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PULMONARY HYPERTENSION AND RIGHT VENTRICULAR DYSFUNCTION: PROGNOSTIC IMPLICATIONS IN PATIENTS WITH DIFFERENT CLINICAL PHENOTYPES OF ISCHEMIC HEART FAILURE

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1. INTRODUCTION

Heart failure (HF) is a heterogeneous syndrome with a poor prognosis. Its prevalence is 17.2 per 1000 individuals [1], varying between 1% - 3% of the adult population [2,3]. In terms of HF phenotype, the reported prevalence of HF with preserved ejection fraction (HFpEF) is continuously increasing, while the rate of HF with reduced ejection fraction (HFrEF) remains stable or gradually decreases [2]. Among the multiple causes of HF, coronary artery disease (CAD) represents the predominant etiology, accounting for 26% of the total burden [2,4].

The prognosis of HF has improved following the implementation of guideline-directed medical therapy. Nevertheless, the mortality rate remains elevated, ranging between 6.4% - 17.4% [2], while HF hospitalization accounts for approximately 1% – 2% of all-cause admissions, representing the leading cause of hospitalization among individuals aged over 65 years [4]. Although multiple scores for estimating mortality risk in HF are available, there are currently no reliable tools for assessing the risk of HF-related hospitalization or worsening HF (WHF) episodes [5], which are unfavourable outcomes with an enormous social and economic burden.

The development of pulmonary hypertension (PH) represents a turning point in the natural course of HF [6], worsening its prognosis regardless of the HF phenotype. PH is further associated with an increased risk of both mortality [7–9] and morbidity [7,10]. The prevalence of PH associated with left heart disease (PH-LHD) varies between 36% - 83% in patients with HF [7,10]. The gold standard for the evaluation of pulmonary hemodynamics is right heart catheterization; however, as an invasive diagnostic method, it is often unjustified in subjects with LHD. Echocardiographic estimation of the PH probability (PHpr) is recommended in this category of patients, despite the fact that echocardiography has the capacity to both underestimate and overestimate pulmonary artery pressure [11].

PH-LHD can be stratified according to pulmonary vascular resistance (PVR) into isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH) [11,12]. Studies and meta-analyses have demonstrated a significant negative prognostic impact and reduced survival in patients with Cpc-PH [7,13]. Attempts have been made to identify non-invasive indicators that could estimate the presence of a precapillary component within PH-LHD [14,15]; however, their correlation with invasively measured parameters is not well demonstrated or validated, and their prognostic impact is supported by limited evidence.

Despite being recognized in recent decades, the importance of right ventricular (RV) function and its prognostic role remains significantly underestimated. There is no unanimously accepted definition of right ventricular dysfunction (RVD). Thus, while some expert recommendations define it as the determination of a parameter that characterizes RV function outside the reference range [16], other sources emphasize the differentiation between RVD, which involves RV structural or functional abnormalities without hemodynamic compromise, and RV failure, caused by reduced filling and/or RV output [17,18]. The prevalence of RVD shows significant variability across studies and meta-analyses, ranging from 19% to 77%, due to the use of varying diagnostic criteria [21–24]. It is associated with a poor prognosis, independent of the underlying pathogenetic mechanism: throughout the entire spectrum of HF phenotypes [18,21,22], after cardiac surgery [23], acute myocardial infarction (AMI) [24] and PH [11].

Surgical or percutaneous myocardial revascularization has made remarkable progress in managing obstructive CAD. Percutaneous coronary intervention (PCI) has a clear benefit in improving survival in patients with AMI [25], while coronary artery bypass grafting (CABG) has proven effective in reducing cardiovascular (CV) mortality and hospitalization over a 10-year

period in patients with severe left ventricular (LV) systolic dysfunction [26]. However, studies comparing the outcomes of patients undergoing CABG [26] or PCI [25,27] with optimal medical therapy, as well as those evaluating the two types of myocardial revascularization [28,29], have primarily focused on endpoints such as mortality, CV-related hospitalization, and the risk of AMI or stroke. Limited studies have explored the long-term evolution of ischemic HF and its phenotypes, so the impact of myocardial revascularization on HF prognosis remains insufficiently elucidated. Although some small studies have analyzed RV function or PH in patients undergoing CABG or PCI, these have primarily focused on the early postoperative stage, as well as their short-term prognostic impact. Thus, the prevalence, evolution and long-term prognostic value of PH and RVD in patients who have undergone myocardial revascularization through CABG or PCI are sparsely and fragmentarily reported in the specialized literature.

The aim of this study was to investigate the characteristics of pulmonary hypertension associated with left heart disease and right ventricular dysfunction in patients with ischemic heart failure, as well as to develop long-term prognostic criteria following myocardial revascularization.

The **objectives of the research** were:

1. To assess the evolution of manifestations defining heart failure phenotypes over 12 months after myocardial revascularization.
2. To analyze the evolution of echocardiographic parameters suggestive of postcapillary pulmonary hypertension and its subtypes 12 months following myocardial revascularization, and to investigate their correlation with heart failure phenotypes
3. To estimate the modifications of right ventricular function parameters over 12 months after myocardial revascularization.
4. To perform a comparative analysis of the evolution of pulmonary hypertension, right and left ventricular dysfunction according to the type of myocardial revascularization: coronary artery bypass grafting or percutaneous coronary intervention.
5. To develop long-term prognostic criteria for the evolution of ischemic heart failure after myocardial revascularization and to determine the impact of pulmonary hypertension and right ventricular dysfunction in this context.

Scientific novelty and originality. The research provided new data on the prevalence of PH in patients with ischemic HF and myocardial revascularization. For the first time in the Republic of Moldova, we performed non-invasive (echocardiographic) diagnosis of postcapillary PH subtypes (IpcPH and CpcPH), with estimation of their prevalence in patients undergoing myocardial revascularization. We established a moderate and statistically significant correlation between echocardiographic parameters defining PH and HF characteristics. The independent impact of the HFrEF phenotype, LV remodeling and diastolic dysfunction parameters, the preexisting early changes within the pulmonary circulation, CV and non-CV comorbidities (arterial hypertension, atrial fibrillation, chronic kidney disease) on the progression of the echocardiographic probability of PH was demonstrated.

Furthermore, we reported the prevalence of RVD in patients with both surgical and percutaneous myocardial revascularization, thus supplementing the existing data in this field. We presented evidence supporting a multifactorial pathophysiological mechanism in the development of RVD in patients with ischemic HF, determined by ventricular interdependence, RV afterload and the impaired RV- pulmonary artery coupling. For the first time in the Republic of Moldova, the cardiopulmonary exercise test (CPET) was conducted in patients with PH and RVD, demonstrating reduced peak oxygen uptake (VO_2p) and ventilatory inefficiency.

As a result of this study, we provided solid evidence of the major prognostic impact of echocardiographic parameters defining PH and RVD on the risk of HF hospitalization and WHF episodes, as well as on the composite endpoint of all-cause mortality and HF-related hospitalization.

The scientific issue addressed in the research consists in identifying the parameters of PH and RVD with prognostic impact and quantifying their contribution in patients with ischemic HF and myocardial revascularization with respect to the defined endpoints – HF hospitalization and WHF episodes, as well as the composite endpoint: all-cause mortality and HF hospitalization. Additionally, prognostic factors determining the progression of the echocardiographic probability of PH at 12 months after the acute cardiac event were identified, thereby revealing the impact of both systolic and diastolic LV dysfunction, early changes in the pulmonary vascular bed and of CV and non-CV comorbidities in the development of PH-LHD. At the same time, prognostic determinants influencing de novo RVD at 12 months after myocardial revascularization were highlighted, emphasizing the importance of RV afterload, RV–pulmonary artery coupling and ventricular interdependence.

The theoretical significance of the research lies in identifying the correlation between PH-LHD, its subtypes and HF phenotypes in patients who underwent myocardial revascularization through CABG or PCI. Additionally, the parameters that demonstrated prognostic impact in the context of progression of the echocardiographic probability of PH 12 months after myocardial revascularization suggest the presence of subtle alterations in pulmonary circulation early after the acute cardiac event. These changes appear to progress under the influence of systolic and diastolic LV dysfunction, interacting with CV comorbidities (arterial hypertension and atrial fibrillation) and non-CV comorbidities (chronic kidney disease). At the same time, the impact of LV morpho-functional characteristics, echocardiographic parameters of PH and its precapillary component on the development of de novo RVD outlines a multifactorial pathophysiological mechanism underlying RVD in patients undergoing myocardial revascularization: ventricular interdependence and increased afterload, with impaired RV–pulmonary artery coupling. Strong arguments were presented in support of the major determining role of PH and RVD in the progression of ischemic HF, enhancing the risk of all-cause mortality, HF-related hospitalization and WHF.

Practical value of the research. The study demonstrated the feasibility of non-invasive echocardiographic differentiation of PH-LHD subtypes: IpcPH and CpcPH. The research emphasized the importance of incorporating parameters characterizing RV morphology and systolic function, as well as PH indices, such as tricuspid regurgitation velocity (TRV) and additional signs suggestive of PH, into the echocardiographic protocol for the follow up examination of patients who underwent CABG or PCI. These parameters have proven to be prognostic determinants in the evolution of HF. Furthermore, the study highlighted the relevance of integrating CPET into the evaluation protocol for patients who underwent myocardial revascularization, both for characterization the evolution of exercise capacity and for the assessment of gas exchange parameters with prognostic significance in this patient population.

As a result of the conducted study, five prognostic methods were developed. Two prediction models estimate the risk of HF-related hospitalization during the first year after myocardial revascularization. Given the negative prognostic impact of WHF, we developed the prognostic method for evaluation the risk of WHF during the first year after myocardial revascularization. Additionally, predictive models were created for assessing the risk of unfavourable evolution of PH and RVD.

Publications related to the thesis topic. The findings of the study have been reflected in 26 publications, including 1 article in a journal with an impact factor of 16.9, 2 articles in SCOPUS – indexed journals where the author is the first author, 5 articles in category B journals, 3 articles in category C journals, 11 abstracts in the proceedings of international scientific congresses and 4 theses in the proceedings of national scientific conferences.

Approval of Scientific Results. The relevant results derived from this research have been presented and discussed at numerous scientific forums, including: the Heart Failure Congress (2020 – online, May 21-24, 2022 in Madrid, Spain; May 20-23, 2023 in Prague, Czech Republic; May 11-14, 2024 in Lisbon, Portugal), ESC Preventive Cardiology Congress (2020 and 2022, online), the National Cardiology Congress (September 21-24, 2022 in Sinaia, Romania); as well as national conferences: the Annual Scientific Conference of USMF "N. Testemițanu" (2021 and 2022 in Chișinău), the scientific conference marking World COPD Day (November 22, 2019, Chișinău), the scientific conference "Pulmonary Hypertension in Daily Clinical Practice" (October 7, 2023, Chișinău) and the Scientific Conference within the International Specialized Exhibition "MoldMedizin & MoldDent" (September 27, 2024, Chișinău).

The results of the thesis were discussed and approved during the meeting of the Chronic Heart Failure Laboratory of the Institute of Cardiology (no. 3 of 27.03.2025) and the Specialized Scientific Seminar 321.03–Cardiology, 321.23–Cardiac Surgery (no. 2 of 02.05.2025).

Keywords: pulmonary hypertension, echocardiographic probability of pulmonary hypertension, right ventricular dysfunction, ischemic heart failure, heart failure phenotypes, ischemic heart disease, myocardial revascularization, prognosis.

2. MATERIALS AND METHODS

In order to achieve the proposed aim, a prospective observational analytical cohort study was conducted during the period 2020-2023 within the Chronic Heart Failure Laboratory of the Institute of Cardiology. The research was carried out with the support of the project 20.80009.8007.40 "*New therapeutic alternatives for improving the long-term prognosis of patients with chronic heart failure through the implementation of surgical, interventional and perioperative recovery strategies - ALTERICC*" within the State Program (2020-2023), the contracting authority: National Agency for Research and Development. The study was approved by the Research Ethics Committee of the „Nicolae Testemițanu" State University of Medicine and Pharmacy, reviewed in the session held on 20.09.2020, with the favourable opinion no. 82 issued on 05.10.2020.

Inclusion criteria for the study were as follows (all criteria were mandatory):

- Patients with a confirmed diagnosis of HF who underwent myocardial revascularization through CABG (with or without left ventricular reconstruction and valve repair) in the context of chronic coronary syndrome, or PCI in the setting of AMI, 3 months after the acute cardiac event
- Age ≥ 18 years
- Subjects who signed the informed consent form.

Exclusion criteria were based on the presence in medical records or patient history of data suggesting other potential causes of PH:

- Idiopathic pulmonary arterial hypertension;
- PH associated with drugs and toxins;
- PH associated with human immunodeficiency virus infection;
- PH associated with portal hypertension;

- Connective tissue diseases;
- Congenital heart diseases;
- Pulmonary veno-occlusive disease;
- Chronic pulmonary disease (forced vital capacity and/or forced expiratory volume in 1 second < 60% of predicted values), including: chronic obstructive pulmonary disease, pulmonary emphysema, restrictive lung disease;
- Acute or previous pulmonary thromboembolism;
- Renal failure with estimated glomerular filtration rate ≤ 15 ml/min/1.73 m².

The study included 275 patients with ischemic HF who underwent myocardial revascularization, of whom 150 patients (54.5%) underwent CABG (with/without LV reconstruction and/or valvular correction) in the setting of chronic coronary syndrome and 125 patients (45.5%) underwent PCI in the context of AMI, being enrolled in the study 3 months after the acute cardiac event. The mean age in the cohort was 63.12±0.54 years, 217 patients were men (78.9%) and 58 subjects were women (21.1%).

At baseline – stage T-3 of the study (3 months after myocardial revascularization) - all patients were evaluated according to a questionnaire that included the subjects' demographic and anthropometric data, risk factors and comorbidities, with the calculation of Charlson Comorbidity Index (CCI). Electrocardiography, echocardiography, laboratory tests, including serum NT-proBNP level, spirometry, 6 minute walk test (6MWT) and CPET were performed.

The syndrome of HF was established according to the recommendations of the ESC Guidelines for the diagnosis and treatment of acute and chronic HF [30], with stratification of HF phenotype based on LV ejection fraction (LVEF) into HFrEF, HFmrEF and HFpEF. The estimation of the echocardiographic probability of PH was performed in accordance with the criteria recommended by the ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension [12], involving the measurement of TRV and the assessment of additional suggestive signs of PH, related to: A. The ventricles: RV/LV end-diastolic diameters ratio >1.0; the ratio between tricuspid annular plane systolic excursion (TAPSE) and pulmonary artery systolic pressure (sPAP) <0.55 mm/mmHg; B. The pulmonary artery: the RV outflow tract acceleration time (RVOT AT) <105 ms; early diastolic pulmonary regurgitation velocity >2.2 m/s; pulmonary artery diameter >25 mm; C. The inferior vena cava (IVC): IVC diameter >21 mm with decreased inspiratory collapse; right atrium end-systolic area >18 cm². Patients with intermediate or high echocardiographic probability of PH formed the study group, whereas those with low probability comprised the control group.

The echocardiographic differentiation of post-capillary PH subtypes was performed by estimating the mean pulmonary artery pressure (mPAP = 79 – 0.45 × RVOT AT), pulmonary artery wedge pressure (PAWP = 1.9 + 1.24 × E/e') and pulmonary vascular resistance (PVR = TRV / RVOT VTI × 10 + 0.16, where RVOT VTI is RV outflow tract velocity time integral) [31].

The following criteria were used for the diagnosis of RVD: TAPSE <17 mm, RV fractional area change (RV FAC) <35%, peak systolic velocity of the lateral tricuspid valve annulus (RV S') <9.5 m/s or RV index of myocardial performance (RIMP Tei) >0.43 [16]. Considering that cardiac surgery, particularly tricuspid valve annuloplasty, may affect annular motion and thereby reduce the accuracy of TAPSE and RV S', RVD was considered present in the case of a combination of two echocardiographic parameters reflecting RV function, or in association with at least one of the following signs of right sided volume or pressure overload: RV end-diastolic diameter >41 mm, RV/LV end-diastolic diameters ratio >1.0, RV free wall thickness >5 mm, TRV >2.8 m/s, IVC diameter >21 mm with reduced inspiratory collapse, or right atrium end-systolic area >18 cm².

In order to achieve the study objectives and to assess the particularities of patients with varying degrees of PH probability, the cohort was stratified into three groups: low PHpr = 115 patients, intermediate PHpr = 72 subjects and high PHpr = 88 patients. Additionally, to explore the characteristics of individuals with RVD, the population was further categorized into two groups: RVD – 108 patients with impaired RV function and non-RVD – 167 patients with preserved RV function.

The subjects enrolled in the study were monitored for 9,63±1,74 months, with 5 patients lost to follow-up. At the 12-month follow-up visit – T-12 stage, the investigations performed at baseline were repeated.

The study endpoints were:

1) all-cause mortality,

2) HF hospitalization,

3) WHF episodes - defined by the presence of any of the following criteria: HF hospitalization, the need for intravenous diuretics in an outpatient setting, escalation of oral diuretic therapy,

4) improvement of LVEF - defined as an increase in LVEF by ≥10% during the follow-up period in patients with baseline LVEF ≤40%, resulting in a follow-up LVEF >40% at the 12-month visit,

5) negative evolution of PH - defined by the progression of PH probability from low to intermediate PHpr or high PHpr, or from intermediate PHpr to high PHpr, during the monitoring period,

6) newly developed RVD - established at the 12-month visit according to the criteria described above in patients with normal baseline RV function.

Methods of statistical analysis. The collected data were analyzed using IBM SPSS Statistics, 21.0 (IBM Corp., Armonk, New York, USA). Descriptive analysis included the determination of the mean, standard deviation and standard error for continuous variables, while for qualitative variables, frequencies and percentages were calculated. Bivariate analysis involved the use of the independent and paired sample Student's t-test, the χ^2 test and ANOVA. The association between parametric variables was assessed using the Bravais-Pearson correlation coefficient (r). Multivariate analysis through logistic regression enabled the identification of predictive factors for the established endpoints, with the odds ratio (OR) and the 95% confidence interval (95%CI) being determined. Discriminant analysis allowed the selection of predictors and the creation of prognostic models for the endpoints. The predictive methods' discriminative ability was evaluated by constructing ROC curves and assessing the area under the curve (AUC). The results of the statistical analysis were presented through tables and graphs (box plot, bar plot, scatter plot, Forest plot).

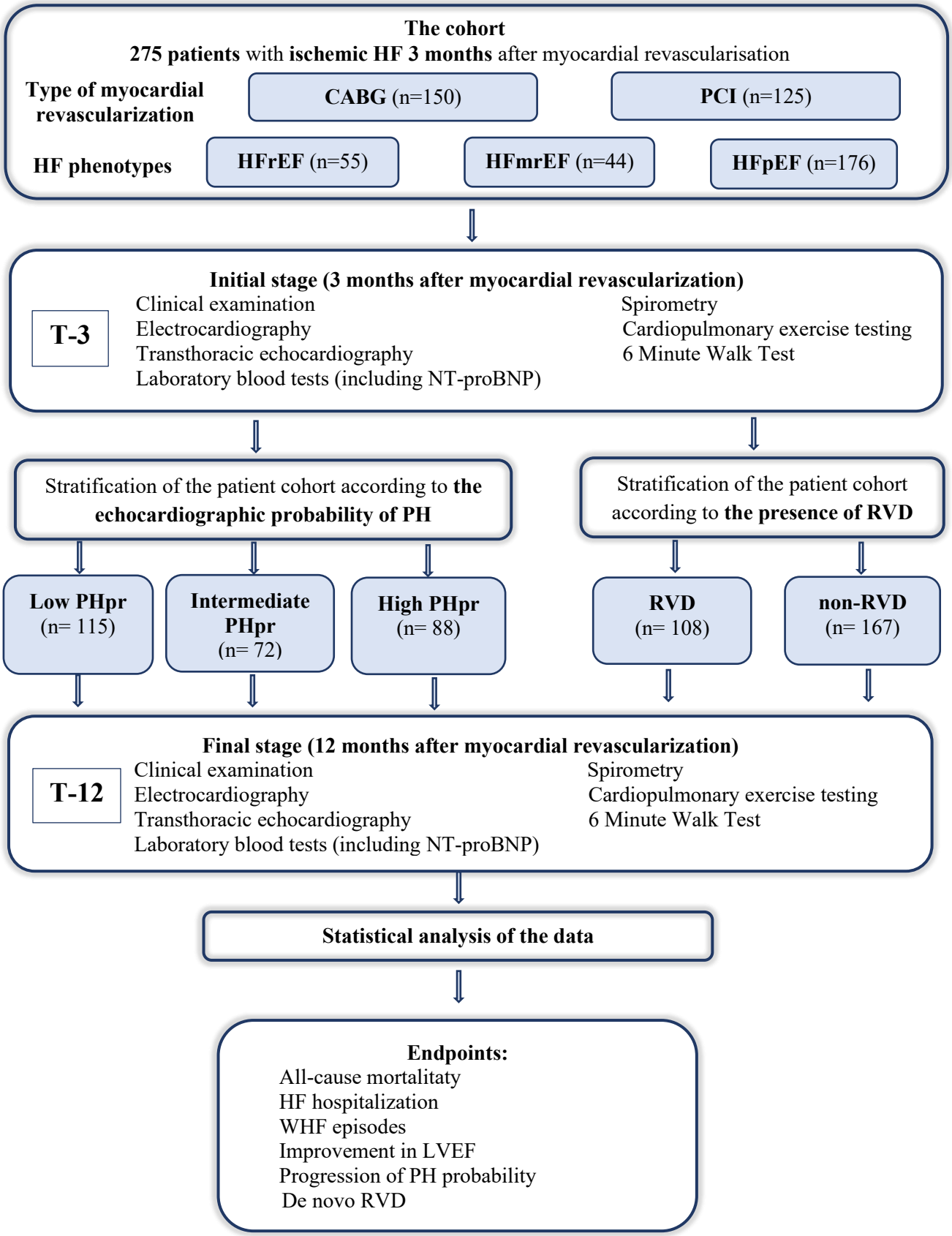


Figure 1. The study design.

Note: CABG – coronary artery bypass grafting, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, LVEF – left ventricular ejection fraction, NT-proBNP – N-terminal pro B-type Natriuretic Peptide, PCI – percutaneous coronary intervention, PHpr – echocardiographic probability of pulmonary hypertension, RVD – right ventricular dysfunction

3. LONGITUDINAL PROFILE OF HEART FAILURE PHENOTYPES, PULMONARY HYPERTENSION AND RIGHT VENTRICULAR DYSFUNCTION AT 12 MONTHS AFTER MYOCARDIAL REVASCULARIZATION

3.1. Evolution of the defining manifestations of heart failure phenotype 12 months after myocardial revascularization

At the 3-month stage after myocardial revascularization, patients were stratified according to the HF phenotype as follows: 64.0% (176 pts) had HFpEF, 16.0% (44 pts) were diagnosed with HFmrEF and 20.0% (55 pts) had HFrEF. The average age was similar across different HF phenotypes: (HFpEF: 63.52±0.67 years, HFmrEF: 63.05±1.18 years, HFrEF: 61.91±1.40 years, $p>0.05$), while the proportion of women was higher in the HFpEF phenotype compared to HFmrEF and HFrEF (26.1%, 46 pts vs 11.4%, 5 pts and 12.7%, 7 pts, respectively, $\chi^2=7.5$, $p<0.05$).

Patients with HFmrEF phenotype had the longest history of CAD compared to HFrEF and HFpEF (2.68±0.84 years vs 1.60±0.38 years vs 0.97±0.1 years, $p<0.01$). The prevalence of previous myocardial infarction (MI) was higher in patients with HFrEF compared to the HFmrEF and HFpEF phenotypes (54.5%, 25 pts vs 36.4%, 16 pts vs 33.0%, 58 pts, $\chi^2=8.35$, $p<0.05$). Additionally, LV aneurysm was more frequently identified in the HFrEF group compared to HFmrEF and HFpEF (34.54%, 19 pts vs 11.36%, 5 pts vs 7.38%, 13 pts, $\chi2=33.16$, $p<0.001$).

Patients with different HF phenotypes did not significantly differ based on the type of myocardial revascularization. Thus, the ratio of CABG or PCI was similar in all three groups (HFpEF: 54.0% vs 46.0%, HFmrEF: 52.3% vs 47.7%, HFrEF: 58.2% vs 41.8%). In contrast, referring to patients who underwent CABG, the majority of those with the HFrEF and HFmrEF phenotypes underwent complex surgical intervention, while its proportion was notably lower in the HFpEF group (90.7%, 29 pts vs 82.5%, 19 pts vs 58.4%, 56 pts, $\chi^2=37.30$, $p<0.001$).

At the end of the study, 71.4% (190 pts) had HFpEF phenotype, 13.6% (36 pts) were attributed to the HFmrEF phenotype, and 15.0% (40 pts) were included in the HFrEF group. Over the monitoring period, we observed a +7,4% increase in the proportion of patients with HFpEF, as well as a -2,4% decrease in the rate of patients with HFmrEF and a -5,0% reduction in the percentage of patients with HFrEF (Figure 2).

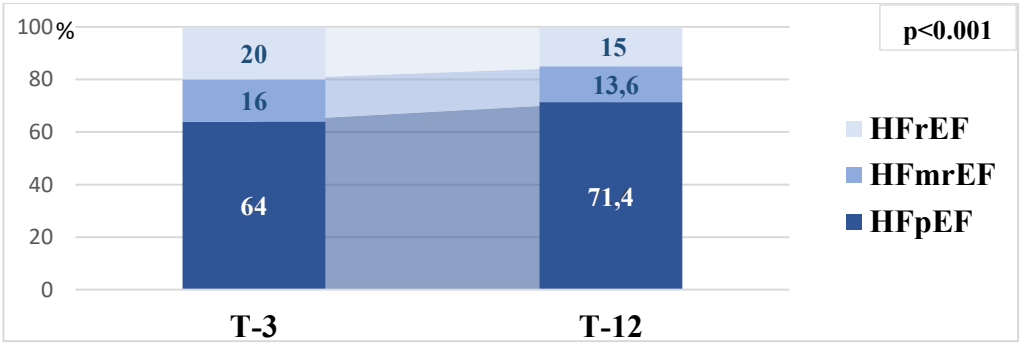


Figure 2. Distribution of HF phenotypes (%) at 3 and 12 months after myocardial revascularization.

HF – heart failure, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction.

LVEF showed a positive evolution at the cohort level, increasing by +1.76±0.43% ($p<0.001$) during the follow-up period, a dynamic observed in all HF phenotypes, albeit with varying magnitudes ($p<0.001$). The most pronounced increase in LVEF was observed in the HFrEF (+5.28±1.36%, $p<0.001$) and HFmrEF (+4.34±0.93%, $p<0.001$) groups, while the increase in the HFpEF group was insignificant (+0.06±0.42%) (Figure 3).

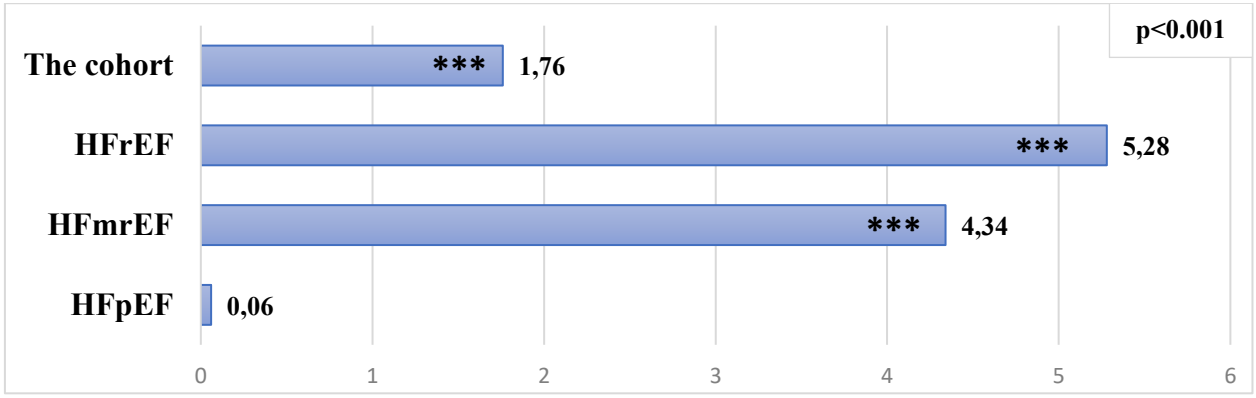


Figure 3. Evolution of LVEF (%) at 12 months after myocardial revascularization according to the HF phenotype

Note: p<0.001 - the statistical significance of dynamics across HF phenotype-stratified patient groups.
**** - p<0.001 – the statistical significance of the dynamics within each group.*
HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, LVEF – left ventricular ejection fraction.

Serum NT-proBNP showed an overall nonsignificant decrease of -146.26±96.49 pg/ml (p>0.05), with a distinct pattern across HF phenotypes (p<0,001): a significant reduction in the HFrEF group (-935.28±406.53 pg/ml, p<0.001) and no notable changes in the HFpEF (+70.24±42.73 pg/ml) and HFmrEF (+27.3±20.5 pg/ml) groups (Figure 4).

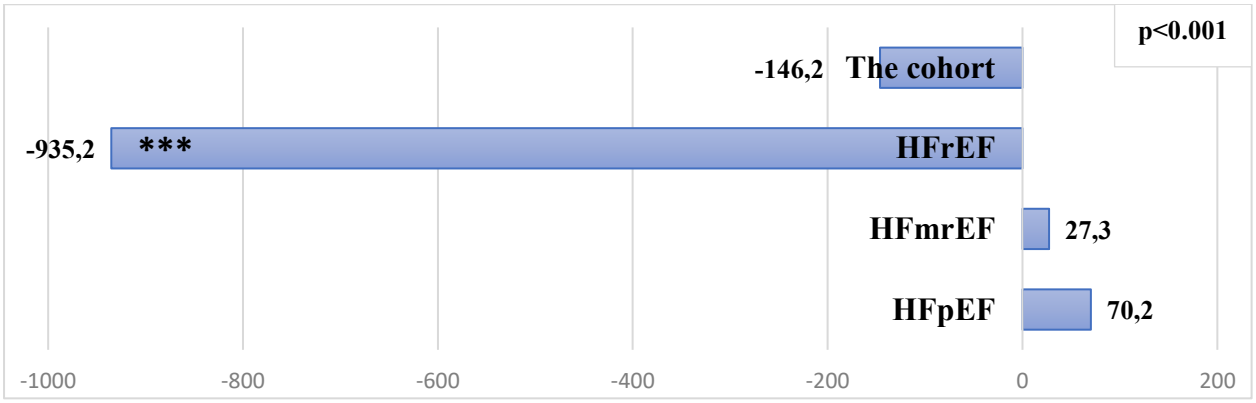


Figure 4. Evolution of NT-proBNP levels (pg/ml) according to the HF phenotype at 12 months after myocardial revascularization

Note: p<0.001 - the statistical significance of dynamics across HF phenotype-stratified patient groups.
**** - p<0.001 – the statistical significance of the dynamics within each group.*
HF – heart failure, HFmrEF – heart failure with mildly reduced ejection fraction, HFpEF – heart failure with preserved ejection fraction, HFrEF – heart failure with reduced ejection fraction, NT-proBNP – N-terminal fragment of B-type natriuretic pro-peptide.

Prognostic determinants of LVEF improvement

Among all patients with reduced LVEF at baseline, improvement was observed in 23.95% of cases by the T-12 stage. The univariate statistical analysis revealed the following parameters as relevant for this patient category: older age (66.0±1.40 years vs 61.41±1.15 years, p<0.05), increased left atrial diameter (46.55±1.11 mm vs 43.69±0.66 mm, p<0.05), elevated TRV (2.96±0.07 m/s vs 2.76±0.03 m/s, p<0.05), enlarged pulmonary artery diameter (28.48±0.64 mm vs 26.74±0.34 mm, p<0.05) and inferior walking distance during the 6MWT (269.29±3.81 m vs 302.46±9.61 m, p=0.055).

The prognostic determinants that influenced the positive dynamics of LVEF are presented in Figure 5.

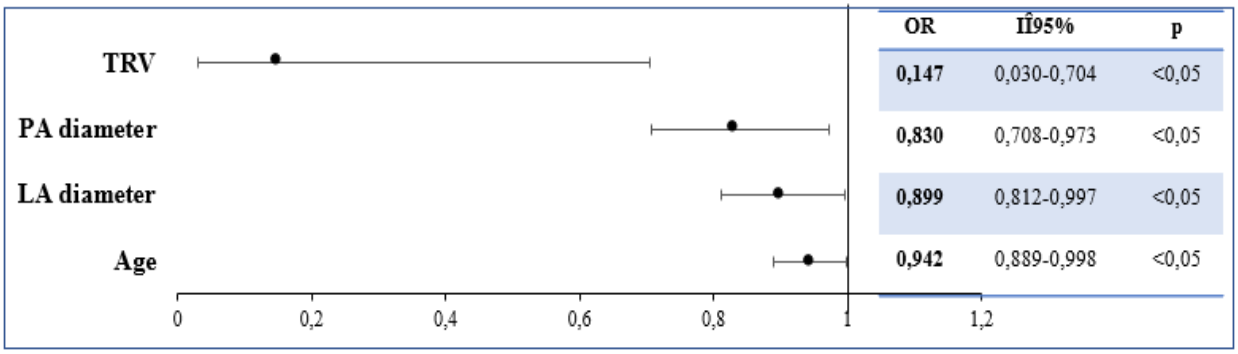


Figure 5. Prognostic determinants of LVEF improvement 12 months after myocardial revascularization.

Note: LA – Left atrium, PA – Pulmonary artery, TRV – Tricuspid regurgitation velocity.

3.2. Modification of parameters suggestive for pulmonary hypertension 12 months after myocardial revascularization

The prevalence of PH at 3 months after myocardial revascularization was 58.1% (160 pts) at the cohort level. Based on the echocardiographic estimation of PH probability, 41.8% (115 pts) of patients were classified as having low PHpr, 26.2% (72 pts) had intermediate PHpr and 32.0% (88 pts) had high PHpr. The delimitation of PH subtypes based on echocardiographic data revealed an IpcPH rate of 43.3% and a CpcPH prevalence of 10.9% at the cohort level. Additionally, all patients with intermediate PHpr were assigned to the IpcPH subtype, while 63.4% (52 pts) of patients with high PHpr had IpcPH and 36.6% (30 pts) were categorized in the CpcPH subtype, χ^2=317.17, p<0.001 (Figure 6).

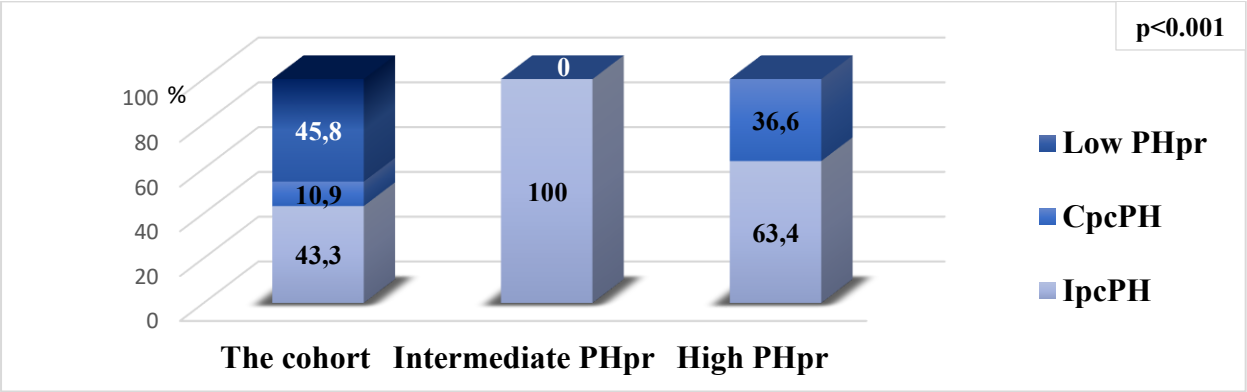


Figure 6. Distribution of patients according to PH subtypes: IpcPH and CpcPH estimated echocardiographically in relation to PH probability, % (n=263).

Note: CpcPH - combined post- and pre-capillary pulmonary hypertension, IpcPH - isolated post-capillary pulmonary hypertension, PH - pulmonary hypertension, PHpr - echocardiographic probability of pulmonary hypertension.

The patients divided according to PH probability did not differ significantly based on age and gender. A history of MI was more frequently found in patients with high and intermediate PHpr compared to those without echocardiographic signs of PH (50.0%, 44 pts vs 43.1%, 31 pts vs 25.2%, 29 pts, χ^2=14.15, p=0.001). The localization of MI was similar across the three groups (χ^2=6.82, p>0.05). The frequency of LV aneurysm was elevated in patients with intermediate or high PHpr (high PHpr: 32.8%, 21 pts vs intermediate: 17.3%, 9 pts vs low: 8.6%, 7 pts, χ^2=13.79, p=0.001). The prevalent type of myocardial revascularization in subjects with PH was CABG (high PHpr: 62.5%, 55 pts vs intermediate: 59.7%, 43 pts vs low: 45.2%, 52 pts, χ^2=7.06, p<0.05). They underwent predominantly complex surgical interventions (high PHpr: 80.0%, 44 pts vs intermediate: 72.7%, 31 pts vs low: 53.8%, 28 pts, χ^2=13.55, p<0.05).

Table 1. Echocardiographic probability of PH and comorbidities

Parameter		Low PHpr (n=115)	Intermediate PHpr (n=72)	High PHpr (n=88)	p
Arterial hypertension, % (n)		81,7% (94)	90,3% (65)	90,9% (80)	0,097
Atrial fibrillation, % (n)	permanent	2,6% (3)	5,6% (4)	21,6% (19)	**<0,001**
	paroxysmal	19,1% (22)	22,2% (16)	17,0% (15)	
Obesity, % (n)		36,5% (42)	44,4% (32)	52,2% (46)	0,08
Anemia, % (n)		9,6% (11)	8,3% (6)	16,1% (14)	0,22
Diabetes mellitus, % (n)		28,7% (33)	30,6% (22)	38,6% (34)	0,302
Chronic kidney disease, % (n)		13,0% (15)	18,1% (13)	20,5% (18)	0,352
Charlson Comorbidity Index, points		3,03 ± 0,13	3,82 ± 0,21	3,97 ± 0,18	**<0,001**

Among the studied comorbidities, only the prevalence of atrial fibrillation was significantly higher in patients with signs of PH, who also exhibited a higher CCI (Table 1).

Investigating the correlation between PH and HF phenotypes in patients who underwent myocardial revascularization, we identified a significant positive interdependence (contingency coefficient χ^2=0.344, p<0.001). Exploring the interrelationships between key PH variables and HF parameters, we found a moderate negative correlation between TRV and LVEF (r = -0.431, p<0.001), as well as a significant positive interconnection with NT-proBNP (r = 0.375, p<0.001). sPAP demonstrated a moderate correlation with LVEF (r = -0.447, p<0.001) and NT-proBNP (r = 0.449, p<0.001) (Figure 7).

Examining the interconnection between post-capillary PH subtypes and HF phenotypes, we identified a significant positive correlation (χ^2=0.377, p<0.001). Echocardiographically estimated parameters underlying the definition of PH subtypes showed statistical significant correlations with the characteristics of HF phenotypes, noting a moderate positive interdependence between PAWP and NT-proBNP (r = 0.492, p<0.001), as well as a significant negative interrelation of mPAP (r= -0.332, p<0.001) and PVR (r = -0.390, p<0.001) with LVEF and positive correlations with NT-proBNP (r = 0.390, p<0.001 – for both).

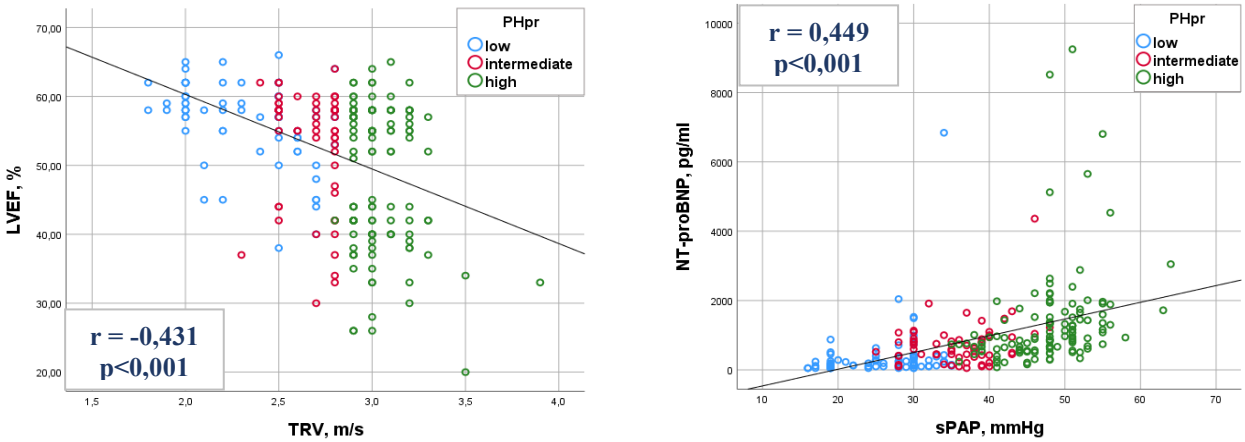


Figure 7. Correlation between TRV and LVEF and between sPAP and NT-proBNP

Note: LVEF – left ventricular ejection fraction, NT-proBNP – N-terminal pro-brain natriuretic peptide fragment, sPAP – pulmonary artery systolic pressure, TRV – tricuspid valve regurgitation velocity.

The functional capacity, evaluated through the distance covered during the 6MWT, was gradually reduced according to PH probability (high PHpr: 294.64±7.95 m, intermediate PHpr: 308.55±9.47 m, low PHpr: 332.65±6.34 m, p=0.001).

The exercise capacity, expressed by VO_2p related to the predicted maximum value and body mass, was lower in patients with echocardiographic signs of PH. Oxygen pulse and

circulatory power were reduced in these subjects, with an early onset of anaerobic threshold being recorded (Table 2). On the other hand, we identified a clear ventilatory inefficiency in patients with echocardiographic signs of PH, expressed by a gradually increased VE/VCO_2 slope, reduced values of ventilatory power and end-tidal CO_2 pressure ($PetCO_2$). The rate of patients exhibiting exercise oscillatory ventilation pattern was significantly higher in these subjects (Table 2).

Table 2. CPET performance depending on PH probability

Parameters	Low PHpr (n=87)	Intermediate PHpr (n=49)	High PHpr (n=61)	F	p
VO_2p, ml/min	1241,18 ± 33,60	1157,41 ± 49,66	1121,61 ± 40,68	2,65	0,073
VO_2%pred, %	59,72 ± 1,36	55,39 ± 1,95	51,98 ± 1,49	6,86	**0,001**
VO_2p/kg, ml/min/kg	15,20 ± 0,39	13,48 ± 0,53	11,96 ± 0,40	15,44	**<0,001**
VO_2 pulse, %	85,55 ± 1,87	81,44 ± 2,65	76,47 ± 2,35	4,53	**0,012**
Anaerobic threshold, %	50,31 ± 1,72	47,18 ± 2,22	39,05 ± 1,62	10,22	**<0,001**
Circulatory power, mmHg*ml/min/kg	2298,89 ± 71,33	2103,26 ± 105,16	1824,97 ± 82,32	8,78	**<0,001**
RER	1,05 ± 0,01	1,05 ± 0,01	0,98 ± 0,01	8,01	**<0,001**
Ventilatory parameters:					
VE/VCO_2	31,15 ± 0,43	35,22 ± 0,58	36,23 ± 0,50	33,06	**<0,001**
Ventilatory power	4,95 ± 0,11	4,46 ± 0,13	4,21 ± 0,11	10,44	**<0,001**
$PetCO_2$, mmHg	38,19 ± 0,50	33,83 ± 0,56	33,57 ± 0,41	29,33	**<0,001**
Exercise oscillatory ventilation, % (n)	32,2% (28)	75,5% (37)	86,9% (53)	-	**<0,001**

Note: $PetCO_2$ – end-tidal carbon dioxide pressure, PHpr – echocardiographic probability of pulmonary hypertension, RER – respiratory exchange ratio, CPET – cardiopulmonary exercise testing, VE/VCO_2 – ventilatory equivalent for carbon dioxide, VO_2p - peak oxygen uptake, VO_2%pred - achieved peak oxygen uptake relative to maximal predicted value, VO_2p/kg – peak oxygen uptake related to body mass.

Evolution of the parameters defining the echocardiographic probability of PH 12 months following myocardial revascularization

The prevalence of PH at 12 months after myocardial revascularization was 67.6% (180 pts), increasing by +9.5% compared to the initial stage of the study. Analyzing the evolution of PH probability during follow-up, we observed a +12.7% increase in the proportion of patients with high PHpr, due to a reduction in the rate of those with intermediate (-3.3%) and low (-9.5%) PH probability (Figure 8).

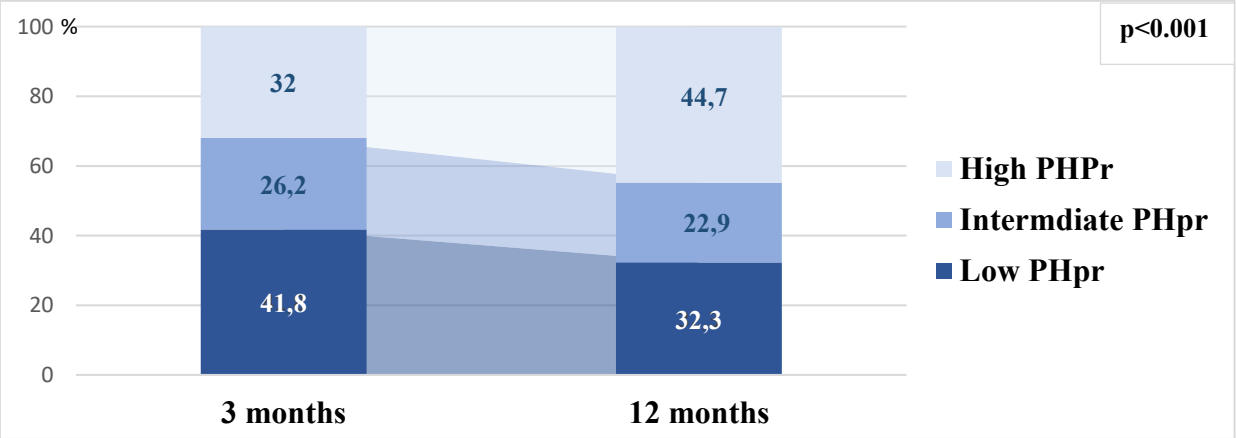


Figure 8. Evolution of the echocardiographic probability of PH 12 months after myocardial revascularization, %

Note: PH – pulmonary hypertension, PHpr – echocardiographic probability of pulmonary hypertension.

Analyzing specifically the parameters defining PH echocardiographic probability that contributed to its negative evolution, we observed an important increase in right atrium area (+2.22±0.42 cm², p<0.001), a marked reduction in RVOT AT (-7.63±1.25 ms, p<0.001) and TAPSE/sPAP ratio (-0.02±0.01 mm/mmHg, p<0.05), while TRV did not change significantly at the cohort level (Figure 9).

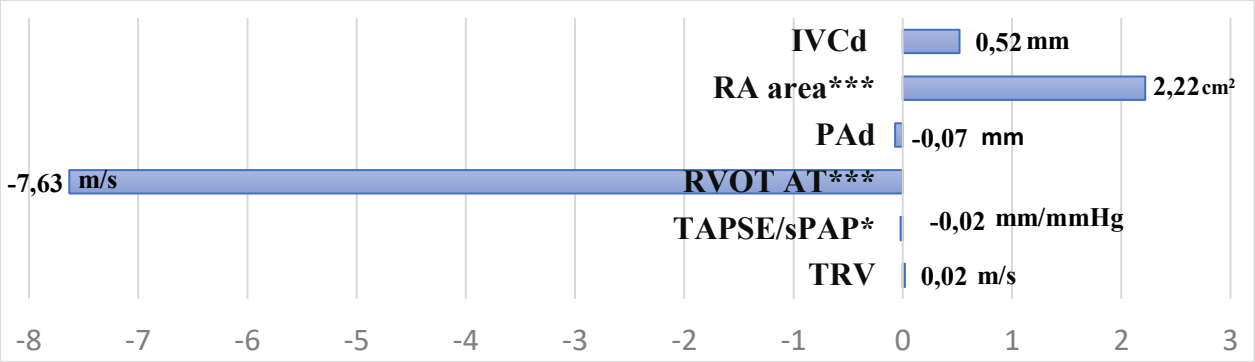


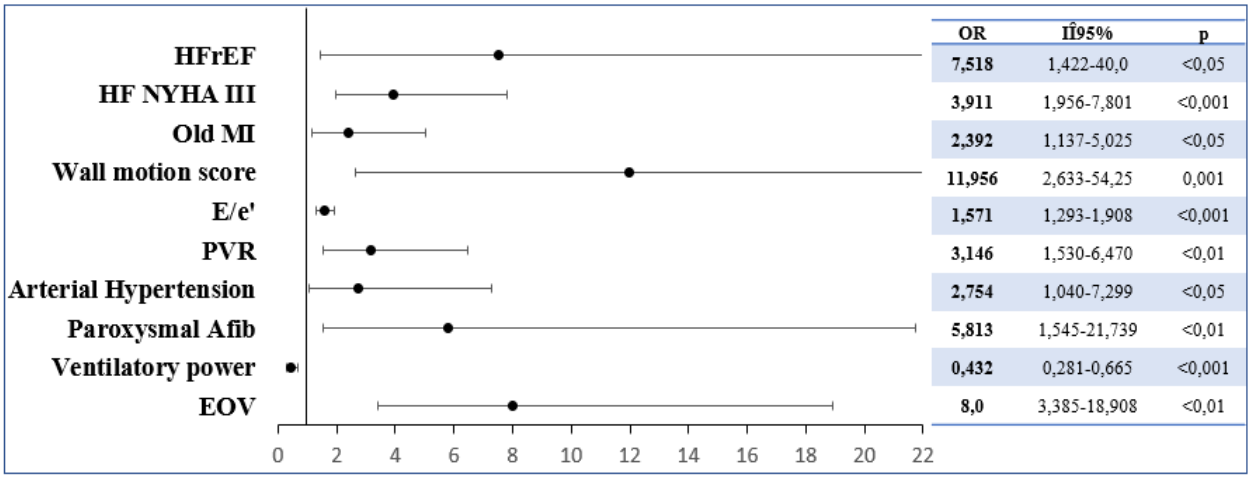
Figure 9. Evolution of the parameters defining the echocardiographic probability of PH.

*Note: * - p<0.05, *** - p<0.001 – statistical significance of parameter dynamics at the cohort level.. IVCd – inferior vena cava diameter, PAd – pulmonary artery diameter, RA – right atrium, RVOT AT – right ventricular outflow tract acceleration time, sPAP – pulmonary artery systolic pressure, TAPSE – tricuspid annular plane systolic excursion, TRV – peak velocity of tricuspid regurgitation.*

The proportion of the CpcPH subtype increased by +5.3% during follow-up, reaching 16.2% (42 cases), while the rate of IpcPH rose by +8.4%, reaching 51.7% (134 cases). The increase in postcapillary PH subtypes was driven by a negative and statistically significant evolution of mPAP (+2.92±0.56 mmHg, p < 0.001) and PVR (+0.24±0.04 WU, p < 0.001).

Progression of the echocardiographic probability of PH 12 months after myocardial revascularization

At the 12-month stage after myocardial revascularization, 81 patients (30.45%) were identified with newly developed echocardiographic signs of PH or who progressed from the intermediate to high PH probability group. The predictors that influenced the progression of the echocardiographic probability of PH during the follow-up period are presented in figure 10.



	OR	ÏÎ95%	p
HFrEF	7,518	1,422-40,0	<0,05
HF NYHA III	3,911	1,956-7,801	<0,001
Old MI	2,392	1,137-5,025	<0,05
Wall motion score	11,956	2,633-54,25	0,001
E/e'	1,571	1,293-1,908	<0,001
PVR	3,146	1,530-6,470	<0,01
Arterial Hypertension	2,754	1,040-7,299	<0,05
Paroxysmal Afib	5,813	1,545-21,739	<0,01
Ventilatory power	0,432	0,281-0,665	<0,001
EOV	8,0	3,385-18,908	<0,01

Figure 10. Prognostic factors for progression of PH echocardiographic probability 12 months after myocardial revascularization

Note: Afib – atrial fibrillation. E/e' - Early diastolic transmitral flow velocity divided by early diastolic mitral annular velocity, EOV – exercise oscillatory ventilation, HF- heart failure, HFrEF – Heart failure with reduced ejection fraction, LVEDD – Left ventricular end-diastolic diameter, MI –myocardial infarction, NYHA – New York Heart Association, PVR – Pulmonary vascular resistance

Discriminant analysis revealed six parameters: age, presence of atrial fibrillation, glomerular filtration rate, right atrium diameter, HF phenotype and duration of hospitalization for cardiac rehabilitation after the acute cardiac event, which constituted the foundational dataset for developing the „*Prediction model for the progression of echocardiographic probability of pulmonary hypertension in patients with ischemic heart failure 12 months after myocardial revascularization"* with a positive predictive value of 74.07%.

Referring to the group of patients who developed PH during the follow-up period compared to those without signs of PH, the following predictive factors were identified: mPAP (OR=1.097, CI=1.029–1.169, p<0.01), RVOT AT (OR=0.968, CI=0.942–0.995, p<0.05), HFrEF phenotype (OR=8.333, CI=1.344–52.631, p<0.01), NYHA III functional class (OR=3,211, IÎ=1,445-7,207, p<0,01), LVEF (OR=0.930, CI=0.883–0.979, p<0.01), LV end-diastolic diameter (OR=1.129, CI=1.024–1.246, p<0.05) and left atrium diameter (OR=1.130, CI=1.025–1.246, p<0.05).

Thus, analyzing the identified prognostic determinants, we conclude that the probable mechanism underlying the onset or progression of PH echocardiographic probability was driven by LV systolic and diastolic dysfunction, preexisting early changes in the pulmonary circulation, CV and non-CV comorbidities.

3.3. Evolution of right ventricular function parameters over 12 months following myocardial revascularization

Prevalence of RVD in the cohort was 39.27% (108 pts), 69.2% (72 pts) of which had RVD without signs of RV failure and 30.8% (36 pts) presented early signs of RV failure. Patients with RVD were older (65.88±0.81 years vs 61.34±0.70 years, p<0.001), with a homogenous distribution by gender. They had a significantly longer history of CAD compared to patients without RVD signs (2.09±0.36 years vs 0.9±0.17 years, p<0.01), and more frequently presented with MI (50.9%, 55 pts vs 29.3%, 49 pts, χ^2=12.99, p<0.001) and LV aneurysm (30.3%, 23 pts vs 11.6%, 14 pts, χ^2=10.69, p=0.001). The rate of inferior or anteroseptal wall MI was similar in patients with and without RVD (χ^2=5.98, p=0.050). Patients with impaired RV function were predominantly revascularized by CABG (72.2%, 78 pts vs 43.1%, 72 pts, χ^2=22.41, p<0.001), while the complexity of the cardiac surgery was homogenous between groups (χ^2=7.52, p=0.057). The structure of comorbidities in patients with RVD was characterized by higher proportions of arterial hypertension, atrial fibrillation, anemia and chronic kidney disease, with their burden confirmed by a higher CCI (Table 3).

Tabel 3. Distribution of patients with RVD according to comorbidities

Parameters		**RVD (n=108)**	**Non-RVD (n=167)**	**χ^2**	**p**
Arterial hypertension, % (n)		93,5% (101)	82,6% (138)	6,82	**0,006**
Atrial Fibrillation, % (n)	Permanent	17,6% (19)	4,2% (7)	20,28	**<0,001**
	Paroxysmal	25,0% (27)	15,6% (26)		
Stroke, % (n)		8,3% (9)	3,0% (5)	4,79	**0,047**
Obesity, % (n)		45,4% (49)	42,5% (71)	0,21	0,366
Anemia, % (n)		18,7% (20)	6,6% (11)	9,52	**0,002**
Diabetes mellitus, % (n)		37,0% (40)	29,3% (49)	1,77	0,115
Chronic kidney disease, % (n)		22,2% (24)	12,0% (20)	11,341	**0,010**
Charlson Comorbidity Index, points		3,99 ± 0,15	3,24 ± 0,12	-	**<0,001**

Analyzing the functional capacity of patients with RVD, we noted a shorter distance covered during the 6MWT compared to the control group (291.01±7.22 m vs 329.41±5.51 m, p<0.001).

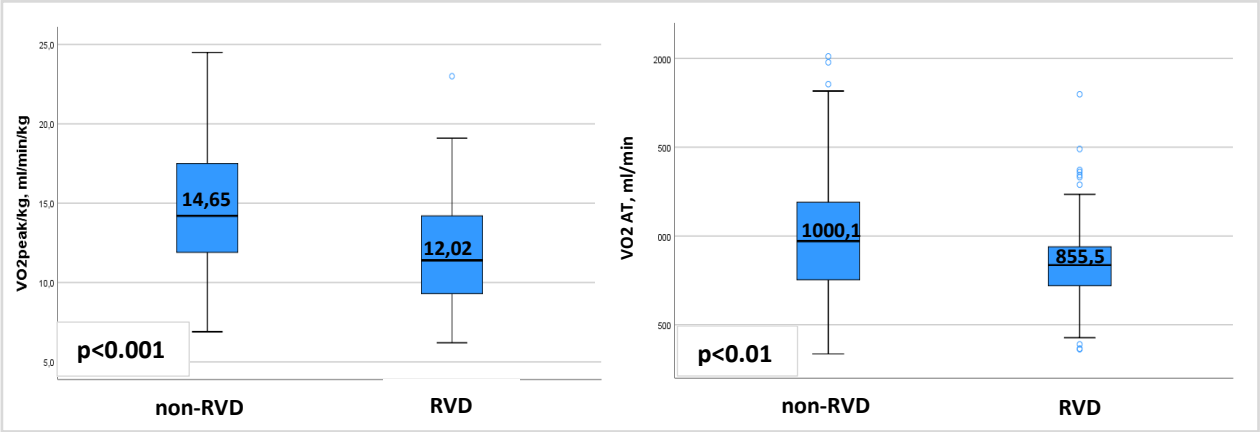


Figura 11. VO_2p/kg (ml/min/kg) and VO_2 determined at the anaerobic threshold (ml/min) in patients with RVD compared to the control group (n=197)

Note: AT – anaerobic threshold, VO_2p/kg - peak oxygen uptake related to body weight

The cardiometabolic profile of patients with RVD showed lower VO_2p both in absolute value and when adjusted for body weight and predicted maximal VO_2, an early onset of the anaerobic threshold and reduced oxygen pulse (Figure 11). Additionally, ventilatory efficiency was impaired, as reflected by elevated VE/VCO_2 slope, decreased ventilatory power and $PetCO_2$, with more frequent occurrence of exercise oscillatory ventilation (Table 4).

Tabel 4. Ventilatory parameters assessed during CPET according to the presence of RVD

Parameters	DVD (n=66)	Non-DVD (n=131)	p
VE/VCO_2 at maximal exercise	36,59 ± 0,50	32,30 ± 0,36	**<0,001**
VE/VCO_2 at anaerobic threshold	38,00 ± 0,63	32,82 ± 0,38	**<0,001**
Ventilatory power	4,04 ± 0,1	4,88 ± 0,08	**<0,001**
$PetCO_2$, mmHg	33,0 ± 0,42	37,03 ± 0,40	**<0,001**
Exercise oscillatory ventilation, % (n)	87,9% (58)	45,8% (60)	**<0,001**

Note: RVD - right ventricular dysfunction, $PetCO_2$ - end-tidal carbon dioxide pressure, CPET - cardiopulmonary exercise test, VE/VCO_2 - ventilatory equivalent for carbon dioxide.

The evolution of RVD 12 months following myocardial revascularization

The prevalence of RVD at 12 months after myocardial revascularization increased by +10%, reaching 49.2% (131 pts), of which 70.8% (92 pts) had RVD without RV failure, while 28.5% (37 pts) showed signs of early RV failure. During follow-up, we observed that 24% (25 pts) of patients with RVD at stage T-3 experienced improvement in RV function by the end of the study, whereas 32.1% (52 pts) of those without RVD at baseline showed deterioration of RV function 12 months after myocardial revascularization ($\chi^2 = 48.75$, $p < 0.001$) (Figure 12).

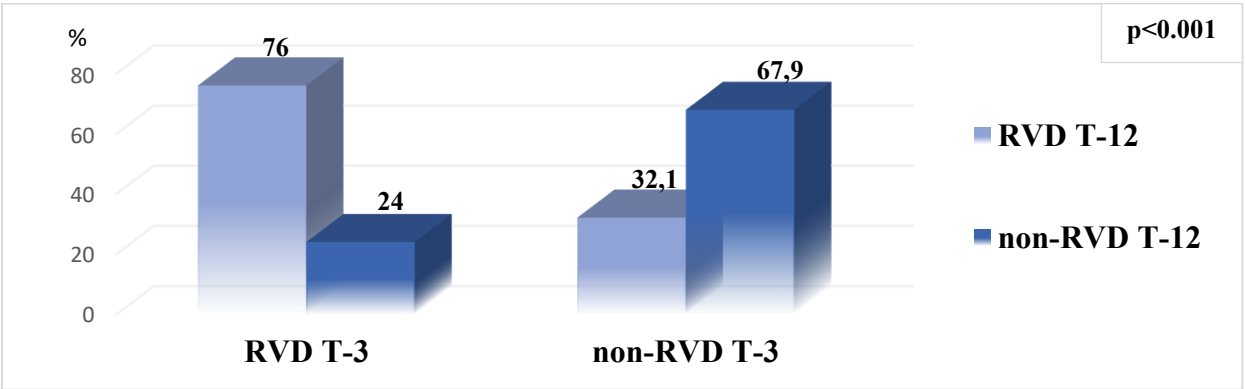


Figure 12. Evolution of RVD 12 months after myocardial revascularization, % (n=266)

The increase in RVD prevalence at the cohort level during the monitoring period occurred as a result of the negative progression of certain echocardiographic parameters characterizing RV morphology and function, such as TAPSE, RV S' and RV free wall thickness (Figure 13).

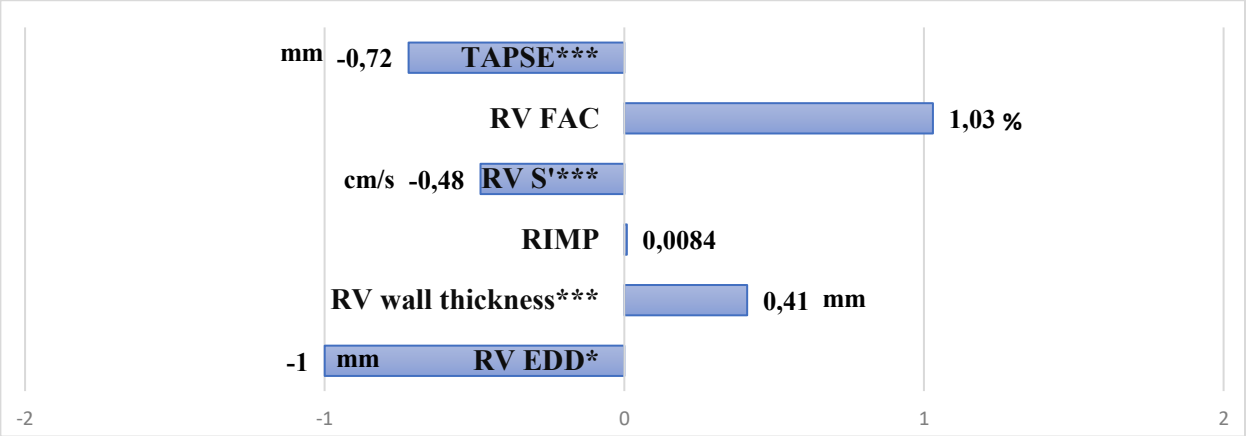


Figure 13. **Dynamics of the structural and functional echocardiographic parameters defining RVD 12 months after myocardial revascularization (n=266)**

*Note: *-p<0.05, **-p<0.01, ***-p<0.001 – statistical significance of parameter dynamics at the cohort level. RIMP – right ventricular index of myocardial performance, RV EDD – right ventricular end-diastolic diameter, RV FAC – right ventricular fractional area change, RV S' – peak systolic velocity at the lateral tricuspid annulus, TAPSE – tricuspid annular plane systolic excursion.*

Prognostic determinants of RVD development 12 months after myocardial revascularization

At the T-12 stage, de novo RVD was identified in 53 patients (19.9%) of the study population. The prognostic factors determining RVD development 12 months following myocardial revascularization are presented in the Figure 14.

Discriminant analysis revealed 4 variables: duration of CAD, NYHA functional class of HF, right atrium diameter and left ventricular end-diastolic diameter, which constituted the foundational dataset for developing the „*Prediction model for the development of right ventricular dysfunction in patients with ischemic heart failure 12 months after myocardial revascularization*", with a positive predictive value of 63,4%.

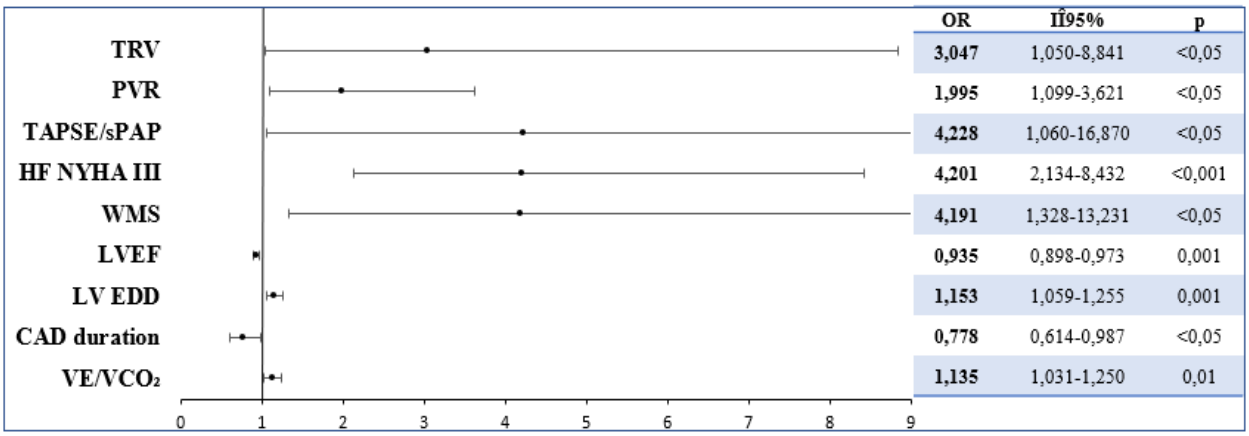


Figure 14. Prognostic determinants of RVD development 12 months after myocardial revascularization

Note: CAD – coronary artery disease, LV EDD – left ventricular end-diastolic diameter, LVEF – left ventricular ejection fraction, HF – heart failure, NYHA – New York Heart Association, sPAP – pulmonary artery systolic pressure, PVR – pulmonary vascular resistance, TAPSE – tricuspid annular plane systolic excursion, TRV – peak tricuspid regurgitation velocity, VE/VCO₂ – ventilatory equivalent for carbon dioxide, WMS – wall motion score.

3.4. Comparative analysis of the evolution of pulmonary hypertension and biventricular dysfunction in relation to the type of myocardial revascularization

3.4.1. Evolution of pulmonary hypertension according to the type of myocardial revascularization 12-months after the acute event

At baseline the prevalence of PH in the CABG group was 65.4% (98 pts), while in the post-PCI group the PH rate was 49.6% (62 pts), p<0.05. The proportion of high PHpr was significantly greater in patients with CABG compared to PCI (36.7%, 55 pts vs 26.4%, 33 pts, χ^2=7.06, p<0.05) (Figure 15). At 12 months after myocardial revascularization, the prevalence of PH increased by +10.7% in the CABG group, reaching 76.1% (112 pts), while in the PCI group the PH rate rose by +7.5%, achieving 57.1% (68 pts). In both groups, the proportion of patients with high PHpr increased steadily, this trend being more pronounced among those who underwent CABG.

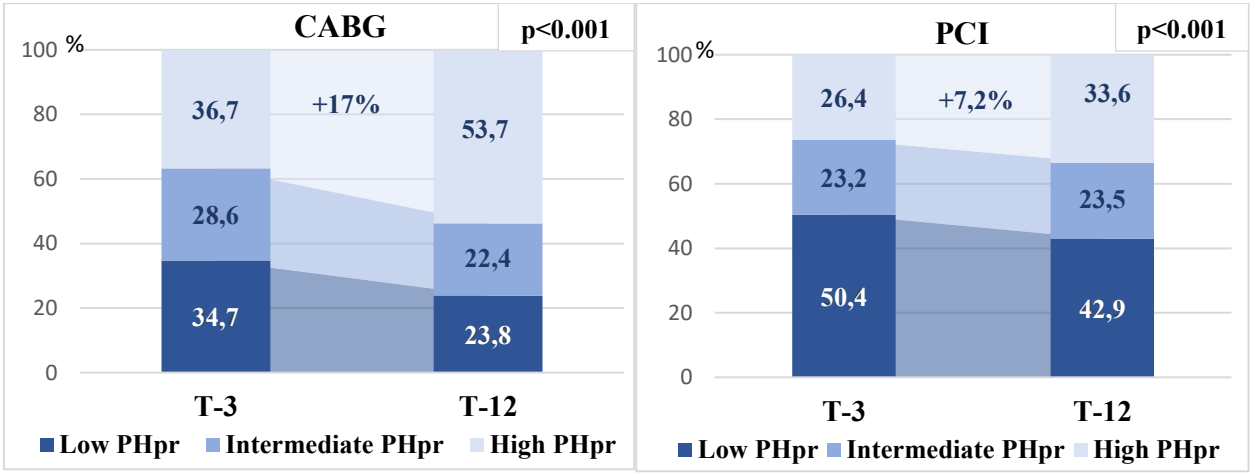


Figure 15. Evolution of the echocardiographic probability of PH according to the type of myocardial revascularization over 12 months after the acute event, %

The echocardiographic parameters whose dynamics accounted for the distinct evolution of PH in patients undergoing CABG were: TRV, right atrium area and TAPSE/sPAP ratio (Table 5).

Table 5. Evolution of echocardiographic parameters defining the probability of PH according to the type of myocardial revascularization

Parameter	Study stage	CABG (n=150)	PCI (n=125)	p_{1-2}
TRV, m/s	T-3	2,73 ± 0,02	2,66 ± 0,03	0,085
	T-12	2,80 ± 0,02** ′	2,63 ± 0,03 ′	**0,002**
sPAP, mmHg	T-3	37,95 ± 0,80	35,06 ± 0,93	**0,019**
	T-12	40,37 ± 0,83**	35,27 ± 1,07	**<0,001**
RVOT AT, ms	T-3	104,97 ± 1,89	111,32 ± 2,18	**0,029**
	T-12	96,72 ± 1,55***	104,95 ± 2,07**	**0,002**
Pulmonary artery diameter, mm	T-3	26,23 ± 0,25	25,06 ± 0,26	**0,002**
	T-12	25,97 ± 0,22	25,21 ±0,27	**0,031**
IVC diameter, mm	T-3	20,04 ± 0,24	19,12 ± 0,32	0,920
	T-12	21,10 ± 0,30**	19,02 ± 0,39	**<0,001**
Right atrium area, cm^2	T-3	21,57 ± 0,47	20,60 ± 0,47	0,149
	T-12	24,78 ± 0,57*** ‴	21,66 ± 0,52 ‴	**<0,001**
TAPSE/sPAP, mm/mmHg	T-3	0,49 ± 0,01	0,60 ± 0,01	**<0,001**
	T-12	0,45 ± 0,01** ″	0,59 ± 0,02 ″	**<0,001**

Note: p1-2 – validity of the differences between groups at the same stage, where: 1 – CABG, 2 - PCI.
- p<0.05, ** - p<0.01, * - p<0.001 – validity of the dynamics between T-3 and T-12 within the same group.*
′ - p<0.05, ″ - p<0.01, ‴ - p<0.001 – validity of the dynamics between patient groups.

The proportion of IpcPH (47.9%, 67 pts vs 42.3%, 52 pts) and CpcPH (15.0%, 21 pts vs 7.3%, 9 pts) was statistically significantly higher at baseline in patients who underwent CABG compared to those post-PCI (χ^2=6.49, p<0.05). The percentage of patients with CpcPH increased during the follow-up period more notably in the PCI group (+6.4%) compared to the CABG group (+3.3%). On the other hand, the proportion of IpcPH increased mainly in patients post-CABG (+10.2%) compared to those post-PCI (+1.9%), in the context of similar negative dynamics of mPAP and PVR (Table 6).

Tabel 6. Evolution of mPAP, PAWP and PVR estimated by echocardiography over 12 months after the acute event in relation to the type of myocardial revascularization

Parameter	Study stage	CABG (n=150)	PCI (n=125)	p_{1-2}
mPAP, mmHg	T-3	31,90 ± 0,83	28,55 ± 0,99	**0,011**
	T-12	35,37 ± 0,71***	30,74 ± 0,98*	**<0,001**
PAWP, mmHg	T-3	16,01 ± 0,32	14,38 ± 0,26	**<0,001**
	T-12	16,02 ± 0,22	15,07 ± 0,25*	**0,005**
PVR, WU	T-3	1,48 ± 0,05	1,37 ± 0,07	0,196
	T-12	1,72 ± 0,05***	1,60 ± 0,06***	0,152

Note: p1-2 – validity of the differences between groups at the same stage, where: 1 - CABG, 2 – PCI.
- p<0.05, ** - p<0.01, * - p<0.001 – validity of the dynamics between stages T-3 and T-12 within the same group.*
CABG – coronary artery bypass grafting, PAWP – pulmonary artery wedge pressure, PCI – percutaneous coronary intervention, mPAP – mean pulmonary artery pressure, PVR – pulmonary vascular resistance, WU – Wood units.

3.4.2. Evolution of right ventricular dysfunction in relation to the type of myocardial revascularization 12 months after the acute event

The prevalence of RVD at 3 months after myocardial revascularization was higher in patients who underwent CABG (52.0%, 78 pts) compared to those post-PCI (24.0%, 30 pts), χ^2=22.41, p<0.001. During the follow-up period, the proportion of RVD increased by +5.1% in post-CABG patients, reaching 57.1% (84 pts), while in subjects who underwent PCI it rose by +15.5%, reaching 39.5% (47 pts), χ^2=8.19, p<0.01 (Figure 16).

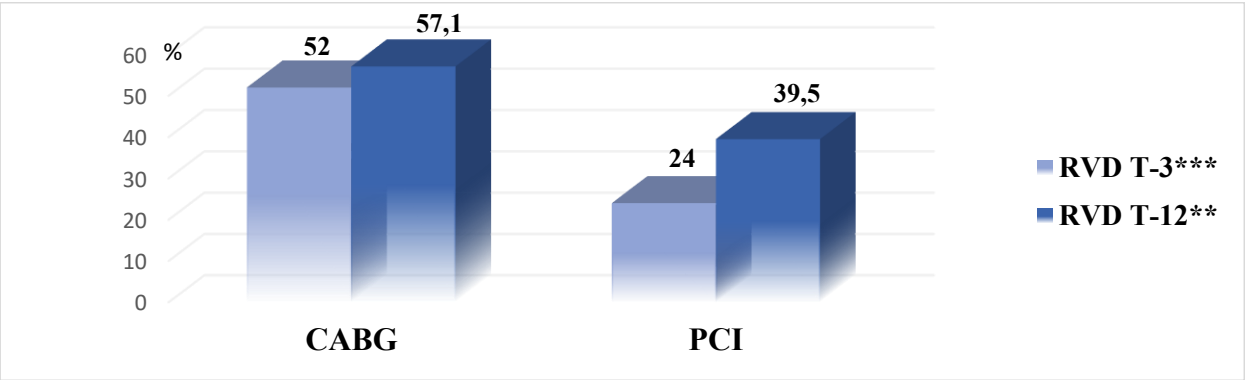


Figure 16. Evolution of RVD in relation to the type of myocardial revascularization 12 months after the acute event, %

*Note: ***-p<0.001, **-p<0.01-significance of the difference between groups at T-3 and T-12, respectively.*
CABG – coronary artery bypass grafting, PCI - percutaneous coronary intervention.

The evolution of RVD was determined by the distinct dynamics between groups of the following echocardiographic parameters: RV S' (p<0.001) and RIMP (p<0.05), which did not change in the post-CABG group, but recorded a statistically significant negative trend in the post-PCI group. The RV end-diastolic diameter decreased significantly in patients who underwent surgical myocardial revascularization and did not change in those with PCI (p<0.01), while RV free wall thickness increased predominantly in the CABG group (p<0.05) (Table 7).

Table 7. Dynamics of RV echocardiographic parameters in relation to the type of myocardial revascularization.

Parameter	Study stage	CABG (n=150)	PCI (n=125)	p_{1-2}
RV end-diastolic diameter, mm	T-3	40,64 ± 0,47	38,69 ± 0,49	**0,005**
	T-12	38,98 ± 0,50* ′′	38,33 ± 0,52 ′′	0,373
RV free wall thickness, mm	T-3	4,63 ± 0,06	4,58 ± 0,05	0,578
	T-12	5,17 ± 0,06 ′	4,86 ± 0,07 ′	**0,002**
TAPSE, mm	T-3	17,36 ± 0,24	19,53 ± 0,34	**<0,001**
	T-12	17,08 ± 0,18	18,42 ± 0,30***	**<0,001**
RV FAC, %	T-3	38,15 ± 0,85	41,11 ± 0,75	**0,010**
	T-12	36,56 ± 0,77	40,89 ± 1,02	**0,001**
RV S', cm/s	T-3	9,79 ± 0,14	11,21 ± 0,25	**<0,001**
	T-12	9,61 ± 0,11 ′′′	10,41 ± 0,18** ′′′	**<0,001**
RIMP	T-3	0,47 ± 0,01	0,38 ± 0,01	**<0,001**
	T-12	0,46 ± 0,01 ′	0,41 ± 0,01* ′	**0,012**

Note: p1-2 – validity of differences between groups at the same stage, where: 1 - CABG, 2 - PCI.
- p<0.05, ** - p<0.01, * - p<0.001 – validity of dynamics between T-3 and T-12 within the same group.*
′ - p<0.05, ′′ - p<0.01, ′′′ - p<0.001 – validity of dynamics between patient groups.
RV FAC –Right ventricular fractional area change, RIMP – Right ventricular index of myocardial performance, RV S′ – Peak systolic velocity at the lateral tricuspid annulus, TAPSE – Tricuspid annular plane systolic excursion, RV – Right ventricle.

3.4.3. The evolution of left ventricular parameters in relation to the type of myocardial revascularization over 12 months following the acute event

At the initial stage of the study, patients categorized according to the type of myocardial revascularization presented a similar distribution based on HF phenotype (CABG: HFpEF - 63.3%, 95 pts; HFmrEF - 15.3%, 23 pts; HFrEF - 21.3%, 32 pts; PCI: HFpEF - 64.8%, 81 pts; HFmrEF - 16.8%, 21 pts; HFrEF - 18.4%, 23 pts, χ^2=0.40, p>0.05). During the monitoring period, the proportion of HFpEF increased in both groups: by +8.8% in patients post-CABG and by +5.8% in patients post-PCI, while the rate of HFrEF decreased by -5% in each group and the percentage of HFmrEF slightly reduced (CABG: -3.7%, PCI: -0.8%). The distribution of patients by HF phenotype remained homogeneous at the end of the study.

Tabel 8. Evolution of left ventricular echocardiographic parameters according to the type of myocardial revascularization over 12 months following the acute event

Parameter	Stage	CABG (n=150)	PCI (n=125)	p_{1-2}
LV ESD, mm	T-3	37,15 ± 0,65	35,32 ± 0,63	**0,045**
	T-12	37,94 ± 0,69	36,52 ± 0,64	0,134
LV EDD, mm	T-3	54,25 ± 0,43	53,04 ± 0,42	**0,049**
	T-12	54,64 ± 0,47	53,04 ± 0,49	**0,021**
LV ESV, ml	T-3	77,83 ± 2,56	71,72 ± 2,60	0,095
	T-12	70,85 ± 2,57**	67,62 ± 2,58	0,377
LV EDV, ml	T-3	150,32 ± 2,92	144,92 ± 3,30	0,221
	T-12	144,08 ± 3,12*	135,72 ± 3,24**	0,065
LVEF, %	T-3	50,01 ± 0,80	51,15 ± 0,84	0,328
	T-12	52,37 ± 0,76***	52,45 ± 0,85*	0,945

Note: p1-2 – validity of differences between groups at the same stage, where: 1 - CABG, 2 - PCI.
*p<0.05, ** - p<0.01, *** - p<0.001 – validity of dynamics between stages T-3 and T-12 within the same group.*
LVEDD- Left ventricular end-diastolic diameter, LVESD- Left ventricular end-systolic diameter, LVEF- Left ventricle ejection fraction, LV EDV- Left ventricular end-diastolic volume, LV ESV- Left ventricular end-systolic volume.

NT-proBNP was higher in the CABG group compared to the PCI group at 3 months after myocardial revascularization (1292±164.57 pg/ml vs 784.62±111.34 pg/ml, p<0.05). During the monitoring period, a reduction in NT-proBNP was observed in the CABG group (-282.95±155.39 pg/ml, p=0.05), while no significant change was noted in the PCI group. Consequently, at T-12, the difference between the groups became statistically insignificant (CABG: 1011.47±92.29 pg/ml vs PCI: 739.25±114.44 pg/ml, p<0.05).

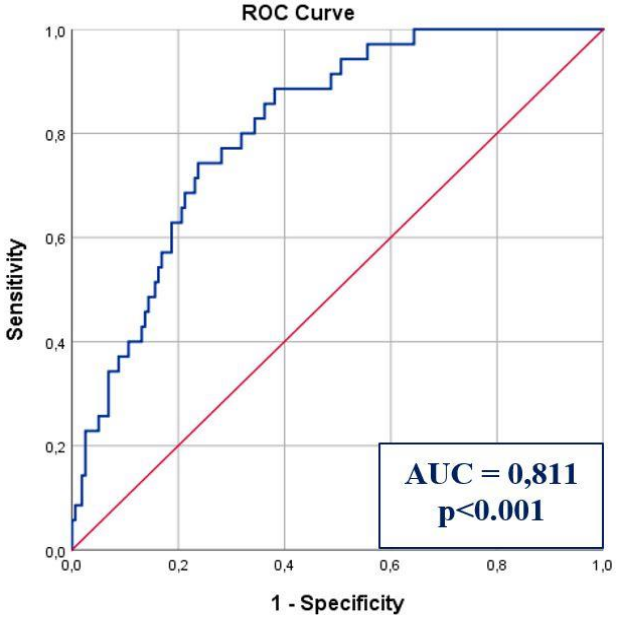
LVEF, determined at the early stage of the study, was comparable regardless of the type of myocardial revascularization (CABG: 50.01±0.80% vs PCI: 51.15±0.84%, p>0.05). It increased significantly in both groups during the follow-up period, with a more pronounced magnitude in patients who underwent CABG (+2.19±0.62%, p<0.001) compared to those post-PCI (+1.24±0.69%, p<0.05). The LVEF values were similar at the end of the research (52.37±0.76% vs 52.45±0.85%, p>0.05).

The evolution of LV echocardiographic parameters is presented in Table 8, showing a positive dynamic of both telesystolic and telediastolic volumes in patients who underwent myocardial revascularization, either by CABG or PCI.

3.5. The prognosis of patients with ischemic heart failure

HF hospitalizations

The HF hospitalization rate during the first year after myocardial revascularization was 18.1% at the cohort level. As a result of discriminant analysis, two methods for predicting the risk of HF hospitalization 12 months after myocardial revascularization were developed. One of these methods: „*Prediction method based on clinical parameters for the risk of heart failure hospitalization during the first year after myocardial revascularization*" involves 9 clinical parameters presented in Table 9, showing a good discriminatory performance: AUC 0.811 (95%CI=0.743–0.879, p<0.001, Figure 17), ensuring correct prediction of HF-related hospitalization in 74.3% of cases and the absence of hospitalization in 75.6% of cases.



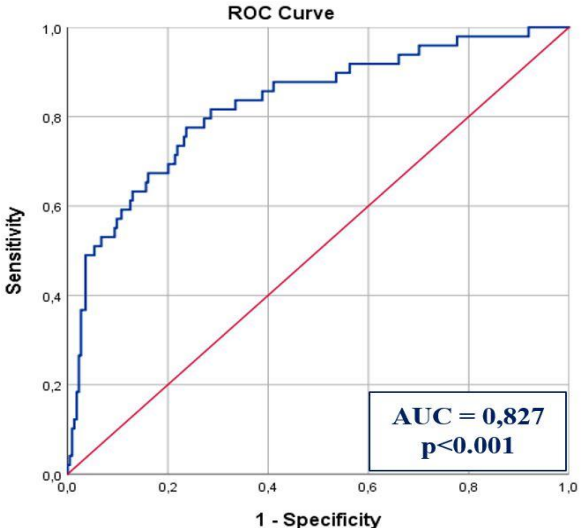
Tabel 9. Clinical predictors of HF hospitalization

Parameter		HF Hosp +	HF Hosp -	p
Age, years		66,060±0,94	62,47±0,62	<0,01
Males, %		82,0	78,2	0,352
CAD history, years		2,72±0,66	1,07±0,15	<0,05
Old MI, %		52,0	34,7	<0,05
LV aneurysm, %		40,0	14,2	0,001
Diabetes mellitus, %		44,0	29,8	<0,05
CKD stage KDIGO, %	G1	26,0	42,2	<0,05
	G2	52,0	43,1	
	G3a, b	16,0	13,8	
	G4	6,0	0,9	
CCI, points		4,36±0,26	3,35±0,10	0,001
Index hosp., days		10,26±0,58	8,71±0,24	<0,05

Figure 17. ROC curve and predictors included in the prognostic method based on clinical parameters for predicting the risk of HF hospitalization 12 months after myocardial revascularization

Note: CAD – coronary artery disease, CKD - chronic kidney disease, CCI - Charlson Comorbidity Index, Hosp. – hospitalization, MI - myocardial infarction, KDIGO - The Kidney Disease: Improving Global Outcomes.

Another method for predicting the risk of HF hospitalization 12 months after myocardial revascularization was based on 7 variables, as shown in Table 10. The "*Prediction method for the risk of heart failure hospitalization during the first year after myocardial revascularization*" exhibited superior prognostic performance: AUC=0.827 (95%CI=0.759-0.895, p<0.001, Figure 18), and its application correctly predicted HF hospitalization in 75.5% of cases and the absence of HF hospitalization in 76.8% of cases.



Tabel 10. Predictors of HF hospitalization

Parameter	HF Hosp +	HF Hosp -	p
Hemoglobin, g/l	129,04±1,7	137,19±0,7	<0,001
eGFR, ml/min/1.73m^2	74,44 ± 3,1	85,37 ± 1,6	<0,01
LVEF, %	43,46 ± 1,5	52,10 ± 0,5	<0,001
TRV, m/s	2,88 ± 0,05	2,65 ± 0,02	<0,001
RV EDD, mm	42,63 ± 0,8	39,12 ± 0,3	<0,001
TAPSE/sPAP, mm/mmHg	0,39 ± 0,02	0,57 ± 0,01	<0,001

Figure 18. ROC curve and predictors included in the prognostic method for assessing the risk of HF hospitalization 12 months after myocardial revascularization

Note: eGFR - estimated glomerular filtration rate, LVEF - left ventricular ejection fraction, RV EDD – right ventricular end-diastolic diameter, sPAP - systolic pulmonary artery pressure, TAPSE - tricuspid annular plane systolic excursion, TRV - peak velocity of tricuspid regurgitation.

Composite endpoint: all-cause mortality and HF-hospitalization

Taking into account the low mortality rate among outpatients with ischemic HF and myocardial revascularization observed in our study (4 patients deceased during follow-up), we considered it appropriate to establish a composite endpoint: all-cause mortality and HF hospitalization. We identified multiple risk factors associated with this outcome, among which we highlight the impact of high PH probability, CpcPH subtype, TRV and PVR, as well as the decisive prognostic role of RVD, along with: TAPSE, RV S', RIMP (Figure 19).

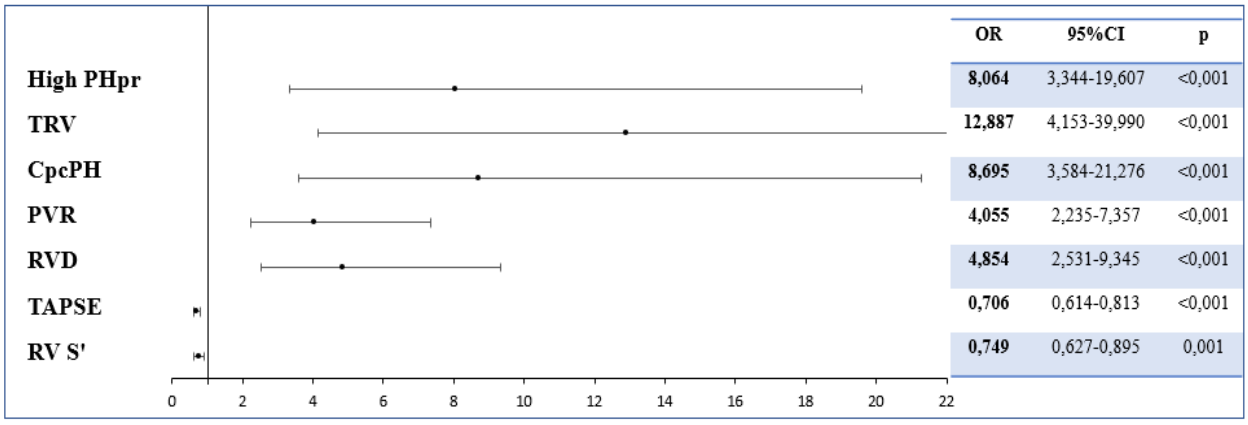


Figure 19. Impact of PH and RVD on the risk of the composite endpoint: all-cause mortality and HF hospitalization

Note: CpcPH- combined post- and precapillary pulmonary hypertension, PHpr- echocardiographic probability of pulmonary hypertension, PVR- pulmonary vascular resistance, RVD- right ventricular dysfunction, RV S'- peak systolic velocity at the lateral tricuspid annulus, TAPSE- tricuspid annular plane systolic excursion, TRV- tricuspid regurgitation velocity.

Worsening heart failure

The proportion of patients with ischemic HF and myocardial revascularization who experienced episodes of WHF was 21.0% at the cohort level. The multivariate statistical analysis highlighted multiple prognostic factors for the occurrence of these episodes during the follow-up, with the most relevant ones shown in the Figure 20.

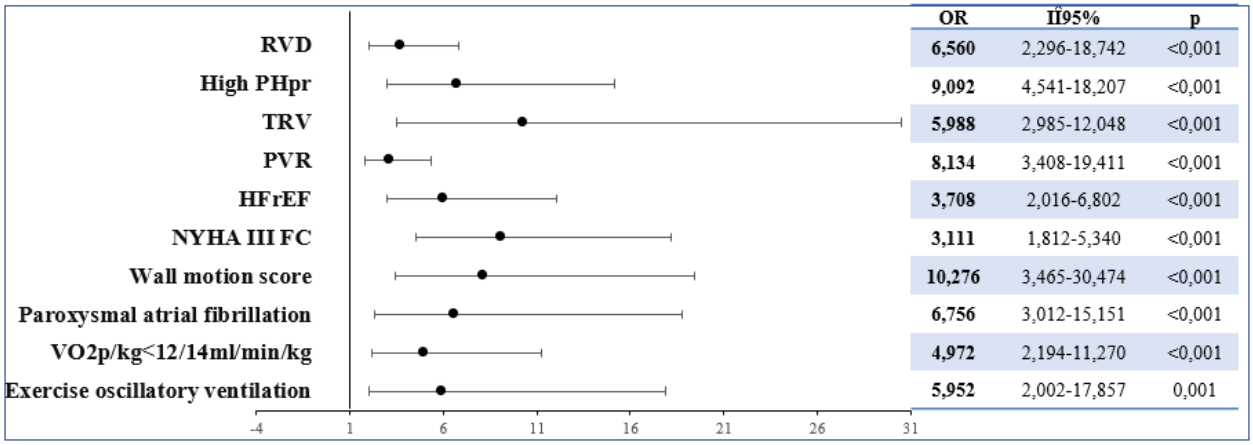


Figure 20. Prognostic factors for the occurrence of WHF episodes 12 months after myocardial revascularization

Note: HFrEF - heart failure with reduced ejection fraction, PHpr - echocardiographic probability of pulmonary hypertension, PVR - pulmonary vascular resistance, RVD - right ventricular dysfunction, TRV – tricuspid regurgitation velocity, VO_2p/kg - peak oxygen consumption relative to body weight.

Discriminant analysis highlighted 8 more relevant parameters: CAD duration, left atrial diameter, left ventricular telediastolic diameter, LVEF, NYHA functional class of HF, LV aneurysm, CCI experessed in points and number of non-CV comorbidities, which formed the basis for developing the *„Method for predicting worsening heart failure episodes one year after myocardial revascularization",* with a positive predictive value of 64% and a negative predictive value of 85.6%.

GENERAL CONCLUSIONS

1. Stratification of HF phenotypes at 3 months post–myocardial revascularization demonstrated a distribution of HFpEF, HFmrEF and HFrEF of 64.0%, 16.0% and 20.0%, respectively. At the end of the follow-up period, an increase in HFpEF prevalence was observed alongside a reduction in HFrEF rate. Defining characteristics of the HF phenotypes, such as LVEF and NT-proBNP, exhibited a more pronounced positive trajectory in patients with HFrEF.
2. The prevalence of PH, determined by echocardiographic criteria, in the ischemic HF cohort was 58.1% at 3 months after myocardial revascularization, rising by 9.5% by the end of the study. The CpcPH and IpcPH subtypes were detected echocardiographically in 10.9% and 43.3% of cases, respectively. Prognostic determinants associated with the progression of PH echocardiographic probability comprised the HFrEF phenotype, LV characteristics (including diastolic dysfunction), PVR and mPAP estimated by echocardiography, comorbidities (atrial fibrillation, arterial hypertension, chronic kidney disease) and ventilatory indices assessed during CPET. Echocardiographic parameters suggestive of PH and its subtypes showed a moderate correlation with variables defining HF phenotypes.
3. The prevalence of RVD in the ischemic HF patient cohort was 39.2% at 3 months after myocardial revascularization, increasing notably by 10% during the monitoring period. Variables suggestive of PH and RV–pulmonary artery coupling, along with defining features

of left-sided HF and VE/VCO_2 slope, demonstrated prognostic value for the development of RVD at 12 months after myocardial revascularization.

4. The comparative analysis between patients undergoing CABG and PCI revealed a higher baseline prevalence of PH in the CABG group, with a continuous increase observed in both groups during follow-up. The rate of RVD was initially higher in post-CABG patients, whereas by the end of follow-up, its increase was more pronounced in the post-PCI group. Left ventricular systolic function was comparable at baseline, showing a more evident positive trajectory in the CABG group over time.
5. The defining features of the echocardiographic probability of PH and CpcPH subtype, along with key parameters of RVD and RV-pulmonary artery coupling, demonstrated substantial prognostic value in the course of ischemic HF 12 months after myocardial revascularization. HF features and left heart characteristics, in combination with CV and non-CV comorbidities, peak oxygen uptake and ventilatory pattern, were also identified as significant predictors.

PRACTICAL RECOMMENDATIONS

1. Estimating the echocardiographic probability of PH as a primary option at all stages of follow-up in patients with ischemic HF and myocardial revascularization through coronary artery bypass grafting or percutaneous coronary intervention.
2. Applying the „*Prediction model for the progression of echocardiographic probability of pulmonary hypertension in patients with ischemic heart failure 12 months after myocardial revascularization"* at an early stage following myocardial revascularization, wich allows the identification of patients at increased risk of PH probability progression, who require close monitoring, timely adjustment of optimal pharmacological therapy and adequate management of comorbidities.
3. The inclusion in the echocardiographic protocol for the assessment of patients with ischemic heart failure of a multiparametric evaluation of the right ventricle (tricuspid annular plane systolic excursion, peak systolic velocity of the lateral tricuspid annulus, fractional area change, myocardial performance index, end-diatolic diameter, free wall thickness) at each stage of follow-up after myocardial revascularization for early identification of right ventricular dysfunction.
4. Using in clinical practice the „*Prediction model for the development of right ventricular dysfunction in patients with ischemic heart failure 12 months after myocardial revascularization"*, which allows the identification of patients at risk of adverse right ventricular functional evolution, in order to optimize therapeutic management.
5. Implementing cardiopulmonary exercise testing in the investigation plan of patients with ischemic HF to quantify cardiorespiratory fitness, metabolic performance and gas exchange at each follow-up stage after myocardial revascularization, both by coronary artery bypass grafting or percutaneous coronary intervention.
6. The application in primary healthcare institutions of the „*Prediction method based on clinical parameters for the risk of heart failure hospitalization during the first year after myocardial revascularization*" and in secondary or tertiary hospital institutions – the use of the „*Prediction method for the risk of heart failure hospitalization during the first year after myocardial revascularization*" and the „*Prediction method for the risk of worsening heart failure during the first year after myocardial revascularization*," for the early identification of patients at increased risk of adverse heart failure evolution, enabling closer monitoring, timely escalation of guideline-directed medical therapy, screening and management of comorbidities.

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LIST OF PUBLICATIONS AND PARTICIPATION IN SCIENTIFIC FORUMS

by Ms. **Janna Cazacu**, doctoral graduate

for her doctoral thesis in medical sciences, with the topic **„Pulmonary hypertension and right ventricular dysfunction: prognostic implications in patients with different clinical phenotypes of ischemic heart failure”,** 321.03-Cardiology

- **Articles in scientific journals abroad:**

✓ **articles in ISI journals, SCOPUS and other international databases:**

1. **Cazacu J.**, Lîsîi D., Priscu O., Bursacovschi D., Dodu S., Guțan I., Botnari N., Oprea C., Costiuc M., Jucovschi C., Vataman E. Prognostic factors influencing all-cause mortality and hospitalizations after inpatient cardiac rehabilitation for acute coronary events. In: Arch Balk Med Union. 2024; 59(2): 174-187. ISSN: 1584-9244. https://doi.org/10.31688/ABMU.2024.59.2.05 (**SCOPUS)**
2. **Cazacu J.**, Jucovschi C., Vataman E. Pulmonary hypertension and right ventricular dysfunction: prognostic impact on heart failure hospitalizations one year after myocardial revascularization. In: Arch Balk Med Union. 2025; 60(1): 32-40. ISSN: 1584-9244. https://doi.org/10.31688/ABMU.2025.60.1.03 (**SCOPUS)**
3. Lund L., Crespo-Leiro M.G., Laroche C., Garcia-Pinilla J., Bennis A., Vataman E., Polovina M., Radovanovic S., Apostolovic S., Asanin M., Gackowski A., Kaplon-Cielicka A., Cabac-Pogorevici I., Anker S., Chioncel O., Coats A., Filippatos G., Lainscak M., McDonagh T., Mebazaa A., Metra M., Piepoli M., Rosano G., Ruschitzka F., Savarese G., Seferovic P., Iung B., Popescu B., Maggioni A., for the ESC EORP HF III National Leaders and Investigators: Bursacovschi D., Lisii D., Paraniuc E., **Cazacu J.**, Dogot M., Botnari N., Grib L., Filimon S., Samohvalov E., Purteanu L., Grivenco A., Revenco V., et. al. Rationale and design of the ESC Heart Failure III Registry – Implementation and discovery. In: European Journal of Heart Failure. 2023; 25(12): 2316-2330. ISSN: 1879-0844. https://doi:10.1002/ejhf.3087 (**IF: 16,9)**

- **Articles in accredited national scientific journals:**

✓ **articles in category B journals**

4. **Cazacu J**., Bursacovschi D., Dogot M., Lîsîi D., Tofan V., Ureche A., Moscalu V.V., Batrînac A., Moscalu V.D., Vataman E. Evoluția perioperatorie a fenotipului de insuficiență cardiacă cronică la pacienții care au suportat intervenție chirurgicală cardiacă. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2022; 1(65): 48-56. ISSN 1857-0011. https://ibn.idsi.md/vizualizare_articol/153755
5. Bursacovschi D., **Cazacu J.,** Lîsîi D., Vataman E. Evaluarea eficacității reabilitării cardiace asupra funcției diastolice ventriculare stângi la pacienții ce au suportat revascularizare coronariana percutană. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2022; 1(72): 23-27. ISSN 1857-0011. https://ibn.idsi.md/ro/vizualizare_articol/153737

6. **Cazacu J.,** Bursacovschi D., Dodu S., Vataman E. Capacitatea de efort la pacienții cu disfuncție de ventricul drept în perioada precoce după revascularizare miocardică. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2023; 1(75): 48-58. ISSN 1857-0011. https://ibn.idsi.md/vizualizare_articol/182165
7. **Cazacu J**., Bursacovschi D., Dodu S., Vataman E. Particularitățile evoluției hipertensiunii pulmonare la pacienții cu insuficiență cardiacă ischemică pe parcursul a 12 luni după revascularizare miocardică. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2024; 1(78): 17-27. ISSN 1857-0011. https://ibn.idsi.md/vizualizare_articol/209821
8. **Cazacu J**., Vataman E. Predictorii dezvoltării disfuncției de ventricul drept la pacienții cu insuficiență cardiacă ischemică la 12 luni după revascularizare miocardică. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2025; 1(81): 22-30. ISSN 1857-0011.

✓ **articles in category C journals:**

9. Vataman E., **Cazacu J**., Lîsîi D., Aprodu S. Prevalența hipertensiunii pulmonare în perioada postrevascularizare miocardică precoce la pacienții cu by-pass aorto-coronarian și angioplastie primară. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2019;3(63): 146-152. ISSN 1857-0011. https://ibn.idsi.md/ro/vizualizare_articol/89839
10. **Cazacu J.** Hipertensiunea pulmonară și disfuncția de ventricul drept în insuficiența cardiacă cu fracția de ejecție prezervată. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2020; 1(65): 165-170. ISSN 1857-0011. https://ibn.idsi.md/ro/vizualizare_articol/115040
11. Lîsîi D., **Cazacu J**., Bursacovschi D., Dogot M., Draganiuc A., Mucovozov V., Vataman E. Determinarea parametrilor prognostici pentru mortalitate la pacienții cu insuficiență cardiacă cronică după revascularizare coronariană. In: Buletinul Academiei de Științe a Moldovei. Științe Medicale. 2020; 1(65): 215-222. ISSN 1857-0011. https://ibn.idsi.md/vizualizare_articol/115067

- **Articles in international or national scientific conference proceedings:**

✓ **international:**

12. **Cazacu J.,** Bursacovschi D., Lîsîi D., Vataman E. Evolution of the residual risk in the post-myocardial revascularization period in patients with ischemic heart failure. In: Heart Failure Association Discoveries, 22-29 iunie 2020, online: European Journal of Heart Failure, 2020; 22(Suppl. S1): p. 206. https://doi:10.1002/ejhf.1963
13. **Cazacu J.,** Bursacovschi D., Lisii D., Vataman E. The effectiveness of structured telephone support in the late phase of rehabilitation at home in patients with myocardial revascularization. In: ESC Preventive Cardiology, 7-9 aprilie 2022, online: European Journal of Preventive Cardiology. 2022; 29(Suppl 1): p. i360. https://doi.org/10.1093/eurjpc/zwac056.254.
14. Bursacovschi D., **Cazacu J**., Lisii D., Vataman E. The effect of surgical ventricular restoration technics on left ventricular remodeling in different heart failure phenotypes. In: European Society of Cardiology. Preventive Cardiology, 7-9 aprilie 2022, online: European Journal of Preventive Cardiology. 2022; 29(Suppl 1): p. i45. https://doi.org/10.1093/eurjpc/zwac056.254
15. **Cazacu J**. Clinical characteristics of patients with heart failure with mildly reduced left ventricular ejection fraction after cardiac surgery. In: MedEspera 2022. Abstract book. The 9th International Medical Congress for Students and Young Doctors, Chișinău: 2022; 9: p. 19. https://conferinte.stiu.md/sites/default/files/evenimente/ABSTRACT%20BOOK%20MedEspera%202022.pdf
16. **Cazacu J.,** Bursacovschi D., Lisii D., Vataman E. Perioperative evolution of serum levels of type B natriuretic peptide in patients with different clinical phenotypes of heart failure and cardiac surgery. In: Heart Failure Congress, 21-24 mai 2022, Madrid, Spania: Eur J Heart Fail. 2022; 24(Suppl. S2): p. 84. https://doi:10.1002/ejhf.2569

17. Bursacovschi D., **Cazacu J.,** Lisii D., Vataman E. The effect of surgical ventricular restoration technics on pulmonary hypertension in different heart failure phenotypes. In: Heart Failure Congress, 21-24 mai 2022, Madrid, Spania: Eur J Heart Fail. 2022; 24(Suppl. S2): p. 152. https://doi:10.1002/ejhf.2569
18. **Cazacu J**., Bursacovschi D., Dodu S., Moscalu V.V., Vataman E. Peak oxygen uptake and ventilatory pattern in patients with heart failure with reduced ejection fraction in the early stage after myocardial revascularization by coronary artery bypass grafting. In: Heart Failure Congress, 20-23 mai 2023, Praga, Cehia: Eur J Heart Fail. 2023, 25(Suppl S2): p. 64. https://doi.org/10.1002/ejhf.2927
19. **Cazacu J.,** Bursacovschi D., Dodu S., Moscalu V.V., Vataman E. The peculiarities of cardiopulmonary exercise testing in patients with pulmonary hypertension and heart failure in the early period after myocardial revascularization. In: Heart Failure Congress, 20-23 mai 2023, Praga, Cehia: Eur J Heart Fail. 2023, 25(Suppl S2): p. 387. https://doi.org/10.1002/ejhf.2927
20. Bursacovschi D., **Cazacu J**,. Lisii D., Priscu O., Gutan I., Vataman E. Ejection fraction trajectory in short-term follow-up study after revascularization of patients with ischemic heart disease. In: Heart Failure Congress, 20-23 mai 2023, Praga, Cehia: Eur J Heart Fail. 2023, 25(Suppl S2): p. 207.
https://doi.org/10.1002/ejhf.2927
21. **Cazacu J.,** Vataman E. Correlation of NT-proBNP and residual ischemic risk in patients with heart failure and myocardial revascularization. Heart Failure Congress, 11-14 mai 2024, Lisabona, Portugalia: Eur J Heart Fail. 2024, 26(Suppl. S2): p. 173. https://doi.org/10.1002/ejhf.3325
22. **Cazacu J**., Bursacovschi D., Vataman E. The correlation between peak oxygen uptake and the distance performed at 6-minute walking test in the assessement of exercise capacity in patients with heart failure and myocardial revascularization. Heart Failure Congress, 11-14 mai 2024, Lisabona, Portugalia: Eur J Heart Fail. 2024, 26(Suppl. S2): p. 258. https://doi.org/10.1002/ejhf.3325

✓ **national:**

23. **Cazacu J.** Evoluția hipertensiunii pulmonare în perioada precoce după by-pass coronarian la pacienții cu insuficiență cardiacă. În: Abstract book. Conferința Științifică Anuală USMF „N. Testemitanu". Cercetare în biomedicină și sănătate: calitate, excelență și performanță, Chișinău: 2021: p. 106. ISBN 978-9975-82-223-7. https://conferinta.usmf.md/wp-content/uploads/ABSTRACT-BOOK-Culegere-de-rezumate_21_10.pdf
24. Bursacovschi D., **Cazacu J.,** Lîsîi D., Vataman E. Impactul comorbidităților non-cardiace asupra consecințelor insuficienței cardiace la pacienți după terapia de revascularizare coronariană. În: Abstract book. Conferința Științifică Anuală USMF „N. Testemitanu". Cercetare în biomedicină și sănătate: calitate, excelență și performanță, Chișinău: 2021: p. 124. ISBN 9789975-82-223-7.
25. **Cazacu J**., Vataman E. Valoarea aplicativă a testului de efort cardiopulmonar după procedurile de revascularizare miocardică. MJHS. Culegere de rezumate. Conferința Științifică Anuală USMF „N. Testemitanu". Cercetare în biomedicină și sănătate: calitate, excelență și performanță. Chișinău: 2022; 29(3): p. 185.
26. Cazacu J. Patternul ventilator evaluat prin test de efort cardiopulmonar la pacienții cu disfuncție de ventricul drept. MJHS. Culegere de rezumate. Conferința Științifică Anuală USMF „N. Testemitanu". Cercetare în biomedicină și sănătate: calitate, excelență și performanță. Chișinău: 2023; 10(3): p. 324.

- **Patents of inventions, innovation, registration certificates, materials at invention fairs:**

✓ **Short term patents of invention:**

27. **Cazacu J**., Jucovschi C., Vataman E. Metodă de prognostic în baza parametrilor clinici al riscului de spitalizare din cauza insuficienței cardiace pe parcursul primului an după revascularizare miocardică. Short term patent of invention MD 1834 Y. BOPI nr. 4/2025, 30.04.2025.

28. **Cazacu J.,** Jucovschi C., Vataman E. Metodă de prognostic al riscului de spitalizare din cauza insuficienţei cardiace pe parcursul primului an după revascularizare miocardică. Short term patent of invention MD 1825. BOPI nr. 3/2025, 31.03.2025.

✓ **Innovation certificates:**

29. **Cazacu Janna**, Jucovschi Constantin, Vataman Eleonora. Model de predicție a progresării probabilității ecocardiografice a hipertensiunii pulmonare la pacienții cu insuficiență cardiacă ischemică pe parcursul a 12 luni după revascularizare miocardică. Innovation certificate: Nr. 6299 din 19.11.2024.
30. **Cazacu Janna**, Jucovschi Constantin, Vataman Eleonora. Metodă de prognostic a exacerbării insuficienței cardiace pe parcursul primului an după revascularizare miocardică. Innovation certificate: Nr. 6300 din 19.11.2024.
31. **Cazacu Janna**, Jucovschi Constantin, Vataman Eleonora. Model de predicție a dezvoltării disfuncției de ventricul drept la pacienții cu insuficiență cardiacă ischemică pe parcursul a 12 luni după revascularizare miocardică. Innovation certificate: Nr. 6301 din 19.11.2024.

- **Participation with communications in scientific forums:**

✓ **International:**

32. **Cazacu J.** Influența disfuncției de ventricul drept asupra capacității de efort în perioada precoce după revascularizare miocardică. Congresul Național de Cardiologie. Sinaia, România, 21-24 septembrie 2022.
33. **Cazacu J.** Stratificarea riscului de spitalizări repetate în primul an după revascularizarea miocardică – abordare prognostică în insuficiența cardiacă ischemică. Comunicarea prezentată la: Congresul Național de Cardiologie; 17-20 septembrie 2025; Sinaia, România.

✓ **National:**

34. **Cazacu J.** Hipertensiunea pulmonară la pacienții cu bronhopneumopatie cronică obstructivă. Conferința științifică în cadrul marcării Zilei Mondiale de luptă împotriva Bronhopneumopatiei Obstructive Cronice cu genericul "Toţi împreună să stopăm BPOC". Chișinău, 22 noiembrie 2019.
35. **Cazacu J.** Evoluția hipertensiunii pulmonare în perioada precoce după by-pass coronarian la pacienții cu insuficiență cardiac. Conferința Științifică Anuală USMF „N. Testemitanu”. Cercetare în biomedicină și sănătate: calitate, excelență și performanță. Chișinău, 20.10.2021.
36. **Cazacu J.** Rolul testului de efort cardiopulmonar în evaluarea capacității de efort, stratificarea riscului. Conferința clinică a IMSP Institutului de Cardiologie. Chișinău, 03 mai 2023.
37. **Cazacu J.** Evoluția riscului pacientului cu hipertensiune pulmonară arterială aplicând terapia combinată secvențială. Caz clinic. Conferința științifică ”Hipertensiunea pulmonară în practica clinică de zi cu zi”, Chișinău, 07 octombrie 2023.
38. **Cazacu J.** Testul de efort cardiopulmonar în aprecierea capacității de efort și dozarea acesteia. Conferința științifico-practică cu genericul „Reabilitarea cardiovasculară la domiciliu după operații pe cord și infarct miocardic acut” în cadrul Expoziției Internaționale Specializate „MoldMedizin & MoldDent” ediția 2024, Chișinău, 27 septembrie 2024.

- **Participation with posters in scientific forums:**

✓ **International:**

39. **Cazacu J.,** Bursacovschi D., Lîsîi D., Vataman E. Evolution of the residual risk in the post-myocardial revascularization period in patients with ischemic heart failure. Heart Failure Association Discoveries. online, 22-29 iunie 2020.
40. Bursacovschi D., Vataman E., **Cazacu J**., Lisii D. The role of cardiac rehabilitation program on left ventricular function in coronary artery disease patients. European Association of Preventive Cardiology Essentials 4 You. online, aprilie 2020.
41. **Cazacu J.**, Bursacovschi D., Lîsîi D., Vataman E. The effectiveness of structured telephone support in the late phase of rehabilitation at home in patients with myocardial revascularization. European Society of Cardiology. Preventive Cardiology. online, 7-9 aprilie 2022.

42. **Cazacu J.,** Bursacovschi D., Lîsîi D., Vataman E. Perioperative evolution of serum levels of type B natriuretic peptide in patients with different clinical phenotypes of heart failure and cardiac surgery. Heart Failure Congress, Madrid, Spania, 21-24 mai 2022.
43. **Cazacu J.,** Bursacovschi D., Dodu S., Moscalu V.V., Vataman E. Peak oxygen uptake and ventilatory pattern in patients with heart failure with reduced ejection fraction in the early stage after myocardial revascularization by coronary artery bypass grafting. Heart Failure Congress, Praga, Cehia, 20-23 mai 2023.
44. **Cazacu J.,** Bursacovschi D., Dodu S., Moscalu V.V., Vataman E. The peculiarities of cardiopulmonary exercise testing in patients with pulmonary hypertension and heart failure in the early period after myocardial revascularization. Heart Failure Congress, Praga, Cehia, 20-23 mai 2023.
45. Bursacovschi D., **Cazacu J.,** Lisii D., Priscu O., Gutan I., Vataman E. Ejection fraction trajectory in short-term follow-up study after revascularization of patients with ischemic heart disease. Heart Failure Congress, Praga, Cehia, 20-23 mai 2023.
46. **J Cazacu,** E Vataman. Correlation of NT-proBNP and residual ischemic risk in patients with heart failure and myocardial revascularization. Heart Failure Congress, Lisabona, Portugalia, 11 mai 2024.
47. **J Cazacu,** D. Bursacovschi, E Vataman. The correlation between peak oxygen uptake and the distance performed at 6-minute walking test in the assessement of exercise capacity in patients with heart failure and myocardial revascularization. Heart Failure Congress, Lisabona, Portugalia, 11 mai 2024.

✓ **national:**

48. **Cazacu J**., Vataman E. Valoarea aplicativă a testului de efort cardiopulmonar după procedurile de revascularizare miocardică. Conferința Științifică Anuală USMF „N. Testemitanu”. Cercetare în biomedicină și sănătate: calitate, excelență și performanță. Chișinău, 19-21 octombrie 2022.

ANNOTATION

to the PhD thesis in medical sciences by doctoral graduate Janna Cazacu:
"Pulmonary hypertension and right ventricular dysfunction: prognostic implications in patients with different clinical phenotypes of ischemic heart failure",
Chișinău, 2025

Relevance of the research. Pulmonary hypertension (PH) and right ventricular dysfunction (RVD) are linked to increased mortality and morbidity across a wide spectrum of clinical conditions; however, their long-term evolution and prognostic impact in patients with ischemic heart failure (HF) after myocardial revascularization remain incompletely elucidated.

Aim of the study: to investigate the characteristics of postcapillary PH and RVD in ischemic HF and to develop long-term prognostic criteria following myocardial revascularization.

Research objectives: 1) to assess the evolution of HF phenotypes at 12 months after myocardial revascularization; 2) to elucidate changes in echocardiographic parameters suggestive of postcapillary PH and its subtypes and to explore their correlations with HF phenotypes; 3) to estimate the modifications of right ventricular (RV) function parameters; 4) to compare the evolution of PH, RV and left ventricular dysfunction according to the type of myocardial revascularization; 5) to develop prognostic criteria for ischemic HF' evolution and to determine the impact of PH and RVD in this context.

Scientific novelty. A non-invasive (echocardiographic) diagnosis of postcapillary PH subtypes: isolated post-capillary PH (IpcPH) and combined post- and pre-capillary PH (CpcPH) was performed. Predictors of the progression of echocardiographic probability of PH and of de novo RVD were identified. Cardiopulmonary exercise testing (CPET) provided a detailed characterization of the cardiometabolic and ventilatory profiles of patients with investigated clinical conditions. PH and RVD significantly influenced ischemic HF prognosis, increasing the risk of HF hospitalizations, worsening HF episodes and were associated with the composite endpoint: all-cause mortality and HF-related admissions.

Theoretical significance. The study highlighted moderate correlations between PH associated with left heart disease (PH-LHD), its subtypes and HF phenotypes. It demonstrated the prognostic role of systolic and diastolic LV dysfunction, preexisting early changes within the pulmonary circulation and comorbidities on the progression of the echocardiographic probability of PH. Study data suggest the presence of a mixed pathophysiological mechanism underlying de novo RVD, based on ventricular interdependence and RV-PA uncoupling. The results support the essential role of PH and RVD in the evolution of ischemic HF.

Practical value. The study demonstrated the feasibility of non-invasive echocardiographic differentiation of PH-LHD subtypes: IpcPH and CpcPH, emphasized multiparametric RV assessment and supported CPET use in the follow-up of patients with ischemic HF who underwent myocardial revascularization. Five predictive models were proposed to estimate the risk of HF hospitalization and worsening HF, adverse PH evolution and de novo RVD 12 months after myocardial revascularization.

Thesis structure includes: introduction, 4 chapters, conclusions, recommendations, 251 references, 11 appendices, 38 figures, 35 tables, and 26 publications related to the thesis topic.

Keywords: pulmonary hypertension, echocardiographic probability of pulmonary hypertension, right ventricular dysfunction, ischemic heart failure, heart failure phenotypes, ischemic heart disease, myocardial revascularization, prognosis.

ADNOTARE

la teza de doctor în științe medicale a absolventei doctoratului Cazacu Janna:

„*Hipertensiunea pulmonară și disfuncția ventriculului drept: implicații prognostice la pacienții cu diferite fenotipuri clinice de insuficiență cardiacă ischemică*”,

Chișinău, 2025

Actualitatea cercetării. HTP și DVD sunt asociate cu risc crescut de mortalitate și morbiditate într-un spectru variat de entități clinice, însă evoluția și impactul prognostic pe termen lung al acestora la pacienții cu IC ischemică și revascularizare miocardică rămâne incomplet elucidat.

Scopul lucrării: cercetarea particularităților HTP-BCS și DVD la pacienții cu IC ischemică și elaborarea unor criterii prognostice pe termen lung după revascularizare miocardică.

Obiectivele cercetării: 1) aprecierea evoluției manifestărilor definitorii ale fenotipurilor IC la 12 luni după revascularizare miocardică; 2) elucidarea modificărilor parametrilor ecocardiografici sugestivi pentru HTP postcapilară și subtipurile sale, cu investigarea corelației acestora cu fenotipurile IC; 3) evaluarea particularităților clinice ale pacienților cu DVD și a dinamicii funcției acestuia; 4) analiza comparativă a evoluției parametrilor ecocardiografici ai HTP, disfuncției VD și VS în raport cu tipul revascularizării miocardice; 5) elaborarea criteriilor de prognostic pe termen lung pentru evoluția IC ischemice după revascularizare miocardică și determinarea impactului HTP și DVD în acest context.

Noutatea științifică. În premieră a fost efectuată diagnosticarea neinvazivă (ecocardiografică) a subtipurilor HTP postcapilare: HTP-Ipc și HTP-Cpc. Au fost identificați factorii prognostici care au determinat progresarea probabilității ecocardiografice a HTP și apariția DVD de novo. Aplicând TECP, fost descris profilul cardiometabolic și ventilator al pacienților cu HTP-BCS și DVD. Studiul a demonstrat un aport prognostic considerabil al HTP și DVD în evoluția IC ischemice, majorând riscul de spitalizări din cauza IC, apariția episoadelor de exacerbare a IC, fiind asociate cu punctul final mixt: mortalitate de orice cauză și spitalizări determinate de IC.

Semnificația teoretică a studiului constă în evidențierea corelației moderate dintre HTP-BCS, subtipurile acesteia și fenotipurile IC. S-a demonstrat impactul prognostic al disfuncției sistolice și diastolice a VS, alterărilor incipiente ale circulației pulmonare și comorbidităților asupra avansării probabilității ecocardiografice de HTP. Datele obținute au sugerat existența unui mecanism fiziopatologic mixt de apariție a DVD de novo, bazat pe interdependența ventriculară și decuplarea VD-AP. Rezultatele susțin rolul esențial al HTP și DVD în evoluția IC ischemice.

Valoarea aplicativă. Studiul a demonstrat fezabilitatea delimitării ecocardiografice a subtipurilor HTP-BCS (HTP-Ipc și HTP-Cpc), a subliniat importanța evaluării multiparametrice a VD și integrării TECP în supravegherea pacienților cu IC și revascularizare miocardică. Au fost elaborate 5 modele predictive, care permit estimarea riscului de spitalizare și exacerbare a IC, evoluției negative a HTP și dezvoltării DVD la 12 luni după revascularizare miocardică.

Implementarea rezultatelor științifice a fost realizată în activitatea clinică a secției Cardiochirurgie și Reabilitare cardiacă, IMSP Institutul de Cardiologie.

Structura tezei cuprinde: introducere, 4 capitole, concluzii generale şi recomandări practice, bibliografie, care constă din 251 de surse științifice, 11 anexe, 120 pagini de text de bază, 38 de figuri, 35 de tabele, 26 de publicații la tema tezei.

Cuvinte-cheie: hipertensiune pulmonară, probabilitate ecocardiografică de hipertensiune pulmonară, disfuncție de ventricul drept, insuficiență cardiacă ischemică, fenotipuri de insuficiență cardiacă, boală cardiacă ischemică, revascularizare miocardică, prognostic.