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Advancing Risk Stratification in HFpEF: Unveiling the Potential of Cardiac Fibrosis Markers for Early Diagnosis and Enhanced Patient Outcomes

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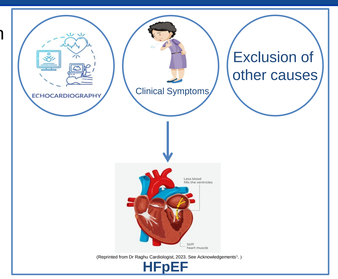
Background

- Heart failure with preserved ejection fraction (HFpEF) presents a significant challenge in clinical management due to its heterogeneous nature.
- Traditional diagnostic criteria, reliant on clinical parameters and echocardiography, may have limitations in early detection and risk stratification.
- The exploration of cardiac fibrosis markers represents a potential paradigm shift in improving diagnostic precision and patient outcomes in HFpEF.



Traditional Diagnostic Criteria

Significance

- Understanding the significance of cardiac fibrosis markers in HFpEF is crucial for advancing clinical practice.
- Traditional criteria may lack sensitivity, leading to delayed diagnosis and suboptimal management.
- The investigation of galectin-3, NT-proBNP, and other biomarkers offers the potential for early detection and improved risk assessment, thus addressing critical gaps in current HFpEF care.

Methods

Search Strategy:

- A systematic literature search was conducted across PubMed, Scopus, ScienceDirect and Google Scholar databases on November 10th, 2023, and yielded different results, as shown in table 1.

Study Selection:

- Sixteen studies were selected based on their relevance to biomarkers, risk stratification, and outcomes in HFpEF. Inclusion criteria involved peer-reviewed articles published until November 10th, 2023, exploring the role of cardiac fibrosis markers in HFpEF. Various study designs, including clinical trials, observational studies, and systematic reviews were considered.

Outcome Measures:

- Primary outcome measures included diagnostic accuracy, prognostic value, and impact on patient outcomes of cardiac fibrosis markers in HFpEF.

Data Extraction:

- Extracted data encompassed study design, participant characteristics, specific cardiac fibrosis markers investigated, traditional diagnostic criteria used, risk stratification outcomes, and patient-related endpoints.
- Figures were extracted from the studies to visually represent key findings.
- No further analysis was done to the extracted data.

Database Searched	Date of search	Keyword String	Number of Results
ScienceDirect	11/10/2023	"heart failure with preserved ejection fraction" AND "fibrosis markers OR biomarkers" AND "diagnosis" AND "risk stratification"	989
PubMed	11/10/2023	"heart failure with preserved ejection fraction" AND "fibrosis markers OR biomarkers" AND "diagnosis" AND "risk stratification"	18
Google Scholar	11/10/2023	"heart failure with preserved ejection fraction" AND "fibrosis markers OR biomarkers" AND "diagnosis" AND "risk stratification"	282
Scopus	11/10/2023	"heart failure with preserved ejection fraction" AND "fibrosis markers OR biomarkers" AND "diagnosis" AND "risk stratification"	24

Table 1: Databases searched and their correlated number of results using a specific keyword string

Results

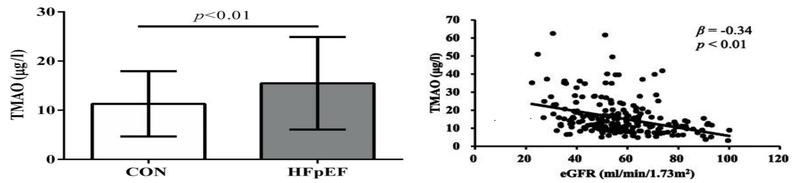


Figure 1: Plasma Trimethylamine N-Oxide (TMAO) and Renal Function
Left: Comparison of plasma TMAO levels in control (CON) and HFpEF groups. Right: Spearman analysis of TMAO levels with eGFR. (Reprinted from Guo et al., BMC Cardiovasc Disord, 2020, with permission[1]. See Acknowledgements.)

- Guo et al. (2020) explored the association between plasma trimethylamine N-oxide (TMAO) and renal function in HFpEF.
- Figure 1 illustrates the correlation between TMAO levels and renal function. The figure suggests that TMAO may provide insights into the systemic implications of HFpEF, emphasizing the multifaceted nature of HFpEF pathophysiology and highlighting TMAO relevance in risk stratification.

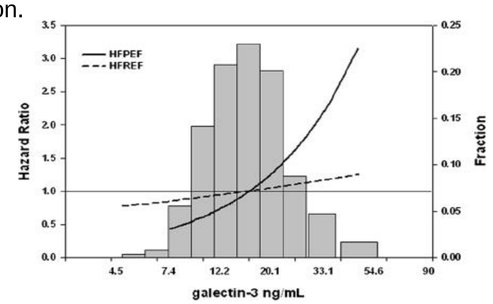


Figure 2: Graphical depiction of the risk estimates for experiencing the primary outcome in patients with HFPEF and HFREF with increasing levels of plasma galectin-3. The distribution of (log-transformed) galectin-3 is depicted in the background in brown bars. A similar increase in galectin-3 causes a much more pronounced increase in risk in patients with HFPEF compared to patients with HFREF. (Reprinted from de Boer et al., Ann Med, 2011, with permission[2]. See Acknowledgements.)

- De Boer et al. (2011) assessed the predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction.
- Figure 2 showcases the potential of galectin-3 as a predictive biomarker, emphasizing its relevance in both HFpEF and heart failure with reduced ejection fraction (HFrEF). This figure supports the notion that galectin-3 could contribute to improved risk stratification.

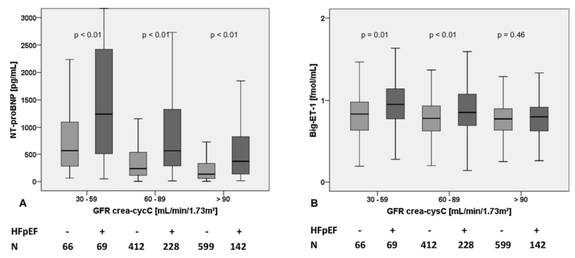


Figure 3: N-Terminal Pro-B-Type Natriuretic peptide (A) and Big-endothelin-1 (B) plasma concentrations in patients without HF (−) and in patients with heart failure with preserved ejection fraction (+) (HFpEF) according to kidney function. Boxes represent interquartile ranges, whereas whiskers indicate 5th and 95th percentiles. Comparisons between groups were conducted with the Mann–Whitney-U ⁻test ($\alpha = 0.05$). ((Reprinted from Gergei et al., Peptides, 2019, with permission[3]. See Acknowledgements.)

- Gergei et al. (2019) investigated the relationship between renal function, NT-proBNP, propeptide big-endothelin, and HFpEF.
- Figure 3, derived from their study, demonstrates potential correlations between these markers and renal function, suggesting their collective utility in risk stratification. This figure highlights the intricate interplay between cardiac and renal dysfunction in HFpEF.

Results (cont.)

- Chirinos et al. (2020) investigated multiple plasma biomarkers for risk stratification in HFpEF.
- Chirinos et al. found that a machine-learning-derived model using a combination of biomarkers (including biomarkers related to calcification, inflammation, liver injury, adipocyte biology, angiogenesis, and extracellular matrix) was strongly predictive of the risk of death or heart failure admission (DHFA) in HFpEF patients.
- Figure 4, adapted from their study, suggests the potential of key pathological biomarkers for enhanced risk stratification beyond traditional criteria.

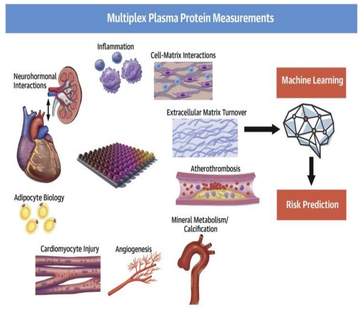


Figure 4: Multimarker-Based Machine Learning Approach for Risk Prediction in Heart Failure With Preserved Ejection Fraction. (Reprinted from Chirinos et al., Journal of the American College of Cardiology, 2020, with permission[4]. See Acknowledgements.)

Discussion

- The results collectively suggest that cardiac fibrosis markers, such as galectin-3, TMAO, and NT-proBNP, hold promise for improving risk stratification in HFpEF.
- The multifactorial nature of HFpEF is reflected in the diverse biomarkers studied, indicating the need for a comprehensive approach to risk assessment.
- Despite these promising findings, challenges remain, including the need for standardization of biomarker measurement and validation in larger, diverse cohorts.
- Additionally, the integration of multiple biomarkers into a clinically applicable risk stratification tool requires further investigation.

Future Direction

- Future research directions should focus on validating and standardizing these cardiac fibrosis markers for widespread clinical use.
- Longitudinal studies are imperative to understand the dynamic changes in these markers over time and their correlation with patient outcomes.
- Exploring the integration of these markers into routine clinical practice and the development of targeted therapies based on markers profiles are essential for advancing HFpEF management.

References and Acknowledgements