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Review Article

Prognostic Stratification in Heart Failure: Emerging Biomarkers and Explainable Artificial Intelligence in Real-World Care

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Abstract

Heart Failure (HF) remains a leading cause of morbidity, mortality, and healthcare utilization worldwide, driven by population ageing, multimorbidity, and improved survival after acute cardiovascular events. Although Left Ventricular Ejection Fraction (LVEF) remains central to classification and therapeutic decision-making, it incompletely captures the biological and clinical heterogeneity of HF-particularly in heart failure with preserved and mildly reduced ejection fraction. Traditional prognostic markers such as natriuretic peptides, renal function, sodium, and anaemia underpin established risk scores but may underestimate vulnerability in older, frail, and socially disadvantaged populations. Emerging markers of biological reserve, systemic inflammation, and nutritional vulnerability-including clinical frailty scales, temporal muscle thickness, neutrophil-to-lymphocyte ratio, and nutritional indices-have gained increasing attention as accessible, low-cost predictors with potential incremental prognostic value.

In parallel, Artificial Intelligence (AI) and machine-learning approaches offer opportunities to integrate multidimensional clinical data, identify phenotypic clusters, and improve prediction of mortality and readmission. However, their clinical adoption requires methodological rigor, transparency, interpretability, and validation in real-world settings. This narrative state-of-the-art review synthesizes contemporary evidence across HF phenotypes, classical and emerging prognostic markers, multidisciplinary HF care models, and explainable AI-enabled prognostication. We highlight key knowledge gaps and discuss clinical and organizational implications for implementing integrated, parsimonious, and interpretable risk stratification tools within multidisciplinary HF units. Together, these dimensions support a translational pathway from multimodal data integration to deployable prognostic tools capable of informing individualized care and optimizing resource allocation in real-world HF management.

Keywords: Heart failure; prognosis; frailty; temporal muscle thickness; inflammation; neutrophil-to-lymphocyte ratio; artificial intelligence; multidisciplinary care

Abbreviations: HF: heart failure; LVEF: left ventricular ejection fraction; HFrEF: heart failure with reduced ejection fraction; HFmrEF: heart failure with mildly reduced ejection fraction; HFpEF: heart failure with preserved ejection fraction; CFS: Clinical Frailty Scale; TMT: temporal muscle thickness; NLR: neutrophil-to-lymphocyte ratio; AI: artificial intelligence

Introduction

Heart Failure (HF) is a complex clinical syndrome and a major public health challenge, associated with high prevalence, recurrent hospitalizations, and persistent mortality despite major therapeutic advances. Its burden continues to rise globally due to population ageing, improved survival after acute cardiovascular events, and increasing multimorbidity. Prognostic stratification is therefore central to HF management, guiding therapeutic intensity, follow-up strategies, and allocation of healthcare resources, particularly during vulnerable transition periods after hospitalization. Although classification based on Left Ventricular Ejection Fraction (LVEF) remains clinically useful and therapeutically actionable, it only partially reflects the underlying pathophysiology and fails to explain substantial within-phenotype heterogeneity. This limitation is particularly evident in HF with preserved and mildly reduced ejection fraction, where systemic comorbidities, inflammation, and biological vulnerability play a dominant role.

In recent years, HF has increasingly been conceptualized as a multisystem syndrome, in which frailty, sarcopenia, inflammation, and nutritional status substantially influence outcomes. However, these domains remain under-integrated into routine prognostic assessment and clinical risk models. At the same time, advances in Artificial Intelligence (AI) and machine learning have enabled the integration of complex, multidimensional clinical data, offering potential improvements in phenotyping and risk prediction. The challenge lies in translating these advances into clinically interpretable and deployable tools. This narrative review provides a clinically oriented synthesis of evidence on prognostic stratification in HF, focusing on the integration of classical and emerging biomarkers, organizational models of care, and explainable AI approaches, with emphasis on real-world applicability within multidisciplinary HF units [1-20].

Discussion

Epidemiology and Burden of Heart Failure

HF affects approximately 1–2% of the adult population and exceeds 10% among individuals older than 70 years. It remains a leading cause of hospitalization and healthcare expenditure, with recurrent admissions representing a major driver of disease burden. In Portugal and other ageing regions, HF prevalence and outcomes are further shaped by multimorbidity, social vulnerability, and geographic dispersion, underscoring the need for structured and proactive care models [21-30].

Pathophysiology and LVEF-Based Phenotypes

Contemporary HF classification recognizes HFrEF, HFmrEF, HFpEF, and HF with recovered ejection fraction. While HFrEF is predominantly characterized by systolic dysfunction and neurohormonal activation, HFpEF is increasingly understood as a multisystem disorder driven by cardiometabolic comorbidities, systemic inflammation, endothelial dysfunction, and impaired reserve. HFmrEF represents a heterogeneous and dynamic phenotype, while recovered EF denotes improvement with therapy but persistent residual risk. These distinctions highlight the limitations of LVEF as a sole prognostic descriptor [31-40].

Prognosis Across Ejection Fraction Phenotypes

Although prognosis varies across LVEF categories, substantial overlap exists. Mortality and rehospitalization remain clinically significant across all phenotypes, particularly in the early post-discharge period. Importantly, non-cardiovascular events contribute substantially to outcomes in HFpEF, reflecting systemic disease burden. These observations support the need for prognostic models that transcend LVEF-based classification [41-50].

Classical Prognostic Predictors

Classical prognostic markers-such as natriuretic peptides, renal dysfunction, hyponatraemia, anaemia, age, and comorbidity burden-form the backbone of existing risk scores. Tools such as the MAGGIC risk score and the Seattle Heart Failure Model integrate these variables to estimate survival. However, their performance may be suboptimal in older, frail, and socially vulnerable populations, where biological reserve and functional status are critical determinants of outcome [51-60].

Emerging Biomarkers of Biological Vulnerability

Frailty and Sarcopenia

Frailty is highly prevalent among HF patients and consistently associated with mortality, rehospitalization, and reduced tolerance to guideline-directed therapies. Sarcopenia and cachexia reflect advanced HF biology and catabolic imbalance, conferring additional risk through inflammatory and metabolic pathways [61-70].

Temporal Muscle Thickness

Temporal Muscle Thickness (TMT), measured opportunistically on routine cranial CT imaging, has emerged as an objective surrogate of sarcopenia and biological reserve. Evidence across clinical contexts supports its association with mortality and adverse outcomes, with good reproducibility and feasibility for automated assessment. In HF populations, TMT offers a pragmatic avenue to quantify vulnerability beyond traditional metrics [71-80].

Systemic Inflammation and Neutrophil-To-Lymphocyte Ratio

Chronic low-grade inflammation is a hallmark of HF, particularly HFpEF. The neutrophil-to-lymphocyte ratio (NLR) integrates innate immune activation and physiological stress and has shown consistent associations with mortality and adverse events in HF. Its low cost and universal availability make it an attractive candidate for routine risk stratification [81-90].

Nutritional Vulnerability

Nutritional indices such as CONUT and the prognostic nutritional index capture malnutrition and inflammatory burden, both independently associated with adverse outcomes in HF. Their integration may be particularly relevant in frail and advanced disease states (Figure 1).

Supplementary materials

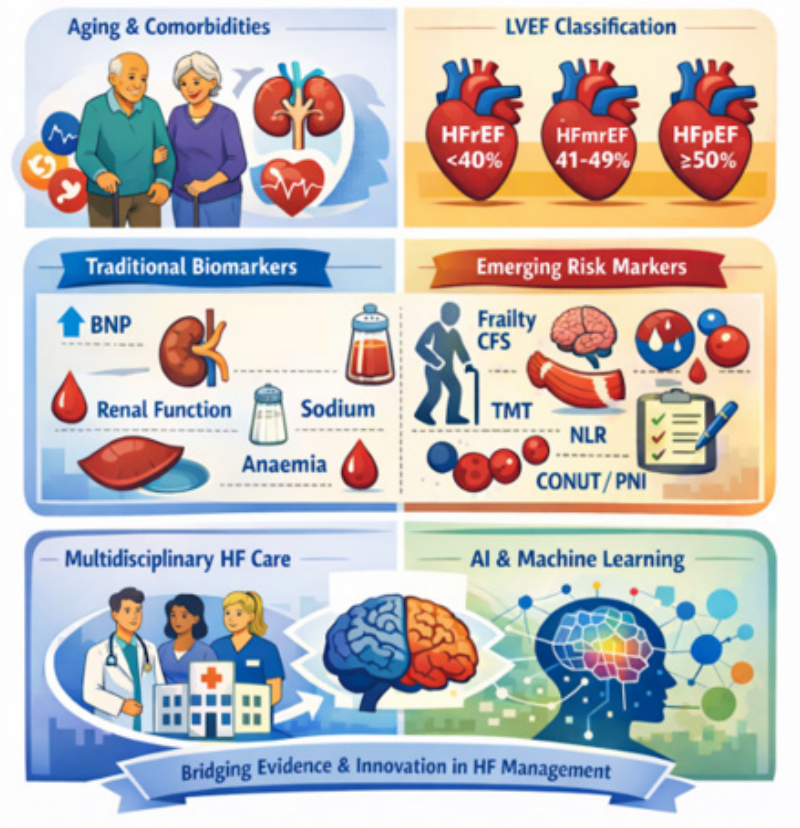

Figure 1: Schematic representation of clinical challenges and emerging prognostic tools into data-driven approaches across the heart failure spectrum.

Multidisciplinary Heart Failure Units and Organization of Care

Dedicated multidisciplinary HF units reduce rehospitalizations and improve outcomes, particularly during post-discharge transitions. These programs facilitate coordinated optimization of therapy, patient education, and structured follow-up. In regions characterized by ageing and social vulnerability, such models may mitigate inequities and prevent avoidable decompensation (Tables 1&2).

Table 1: Classical Prognostic Markers in Heart Failure.

Domain	Marker	Pathophysiological meaning	Prognostic value	Limitations
Haemodynamic stress	NT-proBNP	Ventricular wall stress, congestion	Mortality, rehospitalization	Influenced by age, renal function
Renal function	Creatinine / eGFR	Cardiorenal interaction	Mortality, progression	Non-specific
Electrolytes	Sodium	Neurohormonal activation	Advanced HF prognosis	Late marker
Haematological	Haemoglobin	Oxygen delivery	Functional decline, mortality	Multifactorial

Table 2: Emerging Biomarkers of Biological Vulnerability in Heart Failure.

Biomarker	Domain	Measurement	Key prognostic associations	Clinical advantages
Clinical Frailty Scale	Frailty	Bedside clinical scale	Mortality, rehospitalization	Simple, validated
Temporal Muscle Thickness	Sarcopenia	Opportunistic CT	Mortality, rehospitalization	Objective, reproducible
Neutrophil-to-lymphocyte ratio	Inflammation	Routine blood test	Mortality, adverse outcomes	Low cost, accessible
CONUT / PNI	Nutrition	Laboratory-based	Mortality, vulnerability	Integrates nutrition & inflammation

CT – Computed Tomography

Artificial Intelligence and Explainable Prediction in HF

AI and machine-learning approaches enable the integration of complex multimodal data, supporting phenotyping and risk prediction through non-linear modelling. However, clinical translation requires careful attention to overfitting, bias, calibration, and generalizability. Explainable AI techniques may enhance clinician trust and interpretability but must be applied within rigorous methodological frameworks aligned with reporting standards such as TRIPOD and PROBAST [91-100].

Knowledge Gaps and Research Agenda

Key gaps include under-integration of frailty and sarcopenia into routine risk assessment, limited incorporation of social determinants, and insufficient external validation of AI-based models. Future research should prioritize parsimonious, explainable models evaluated within multidisciplinary care pathways and focused on clinically actionable endpoints [101-110].

Limitations of this Review

As a narrative review, this work does not follow a formal systematic review protocol, and selection bias cannot be fully excluded. Nevertheless, emphasis was placed on high-level evidence, methodological rigor, and real-world applicability (Tables 3&4).

Table 3: Traditional Risk Scores vs AI-Based Prognostic Models.

Feature	Traditional scores	AI-based models
Variables	Limited, predefined	Multidimensional
Interactions	Mostly linear	Non-linear
Interpretability	High	Variable (improving with explainable AI)
Adaptability	Static	Dynamic, updateable
External validation	Established	Often limited

Table 4: Clinically Relevant Prognostic Endpoints in Contemporary HF Care.

Endpoint	Clinical relevance	Strengths	Limitations
90-day HF rehospitalization	Care quality, transitions	Frequent, actionable	Competing risk with death
90-day composite (death or HF admission)	Global instability	Increased power	Requires clear definitions
12-month all-cause mortality	Hard endpoint	Benchmarking	Lower event rate

Conclusion

HF remains a major clinical and organizational challenge characterized by rising prevalence, multimorbidity, and recurrent hospitalization. While LVEF-based phenotyping remains useful, it is insufficient for precise individual prognostication. Classical biomarkers are essential but do not fully capture systemic vulnerability. Emerging markers of frailty, sarcopenia, inflammation, and nutrition-particularly TMT and NLR-offer promising, accessible additions with potential incremental value. Multidisciplinary HF care models provide a compelling framework to operationalize risk-stratified care, while explainable AI approaches may further enhance prognostic precision. Together, these dimensions support the development of integrated, interpretable prognostic tools capable of informing personalized care and optimizing outcomes in real-world HF management.

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Conflict of Interest

The authors declare no conflicts of interest related to this manuscript.

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