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CLINICAL AND IMAGING DIFFERENCES AND SIMILARITIES BETWEEN HEART FAILURE WITH SLIGHTLY REDUCED VERSUS PRESERVED EJECTION FRACTION IN THE ELDERLY

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Cuprins

Introduction

Heart failure (HF) is one of the most common and severe chronic conditions, affecting millions of people worldwide. It is defined as the heart's inability to supply the necessary amount of blood to meet the body's metabolic needs, leading to a series of debilitating symptoms and reduced quality of life. The choice of this research topic is motivated by the alarming increase in the incidence of HF among the elderly and the major impact this condition has on patients and healthcare systems globally.

HF affects approximately 26 million people worldwide and is responsible for a significant number of hospitalizations and deaths. In Romania, the prevalence of HF is about 47%, with a continuously increasing incidence and mortality. Due to the aging population and advances in cardiovascular disease treatments, the number of HF patients is on the rise, making the management of this condition increasingly complex. HF is associated with significant costs for healthcare systems due to frequent hospitalizations, emergency visits, and the need for long-term treatments.

The impact of heart failure on the healthcare system is enormous. The costs associated with managing this condition include expenses for repeated hospitalizations, frequent medical consultations, and long-term medication use. Additionally, HF has a significant impact on patients' quality of life, as they face debilitating symptoms such as dyspnea, extreme fatigue, and edema. For these reasons, early identification of HF and appropriate therapeutic intervention are essential to reduce the burden on patients and healthcare systems.

HF can be classified based on the left ventricular ejection fraction (LVEF) into HF with reduced ejection fraction (HFrEF) – LVEF <40%, heart failure with slightly preserved ejection fraction (LVEF 41-49%), and HF with preserved ejection fraction (HFpEF) – LVEF>50%. Ejection fraction is an important indicator of ventricular function and refers to the volume of blood expelled from the left ventricle with each contraction. This distinction is crucial, influencing both diagnosis, prognosis, and treatment of HF patients.

The importance of studying HF in elderly patients is evident given that this age group presents distinct clinical and paraclinical peculiarities compared to the general population. The elderly often have multiple comorbidities such as hypertension, diabetes mellitus, and chronic kidney disease, which complicate the management of HF.

Additionally, the aging process affects the structure and function of the heart, making these patients more susceptible to developing HF. Therefore, it is essential to identify effective diagnostic and personalized treatment methods for this vulnerable category.

The novelty and relevance of the topic derive from the need to better understand the mechanisms underlying HF with slightly reduced ejection fraction (HFmrEF) compared to HF with preserved ejection fraction (HFpEF). HF with HFmrEF represents a category of heart failure that exhibits characteristics of both patients with preserved and reduced EF. A special category is represented by HF with reversible EF, where patients show significant improvement in EF following treatment. Early identification of these patients and the application of appropriate therapeutic interventions can lead to symptom relief and improved long-term prognosis.

In the context of international and national concerns, the theme aligns perfectly with ongoing efforts to improve the prognosis of HF patients. Globally, numerous studies focus on identifying biomarkers and clinical factors that can predict HF progression and response to treatment. In Romania, heart failure is a major public health issue, and local research contributes to the consolidation of knowledge and the development of appropriate clinical guidelines.

2. Special part. Personal Contributions

Working Hypothesis and Study Objectives

In Europe, the prevalence of HF follows a similar pattern, being estimated at 10% among people over the age of 70. European studies show a growing prevalence as the population ages and treatments for acute cardiovascular diseases improve, allowing for long-term survival but with an increased predisposition to develop chronic HF. (Ponikowski 2016; Mosterd 2007)

In Romania, available epidemiological data show a significant prevalence of HF among the elderly. According to recent studies, the prevalence of HF in the general population is approximately 4.7%, and this figure rises to over 15% among people over the age of 65. Common cardiovascular risk factors in Romania, such as hypertension, diabetes mellitus, and coronary artery disease, significantly contribute to the development of HF in the elderly. Effective management of HF in this age group is crucial, considering its impact on morbidity, mortality, and patients' quality of life (Romanian Society of Cardiology 2019).

The working hypothesis is based on the premise that elderly patients with heart failure with preserved or slightly reduced ejection fraction (HFpEF and HFmrEF) present distinct clinical and paraclinical characteristics that can be identified early to allow specific therapeutic interventions. Identifying these characteristics can contribute to improving the prognosis and quality of life of patients through personalized treatment.

Objectives:

1. Identifying the clinical and paraclinical characteristics of elderly patients with HFpEF and HFmrEF.
    - Analyzing the demographic profile and risk factors associated with HFpEF and HFmrEF.
    - Evaluating specific echocardiographic parameters and biomarkers (e.g., longitudinal strain, NT-proBNP) in this category of patients.

2. Establishing a predictive model for identifying elderly patients at high risk of developing HFpEF and HFmrEF.
    - Creating a clinical and paraclinical profile based on collected data.
    - Using statistical analysis to develop a predictive model to help in early identification of high-risk patients.

3. Formulating clinical recommendations for the optimal management of heart failure with preserved and slightly reduced ejection fraction in the elderly.

- Developing guidelines based on the evidence obtained in the study.
- Promoting an interdisciplinary approach in the treatment of elderly patients with HFpEF and HFmrEF.

2.1. Study Materials and Methods

Study Objective

The objective of this study is to identify and characterize the clinical and paraclinical profile of elderly patients with heart failure and preserved or slightly reduced ejection fraction. By thoroughly evaluating these patients, we aim to develop a predictive model that allows early identification of high-risk patients and to formulate specific therapeutic strategies to improve ejection fraction and quality of life.

Study Rationale

Heart failure is one of the leading causes of morbidity and mortality among the elderly population. Managing this condition is complex and requires a personalized approach, especially in patients with preserved or slightly reduced ejection fraction. Early identification of high-risk patients and appropriate therapeutic intervention can prevent decompensations, reduce hospitalizations, and improve long-term prognosis. Our study aims to contribute to a deeper understanding of the risk factors and specific clinical characteristics of this patient group, thus providing scientific support for clinical guidelines and personalized therapeutic decisions.

Study Cohort

Our study was conducted on a representative sample of elderly patients diagnosed with heart failure with preserved and slightly reduced ejection fraction (HFpEF and HFmrEF). The study was conducted at the Dr. Pompei Samarian County Emergency Hospital in Călărași, the Central Military Emergency University Hospital "Dr. Carol Davila" in Bucharest, and the "Prof. Dr. Th. Burghele" Clinical Hospital in Bucharest. This was a prospective and retrospective observational, non-randomized study on a sample of 127 patients diagnosed with heart failure. One group of patients (group A, 63 patients) had slightly reduced left ventricular ejection fraction, and the other group of patients (group B,

64 patients) had preserved left ventricular ejection fraction. The sample was representative of a population of patients diagnosed and treated in the mentioned hospitals.

Inclusion Criteria

- Patients aged 65-74 years.
- Symptomatic patients with HFpEF (LVEF ≥ 50%) or HFmrEF (LVEF between 40% and 49%).
- Hemodynamically stable without recent acute decompensations (within the last 4 weeks).
- Controlled hypertension.
- Patients with asymptomatic chronic ischemic heart disease with EKG changes (horizontal ST segment depression >1mm but <3mm and/or negative T waves in leads concordant with the coronary territory).
- No express indication for coronary angiography at the time of inclusion in the study.
- Patients on chronic treatment with beta-blockers, angiotensin-converting enzyme inhibitors (ACEI), or angiotensin receptor blockers (ARB), loop diuretics, and mineralocorticoid receptor antagonists, dosed according to tolerance and in the absence of contraindications.

Exclusion Criteria

- Patients with heart failure with reduced ejection fraction (LVEF < 40%).
- Acute decompensations of HF in the last 4 weeks.
- Symptomatic ischemic heart disease or previous myocardial infarction.
- Patients with severe valvular disease.
- Patients with dilated, restrictive, hypertrophic obstructive, or idiopathic cardiomyopathy.
- Patients with atrioventricular or intramyocardial conduction disorders.
- Severe uncontrolled comorbidities (e.g., stage IV-V chronic kidney disease, active neoplastic diseases, severe chronic respiratory failure, chronic liver diseases).
- Patients with severe cognitive disorders that could affect treatment compliance and study participation.

Study Methods

To achieve the study's goals and objectives, two distinct protocols were used.

Situation 1

- Patients hospitalized or consulted on an outpatient basis in the clinics where the study was conducted without recent previous evaluations were initially assessed clinically, paraclinically, and non-invasively according to the study protocol.
- Patients were periodically reevaluated in the first 3 months.
- At 6 months from the initial evaluation, patients were reevaluated clinically (degree of dyspnea, presence of edema, hepatomegaly), paraclinically (NT-proBNP), and imagistically (chest X-ray, echocardiography for reassessment of LVEF, longitudinal strain of the left ventricle, electromechanical dispersion of the left ventricle, MAPSE). The data were entered into the database.
- At 12 months, patients were reevaluated following the same protocol as at 12 months.

Situation 2

- Patients known to the clinics where the study was conducted.
- Patients were periodically reevaluated by the attending physician in the year prior to inclusion in the study.
- The evaluation performed 12 months prior was considered the baseline moment. Data collection included clinical (degree of dyspnea, presence of edema, hepatomegaly), paraclinical (at 12 months – NT-proBNP, lipid profile, glycemic profile, serum creatinine and NT-proBNP at 6 months), and imagistic (chest X-ray, echocardiography for reassessment of LVEF, longitudinal strain of the left ventricle, electromechanical dispersion of the left ventricle, MAPSE) obtained 6 and 12 months prior to inclusion in the study.
- Clinical, paraclinical, and imagistic evaluation of patients at the time of inclusion.

In the end, the patients' data were included in a Microsoft EXCEL database that contained the necessary information for analysis and obtaining relevant conclusions.

Patients included in the study were examined by the attending physician and the study physician on an outpatient basis, through day hospitalization or continuous hospitalization. They underwent a complete clinical, paraclinical, and imagistic examination, allowing the identification of patients who met the inclusion and exclusion criteria and their inclusion in the study. The data obtained were entered into the patient's observation sheet or the medical discharge letter.

The anamnesis confirmed the presence of heart failure symptoms, ruled out the presence of angina, risk factors, comorbidities, and previous treatment (beta-blockers, ACE

inhibitors or ARBs, loop diuretics, and mineralocorticoid receptor antagonists). The clinical examination provided information on the presence of dyspnea, effort tolerance, peripheral edema, hepatomegaly, and data on depression or cognitive disorders.

Laboratory tests were collected upon admission (day or continuous hospitalization) and included blood glucose, serum creatinine, complete lipid profile (total serum cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), heart failure biomarker (NT-proBNP).

Electrocardiography was performed on all patients to confirm the diagnosis of chronic coronary syndrome (horizontal ST segment depression >1mm but <3mm and/or negative T waves in leads concordant with the coronary territory) and to confirm the absence of intramyocardial conduction disorders.

Echocardiography was performed on all patients using a General Electric or Philips ultrasound machine. The study followed:

- Measurement of cavity diameters
- Measurement of posterior wall dimensions of the left ventricle and interventricular septum
- Measurement of left atrial volume
- Automatic calculation of LVEF
- Measurement of MAPSE
- Measurement of the longitudinal strain of the left ventricle and electromechanical dispersion of the left ventricle
- Quantification of the degree of mitral regurgitation
- Identification of delayed relaxation type diastolic dysfunction

The data collected were analyzed using appropriate statistical methods to identify differences and similarities between the two patient groups (HFpEF and HFmrEF), as well as to evaluate the evolution of heart failure and factors associated with the improvement of ejection fraction.

Results – Analysis of the Study Cohort

Descriptive Analysis of the Cohort

The first research direction consisted of a comparative inferential analysis of the variables followed in the study. Patients were divided into two study groups: group A, including patients with LVEF 41-49%, and group B, including patients with LVEF > 50%.

Table 2.1. Comparative Inferential Analysis of Demographic Data by Groups

Variable	**Group A**, N = 63	**Group B**, N = 64	**p-Value**[1]
Age, Mean (SD)	68.94 (3.34)	68.61 (3.23)	0.58
Age, n (%)			0.86
65	17 (27%)	19 (29.7%)	
66	5 (7.9%)	4 (6.2%)	
67	4 (6.3%)	6 (9.4%)	
68	5 (7.9%)	5 (7.8%)	
69	2 (3.2%)	4 (6.2%)	
70	7 (11.1%)	6 (9.4%)	
71	5 (7.9%)	3 (4.7%)	
72	6 (9.5%)	5 (7.8%)	
73	3 (4.8%)	7 (10.9%)	
74	9 (14.3%)	5 (7.8%)	
Gender, n (%)			0.77
Male	12 (19%)	21 (32.8%)	
Female	51 (81%)	43 (67.2%)	
Origin, n (%)			0.8
Rural	16 (25.4%)	15 (23.4%)	
Urban	47 (74.6%)	49 (76.6%)	

[1] Welch Two Sample t-test; Fisher's exact test; Pearson's Chi-squared test

The table shows a trend where female patients are better represented in the group with slightly reduced ejection fraction, with no significant differences in age. The observed difference is close to statistical significance ($p = 0.07$).

Tabel 2.5. Comparative Inferential Analysis of Echocardiographic Parameters by Groups

Variable	**Group A N = 63**	**Group B N = 64**	**p-value[1]**
Mean LVEF (SD)	45.7 (2.08)	53.64 (1.92)	2.53e-45
Mean Longitudinal Strain (SD)	-16.46 (0.91)	-21.86 (0.94)	2.69e-63
Mean PSD (SD)	57.13 (11.34)	37.41 (1.48)	1.10e-20
Mean MAPSE (SD)	1.04 (0.11)	1.28 (0.08)	4.91e-26
Mean LVEDD (SD)	5.06 (0.23)	5 (0.22)	0.141
Mean PWTd (SD)	0.97 (0.16)	1 (0.17)	0.175
Mean IVS (SD)	1.2 (0.19)	1.16 (0.19)	0.282
Mean LV Mass (SD)	210.47 (57.45)	207.12 (55.67)	0.739
Mitral Regurgitation n(%)			0.042
Grade I	34 (54%)	47 (73%)	
Grade II	27 (43%)	17 (27%)	
Grade III	2 (3%)	0 (0%)	
Increased LA Volume n(%)			0.51
No	56 (89%)	60 (94%)	
Yes	7 (11%)	4 (6%)	
LVH n(%)			0.27
No	16 (25%)	23 (36%)	
Yes	47 (75%)	41 (64%)	

[1] Pearson’s Chi-squared test

The table presents the mean and standard deviation for selected echocardiographic parameters in groups A and B, along with p-values to assess the statistical significance of observed differences.

- **LVEF (%)**: Group A has a mean LVEF of 45.7% (SD = 2.08), while group B has a significantly higher mean of 53.64% (SD = 1.92). The extremely low p-value (2.53e-45) indicates a statistically significant difference between the two groups, suggesting a much better left ventricular function in group B.

- **Longitudinal Strain (%)**: The mean for group A is -16.46 (SD = 0.91) and for group B is -21.86 (SD = 0.94). The highly significant p-value (2.69e-63) indicates a more pronounced longitudinal deformation in group B.
- **PSD**: Group A has a mean of 57.13 (SD = 11.34) compared to 37.41 (SD = 1.48) in group B. The p-value (1.10e-20) suggests greater variability in ventricular activation time in group A.
- **MAPSE**: The mean in group A is 1.04 (SD = 0.11) and in group B is 1.28 (SD = 0.08). The significant p-value (4.91e-26) suggests better mitral annular plane systolic excursion in group B.

Identification of Potential Predictors for Heart Failure

The second research direction aims to identify potential predictors that increase the risk of heart failure through left ventricular systolic dysfunction. This analysis used various statistical methods to explore and validate risk factors associated with heart failure.

We constructed an initial logistic model to evaluate the influence of different risk factors on heart failure, including demographic, clinical, and biological variables. To address potential collinearity issues among included variables, we calculated the Variance Inflation Factor (VIF), confirming the absence of significant collinearity.

To optimize the model and identify the most relevant set of variables, we used the stepwise method, which allows iterative variable selection based on the Akaike Information Criterion (AIC).

Additionally, we focused on identifying risk factors contributing to reduced left ventricular ejection fraction (LVEF). We used a linear regression model to evaluate how different factors influence the initial LVEF value. Variables included in the analysis were age, BMI, menopause before 45 years, hypertension (HTN), atrial fibrillation (AF), depression, serum cholesterol, dyslipidemia, and metabolic syndrome.

This analysis demonstrated that the analyzed variables did not have a significant influence on the left ventricular ejection fraction. The linear regression model explained very little of the observed variability in LVEF. It is necessary to explore other risk factors or use more advanced modeling methods to identify factors that significantly influence LVEF.

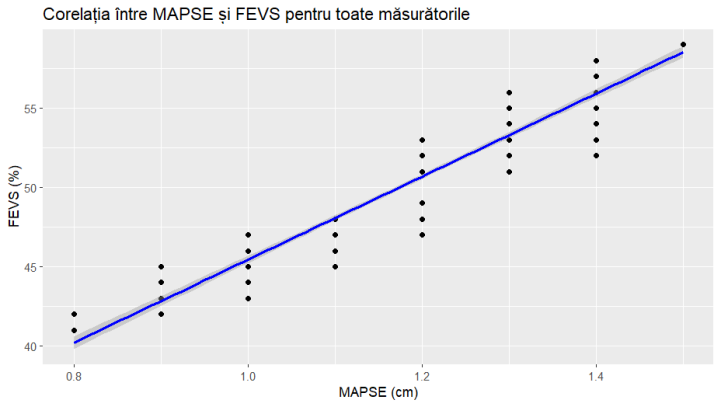

Figura 2.50. Correlation Between Global MAPSE Values and LVEF

The scatter plot combining all measurements (initial, 6 months, and 12 months) shows a strong linear correlation between MAPSE and LVEF.

Tabel 2.13. Pearson Correlation Coefficients for MAPSE and LVEF

Measurement	**Pearson Correlation Coefficient (r)**	**Statistical Significance (p-value)**
MAPSE vs. FEVS	0.95	< 0.001
MAPSE 6L vs. FEVS 6M	0.94	< 0.001
MAPSE 12L vs. FEVS 12M	0.93	< 0.001
Total (all measurements)	0.94	< 0.001

Pearson correlation coefficients for MAPSE and LVEF at all time intervals are very close to 1, indicating a strong linear correlation. P-values < 0.001 suggest these correlations are statistically significant, indicating that MAPSE can be reliably used to estimate LVEF.

The third research direction was a descriptive statistical analysis of the variables monitored in the study – a secondary objective of the study. This analysis presented the characteristics of the patient cohort by reporting the mean, median, standard deviation (SD), minimum, and maximum distribution for continuous variables, while relative and absolute frequencies were reported for categorical variables.

The descriptive statistical analysis provided a detailed overview of the demographic, behavioral, and clinical characteristics of the patient cohort. The patients presented a high prevalence of cardiovascular risk factors such as hypertension and dyslipidemia. Additionally, elevated values of NT-proBNP and reduced LVEF indicated significant cardiac dysfunction among the patients. These data underscore the importance of monitoring and carefully managing these patients to prevent cardiovascular complications.

Fourth Research Direction: Identifying Clinical, Biological, and Imaging Factors for Stratification

This research direction aimed to stratify patients by identifying clinical, biological, and imaging factors to predict those with slightly reduced ejection fraction (FEur) who may progress to reversible or reduced ejection fraction (FE).

Patients were re-evaluated at 6±1 months and 12±2 months, with attention to:

- **Clinical parameters**: dyspnea, effort tolerance, hepatomegaly, NYHA class
- **Biological markers**: NT-proBNP
- **Imaging parameters**: presence of stasis hilums, LVEF, MAPSE, longitudinal strain of the left ventricle, electromechanical dispersion (PSD) of the left ventricle

Tabel 2.20. Number of Patients at 6 and 12 Months by LVEF Evolution

Interval	**LVEF > 50%**	**LVEF Maintained**	**LVEF Reduced**
6 months	24 (43.6%)	31 (56.4%)	7 (12.7%)
12 months	13 (22.0%)	30 (50.8%)	18 (30.5%)

We analyzed the influence of initial NT-proBNP values on the evolution of LVEF values.

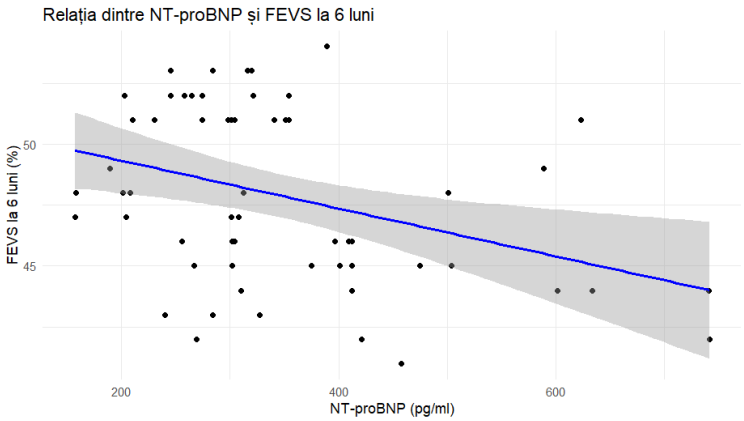

Figura 2.94. Correlation Between NT-proBNP and LVEF at 6 Months

This graph shows the relationship between NT-proBNP values and LVEF at 6 months. The blue line represents the regression line, and the gray band represents the confidence interval. A descending trend suggests higher NT-proBNP values are associated with lower LVEF at 6 months. Linear regression confirms that NT-proBNP is a significant negative predictor of LVEF at 6 months ($p < 0.001$).

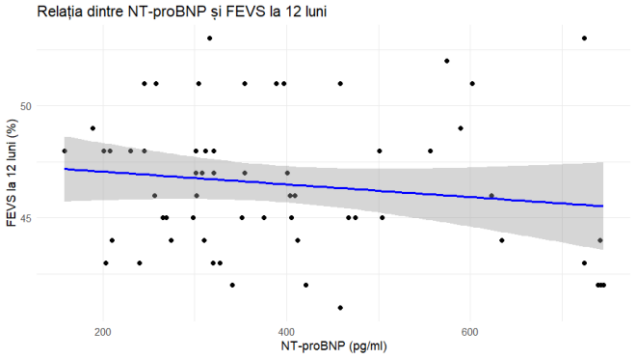

Figura 2.95. Correlation Between NT-proBNP and LVEF at 12 Months

This graph illustrates the relationship between NT-proBNP values and LVEF at 12 months. Similar to the previous graph, a descending trend indicates that higher NT-proBNP values are associated with lower LVEF at 12 months. Linear regression results confirm this negative relationship ($p < 0.001$).

Regression Analysis

Regression analysis demonstrates that NT-proBNP is a significant predictor for the likelihood of having an LVEF > 50% at 6 months with a p-value of 0.019. The coefficient of -2.345 indicates a strong influence on the modification of LVEF.

Tabelul 2.101. ROC Curve Results for NT-proBNP and LVEF at 6 Months

Measure	**Value**
AUC	0.6791
Threshold (logit)	0.473
Threshold (absolute)	370.94 pg/ml
Sensitivity	0.75
Specificity	0.63

The ROC curve for the logistic model shows the model's ability to discriminate between patients with LVEF > 50% and those with LVEF ≤ 50% at 6 months. An AUC (Area Under the Curve) of 0.6791 indicates a moderate discriminative ability. Threshold values for NT-proBNP suggest that patients with NT-proBNP below 370.94 pg/ml have a higher likelihood of having an LVEF > 50% at 6 months, with a sensitivity of 52.17% and a specificity of 80.56%. This means NT-proBNP can be used to identify patients at risk of reduced LVEF.

Tabelul 2.102. ROC Curve Results for NT-proBNP and LVEF at 12 Months

Measure	Value
AUC	0.7117
Threshold (logit)	0.5436
Threshold (absolute)	227.92 pg/ml
Sensitivity	0.65
Specificity	0.70

Threshold values for NT-proBNP suggest that patients with NT-proBNP below 227.92 pg/ml have a higher likelihood of having an LVEF > 50% at 12 months, with a sensitivity of 90.91% and a specificity of 52.08%. This means NT-proBNP can be used to identify patients at risk of reduced LVEF.

Analyzing the Influence of Initial LVEF Values

Initial LVEF values are significant predictors for achieving an LVEF > 50% at 6 months, for reducing LVEF at 12 months, and for reducing LVEF at 12 months compared

to 6 months. Initial LVEF values are not significant predictors for achieving an LVEF > 50% at 12 months or for reducing LVEF at 6 months.

Analyzing the Influence of Longitudinal Strain on LVEF Evolution

Linear regression at 6 months shows a significant negative relationship between longitudinal strain and LVEF at 6 months. The coefficient for strain is -2.7568, indicating that as strain decreases, LVEF at 6 months tends to increase. This result is statistically significant with a very low p-value (2.36e-08). The R-squared value of 0.413 indicates that approximately 41.3% of the variability in LVEF at 6 months can be explained by strain values.

At 12 months, the coefficient for strain is -1.1183, indicating a negative relationship between strain and LVEF at 12 months, but this relationship is weaker than at 6 months. The p-value of 0.017818 means the result is statistically significant, but the R-squared value of 0.09458 indicates a lower explanatory power.

Regression Analysis at 6 Months

Logistic regression at 6 months demonstrates that longitudinal strain is a significant predictor for the likelihood of having an LVEF > 50% at 6 months. A negative coefficient of -1.12 suggests that an increase (less negative value) in strain is associated with a lower likelihood of having an LVEF > 50%.

At 12 months, longitudinal strain is a significant predictor for LVEF reduction. A coefficient of 0.9352 and a p-value of 0.0442 indicate statistical significance ($p < 0.05$). This means that increasing strain values are associated with a higher likelihood of LVEF reduction at 12 months.

Tabel 2.112. ROC Curve Results and Threshold for Longitudinal Strain and LVEF at 6 Months

Metric	Value
Area Under Curve (AUC)	0.7059
Threshold	0.3661
Threshold (absolute)	-16.97%
Sensitivuty	0.7826
Specificity	0.5789

The ROC curve and thresholds for longitudinal strain of the left ventricle and LVEF at 6 months indicate a moderate discriminative ability of the logistic model. Threshold values for strain suggest that patients with a strain greater than -16.97 have a higher likelihood of having an LVEF > 50% at 6 months, with a sensitivity of 78.26% and a specificity of 58.33%. This indicates that strain can be a useful indicator of ventricular function at 6 months.

Tabel 2.114. ROC Curve Results and Thresholds for Longitudinal Strain and LVEF at 12 Months

Metric	Value
Area Under Curve (AUC)	0.7159
Threshold	0.1675
Threshold (absolute)	-16.53%
Sensitivity	0.9091
Specificity	0.5208

The ROC curve and thresholds for longitudinal strain of the left ventricle and LVEF at 12 months indicate a moderate discriminative ability. Threshold values for strain suggest that patients with a strain greater than -16.53 have a higher likelihood of having an LVEF > 50% at 12 months, with a sensitivity of 78.26% and a specificity of 58.33%. This indicates that strain can be a useful indicator of ventricular function at 12 months.

Evaluating the Influence of Electromechanical Dispersion on LVEF

We also analyzed the influence of electromechanical dispersion (PSD) of the left ventricle on the evolution of LVEF.

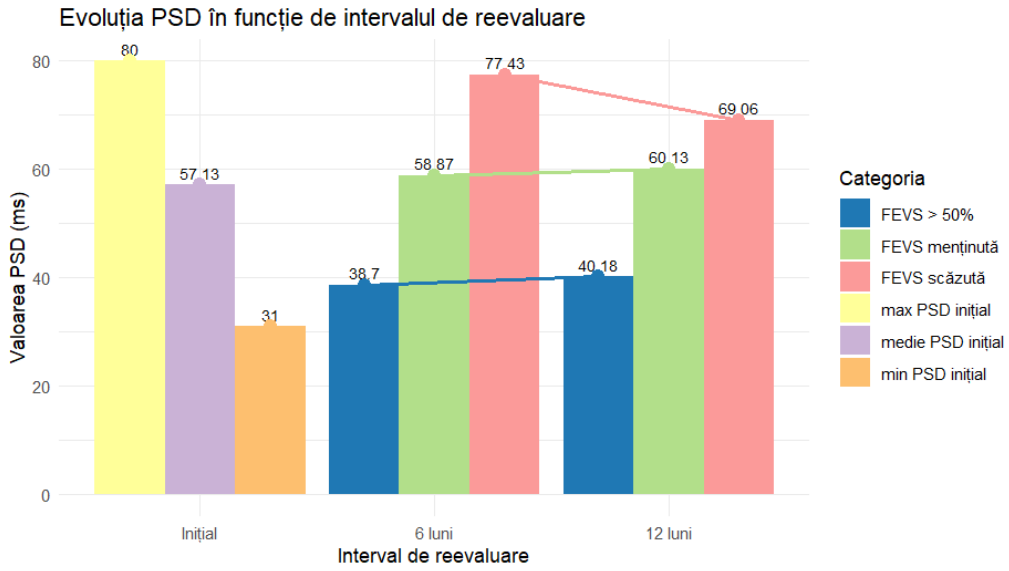

Figura 2.102. Evolution of PSD Values Based on Re-evaluation Intervals

In this graph, we can observe:

1. **Initial Evaluation**:
    - Initial PSD values show high variability, with a maximum value of 80 and a minimum value of 31. The average value of 57.13 indicates a general tendency toward moderate PSD values among patients.
2. **At 6 Months**:
    - Patients who had a recovery of LVEF (LVEF > 50%) showed a significant decrease in PSD, suggesting an improvement in ventricular function.
    - Patients with maintained LVEF had similar PSD values compared to the initial value, indicating stabilization of their condition.
    - Patients with decreased LVEF had a significant increase in PSD, suggesting a deterioration of ventricular function.
3. **At 12 Months**:
    - PSD values in patients with LVEF > 50% remained relatively constant compared to 6 months, indicating stabilization of improvement.
    - Patients with maintained LVEF had values similar to those at 6 months, indicating continued stabilization.
    - Patients with decreased LVEF showed a slight decrease in PSD compared to 6 months, but values remained higher than initial, suggesting persistent deterioration.

In conclusion, the graph suggests that medical interventions and management of patients with heart failure and slightly reduced ejection fraction can significantly impact ventricular function, measured through PSD. ANOVA analysis can provide additional insights into the statistical significance of these differences between groups.

Tabel 2.116. ANOVA Results for PSD Values Evolution

	Df	Sum Sq	Mean Sq	F value	Pr(>F)
Interval	2	18	8.9		>0.05
Category	5	4561	912.1		>0.05
Interval:Category	10	219	21.9		>0.05

According to the ANOVA test, the patient's category significantly impacts PSD values, while the time interval and the interaction between interval and category do not appear to be significant factors. These results suggest that differences in PSD values are more likely determined by the initial condition of the patients rather than the reevaluation period.

Linear Regression for LVEF at 6 and 12 Months

The linear regression for LVEF at 6 months indicates a coefficient of -0.26896 for the electromechanical dispersion of longitudinal fibers of the LV, suggesting that for each unit increase in PSD, LVEF at 6 months decreases by approximately 0.27%. This coefficient is statistically significant ($p < 0.001$).

The linear regression for LVEF at 12 months indicates a coefficient of -0.12325 for the electromechanical dispersion of longitudinal fibers of the LV, suggesting that for each unit increase in PSD, LVEF at 12 months decreases by approximately 0.12%. This coefficient is statistically significant ($p < 0.001$).

Tabel 2.121. ROC Curve Results and Threshold for LVEF at 6 Months

Parametru	**Valoare**
Area Under Curve (AUC)	0.9336
Threshold	0.3786 (normalized units) =59.5ms
Sensitivity	0.870
Specificity	0.905

The optimal threshold for PSD is approximately 59.5ms, with a sensitivity of 87% and a specificity of 91%. This indicates that patients with PSD below this threshold have a higher probability of having LVEF > 50% at 6 months, indicating favorable evolution.

Tabel 2.122. ROC Curve Results and Threshold for LVEF at 12 Months

Metric	Value
Area Under Curve (AUC)	0.7117
Threshold	0.5436 (normalized units) = 62,3ms
Sensitivity	0.650
Specificity	0.700

The optimal threshold for PSD is approximately 62.3ms, with a sensitivity of 65% and a specificity of 70%. This indicates that patients with PSD below this threshold have a higher probability of having LVEF > 50% at 12 months, indicating favorable evolution.

3. Conclusions and Personal Contributions

This study evaluated a diverse set of clinical, biological, and imaging parameters to better understand the characteristics and evolution of patients with heart failure with preserved and slightly reduced ejection fraction.

1. **HF with Slightly Reduced and Preserved EF**: Both have similar clinical and paraclinical characteristics but significant differences in prognosis.
2. **Slightly Reduced EF**: An independent entity with potential for reversibility or worsening.
3. **MAPSE and LVEF**: Significant correlation encourages the use of MAPSE as an element for quantifying LV systolic function in patients with poor echocardiographic windows.
4. **Modern Echocardiographic Parameters**: Longitudinal strain and electromechanical dispersion of LV are superior in quantifying systolic function and risk stratification compared to classic parameters (LVEF).

5. **Clinical and Paraclinical Correlation**: The correlation between clinical parameters (dyspnea), paraclinical markers (NT-proBNP), and echocardiographic parameters (LVEF, longitudinal strain, electromechanical dispersion) is important for early identification of HF patients with reversible potential.
6. **Significant Clinical Factors**: Edema and dyspnea were identified as significant clinical factors in determining the decrease of LVEF at 6 months.
7. **Hypertension Influence**: Significant impact on LVEF reduction at 6 months (-2.31%) but not at 12 months.
8. **NT-proBNP**: Identified as a significant predictive biomarker for LVEF evolution. Threshold values below 370.94 pg/mL at 6 months and below 227.92 pg/mL at 12 months were associated with a higher probability of LVEF improvement.
9. **Longitudinal Strain**: Demonstrated important predictive capacity, with GLS values below -18% at 6 months and below -19% at 12 months correlated with LVEF improvement.
10. **Electromechanical Dispersion**: A valuable indicator for risk stratification, with dispersion values below 55 ms at 6 months and below 50 ms at 12 months associated with LVEF improvement.

3.1. Clinical Implications of the Results

3.1.1. Clinical Profile of Patients with Slightly Reduced EF with Potential to Evolve to Preserved EF

Clinical Profile:

- Elderly patient, male or female, from urban or rural areas, smoker or non-smoker, with asymptomatic ischemic heart disease.
- Good control of hypertension.
- No signs and symptoms of heart failure – moderate exertional dyspnea or peripheral edema.
- Chronic treatment with beta-blockers, ACE inhibitors or ARBs, loop diuretics, and mineralocorticoid receptor antagonists, dosed according to tolerance and in the absence of contraindications.

Biological Profile:

- Initial NT-proBNP below 370.94 pg/mL suggests favorable evolution at 6 months and below 227.92 pg/mL at 12 months.
- Metabolic and renal parameters within normal limits.

Imaging Profile:

- Initial LV longitudinal strain (GLS) below -18% suggests favorable evolution at 6 months and below -19% at 12 months, indicating good subclinical systolic function.
- Electromechanical dispersion below 55 ms for 6 months evolution and below 50 ms at 12 months, indicating good synchronization of myocardial contractions.
- MAPSE > 10 mm.

3.1.2. Clinical Profile of Patients with Slightly Reduced EF with Potential to Evolve to Reduced EF

Clinical Profile:

- Elderly patient, male or female, from urban or rural areas, smoker or non-smoker, with asymptomatic ischemic heart disease, with multiple comorbidities such as hypertension, dyslipidemia, depression.
- Presence of heart failure signs and symptoms - dyspnea and peripheral edema.
- History of atrial fibrillation.
- Chronic treatment with beta-blockers, ACE inhibitors or ARBs, loop diuretics, and mineralocorticoid receptor antagonists, dosed according to tolerance and in the absence of contraindications.

Biological Profile:

- Initial NT-proBNP above 370.94 pg/mL, indicating volume overload and ventricular dysfunction.
- Metabolic syndrome.

Imaging Profile:

- Initial myocardial strain (GLS) above -17% suggests an unfavorable potential evolution at 6 months and above -16% at 12 months, indicating subclinical systolic dysfunction.
- Electromechanical dispersion above 60 ms, indicating ventricular dyssynchrony.
- MAPSE < 10 mm, suggesting reduced systolic function of the left ventricle.

Clinical Implications

1. **Patients with Potential to Evolve to Preserved LVEF**: These patients may benefit from regular monitoring and therapy adjustments to maintain good control of comorbidities. Early interventions and therapeutic adjustments can prevent heart failure progression.
2. **Patients with Potential to Evolve to Reduced LVEF**: These patients require intensive monitoring and more aggressive therapeutic interventions. Frequent

evaluation of clinical, biological, and imaging parameters is essential for early identification of deterioration and treatment adjustment.

3. **Personalized Management**: Using NT-proBNP, myocardial strain, and electromechanical dispersion in clinical practice can improve risk stratification and treatment personalization for patients with heart failure and slightly reduced LVEF.
4. **Early Interventions**: Identifying patients with critical parameter values allows for more aggressive therapeutic interventions and intensive monitoring, thereby preventing the worsening of heart failure.
5. **Comprehensive Evaluation**: Integrating clinical, biological, and imaging evaluations offers a more comprehensive approach to patient management, improving prognosis and quality of life.
6. **Modern Systolic Function Parameters**: Modern parameters for quantifying LV systolic function (LV longitudinal strain and electromechanical dispersion) are superior and more sensitive than LVEF in identifying patients who can transition from slightly reduced to preserved LVEF.
7. **Identifying Reversible Patients**: Patients with NT-proBNP <370 pg/ml, longitudinal strain >16.5%, and PSD <59.5 ms have the potential for LVEF reversibility. Implementing maximal treatment with the 5 pillars (according to ESC guidelines) is recommended for these patients.
8. **Therapeutic Interventions Based on Early Stratification**: Early therapeutic interventions based on early stratification of patients with slightly reduced LVEF can reduce hospitalization rates and improve patient quality of life.

Recommendations for Practice

1. **Implementation of Screening Protocols**: Implement biomarker screening protocols within elderly heart failure patient care programs.
2. **Development of Clinical Guidelines**: Develop clinical guidelines that include NT-proBNP, longitudinal strain, and PSD as standard evaluation tools.

Study Limitations

1. **Sample Size**: The study had a relatively small sample size, which may limit the generalizability of the results.
2. **Monitoring Duration**: Patient monitoring was limited to 12 months, not allowing for long-term evaluation of therapy effects and disease evolution.
3. **Imaging Methodology**: Variability in echocardiographic techniques and result interpretation can influence the accuracy of strain and dispersion measurements.

Future Research Directions

1. **Long-Term Studies**: Evaluate the long-term effects of therapeutic interventions and monitor LVEF evolution over extended periods (24-36 months).
2. **Larger Samples**: Conduct studies with larger sample sizes to confirm results and allow for more detailed subgroup analyses.
3. **Advanced Techniques**: Integrate new imaging technologies and emerging biomarkers to improve diagnostic accuracy and risk stratification.
4. **Therapeutic Interventions**: Evaluate the efficacy of different therapeutic regimens and medication combinations to optimize treatment for patients with slightly reduced LVEF.

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Listă lucrări științifice publicate

Articole publicate în reviste de specialitate:

1. *Romanian Journal of Internal Medicine*, Vol. XIX, No. 2, pag 7-15, Titlul: The Association Between Heart Failure with Preserved and Mildly Reduced Ejection Fraction and Depression in the Elderly Patient. Autori: **Irina Ispas,** Alice Munteanu, Andreea Stoica
    - link: https://sciendo.com/article/10.2478/inmed-2022-0214
2. Romanian Journal of Gerontology and Geriatrics 2023, Vol 11, No 1-2, pag. 15-20. Titul: Heart failure with preserved and mildly reduced ejection fraction in elderly. Autori: **Irina Ispas,** Alice Munteanu, Andreea Stoica
    - link: https://rjgg.ro/pdf/2022_v11.3p15.pdf