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# Beyond unrecognized: heart failure with supranormal ejection fraction — a review of current knowledge on a novel heart failure phenotype

## Niewydolność serca z supranormalną frakcją wyrzutową — przegląd aktualnej wiedzy o nowym fenotypie niewydolności serca

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### Abstract

Heart failure with supranormal ejection fraction (HFsnEF) is a newly recognized and distinct phenotype in cardiology, specifically refers to the coexistence of heart failure symptoms with an ejection fraction ≥ 65%. HFsnEF patients, predominantly women, exhibit smaller left ventricular volumes, lower NT-proBNP levels, and lower rates of coronary artery disease (CAD) and atrial fibrillation (AF) compared to other HF with preserved ejection fraction subgroups. Treatment options for HFsnEF are limited, with suboptimal response to standard pharmacotherapy. Prognosis in HFsnEF is associated with increased mortality rates as ejection fraction exceeds 60–65%. Refinement of diagnostic and treatment approaches is crucial for improving outcomes in this challenging patient group.

Key words: echocardiography, heart failure, pharmacotherapy

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## Introduction

Heart failure (HF) has been divided into distinct phenotypes using the measurement of left ventricular ejection fraction (LVEF). HF is distinguished by reduced ejection fraction (HFrEF), mildly reduced ejection fraction (HFmrEF), and preserved ejection fraction (HFpEF) [1]. In 2019, it was observed for the first time that there is a significant correlation between the increase in mortality rate and an increase in LVEF above 60–65% [2]. HF with a supra-normal ejection fraction (HFsnEF), a newly recognized phenotype, refers to patients with an EF of ≥ 65% [3], capturing significant interest in modern cardiology.

Some studies suggest that HFsnEF may be a distinct clinical entity with its own unique characteristics, while others propose that it may be a variant of HFpEF or a result of other underlying medical conditions. Currently, there is no widely accepted diagnostic method or treatment strategy for HFsnEF, and the management of this condition typically involves addressing the underlying causes of the symptoms, such as hypertension, valvular disease, or other cardiac disorders. It is worth noting that the current ESC

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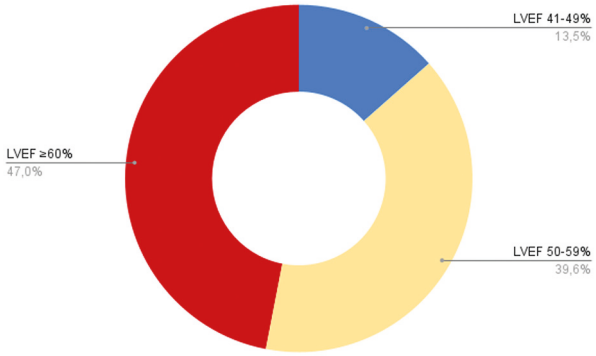


**Figure 1.** Percentage of hospitalized patients with heart failure and LVEF > 40% (N = 47,026) based on their ejection fraction [7]

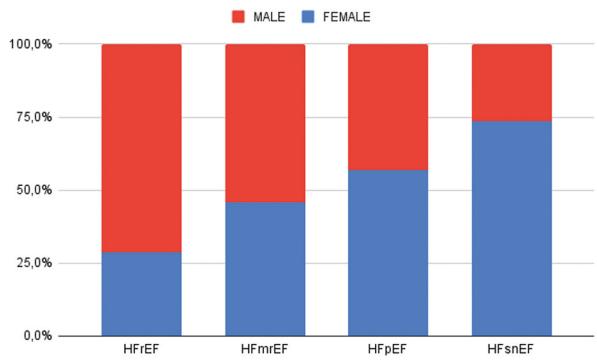


**Figure 2.** The increasing percentage of women in patient groups with heart failure and higher ejection fraction in the RELAX-AHF-2 study [9]

guidelines on HF do not indicate a distinct patient group with EF > 65% but acknowledge the ongoing need to further understand the characteristics of patients with HFpEF based on evidence gaps [1].

## Definition

The topic of HFsnEF is unexplored therefore an exact definition describing this group of patients has not been established yet. Based on the available literature, where a changed clinical profile has been delineated in patients, characterized by LVEF > 60%, > 65%, and > 70% (depending on the study), one can hypothesize that this group includes patients diagnosed with HF, whose LVEF is > 60%. The authors propose their definition based on combined ESC guidelines (with HF classification including LVEF) [1] and the Universal Definition of HF [4], where HFsnEF should be defined as a clinical syndrome consisting of typical symptoms (that may be accompanied by signs) in patients with established LVEF > 60% and objective evidence of cardiac structural and/or functional abnormalities, including elevated natriuretic peptides.

## Epidemiology and HFsnEF phenotype

Despite previous underestimations, it appears that HFpEF accounts for 50–60% of all cases of HF [3, 5]. Various methods of calculating EF make it challenging to accurately determine the prevalence of HFsn and the available data are confusing [6]. Based on published studies involving patients with HFpEF, it has been estimated that patients with EF ≥ 60% comprise around 15% of all patients with HF [7]. These estimates, however, remain uncertain, as evidenced by a study published in Circulation (2023) — among a population of over 47,000 hospitalized patients with HF with LVEF > 40%, a substantial 47% exhibited an LVEF ≥ 60% [8] (Fig. 1), and on the other hand the RELAX-AHF-2 study among patients admitted to the hospital due to HF recorded only 2.5% of patients with HFsnEF [9].

Even though the cutoff point for HFsnEF is sometimes set at an EF of 65%, changes in patient population and their clinical profiles are observed starting from EF ≥ 60%. In the whole spectrum of EF, this subgroup has been shown to have the highest female-to-male ratio (64.9%), stands out with the lowest concentration of NT-proBNP (median of 2234 pg/mL) and the lowest incidence rates of CAD (31.5%) and atrial fibrillation (34.4%) [8]. Indeed, it appears that the increase of EF increases the proportion of women. In the study of Bart J. van Essen et al. [10] women accounted for 57% of the HFpEF group and 73.5% of the HFsnEF group (Fig. 2). Horiuchi et al. [11], reported that patients with HFsnEF have smaller left ventricular volume compared to other subgroups of HF also another study described that patients with HF and LVEF > 60% present lower left ventricle end-diastolic volumes and end-systolic volumes, but with the comparison to the LVEF 50–60% group [12]. In this study, a significant portion of the HFsnEF patients had aortic stenosis and left ventricular hypertrophy that may impact the smaller size of the left ventricle and higher EF [13]. Moreover, LVEF > 65% is relatively common in the population undergoing transcatheter aortic valve replacement [14]. In the HFsnEF subgroup non-ischaemic aetiology of HF is more common compared to the whole HFpEF group (73.3% vs 60.6%, $p < 0.01$) and non-cardiovascular mortality is higher (6.4% vs 3.8%, $p < 0.01$) [10].

Recently, cardiac amyloidosis has been increasingly recognized as one of the various causes of HFpEF [15, 16], but no statistically significant association between cardiac amyloidosis and HFsnEF have been found until now [17].

## Diagnostics

At present, the major attention is directed at the limitations associated with the under-recognition of HFpEF including

HFsnEF [6]. The probability of HF is based on the patient's prior clinical history (e.g., CAD, AH, diuretic use), presenting symptoms (e.g., orthopnoea), physical examination (e.g., bilateral oedema, increased jugular venous pressure, displaced apical beat) and resting ECG [1].

The second step in the diagnostic strategy is the detection of elevated levels of natriuretic peptides (BNP > 35 pg/mL and/or NT-proBNP > 125 pg/mL) [3].

If the probability of HF is likely, echocardiography with assessment of cardiac functional and structural abnormalities, evaluation of EF should be performed and identification of HFrEF, HFmrEF or HFpEF accomplished. Despite the existence of various diagnostic tools for HFpEF (e.g., HFA-PEFF), it appears to be suboptimal for diagnosing HFsnEF [18]. Still, there are no diagnostic scoring systems for separate HFsnEF detection [6].

## Treatment

One of the most characteristic features of HFsnEF is a less effective response to pharmacological treatment. The post-hoc analysis of combined data from big randomized, placebo-controlled trials — PARADIGM-HF and PARAGON-HF have provided us with data on the impact of ARNI in the group of patients with HFsnEF. The hazard ratio (HR) for hospitalization due to HF was higher in patients with LVEF > 60% (1.04 [0.76–1.44]) than in patients with LVEF 50–60% (0.81 [0.63–1.05]) [19, 20]. Similar observations come from a post-hoc analysis of the TOPCAT study. It showed that the protective impact of spironolactone against cardiovascular death or HF-related hospitalization was stronger in patients with LVEF 50–60% (HR = 1.03 [0.80–1.32]) than in patients with LVEF > 60% (HR = 0.89 [0.74–1.06]) [21].

Candesartan in CHARM-Preserved trial was more effective in the reduction of CV death or HF-associated hospitalization in patients with LVEF < 40% (HR 0.95 [0.79–1.14]) than in patients with LVEF 50–60% (HR 0.82 [0.75–0.91]) [22].

Concluding, it has been demonstrated that the beneficial effect of ARNI (sacubitril/valsartan), ARB (candesartan), and MRA (spironolactone) decreases with the increase of EF [23]. In a group of over 290,000 patients, beta-blockers not only failed to improve survival in patients with HF > 60% but resulted in an increased rate of hospitalizations [24].

When it comes to SGLT-2 inhibitors which are currently among the most important medications in the pharmacotherapy of HFpEF, empagliflozin demonstrated a decreased effect where EF exceeds 60%, while dapagliflozin was effective even at higher values of EF. In the DELIVER and EMPEROR-preserved trials, patients with HFpEF treatment with dapagliflozin and empagliflozin showed HR of 0.79 (0.64–0.98) and 0.80 (0.64–0.99) respectively for cardiovascular events. In the subgroup of patients with LVEF ≥ 60%, in the DELIVER trial, the HR was 0.76 (0.60–0.96) and in the EMPEROR-preserved trial 0.87 (0.69–1.10) [25].

Based on the data provided, it can be concluded that dapagliflozin/empagliflozin, are effective medications in the group of patients with LVEF ≥ 60%, with a combined HR of 0.81 (0.69–0.96) [26, 27]. However, it is important to note that the use of these specific drugs should be based on their proven efficacy and clinical indications.

It seems that GLP-1 analogues will also become the mainstay of pharmacotherapy for HFpEF. The STEP-HFpEF study indicates that annual treatment with these drugs not only allows for a significant reduction in HF symptoms (increase in KCCQ-CSS by 7.8 (4.8 to 10.9) p < 0.001 vs placebo) but also achieves a substantial decrease in hospitalizations or urgent visits due to HF, with a value of 0.08 (0.00 to 0.42). This is also a significant study for HFsnEF patients since 43.3% of patients enrolled in the STEP-HFpEF study exhibited LVEF ≥ 60% [28].

The important aspect of the treatment of patients with HF is improving their quality of life. In the EMPEROR-preserved trial, in HFsnEF group the reduction in symptom scores after a 52-week therapy with empagliflozin as measured by the Kansas City Cardiomyopathy Questionnaire was 3.93 (2.86–4.99) and differed from placebo by 0.64 (–0.86–2.13) whereas in the HFpEF subgroup, reduction in symptom scores was 4.54 (3.51–5.58), and they differed from placebo by 2.26 (0.79–3.73) (p = 0.39) [29]. It seems that in the HFpEF patient group, it is more challenging to alleviate heart failure symptoms when the ejection fraction is above 60%.

## Prognosis

According to the available data from recent literature, HFpEF is associated with increased mortality as EF exceeds 60–65%.

In the study of Wehner et al. [2], in a population of over 200,000 patients, the adjusted HR for all-cause mortality in the groups of patients distinguished by EF was: 1.73 (1.66–1.80) in the group with EF 35–40%, 1.06 (1.04–1.0 8), in the group with EF 55–60%, 1.17 (1.14–1.20), in the group with EF 65–70%, and 1.73 (1.66–1.80), in the group with EF > 70%. The HR for all-cause mortality in patients with EF > 70 % reached a that noted in the group with EF 35–40%, with an HR of 1.71 (1.64–1.77) [2].

Several interesting observations come from small studies. Supranormal EF in patients without cardiovascular diseases but with lower stroke volume was shown to be associated with an increased risk of cardiovascular events [30], women with HFsnEF had a significantly higher rate of major adverse cardiac events compared to women with LVEF 55–65% (p < 0.001), while no such association was observed in men (p = 0.74) [31]. Imamura et al. [14]

indicate that LVEF > 65% is associated with higher all-cause mortality and HF hospitalization during a 3-year observation period after transcatheter aortic valve replacement, with an adjusted HR of 1.16 (1.02–1.31). Genetic and phenotypic profiling suggest that the mere presence of genes associated with HFsnEF is responsible for decreased survival [13].

## Conclusion

Modern cardiology encounters challenges in effectively treating patients with HFsnEF, as they do not conform to standard treatment protocols, and there is a significant need to improve their outcomes. The current management approach for this patient group, similar to that of HFpEF patients, appears to be outdated and unfavourable based on recent research. Improperly matched medications are approaching the effectiveness of a placebo and may even be harmful, considering their adverse effects. It is also worth considering expanding the borderline values of EF for HFsnEF, as typical changes associated with this phenotype are already observed at EF > 60%. Emerging the subgroup of patients with HFsnEF in future studies might contribute to the development of specific diagnostic and therapeutic algorithms tailored precisely to this group. It is also important to accurately estimate the significance of the problem being faced, as current data on the proportion of patients with HFsnEF within the overall HF population are confusing. Special registries of HF patients conducted in many countries are needed. Moreover, the heterogeneity of the HFpEF group appears to extend beyond just HFsnEF patients [32], which further complicates both diagnosis and treatment. It's worth noting again that in healthy individuals without concomitant cardiac diseases, LVEF > 78% has been associated with a statistically significant deterioration in prognosis [30]. This also warrants a broader examination of the healthy population with supranormal left ventricular ejection fraction (snLVEF) and assessing this value in terms of risk criteria for the development of cardiovascular diseases. Finally, EF — a simple parameter assessed with echocardiography may be in future replaced by some other measurement and technique to identify the severity of HF.

## Additional information

### Author contribution

PM — data collection, drafting of the article; RM, KP, JD — substantive supervision, correction

### Conflict of interests

The authors declare no conflict of interest.


### Streszczenie

Niewydolność serca z supranormalną frakcją wyrzutową jest nowym i dość odmiennym fenotypem, który dotyczy pacjentów z niewydolnością serca przy jednoczesnym stwierdzeniu frakcji wyrzutowej lewej komory ≥ 65%. Jest to grupa pacjentów, zazwyczaj kobiet, którzy charakteryzują się mniejszą objętością lewej komory, niższymi stężeniami NT-proBNP a także rzadszym występowaniem choroby wieńcowej czy migotania przedsionków w porównaniu do pozostałej populacji pacjentów, którzy chorują na niewydolność serca z zachowaną frakcją wyrzutową. Na ten moment leczenie populacji pacjentów z supranormalną frakcją wyrzutową stanowi duże wyzwanie, a odpowiedź na standardowe leczenie zazwyczaj jest ograniczona. W tej populacji pacjentów śmiertelność wzrasta wraz ze wzrostem frakcji wyrzutowej powyżej 60–65%. Udoskonalenie metod diagnostycznych i leczniczych w tej grupie pacjentów zdaje się być kluczem do poprawy ich rokowania.



Słowa kluczowe: echokardiografia, niewydolność serca, farmakoterapia

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## References


1. McDonagh Th, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
2. Wehner GJ, Jing L, Haggerty CM, et al. Routinely reported ejection fraction and mortality in clinical practice: where does the nadir of risk lie? Eur Heart J. 2020; 41(12): 1249–1257, doi: 10.1093/eurheartj/ehz550, indexed in Pubmed: 31386109.
3. Huang Z, Jiang Y, Zhou Y. Heart failure with supra-normal left ventricular ejection fraction: state of the art. Arq Bras Cardiol. 2021; 116(5): 1019–1022, doi: 10.36660/abc.20190835, indexed in Pubmed: 34008831.
4. Bozkurt B, Coats A, Tsutsui H, et al. Universal definition and classification of heart failure: a report of the Heart Failure Society of America, Heart Failure Association of the European Society of Cardiology, Japanese Heart Failure Society and Writing Committee of the Universal Definition of Heart Failure. European Journal of Heart Failure. 2021; 23(3): 352–380, doi: 10.1002/ejhf.2115, indexed in Pubmed: 33605000.
5. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol. 2017; 14(10): 591–602, doi: 10.1038/nrcardio.2017.65, indexed in Pubmed: 28492288.
6. Kittleson M, Panjrath G, Amancherla K, et al. 2023 ACC expert consensus decision pathway on management of heart failure with preserved ejection fraction. Journal of the American College of Cardiology. 2023; 81(18): 1835–1878, doi: 10.1016/j.jacc.2023.03.393, indexed in Pubmed: 37137593.
7. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022; 400(10354): 757–767, doi: 10.1016/S0140-6736(22)01429-5, indexed in Pubmed: 36041474.
8. Greene SJ, Spertus JA, Tang W, et al. Heart failure across the range of mildly reduced and preserved ejection fraction in the united states. Circ Heart Fail. 2023; 16(5): e010430, doi: 10.1161/CIRCHEARTFAILURE.123.010430, indexed in Pubmed: 37078276.
9. Metra M, Teerlink J, Cotter G, et al. Effects of serelaxin in patients with acute heart failure. N Engl J Med. 2019; 381(8): 716–726, doi: 10.1056/nejmoa1801291, indexed in Pubmed: 31433919.
10. van Essen BJ, Tromp J, Ter Maaten JM, et al. Characteristics and clinical outcomes of patients with acute heart failure with a supranormal left ventricular ejection fraction. Eur J Heart Fail. 2023; 25(1): 35–42, doi: 10.1002/ejhf.2695, indexed in Pubmed: 36114655.
11. Horiuchi Yu, Asami M, Ide T, et al. Prevalence, characteristics and cardiovascular and non-cardiovascular outcomes in patients with heart failure with supra-normal ejection fraction: Insight from the JROADHF study. Eur J Heart Fail. 2023; 25(7): 989–998, doi: 10.1002/ejhf.2895, indexed in Pubmed: 37191180.
12. Rosch S, Kresoja KP, Besler C, et al. Characteristics of heart failure with preserved ejection fraction across the range of left ventricular ejection fraction. Circulation. 2022; 146(7): 506–518, doi: 10.1161/CIRCULATIONAHA.122.059280, indexed in Pubmed: 35862208.
13. Forrest IS, Rocheleau G, Bafna S, et al. Genetic and phenotypic profiling of supranormal ejection fraction reveals decreased survival and underdiagnosed heart failure. Eur J Heart Fail. 2022; 24(11): 2118–2127, doi: 10.1002/ejhf.2482, indexed in Pubmed: 35278270.
14. Imamura T, Hida Y, Ueno H, et al. Clinical implication of supra-normal left ventricular ejection fraction in patients undergoing transcatheter aortic valve replacement. J Clin Med. 2023; 12(23), doi: 10.3390/jcm12237429, indexed in Pubmed: 38068484.
15. Murat S, Cavusoglu Y, Yalvac HE, et al. Assessment of clinical characteristics of cardiac amyloidosis as a potential underlying etiology in patients diagnosed with heart failure with preserved ejection fraction. Kardiol Pol. 2022; 80(6): 672–678, doi: 10.33963/KP.a2022.0098, indexed in Pubmed: 35390167.
16. Oghina S, Bougouin W, Bézard M, et al. The impact of patients with cardiac amyloidosis in hfpef trials. JACC Heart Fail. 2021; 9(3): 169–178, doi: 10.1016/j.jchf.2020.12.005, indexed in Pubmed: 33549560.
17. Martens P, Hanna M, Valent J, et al. Supra-normal left ventricular ejection fraction in cardiac amyloidosis. Clin Res Cardiol. 2023; 112(3): 441–443, doi: 10.1007/s00392-022-02043-w, indexed in Pubmed: 35639149.
18. Pieske B, Tschöpe C, de Boer RA, et al. How to diagnose heart failure with preserved ejection fraction: the HFA-PEFF diagnostic algorithm: a consensus recommendation from the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur Heart J. 2019; 40(40): 3297–3317, doi: 10.1093/eurheartj/ehz641, indexed in Pubmed: 31504452.
19. McMurray JJV, Packer M, Desai AS, et al. PARADIGM-HF Investigators and Committees. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11): 993–1004, doi: 10.1056/NEJMoa1409077, indexed in Pubmed: 25176015.
20. Solomon S, McMurray J, Anand I, et al. Angiotensin–Neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med. 2019; 381(17): 1609–1620, doi: 10.1056/nejmoa1908655, indexed in Pubmed: 31475794.
21. Solomon SD, Claggett B, Lewis EF, et al. TOPCAT Investigators. Influence of ejection fraction on outcomes and efficacy of spironolactone in patients with heart failure with preserved ejection fraction. Eur Heart J. 2016; 37(5): 455–462, doi: 10.1093/eurheartj/ehv464, indexed in Pubmed: 26374849.
22. Lund LH, Claggett B, Liu J, et al. Heart failure with mid-range ejection fraction in CHARM: characteristics, outcomes and effect of candesartan across the entire ejection fraction spectrum. Eur J Heart Fail. 2018; 20(8): 1230–1239, doi: 10.1002/ejhf.1149, indexed in Pubmed: 29431256.
23. Ferreira JP, Packer M, Butler J, et al. Reconsidering the ejection fraction centric view of pharmacologic treatment for heart failure. Eur J Heart Fail. 2022; 24(7): 1148–1153, doi: 10.1002/ejhf.2457, indexed in Pubmed: 35191586.
24. Arnold SV, Silverman DN, Gosch K, et al. Beta-Blocker use and heart failure outcomes in mildly reduced and preserved ejection fraction. JACC Heart Fail. 2023; 11(8 Pt 1): 893–900, doi: 10.1016/j.jchf.2023.03.017, indexed in Pubmed: 37140513.
25. Vaduganathan M, Docherty KF, Claggett BL, et al. SGLT-2 inhibitors in patients with heart failure: a comprehensive meta-analysis of five randomised controlled trials. Lancet. 2022; 400(10354): 757–767, doi: 10.1016/S0140-6736(22)01429-5, indexed in Pubmed: 36041474.
26. Empagliflozin in heart failure with a preserved ejection fraction. N Engl J Med. 2022; 386(21): e57, doi: 10.1056/nejmc2118470, indexed in Pubmed: 35613032.

27. McMurray J, Solomon S, Inzucchi S, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med . 2019; 381(21): 1995–2008, doi: 10.1056/nejmoa1911303, indexed in Pubmed: 31535829.
28. Kosiborod MN, Petrie MC, Borlaug BA, et al. STEP-HFpEF DM Trial Committees and Investigators, STEP-HFpEF Trial Committees and Investigators. Semaglutide in patients with heart failure with preserved ejection fraction and obesity. N Engl J Med. 2023; 389(12): 1069–1084, doi: 10.1056/NEJMoa2306963, indexed in Pubmed: 37622681.
29. Siddiqi TJ, Anker SD, Filippatos G, et al. Health status across major subgroups of patients with heart failure and preserved ejection fraction. Eur J Heart Fail. 2023; 25(9): 1623–1631, doi: 10.1002/ejhf.2831, indexed in Pubmed: 36974746.
30. Shah S, Segar MW, Kondamudi N, et al. Supranormal left ventricular ejection fraction, stroke volume, and cardiovascular risk: findings from population-based cohort studies. JACC Heart Fail. 2022; 10(8): 583–594, doi: 10.1016/j.jchf.2022.05.007, indexed in Pubmed: 35902163.
31. Maredziak M, Bengs S, Portmann A, et al. Microvascular dysfunction and sympathetic hyperactivity in women with supra-normal left ventricular ejection fraction (snLVEF). Eur J Nucl Med Mol Imaging. 2020; 47(13): 3094–3106, doi: 10.1007/s00259-020-04892-x, indexed in Pubmed: 32506162.
32. Uijl A, Savarese G, Vaartjes I, et al. Identification of distinct phenotypic clusters in heart failure with preserved ejection fraction. Eur J Heart Fail. 2021; 23(6): 973–982, doi: 10.1002/ejhf.2169, indexed in Pubmed: 33779119.