Breha[1,2]**, Caterina Delcea[1,2], Andreea Cristina Ivanescu[1,2], Gheorghe Andrei Dan [1,2,3]The Prognostic Value of Troponin Levels Adjusted for Renal Function in Heart Failure - A Systematic Review Romanian Journal of Internal Medicine 2025 (Chapter 5)

2. **Anca Breha[1,2]**, Caterina Delcea[1,2], Andreea Cristina Ivanescu[1,2], Gheorghe Andrei Dan [1,2,3] NT-proBNP as an Independent Predictor of Long-term All-cause Mortality in Heart Failure across the eGFR spectrum Journal of Internal Medicine 2025 (Chapter 6)

1.INTRODUCTION

Heart failure and chronic kidney disease are two highly prevalent pathological conditions, with a significant impact on public health at the global, European, and national levels. Their coexistence indicates a complex pathophysiological interaction that worsens patient prognosis, requiring a multidisciplinary and personalized clinical approach. In recent years, the importance of identifying and utilizing biomarkers in the diagnosis and prognosis of these diseases has increased considerably; however, their integration into clinical practice remains a challenge.

Heart Failure, recognized as one of the leading causes of global mortality, evolves within the context of shared pathophysiological mechanisms with chronic kidney disease, such as endothelial dysfunction, activation of neurohormonal systems, and inflammation. The kidney's role in electrolyte homeostasis, blood pressure regulation, and renal blood flow supports the close connection between these organs. Thus, renal dysfunction not only worsens HF but may also have a causal role in its progression, being associated with a diminished treatment response and an increased risk of mortality.

In the context of these interdependencies, cardiac biomarkers such as NT-proBNP and troponins are essential for prognostic assessment; however, their interpretation is complicated by the influence of renal impairment on the clearance and secretion of these peptides. Recent studies suggest that measuring these biomarkers, combined with clinical parameters and the assessment of renal dysfunction severity, can play an important role in risk stratification for patients with these conditions. Nonetheless, uncertainties remain regarding threshold values for different degrees of renal impairment and their impact on long-term prognosis.

This thesis was motivated by the frequent difficulties encountered in clinical practice when evaluating patients with heart failure (HF) and concomitant chronic kidney disease (CKD). Often, these patients present atypical symptoms, laboratory test results are difficult to interpret, and the prognosis is uncertain. Establishing a positive diagnosis, accurately assessing risk, and tailoring treatment are challenging aspects due to the complex interactions between the two conditions and the limitations of available evaluation methods.

This thesis aims to contribute to existing knowledge by assessing the prognostic impact of hs-TnT and NT-proBNP in a specific cohort of patients with HF, seeking to determine the practical value of combining these biomarkers in mortality prediction. The study will

highlight differences in predictive performance based on the severity of renal dysfunction (evaluated through eGFR) and will establish specific threshold values for various degrees of renal impairment. Furthermore, the analysis will adopt an innovative approach by separately analyzing patients from distinct eGFR groups, thereby identifying different independent parameters for those with more progressed renal dysfunction. Through this approach, the thesis aims to provide a more nuanced understanding of the role of biomarkers in risk stratification and management of patients with HF and CKD, with the goal of improving long-term clinical outcomes.

Within the retrospective study, the focus is on highlighting differences in predictive performance according to the severity of renal dysfunction, evaluated through eGFR, and establishing relevant threshold values for different levels of renal impairment.

This research aligns with both international and national efforts to improve prognosis in heart failure, contributing to a deeper understanding of the role of biomarkers in the context of cardiorenal pathology. Through an interdisciplinary approach, combining cardiology, nephrology, and molecular biology, it opens new perspectives for personalized evaluation and treatment strategies aimed at reducing mortality and complications.

The obtained results will provide clinical support for adjusting diagnostic and prognostic thresholds and for developing integrated risk models that can be implemented in current practice, facilitating more precise management of patients with heart failure and renal dysfunction. At the same time, the importance of future research to validate and extend these findings in larger populations and prospective studies is acknowledged.

2. Current State of Knowledge

2.1 The Pathophysiological Interaction between Heart Failure and Chronic Kidney Disease

Heart failure and chronic kidney disease are two highly prevalent pathological conditions with a significant impact on public health. Their coexistence indicates a complex pathophysiological interdependence that worsens patient prognosis and requires a multidisciplinary and personalized approach to therapeutic management[2].

Heart failure, according to the European Guidelines of 2021, is a clinical syndrome characterized by symptoms such as dyspnea, peripheral edema, and fatigue during exertion, caused by a structural or functional abnormality of the heart that leads to increased intracardiac pressures and/or inadequate cardiac output. It can be of an acute or chronic nature and is classified based on the left ventricular ejection fraction: reduced (≤40%), moderately reduced (41-49%), or preserved (≥50%). The etiology is diverse, including myocardial dysfunction, valvular diseases, arrhythmias, or other anomalies. Epidemiologically, heart failure is a major cause of hospitalizations and mortality, with recent trends showing an increase in cases among younger individuals, a reduction in mortality, but also an increase in hospitalizations[3],[5]. Heart failure is classified into chronic heart failure and acute heart failure. [4]

Chronic Kidney Disease is defined, according to the KDIGO 2024 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease, as a progressive deterioration of kidney function over a period of three months or longer, characterized by abnormalities in the structure or function of the kidneys, with implications for health[9].

The classification into five stages, based on eGFR, allows for the assessment of severity; from normal stage (eGFR ≥90 ml/min/1.73 m^2) to end-stage renal failure (eGFR <15 ml/min/1.73 m^2). CKD, especially in advanced stages, emphasizes cardiovascular risk, contributing significantly to the overall number of deaths and increasingly ranking high in global mortality statistics. Kidney lesions are caused by factors such as hypertension, hyperfiltration, and glomerular damage, impacting both cardiovascular diseases and overall mortality.

The cardiorenal interdependence is also reflected in the high cardiovascular (CV) mortality among patients with end-stage renal disease (ESRD), which reaches up to 50% of cases, a markedly higher incidence compared to the general population.[13]. In patients aged 25 to

34 years, cardiovascular fatality rates are 500 times higher than in individuals of the same age with normal kidney function [13]. Additionally, most patients with CKD stages 3 to 4 (GFR <60 mL/min/1.73 m²) die from cardiovascular causes rather than progressing to end stage renal disease[13].

2.2.Pathophysiological Mechanisms and Biomarker Involvement

Heart failure and chronic kidney disease share similar pathophysiological mechanisms, such as endothelial dysfunction, activation of the sympathetic neurohormonal system, inflammation, and oxidative stress. The vital role of the kidneys in electrolyte and protein homeostasis, as well as in blood pressure regulation, requires a high perfusion rate (20–25% of cardiac output), which is proportionally higher than that of other organs. This substantial blood flow supports the function of approximately one million nephrons[14]. The heart and kidneys communicate through multiple regulatory pathways, including the renin-angiotensin-aldosterone system, the sympathetic nervous system, antidiuretic hormone, endothelin, and natriuretic peptides. In heart failure, renal hypoperfusion activates renin-angiotensin-aldosterone system and the sympathetic nervous system, leading to vasoconstriction, sodium and fluid retention, and contributing to volume overload, renal interstitial hypertension, and worsening of cardiac and renal dysfunction, creating a vicious cycle that deteriorates the patient's condition[4]. Although sodium retention in heart failure is not primarily caused by the kidneys, it results from impaired renal function, activation of the renin-angiotensin-aldosterone system and sympathetic nervous system, as well as diminished response of natriuretic peptides. Additionally, chronic kidney disease accelerates the processes of atherosclerosis, myocardial disease, valvulopathies, and increases the incidence of cardiac arrhythmias. Anemia is commonly observed in both heart failure and chronic kidney disease, caused by reduced erythropoietin production, which is insufficiently activated by inflammation, and by increased cytokines that stimulate hepatic hepcidin and reduce iron absorption and mobilization, thus worsening anemia and potential cardiovascular complications[15], [16], [17],[18].

2.3. The prognostic significance of NT-proBNP and troponin

European (ESC) and American (AHA) guidelines recommend measuring natriuretic peptides for the exclusion and diagnosis of heart failure; however, the interpretation of results must be adjusted according to conditions such as atrial fibrillation, obesity, age, and chronic kidney disease, as these influence plasma NT-proBNP levels. As renal function

declines, NT-proBNP levels increase exponentially, affected by both decreased renal clearance and additional secretion caused by preload and afterload[25] [26],[27], [28], [29]. Recent evidence shows that elevated levels of N-terminal pro-brain natriuretic peptide are associated with the progression of heart failure, cardiovascular mortality, and overall adverse outcomes, regardless of the stage of renal impairment, although the thresholds for validity require adjustment to reflect the severity of renal dysfunction. In patients with an estimated glomerular filtration rate less than fifteen milliliters per minute per one point seventy-three square meters, levels can reach extremely high values (up to11.215 pg/ml), which can complicate clinical interpretations [34],[35].

High-sensitivity troponin T (hs-TnT) is a valuable biomarker for the prognosis of patients with heart failure, especially in the context of renal impairment, as elevated levels can indicate subclinical myocardial injury or inflammatory activation, even without obvious myocardial damage. Elevated troponin levels are associated with the severity of ventricular dysfunction, reduced survival, and an increased risk of death or re-hospitalization. Dynamic monitoring and adjustment of thresholds to account for the relative impact of renal function are essential for accurate interpretation.

2.4. The role of renal dysfunction in modifying biomarker values

Recent studies highlight that increased levels of troponin T and troponin I correlate with the severity and risk of progression in heart failure, including in patients with chronic kidney disease. In patients on dialysis, elevated troponin T has significant prognostic value, being associated with the risk of congestion and mortality, but the exact relationship with renal function and myocardial injury remains controversial and requires further investigation. Additionally, these biomarkers can independently predict progression to advanced stages of chronic kidney disease, indicating a connection between cardiac impairment and renal deterioration.

Although concentrations of brain natriuretic peptide and N-terminal pro-brain natriuretic peptide increase as the severity of renal dysfunction advances, biological variability and non-cardiac influences complicate their interpretation, especially in advanced stages. The authors recommend serial monitoring of these biomarkers for more accurate evaluation, adjusted according to renal function, to avoid overdiagnosis and improve the management of these patients[98],[99],[100],[53].

3. The hypothesis and objectives of the research

3.1 The hypothesis and objectives of the research

The aim of this work is to evaluate the prognostic impact of troponin and NT-proBNP levels in patients with heart failure and associated renal dysfunction.

3.2 Research objectives

To assess the prognostic value of high-sensitivity cardiac troponin (hs-TnT) and NT-proBNP measured upon admission for predicting all-cause mortality in patients with heart failure and renal dysfunction.

To compare the predictive value of the combination of hs-TnT and NT-proBNP with that of individual biomarkers and traditional clinical variables (e.g., NYHA class, ejection fraction, risk scores) in predicting mortality from any cause.

To analyze the impact of the severity of renal dysfunction (assessed by estimated glomerular filtration rate) on the association between biomarker levels (hs-Troponin and NT-proBNP) measured at admission and the prognosis of patients with heart failure.

To determine cutoff values for various stages of renal impairment.

4. Materials and Methods

4.1. Study design

Our study is an observational, retrospective cohort study. The study protocol complies with the ethical principles of the Declaration of Helsinki and was approved by the Ethics Committee of the Colentina Clinical Hospital.

4.2. Study population and Inclusion/ Exclusion criteria

Adult patients aged 18 years or older with heart failure, consecutively hospitalized in our department between June 2018 and March 2020, were enrolled in the VIVA-HF (surVIVAI in Heart Failure) cohort and considered for inclusion. Exclusion criteria included in-hospital mortality, re-hospitalization of the same patient, and pregnancy. All patients with measured NT-proBNP and creatinine levels within the first 24 hours of admission and who underwent an echocardiographic evaluation during the index hospitalization were included..

4.3. Evaluated Parameters and Analysis Methods

For each patient, demographic data, comorbidities, clinical findings, laboratory results (including NT-proBNP, creatinine, troponin, lipid profile, and other parameters), echocardiographic parameters, and medication history were collected. Data documented included age, sex, New York Heart Association (NYHA) class, hypertension, coronary artery disease, diabetes, obesity, stroke, anemia, lung diseases, liver diseases, thyroid disorders, coronary syndromes, and other pathologies. During hospitalization, vital signs and clinical signs such as edema, pulmonary rales, and jugular venous distension were measured. Laboratory results included, besides NT-proBNP and creatinine, uric acid, urea, liver function tests, electrolytes, HbA1c, complete blood count, and thyroid function tests. Echocardiographic assessment focused on chamber sizes, ejection fraction, diastolic function, valvulopathies, and ventricular wall motion. Additionally, information on pharmacological treatment (ACE inhibitors, beta-blockers, diuretics, anticoagulants, etc.) was collected, and the estimated glomerular filtration rate was calculated using the CKD-EPI formula.

4.4. Statistical Analysis

Statistical analyses were performed using Epi Info 7.2.6.0, SPSS30.0.0.0 and MedCalc23.2.1software. Descriptive statistics were calculated for the demographic and clinical characteristics of the study population. Continuous variables with a Gaussian

distribution were expressed as mean ± standard deviation and evaluated with the appropriate test. Variables with a non-Gaussian distribution were presented as median and interquartile range and evaluated using the Kruskal-Wallis test. The relationships between categorical variables were verified using the Chi-square test, with Yates correction applied when necessary. Risk ratios were calculated for groups with at least fifty patients, while odds ratios were used for groups with smaller numbers. The predictive performance of prognostic indicators was analyzed using receiver operating characteristic curves and cutoff points, utilizing the Youden index. Survival analysis was performed using the Kaplan-Meier method, and the Cox proportional hazards model was applied to determine the impact of significant predictors, selected through a conditional approach. NT-proBNP values were log-transformed using base 10 for multivariable analysis, included both as continuous variables and as dichotomous variables based on previously established cutoff values. A p-value of less than 0.05 was considered statistically significant.

5. Results

5.1. Characteristics of the Studied Population

The VIVA-HF cohort included 716 patients with heart failure, with an average age of 71±10 years, of whom 49% were men. The majority had heart failure with preserved ejection fraction (58.65%), and 68.1% were classified as NYHA class II. Renal function, assessed through creatinine and estimated glomerular filtration rate, indicates a population generally with moderate impairment, with an average eGFR of 69.6 mL/min/1.73 m². The prevalence of comorbidities was high: hypertension (86.7%), diabetes (34.9%), dyslipidemia (76.8%), atrial fibrillation (58.5%), and previous cardiovascular diseases.

Echocardiographic parameters showed an average ejection fraction of 46.5%, with variations depending on the severity of renal dysfunction.

5.2. Correlation between Biomarkers and severity of Renal Dysfunction

NT-proBNP levels increase significantly as renal function declines and are correlated with eGFR. High-sensitivity troponin T (hs-TnT) also shows an increasing distribution in advanced stages of chronic kidney disease, but with substantial variability between sexes and stages, influenced by reduced renal clearance. Elevated levels of both biomarkers indicate faster disease progression and are associated with a higher incidence of complications and mortality.

5.3. Threshold Values for NTproBNP and Troponin in Different Stages of Renal Impairement

Receiver operating characteristic analysis shows that the thresholds for predicting mortality risk are: greater than 1837 pg/mL for eGFR above 60 mL/min, greater than 1413 pg/mL for eGFR 30-60 mL/min, and greater than 6415 pg/mL for eGFR less than 30 mL/min/1.73 m². In groups with severe renal impairment, these thresholds are significantly higher, and the predictive accuracy increases. Troponin T levels above 48.94 pg/mL are associated with a poorer prognosis, especially in advanced stages of chronic kidney disease, and correlate with case severity.

Table 5.3 ROC analysis and cut off values of Nt proBNP across entire eGFR spectrum.

eGFR	AUC (95%CI)	Cut-off Value Sensitivity, Specificity	p value

Entire cohhort	0.726 0.692 – 0.759	> 1991 55.78%, 78.91%	< 0.001
> 60	0.684 0.640 – 0.726	> 1837 50.4%, 80.1%	< 0.001
30 – 60 ml/min	0.717 0.651 – 0.777	> 1413 74.73%, 58.82%	< 0.001
< 30 ml/min	0.850 0.686 – 0.949	> 6415 58.33%, 100%	< 0.001

ROC analysis and cut-off values of troponin across the entire eGFR spectrum			
eGFR	AUC (95%CI)	Cut-off value	p value
Entire cohort	0.646(0.559-0.726)	>12,78pg/ml	0.0032
> 60 ml/min/1.73m2	0.622(0.515-0.72)	>12.78pg/ml	0.04
< 60 ml/min/1.73m2	0.78(0.625-0.893)	>48.94pg/ml	0.001

Table 5.3 ROC analysis and cut off values of Nt proBNP and troponin across entire eGFR spectrum.

5.4. Survival Analysis – Prognostic Models

The Kaplan-Meier analysis demonstrates a correlation between decreasing eGFR and reduced survival duration ($p<0.001$). In patients with eGFR greater than 60 mL/min, troponin T levels above 12.78 pg/mL are associated with significantly shorter survival ($p=0.026$), and in those with severe impairment (eGFR >60 mL/min and troponin T >48.94 pg/mL), the differences are highly significant ($p<0.001$). Using the previously established cutoff values of NT-proBNP, the progressive decline in eGFR was associated with decreased survival duration, with significant differences observed between subgroups based on renal function.

	Cut off value of Troponin hs	survival	Deceased	Chi square	Logrank p
>60ml/min	>12,78pg/ml	74.64±3.56	58.71±3.688	4.973	0.026
<60ml/min	>48.94pg/ml	71.9±3.83	25.6±9.41	21.62	<0.001

	NTproBNP	Survival	Deceased	Chi square	Logrank p value
> 60	> 1837	71.46 ± 1.22	50.92 ± 2.85	55.47	< 0.001
30 – 60 ml/min	> 1413	69.81 ± 2.16	46.21 ± 2.96	29.69	< 0.001
< 30 ml/min	> 6415	46.45 ± 5.53	20.57 ± 6.39	8.99	0.003

Table5.4 Kaplan-Meier survival analysis

5.5. Multivariate Analysis and Predictive Independence

The Cox model identified independent risk factors for mortality: male sex, NYHA class III/IV, hemoglobin level, NT-proBNP level, and pulmonary artery pressures, depending on the severity of chronic kidney disease. Notably, NT-proBNP, when analyzed as a continuous variable, demonstrated its independence as a predictor, surpassing ejection fraction and age, especially in patients with eGFR less than 30 mL/min.

6. Discussions

6.1. Main findings interpretation

Analysis of this cohort of hospitalized patients with heart failure, with or without renal impairment, showed that NT-proBNP levels increase as eGFR decreases, but they remain an independent predictor of long-term mortality from all causes across the entire spectrum of renal impairment. Reference thresholds for prediction were adjusted according to the degree of renal deterioration, with higher levels in patients with advanced renal dysfunction. A sharp increase in the cutoff point was observed in patients with eGFR less than 30 mL/min, where the cutoff value for mortality prediction was 6415 pg/mL. [131]. Furthermore, as eGFR decreases, the number of clinical or non-clinical parameters that remain independently associated with the outcome becomes increasingly limited[131].

6.2. Comparison with other relevant studies

Our findings are in accordance with previous data, which confirm the increase in natriuretic peptide levels in the progressively more advanced stages of renal dysfunction. Similarly, troponin levels, which reflect myocardial injury and the burden of comorbidities that can lead to cardiac damage, have been demonstrated to be independent predictors of survival and re-hospitalizations in patients with heart failure and kidney disease, according to recent systematic reviews [1].

T-proBNP concentrations have been shown to be inversely correlated with eGFR among patients with renal impairment. In a cohort of 177 non-diabetic patients with mild to moderate chronic kidney disease, NT-proBNP levels increased proportionally with decreasing eGFR, and a cutoff value of 213 ng/L was predictive of chronic kidney disease progression[132]. Additionally, higher median levels of NT-proBNP were reported by Fandini and colleagues in patients with CKD compared to those without, respectively 238.5 pg/mL versus 44.0 pg/mL ($p < 0.001$)[133]. An analysis of the CRIC and SPRINT cohorts, which included patients without a prior diagnosis of heart failure, showed that the 95th percentile NT-proBNP values increased from 682 pg/mL in subjects with eGFR between 45-59 mL/min/1.73 m^2, to 1130 pg/mL for those with eGFR between 30-44 mL/min/1.73 m^2, and up to 2523 pg/mL in patients with eGFR less than 30 mL/min/1.73 m^2 [134].

This consistent increase in NT-proBNP levels can be partially attributed to the impaired renal function's inability to eliminate these peptides from circulation, which enhances its reliability

as a prognostic marker. Moreover, for patients with cardiovascular disease and an estimated glomerular filtration rate less than 30 mL/min/1.73 m², the optimal cutoff for predicting all-cause mortality and major cardiovascular events was established at much higher values, at 5809.0 pg/mL, compared to 258.6 pg/mL in those with eGFR ≥ 30 mL/min/1.73 m²[70].

Consistent with our findings, another systematic review and meta-analysis examining the clinical utility of NT-proBNP for acute decompensated heart failure demonstrated that this biomarker retains its diagnostic and prognostic value in patients with renal dysfunction, presenting higher levels than in the normal population [62]. In a cohort of 341 patients with stable chronic heart failure, the cutoff values for NT-proBNP in predicting cardiac events or hospitalizations due to worsening heart failure were ≥1474 pg/mL for those with eGFR less than 60 mL/min [135], Similar to the cutoff identified in our sample for all-cause mortality in patients with the same GFR. Chinese patients with coronary artery disease followed for 417 days showed different cutoff points for those with and without chronic kidney disease[136]. In this cohort, for patients with eGFR less than 60 mL/min/1.73 m², NT-proBNP levels greater than 370 pg/mL represented the cutoff for poorer prognosis, while for those with eGFR ≥ 60 mL/min/1.73 m², the threshold was much higher, with NT-proBNP > 2584 pg/mL. [72]. Confirming our findings in patients with eGFR less than 30 mL/min/1.73 m²[131], Horii and colleagues found that NT-proBNP levels greater than 5809 pg/mL were significantly associated with all-cause mortality [70].

6.3. Clinical Implications and Practical Applications

We support the clinical use of NT-proBNP as a predictor of long-term all-cause mortality in patients with heart failure and chronic kidney disease, given that this biomarker has maintained its prognostic value across all eGFR subgroups [131].

This study confirmed that NT-proBNP, a key marker of myocardial dysfunction and renal impairment, and pulmonary artery systolic pressure, an indicator of right heart failure and pulmonary hypertension, were the two consistent independent predictors of long-term all-cause mortality across all eGFR subgroups[131]. Previous data have shown that in patients with chronic kidney disease, the incidence of pulmonary hypertension is determined by age, anemia, reduced left ventricular ejection fraction, and left ventricular hypertrophy [137]. In accordance with our findings, increased pulmonary artery systolic pressure and the presence of pulmonary hypertension have previously been independently associated with a higher risk of death in patients with chronic kidney disease [137], as well as among patients in end-stage

renal disease [138], thereby consolidating the role of pulmonary hypertension as a crucial risk factor for mortality in this patient population.

A multitude of new biomarkers have been evaluated with the aim of improving the prognosis of heart failure [139], [140], [141], [142], along with multiparametric risk models that seek to enhance the predictive accuracy [143], [144]. In a recent comparison, the BCN-Bio-HF score, which includes NT-proBNP levels along with renal function, clinical variables, and other laboratory parameters, demonstrated the best analytical performance among other prognostic scores, highlighting the prognostic value of the biomarker [145].

A novel aspect of our study is the separate analysis for patients in different eGFR groups, highlighting different independent parameters for those with progressively worse renal function. Our results emphasize the importance of heart failure severity, both of the left and right ventricles, alongside the severity of renal dysfunction, particularly in patients with eGFR less than 30 mL/min/1.73 m². For these patients, other commonly used predictors have lost their independent prognostic value. For example, in patients with eGFR greater than 90 mL/min/1.73 m² or between 30-60 mL/min/1.73 m², hemoglobin levels were independently associated with mortality, according to previous studies[96], whereas in patients with eGFR less than 30 mL/min/1.73 m², this correlation was no longer maintained in multivariate analysis[131]. The triad of heart failure, chronic kidney disease (CKD), and anemia is well known for its significant impact on survival prognosis [146]; However, one could argue that its predictive role is less reliable in advanced stages of cardiac and renal disease, where the two pathologies become the primary determinants of mortality risk. Concordant findings have also been reported for patients with acute cardio-renal syndrome, in which renal function at admission constitutes an essential predictor of prognosis [147].

Troponin levels are strong independent predictors of cardiovascular and all-cause mortality in patients with heart failure, after adjusting for renal function. Notably, renal dysfunction modifies the prognostic value of troponin, with the highest risk observed among patients presenting both elevated troponin levels and impaired renal function. In patients with chronic heart failure, elevated high-sensitivity troponin T levels are particularly relevant as independent markers for all-cause mortality, regardless of renal function index [104], [105], [117][106], [109][148][119], [149][26], [60][116].

A crucial aspect of this analysis is the strong association between elevated high-sensitivity troponin T (hs-cTnT) levels and all-cause mortality; Jungbauer and colleagues reported that

patients in the highest quartile had a hazard ratio (HR) of 2.6 for mortality, after adjusting for renal function, demonstrating the importance of troponin as a prognostic marker in the management of heart failure [117].

Additionally, understanding the relationship between cardiac and renal function is essential, as elevated troponin levels often indicate myocardial injury but also reflect worsening renal function. For example, Tentzeris et al. demonstrated that increased levels of high-sensitivity troponin T are correlated with renal failure, highlighting the need for a comprehensive assessment of both the heart and kidneys[116].

Our results corroborate these observations and extend this knowledge: survival analysis in the subgroup of patients with heart failure and the determination of high-sensitivity troponin T (hs-TnT) levels at admission revealed significant clinico-biological differences between surviving and deceased patients, reinforcing the idea that troponin levels are an important predictor of long-term prognosis in this vulnerable population.

Levels above the threshold of 12.78 pg/mL (the cutoff recommended by previous studies) are associated with a higher mortality rate, especially in patients with impaired renal function (eGFR below 60 mL/min/1.73 m^2). In our cohort, patients with troponin levels above 12.78 pg/mL had a higher average age compared to those below the threshold; however, this difference was not statistically significant ($p=0.13$), suggesting that troponin levels, independent of age or other clinical variables, may have prognostic value.

Furthermore, clinical and laboratory characteristics indicate that deceased patients, on average, had higher leukocyte and neutrophil counts, suggesting a possibly more pronounced inflammatory state or stronger immune reaction—factors recognized for their negative impact on prognosis in acute and chronic heart failure. Similarly, troponin levels above the threshold of 12.78 pg/mL correlated with a significant reduction in left ventricular ejection fraction, indicating severe deterioration of myocardial function.

Importantly, in the Kaplan-Meier analysis, differences in survival patterns were observed in both subgroups: in patients with eGFR > 60 mL/min/1.73 m^2, troponin levels above 12.78 pg/mL were associated with a significant decrease in survival ($p=0.026$), while in those with eGFR < 60 mL/min/1.73 m^2, this threshold of 48.94 pg/mL highlighted a highly significant difference between groups ($p<0.001$)

7.Study limitations

Among the main limitations are the retrospective and observational nature of the study, which restricts causal inference and may introduce selection bias. The relatively small size of the subgroup with severe renal impairment (eGFR <30 mL/min/1.73 m²) limits the generalizability and robustness of the conclusions for this population. Additionally, biomarker values were only assessed at admission, without dynamic follow-up, which limits interpretation of temporal changes. Non-cardiac factors, such as comorbidities or administered treatments, may influence these marker levels and were not fully controlled.

The study was conducted at a single center. While this allowed us to include a larger number of patients and to have a follow-up period of over four years, it restricted the number of variables that could be evaluated. Nevertheless, for the purpose of identifying the utility and cutoff values of NT-proBNP in different eGFR subgroups for predicting all-cause mortality, we managed to include in the multivariable analysis the main cardiovascular and non-cardiovascular factors that could potentially act as confounders.

8. Conclusions and Personal Contributions

The conducted research achieved the proposed objectives, demonstrating a significant impact of NT-proBNP and high-sensitivity troponin T biomarkers on the prognosis of heart failure in patients with renal dysfunction. Our study confirms that NT-proBNP levels measured at admission are significant predictors of long-term mortality, independent of the eGFR groups associated with renal impairment. The cutoff values for NT-proBNP ranged between >1413 and 1991 pg/mL for the general cohort and for groups with eGFR >30 mL/min/1.73 m², with a recommendation to use a threshold of >6415 pg/mL for patients with eGFR <30 mL/min/1.73 m².[131].

his finding highlights the critical role of NT-proBNP levels and suggests using high-sensitivity troponin T levels as a valuable marker in risk stratification for mortality in heart failure. It is important that cutoff values be adjusted according to the degree of renal impairment and monitored longitudinally to enhance prediction accuracy.
The technical and economic advantages include precise risk stratification, which can lead to personalized patient management. Remaining unresolved issues involve the need for integrated predictive models and prospective validation in larger populations.

Own Contributions:

1. Establishing adjusted cutoff values for NT-proBNP across various levels of renal function, detailed in chapter 5
2. Confirming the role of NT-proBNP and high-sensitivity Troponin T as independent predictors of mortality in heart failure with renal dysfunction, discussed in chapter 5
3. Introducing variable cutoff values for high-sensitivity Troponin T, depending on eGFR, and advocating for their integration into clinical protocols, highlighted in chapter 5
4. Demonstrating the predictive capacity of biomarkers for mortality and emphasizing the importance of continuous monitoring, developed in chapter 5.
5. Providing a framework for adjusting biomarker values based on the presence of renal dysfunction, open for future research and extended clinical applicability.

These contributions highlight the potential impact of biomarkers in the management of heart and kidney failure, providing guidance for improving treatment strategies and risk assessment.

9.References

[1] A. Breha, C. Delcea, A. C. Ivanescu, and G. A. Dan, "The Prognostic Value of Troponin Levels Adjusted for Renal Function in Heart Failure - A Systematic Review," *Rom. J. Intern. Med.*, Apr. 2025, doi: 10.2478/RJIM-2025-0006.

[2] A. I. Guaricci *et al.*, "Assessment and management of heart failure in patients with chronic kidney disease," *Heart Fail. Rev.*, vol. 29, no. 2, pp. 379–394, 2024, doi: 10.1007/s10741-023-10346-x.

[3] T. A. McDonagh *et al.*, "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure," Sep. 21, 2021, *Oxford University Press*. doi: 10.1093/eurheartj/ehab368.

[4] "braundwald's heart disease tenth's edition," in *braundwald's heart disease*, 2015, pp. 1909–1942.

[5] T. A. McDonagh *et al.*, "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure," *Eur. Heart J.*, vol. 42, no. 36, pp. 3599–3726, 2021, doi: 10.1093/eurheartj/ehab368.

[6] A. Mosterd and A. W. Hoes, "Clinical epidemiology of heart failure," *Heart*, vol. 93, no. 9, pp. 1137–1146, 2007, doi: 10.1136/hrt.2003.025270.

[7] A. Barasa, M. Schaufelberger, G. Lappas, K. Swedberg, M. Dellborg, and A. Rosengren, "Heart failure in young adults: 20-year trends in hospitalization, aetiology, and case fatality in Sweden," *Eur. Heart J.*, vol. 35, no. 1, pp. 25–32, 2014, doi: 10.1093/eurheartj/eht278.

[8] S. J. Pocock *et al.*, "Predicting survival in heart failure: A risk score based on 39 372 patients from 30 studies," *Eur. Heart J.*, vol. 34, no. 19, pp. 1404–1413, 2013, doi: 10.1093/eurheartj/ehs337.

[9] P. E. Stevens *et al.*, "KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease," *Kidney Int.*, vol. 105, no. 4S, pp. S117–S314, Apr. 2024, doi: 10.1016/J.KINT.2023.10.018.

[10] M. S. Matovinović, "M. Sabljar Matovinović Pathophysiology and classification of

kidney disease 1. PATHOPHYSIOLOGY AND CLASSIFICATION OF KIDNEY DISEASES," *J. Int. Fed. Clin. Chem. Lab. Med.*, vol. 20, no. 1, pp. 2–11, 2020, [Online]. Available: http://www.ifcc.org

[11] V. L. Roger, "Of Probabilities and Uncertainties: Current Challenges of the Heart Failure Epidemic," *JACC Hear. Fail.*, vol. 6, no. 8, pp. 686–688, Aug. 2018, doi: 10.1016/J.JCHF.2018.05.003.

[12] K. Damman, M. A. E. Valente, A. A. Voors, C. M. O'Connor, D. J. Van Veldhuisen, and H. L. Hillege, "Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis," *Eur. Heart J.*, vol. 35, no. 7, pp. 455–469, Feb. 2014, doi: 10.1093/EURHEARTJ/EHT386.

[13] E. L. Schiffrin, M. L. Lipman, and J. F. E. Mann, "Chronic kidney disease: Effects on the cardiovascular system," *Circulation*, vol. 116, no. 1, pp. 85–97, Jul. 2007, doi: 10.1161/CIRCULATIONAHA.106.678342/ASSET/C7519541-21D4-4F72-94D7-BBC93CAB2252/ASSETS/GRAPHIC/25FF1.JPEG.

[14] M. T. Sweetwyne, J. Tao, and K. Susztak, "Kick it up a notch: Notch signaling and kidney fibrosis," *Kidney Int. Suppl.*, vol. 4, no. 1, pp. 91–96, 2014, doi: 10.1038/kisup.2014.17.

[15] X. Li and B. Lindholm, "Cardiovascular Risk Prediction in Chronic Kidney Disease," *Am. J. Nephrol.*, vol. 53, no. 10, pp. 730–739, 2023, doi: 10.1159/000528560.

[16] C. Zoccali *et al.*, "Cardiovascular complications in chronic kidney disease: a review from the European Renal and Cardiovascular Medicine Working Group of the European Renal Association," *Cardiovasc. Res.*, vol. 119, no. 11, pp. 2017–2032, 2023, doi: 10.1093/cvr/cvad083.

[17] A. S. Go *et al.*, *Heart Disease and Stroke Statistics - 2014 Update: A report from the American Heart Association*, vol. 129, no. 3. 2014. doi: 10.1161/01.cir.0000441139.02102.80.

[18] D. S. Silverberg, "The role of erythropoiesis stimulating agents and intravenous (IV) iron in the cardio renal anemia syndrome," *Heart Fail. Rev.*, vol. 16, no. 6, pp. 609–614, 2011, doi: 10.1007/s10741-010-9194-2.

[19] R. T. Cole, A. Masoumi, F. Triposkiadis, G. Giamouzis, V. Georgiopoulou, and A. Kalogeropoulos, “R e nal D ysf u n c t i o n i n He a rt Fa i l ure,” vol. 96, pp. 955–974, 2012.

[20] N. G. Vallianou, S. Mitesh, A. Gkogkou, and E. Geladari, “Chronic Kidney Disease and Cardiovascular Disease: Is there Any Relationship?,” *Curr. Cardiol. Rev.*, vol. 15, no. 1, pp. 55–63, 2018, doi: 10.2174/1573403x14666180711124825.

[21] Y. Zhang *et al.*, “Clinical and serum-based markers are associated with death within 1 year of de novo implant in primary prevention ICD recipients,” *Hear. Rhythm*, vol. 12, no. 2, pp. 360–366, 2015, doi: 10.1016/j.hrthm.2014.10.034.

[22] M. Naghavi *et al.*, “Global, regional, and national age-sex specific all-cause and cause-specific mortality for 240 causes of death, 1990-2013: A systematic analysis for the Global Burden of Disease Study 2013,” *Lancet*, vol. 385, no. 9963, pp. 117–171, 2015, doi: 10.1016/S0140-6736(14)61682-2.

[23] C. W. Yancy *et al.*, “2013 ACCF/AHA guideline for the management of heart failure: A report of the American college of cardiology foundation/american heart association task force on practice guidelines,” *J. Am. Coll. Cardiol.*, vol. 62, no. 16, pp. e147–e239, 2013, doi: 10.1016/j.jacc.2013.05.019.

[24] T. J. Bunch *et al.*, “Effect of beta-blocker therapy on mortality rates and future myocardial infarction rates in patients with coronary artery disease but no history of myocardial infarction or congestive heart failure,” *Am. J. Cardiol.*, vol. 95, no. 7, pp. 827–831, 2005, doi: 10.1016/j.amjcard.2004.12.008.

[25] R. S. Gardner, F. Özalp, A. J. Murday, S. D. Robb, and T. A. McDonagh, “N-terminal pro-brain natriuretic peptide: A new gold standard in predicting mortality in patients with advanced heart failure,” *Eur. Heart J.*, vol. 24, no. 19, pp. 1735–1743, 2003, doi: 10.1016/j.ehj.2003.07.005.

[26] C. Mueller *et al.*, “Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations,” *Eur. J. Heart Fail.*, vol. 21, no. 6, pp. 715–731, 2019, doi: 10.1002/ejhf.1494.

[27] T. G. Harrison *et al.*, “Association of NT-proBNP and BNP With Future Clinical Outcomes in Patients With ESKD: A Systematic Review and Meta-analysis,” *Am. J. Kidney Dis.*, vol. 76, no. 2, pp. 233–247, 2020, doi: 10.1053/j.ajkd.2019.12.017.

[28] S. Niizuma *et al.*, “Impact of left ventricular end-diastolic wall stress on plasma B-type natriuretic peptide in heart failure with chronic kidney disease and end-stage renal disease,” *Clin. Chem.*, vol. 55, no. 7, pp. 1347–1353, 2009, doi: 10.1373/clinchem.2008.121236.

[29] H. Takase and Y. Dohi, “Kidney function crucially affects B-type natriuretic peptide (BNP), N-terminal proBNP and their relationship,” *Eur. J. Clin. Invest.*, vol. 44, no. 3, pp. 303–308, 2014, doi: 10.1111/eci.12234.

[30] J. P. Goetze, G. Jensen, S. Møller, F. Bendtsen, J. F. Rehfeld, and J. H. Henriksen, “BNP and N-terminal proBNP are both extracted in the normal kidney,” *Eur. J. Clin. Invest.*, vol. 36, no. 1, pp. 8–15, 2006, doi: 10.1111/j.1365-2362.2006.01594.x.

[31] P. A. McCullough *et al.*, “B-type natriuretic peptide and renal function in the diagnosis of heart failure: An analysis from the Breathing Not Properly Multinational Study,” *Am. J. Kidney Dis.*, vol. 41, no. 3, pp. 571–579, 2003, doi: 10.1053/ajkd.2003.50118.

[32] L. Jafri *et al.*, “B-type natriuretic peptide versus amino terminal pro-B type natriuretic peptide: Selecting the optimal heart failure marker in patients with impaired kidney function,” *BMC Nephrol.*, vol. 14, no. 1, 2013, doi: 10.1186/1471-2369-14-117.

[33] W. G. Guntheroth, “Decompensated Heart Failure and Diuretic Resistance,” *J. Am. Coll. Cardiol.*, vol. 48, no. 5, pp. 1059–1060, 2006, doi: 10.1016/j.jacc.2006.06.010.

[34] X. Han *et al.*, “Cardiac biomarkers of heart failure in chronic kidney disease,” *Clin. Chim. Acta*, vol. 510, no. May, pp. 298–310, 2020, doi: 10.1016/j.cca.2020.07.040.

[35] R. R. J. van Kimmenade *et al.*, “Amino-Terminal Pro-Brain Natriuretic Peptide, Renal Function, and Outcomes in Acute Heart Failure. Redefining the Cardiorenal Interaction?,” *J. Am. Coll. Cardiol.*, vol. 48, no. 8, pp. 1621–1627, 2006, doi: 10.1016/j.jacc.2006.06.056.

[36] G. M. Felker *et al.*, “Effect of natriuretic peptide–guided therapy on hospitalization or cardiovascular mortality in high-risk patients with heart failure and reduced ejection fraction: A randomized clinical trial,” *JAMA - J. Am. Med. Assoc.*, vol. 318, no. 8, pp. 713–720, 2017, doi: 10.1001/jama.2017.10565.

[37] P. A. Heidenreich *et al.*, “2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines,” May 03, 2022, *Lippincott Williams and Wilkins*. doi: 10.1161/CIR.0000000000001063.

[38] J. A. J. G. van den Brand, G. A. J. van Boekel, H. L. Willems, L. A. L. M. Kiemeney, M. den Heijer, and J. F. M. Wetzels, “Introduction of the CKD-EPI equation to estimate glomerular filtration rate in a Caucasian population.,” *Nephrol. Dial. Transplant*, vol. 26, no. 10, pp. 3176–3181, 2011, doi: 10.1093/ndt/gfr003.

[39] N. Lee *et al.*, “Impact of Cardiac Troponin Elevation on Mortality of Patients with Acute Heart Failure: Insights from the Korea Acute Heart Failure (KorAHF) Registry,” *J. Clin. Med.*, vol. 11, no. 10, pp. 1–13, 2022, doi: 10.3390/jcm11102800.

[40] T. Tsutamoto *et al.*, “Relationship between renal function and serum cardiac troponin T in patients with chronic heart failure,” *Eur. J. Heart Fail.*, vol. 11, no. 7, pp. 653–658, 2009, doi: 10.1093/eurjhf/hfp072.

[41] R. Latini *et al.*, “Prognostic Value of Very Low Plasma Concentrations of Troponin T in Patients With Stable Chronic Heart Failure,” 2007, doi: 10.1161/CIRCULATIONAHA.106.655076.

[42] V. Nagarajan, A. V. Hernandez, and W. H. W. Tang, “Prognostic value of cardiac troponin in chronic stable heart failure: a systematic review,” *Heart*, vol. 98, no. 24, pp. 1778–1786, Dec. 2012, doi: 10.1136/HEARTJNL-2012-301779.

[43] S. Seliger, “The Cardiorenal Syndrome: Mechanistic Insights and Prognostication with Soluble Biomarkers,” *Curr. Cardiol. Rep.*, vol. 22, no. 10, 2020, doi: 10.1007/s11886-020-01360-8.

[44] J. O. Burton, H. J. Jefferies, N. M. Selby, and C. W. McIntyre, “Hemodialysis-induced cardiac injury: determinants and associated outcomes,” *Clin. J. Am. Soc. Nephrol.*, vol. 4, no. 5, pp. 914–920, May 2009, doi: 10.2215/CJN.03900808.

[45] C. Hall, “NT-ProBNP: the mechanism behind the marker.,” *J. Card. Fail.*, vol. 11, no. 5 Suppl, pp. 81–83, 2005, doi: 10.1016/j.cardfail.2005.04.019.

[46] W. ling Yang, M. Fahim, and D. W. Johnson, “Pathophysiology and significance of natriuretic peptides in patients with end-stage kidney disease,” *Clin. Biochem.*, vol.

83, no. May, pp. 1–11, 2020, doi: 10.1016/j.clinbiochem.2020.05.013.

[47] W. E. Hopkins, Z. Chen, N. K. Fukagawa, C. Hall, H. J. Knot, and M. M. LeWinter, "Increased atrial and brain natriuretic peptides in adults with cyanotic congenital heart disease: Enhanced understanding of the relationship between hypoxia and natriuretic peptide secretion," *Circulation*, vol. 109, no. 23, pp. 2872–2877, 2004, doi: 10.1161/01.CIR.0000129305.25115.80.

[48] W. Yan, F. Wu, J. Morser, and Q. Wu, "Corin, a transmembrane cardiac serine protease, acts as a pro-atrial natriuretic peptide-converting enzyme," *Proc. Natl. Acad. Sci. U. S. A.*, vol. 97, no. 15, pp. 8525–8529, 2000, doi: 10.1073/pnas.150149097.

[49] J. Magga, M. Marttila, P. Mäntymaa, O. Vuolteenaho, and H. Ruskoaho, "Brain natriuretic peptide in plasma, atria, and ventricles of vasopressin- and phenylephrine-infused conscious rats," *Endocrinology*, vol. 134, no. 6, pp. 2505–2515, Jun. 1994, doi: 10.1210/endo.134.6.8194476.

[50] T. Tsuruda *et al.*, "Brain natriuretic peptide is produced in cardiac fibroblasts and induces matrix metalloproteinases," *Circ. Res.*, vol. 91, no. 12, pp. 1127–1134, 2002, doi: 10.1161/01.RES.0000046234.73401.70.

[51] M. Harada *et al.*, "Interaction of myocytes and nonmyocytes is necessary for mechanical stretch to induce ANP/BNP production in cardiocyte culture.," *J. Cardiovasc. Pharmacol.*, vol. 31 Suppl 1, pp. S357-9, 1998, doi: 10.1097/00005344-199800001-00100.

[52] R. E. Klabunde, *Cardiovascular Physiology Concepts, 3e*. Lippincott Williams & Wilkins, a Wolters Kluwer business, 2022.

[53] P. Srisawasdi, S. Vanavanan, C. Charoenpanichkit, and M. H. Kroll, "The effect of renal dysfunction on BNP, NT-proBNP, and their ratio," *Am. J. Clin. Pathol.*, vol. 133, no. 1, pp. 14–23, 2010, doi: 10.1309/AJCP60HTPGIGFCNK.

[54] M. Packer *et al.*, "Empagliflozin in Patients With Heart Failure, Reduced Ejection Fraction, and Volume Overload: EMPEROR-Reduced Trial," *J. Am. Coll. Cardiol.*, vol. 77, no. 11, pp. 1381–1392, Mar. 2021, doi: 10.1016/J.JACC.2021.01.033.

[55] L. J. Sokoll *et al.*, "Multicenter analytical performance evaluation of the Elecsys®

proBNP assay," *Clin. Chem. Lab. Med.*, vol. 42, no. 8, pp. 965–972, 2004, doi: 10.1515/CCLM.2004.157.

[56] P. J. Hunt, A. M. Richards, M. G. Nicholls, T. G. Yandle, R. N. Doughty, and E. A. Espiner, "Immunoreactive amino-terminal pro-brain natriuretic peptide (NT-PROBNP): A new marker of cardiac impairment," *Clin. Endocrinol. (Oxf).*, vol. 47, no. 3, pp. 287–296, 1997, doi: 10.1046/j.1365-2265.1997.2361058.x.

[57] P. O. Collinson, S. C. Barnes, D. C. Gaze, G. Galasko, A. Lahiri, and R. Senior, "Analytical performance of the N terminal pro B type natriuretic peptide (NT-proBNP) assay on the Elecsys™ 1010 and 2010 analysers," *Eur. J. Heart Fail.*, vol. 6, no. 3, pp. 365–368, 2004, doi: 10.1016/j.ejheart.2004.01.011.

[58] R. S. Society, "Referência 47," vol. 145, no. 4, pp. 510–511, 2014.

[59] S. Niizuma, Y. Iwanaga, T. Yahata, and S. Miyazaki, "Renocardiovascular Biomarkers: from the Perspective of Managing Chronic Kidney Disease and Cardiovascular Disease," *Front. Cardiovasc. Med.*, vol. 4, no. March, 2017, doi: 10.3389/fcvm.2017.00010.

[60] H. Bosselmann *et al.*, "Prognostic significance of cardiovascular biomarkers and renal dysfunction in outpatients with systolic heart failure: A long term follow-up study," *Int. J. Cardiol.*, vol. 170, no. 2, pp. 202–207, 2013, doi: 10.1016/j.ijcard.2013.10.064.

[61] S. Vickery *et al.*, "B-type natriuretic peptide (BNP) and amino-terminal proBNP in patients with CKD: Relationship to renal function and left ventricular hypertrophy," *Am. J. Kidney Dis.*, vol. 46, no. 4, pp. 610–620, 2005, doi: 10.1053/j.ajkd.2005.06.017.

[62] J. A. Schaub, S. G. Coca, D. G. Moledina, M. Gentry, J. M. Testani, and C. R. Parikh, "Amino-Terminal Pro-B-Type Natriuretic Peptide for Diagnosis and Prognosis in Patients With Renal Dysfunction: A Systematic Review and Meta-Analysis," *JACC Hear. Fail.*, vol. 3, no. 12, pp. 977–989, 2015, doi: 10.1016/j.jchf.2015.07.014.

[63] C. Chenevier-Gobeaux, Y. E. Claessens, S. Voyer, D. Desmoulins, and O. G. J. C. Ekindjian, "Influence of renal function on N-terminal pro-brain natriuretic peptide (NT-proBNP) in patients admitted for dyspnoea in the Emergency Department:

Comparison with brain natriuretic peptide (BNP)," *Clin. Chim. Acta*, vol. 361, no. 1–2, pp. 167–175, 2005, doi: 10.1016/j.cccn.2005.05.021.

[64] S. Anwaruddin *et al.*, "Renal function, congestive heart failure, and amino-terminal pro-brain natriuretic peptide measurement: Results from the ProBNP investigation of dyspnea in the emergency department (PRIDE) study," *J. Am. Coll. Cardiol.*, vol. 47, no. 1, pp. 91–97, 2006, doi: 10.1016/j.jacc.2005.08.051.

[65] A. Çolak, S. Çuhadar, B. Gölcük, Y. Gölcük, Ö. Özdoğan, and I. Çoker, "Effect of renal failure on N-terminal pro-brain natriuretic peptide in patients admitted to emergency department with acute dyspnea," *Anadolu Kardiyol. Derg.*, vol. 14, no. 6, pp. 519–524, 2014, doi: 10.5152/akd.2014.4944.

[66] C. DeFilippi *et al.*, "Interpreting Cardiac Troponin Results from High-Sensitivity Assays in Chronic Kidney Disease without Acute Coronary Syndrome," *Clin. Chem.*, vol. 58, no. 9, pp. 1342–1351, Sep. 2012, doi: 10.1373/CLINCHEM.2012.185322.

[67] I. Coquet *et al.*, "Performance of N-terminal-pro-B-type natriuretic peptide in critically ill patients: A prospective observational cohort study," *Crit. Care*, vol. 12, no. 6, pp. 1–6, 2008, doi: 10.1186/cc7110.

[68] H. H. Leuchte *et al.*, "N-terminal pro-brain natriuretic peptide and renal insufficiency as predictors of mortality in pulmonary hypertension," *Chest*, vol. 131, no. 2, pp. 402–409, 2007, doi: 10.1378/chest.06-1758.

[69] H. J. Park *et al.*, "Direct comparison of B-type natriuretic peptide and N-terminal pro-BNP for assessment of cardiac function in a large population of symptomatic patients," *Int. J. Cardiol.*, vol. 140, no. 3, pp. 336–343, 2010, doi: 10.1016/j.ijcard.2008.11.107.

[70] M. Horii *et al.*, "Prognostic value of B-type natriuretic peptide and its amino-terminal proBNP fragment for cardiovascular events with stratification by renal function," *J. Cardiol.*, vol. 61, no. 6, pp. 410–416, 2013, doi: 10.1016/j.jjcc.2013.01.015.

[71] B. C. Astor *et al.*, "N-terminal prohormone brain natriuretic peptide as a predictor of cardiovascular disease and mortality in blacks with hypertensive kidney disease: The African American Study of Kidney Disease and Hypertension (AASK),"

Circulation, vol. 117, no. 13, pp. 1685–1692, 2008, doi: 10.1161/CIRCULATIONAHA.107.724187.

[72] S. Fu *et al.*, "The ability of NT-proBNP to detect chronic heart failure and predict all-cause mortality is higher in elderly Chinese coronary artery disease patients with chronic kidney disease," *Clin. Interv. Aging*, vol. 8, pp. 409–417, 2013, doi: 10.2147/CIA.S42700.

[73] M. S. Parmacek and R. J. Solaro, "Biology of the troponin complex in cardiac myocytes," *Prog. Cardiovasc. Dis.*, vol. 47, no. 3, pp. 159–176, 2004, doi: 10.1016/j.pcad.2004.07.003.

[74] A. H. B. Wu and R. H. Christenson, "Analytical and assay issues for use of cardiac troponin testing for risk stratification in primary care," *Clin. Biochem.*, vol. 46, no. 12, pp. 969–978, 2013, doi: 10.1016/j.clinbiochem.2013.04.013.

[75] R. A. Byrne *et al.*, "2023 ESC Guidelines for the management of acute coronary syndromes," *Eur. Heart J.*, vol. 44, no. 38, pp. 3720–3826, 2023, doi: 10.1093/eurheartj/ehad191.

[76] M. J. Conrad and P. Jarolim, "Cardiac troponins and high-sensitivity cardiac troponin assays," *Clin. Lab. Med.*, vol. 34, no. 1, pp. 59–73, 2014, doi: 10.1016/j.cll.2013.11.008.

[77] C. Mueller *et al.*, "Rapid rule out of acute myocardial infarction: novel biomarker-based strategies," *Eur. Hear. J. Acute Cardiovasc. Care*, vol. 6, no. 3, pp. 218–222, 2017, doi: 10.1177/2048872616653229.

[78] M. Roffi *et al.*, "2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent st-segment elevation: Task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of ," Jan. 2016, *Eur Heart J.* doi: 10.1093/eurheartj/ehv320.

[79] M. Möckel *et al.*, "Editor's Choice-Rule-in of acute myocardial infarction: Focus on troponin," *Eur. Hear. J. Acute Cardiovasc. Care*, vol. 6, no. 3, pp. 212–217, 2017, doi: 10.1177/2048872616653228.

[80] T. Reichlin *et al.*, "One-hour rule-out and rule-in of acute myocardial infarction

using high-sensitivity cardiac troponin T," *Arch. Intern. Med.*, vol. 172, no. 16, pp. 1211–1218, 2012, doi: 10.1001/archinternmed.2012.3698.

[81] C. Mueller, "Biomarkers and acute coronary syndromes: An update," *Eur. Heart J.*, vol. 35, no. 9, pp. 552–556, 2014, doi: 10.1093/eurheartj/eht530.

[82] J. Boeddinghaus *et al.*, "Clinical use of a new high-sensitivity cardiac troponin I assay in patients with suspected myocardial infarction," *Clin. Chem.*, vol. 65, no. 11, pp. 1426–1436, 2019, doi: 10.1373/clinchem.2019.304725.

[83] D. Logeart *et al.*, "Evidence of cardiac myolysis in severe nonischemic heart failure and the potential role of increased wall strain," *Am. Heart J.*, vol. 141, no. 2, pp. 247–253, 2001, doi: 10.1067/mhj.2001.111767.

[84] M. Torre and P. Jarolim, "Cardiac troponin assays in the management of heart failure," Feb. 04, 2015, *Elsevier*. doi: 10.1016/j.cca.2014.12.027.

[85] A. P. Maggioni *et al.*, "The New England Journal of Medicine Downloaded from nejm.org at UC SHARED JOURNAL COLLECTION on February 14, 2011. For personal use only. No other uses without permission. Copyright © 1993 Massachusetts Medical Society. All rights reserved.," *N. Engl. J. Med.*, vol. 329, no. 20, pp. 1442–1448, 1993.

[86] A. H. Failure, "H 1182 ̈," *J. Med.*, 1996.

[87] E. R. Perna *et al.*, "Ongoing myocardial injury in stable severe heart failure: Value of cardiac troponin T monitoring for high-risk patient identification," *Circulation*, vol. 110, no. 16, pp. 2376–2382, 2004, doi: 10.1161/01.CIR.0000145158.33801.F3.

[88] C. Roongsritong, I. Warraich, and C. Bradley, "Common causes of troponin elevations in the absence of acute myocardial infarction: Incidence and clinical significance," *Chest*, vol. 125, no. 5, pp. 1877–1884, 2004, doi: 10.1378/chest.125.5.1877.

[89] A. V. Gomes, J. D. Potter, and D. Szczesna-Cordary, "The role of troponins in muscle contraction," *IUBMB Life*, vol. 54, no. 6, pp. 323–333, 2002, doi: 10.1080/15216540216037.

[90] A. F. Huxley, "Cross-bridge action: Present views, prospects, and unknowns," *J. Biomech.*, vol. 33, no. 10, pp. 1189–1195, 2000, doi: 10.1016/S0021-

9290(00)00060-9.

[91] R. Maytum, S. S. Lehrer, and M. A. Geeves, “Maytum1999.pdf,” pp. 1102–1110, 1999.

[92] A. M. Gordon, E. Homsher, and M. Regnier, “Regulation of contraction in striated muscle,” *Physiol. Rev.*, vol. 80, no. 2, pp. 853–924, 2000, doi: 10.1152/physrev.2000.80.2.853.

[93] A. Michailovich Chaulin, “Diagnostic Role and Methods of Detection of Cardiac Troponins: An Opinion from Historical and Current Points of View,” *Curr. Cardiol. Rev.*, vol. 19, no. 1, 2022, doi: 10.2174/1573403x18666220610164946.

[94] J. Ledwoch *et al.*, “Prognostic impact of high-sensitive troponin on 30-day mortality in patients with acute heart failure and different classes of left ventricular ejection fraction,” *Heart Vessels*, vol. 37, no. 7, pp. 1195–1202, 2022, doi: 10.1007/s00380-022-02026-x.

[95] T. Tsutamoto *et al.*, “Prognostic role of highly sensitive cardiac troponin I in patients with systolic heart failure,” *Am. Heart J.*, vol. 159, no. 1, pp. 63–67, 2010, doi: 10.1016/j.ahj.2009.10.022.

[96] H. Wada *et al.*, “Impact of Chronic Kidney Disease on the Associations of Cardiovascular Biomarkers With Adverse Outcomes in Patients With Suspected or Known Coronary Artery Disease: The EXCEED-J Study,” *J. Am. Heart Assoc.*, vol. 11, no. 3, 2022, doi: 10.1161/JAHA.121.023464.

[97] J. Ledwoch *et al.*, “Accuracy of high-sensitive troponin depending on renal function for clinical outcome prediction in patients with acute heart failure,” *Heart Vessels*, vol. 37, no. 1, pp. 69–76, 2022, doi: 10.1007/s00380-021-01890-3.

[98] Y. Xue, P. Clopton, W. F. Peacock, and A. S. Maisel, “Serial changes in high-sensitive troponin i predict outcome in patients with decompensated heart failure,” *Eur. J. Heart Fail.*, vol. 13, no. 1, pp. 37–42, 2011, doi: 10.1093/eurjhf/hfq210.

[99] S. Chen, C. Huang, B. Wu, X. Lian, X. Mei, and J. Wan, “Cardiac troponin i in non-acute coronary syndrome patients with chronic kidney disease,” *PLoS One*, vol. 8, no. 12, pp. 1–7, 2013, doi: 10.1371/journal.pone.0082752.

[100] N. Bansal *et al.*, “High-sensitivity troponin T and N-terminal pro-B-type natriuretic

peptide (NT-proBNP) and risk of incident heart failure in patients with CKD: The chronic renal insufficiency cohort (CRIC) study," *J. Am. Soc. Nephrol.*, vol. 26, no. 4, pp. 946–956, 2015, doi: 10.1681/ASN.2014010108.

[101] C. Kawahara *et al.*, "Prognostic value of serial measurements of highly sensitive cardiac troponin i in stable outpatients with nonischemic chronic heart failure," *Am. Heart J.*, vol. 162, no. 4, pp. 639–645, 2011, doi: 10.1016/j.ahj.2011.07.007.

[102] R. Zymliński *et al.*, "Elevated troponin I level assessed by a new high-sensitive assay and the risk of poor outcomes in patients with acute heart failure," *Int. J. Cardiol.*, vol. 230, pp. 646–652, 2017, doi: 10.1016/j.ijcard.2017.01.012.

[103] B. G. Demissei *et al.*, "A multimarker multi-time point-based risk stratification strategy in acute heart failure: results from the RELAX-AHF trial," *Eur. J. Heart Fail.*, vol. 19, no. 8, pp. 1001–1010, 2017, doi: 10.1002/ejhf.749.

[104] S. Masson *et al.*, "Serial measurement of cardiac troponin T using a highly sensitive assay in patients with chronic heart failure: Data from 2 large randomized clinical trials," *Circulation*, vol. 125, no. 2, pp. 280–288, 2012, doi: 10.1161/CIRCULATIONAHA.111.044149.

[105] S. Barlera *et al.*, "Predictors of mortality in 6975 patients with chronic heart failure in the gruppo italiano per lo studio della streptochinasi nell'infarto miocardico-heart failure trial proposal for a nomogram," *Circ. Hear. Fail.*, vol. 6, no. 1, pp. 31–39, 2013, doi: 10.1161/CIRCHEARTFAILURE.112.967828.

[106] J. Lupón *et al.*, "Combined use of the novel biomarkers high-sensitivity troponin t and st2 for heart failure risk stratification vs conventional assessment," *Mayo Clin. Proc.*, vol. 88, no. 3, pp. 234–243, 2013, doi: 10.1016/j.mayocp.2012.09.016.

[107] A. Bayes-Genis *et al.*, "Soluble ST2 serum concentration and renal function in heart failure," *J. Card. Fail.*, vol. 19, no. 11, pp. 768–775, 2013, doi: 10.1016/j.cardfail.2013.09.005.

[108] Y. U. HORIUCHI *et al.*, "Potential Utility of Cardiorenal Biomarkers for Prediction and Prognostication of Worsening Renal Function in Acute Heart Failure," *J. Card. Fail.*, vol. 27, no. 5, pp. 533–541, 2021, doi: 10.1016/j.cardfail.2020.11.025.

[109] M. Egstrup *et al.*, "Prediction of outcome by highly sensitive troponin T in

outpatients with chronic systolic left ventricular heart failure," *Am. J. Cardiol.*, vol. 110, no. 4, pp. 552–557, 2012, doi: 10.1016/j.amjcard.2012.04.033.

[110] A. Aimo *et al.*, "Admission high-sensitivity troponin T and NT-proBNP for outcome prediction in acute heart failure," *Int. J. Cardiol.*, vol. 293, pp. 137–142, 2019, doi: 10.1016/j.ijcard.2019.06.005.

[111] A. Fabbri *et al.*, "Acute heart failure in the emergency department: a follow-up study," *Intern. Emerg. Med.*, vol. 11, no. 1, pp. 115–122, 2016, doi: 10.1007/s11739-015-1336-z.

[112] M. E. Guisado Espartero *et al.*, "Troponin T in acute heart failure: Clinical implications and prognosis in the Spanish National Registry on Heart Failure," *Eur. J. Intern. Med.*, vol. 25, no. 8, pp. 739–744, 2014, doi: 10.1016/j.ejim.2014.08.005.

[113] C. Bjurman, J. Jensen, M. Petzold, O. Hammarsten, and M. L. X. Fu, "Assessment of a multimarker strategy for prediction of mortality in older heart failure patients: A cohort study," *BMJ Open*, vol. 3, no. 3, 2013, doi: 10.1136/bmjopen-2012-002254.

[114] J. Aulin *et al.*, "Biomarkers and heart failure events in patients with atrial fibrillation in the ARISTOTLE trial evaluated by a multi-state model," *Am. Heart J.*, vol. 251, pp. 13–24, 2022, doi: 10.1016/j.ahj.2022.03.009.

[115] C. M. O'Connor *et al.*, "Impact of serial troponin release on outcomes in patients with acute heart failure: Analysis from the protect pilot study," *Circ. Hear. Fail.*, vol. 4, no. 6, pp. 724–732, 2011, doi: 10.1161/CIRCHEARTFAILURE.111.961581.

[116] A. Aimo *et al.*, "High-sensitivity troponin T, NT-proBNP and glomerular filtration rate: A multimarker strategy for risk stratification in chronic heart failure," *Int. J. Cardiol.*, vol. 277, pp. 166–172, 2019, doi: 10.1016/j.ijcard.2018.10.079.

[117] C. G. Jungbauer *et al.*, "Panel of emerging cardiac biomarkers contributes for prognosis rather than diagnosis in chronic heart failure," *Biomark. Med.*, vol. 8, no. 6, pp. 777–789, 2014, doi: 10.2217/bmm.14.31.

[118] G. Michael Felker *et al.*, "Troponin i in acute decompensated heart failure: Insights from the ASCEND-HF study," *Eur. J. Heart Fail.*, vol. 14, no. 11, pp. 1257–1264, 2012, doi: 10.1093/eurjhf/hfs110.

[119] K. McDowell *et al.*, "Incremental prognostic value of biomarkers in PARADIGM-

HF," *Eur. J. Heart Fail.*, vol. 25, no. 8, pp. 1406–1414, 2023, doi: 10.1002/ejhf.2887.

[120] I. Tentzeris *et al.*, "Complementary role of copeptin and high-sensitivity troponin in predicting outcome in patients with stable chronic heart failure," *Eur. J. Heart Fail.*, vol. 13, no. 7, pp. 726–733, 2011, doi: 10.1093/eurjhf/hfr049.

[121] K. Oyama *et al.*, "Serial assessment of biomarkers and heart failure outcomes in patients with atrial fibrillation," *Eur. J. Heart Fail.*, vol. 25, no. 6, pp. 832–841, 2023, doi: 10.1002/ejhf.2844.

[122] B. Ky *et al.*, "Multiple biomarkers for risk prediction in chronic heart failure," *Circ. Hear. Fail.*, vol. 5, no. 2, pp. 183–190, 2012, doi: 10.1161/CIRCHEARTFAILURE.111.965020.

[123] V. Nauffal *et al.*, "Predictors of mortality, LVAD implant, or heart transplant in primary prevention cardiac resynchronization therapy recipients: The HF-CRT score," *Hear. Rhythm*, vol. 12, no. 12, pp. 2387–2394, 2015, doi: 10.1016/j.hrthm.2015.07.026.

[124] D. McGill, G. Talaulikar, J. M. Potter, G. Koerbin, and P. E. Hickman, "Over time, high-sensitivity TnT replaces NT-proBNP as the most powerful predictor of death in patients with dialysis-dependent chronic renal failure," *Clin. Chim. Acta*, vol. 411, no. 13–14, pp. 936–939, 2010, doi: 10.1016/j.cca.2010.03.004.

[125] J. C. Schefold, G. Filippatos, G. Hasenfuss, S. D. Anker, and S. Von Haehling, "Heart failure and kidney dysfunction: Epidemiology, mechanisms and management," *Nat. Rev. Nephrol.*, vol. 12, no. 10, pp. 610–623, 2016, doi: 10.1038/nrneph.2016.113.

[126] A. Y. M. Wang and C. Wai-Kei Lam, "The Diagnostic Utility of Cardiac Biomarkers in Dialysis Patients," *Semin. Dial.*, vol. 25, no. 4, pp. 388–396, 2012, doi: 10.1111/j.1525-139X.2012.01099.x.

[127] R. MICHA, "乳鼠心肌提取 HHS Public Access," *Physiol. Behav.*, vol. 176, no. 1, pp. 100–106, 2017, doi: 10.1177/0022146515594631.Marriage.

[128] P. Ponikowski *et al.*, "2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure," *Eur. Heart J.*, vol. 37, no. 27, pp. 2129-2200m, 2016,

doi: 10.1093/eurheartj/ehw128.

[129] D. Murphy, V. Jha, and D. Banerjee, “Diabetes and CKD,” *Manag. Kidney Dis.*, vol. 105, no. 4, pp. 147–166, 2023, doi: 10.1007/978-3-031-09131-5_10.

[130] I. C. Van Gelder *et al.*, “2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS),” *Eur. Heart J.*, pp. 3314–3414, 2024, doi: 10.1093/eurheartj/ehae176.

[131] A. Breha, C. Delcea, A. C. Ivanescu, and G. A. Dan, “NT-proBNP as an Independent Predictor of Long-term All- cause Mortality in Heart Failure across the eGFR spectrum,” pp. 1–17, 2025.

[132] K. S. Spanaus *et al.*, “B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: The mild-to-moderate kidney disease study,” *Clin. Chem.*, vol. 53, no. 7, pp. 1264–1272, 2007, doi: 10.1373/clinchem.2006.083170.

[133] G. P. Fadini, B. M. Bonora, M. Albiero, M. Zaninotto, M. Plebani, and A. Avogaro, “DPP-4 inhibition has no acute effect on BNP and its N-terminal pro-hormone measured by commercial immune-assays. A randomized cross-over trial in patients with type 2 diabetes,” *Cardiovasc. Diabetol.*, vol. 16, no. 1, pp. 1–7, 2017, doi: 10.1186/s12933-017-0507-9.

[134] N. Bansal *et al.*, “Kidney Function Specific Reference Limits for N-terminal Pro Brain Natriuretic Peptide and High Sensitivity Troponin T: The Systolic Blood Pressure Intervention Trial,” *Kidney Med.*, vol. 4, no. 9, p. 100517, 2022, doi: 10.1016/j.xkme.2022.100517.

[135] C. Bruch, C. Fischer, J. Sindermann, J. Stypmann, G. Breithardt, and R. Gradaus, “Comparison of the Prognostic Usefulness of N-Terminal Pro-Brain Natriuretic Peptide in Patients With Heart Failure With Versus Without Chronic Kidney Disease,” *Am. J. Cardiol.*, vol. 102, no. 4, pp. 469–474, 2008, doi: 10.1016/j.amjcard.2008.03.082.

[136] P. Jarolim, “High sensitivity cardiac troponin assays in the clinical laboratories,” *Clin. Chem. Lab. Med.*, vol. 53, no. 5, pp. 635–652, 2015, doi: 10.1515/cclm-2014-0565.

[137] S. D. Navaneethan *et al.*, “Prevalence , Predictors , and Outcomes of Pulmonary Hypertension in CKD,” pp. 877–886, 2016, doi: 10.1681/ASN.2014111111.

[138] M. Yigla, O. Fruchter, D. Aharonson, N. Yanay, S. A. Reisner, and M. Lewin, “Pulmonary hypertension is an independent predictor of mortality in hemodialysis patients,” *Kidney Int.*, vol. 75, no. 9, pp. 969–975, 2009, doi: 10.1038/ki.2009.10.

[139] A. M. Vrabie, S. Totolici, C. Delcea, and E. Badila, “Biomarkers in Heart Failure with Preserved Ejection Fraction: A Perpetually Evolving Frontier,” *J. Clin. Med.*, vol. 13, no. 16, Aug. 2024, doi: 10.3390/JCM13164627.

[140] M. Grigore, A. M. Grigore, and A. M. Ilieșiu, “Portal Vein Pulsatility: A Valuable Approach for Monitoring Venous Congestion and Prognostic Evaluation in Acute Decompensated Heart Failure,” *Diagnostics (Basel, Switzerland)*, vol. 14, no. 18, Sep. 2024, doi: 10.3390/DIAGNOSTICS14182029.

[141] C. Delcea, C. Adrian Buzea, D. Dobrev, and G. Andrei Dan, “Prognostic roles of neutrophil–lymphocyte, monocyte-lymphocyte and platelet-lymphocyte ratios for long-term all-cause mortality in heart failure,” *IJC Hear. Vasc.*, vol. 54, no. July, p. 101502, 2024, doi: 10.1016/j.ijcha.2024.101502.

[142] V. Turi *et al.*, “Correlations between left ventricle ejection fraction, global longitudinal strain by two-dimensional speckle tracking and pulse wave velocity in coronary artery disease,” *Med. Evol.*, vol. 26, no. 2, pp. 104–110, Jun. 2020, doi: 10.70921/MEDEV.V26I2.1194.

[143] M. Canepa *et al.*, “Performance of Prognostic Risk Scores in Chronic Heart Failure Patients Enrolled in the European Society of Cardiology Heart Failure Long-Term Registry,” *JACC Hear. Fail.*, vol. 6, no. 6, pp. 452–462, Jun. 2018, doi: 10.1016/J.JCHF.2018.02.001.

[144] A. C. Ivănescu and G.-A. Dan, “Stroke risk scores to predict hospitalization for acute decompensated heart failure in atrial fibrillation patients,” *ROM. J. INTERN. MED*, vol. 59, pp. 73–82, 2021, doi: 10.2478/rjim-2020-0032.

[145] P. Codina *et al.*, “Head-to-head comparison of contemporary heart failure risk scores,” *Eur. J. Heart Fail.*, vol. 23, no. 12, pp. 2035–2044, 2021, doi: 10.1002/ejhf.2352.

[146] S. A. Virani, A. Khosla, and A. Levin, “Chronic kidney disease, heart failure and anemia,” *Can. J. Cardiol.*, vol. 24, no. SUPPL. B, pp. 22B-24B, 2008, doi: 10.1016/s0828-282x(08)71026-2.

[147] G. Aletras *et al.*, “Unraveling Acute Cardiorenal Syndrome: Predictors and Consequences in Acute Heart Failure,” *J. Clin. Med. 2025, Vol. 14, Page 2270*, vol. 14, no. 7, p. 2270, Mar. 2025, doi: 10.3390/JCM14072270.

[148] D. J. Lok *et al.*, “Incremental prognostic power of novel biomarkers (growth-differentiation factor-15, high-sensitivity C-reactive protein, galectin-3, and high-sensitivity troponin-T) in patients with advanced chronic heart failure,” *Am. J. Cardiol.*, vol. 112, no. 6, pp. 831–837, 2013, doi: 10.1016/j.amjcard.2013.05.013.

[149] G. M. Yilmaz Oztekin and A. Genç, “Prognostic Significance of High-Sensitivity Troponin T in Nonischemic Heart Failure with Reduced Ejection Fraction,” *Turk Kardiyol. Dern. Ars.*, vol. 51, no. 2, pp. 129–134, Mar. 2023, doi: 10.5543/tkda.2023.26900.