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MULTIDIMENSIONAL APPROACH TO CHRONIC HEART FAILURE FOR THE DEVELOPMENT OF AN INDIVIDUALIZED EVALUATION MATRIX

321.03 CARDIOLOGY

Summary of the habilitation thesis in medical sciences

Chișinău, 2026

The thesis was developed within the Discipline of Cardiology, Department of Internal Medicine, Nicolae Testemițanu State University of Medicine and Pharmacy.

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The public defense will take place on 09.09.2026, 14:00 at Nicolae Testemițanu State University of Medicine and Pharmacy, 165 Ștefan cel Mare și Sfânt Blvd., Office 205, during the meeting of the Public Defense Committee for the Habilitated Doctoral Thesis, approved by the decision of the Scientific Council of the Consortium dated 22.06.2026 (Minutes No. 5/7).

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INTRODUCTION

Despite continuous progress in cardiovascular medicine, heart failure (HF) remains one of the leading causes of mortality and morbidity worldwide. The number of affected patients is increasing, and the economic burden associated with recurrent hospitalizations and complex treatments represents a major challenge for healthcare systems. Population ageing, the rising prevalence of metabolic diseases, and cardiovascular comorbidities contribute to an alarming expansion of HF in Europe and the United States. Current estimates indicate more than 15 million patients in Europe and approximately 8 million in the United States [1]. This reality necessitates the development of early diagnostic strategies, individualized interventions, and predictive models capable of reducing long-term risks [2].

The classification of heart failure has evolved significantly, reflecting differences in pathophysiology, prognosis, and response to treatment. In addition to heart failure with reduced ejection fraction (HFrEF) and heart failure with preserved ejection fraction (HFpEF), recent guidelines have introduced the category of heart failure with mildly reduced ejection fraction (HFmrEF), which requires further research to establish clear therapeutic recommendations [3].

HFrEF (EF <40%) is the most extensively studied form, for which cornerstone therapies—renin–angiotensin system blockers, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors—have demonstrated major benefits in reducing mortality and hospitalizations.

HFpEF (EF ≥50%) represents a heterogeneous entity, characterized by diastolic dysfunction, systemic inflammation, and increased myocardial stiffness. Although it is as prevalent as HFrEF, the lack of therapies with clear mortality benefits makes it an insufficiently defined area of modern cardiology [4].

HFmrEF (EF 40–49%) represents an intermediate group, sharing pathophysiological features with both major categories. Available data suggest a possible therapeutic response similar to that observed in HFrEF; however, the evidence remains inconclusive [5].

A relatively recent concept is that of "recovered ejection fraction," observed in patients with HF who initially presented with severe systolic dysfunction but, under optimal therapy, improved their ventricular function. Despite this recovery, these patients remain at increased risk for adverse cardiovascular events and require continuous monitoring [6].

Comorbidities represent a major determinant of heart failure evolution, contributing to clinical heterogeneity and increasing the complexity of patient management. Conditions such as arterial hypertension, diabetes mellitus, chronic kidney disease, obesity, and chronic obstructive pulmonary disease are frequently associated and influence both pathophysiological mechanisms and prognosis [7]. The interaction between these conditions leads to increased filling pressures, endothelial dysfunction, systemic inflammation, and impaired myocardial function, resulting in a more severe disease course [8]. Furthermore, the presence of multimorbidity complicates the selection and titration of therapy, increasing the risk of adverse effects and drug interactions, which necessitates an integrated and individualized approach [9].

Modern strategies emphasize comprehensive patient evaluation and integration of comorbidities into the decision-making algorithm, with treatment tailored according to the individual clinical profile and patient-specific characteristics [9,10]. A central role in the evolution of modern cardiology is played by the integration of artificial intelligence (AI) in the diagnosis and management of HF. Machine learning algorithms facilitate early identification of myocardial dysfunction, enable automated interpretation of ECGs and cardiac imaging, reduce inter-observer

variability, and allow individualized prediction of disease evolution [11]. Smart wearable devices complement this approach by ensuring continuous monitoring and early intervention.

Advanced echocardiography remains an essential tool in HF evaluation. Techniques such as speckle-tracking and tissue Doppler imaging allow quantification of myocardial deformation and early detection of subclinical dysfunction. Global longitudinal strain has proven to be an independent predictor of mortality, regardless of ejection fraction [12].

The role of AI in the analysis of echocardiographic images is becoming increasingly evident. Algorithms can identify pathological patterns with accuracy comparable to human experts, analyze large volumes of imaging data, and predict disease progression [13,14,15]. This integration reduces variability in interpretation and increases access to high-precision assessments, including in resource-limited centers [16,17].

In the Republic of Moldova, epidemiological data on heart failure are limited, which restricts the development of effective prevention and treatment strategies. The lack of national registries for HF and atrial fibrillation makes it difficult to estimate the true burden on the healthcare system and to plan appropriate interventions. This deficit highlights the need for systematic national-level studies.

Adherence to international guidelines developed by ESC and AHA varies across regions and depends on resources, infrastructure, and access to modern therapies [2,3]. In Moldova, these limitations may reduce the applicability of recommendations, highlighting the need to strengthen continuous medical education and modernize healthcare infrastructure.

In conclusion, heart failure remains a major issue in contemporary cardiology, requiring an integrative approach based on precision medicine, advanced imaging, and modern analytical algorithms. Identifying the subtle mechanisms underlying the interaction between HF, atrial fibrillation, and comorbidities, as well as developing robust predictive models, is essential for improving prognosis and patients' quality of life.

Aim of the study:

To elucidate the clinical and evolutionary characteristics and management strategies of heart failure through the integration of advanced echocardiographic techniques and artificial intelligence algorithms, with the purpose of developing a individualized management matrix.

Objectives:

1. To characterize the clinical, hemodynamic, biological, and evolutionary features of patients with chronic heart failure.
2. To identify specific types and phenotypes of patients with chronic heart failure and to analyze clinical outcomes according to the type of heart failure.
3. To analyze the role of conventional echocardiography and advanced echocardiographic techniques in the diagnosis, risk stratification, and monitoring of patients with heart failure.
4. To assess the impact of comorbidities on the clinical, hemodynamic manifestations and the evolution of patients with chronic heart failure.
5. To analyze the therapeutic strategies applied in patients with heart failure and to compare them with current recommendations from international clinical practice guidelines.
6. To evaluate the impact of artificial intelligence tools in risk stratification of patients with different types of heart failure.
7. To develop an integrated digital matrix for individualized management of patients with heart failure by combining clinical and hemodynamic parameters, advanced echocardiographic techniques, and artificial intelligence algorithms.

Scientific novelty and originality

The conducted study provides an original contribution through the integration of a multidimensional approach that combines clinical, hemodynamic, echocardiographic, biological factors, and advanced data analysis technologies for the comprehensive characterization of patients with heart failure. The evaluation of clinical, hemodynamic, demographic, and biological features, in correlation with the type of heart failure (HFrEF, HFmrEF, HFpEF), enabled the identification of patterns specific to each subgroup and the determination of dominant risk factors. Thus, the analysis of clinical phenotypes went beyond the traditional classification based solely on ejection fraction, contributing to a more nuanced understanding of disease heterogeneity and the impact of comorbidity profiles. The results demonstrated that advanced echocardiographic techniques provide superior capacity for early detection of subclinical myocardial dysfunction through sensitive assessment of diastolic function, myocardial deformation, and cardiac chamber interactions.

Theoretical significance

The proposed study has significant theoretical value by advancing the understanding of pathogenic mechanisms in heart failure and identifying risk factors influencing disease progression. A clearer understanding was achieved regarding the relationships between clinical, hemodynamic, and echocardiographic characteristics of patients with different types of HF, as well as how these variables determine prognosis and response to treatment. The integration of advanced echocardiographic techniques, such as speckle-tracking, contributes to defining relevant parameters for early diagnosis and risk stratification, offering new insights into the pathophysiology of subclinical myocardial dysfunction.

Practical value

The proposed study has substantial practical value, with direct impact on clinical practice and heart failure management strategies. The results facilitated optimization of diagnosis by demonstrating the superiority of advanced echocardiography in the early detection of subclinical myocardial dysfunction, allowing clinicians to identify patients at early stages and initiate effective treatment promptly.

Through precise risk stratification and characterization of clinical phenotypes, the study contributes to treatment individualization, adaptation of therapeutic interventions, and optimization of monitoring. Through these contributions, the study supports the implementation of individualized medicine based on robust data and modern tools, with a positive impact on quality of care and patient prognosis.

Implementation of results

The research results were presented at 58 national and international scientific forums.

The thesis was discussed, approved, and recommended for public defense at the joint meeting of the Department of Internal Medicine – Discipline of Cardiology, Nicolae Testemițanu State University of Medicine and Pharmacy, Republic of Moldova (Minutes No. 19, April 24, 2026), and within the Scientific Seminar in Specialty 321.03 – Cardiology (Minutes No. 2, May 29, 2026).

Publications related to the thesis. The research findings were disseminated through 63 scientific publications, including articles in peer-reviewed journals, conference abstracts, and presentations at national and international scientific meetings.

The thesis comprises 228 pages of electronic text and is structured into an introduction, six chapters of original research, conclusions, and practical recommendations. The bibliography includes 369 references. The thesis is illustrated with 36 tables, 65 figures, and 16 appendices.

Keywords: heart failure, clinical phenotypes, cardiac remodeling, advanced imaging, speckle-tracking, comorbidities, atrial fibrillation, artificial intelligence, risk stratification, individualized evaluation matrix.

The first chapter presents the conceptual framework of heart failure as a complex syndrome, determined by the interaction between myocardial dysfunction, cardiac remodeling, and activation of neurohormonal mechanisms, while also discussing the limitations of classification based solely on ejection fraction.

The second chapter addresses the major role of comorbidities (diabetes, hypertension, atrial fibrillation, chronic kidney disease, chronic obstructive pulmonary disease, anemia, obesity), highlighting their impact on prognosis and on the development of distinct clinical phenotypes.

The third chapter provides a clinical, biological, and hemodynamic characterization of the study population, emphasizing the heterogeneity and complexity of real-world patients.

The fourth chapter analyzes the contribution of cardiac imaging, particularly advanced speckle-tracking techniques, in the assessment of myocardial function and risk stratification, through the integration of imaging data with clinical and biological parameters.

The fifth chapter evaluates the implementation of guideline-directed therapy, highlighting the increased use of modern treatments (including SGLT2 inhibitors and mineralocorticoid receptor antagonists) and their impact on the risk profile, as well as existing limitations in access to certain therapies.

The sixth chapter describes the evolution of management over time, demonstrating an improvement in risk profile associated with more frequent use of modern therapies and the progressive implementation of guideline recommendations.

The seventh chapter develops an artificial intelligence-based risk stratification model, identifying distinct clinical phenotypes based on key variables (LVEF, biomarkers, renal function, sodium, hemoglobin, age, systolic blood pressure).

The eighth chapter integrates the results into a individualized evaluation matrix, demonstrating the utility of combining clinical, biological, imaging data, and artificial intelligence for optimizing the management of patients with heart failure.

The Discussion chapter integrates the obtained results within the context of existing literature, highlighting the relationships between clinical phenotypes, comorbidities, imaging parameters, and therapeutic strategies, as well as the practical implications of artificial intelligence-based phenotyping.

The Conclusions chapter synthesizes the main findings, emphasizing the heterogeneity of heart failure and the importance of a multidimensional approach integrating clinical, imaging, and biological data for optimizing individualized management.

1. GENERAL AND SPECIAL METHODS FOR THE EXAMINATION OF PATIENTS IN THE STUDY GROUPS

The research was conducted at the Institute of Cardiology, General Cardiology Department, the clinical base of the Cardiology Discipline of Nicolae Testemițanu State University of Medicine and Pharmacy. The study was carried out in accordance with international ethical principles for biomedical research, the protocol being approved by the Ethics Committee of Nicolae Testemițanu State University of Medicine and Pharmacy (Approval No. 25/1 of 13.05.2025).

The study period covered 2019–2025, including both the patient enrollment phase and longitudinal follow-up, with evaluations performed at baseline, as well as at 12 months and/or 60 months. This longitudinal approach allowed the assessment of clinical evolution, changes in risk profile, and the impact of therapeutic strategies on the prognosis of patients with heart failure.

From a methodological perspective, the research was designed as an observational, analytical cohort study conducted in real-world clinical practice conditions. The study design included several successive stages: patient selection and enrollment, comprehensive baseline characterization, cross-sectional analysis of clinical and paraclinical parameters, longitudinal follow-up, and integrative analysis, including patient phenotyping and risk stratification using statistical methods and artificial intelligence algorithms.

The study group consisted of patients with heart failure, systematically investigated according to a standardized protocol. Data were collected using a dedicated study questionnaire, validated and approved by the Ethics Committee, and subsequently entered into coded databases, allowing for rigorous and reproducible analysis.

The instruments used in the study were multidimensional and included detailed clinical, paraclinical, and imaging assessments. The study questionnaire included information on personal and socio-demographic data, cardiovascular risk factors (modifiable and non-modifiable), cardiovascular and non-cardiovascular comorbidities, chronic treatment (cardiovascular and non-cardiovascular), as well as treatment adherence.

Clinical evaluation included the assessment of anthropometric and functional parameters such as body mass index, peripheral oxygen saturation, heart rate, blood pressure, and the 6-minute walk test. Paraclinical investigations included electrocardiography, while imaging evaluation was performed using conventional and advanced echocardiography, including the determination of left ventricular ejection fraction and classification of heart failure accordingly (HFrEF, HFmrEF, HFpEF), analysis of diastolic function (E/A, lateral and septal e′, E/e′), assessment of indexed left atrial volume, and evaluation of right ventricular function. Lung ultrasound and additional imaging investigations were also performed when necessary.

Laboratory analysis included the determination of biomarkers specific to heart failure, particularly NT-proBNP, as well as evaluation of lipid profile, renal function, metabolic parameters, and inflammatory markers. The obtained data were analyzed using conventional and multivariate statistical methods and subsequently integrated into advanced analytical models. A distinctive element of the study is the use of artificial intelligence technologies, including machine learning algorithms, dimensionality reduction techniques, and clustering methods, which enabled the identification of clinical phenotypes and the development of risk stratification models. The integration of these methods with clinical, imaging, and biological data formed the basis for the development of a digital matrix for individualized evaluation of patients with heart failure. Through this complex, staged, and multidimensional approach, the research enabled an in-depth characterization of patients with heart failure and provided scientific support for the development of modern evaluation and individualized management strategies .

To achieve the aim and objectives of the study, the representative sample size was calculated using Cochran's formula:

$n = d[\tilde{\pi}(1-\tilde{\pi})]*(z\alpha/w)^2$

where:

d – design effect = 5

$\tilde{\pi} = 0.02$ (prevalence of chronic heart failure in the Republic of Moldova)

$z\alpha = 1.96$

w – margin of error corresponding to a 95% confidence interval, ES = 0.05

$n = 2 \times [0.02 \times 0.98] \times (1.96/0.05)^2 = 151$; after adjustment for a 10% non-response rate, 166 patients with chronic heart failure were required.

The study included patients with chronic heart failure admitted to the Institute of Cardiology between 2019 and 2025, in accordance with inclusion and exclusion criteria.

The results of clinical, paraclinical, and instrumental examinations, conducted within an observational cross-sectional study, allowed the classification of patients with chronic heart failure into three groups according to ejection fraction: preserved, mildly reduced, and reduced.

To demonstrate the impact of comorbidities on clinical prognosis, sample size was calculated using EpiInfo 7.2.2.6 (StatCalc – Sample Size and Power), based on a 95% confidence interval, 80% statistical power, an estimated 15% difference in favorable prognosis between patients with LVEF <50% and ≥50%, relative risk RR = 2, and a 1:1 group ratio. The estimated sample size was 268 patients, which increased to 295 after adjustment for a 10% non-response rate. Subsequently, to evaluate prognostic factors, sample size was recalculated using the Freedman (1982) formula for survival studies, considering: $\alpha = 0.05$ (two-sided), 80% power, hazard ratio = 1.6, 1:1 group ratio, and a cumulative incidence of major cardiovascular events of 32.4% at 5 years. The required number of events was 142, corresponding to a total sample size of 400 patients after adjusting for 10% loss to follow-up.

This sample size ensured adequate statistical power to detect significant differences between subgroups and to robustly assess the prognostic value of advanced echocardiographic parameters.

Inclusion criteria:

• diagnosis of chronic heart failure;
• patient consent;
• age >18 years.

Exclusion criteria:

• acute coronary syndromes;
• status post renal, cardiac, or pulmonary transplantation;
• acute or chronic obstructive nephropathies/uropathies;
• myelodysplastic syndromes; malignancies;
• refusal of informed consent.

Data collection was performed using a standardized protocol based on a study-specific questionnaire approved by the Ethics Committee, recording general patient data (including age at visit and onset), duration of symptoms, family history, comorbidities, cardiovascular risk factors, lifestyle factors, and treatment adherence.

Collected data included demographic (age, sex, occupation, residence, marital status), clinical (symptoms, BMI, SpO_2, heart rate, blood pressure, pulse, 6-minute walk test), and paraclinical parameters: functional (conventional and advanced echocardiography), extracerebral arterial Doppler, abdominal ultrasound, lung ultrasound, ECG, 24-hour ECG Holter and ambulatory blood pressure monitoring, and exercise ECG when needed; laboratory (creatinine, urea, electrolytes, glucose, HbA1c, insulin, HOMA index, lipid profile, INR, NT-proBNP, fibrinogen, uric acid); imaging (chest X-ray).

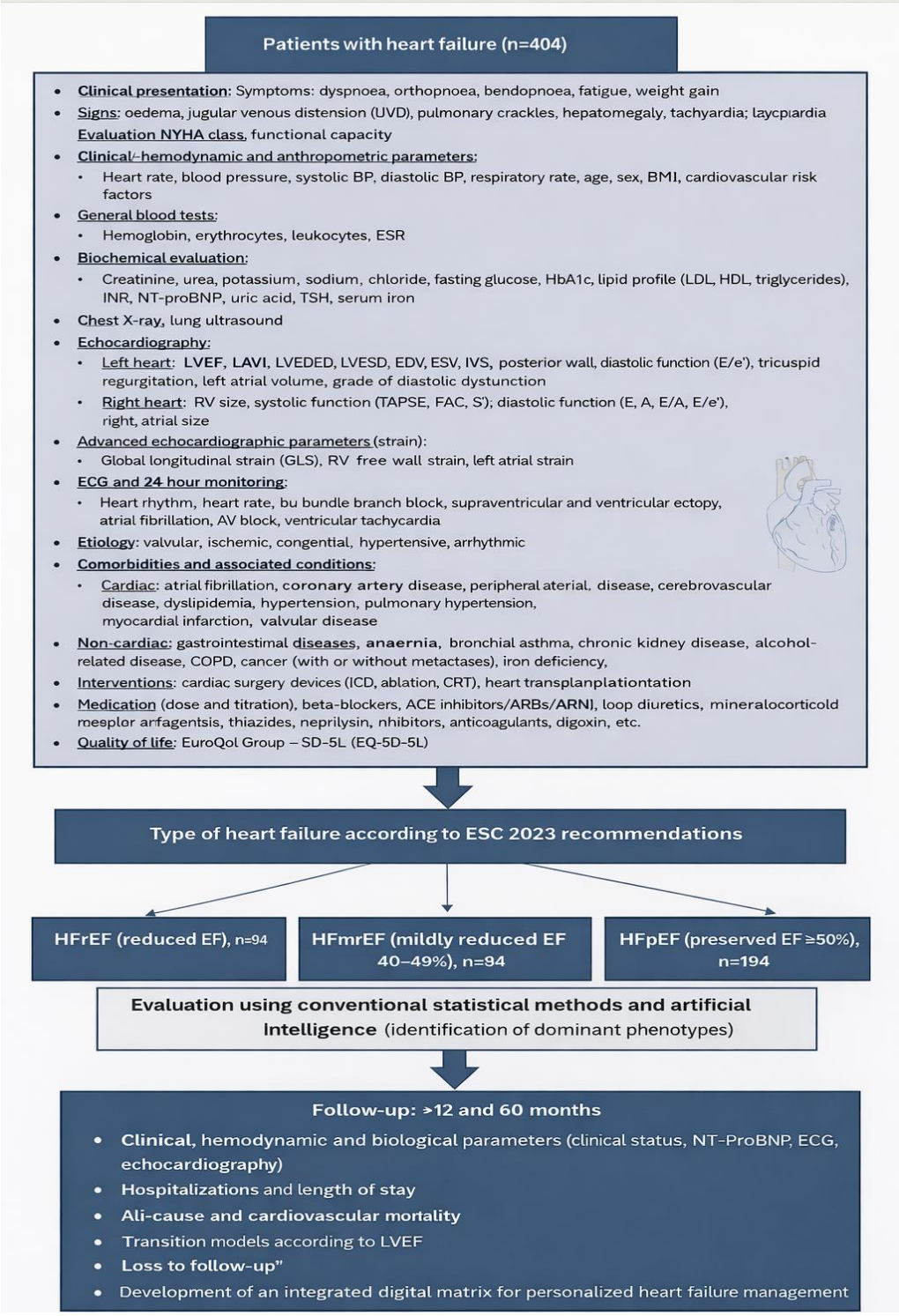


Figure 1. Logical pattern of the study

Patients were followed for 12 and 60 months to assess disease evolution and prognosis. Outcomes included hospitalizations, cardiovascular events (MI, stroke, TIA, pulmonary embolism), bleeding events, and mortality.

Artificial intelligence algorithms were used for clustering and classification (Random Forest, XGBoost, ANN), identifying clinical phenotypes and predicting outcomes such as changes in LVEF. Survival analysis included Kaplan–Meier curves and Cox regression. Statistical analysis was performed using SPSS, R, and Python, with significance set at $p < 0.05$.

2. PROFILE OF HEART FAILURE MANIFESTATIONS ASSESSED BY CLINICAL, IMAGING, AND BIOMARKER TOOLS

2.1 General characteristics of the study cohort

This chapter presents the results of the evaluation of a cohort of patients with heart failure included in an observational, analytical cohort study, based on standardized clinical, paraclinical, and imaging investigations. The assessment was performed at baseline (inclusion) and during follow-up at 12 and/or 60 months. Patients underwent a comprehensive evaluation, and data were collected according to a standardized protocol and a dedicated questionnaire approved by the Ethics Committee of the Nicolae Testemițanu State University of Medicine and Pharmacy (Approval No. 25/1, dated 13.05.2025).

The questionnaire included socio-demographic data, cardiovascular risk factors, comorbidities, treatment and adherence, as well as clinical parameters (BMI, SpO_2, heart rate, blood pressure, 6-minute walk test), ECG, conventional and advanced echocardiography (LVEF, classification into HFrEF/HFmrEF/HFpEF, diastolic function, E/A, e′, E/e′, LAVI, right ventricular function), lung ultrasound, additional imaging investigations, and biological markers (including NT-proBNP, lipid profile, renal function, and metabolic and inflammatory parameters).

The study cohort included 404 patients, with a relatively balanced sex distribution (53.1% male) and a median age of 66.0 years (IQR = 12.0). From an anthropometric perspective, the median BMI was 29.0 kg/m² (IQR = 6.5), with the majority of patients being overweight or obese. Most patients were living with their families (82.4%), and retirees predominated (57.8%).

The history of heart failure revealed a predominance of previously diagnosed cases (96.0%), with a disease duration of more than 12 months in most patients. Etiological analysis demonstrated a heterogeneous distribution, with a clear predominance of ischemic etiology (over 50% of cases), followed by hypertension and valvular disease, while other causes had a lower prevalence. The main reasons for hospitalization or clinical evaluation were most frequently myocardial ischemia (41.6%) and dyspnoea (38.4%), followed by atrial fibrillation and uncontrolled hypertension.

The distribution according to heart failure phenotype showed a predominance of HFpEF (52.2%), followed by HFrEF (25.3%) and HFmrEF (22.6%). Sex distribution differed between subgroups, with male predominance in HFrEF and female predominance in HFpEF, while HFmrEF showed a relatively balanced distribution (Figure 2).

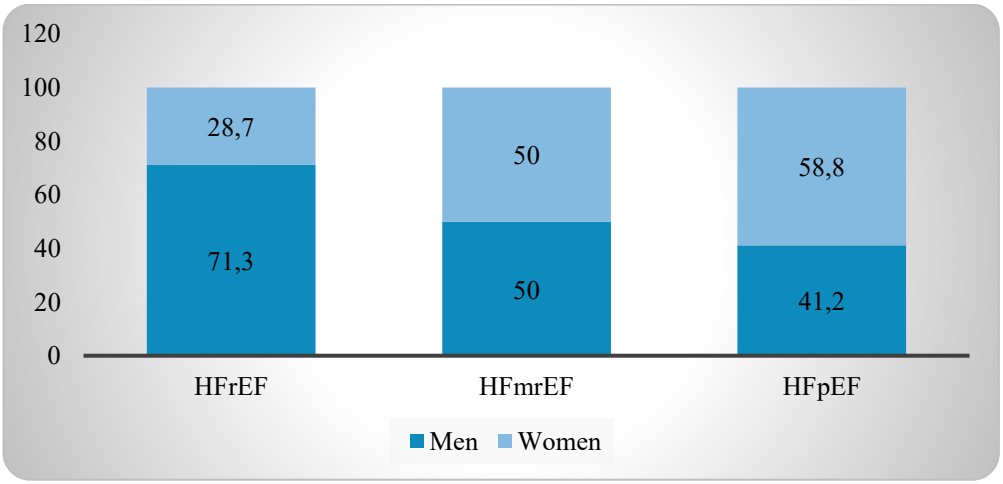


Figure 2. Sex distribution profile across heart failure phenotypes, (%)

The ages showed similar median values, with wide ranges across groups: 63.0 years (35–87; IQR 13.0) in HFrEF, 67.0 years (40–89; IQR 12.0) in HFmrEF, and 66.0 years (39–94; IQR 12.0) in HFpEF (Figure 4).

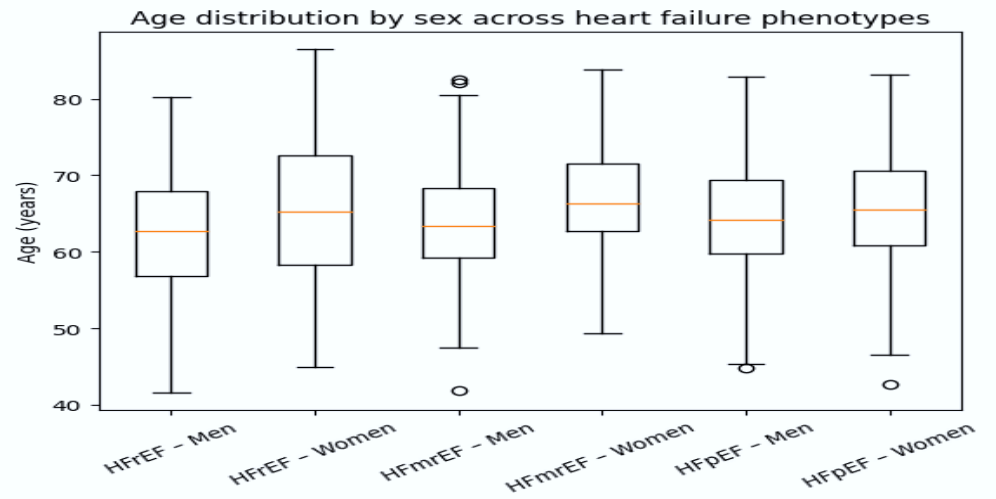


Figure 3. Comparative age distribution according to heart failure phenotype and sex.

From an anthropometric perspective, all subgroups exhibited an increased body weight profile, with median BMI values of 28.4 kg/m² in HFrEF, 28.7 kg/m² in HFmrEF, and 29.3 kg/m² in HFpEF. Distribution across BMI categories confirmed the predominance of overweight and obesity in all groups, with a relatively higher proportion of obesity observed in HFpEF. A prior history of heart failure was predominant across all subgroups, showing a progressive increase from HFrEF (69.9%) to HFpEF (85.8%), while de novo cases were more frequent in HFrEF. A disease duration of more than 12 months represented the dominant form in all groups and increased progressively from HFrEF to HFpEF. The etiological profile revealed clear differences between subgroups: coronary artery disease predominated in HFrEF and HFmrEF, arterial hypertension had a similar prevalence in HFmrEF and HFpEF, while valvular disease was more frequent in HFpEF. Other etiologies had a minor contribution (Figure 4).

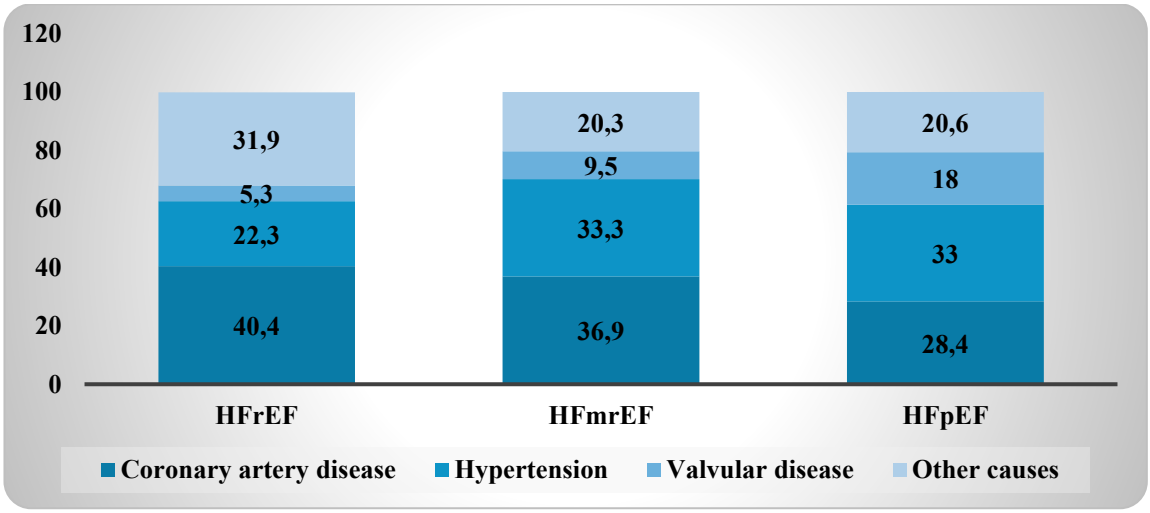


Figure 4. Etiological profile across heart failure phenotypes, (%)

The reasons for presentation followed a similar pattern: myocardial ischemia predominated in HFrEF (48.9%) and remained frequent in HFmrEF (41.7%), whereas in HFpEF it became secondary (33.5%), in the context of more prominent dyspnoea and decompensation (42.8%) (Figure 5).

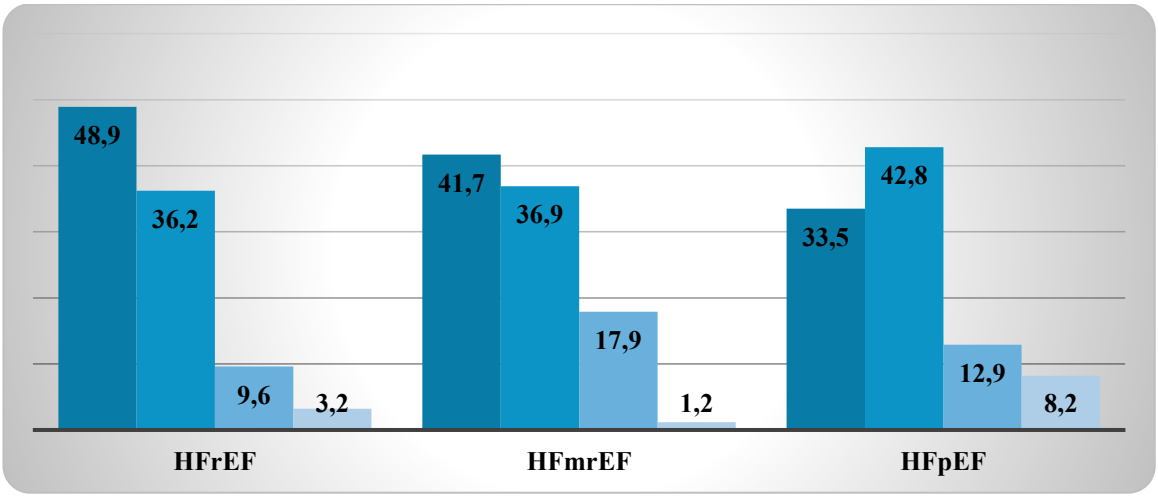


Figure 5. Reason for presentation according to heart failure phenotype.

Atrial fibrillation was more frequent in HFmrEF (17.9%) and HFpEF (12.9%) compared to HFrEF (9.6%), while uncontrolled hypertension was more prevalent in HFpEF (8.2%) compared to HFmrEF (1.2%) and HFrEF (3.2%).

2.2 Clinical, paraclinical, and laboratory parameters of the study cohort

Symptom severity (NYHA class) at admission was available for 404 patients: class II – 48 patients (11.9%), class III – 353 patients (87.4%), and class IV – 3 patients (0.7%).

The distribution of the "clinical profile" was available for 403 patients: profile 1 – 142 patients (35.2%), profile 2 – 161 patients (39.9%), profile 3 – 59 patients (14.6%), and profile 4 – 41 patients (10.2%) (Figure 6).

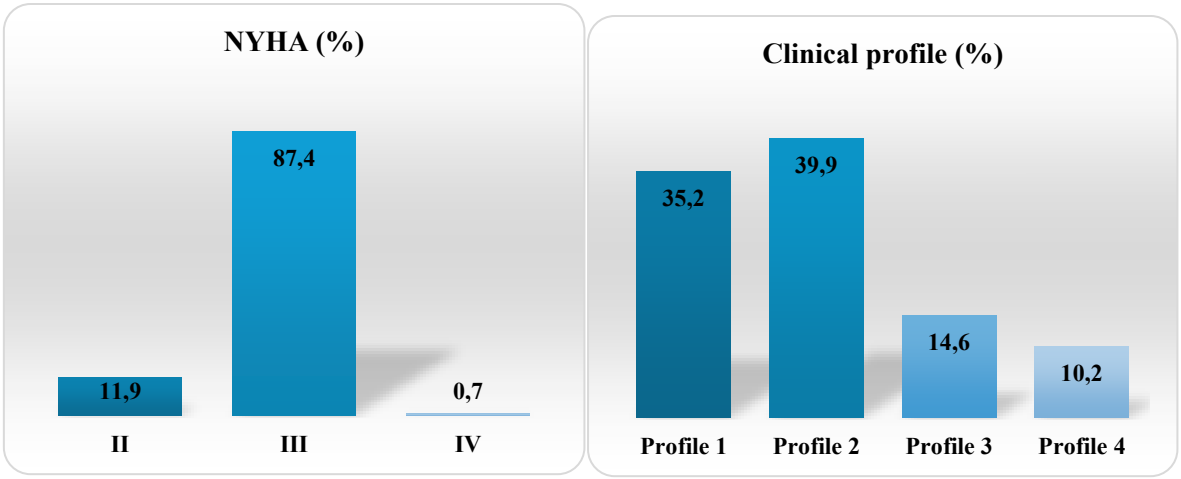


Figure 6. Clinical characterization of the study cohort: distribution of NYHA functional classes and clinical profiles in patients with heart failure, (%)

Systolic blood pressure had a median value of 120 mmHg (IQR = 10; range 90–240 mmHg). Diastolic blood pressure had a median of 80 mmHg (IQR = 0; range 50–120 mmHg). Heart rate showed a median of 73 beats per minute (IQR = 15; range 42–150) (Figure 7).

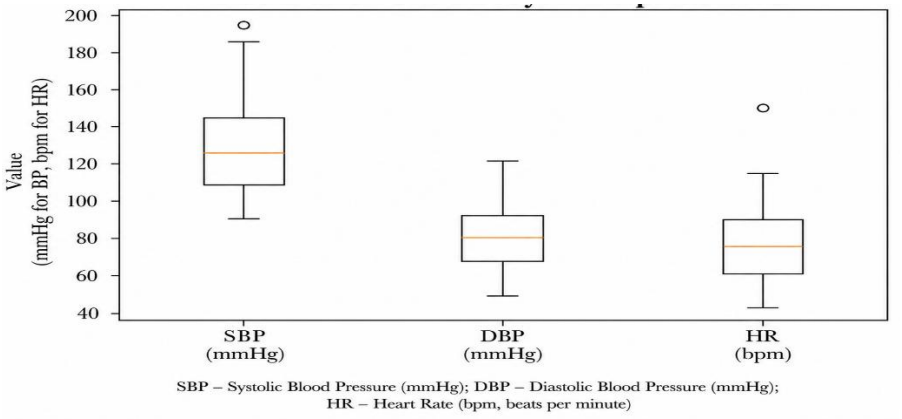


Figure 7. Hemodynamic profile of patients at admission, illustrated by the distribution of blood pressure and heart rate.

At examination/history, the frequencies of signs and symptoms were as follows: peripheral oedema – 214/404 (53.0%), dyspnoea at rest – 174/404 (43.1%), orthopnoea – 99/404 (24.5%), pulmonary crackles – 74/404 (18.3%), and jugular venous pulse – 26/402 (6.5%) (Figure 8). Laboratory profiles were consistent with a decompensation syndrome in a relevant subgroup: hemoglobin – median 132.0 g/L (IQR 21.0; 69.0–203.0), leukocytes – median 6.9 G/L (IQR 2.5; 2.22–25.50), creatinine – median 96.5 µmol/L (IQR 40.0; 39.9–725.0), urea – median 7.3 mmol/L (IQR 4.7; 1.4–64.0), sodium – median 138.0 mmol/L (IQR 4.0; 118.0–156.0), potassium – median 4.3 mmol/L (IQR 0.8; 2.0–7.2), NT-proBNP – median 3,361.0 pg/mL (IQR 7,598.0; 28.0–54,230.0), quantitative troponin – median 4.0 ng/L (IQR 7.0; 2.0–81,222.0), and C-reactive protein – median 6.0 mg/L (IQR 6.0; 0.1–153.0) (Figure 9).

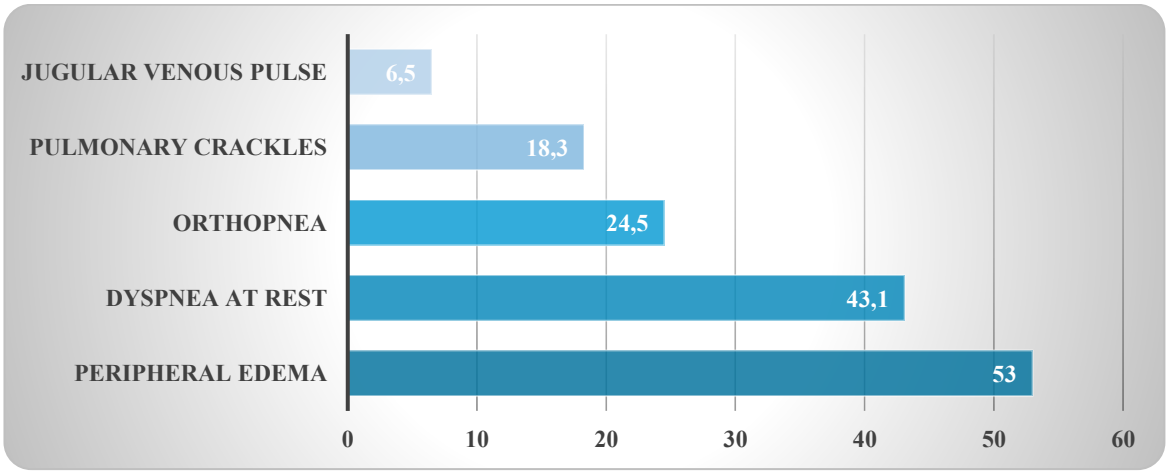


Figure 8. Symptomatic profile of patients with heart failure at the time of admission, (%)

Metabolic and biochemical parameters showed median values of: glucose 5.9 mmol/L, total cholesterol 4.7 mmol/L, LDL-cholesterol 2.7 mmol/L, albumin 3.6 g/dL, serum iron 10.6 µmol/L, uric acid 7.2 mg/dL, and total bilirubin 15.0 mmol/L. Anemia was present in 20.8% of patients, while hyperkalemia was relatively frequent (14.2% for K^+ >5.0 mmol/L), a finding relevant for RAAS inhibitor/MRA therapy titration. Dyslipidemia was identified in 57.0% of patients, and most did not achieve recommended LDL targets (LDL >1.8 mmol/L in 88.8% and >1.4 mmol/L in 96.2%), highlighting the need for optimization of lipid-lowering therapy. Iron deficiency was present in 15.4% of patients, likely underestimated in the absence of specific biomarkers.

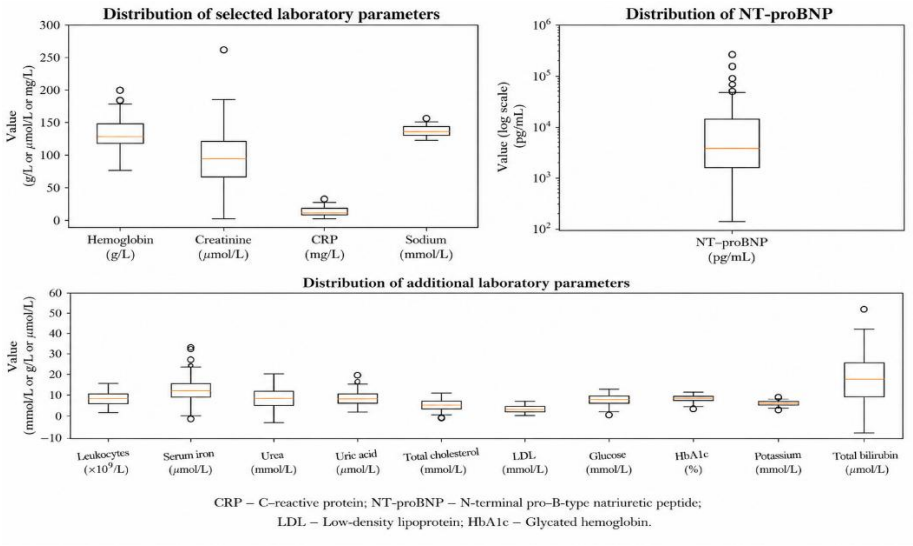


Figure 9. Overall profile of laboratory parameters in the study population, illustrated by boxplots (median and interquartile range).

Patients were classified into clinico-hemodynamic profiles (warm/dry, warm/wet, cold/dry, cold/wet), with prognostic and therapeutic relevance. Analysis of biological parameters showed limited differences between profiles. Hemoglobin exhibited a relatively uniform distribution ($p = 0.068$), without significant differences. In contrast, creatinine varied significantly across profiles ($p = 0.030$), with the highest values observed in the cold/wet profile, suggesting more severe renal impairment in this subgroup. Sodium showed minimal variation between profiles, without clear clinical relevance despite statistical significance ($p = 0.031$). Potassium and glucose did not differ significantly between groups, reflecting a heterogeneous but comparable metabolic distribution. Overall, creatinine was the only biological parameter that discriminated between profiles, while the other markers showed similar distributions, suggesting that profile differentiation is driven predominantly by hemodynamic and perfusion status rather than isolated biochemical variations.

2.3 Analysis of the study cohort according to left ventricular ejection fraction

To highlight differences between HFrEF (<40%), HFmrEF (40–49%), and HFpEF (≥50%), parameters were analyzed as mean ± standard deviation. The Kruskal–Wallis test was used for overall comparisons, followed by Dunn's post-hoc test with Bonferroni correction for $P < 0.05$. Hemoglobin values were comparable across groups (HFrEF 132.0 ± 21.1; HFmrEF 133.1 ± 18.3; HFpEF 131.2 ± 18.5; $P = 0.640$). In contrast, creatinine showed significant differences (HFrEF 121.8 ± 108.9; HFmrEF 109.4 ± 78.0; HFpEF 102.9 ± 83.5; $P = 0.027$), with the difference remaining significant only between HFrEF and HFpEF in post-hoc analysis.

Sodium ($P = 0.515$), potassium ($P = 0.089$), and glucose ($P = 0.557$) did not show significant differences between groups, and no relevant overall differences were observed for NT-proBNP ($P \geq 0.05$). Overall, creatinine was the only parameter that significantly differentiated subgroups according to ejection fraction, with higher values in HFrEF compared to HFpEF, suggesting more pronounced renal impairment in this category. The other biological parameters showed similar distributions across groups (Figure 10).

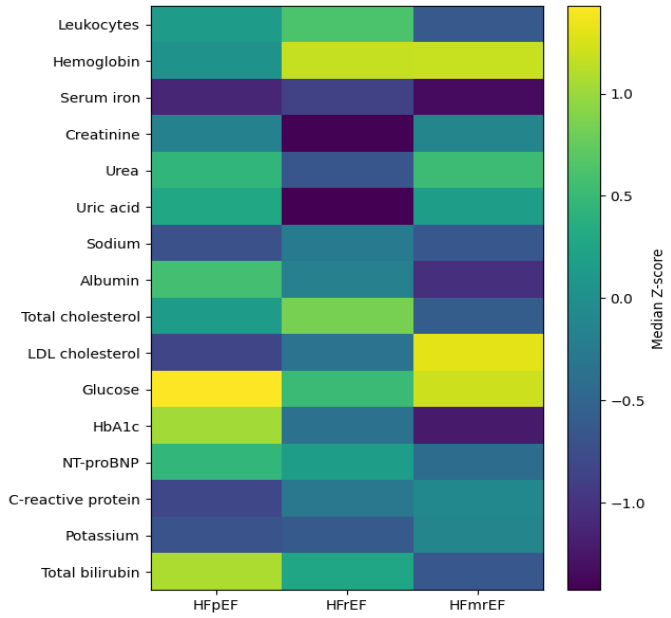


Figure 10. Heatmap representation of the biological profile according to heart failure phenotypes, highlighting the relative variations in laboratory parameters (Z-score).

Approximately half of the patients presented with chest radiographic abnormalities (50.4%; 95% CI 44.1–56.7), with no significant differences between heart failure phenotypes (HFrEF 60.3%, HFmrEF 50.0%, HFpEF 49.1%; P = 0.38). In contrast, the clinical congestion score (0–8) was significantly higher in HFrEF (1.8 ± 2.5) compared to HFmrEF (0.9 ± 1.5) and HFpEF (0.5 ± 1.1) (P = 0.002), suggesting a greater congestion burden in patients with reduced ejection fraction. Lung ultrasound (LUS) showed a mean score of 9.2 ± 7.3, with a predominance of mild-to-moderate forms and a rare absence of congestion, reflecting the selection of symptomatic patients. The LUS score was significantly higher in HFrEF (12.1 ± 8.5) compared to HFmrEF (9.1 ± 6.0) and HFpEF (4.9 ± 5.4) (P < 0.001), confirming more pronounced interstitial pulmonary congestion in this subgroup. Clinical signs of congestion showed robust correlations with imaging parameters and ventricular function. Pulmonary crackles were associated with radiographic abnormalities ($\rho \approx 0.41$; P < 0.001), while LUS score and grade were inversely correlated with LVEF ($\rho \approx -0.34$ to -0.38; P < 0.001). Peripheral oedema, orthopnoea, and jugular venous distension were associated with lower LVEF values ($|\rho| \approx 0.19$–0.29; $P \leq 0.001$). NYHA class correlated significantly with hemodynamic profile and congestion scores ($\rho = 0.19$–0.48; $P \leq 0.02$), and "wet/cold" profiles were associated with more severe symptomatology and more pronounced systolic dysfunction ($\rho = -0.24$; P < 0.001).

Clinico-imaging correlations were of moderate strength: peripheral oedema was associated with radiological abnormalities and LUS score, while dyspnoea and jugular venous distension were associated with the severity of congestion assessed by imaging, confirming concordance between clinical and imaging evaluation. In longitudinal analysis, a significant clinical improvement was observed, reflected by a reduction in body weight of 1.18 kg (95% CI −1.64 to −0.71; P < 0.001), from 86.09 ± 14.45 kg to 84.78 ± 13.90 kg (n = 105) (Figure 11).

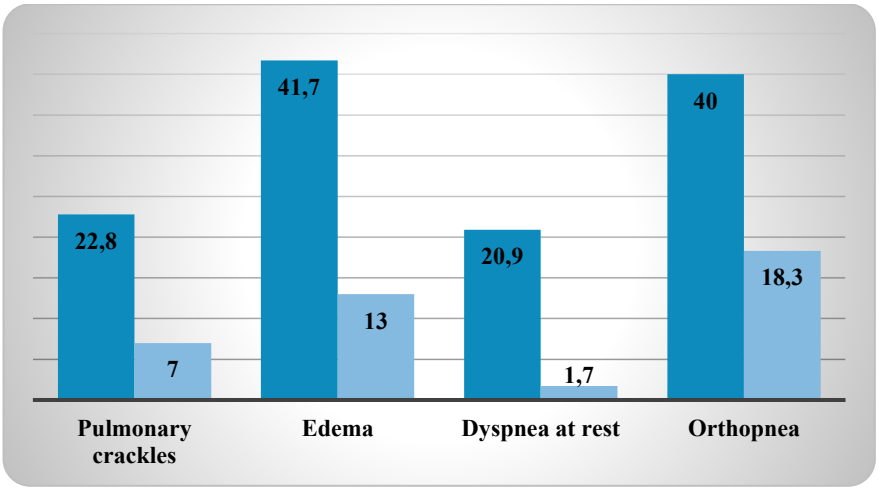


Figure 11. Evolution of clinical parameters before and after discharge.

Objective signs of congestion significantly decreased: pulmonary crackles from 22.8% to 7.0% ($P < 0.001$; n = 114), peripheral oedema from 41.7% to 13.0% ($P < 0.001$; n = 115), dyspnoea at rest from 20.9% to 1.7% ($P < 0.001$; n = 115), and orthopnoea from 40.0% to 18.3% ($P < 0.001$; n = 115). The proportion of patients with available chest radiography was higher at discharge (39.5% vs. 78.9%; $P < 0.001$; n = 114), reflecting completion of investigations during hospitalization. However, in the subgroup with paired data, the proportion of radiographic abnormalities did not differ significantly (57.6% vs. 66.7%; $P = 0.628$; n = 33). Overall, these findings confirm a clear clinical decongestion and functional improvement by the time of discharge, accompanied by moderate weight reduction and improvement in NYHA class.

2.4 Clinical evolution during follow-up of the study cohort

At 12 months, the main parameters were as follows: body weight 81.43 ± 13.69 kg, with a median of 80.00 kg (IQR 72.00–90.00), range 52.00–126.00 (n = 279); heart rate 67.18 ± 6.78 bpm, median 68 bpm (IQR 62–72), range 50–92 (n = 279); systolic blood pressure 118.21 ± 7.43 mmHg, median 120 mmHg (IQR 113–123), range 100–140 (n = 280); and diastolic blood pressure 75.36 ± 5.81 mmHg, median 75 mmHg (IQR 71–79), range 60–95 (n = 280).

From a functional perspective, the distribution of NYHA classes was clearly favorable: NYHA class II predominated (255 patients; 91.1%), while NYHA class I was rare (6 patients; 2.1%) and NYHA class III remained at a low proportion (19 patients; 6.8%). This pattern indicates clinical stabilization with mild-to-moderate limitation of physical activity in the vast majority of patients and is consistent with sustained decongestion following discharge (Figure 12).

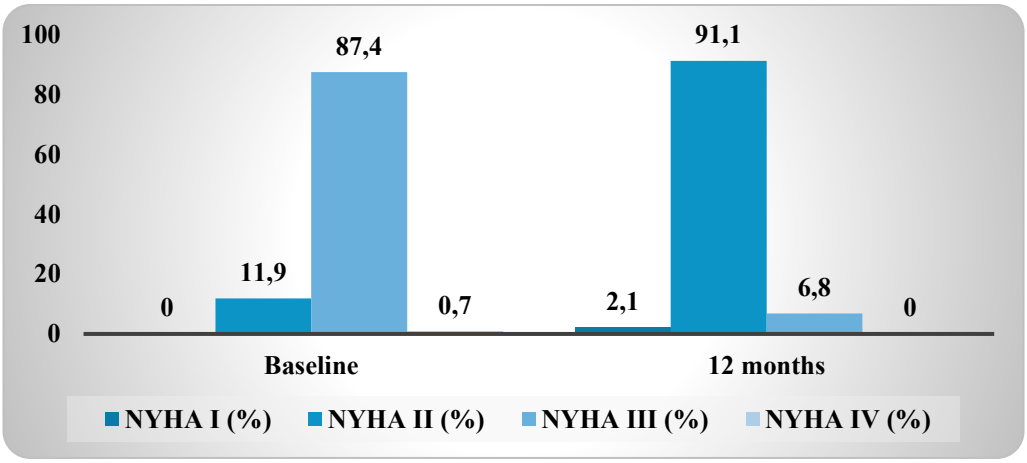


Figure 12. Functional class of heart failure (NYHA) at baseline versus 12 months after discharge, (%)

Compared with baseline, the overall trend indicates maintenance of clinical improvement: the weight reduction achieved during the acute episode is sustained, and functionally, patients remain predominantly in NYHA class II, suggesting adequate control of symptoms and signs of congestion over time. In subsets where variables could be paired between baseline and 1-year follow-up, the direction of changes is consistent with clinical observations, showing improved functional status and a lower frequency of congestion markers. Event burden was modest: the number of heart failure hospitalizations was 0.49 ± 0.70 (median 0; IQR 0–1; range 0–3), and the total duration of hospitalization was 2.68 ± 3.95 days (median 0; IQR 0–5; range 0–20). Quality of life (EQ-5D) indicated generally good overall functioning, with predominance of mild impairment in mobility and self-care and moderate impairment in usual activities and pain. The visual analogue scale (VAS) for health status was 77.41 ± 4.41 (median 80; IQR 70–80). Access to specialized care was high and stable: regular contact with the heart failure management team was reported in 95.1% at baseline and 96.9% at 1 year, while participation in exercise programs remained constant (~37%). These findings suggest good continuity of care and stable adherence to non-pharmacological interventions.

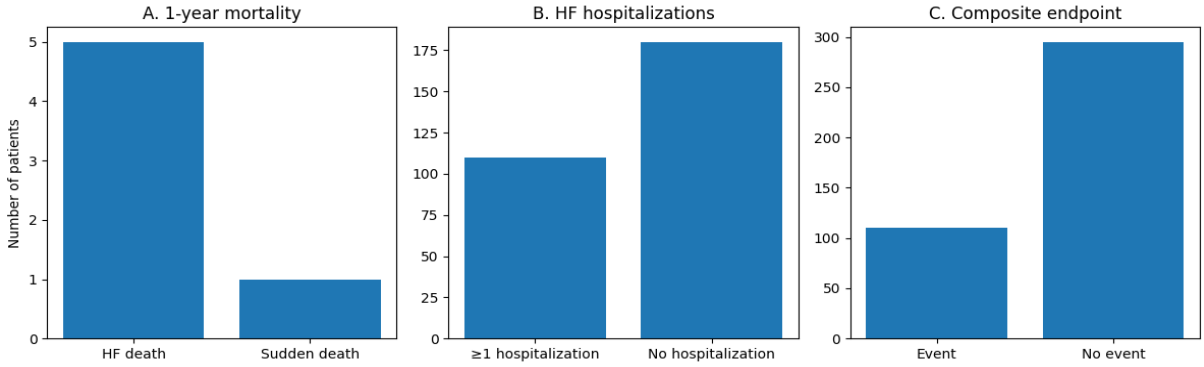


Figure 13. Clinical events at 1 year in the study cohort: mortality, hospitalizations, and composite endpoint, (%)

During the 1-year follow-up period, 6 deaths were recorded (2.10%; 95% CI: 0.96–4.50), predominantly of cardiac origin (83.3%), corresponding to 1.75% of the cohort, while sudden cardiac death accounted for 0.35%. Heart failure hospitalizations were frequent (38.25%), with a mean of 0.49 ± 0.70 episodes per patient (median 0; IQR 0–1) and a total hospitalization duration of 2.68 ± 3.95 days per patient (median 0; IQR 0–5). The composite endpoint had an incidence of 39.7%, while hospitalization-free survival was 61.8% (Figure 13).

The distribution across heart failure phenotypes showed a shift toward less severe forms: HFrEF decreased from 20.9% to 14.2%, HFmrEF increased to 24.3%, and HFpEF to 61.6%, suggesting an overall improvement in left ventricular function. Transitions between categories confirmed this trend: among HFrEF patients, 33.9% transitioned to HFmrEF, with no direct conversions to HFpEF; among HFmrEF patients, 25.8% progressed to HFpEF, while regression was rare. Among HFpEF patients, nearly all remained stable. Overall, 13.1% of patients transitioned to a less severe category, while deterioration was uncommon (0.7%).

LVEF analysis supported these findings: 48.5% of patients showed an increase, including 14.2% with a significant improvement (≥5 percentage points), while 45.1% remained stable and only 6.3% experienced a significant decline (Figure 14).

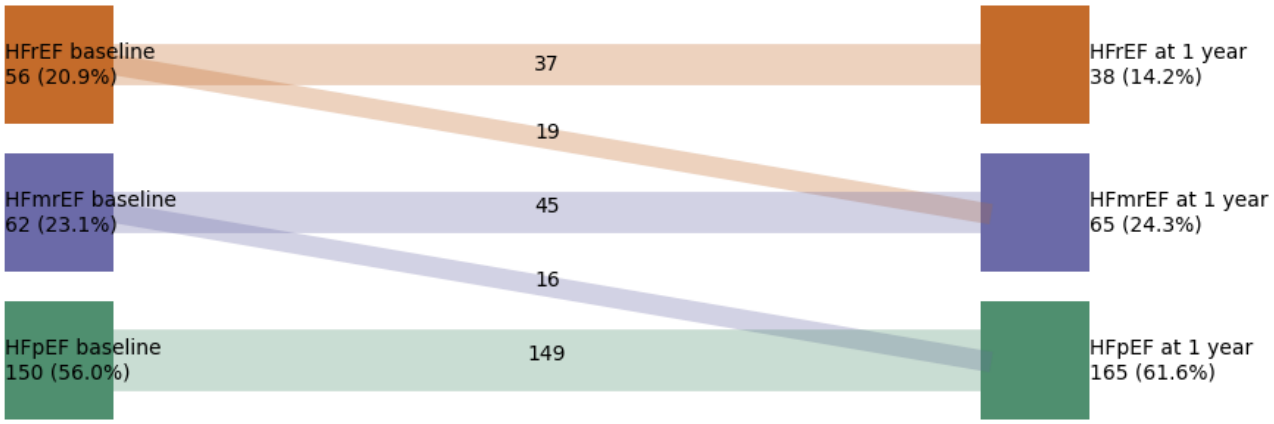


Figure 14. Transition of heart failure phenotypes between baseline and 1 year, according to ejection fraction.

From a clinical perspective, the cohort was characterized by stabilization and recovery: the proportion of HFrEF decreased, while HFpEF increased, with approximately one in eight patients transitioning to a more favorable category (Figure 14).

At 5 years (n = 174), LVEF remained relatively stable at the group level (mean ~48.5%; median 52%, IQR 45–55), with predominance of HFpEF (63.2%), followed by HFmrEF (21.8%) and HFrEF (14.9%). This profile suggests favorable cardiac remodeling; however, the persistence of HFrEF indicates a vulnerable subgroup requiring close monitoring and optimization of therapy (Figure 15).

Despite this profile, symptomatic status remained significant: most patients were in NYHA classes II–III, with high prevalence of dyspnoea (95.2%), exercise limitation (89.0%), fatigue (87.2%), and peripheral oedema (89.7%), while palpitations were also frequent (68.3%). Quality of life (EQ-5D) indicated mild-to-moderate limitations, with a modest overall health perception (~58/100), outlining a symptomatic population dominated by congestion and exercise intolerance.

Five-year mortality was substantial: 36.9% all-cause mortality, predominantly cardiovascular (34.5%), while non-cardiovascular mortality was low (2.4%). Over 93% of deaths were of cardiovascular origin, confirming the dominant role of cardiovascular risk and the need for continuous optimization of heart failure-specific therapy and secondary prevention.

The distribution of rehospitalizations was heterogeneous. Although most patients did not experience hospitalizations for heart failure (median 0; IQR 0–1), approximately 40–45% had at least one episode, and a small subgroup experienced recurrent admissions (≥2–5), disproportionately contributing to healthcare resource utilization (Figure 16).

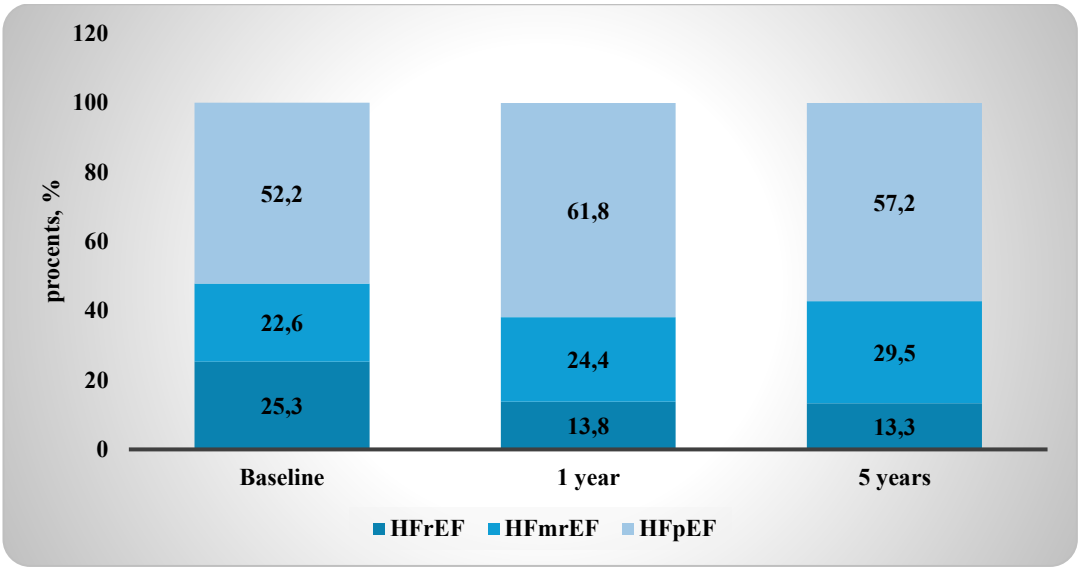


Figure 15. Evolution of the distribution of heart failure phenotypes defined by ejection fraction (baseline, 1 year, and 5 years), (%)

A similar pattern was observed for non–heart failure rehospitalizations, suggesting the impact of comorbidities. Overall, a bimodal distribution emerges: stable patients without rehospitalizations versus a core group of "frequent users" with an unstable clinical course. This subgroup represents the primary target for intensive interventions, including optimization of guideline-directed medical therapy (GDMT), use of SGLT2 inhibitors, rhythm and rate control, and implementation of structured post-discharge monitoring strategies. The low proportion of non-cardiovascular mortality confirms that cardiovascular risk remains the main determinant of 5-year prognosis.

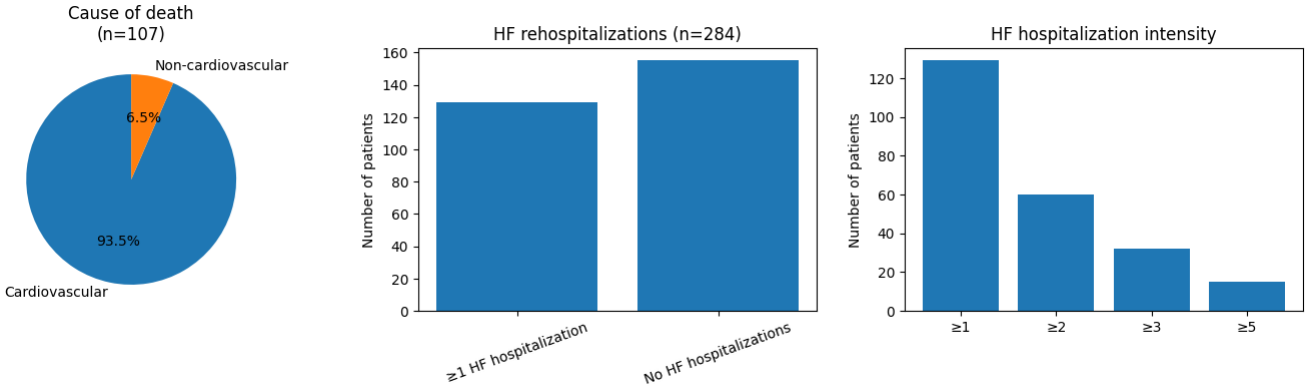


Figure 16. Five-year outcomes: mortality and hospitalization burden in the heart failure cohort. Distribution of deaths (cardiovascular vs non-cardiovascular) and frequency of heart failure rehospitalizations.

At 5 years, mortality shows a gradient influenced by heart failure phenotype and LVEF dynamics, suggesting its prognostic value over the medium term. At baseline, mortality was higher in HFrEF (41.0%) and HFmrEF (39.7%) compared with HFpEF (35.5%), with all deaths being of cardiovascular origin.

At 1 year, persistence of HFrEF was associated with the highest risk (47.4%), compared with HFmrEF (35.8%) and HFpEF (38.2%), indicating a more favorable prognosis with higher LVEF values (Figure 16). The same trend persisted at 5 years (HFrEF 48.7%; HFmrEF 36.0%; HFpEF 38.2%), although interpretation is influenced by survivor selection (Figure 17). From the perspective of LVEF dynamics, deterioration (≥5 percentage points) was associated with the

highest mortality (47.1%), whereas moderate improvement or stability showed comparable risks (~37–38%). Marked increases in LVEF were not uniformly associated with a favorable prognosis, likely reflecting baseline disease severity.

Multivariate analysis confirmed the role of LVEF at 1 year as a major predictor: each 5-percentage-point increase was associated with an approximately 55% reduction in 5-year mortality risk (OR 0.45; p = 0.046), while LVEF variation itself was not statistically significant. Overall, LVEF at 1 year represents an integrative marker of disease trajectory, and persistence of HFrEF identifies patients at the highest prognostic risk.

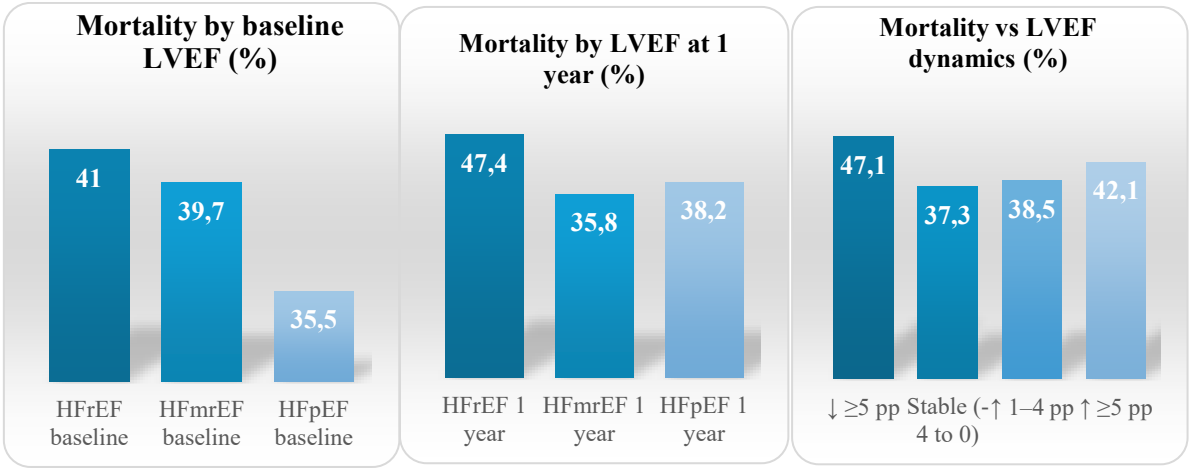


Figure 17. Five-year mortality according to heart failure phenotype and the dynamics of left ventricular ejection fraction.

At 1 year, loss to follow-up for LVEF assessment was low (≈4.5–5.2%). At 5 years, retention for vital status was very good (losses 2.1%), while the absence of echocardiographic evaluation was 6.9% in the overall cohort and 8.5% among survivors.

Heart failure emerges as a heterogeneous condition in which disease trajectory is driven by the interplay between ventricular function, congestion status, and response to therapy. Clinical evolution is unevenly distributed, with a small subgroup accounting for the majority of recurrent hospitalizations, supporting the need for structured post-discharge interventions. LVEF at 1 year represents a major determinant of prognosis: persistence of HFrEF is associated with increased risk, whereas transition to higher LVEF values is linked to more favorable outcomes. A 5-percentage-point increase in LVEF significantly reduces mortality risk, while deterioration in ventricular function identifies patients with poor prognosis. Congestion control remains a central pillar of stabilization, and guided decongestion—including lung ultrasound-based strategies—represents an effective approach to reducing recurrences. Overall, heart failure is associated with a severe prognosis (36.9% 5-year mortality, predominantly cardiovascular), and optimization of guideline-directed therapy, achieving the best possible LVEF at 1 year, and active congestion management can significantly reduce long-term event burden.

3. DESCRIPTION OF PHENOTYPES IN THE HEART FAILURE COHORT

3.1 Phenotyping of patients with heart failure

The analyzed cohort included 404 patients with heart failure, from which, after data cleaning and filtering, 253 relevant numerical variables were retained. These were grouped into: left ventricular (LV) systolic and diastolic function (LVEF, E/e′, LA), right ventricular (RV) function and pulmonary hypertension (TAPSE, PAP), biomarkers (NT-proBNP, creatinine, Na, K, Hb), clinical parameters (blood pressure, heart rate, congestion score), and

comorbidities/treatments. For conventional phenotyping (K-means, k = 4), data were imputed (median) and standardized (z-score), and clustering identified four distinct phenotypes:

C1 – Metabolic–hypertensive HFpEF (N = 135): preserved LVEF (~56%), increased BMI (~29.7), moderate NT-proBNP (~954 pg/mL), minimal congestion, relatively preserved renal function; hypertension ~94%, diabetes ~25%. A "dry" phenotype dominated by metabolic and hypertensive components.

C2 – Severe systolic HFrEF (N = 88): reduced LVEF (~38%), elevated NT-proBNP (~1933 pg/mL), early renal impairment, low congestion; reduced TAPSE (~14.8 mm). A "systolic-dominant" phenotype, associated with arrhythmic risk and requiring full guideline-directed medical therapy (GDMT).

C3 – Cardiorenal congestive HFrEF (N = 116): high congestion score (~3.8), maximal NT-proBNP (~3031 pg/mL), increased creatinine (~131 μmol/L). A "wet" phenotype characterized by volume overload and cardiorenal syndrome.

C0 – Post-ischemic/anemic HFrEF (N = 65): moderately reduced LVEF (~45.8%), elevated NT-proBNP (~3081 pg/mL), low hemoglobin, low congestion, coronary profile; younger age (~60 years). An ischemic/anemic phenotype with risk of decompensation in the presence of intercurrent stressors.

The phenotypes were validated using Δz values and clinical criteria, confirming coherent separation across systolic, congestive, metabolic, and cardiorenal axes.

Phenotyping using artificial intelligence

Data were preprocessed (cleaning, median imputation, standardization), reduced in dimensionality using principal component analysis (PCA; ~90% explained variance), and analyzed using a Bayesian Gaussian Mixture Model (Dirichlet Process), allowing automatic identification of clusters and probabilistic assignment.

Seven phenotypes were identified:

AI-0 – Cardiorenal congestive HFrEF (N = 115): marked congestion (~3.77), very high NT-proBNP (~3031 pg/mL), increased creatinine (~131 μmol/L). A high-risk "wet" phenotype.

AI-1 – Stable metabolic–hypertensive HFpEF (N = 68): LVEF ~54%, moderate NT-proBNP (~970 pg/mL), no congestion, preserved renal function; hypertension ~92%. A stable, euvolemic phenotype.

AI-2 – Metabolic HFpEF (obese/diabetic) (N = 55): LVEF ~51.6%, BMI ~30.6, moderate NT-proBNP (~1087 pg/mL), mildly increased creatinine; hypertension ~98%, diabetes ~35%. An advanced metabolic phenotype.

AI-3 – Severe systolic HFrEF (N = 51): LVEF ~33%, elevated NT-proBNP (~2288 pg/mL), increased creatinine (~131 μmol/L), low congestion. A phenotype with severe systolic dysfunction and major prognostic risk.

AI-4 – Mixed ischemic/arrhythmic/metabolic HFrEF (N = 49): LVEF ~47.5%, NT-proBNP ~1871 pg/mL, very high prevalence of atrial fibrillation (~68%), hypertension ~96%, diabetes ~47%. A phenotype dominated by arrhythmia and metabolic substrate.

AI-5 – Biomarker-high HFrEF (N = 38): LVEF ~46.8%, very high NT-proBNP (~3562 pg/mL) disproportionate to congestion, relatively preserved renal function. A phenotype with high risk of rapid decompensation.

AI-6 – Stable hypertensive HFpEF without AF (N = 28): LVEF ~59%, moderate NT-proBNP (~1120 pg/mL), minimal creatinine (~82 μmol/L), absence of atrial fibrillation. A "robust" phenotype with low risk.

3.2 Individualization of treatment according to identified phenotypes

Based on phenotypes identified through integrated statistical and artificial intelligence analysis, individualized therapeutic strategies were formulated, adapted to the clinico-echocardiographic profile and patient comorbidities.

For phenotype AI-0 – cardiorenal congestive HFrEF, the primary objective is effective decongestion using loop diuretics, potentially in sequential strategies, with careful monitoring of volume and electrolyte status. After stabilization, full implementation of guideline-directed therapy (ARNI/ACEi/ARB, beta-blockers, MRAs, SGLT2 inhibitors) is recommended, adjusted according to renal function and blood pressure, along with correction of iron deficiency.

For phenotype AI-1 – stable metabolic–hypertensive HFpEF, management includes SGLT2 inhibitors, strict blood pressure control, and optimization of the metabolic profile through weight reduction and physical activity. In the presence of atrial fibrillation, anticoagulation and individualized rhythm or rate control strategies are required, with periodic monitoring of NT-proBNP and renal function.

Phenotype AI-2 – metabolic HFpEF (obese/diabetic) follows similar principles, with emphasis on intensive metabolic management, SGLT2 inhibitors, and in selected patients GLP-1 receptor agonists, alongside strict diabetes and hypertension control.

For phenotype AI-3 – severe systolic HFrEF, rapid initiation and titration to target doses of GDMT is essential. Ivabradine may be used in patients with elevated heart rate, and in selected cases cardiac resynchronization therapy or ICD implantation is indicated according to standard criteria.

Phenotype AI-4 – mixed ischemic/arrhythmic/metabolic HFrEF requires, in addition to full HFrEF therapy, prioritized management of atrial fibrillation (anticoagulation and rhythm/rate control), evaluation of ischemic substrate, and intervention on metabolic risk factors.

For phenotype AI-5 – biomarker-high HFrEF, management includes full GDMT combined with intensive monitoring and patient education for early diuretic adjustment; evaluation of adherence and triggers of decompensation is essential.

For phenotype AI-6 – stable hypertensive HFpEF, strict blood pressure control, SGLT2 inhibitor use, lifestyle interventions, and periodic monitoring are recommended, with vigilance for the development of atrial fibrillation.

3.3 Distribution of comorbidities across heart failure phenotypes

The analysis of comorbidities highlights that hypertension remains the central comorbidity, being universal in hypertensive HFpEF without atrial fibrillation (AI-6, 100%) and highly prevalent in other HFpEF phenotypes (AI-2: 66.1%; AI-1: 58.2%). In HFrEF, its prevalence is more heterogeneous, ranging from 96.6% in AI-4 to 17.9% in the cardiorenal phenotype (AI-0), where the congestive axis predominates.

Diabetes mellitus delineates the metabolic axis, reaching its highest prevalence in AI-2 (37.5%) and remaining relevant in AI-6 (29.3%) and in intermediate HFrEF phenotypes. The absence of diabetes in AI-1 underscores the heterogeneity of HFpEF.

Atrial fibrillation clearly defines AI-4 (100%), but remains frequent in AI-1, AI-2, AI-5, and AI-3 (approximately 40–60%), suggesting the role of elevated filling pressures and atrial remodeling. It is absent in AI-6 and rare in AI-0.

Respiratory comorbidities are moderately represented (COPD more frequent in HFrEF), while sleep apnea is likely underdiagnosed.

The ischemic component predominates in HFrEF, particularly in AI-3, with high rates of myocardial infarction, angina, PCI, and CABG, indicating the need for optimization of revascularization strategies and secondary prevention.

Vascular and thromboembolic comorbidities are more frequent in phenotypes with atrial fibrillation and elevated biomarkers (AI-4, AI-5), while treated valvular disease is also concentrated in AI-4 and AI-3. Thyroid dysfunction and behavioral factors (smoking, alcohol consumption) are more pronounced in severe HFrEF.

Overall, three major axes emerge:

– the **hypertensive axis** (dominant in HFpEF),

– the **metabolic axis** (AI-2, partially AI-6),

– the **arrhythmic axis** (AI-4, but present across phenotypes).

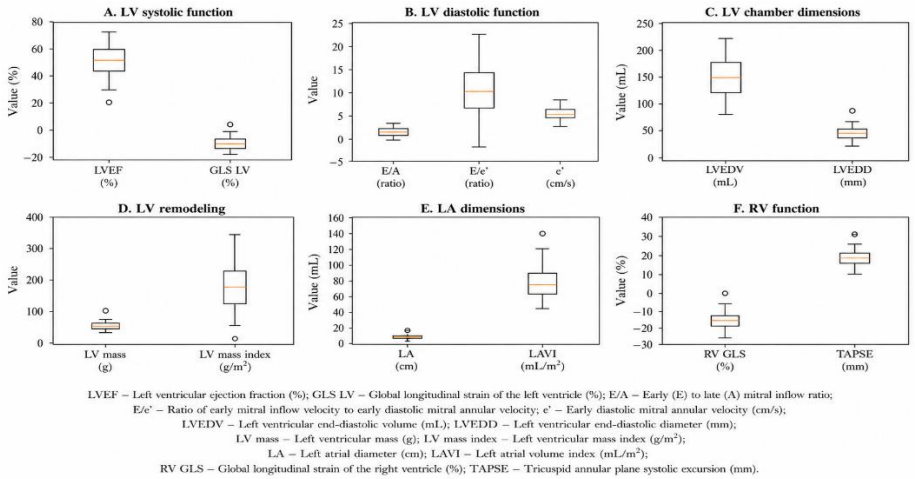
The ischemic phenotype (AI-3) requires optimization of GDMT and revascularization, while the cardiorenal phenotype (AI-0) requires decongestion strategies and renal protection.

The application of K-means clustering and AI models (PCA + Bayesian Gaussian mixture) generated stable and clinically relevant phenotypes. AI-based analysis enabled finer stratification (7 subgroups vs. 4 classical clusters), highlighting distinct pathophysiological axes and facilitating individualized prognosis and therapy.

4. EVALUATION OF CONVENTIONAL AND ADVANCED ECHOCARDIOGRAPHIC PARAMETERS IN HEART FAILURE PATIENTS

4.1 Analysis of conventional echocardiographic parameters

Conventional echocardiographic evaluation revealed a heterogeneous morpho-functional profile, dominated by mild-to-moderate systolic dysfunction (mean LVEF 46.9 ± 11.8%), with a balanced distribution between reduced (26.2%), mildly reduced (25.2%), and preserved ejection fraction (48.6%). Left ventricular remodeling was frequent, characterized by chamber dilation and increased myocardial mass, suggesting a predominance of concentric geometry. Diastolic dysfunction was widespread, with most patients presenting a pseudonormal pattern (72.6%), while elevated filling pressures (E/e′ ≥14) were identified in 24.8%. Myocardial relaxation was consistently impaired, with reduced tissue Doppler velocities in more than 85–90% of patients. The left atrium was markedly dilated (LAVI ≥34 mL/m² in 72.9%), reflecting chronic pressure overload. Valvular involvement was predominantly regurgitant, of mild-to-moderate severity, without significant severe aortic lesions. Right ventricular function was frequently at the lower limit of normal (TAPSE <17 mm in 38.8%), and pulmonary pressures were elevated in the majority of patients (≥35 mmHg in ~70%), suggesting mild pulmonary hypertension associated with left ventricular dysfunction (Figure 18). Overall, these data describe a profile dominated by structural remodeling, diastolic dysfunction, and chronic hemodynamic overload, with concomitant involvement of the right ventricle and pulmonary circulation.



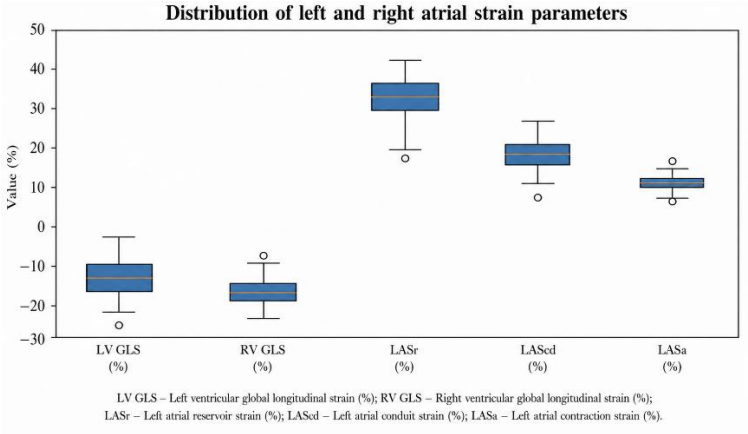
LVEF – Left ventricular ejection fraction (%); GLS LV – Global longitudinal strain of the left ventricle (%); E/A – Early (E) to late (A) mitral inflow ratio; E/e' – Ratio of early mitral inflow velocity to early diastolic mitral annular velocity; e' – Early diastolic mitral annular velocity (cm/s); LVEDV – Left ventricular end-diastolic volume (mL); LVEDD – Left ventricular end-diastolic diameter (mm); LV mass – Left ventricular mass (g); LV mass index – Left ventricular mass index (g/m²); LA – Left atrial diameter (cm); LAVI – Left atrial volume index (mL/m²); RV GLS – Global longitudinal strain of the right ventricle (%); TAPSE – Tricuspid annular plane systolic excursion (mm).

Figure 18. Distribution of conventional structural and functional echocardiographic parameters in the study cohort.

Conventional echocardiography revealed a characteristic heart failure profile dominated by frequently concentric left ventricular remodeling, mild-to-moderate systolic dysfunction, and diastolic dysfunction associated with chronic left atrial dilation.

4.2 Evaluation of advanced echocardiographic parameters in heart failure patients

Advanced echocardiographic assessment (speckle tracking) enabled direct quantification of myocardial function, providing superior sensitivity compared with conventional parameters. Global longitudinal strain of the left ventricle (LV GLS) had a mean value of −15.61 ± 3.92% (median −16.0%; IQR −18.6 to −13.0), suggesting reduced contractile reserve in a subgroup of patients, including those with apparently preserved ejection fraction.



LV GLS – Left ventricular global longitudinal strain (%); RV GLS – Right ventricular global longitudinal strain (%); LASr – Left atrial reservoir strain (%); LAScd – Left atrial conduit strain (%); LASa – Left atrial contraction strain (%).

Figure 19. Distribution of advanced echocardiographic parameters in the study cohort (boxplots).

Right ventricular function was relatively well preserved, with RV GLS of −19.81 ± 1.91% (median −20.0%), showing low variability and indicating less pronounced longitudinal impairment compared with the left ventricle. Left atrial strain analysis demonstrated a reduction in both the reservoir component (LASr 31.65 ± 5.60%) and the conduit component (LAScd 19.37 ± 4.76%), suggesting increased atrial stiffness and impaired ventricular relaxation. In contrast, active contractile function (LASa 12.29 ± 1.93%) remained relatively preserved, with a compensatory trend in a subset of patients. This profile is consistent with predominant diastolic dysfunction, left atrial stiffness, and elevated filling pressures, explaining reduced exercise tolerance and a predisposition to congestion episodes (Figure 19).

4.3 Correlations between conventional and advanced echocardiographic parameters

Comparison of conventional echocardiographic parameters with myocardial deformation indices revealed consistent correlations between global function and longitudinal mechanics. A strong inverse correlation was observed between ejection fraction and LV global longitudinal strain (ρ = −0.83), as well as between TAPSE and RV strain (ρ = −0.89), confirming concordance between classical and advanced markers. Cross-relationships (LVEF–RV GLS: ρ = −0.46; TAPSE–LV GLS: ρ = −0.49) support the concept of biventricular functional interdependence.

In the diastolic domain, increased filling pressures were associated with reduced atrial function, reflected by inverse correlations between E/e′ and LAScd (ρ = −0.40) and LASr (ρ = −0.36), as well as between LAVI and LAScd (ρ = −0.40) and LASr (ρ = −0.31). Consistently, myocardial relaxation (septal e′) correlated directly with atrial performance (ρ ≈ 0.34–0.40). Additionally, atrial dilation (LAVI) was associated with less negative GLS values (ρ = 0.26), suggesting subtle longitudinal impairment in the context of chronic loading.

Overall, these correlations confirm the coherence between conventional and strain-derived parameters and highlight the complementary value of advanced echocardiography in the integrated assessment of cardiac function (Figure 20).

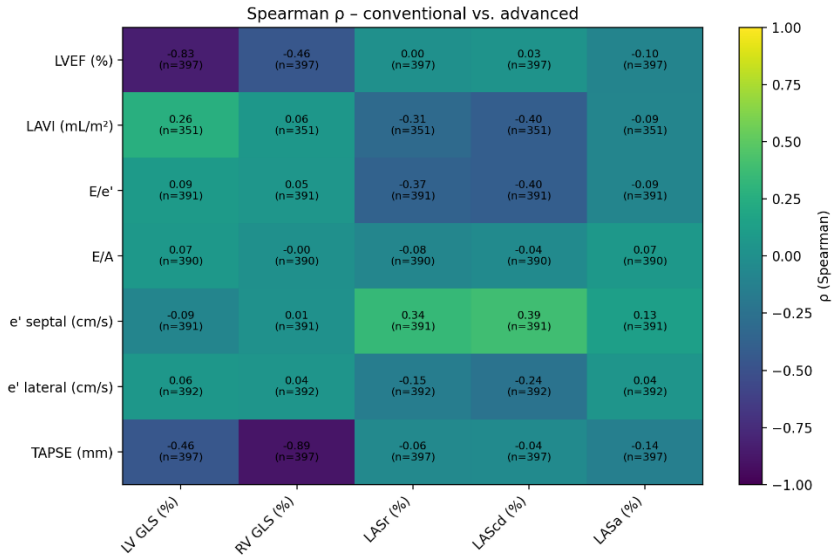


Figure 20. Correlations between conventional and advanced echocardiographic parameters

At the level of active atrial contraction, an inverse correlation was observed between tricuspid annular plane systolic excursion (TAPSE, mm) and atrial contractile strain (LASa, %) (ρ = −0.14), as well as a direct correlation between septal e′ velocity (cm/s) and LASa (%) (ρ = 0.13).

These associations highlight the role of atrial contraction as a compensatory mechanism during late diastole, particularly in situations where passive ventricular filling is impaired.

4.4 Correlative analysis between echocardiographic and clinical parameters in patients with heart failure

The correlation analysis highlights an integrative pathophysiological mechanism in which longitudinal dysfunction and increased diastolic load determine clinical severity, congestion, and neurohormonal activation in heart failure.

LV GLS correlates directly with NT-proBNP (ρ = 0.33, p < 0.001), while LVEF shows an inverse correlation (ρ = −0.14, p = 0.011), confirming the association between myocardial dysfunction and neurohormonal activation. Similar relationships are observed for the right ventricle (RV GLS: ρ = 0.14), suggesting biventricular involvement. Signs of congestion (rales, oedema) are associated

with impaired longitudinal function (LV GLS up to ρ = 0.31; RV GLS up to ρ = 0.18) and with reduced LVEF (ρ ≈ −0.16 to −0.17), while TAPSE correlates inversely with congestion (ρ = −0.18), reflecting right ventricular dysfunction. Respiratory symptoms (dyspnoea, orthopnoea) predominantly reflect diastolic loading and atrial remodeling, correlating with LAScd (ρ up to 0.36), LV GLS (ρ up to 0.32), as well as with LAVI and E/e′.

The left atrium plays a central role: clinical severity (NYHA class) correlates directly with LAScd (ρ = 0.47), inversely with LASr (ρ = −0.23), and directly with LASa (ρ = 0.17), suggesting increased atrial stiffness and compensatory mechanisms. Central venous pressure and the overall clinical profile follow a similar pattern, correlating with GLS and diastolic parameters. Hemodynamic variables further support these relationships: heart rate is associated with worsening longitudinal function (LV GLS: ρ = 0.28; RV GLS: ρ = 0.18) and inversely with LVEF and TAPSE (ρ = −0.18).

Markers of myocardial injury (troponin) correlate with longitudinal impairment and atrial function (ρ up to 0.23) (Figure 21).

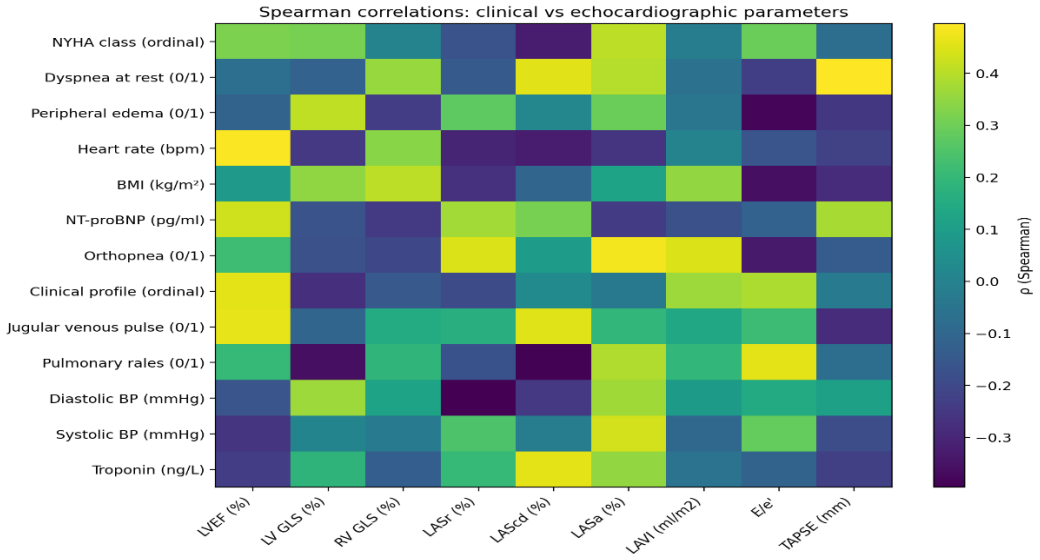


Figure 21. Correlations between echocardiographic and clinical parameters

Overall, these correlations confirm that longitudinal dysfunction and increased diastolic load represent the central mechanisms determining clinical severity and the hemodynamic profile.

4.5 Identification of echocardiographic parameters with predictive value for clinical outcomes in patients with heart failure

The correlation analysis between advanced echocardiographic parameters and clinical status highlights a coherent relationship between longitudinal dysfunction, diastolic loading, and clinical severity. Left ventricular global longitudinal strain (LV GLS) correlated directly with NT-proBNP (ρ = 0.33, p < 0.001), while ejection fraction showed an inverse correlation (ρ = −0.14, p = 0.011), confirming the link between myocardial dysfunction and neurohormonal activation. Similar, though weaker, relationships were also observed for the right ventricle.

Signs of congestion and respiratory symptoms were consistently associated with impaired longitudinal function and diastolic parameters, while left atrial function showed a strong correlation with clinical severity (NYHA: LAScd ρ = 0.47; LASr ρ = −0.23), highlighting the central role of the left atrium in determining exercise tolerance. Hemodynamic parameters and heart rate followed the same pattern, reflecting a compensatory response to reduced myocardial performance. In the analysis of quality of life, LV GLS and LVEF showed significant correlations after FDR correction with the domains of Mobility, Pain/Discomfort, and Anxiety/Depression (ρ

≈ 0.22–0.27; q = 0.008–0.034), confirming the direct impact of longitudinal function on daily life. From a prognostic perspective, univariate analysis showed that less negative LV GLS, reduced LASr/LAScd, and increased NT-proBNP were associated with a higher risk of cardiovascular mortality and rehospitalizations. Multivariate models (LVEF, LV GLS, LASr, LAScd, NT-proBNP) demonstrated modest discriminative capacity (AUC ~0.55 for mortality and ~0.57 for rehospitalizations), suggesting a real but distributed prognostic signal across variables (Figure 22).

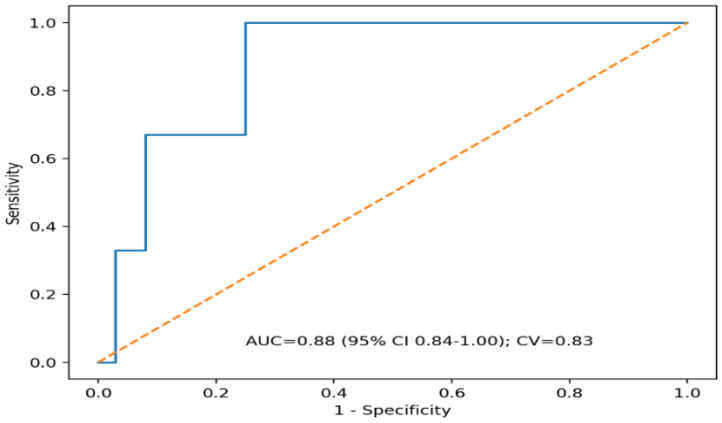


Figure 22. Echocardiographic predictors in multivariate analysis (LVEF, LV GLS, RV GLS, NT-proBNP, LASr, LASd) for heart failure rehospitalizations.

Overall, LV GLS, atrial parameters, and NT-proBNP emerge as the most consistent risk markers, outperforming ejection fraction in predicting clinical events. Their integration with conventional parameters (E/e′, LAVI, TAPSE, PASP) provides a robust framework for stratification and monitoring of patients with heart failure, although their utility for individual decision-making remains limited in the absence of stronger multivariate models.

5. EVALUATION OF THE IMPACT OF COMORBIDITIES ON CLINICAL, HEMODYNAMIC MANIFESTATIONS AND OUTCOMES IN PATIENTS WITH HEART FAILURE

5.1 Analysis of comorbidity prevalence in patients with heart failure

In the context of the multidimensional nature of heart failure, the analysis of comorbidities highlights a high and heterogeneous burden, with a major impact on clinical evolution and prognosis. Within the cardiovascular domain, hypertension predominates (86.9%), followed by coronary artery disease (65.3%) and prior myocardial infarction (29.5%), reflecting a significant residual ischemic risk. Atrial fibrillation is frequent (35.6%), with an additional 18.3% having a prior history, underscoring the need for rigorous anticoagulation management.

Revascularization procedures are present in approximately 15% of patients, while significant valvular disease is less frequent (Figure 23).

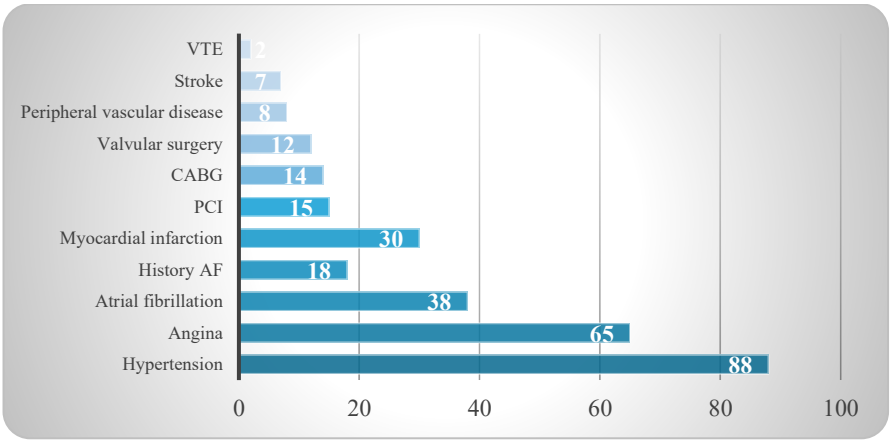


Figure 23. Prevalence of cardiovascular comorbidities, (%)

The systemic atherosclerotic burden is further supported by the presence of peripheral vascular disease and stroke/TIA (both 7.4%), while venous thromboembolism remains rare (1.7%). Within the non-cardiovascular domain, diabetes is present in 22.8% of patients (with an additional 6.4% controlled cases), and COPD in 10.1%, both contributing to respiratory symptomatology. Hepatic dysfunction (5.7%), dialysis (1.5%), and active malignancy (1.0%) identify vulnerable subgroups, while neuropsychiatric comorbidities, although less frequent (depression 2.2%, cognitive impairment 1.2%), may influence adherence and quality of life (Figure 24).

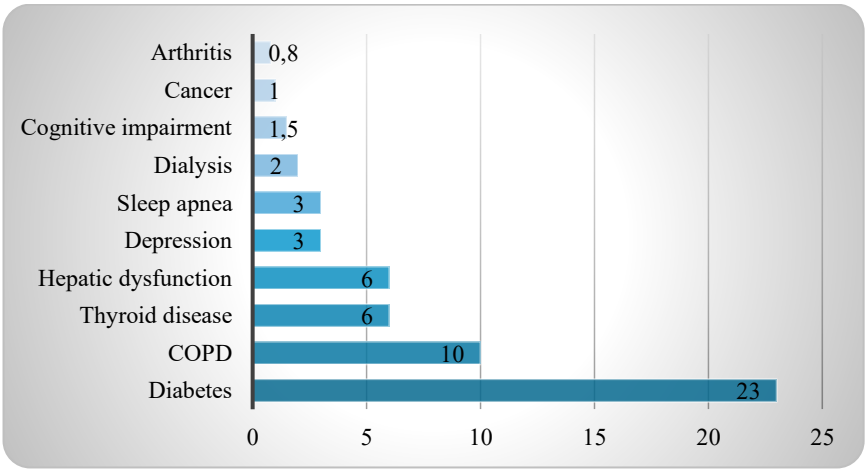


Figure 24. Prevalence of non-cardiovascular comorbidities.

Sleep apnea is likely underdiagnosed (2.0%, with CPAP use in 0.2%). Lifestyle factors remain relevant: active smoking is present in 7.2% of patients, while problematic alcohol consumption is observed in approximately 5–6%, representing important opportunities for intervention. Overall, the coexistence of hypertension, coronary artery disease, and atrial fibrillation, on a background of metabolic and respiratory comorbidities, explains the increased risk of decompensation and rehospitalization. These findings support the need for an integrated approach focused on risk factor control, optimization of therapy, and multidisciplinary management of the patient.

5.2 Analysis of the distribution of comorbidities according to heart failure type

Comparative analysis of comorbidities across phenotypes defined by ejection fraction reveals physiologically relevant differences. The ischemic component follows a decreasing gradient from HFrEF to HFpEF: myocardial infarction is present in 49.0% of HFrEF patients, 31.9% in HFmrEF, and 18.4% in HFpEF ($p < 0.0001$), supporting the dominant role of the ischemic substrate in the reduced ejection fraction phenotype (Figure 25). Atrial fibrillation is frequent across all groups, but reaches its highest prevalence in HFmrEF (67.0%) and HFrEF (54.8%),

compared with HFpEF (47.6%) (p = 0.007), highlighting a greater arrhythmic burden in reduced and mid-range ejection fraction phenotypes.

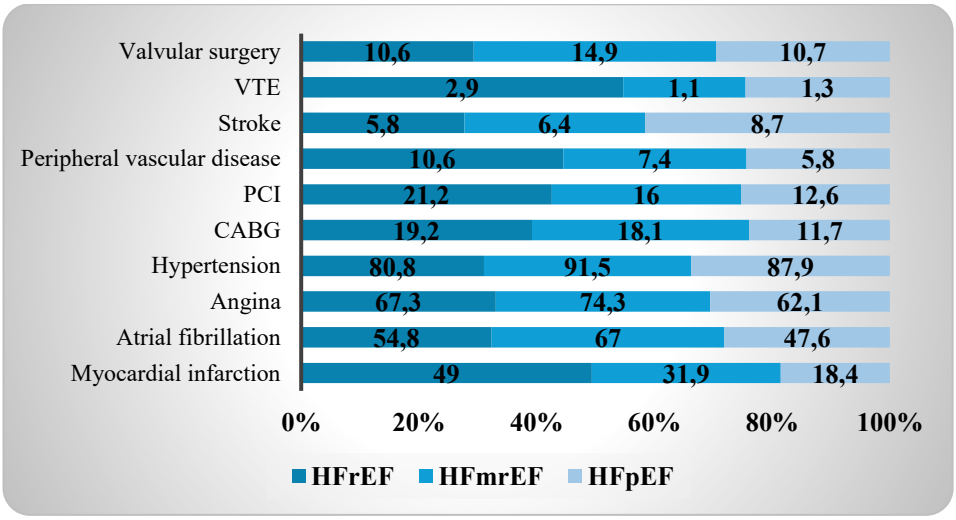


Figure 25. Distribution of the prevalence of cardiovascular comorbidities according to heart failure type, (%)

Hypertension remains ubiquitous (80.8–91.5%) without significant differences between groups, while angina and revascularization procedures do not clearly discriminate between phenotypes.

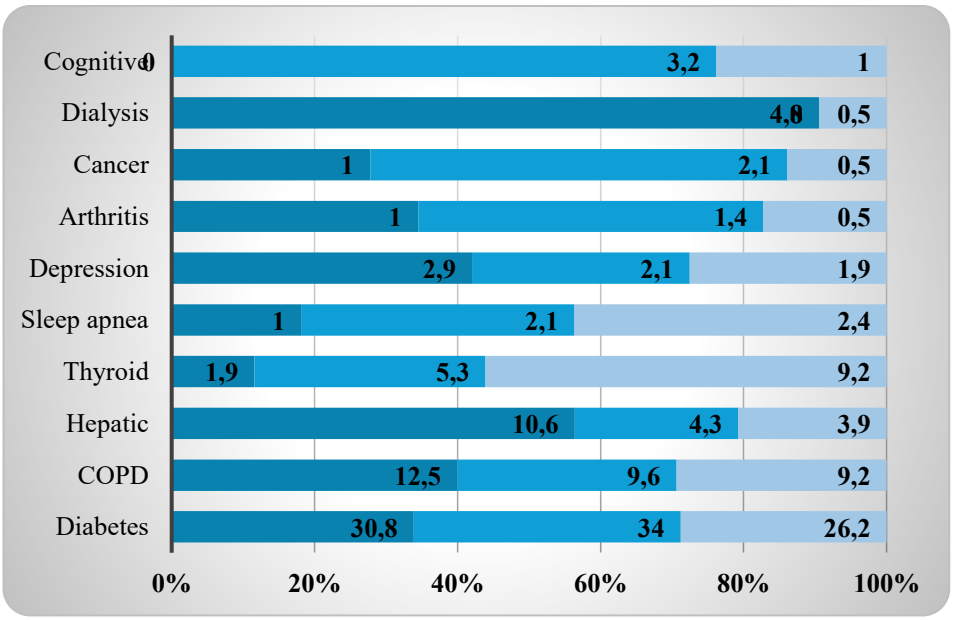


Figure 26. Distribution of the prevalence of non-cardiovascular comorbidities according to heart failure type, (%)

Within the non-cardiovascular domain, hepatic dysfunction is more frequent in HFrEF (10.6% vs ~4%, p = 0.044), reflecting systemic congestion, while thyroid dysfunction is more prevalent in HFmrEF/HFpEF (~9%) than in HFrEF (~5%). Diabetes (≈26–34%) and COPD (≈9–12%) do not differ significantly between groups, suggesting a transversal role of these comorbidities (Figure 26). Overall, HFrEF is characterized by a pronounced ischemic and congestive profile, HFmrEF by a maximal arrhythmic burden, and HFpEF by the predominance of pressure overload and metabolic comorbidities. These differences support the need for a phenotype-adapted therapeutic approach.

5.3 Analysis of the distribution of comorbidities across age groups in patients with heart failure

Age group stratification (<65 years, 65–74 years, ≥75 years) highlights relevant differences in the comorbidity profile. Hypertension remains nearly universal (89.6–93.8%) without significant variation, while atrial fibrillation shows a relatively constant prevalence (51.9–56.5%), suggesting a stable arrhythmic burden across age groups. The ischemic component increases with age, with stable angina showing an ascending gradient from 60.1% (<65 years) to 73.6% (65–74 years) and 85.5% (≥75 years) ($p = 0.0006$), while myocardial infarction reaches 35.5% in elderly patients. Cerebrovascular events and peripheral vascular disease increase moderately in patients ≥75 years (~11.3%), reflecting the cumulative atherothrombotic risk. Invasive procedures vary by age: percutaneous interventions remain relatively constant (~15–18%), whereas bypass surgery and valvular surgery decrease significantly in patients ≥75 years (8.2% and 1.6% vs 21.1% and 17.9% in those <65 years; $p < 0.05$), suggesting treatment selection based on frailty. Among non-cardiovascular comorbidities, diabetes peaks in the 65–74-year group (35.1%), COPD remains relatively constant (~23–25%), and hepatic dysfunction is more frequent in patients ≥65 years (≈14–18%). Lifestyle factors (smoking ~15–21%, alcohol consumption ~11–12%) remain relatively stable across age groups. Advanced age is associated with an increased ischemic and atherothrombotic burden and reduced use of invasive interventions, while hypertension and atrial fibrillation remain transversal determinants, supporting the need for an age-adapted clinical approach (Figure 27).

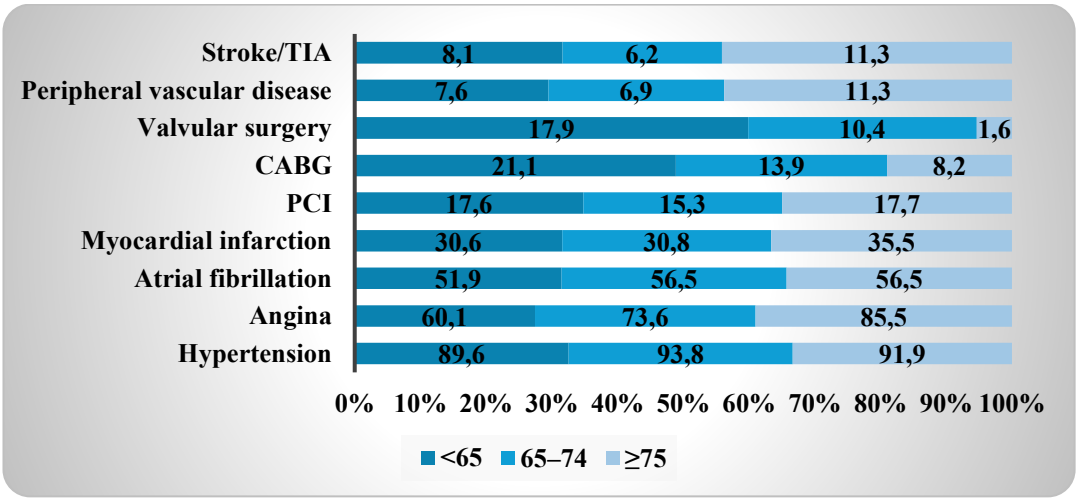


Figure 27. Prevalence of cardiovascular comorbidities according to age groups in patients with heart failure, (%)

Depression is more frequent in patients <65 years (8.1%), compared with 6.0% in those aged 65–74 years, and is absent in patients ≥75 years; however, the wide confidence intervals suggest considerable variability. Cognitive dysfunction occurs predominantly after the age of 65 (5.9% in the 65–74 age group and 2.9% in those ≥75 years), with relevant clinical impact through impaired adherence. Rheumatoid arthritis remains rare (≈1.5–2.9%) across all age groups. Sleep apnea shows low prevalence (3.0–6.5%), without a clear gradient, while CPAP use is very limited, suggesting possible underdiagnosis and undertreatment. Anemia increases progressively with age (24.3% in <65 years, 32.0% in 65–74 years, 40.3% in ≥75 years), accompanied by a decline in hemoglobin levels (13.5 → 12.9 g/dL; $p = 0.0156$). Renal function deteriorates significantly (eGFR 77 → 54 mL/min/1.73 m²), and the prevalence of chronic kidney disease increases from 22.3% to 62.9% ($p < 0.0001$), highlighting the cumulative biological burden (Figure 28).

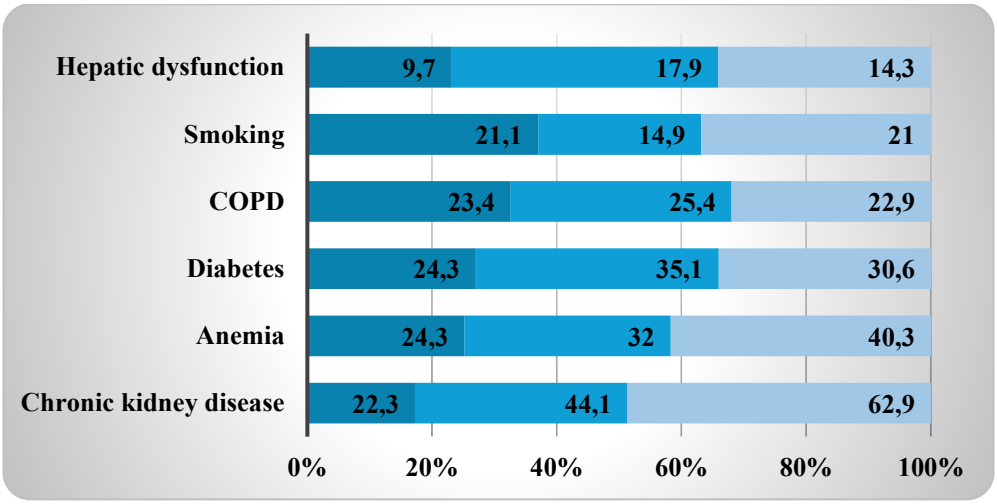


Figure 28. Prevalence of non-cardiovascular comorbidities according to age groups in patients with heart failure, (%)

Overall, multimorbidity is nearly universal (99.3%), with a mean of 7.0 ± 2.3 comorbidities per patient, without major differences between age groups, highlighting the need for an integrated and individualized approach.

5.4 Analysis of the prognostic value of comorbidities on the clinical outcomes of patients with heart failure

The analysis of the prognostic value of comorbidities at 5 years reveals a differentiated impact on rehospitalizations and mortality. In the analyzed cohort (N = 284 for mortality), 99 cardiovascular deaths (34.86%) and 129 rehospitalizations (31.93%) were recorded.

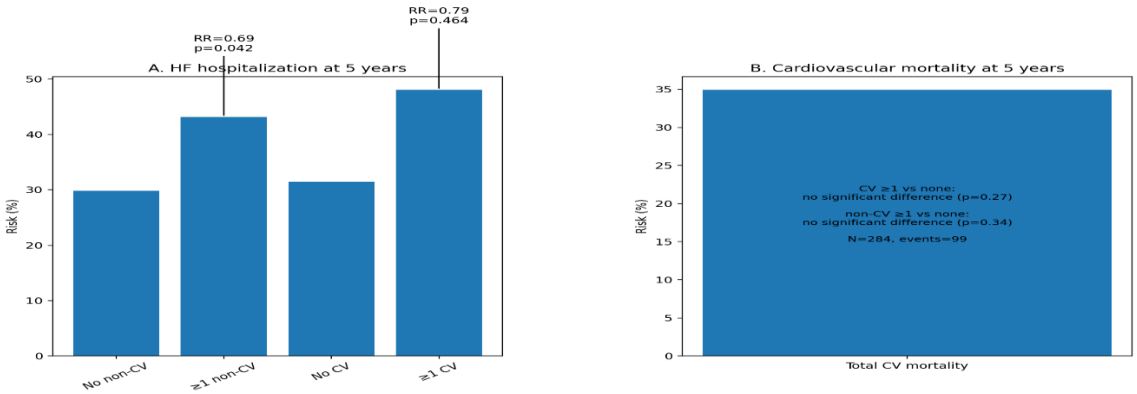


Figure 29. Impact of cardiovascular and non-cardiovascular comorbidities on the risk of heart failure hospitalization at 5 years.

For rehospitalization, certain comorbidities were significantly associated with increased risk: COPD (34.15% vs 12.60%; RR = 2.71; p = 0.0039) and chronic kidney disease (37.70% vs 27.54%; p = 0.0325). In contrast, diabetes mellitus was paradoxically associated with a lower risk (RR = 0.67; p = 0.0256). Aggregate analysis showed that the presence of ≥1 non-cardiovascular comorbidity was associated with a lower risk of rehospitalization (29.79% vs 43.08%; RR = 0.69; p = 0.042), while cardiovascular comorbidities did not significantly influence this risk (p = 0.464) (Figure 29).

For 5-year cardiovascular mortality, no robust associations were identified either for individual comorbidities or for grouped categories (p = 0.279 for cardiovascular; p = 0.348 for non-cardiovascular), suggesting a limited influence in the context of a high overall event rate. Multimorbidity was nearly universal (99.3%), with a mean of 7.0 ± 2.3 comorbidities per patient, highlighting the clinical complexity of the cohort. In this context, COPD emerges as a marker of

risk for rehospitalization, while other comorbidities show heterogeneous effects, and their overall impact on mortality remains limited.

6. ANALYSIS OF THERAPEUTIC MANAGEMENT IN PATIENTS WITH HEART FAILURE

6.1 Medication administered to patients at study enrollment

In the 2019–2020 cohort, treatment at admission was nearly universal (99.0%), dominated by diuretics (85.8%), RAAS blockade (70.8%), beta-blockers (69.8%), and MRAs (58.3%), outlining a solid neurohormonal therapeutic foundation. ARNI use was almost absent (0.7%), and SGLT2 inhibitors were not yet implemented. Anticoagulation was frequent (53.5%), predominantly with vitamin K antagonists, while statins were used in 69.1% of patients.

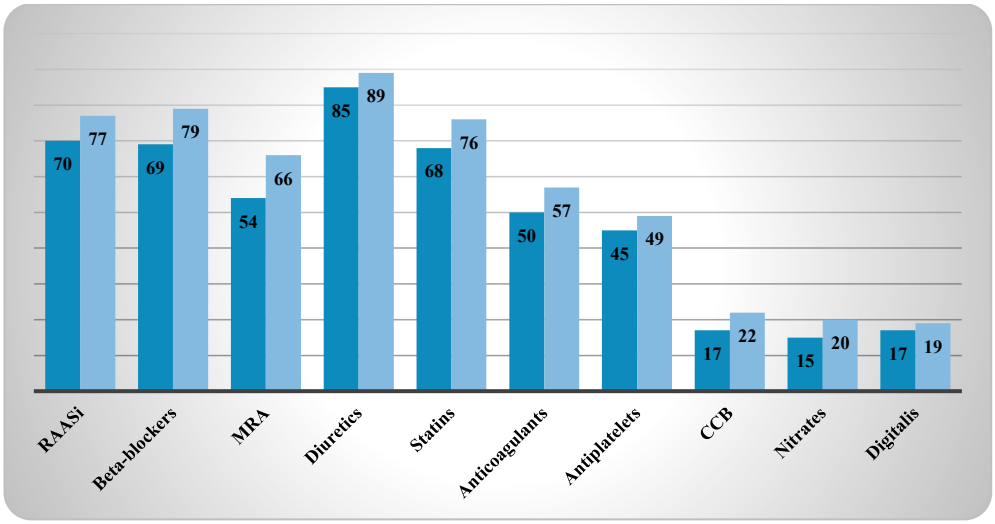


Figure 30. Rate of cardiovascular medication prescription at admission and after discharge in patients with heart failure, (%)

At discharge, treatment coverage becomes complete (100%), with clear intensification of therapy: beta-blockers increase to 79.9% (+10.1 pp), MRAs to 67.4% (+9.0 pp), RAAS blockade to 77.4% (+6.6 pp), and statins to 76.7% (+7.6 pp). Anticoagulant use increases to 58.0%, with expansion of DOAC use (14.9%), while diuretics rise to 89.9% (Figure 30). ARNI use remains marginal (1.7%), and SGLT2 inhibitors are absent.

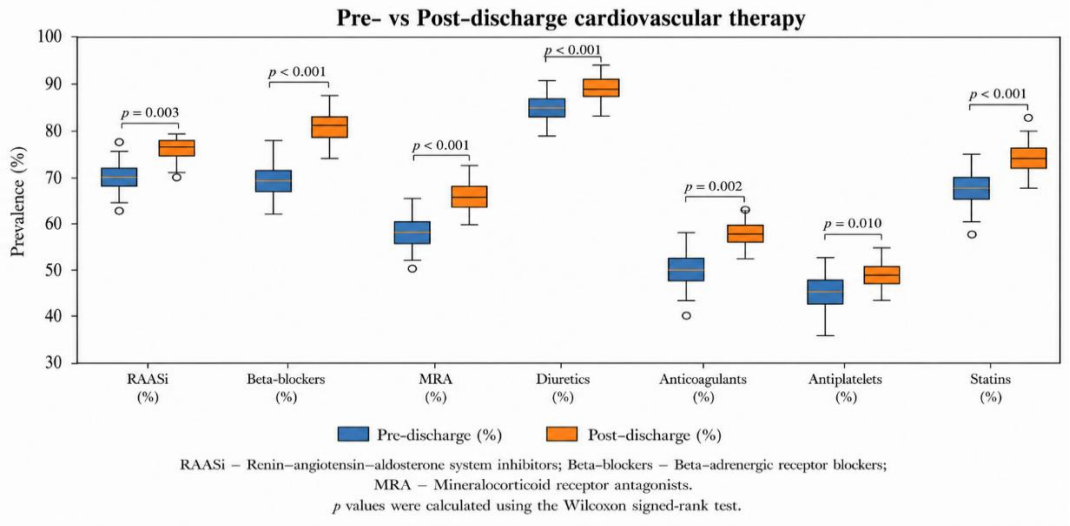


Figure 31. Boxplot of the distribution of prescription rates for major therapeutic classes, highlighting treatment optimization between admission and discharge (Δ, %).

Regarding the achievement of target doses, proportions remain moderate: beta-blockers 49.8%, ACE inhibitors 42.4%, MRAs 37.6%, and ARBs 30.8%, with no patients reaching target doses for ARNI, suggesting only partial optimization at discharge. Guideline-directed therapy combinations show improvement, with triple therapy increasing from 15.9% to 18.0%, while dual therapies expand moderately and monotherapy decreases (Figure 31). The therapeutic profile at discharge is better aligned with guideline recommendations; however, there remains significant potential for further titration and full implementation, particularly for ARNI and SGLT2 inhibitors. Oral antidiabetic therapy remains stable, with a slight increase from 22.6% (65/288) to 23.3% (67/288; +0.7 pp), suggesting minor adjustments without major class changes. Insulin use remains relatively constant, with a slight decrease from 6.9% to 6.6% (−0.3 pp), possibly reflecting a selective transition toward oral therapies.

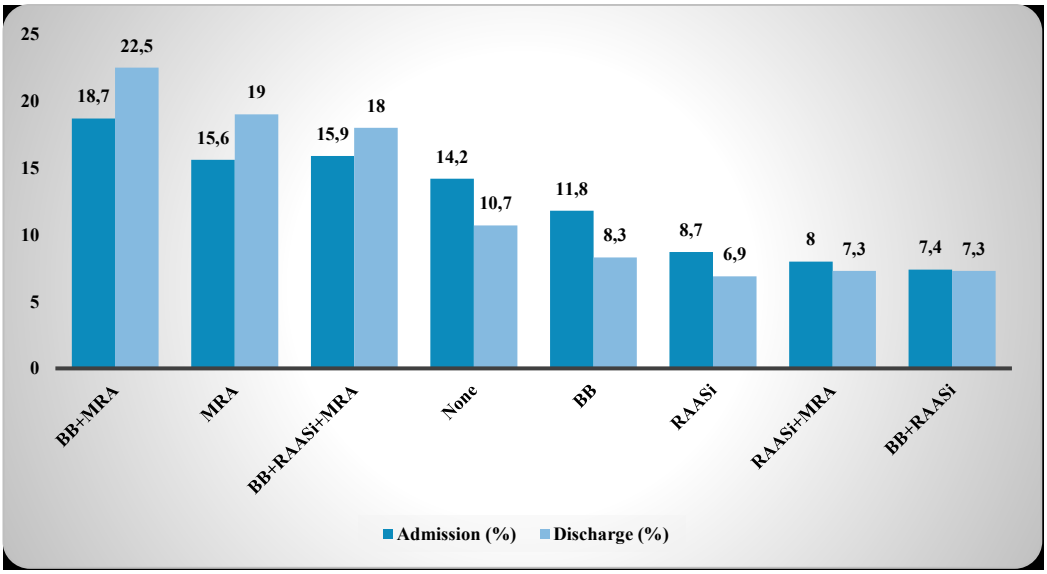


Figure 32. Distribution of therapeutic combinations at admission and discharge, highlighting changes in treatment strategies, (%)

Modern drug classes show minimal penetration: SGLT2 inhibitors and DPP-4 inhibitors are absent (0%), while GLP-1 receptor agonists are used only sporadically (0.3%), reflecting limited access and adoption during the analyzed period. Non-cardiovascular medication use is low and stable: allopurinol 0.7%, NSAIDs and systemic corticosteroids with a minimal increase from 0.3% to 0.7%, and inhaled corticosteroids remaining constant (1.4%). Psychiatric and analgesic treatments remain marginal (≤1.4%), without significant variation. Intravenous iron is the only intervention with a clear increase, from 0.3% to 1.0% (+0.7 pp), suggesting active correction of iron deficiency during hospitalization. Overall, the non-cardiovascular therapeutic burden is low (mean 1.09 ± 0.36; median 1). According to phenotype, oral diuretics are nearly universal in HFrEF (96.8%) and HFmrEF (95.3%), compared with HFpEF (84.5%), highlighting a higher congestion burden in reduced ejection fraction forms.

6.2 Medication at enrollment according to heart failure type

The synthesis of discharge prescriptions according to heart failure type in the 2019–2020 cohort highlights relevant differences between phenotypes. Decongestion remains the dominant component, especially in reduced ejection fraction: oral diuretics are nearly universal in HFrEF (96.8%) and HFmrEF (95.3%), compared with HFpEF (84.5%), suggesting a higher congestion burden in reduced EF forms. Disease-modifying therapy is more intensively used in patients with

lower EF. RAAS blockade reaches 80.6% in HFrEF and 79.7% in HFmrEF, compared with 74.8% in HFpEF, while beta-blockers follow a similar pattern (85.5%, 82.8%, 76.1%).
The most pronounced difference is observed for MRAs (87.1% in HFrEF; 82.8% in HFmrEF; 53.5% in HFpEF), reflecting a more selective use in HFpEF.
In secondary prevention, statins are more frequent in HFmrEF and HFpEF (~79%) compared with HFrEF (67.7%). Anticoagulants predominate in HFmrEF (75.0%) and HFrEF (59.7%), while antiplatelets are more commonly used in HFpEF (55.5%), suggesting differences in ischemic and arrhythmic profiles (Figure 33).
Symptomatic therapy shows an EF-dependent gradient: calcium channel blockers increase with EF (26.5% in HFpEF vs 16.1% in HFrEF), while nitrates and digitalis are more frequent in HFrEF (33.9% and 40.3%), reflecting a greater need for symptom and rate control.

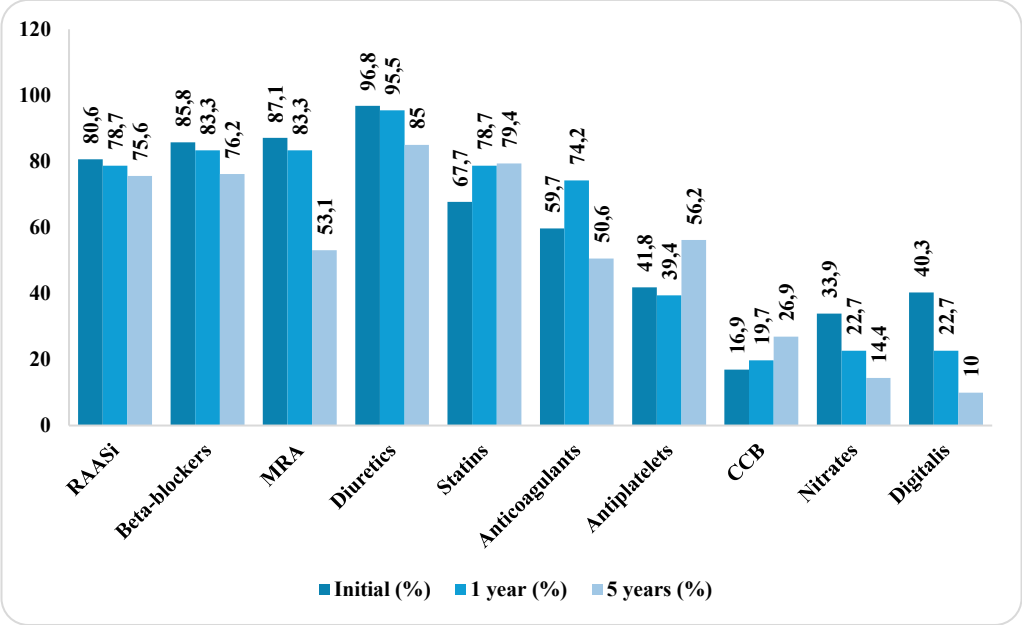


Figure 33. Rate of cardiovascular medication prescription according to heart failure type, (%)

Overall, ejection fraction phenotype consistently shapes therapeutic strategy: intensification of disease-modifying therapy in HFrEF/HFmrEF and a more blood pressure– and ischemia-oriented approach in HFpEF, with decongestion as a central element across all phenotypes. Analysis of the impact of the number of GDMT classes at discharge on 1-year outcomes shows very low mortality (0.7%), precluding robust modeling. For heart failure hospitalizations, each additional GDMT class is associated with an IRR ≈ 1.23 (95% CI 1.00–1.52; $p = 0.055$), and for total days of hospitalization IRR = 1.21 (95% CI 1.10–1.32; $p < 0.001$).
These associations must be interpreted in the context of confounding by indication: patients with more severe disease receive more therapeutic classes and inherently have a higher risk of events. Therefore, severity-adjusted models and robust statistical approaches (e.g., negative binomial models or propensity score weighting) are required for a more accurate assessment of the relationship between GDMT and prognosis.

6.3 Medication at 5 years after study enrollment

At 5 years, in the analyzed cohort (n = 186), beta-blocker use remains high (78.4%), with bisoprolol predominating (39.5%), significantly more frequent than metoprolol (19.5%).
RAAS blockade is mainly sustained by ACE inhibitors (45.4%), more frequently used than ARBs (29.7%), while ARNI remain marginal (1.1%). MRAs are used in 61.6% of patients, and SGLT2 inhibitors in 58.1%, predominantly dapagliflozin, without significant differences between these

classes. Diuretics remain frequently used (75.1%), with torasemide predominating (50.3%). Anticoagulation is present in 50.8% of patients, predominantly with DOACs, especially rivaroxaban (44.9%), while vitamin K antagonists are rare (<5%).

Antiplatelet therapy is observed in 41.1% of patients, mainly aspirin. Calcium channel blockers (26.5%) and statins (69.7%) are frequently used, while digoxin and antiarrhythmic agents remain at approximately 15%. Nitrates are reported very frequently (97.3%), largely reflecting "as-needed" use. In the non-cardiovascular domain, antidiabetic agents (excluding SGLT2 inhibitors) are used in 20.5% of patients, predominantly metformin, while respiratory and psychiatric therapies remain limited. At the patient level, four-pillar therapy (BB + RAAS blockade + MRA + SGLT2 inhibitors) is the most frequent regimen (25.1%), followed by three-pillar combinations (~33% cumulatively), while monotherapy or absence of therapy remains below 15%. Compared with discharge (2019–2020), most therapeutic classes remain stable (beta-blockers, ACE inhibitors/ARBs, diuretics, statins, and anticoagulation), with only minor and statistically non-significant changes. The most important change is the introduction of SGLT2 inhibitors, from complete absence to 58.1% ($p < 0.001$), marking the transition toward modern heart failure therapy (Figure 34).

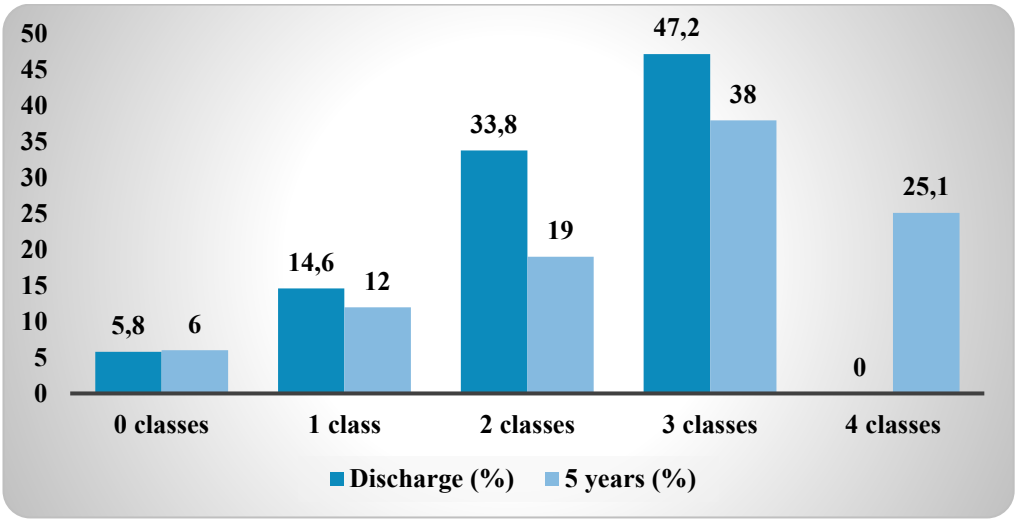


Figure 34. Distribution of therapeutic combinations (0–4 classes) at discharge and at 5 years, (%)

Additionally, the structure of anticoagulation shifts in favor of DOACs, while the apparent increase in nitrate use mainly reflects intermittent administration. Overall, there is a clear transition from the classical triple therapy regimen toward guideline-directed quadruple therapy, with the integration of SGLT2 inhibitors and the maintenance of beta-blockers and RAAS blockade as foundational elements.

6.4 Medication administered to patients enrolled in 2025

Discharge represents a key moment for therapeutic optimization, with significant increases across all major drug classes. RAAS blockade increased from 71.8% to 89.7% (+17.9 pp; $p = 0.0012$), beta-blockers from 76.1% to 92.3% (+16.2 pp; $p = 0.0002$), and MRAs from 53.0% to 79.5% (+26.5 pp; $p < 0.001$). The most substantial increase was observed for SGLT2 inhibitors, from 29.1% to 72.7% (+43.6 pp; $p < 0.001$), reflecting their rapid integration into clinical practice. Diuretics increased from 49.6% to 80.4% (+30.8 pp; $p < 0.001$), confirming the intensification of decongestive therapy. Other therapeutic classes remained stable: digitalis (21.4% vs 23.1%; $p = 0.45$), statins (~79%; $p = 0.81$), and antiplatelet therapy (~64%; $p = 0.64$). Overall anticoagulation increased (51% → 68%; $p = 0.032$), driven by a shift toward DOACs, accompanied by a reduction

in vitamin K antagonists. Calcium channel blockers, nitrates, and antiarrhythmic agents showed low and stable utilization. In the non-cardiovascular domain, there is a shift toward therapies with cardio-renal benefit, with a modest increase in oral antidiabetic agents and stable insulin use. The use of NSAIDs and systemic corticosteroids decreased significantly, while intravenous iron administration increased (+9 pp; p = 0.03), suggesting a more systematic approach to iron deficiency management. At the level of therapeutic combinations, a clear shift toward multi-pillar regimens is observed: the proportion of patients without any pillar decreases (9.4% → 0.9%), while complete four-pillar therapy increases from 28.2% to 47.9% (+19.7 pp). Two-pillar combinations decline, being replaced by three- and four-pillar regimens, reflecting treatment intensification during hospitalization.

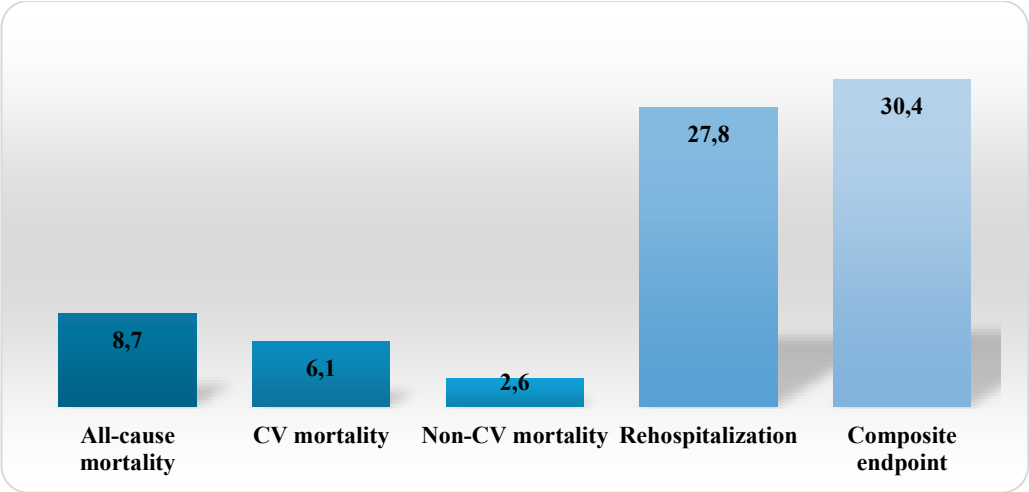


Figure 35. Evolution of clinical events at 1 year. Distribution of mortality, rehospitalizations, and the composite endpoint in the analyzed cohort (%).

At follow-up, the initial therapeutic optimization is largely maintained. Beta-blockers remain at high rates (92.3%), MRAs and RAAS blockade are sustained above 75–80%, and SGLT2 inhibitors continue to increase (up to ~57%). Diuretics and statins remain frequently used, while anticoagulation confirms the shift toward DOACs. Clinical evolution at 1 year shows moderate mortality (8.7%), predominantly cardiovascular (6.1%), but a relatively high rehospitalization rate (27.8%), with a composite endpoint of 30.4% (Figure 35). This profile indicates relatively controlled mortality but persistent morbidity, driven mainly by recurrent decompensations.

Overall, hospitalization acts as a true "window of opportunity" for optimization, with significant increases in prognostically relevant therapies and a shift toward complete therapeutic combinations. However, implementation remains incomplete for ARNI, primarily due to access limitations, while SGLT2 inhibitors represent the major advancement of the recent period. Temporal trends demonstrate clear alignment with guideline recommendations in recent years, with expansion of modern therapies and integration of multidisciplinary care, while heart failure phenotype continues to modulate therapeutic decision-making.

7. EVALUATION OF THE IMPACT OF ARTIFICIAL INTELLIGENCE TOOLS IN RISK STRATIFICATION OF PATIENTS WITH HEART FAILURE

7.1 Algorithm for the use of AI tools in patients with heart failure

We developed an artificial intelligence pipeline for phenotyping and risk stratification in patients with heart failure, integrating clinical and biological variables, comorbidities, and GDMT status into an unsupervised clustering model.

The model identified three risk levels (high, intermediate, and low), arranged along a coherent biological gradient primarily driven by NT-proBNP, ejection fraction, and cardio-renal function
The distribution was unbalanced but clinically plausible: high risk ≈1.3%, intermediate risk ≈2.8%, and low risk ≈95.9%. Phenotypic profiling revealed a clear gradient: the high-risk cluster is characterized by markedly elevated NT-proBNP (~13,500 pg/mL), renal impairment, and tachycardia, whereas the low-risk group corresponds to a stable hemodynamic profile, with low NT-proBNP (~900 pg/mL) and better renal function. The intermediate cluster occupies a transitional position, with residual risk that may be amenable to improvement.

AI-based profiling highlights a biologically coherent stratification, with severity increasing from C2 → C1 → C0, and risk primarily driven by neurohormonal activation (NT-proBNP), renal function, and hemodynamic status. Clinical validity is supported by the distribution of events: hospitalization rates increase progressively from 12.0% in the low-risk group to 20.7% in the intermediate group and 30.8% in the high-risk group, in line with the biological gradient. GDMT status further differentiates phenotypes: low-risk patients show better implementation (particularly beta-blockers, MRAs, and SGLT2 inhibitors), while underutilization of ARNI remains consistent, reflecting access limitations. Temporal analysis demonstrates a favorable redistribution of risk in 2025, in parallel with increased penetration of SGLT2 inhibitors and MRAs. From a practical perspective, AI-based stratification enables a differentiated approach: high-risk patients require rapid titration and intensive monitoring, intermediate-risk patients represent the main target for GDMT optimization, while low-risk patients require maintenance and preventive strategies.Overall, the AI tool provides robust and explainable phenotyping, with direct clinical utility in the early identification of vulnerable patients, prioritization of interventions, and monitoring of therapeutic performance, representing a valuable support for individualized medicine in heart failure.

7.2 Digital tool for risk stratification in heart failure – methodology, rationale, formulas, and applicability

We developed an explainable digital tool for estimating the risk of hospitalization and cardiovascular mortality at 1 and 5 years, based on the integration of clinical, biological, and echocardiographic variables. The variable set included parameters with pathophysiological relevance and routine clinical availability (age, LVEF, GLS_abs, E/e′, LAVI, NT-proBNP, TAPSE, sodium, hemoglobin, creatinine), while treatment variables were incorporated separately within a decision-support component. Data were preprocessed using robust standardization and median imputation, reducing the influence of extreme values. Phenotyping was performed using k-means clustering (k = 3), resulting in three risk clusters defined by centroid profiles (μ, s) and visually validated using principal component analysis (PCA). Assignment of a new patient is performed using a robust nearest-centroid rule, based on standardized distance to cluster profiles, using only available variables. This approach is transparent and allows tracking of each variable's contribution. Risks (hospitalization and mortality at 1 and 5 years) are estimated through local calibration, as observed proportions within each cluster, and are directly mapped to the patient according to the assigned cluster.

Implementation in Excel ensures accessibility and reproducibility: simple data entry, automatic classification, percentage-based risk output, and visual interpretation through color coding, complemented by orientative recommendations.

Overall, the tool provides robust and explainable risk stratification, surpassing classification based solely on ejection fraction. Separation is primarily driven by neurohormonal

and cardio-renal markers, while differences in risk reflect both biological severity and the degree of GDMT implementation. Underutilization of ARNI remains an important limitation in achieving full guideline-directed therapy. Due to its simplicity and transparency, the tool can be easily integrated into clinical practice, facilitating the identification of vulnerable patients, prioritization of interventions, and support of individualized therapeutic decision-making.

GENERAL CONCLUSIONS

1. Multidimensional assessment of patients with heart failure demonstrated substantial clinical, biological, and imaging heterogeneity of the disease. Patients with HFrEF exhibited the most severe hemodynamic and biological impairment, higher levels of cardiac biomarkers, and the least favorable clinical outcomes, whereas patients with HFpEF were characterized by a greater burden of metabolic and hypertensive comorbidities.
2. Patient phenotyping using conventional statistical methods and artificial intelligence algorithms enabled the identification of distinct subgroups characterized by different clinical, biological, and prognostic profiles. Classification based solely on ejection fraction proved insufficient to capture the complexity of heart failure, while the identified phenotypes provided additional information relevant for risk stratification and treatment individualization.
3. Advanced echocardiographic techniques based on myocardial deformation analysis provided a more sensitive and comprehensive characterization of cardiac dysfunction compared with conventional parameters. Ventricular and atrial strain parameters were associated with heart failure severity, functional status, congestion markers, and neurohormonal biomarkers, offering complementary information to standard echocardiographic assessment and contributing to prognostic evaluation.
4. Cardiovascular and non-cardiovascular comorbidities were highly prevalent in heart failure and significantly influenced both clinical presentation and disease progression. The presence of at least one non-cardiovascular comorbidity was associated with an increased risk of heart failure hospitalization, highlighting the important role of multimorbidity in determining long-term prognosis.
5. Analysis of therapeutic management demonstrated a progressive improvement in the implementation of guideline-directed medical therapy. At the 5-year evaluation, a significant increase in the use of SGLT2 inhibitors and direct oral anticoagulants was observed, together with a reduction in vitamin K antagonist use, reflecting the gradual alignment of clinical practice with contemporary recommendations.
6. Longitudinal analysis demonstrated that patients who experienced improvement in left ventricular ejection fraction towards HFmrEF or HFpEF had a more favorable prognosis compared with patients with persistent HFrEF. Overall 5-year mortality was 36.9%, while the risk of adverse outcomes was concentrated in subgroups characterized by severe ventricular dysfunction, elevated biomarker levels, and a high burden of comorbidities.
7. The application of artificial intelligence algorithms enabled the identification of phenotypes with differentiated risk profiles and the development of an integrated digital matrix for individualized assessment. The integration of clinical, biological, echocardiographic, and therapeutic variables into a single model demonstrated the feasibility of artificial intelligence for risk stratification and clinical decision support in heart failure..

PRACTICAL RECOMMENDATIONS

1. At the primary healthcare level, systematic and periodic assessment of cardiovascular and non-cardiovascular comorbidities in patients with heart failure should be implemented, considering the major impact of multimorbidity on clinical severity, hospitalization risk, and long-term prognosis. Early identification and active monitoring of hypertension, diabetes mellitus, atrial fibrillation, chronic kidney disease, obesity, and chronic pulmonary diseases should be integrated into routine patient management.
2. In cardiology practice, a multidimensional approach to heart failure assessment should be adopted, complementing ejection fraction-based classification with the integration of clinical, biological, hemodynamic, and advanced imaging parameters. The use of ventricular and atrial myocardial deformation techniques should be encouraged for more precise phenotypic characterization, disease severity assessment, and optimization of risk stratification.
3. Echocardiography laboratories should progressively incorporate left ventricular, right ventricular, and left atrial strain analysis into standard heart failure assessment protocols. Integration of myocardial deformation parameters with conventional echocardiographic evaluation may improve the assessment of cardiac remodeling, diastolic function, and mechanisms involved in disease progression.
4. Strengthening multidisciplinary collaboration among cardiologists, primary care physicians, diabetologists, nephrologists, pulmonologists, internal medicine specialists, and cardiovascular rehabilitation professionals is encouraged to develop integrated heart failure management strategies. Such an approach may contribute to better comorbidity control, reduced decompensations and rehospitalizations, and improved quality of life.
5. Longitudinal monitoring programs integrating periodic clinical, biological, and imaging assessments, including ventricular and atrial longitudinal function parameters, should be implemented. This approach may facilitate the early identification of high-risk patients and support individualized therapeutic and follow-up strategies.
6. The development and integration of digital tools and artificial intelligence algorithms into the assessment and monitoring of patients with heart failure should be encouraged to support risk stratification and individualized therapeutic management. Platforms combining clinical, biological, imaging, and comorbidity-related data may represent an important step toward precision medicine and more efficient use of healthcare resources.

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List of publications related to the thesis topic

1. Contributions to monographs

1.1. POP-MOLDOVAN, A., TROFENCIUC, N.M., PUȘCHIȚA, M, DĂRĂBANȚIU, D.A., MERCEA, S., HRENIUC, C., F. ONEL, M., REVENCO, V., **CABAC-POGOREVICI, I**., et al. New biomarkers in screening anthracycline induced cardiotoxicity only with peripheral blood sampling. In: TechOpen Book. 2019, pp. 140-152, ISBN 978-1-78984-238-8.

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3. Articole în reviste științifice naționale acreditate:

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3.1.7. **CABAC-POGOREVICI, I**., REVENCO, V. Hemodinamica intrarenală în hipertensiunea arterială și insuficiența cardiacă cu fracția de ejecție păstrată. In: Arta Medica. Chișinău, 2020, nr. 3(76), pp. 28-34. ISSN 1810-1852.

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3.1.14. **CABAC-POGOREVICI, I**., REVENCO, V. Metodele imagistice în diagnosticul fenotipurilor afectării viscerale la pacienții cu sindrom metabolic. In: Sănătate Publică, Economie și Management în Medicină. Chișinău, 2016, nr. 4(68), pp. 123-129. ISSN 1729-8687.

4. Alte materiale didactice

7.1. Autor național al Atlasului Epidemiologic European de dedicat Insuficienței Cardiace „HFA Atlas", rezultatele preliminare fiind publicate: Task Force of the HFA Atlas, and the ESC Atlas of Cardiology leadership, developed in collaboration with the National Heart Failure Societies of the ESC member and ESC affiliated member countries (**CABAC-POGOREVICI, I**. VATAMANU E.) The

Heart Failure Association Atlas: rationale, objectives, and methods. J Heart Fail. 2020, nr. 22, 638-645. doi:10.1002/ejhf.1768.
7.2. **CABAC-POGOREVICI, I**, Cobeț V. Noțiuni de fiziologie clinică a sistemului cardiovascular. In: Revenco V, Grib L, autori coordonatori. Manual de cardiologie. Vol. 1. Chișinău: Print-Caro; 2025. p. 27-56. ISBN: 978-5-85748-219-3.

5. Brevete de invenţii, patente, certificate de înregistrare, materiale la saloanele de invenţii

8.1. **CABAC-POGOREVICI, I**., REVENCO V. Model integrat de evaluare ecocardiografică convențională și avansată în diagnosticul, stratificarea riscului și monitorizarea pacienților cu insuficiență cardiacă cronică. Certificat de inovator nr. 6444
8.2. **CABAC-POGOREVICI, I**., REVENCO V. Model integrat de fenotipare clinică și analiză evolutivă a pacienților cu insuficiență cardiacă cronică prin stratificare multidimensională și utilizarea algoritmilor de inteligență artificială. Certificat de inovator nr. 6445

Participări active la forumuri științifice

6. Participări cu comunicări la forumuri științifice:

6.1. Internaţionale

6.1.1. SAVCA D., AVRAM V., JITARI I., CHEIBAȘ D., **CABAC-POGOREVICI, I**., REVENCO V. Skin and heart fragility: cardiovascular involvement in epidermolysis bullosa. Congresul European de Cardiologie 2025, Madrid, Spania, 29 august - 01 septembrie 2025.
6.1.2. JITARI, I., **CABAC-POGOREVICI, I**. Caz clinic: Povestea unei inimi: cardiomiopatia hipertrofică în oglinda unei familii. (pag.35). Conferința de Primăvară a SRC, Sibiu, România, 7-10 mai 2025.
6.1.3. **CABAC-POGOREVICI, I**. Tratamentul insuficienței cardiace cronice: între imperativul normat și realitatea clinică. Congresul Național de Cardiologie, Sinaia, România, 17-20 septembrie 2025.
6.1.4. **CABAC-POGOREVICI, I**., REVENCO, V., MIHALACHE, G., JITARI, I. Hemodinamica intrarenală și carotidiană la pacienții cu insuficiență cardiacă și fracție de ejecție ușor redusă (HFmrEF)/Intrarenal and carotid haemodynamics in patients with heart failure and mildly reduced ejection fraction (HFmrEF). Culegere de rezumate. Congresul Național de Cardiologie, Sinaia, Romania, 2022.
6.1.5. **CABAC-POGOREVICI, I**. Promising novel drugs in cardiovascular medicine. 43rd Annual Congress of the Hellenic Society of Cardiology, 20-22 Octombrie 2022, Atena, Grecia (Megaron the Athens Concert Hall).
6.1.6. **CABAC-POGOREVICI, I**. Me and my AI clinical advisor. What about our disagreements? Athens Academic Forum, 10-11 iunie 2022, Atena, Grecia
6.1.7. **CABAC-POGOREVICI, I**. Cardiorezidențiatul de peste Prut. Cardioculture – Conferința virtuală a Institutului de Boli Cardiovasculare din Timișoara, Sesiunea Tinerilor Cardiologi, Masă rotundă „Căi de optimizare a rezidențiatului de Cardiologie”, 22 octombrie 2021, Timișoara, România (online).
6.1.8. **CABAC-POGOREVICI, I**. Caz clinic. Conduita unui pacient cu insuficiență cardiacă. Congresul Național de Cardiologie, Sesiunea Comună a Tinerilor Cardiologi din Republica Moldova și România, Sinaia România, 19.09.2019

6.2. Naţionale

6.2.1. AVRAM V., **CABAC-POGOREVICI, I**. Hipertensiunea arterială secundară: provocări diagnostice și implicații terapeutice. Conferința “ZIUA MONDIALĂ A HORMONULUI”, Moldova, 6 mai 2025.
6.2.2. **CABAC-POGOREVICI, I**. Apneea obstructiva în somn-aceeasi boală, pacienți diferiți: drumul spre medicina individualizată. Congresul aniversar USMF “80 de ani de inovație în sănătate și educație medicală”, Chișinău, 20-22 octombrie 2025.
6.2.3. **CABAC-POGOREVICI, I**. Aspectul genetic al dislipidemiilor și rezultatul tratamentului cu rosuvastatină. Societatea medicilor de familie în cadrul Congresului aniversar USMF “80 de ani de inovație în sănătate și educație medicală”, Chișinău, 20-22 octombrie 2025.
6.2.4. **CABAC-POGOREVICI, I**. Individualizarea terapiei antitrombotice la pacienții cu cancer: ce ar trebui să știe orice cardiolog. Al 2-lea congres a Societății de Tromboză și Hemostază, Chișinău, 30-31 mai 2025.

6.2.5. JITARI, I., SAVCA, D., AVRAM, V., REVENCO, V., **CABAC-POGOREVICI, I**. Caz clinic: Tromboembolism recurent la o pacientă tânără: algoritm ghidat sau ghid ignorat? Al 2-lea congres a Societatii de Tromboza si Hemostaza, Chișinău, 30-31 mai 2025.
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6.2.9. **CABAC-POGOREVICI, I**. Sindroame coronariene acute. Congresul V al Medicilor de Familie din Republica Moldova. Chișinău, 17 mai 2024.
6.2.10. **CABAC-POGOREVICI, I**. A IX-a ediție a Simpozionului Național de Cardiologie De ce au fost necesare actualizări în conduita insuficienței cardiace la o distanță de numai doi ani de la ghidul precedent. Ghidul Societății Europene de Cardiologie 2023. Chișinău 2023.
6.2.11. **CABAC-POGOREVICI, I**. A VIII-a ediție a Simpozionului Național de Cardiologie Evaluarea cardiovasculară și managementul pacienților supuși intervențiilor chirurgicale non-cardiace. Ghidul Societății Europene de Cardiologie 2022. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu", Chișinău 2022.
6.2.12. BURSACOVSCHI, D., CAZACU, J., **CABAC-POGOREVICI, I**., ROBU, M. Importanța indicelui de comorbiditate și prevalenței fragilității în evoluția limfoamelor non-Hodgkin cu celule B. . Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu", Chișinău 2022.
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6.2.14. SAVCA, D.; **CABAC-POGOREVICI, I**. Sindromul Wellens. Prezentare de caz clinic. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu", 19–21 octombrie 2022, Chișinău, Republica Moldova.
6.2.15. **CABAC-POGOREVICI, I**. Sindroamele coronariene cronice: modificarea conceptului pentru depășirea lacunelor. Simpozionul Național de Cardiologie cu genericul: „Actualități în cardiologie prin prisma ghidurilor noi ale Societății Europene de Cardiologie 2019" în cadrul Zilelor Universității de Stat de Medicină și Farmacie "Nicolae Testemițanu". Chișinău, Republica Moldova 17.10.2019.
6.2.16. **CABAC-POGOREVICI, I**. Filosofia ghidului versus viața reală. (Guide is not God?). Simpozionul Național de Cardiologie cu genericul: „Actualități în cardiologie prin prisma ghidurilor noi ale Societății Europene de Cardiologie 2019" în cadrul Zilelor Universității de Stat de Medicină și Farmacie "Nicolae Testemițanu". Chișinău, Republica Moldova 17.10.2019

7. Participări cu postere la forumuri ştiinţifice:

7.1. Internaţionale

7.1.1. JITARI, I., **CABAC-POGOREVICI, I**., REVENCO, V. Echoes of the heart and kidneys: exploring intrarenal hemodynamics in heart failure with preserved ejection fraction. Congresul European de Cardiologie, Madrid, Spania, 29 august – 01 septembrie 2025.
7.1.2. JITARI, I., SAVCA, D., COTONEȚ, T., AVRAM, V.,REVENCO, V., CABAC- POGOREVICI, I. Valoarea prognostică a hemodinamicii intrarenale în insuficiența cardiacă cu fracție de ejecție păstrată. Al 64-lea Congres Național de Cardiologie, Societatea Română de Cardiologie, Romania, 17-20 septembrie 2025.
7.1.3. AVRAM V., **CABAC-POGOREVICI, I**., REVENCO V. Manifestare severă a miopericarditei acute la o pacientă de 18 ani: de la simptome inițiale la complicații amenințătoare de viață / Severe manifestation of acute myopericarditis in an 18-years-old female patient: from initial symptoms to life-threatening complications. Al 64-lea Congres Național de Cardiologie, Societatea Română de Cardiologie, România, 17-20 septembrie 2025.

7.1.4. **CABAC-POGOREVICI, I**., REVENCO, V. Legătura complexă între afectarea vasculară și remodelarea ventriculului stâng în insuficiența cardiacă cu fracția de ejecție ușor redusă. Al 63-lea Congres Național de Cardiologie, Societatea Română de Cardiologie, Romania, 18-21 septembrie 2024. (poster)
7.1.5. **CABAC-POGOREVICI, I**., JITARI, I., SAVCA, D., REVENCO, V. Conexiune complexă între afectarea macrovasculară și hemodinamica intrarenală în hipertensiunea arterială și disglicemie. Al 63-lea Congres Național de Cardiologie, Societatea Română de Cardiologie, Romania, 18-21 septembrie 2024. (poster)
7.1.6. JITARI, I., **CABAC-POGOREVICI, I**., SAVCA, D., REVENCO, V. The intricate connection between macrovascular damage and intrarenal hemodynamics in arterial hypertension and dysglycemia. Congresul European de Cardiologie, Societatea Europeană de Cardiologie, Londra, Marea Britanie, 30 august - 02 septembrie 2024. (poster)
7.1.7. **CABAC-POGOREVICI, I**., REVENCO, V., JITARI, I. The intricate link between COVID-19 and heart failure events. Congresul Asociației Europene de Insuficiență Cardiacă 2023, Praga Cehia https://esc365.escardio.org/session/40366?query=cabac-pogorevici
7.1.8. **CABAC-POGOREVICI, I**., REVENCO, V. Left ventricular geometry and carotid hemodynamics in heart failure with midly reduced ejection fraction. Congresul Asociației Europene de Insuficiență Cardiacă 2023, Praga Cehia. https://esc365.escardio.org/results?query=cabac-pogorevici&page=
7.1.9. **CABAC-POGOREVICI, I**., REVENCO, V., SARS-COV2 infection and heart failure an intricate link of mutual impact. Congresul Societății Europene de Cardiologie, 2023, Amsterdam, Olanda https://esc365.escardio.org/presentation/233595?query=cabac-pogorevici
7.1.10. **CABAC-POGOREVICI, I**., REVENCO, V., JITARI, I. Left ventricular remodelling and carotid hemodynamics in heart failure with preserved ejection fraction. Congresul Asociației Europene de Insuficiență Cardiacă 2022, 21-24 mai, Spania Madrid
7.1.11. **CABAC-POGOREVICI, I**., REVENCO, V. The complex interconnection between SARS-COV2 infection and heart failure events. Congresul Asociației Europene de Insuficiență Cardiacă 2022, 21-24 mai, Spania Madrid
7.1.12. SAVCA, D., **CABAC-POGOREVICI, I**. Sindromul Wellens. Prezentare de caz clinic/Wellens syndrome. A case report. Congresul Național de Cardiologie, 2022, 21-24 septembrie, Sinaia, Romania.
7.1.13. JITARI, I., **CABAC-POGOREVICI, I**. Teratom mediastinal anterior ce mimează boală cardiacă valvulară / Anterior mediastinal teratoma mimicking valvular heart disease. Congresul Național de Cardiologie, 2022, 21-24 septembrie, Sinaia, Romania.
7.1.14. **CABAC-POGOREVICI, I**., REVENCO, V. Evenimentele asociate insuficienței cardiace în infecția SARS-CoV-2 / Heart failure associated events in SARS-CoV-2 infection. Congresul Național de Cardiologie, 2022, 21-24 septembrie, Sinaia, Romania.
7.1.15. **CABAC-POGOREVICI, I**.; REVENCO, V.; JITARI, I. Left ventricular remodelling and carotid hemodynamics in heart failure with preserved ejection fraction. Annual Congress of the Heart Failure Association of the ESC and World Congress on Acute Heart Failure, 21–24 mai 2021, Madrid, Spania.
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7.1.17. **CABAC-POGOREVICI, I**.; REVENCO, V.; MIHALACHE, G.; OCHIȘOR, V.; JITARI, I.; OPREA, C. Interacțiunile complexe ale hemodinamicii intrarenale cu hipertensiunea arterială și insuficiența cardiacă cu fracția de ejecție păstrată. Al 60-lea Congres Național de Cardiologie (Societatea Română de Cardiologie), 22–25 septembrie 2021, Sinaia, România.
7.1.18. **CABAC-POGOREVICI, I**.; JITARI, I. Hipertensiune arterială și demență – relație de dublă cauzalitate. Al 60-lea Congres Național de Cardiologie (Societatea Română de Cardiologie), 22–25 septembrie 2021, Sinaia, România
7.1.19. **CABAC-POGOREVICI, I**.; REVENCO, V. Indicele de rezistență renal și carotidian la pacienții cu hipertensiune arterială. Al 60-lea Congres Național de Cardiologie (Societatea Română de Cardiologie), 22–25 septembrie 2021, Sinaia, România.

7.1.20. JITARI, I.; **CABAC-POGOREVICI, I**.; CAZACU, A.; OPREA, C.; MOSCALU, V.; URECHE, A.; MOSCALU, V. D.; REVENCO, V. Provocări și soluții în diagnosticarea displaziei valvulare congenitale tricuspidiene. Al 60-lea Congres Național de Cardiologie (Societatea Română de Cardiologie), 22–25 septembrie 2021, Sinaia, România.
7.1.21. **CABAC-POGOREVICI, I**., REVENCO V. The affinity of the nictemeral blood pressure variability patterns to intrarenal hemodynamics in patients with HFpEF. HFA Discoveries 2020 (epublication)
7.1.22. **CABAC-POGOREVICI, I**., REVENCO V., MIHALACHE G., OCHIȘOR V., COJUHARI I. Intrarenal and carotid haemodynamics in patients with heart failure and preserved ejection fraction. HFA Discoveries 2020 (epublication)
7.1.23. **CABAC-POGOREVICI, I**., REVENCO V. Renal and carotid resistive indexes and left ventricular remodelling in arterial hypertension. Congresul European de Radiologie 1-4 martie 2019, Viena, Austria
7.1.24. **CABAC-POGOREVICI, I**., REVENCO V. Miscellaneous clinical manifestations of an intracardiac tumour. Congresul Asociației Europene de Insuficiență Cardiacă mai 2019, Atena, Grecia
7.1.25. **CABAC-POGOREVICI, I**., REVENCO V. Clinical determinants of Doppler derived intrarenal hemodynamics in patients with HFpEF. Congresul Asociației Europene de Insuficiență Cardiacă mai 2019, Atena, Grecia
7.1.26. **CABAC-POGOREVICI, I**., REVENCO V. Arterial hypertension, right heart remodelling and intrarenal haemodynamics: the mysterious triangle in the cardiovascular continuum. Congresul Societății Europene de Cardiologie august 2019, Paris Franța

7.2. naţionale

7.2.1. AVRAM V., SAVCA D., JITARI I., **CABAC-POGOREVICI, I**., REVENCO V. Manifestare severă a miopericarditei acute la o pacientă de 18 ani: de la simptome inițiale la complicații amenințătoare de viață / Severe manifestation of acute myopericarditis in an 18-year-old female patient: from initial symptoms to life-threatening complications. Congresul aniversar „80 de ani ai Universității de Stat de Medicină și Farmacie „Nicolae Testemițanu" din Republica Moldova", Chișinău, Republica Moldova, 20–22 octombrie 2025.
7.2.2. REVENCO, V., **CABAC-POGOREVICI, I**. Indicele de rezistență carotidian la pacienții cu hipertensiune arterială. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu", Chișinău 2022.
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7.2.4. **CABAC-POGOREVICI, I**., REVENCO, V. COVID-19 și evenimentele asociate insuficienței cardiace. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu" 19-21 octombrie 2022, Chișinău, Republica Moldova.
7.2.5. SAVCA, D., **CABAC-POGOREVICI, I**. Sindromul Wellens. Prezentare de caz clinic. Conferința științifică anuală „Cercetarea în biomedicină și sănătate: calitate, excelență și performanță", USMF „Nicolae Testemițanu", 19-21 octombrie 2022, Chișinău, Republica Moldova.

ADNOTARE

CABAC-POGOREVICI Irina. ***Abordarea multidimensională a insuficienței cardiace cronice pentru elaborarea unei matrice de evaluare individualizată.*** **Teză de doctor habilitat în științe medicale, Chișinău, 2026.**

Structura tezei. Lucrarea este expusă pe 281 pagini de text electronic și este compartimentată în: introducere, cinci capitole de cercetări originale, concluzii și recomandări, indice bibliografic (369 titluri), 64 figuri, 36 tabele și 15 anexe. Rezultatele cercetării au fost prezentate în xx publicații științifice**. Cuvinte-cheie:** insuficiență cardiacă, fenotipare, comorbidități, remodelare cardiacă, imagistică avansată, inteligență artificială, matrice de evaluare, risc cardiovascular. **Domeniul de studiu**: Cardiologie.

Scopul studiului. Elucidarea particularităților clinico-evolutive și strategiilor de conduită a insuficienței cardiace prin integrarea tehnicilor ecocardiografice avansate și algoritmilor de inteligență artificială în vederea elaborării unei matrice de abordare individualizată.

Obiectivele studiului. Evocarea caracteristicilor clinico-hemodinamice, biologice și evolutive ale pacienților cu insuficiență cardiacă cronică; Evidențierea tipurilor și fenotipurilor specifice ale pacienților cu insuficiență cardiacă cronică și analiza evoluției clinice în funcție de tipul insuficienței cardiace; Analiza rolului ecocardiografiei convenționale și a tehnicilor ecocardiografice avansate în diagnosticul, stratificarea riscului și monitorizarea pacienților cu insuficiență cardiacă; Evaluarea impactului comorbidităților asupra manifestărilor clinice, hemodinamice și evoluției pacienților cu insuficiență cardiacă cronică; Analiza strategiilor terapeutice aplicate pacienților cu insuficiență cardiacă și compararea acestora cu recomandările actuale ale ghidurilor internaționale de practică medicală; Aprecierea impactului instrumentelor de inteligență artificială în stratificarea riscului pacienților cu diferite tipuri de IC; Elaborarea unei matrice digitale integrate de abordare individualizata a pacienților cu insuficiență cardiacă prin îmbinarea parametrilor clinico-hemodinamici, tehnicilor ecocardiografice avansate și algoritmilor de inteligență artificială.

Noutatea și originalitatea științifică. Lucrarea abordează insuficiența cardiacă printr-o perspectivă multidimensională, integrând date clinice, imagistice avansate și analitice cu metode moderne de analiză multivariable și clustering. A fost elaborată o matrice originală de evaluare individualizată, capabilă să diferențieze fenotipuri clinice și să identifice pacienții cu risc înalt. Teza propune un model inovator care corelează remodelarea cardiacă cu comorbiditățile, biomarkerii și parametrii speckle-tracking, realizând pentru prima dată o integrare sistematică a indicatorilor clinici, metabolici și imagistici într-o arhitectură analitică unitară cu aplicabilitate directă în stratificarea riscului.

Problema științifică importantă soluționată. A fost fundamentat și validat un model holistic de evaluare a insuficienței cardiace, care permite definirea fenotipurilor clinice și identificarea pacienților cu risc crescut de spitalizare și mortalitate, oferind suport pentru individualizarea conduitei terapeutice.

Semnificația teoretică. Teza clarifică mecanismele contemporane ale evoluției insuficienței cardiace în contextul comorbidităților, contribuind la actualizarea conceptelor de fenotipare prin integrarea markerilor imagistici, clinici și funcționali. Lucrarea aprofundează relația dintre remodelare, disfuncția ventriculară și heterogenitatea fenotipurilor bolii.

Valoarea aplicativă. Matricea de evaluare elaborată oferă un instrument practic pentru stratificarea riscului, individualizarea tratamentului și optimizarea managementului clinic. Rezultatele pot fi implementate în instruirea profesională, în registre clinice și în dezvoltarea unor instrumente digitale de suport decizional.

Implementarea rezultatelor. Rezultatele au fost aplicate în activitatea didactică și clinică a Disciplinei de Cardiologie ale USMF „Nicolae Testemițanu”, în practica Institutului de Cardiologie și în inițiativele de digitalizare a evaluării pacientului cardiac, constituind baza unor prototipuri algoritmice pentru stratificarea riscului la pacienții cu insuficiență cardiacă.

SUMMARY

CABAC-POGOREVICI Irina. A Multidimensional Approach to Chronic Heart Failure for the Development of a Individualized Evaluation Matrix. Habilitation thesis in medical sciences, Chișinău, 2026.

Structure of the thesis. The work comprises ***281*** pages of electronic text and is structured into: an introduction, five chapters of original research, conclusions and recommendations, a bibliographic index (***369*** titles), ***64*** figures, ***36*** tables and ***15*** annexes. The research findings have been presented in ***xx*** scientific publications. *Keywords:* heart failure, phenotyping, comorbidities, cardiac remodeling, advanced imaging, artificial intelligence, evaluation matrix, cardiovascular risk. *Field of study:* Cardiology.

Purpose of the study. To elucidate the clinical-evolutionary features and management strategies of chronic heart failure through the integration of advanced echocardiographic techniques and artificial intelligence algorithms, with the aim of developing a individualized evaluation matrix.

Objectives of the study. To describe the clinical, hemodynamic, biological and evolutionary characteristics of patients with chronic heart failure; to identify specific types and phenotypes of heart failure and analyze their clinical evolution; to assess the role of conventional and advanced echocardiography in diagnosis, risk stratification and follow-up; to evaluate the impact of comorbidities on clinical presentation, hemodynamics and outcomes; to analyze therapeutic strategies applied to heart failure patients in comparison with current international guidelines; to assess the contribution of artificial intelligence tools to risk stratification across different heart failure phenotype.

Scientific novelty and originality. The thesis investigates heart failure from a multidimensional perspective, integrating clinical data with advanced imaging and analytical methods, including multivariable modelling and unsupervised clustering. An original individualized evaluation matrix has been developed, capable of differentiating clinically relevant phenotypes and identifying patients at high risk. The study introduces an innovative model that correlates cardiac remodeling with comorbidities, biomarkers, and speckle-tracking parameters, achieving for the first time a systematic integration of clinical, metabolic and imaging indicators within a unified analytical architecture with direct applicability in risk stratification.

The important scientific problem solved. The thesis establishes and validates a holistic model for assessing heart failure, enabling the definition of clinical phenotypes and the identification of patients at increased risk of hospitalization and mortality, thereby supporting individualized therapeutic decision-making.

Theoretical significance. The findings elucidate contemporary mechanisms of heart failure evolution in the context of comorbidities and contribute to updating phenotyping concepts through the integration of imaging, clinical and functional markers. The work deepens understanding of the relationship between cardiac remodeling, ventricular dysfunction and the heterogeneity of disease phenotypes.

Practical value. The developed evaluation matrix provides a practical tool for risk stratification, treatment individualization and optimization of clinical management. The results can be applied in professional training programs, clinical registries and the development of digital decision-support instruments.

Implementation of results. The outcomes have been incorporated into the teaching and clinical activities of the Cardiology Departments of the "Nicolae Testemițanu" State University of Medicine and Pharmacy, in the clinical practice of the Institute of Cardiology, and in initiatives aimed at digitalizing cardiac patient evaluation, forming the basis for algorithmic prototypes for risk stratification in heart failure patients.