

Biomarkers in the Prediction of Mortality and Prognosis in Patients with Heart Failure

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The PhD thesis addresses a highly relevant topic in contemporary cardiology, namely the refinement of risk stratification and optimization of prognostic assessment in patients with chronic heart failure. The importance of this subject derives from the substantial burden expressed by heart failure, as reflected by its high prevalence, marked impact on quality of life, frequent hospitalizations and readmissions, and considerable associated mortality, despite the therapeutic advances achieved over recent decades.

Heart failure should be regarded as a systemic syndrome resulting from the complex interplay between myocardial injury, cardiorenal dysfunction, chronic inflammation, endothelial dysfunction, neurohormonal activation, and protein-metabolic abnormalities. This perspective illustrates the marked clinical heterogeneity of this clinical syndrome and the variability of its course, ranging from stable chronic forms to episodes of acute decompensation associated with life-threatening risk. In this context, the identification of biomarkers capable of capturing not only hemodynamic severity, but also the complexity of the systemic pathophysiological mechanisms underlying heart failure, becomes essential for the individualization of clinical management.

The thesis is based on the premise that established biomarkers, although indispensable, are not always sufficient for a comprehensive assessment and stratification of risk. N-terminal pro-B-type natriuretic peptide (NT-proBNP) currently represents the reference standard in the diagnosis and management of heart failure; however, its prognostic utility may be enhanced by integrating additional biological parameters that reflect renal function, inflammation, hematological disturbances, and inflammatory-nutritional status. The central hypothesis of this research is that novel composite biomarkers, only partially explored, derived from routine laboratory parameters and readily available in daily clinical practice, may improve diagnostic accuracy, risk stratification, prognostic assessment, and the management of patients admitted for chronic heart failure.

In line with this hypothesis, the objectives of the thesis focused on the integrated evaluation of biomarkers relevant to the principal pathophysiological mechanisms involved in chronic heart failure. The prognostic value of the neutrophil-to-lymphocyte ratio (NLR) and the platelet-to-lymphocyte ratio (PLR), as markers of systemic inflammation, were assessed in relation to length of hospital stay and readmission risk. In addition, the relationships between inflammatory biomarkers, NT-proBNP, and various clinical and prognostic parameters were investigated. A central objective was the assessment of the NT-proBNP-to-albumin ratio (NTAR) as a composite biomarker of myocardial stress and inflammatory-nutritional status for the prediction of all-cause in-hospital mortality. Emerging biomarkers, such as NTAR, the red cell distribution width-to-estimated glomerular filtration rate ratio (RGR), and the red cell distribution width-to-fibrinogen ratio (RFR), were evaluated against established biomarkers, including albumin, NT-proBNP, NLR, the fibrinogen-to-albumin ratio (FAR), the neutrophil percentage-to-albumin ratio (NPAR), and the red cell distribution width-to-albumin ratio (RAR), for the prediction of length of hospital stay (LOS), in-hospital mortality, and 6-months all-cause mortality.

The theoretical foundation of the thesis consists of a critical analysis of the main biomarkers currently used in daily cardiological practice: natriuretic peptides, high-sensitivity cardiac troponins, soluble ST2, galectin-3, and mid-regional pro-atrial natriuretic peptide. This analysis highlights the superiority of an integrated assessment encompassing multiple pathophysiological dimensions over the isolated interpretation of a single biomarker.

The original research was based on a local clinical database from the Department of Internal Medicine II – Cardiology Unit of the Târgu Mureș County Emergency Clinical Hospital, Romania. The studies employed different designs —retrospective, observational, and hypothesis-generating— and data were collected between January 1, 2022 and August 31, 2024. The primary cohort comprised a total of 3,237 consecutive hospitalizations. The original contribution of this doctoral research was structured around three studies published in international Web of Science-indexed journals, two in Q1 journals and one in a Q2 journal. According to predefined protocols, the first study included 427 hospitalizations corresponding to 355 patients and evaluated NLR and PLR as potential predictors of length of hospital stay and readmission. Similarly, the second study included 382 patients and comparatively assessed NTAR, RGR, and RFR in relation to the LOS, in-hospital mortality, and 6-months all-cause mortality. The third study included 542 hospitalizations and specifically investigated the value of NTAR in predicting all-cause in-hospital mortality, including sex-stratified analyses.

Patients with associated diseases (including acute infection, active inflammation, sepsis, active malignancy, autoimmune disease, primary liver disease, hematological malignancy, end-stage chronic kidney disease, acute or subacute venous thromboembolism), likely to independently influence the new-proposed investigated biomarkers were excluded, as well as cases with incomplete data. Laboratory measurements were performed within the first two hours after admission, and the indices NLR, PLR, NPAR, RAR, FAR, NTAR, RFR, and RGR were calculated based on the recorded biological parameters. Imaging assessment included transthoracic echocardiography; patients were stratified according to left ventricular ejection fraction in accordance with the 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Advanced statistical analyses included descriptive and inferential tests, logistic regression models, ROC curve analysis, DeLong comparisons, Kaplan–Meier survival analysis, Cox proportional hazards models, and Schoenfeld residual analysis.

The results of the first study showed that NLR was associated with the clinical severity of heart failure and had limited yet genuine utility in estimating length of hospital stay, whereas PLR did not demonstrate comparable value in this respect. Although neither NLR nor PLR was significantly associated with the total number of readmissions at 90 days, higher NLR values tended to correlate with a shorter time to readmission, suggesting a relationship between inflammatory status and clinical vulnerability.

The second study highlighted the utility of novel composite biomarkers derived from the combination of routine biological parameters. Albumin, NT-proBNP, NTAR, RAR, and RGR emerged as relevant markers for estimating clinical outcomes. Albumin was negatively associated with LOS and all-cause mortality, whereas NT-proBNP was positively associated with prolonged hospitalization and all-cause mortality. NTAR provided superior prognostic insight, suggesting that integrating myocardial stress with information related to inflammation and nutritional status enhances mortality discrimination. Among the emerging biomarkers, RGR was particularly noteworthy, being significantly associated with both all-cause in-hospital mortality and 6-month all-cause mortality; in certain analyses, it remained the sole independent predictor of in-hospital death. By contrast, RFR showed more limited utility for the outcomes under investigation.

The third line of the research further explored the value of NTAR in the prediction of all-cause in-hospital mortality. The findings demonstrated that NTAR has important prognostic value in comparison with its individual components, particularly in male patients, in whom it emerged as an independent predictor of in-hospital death. In the female subgroup, NTAR also showed predictive value; however, the final model was superseded by the performance of albumin and diastolic blood pressure, suggesting the existence of sex-related biological and clinical differences.

Taken together, the results of this doctoral research support the concept that chronic heart failure should be evaluated using an integrative, multimarker approach. Simple inflammatory biomarkers such as NLR may provide complementary information, but their prognostic performance remains limited. By contrast, composite biomarkers, particularly NTAR and RGR, appear to capture more accurately the complexity of heart failure and to provide superior predictive value for major clinical outcomes.

The value of RGR was further explored in an additional dedicated study on chronic heart failure published in a Q1 journal, whereas the utility of RGR and NTAR was also confirmed in pulmonary arterial hypertension and chronic thromboembolic pulmonary hypertension in a Q1 journal. Collectively, these findings support the potential of the newly proposed biomarkers to contribute to the development of an expanded prognostic panel applicable across a variety of cardiovascular and possible non-cardiovascular conditions.

The originality of the thesis lies in the application of the composite biomarker concept to chronic heart failure and in demonstrating its practical potential, given that the analyzed markers are calculated from widely available laboratory parameters and may be easily incorporated into routine clinical assessment. At the same time, the thesis acknowledges its methodological limitations, related to the retrospective and single-center design of the studies, the lack of serial biomarker measurements, and the impossibility of systematically assessing the influence of treatment on biomarker dynamics.

In conclusion, this PhD thesis demonstrates that prognostic assessment and risk stratification in patients with chronic heart failure can be improved by means of a multimarker approach capable of integrating information on myocardial and cardiorenal injury, chronic inflammation, endothelial dysfunction, neurohormonal activation, and protein-metabolic abnormalities. The newly proposed composite biomarkers, particularly NTAR and RGR, proved promising for the prediction of prolonged hospitalization and all-cause mortality, surpassing, in certain contexts, the performance of traditional biomarkers assessed individually. Through its methodological coherence, clinical relevance, and practical applicability, the thesis makes an original contribution to the field of cardiology and outlines future directions for research and potential clinical implementation.