UNIVERSITATEA DE MEDICINĂ ȘI FARMACIE

"CAROL DAVILA" din BUCUREȘTI

UNIVERSITY OF MEDICINE AND PHARMACY

"CAROL DAVILA", BUCURESTI

DOCTORAL SCHOOL

FIELD: MEDICINE

IMPACT OF NON-CARDIAC COMORBIDITIES ON THE OUTCOME OF HEART FAILURE PATIENTS WITH LOW LEFT VENTRICULAR EJECTION FRACTION COMPARED TO HEART FAILURE PATIENTS WITH PRESERVED LEFT VENTRICULAR EJECTION FRACTION

PhD SUPERVISOR:

PROF. UNIV. DR. CRINA JULIETA SINESCU

PhD STUDENT:

CEZARA ANDREEA SOYSALER

2024

3. WORKING HYPOTHESIS AND GENERAL OBJECTIVES

Non-cardiac comorbidities are central to the progression of Heart Failure (HF) and their effective management is crucial in the proper care of patients. Diabetes mellitus (DM), hypertension, obesity and hypercholesterolemia are important risk factors in the development of HF, and addressing them appropriately, together with the use of artificial intelligence (AI) and machine learning (ML), can improve prognosis and prevent complications.

AI and ML can be used to optimize the management of patients with HF, both by early identification of comorbidities and by providing personalized treatment strategies. These technologies can manage large volumes of data and help close gaps in diagnosis and treatment. Therefore, comprehensively addressing cardiovascular risk factors and comorbidities, particularly in the case of DM, hypertension, obesity and hypercholesterolemia, is a key part of the management of HF patients, and AI and ML can play a significant role in this process.

The focus of this thesis is to better understand HF through the lens of comorbidities and how they influence disease progression. We have pursued three objectives which are found within the three chapters in the results part of the 'Own contributions' chapter:

Ø To develop an ML algorithm based on which to identify the comorbidities with the strongest impact on left ventricle ejection fraction (LVEF) in order to eliminate and/or treat them to prevent complications or worsening of the disease;

Ø Generate an ML algorithm to group HF patients admitted to hospital into subsets based on comorbidities and disease progression to more easily identify high-risk patients and prevent major episodes impacting survival and quality of life;

Ø Statistical analysis of the impact of demographic factors (gender and education) as well as comorbidities (valvopathy, ischemia, smoking, obesity, high cholesterol and diabetes) on HF progression.

4. GENERAL RESEARCH METHODOLOGY

The three studies took place in the Cardiology Clinic of the Emergency Hospital "Bagdasar-Arseni", Bucharest, Romania. The study type was prospective and data were collected from 201 patients between October 2019 and October 2020.

Inclusion criteria were as follows:

- Patients over 18 years of age,

- CHF with preserved or reduced LVEF

- presence of cardiovascular and non-cardiovascular comorbidities (diabetes, dyslipidemia, obesity, associated ischemic pathology, hypertension)

Exclusion criteria were as follows:

- Refusal to sign informed consent at study enrolment.

- neuropsychiatric diseases

- life expectancy under 1 year

Participation in these studies was voluntary, unconditional, unpaid, was done after discussion with the treating physician and did not affect the setting of clinical assessments and treatment protocols. Patients who agreed to enrollment signed informed consent. All steps involving humans were carried out in accordance with the good practice guidelines of the Declaration of Helsinki (October 2008).

STUDY NO.1. RELATIONSHIP OF BEHAVIOURAL, SOCIAL AND DIABETES FACTORS WITH LEFT VENTRICULAR EJECTION FRACTION MEASURED USING MACHINE LEARNING TECHNIQUES

HF remains one of the most important public health problems, a major cause of death and readmission, with an increasing incidence and a mostly poor prognosis requiring new therapeutic options appropriate to each subgroup of patients. Various mechanisms contribute to the development of HF with reduced ejection fraction, many of which are under-researched. Obesity, hypertension, sedentary lifestyle and metabolic syndrome have been identified as important risk factors for various cardiovascular diseases, including HF with reduced ejection fraction. Hospitalizations remain relevant because of their relatively easily quantifiable costs and as a marker for disease severity, quality of life and prognosis. In 2012, Cook et al. assessed the global annual burden of HF from all published sources and estimated it at $108 billion annually. The immediate average HF burden for high-income countries was 1.42% versus 0.11% for low- and middle-income countries (1).

The aim of this study is prevention, early diagnosis and intervention to reduce risk factors, including in the context of co-morbidities, which aim to be better understood. The ultimate goal is to improve the prognosis of HF patients and provide better recommendations. We also aimed to identify the main risk factors for HF, factors that are subsequently used to estimate disease progression and survival. Data of patients admitted to hospital for acute HF were assessed and analysed from the first day of admission to the day of discharge. We demonstrated that smoking, poor education and obesity are the most harmful factors, while diabetes controlled by diet or medication does not significantly affect LVEF.

This research is just the tip of the iceberg in terms of measuring and understanding in depth how certain factors affect HF. However, we believe that this approach in which we combine classical and modern ML technologies together with more data could lead to significant advances, combined with other findings from different fields such as genetics.

Many factors are known to be major or minor contributors to the development of HF. Certain causes include coronary artery disease, hypertension, cardiomyopathies, valvular and congenital heart disease, arrhythmias, alcohol and drugs, increased flow insufficiency (anaemia, thyrotoxicosis, Paget's disease, etc.), pericardial disease and primary right-sided

HF. A meta-analysis by Jones et al. (2) found an improvement in secondary CHF survival rates over the last 70 years. The estimated 1-year survival rate was 85.5%; however, the 5- and 10-year survival rates were 56.7% and 34.9%, and most patients died of HF or cardiovascular diseases (CVD).

We believe that our study has several limitations: it was a prospective study, which did not make it possible to establish an unbiased design for patient selection. The study sample was small, especially for a powerful and complex machine learning classification algorithm such as XGB, and the results obtained are preliminary, which is why further research is needed to certify the results presented.

We believe that disseminating these findings from our study will confer more knowledge to clinicians by exploring the relationship between LVEF and behavioral, social, or comorbid factors and predictors of LVEF in these patients.

An extension of the studies to larger sample groups, covering the diversity of geographic and demographic regions, may provide a more complete perspective on the relationships between the factors investigated and LVEF. A comprehensive data-driven approach and multidimensional analyses could provide not only a more detailed understanding, but also the possibility of identifying patterns or trends that may have escaped detection in narrower studies.

In the future, improving this method of investigation could also involve integrating emerging technologies such as AI and ML to manage and analyse massive amounts of data in real-time. The use of advanced sensors and continuous monitoring systems could provide real-time data, thus contributing to a more accurate assessment of changes in LVEF dynamics and the timely identification of critical factors.

In terms of the limitations of the study, a possible development would be to transform it into a prospective study, where a more rigorous and unbiased design can be adopted for the selection of participants. Also, expanding the study sample and using more sophisticated ML algorithms may help to strengthen the findings and obtain more robust results.

STUDY NO.2. PATTERNS OF COMORBIDITY ASSOCIATIONS IN HOSPITALISED PATIENTS WITH CARDIOVASCULAR DISEASESTUDY NO.2. PATTERNS OF COMORBIDITY ASSOCIATIONS IN HOSPITALISED PATIENTS WITH CARDIOVASCULAR DISEASE

The aim of the current study was to identify the most relevant patterns for hospitalized patients, taking into account some dimensions of their comorbidities, such as triglyceride levels, cholesterol, diabetes, hypertension and obesity. To do this, several clusters were made taking into account the dimensions of comorbidity and the number of patients.

After analysing the existing data, we established three main patterns of patients presenting to hospital: cluster 3 (36%) had triglyceride and cholesterol levels within acceptable parameters and controlled diabetes, but fairly severe LVEF and obesity; cluster 2 (44%) had severe comorbidities; cluster 1 was the most stable group, with 20% of patients having not very severe comorbidities.

Atherogenic dyslipidaemia, hyperglycaemia, obesity and hypertension tend to occur in clusters in similar individuals. The high prevalence of dyslipidemia reported in this study is consistent with this expectation. Hypertension, DM, obesity and hyperlipidaemia are common in HF patients and affect clinical outcomes. Although these comorbidities are associated with the development of HF in the general population and in patients with established HF, their contributory roles are not predictable and their management is quite difficult.

These findings indicate that health education should be promoted among patients to prevent the onset and early detection of complications of dyslipidemia, diabetes mellitus, hypertension and obesity. Overall, the findings of this study show that prevention and treatment of dyslipidaemia, DM, hypertension and obesity should be a priority in the at-risk population.

The main limitations of the study relate to the sample. We had relatively few patients from a single site. Thus, the patterns obtained could be different in other areas or even over time. For a better estimation of how these comorbidities are identified in patients admitted with CVD, more studies should be done, recruiting more patients from more hospitals.

Recent guidelines have addressed the role of lifestyle modification, correction of plasma cholesterol values and management of overweight and obesity in the general population and in patients at high cardiovascular risk. These guidelines, however, do not specifically address the management of such comorbidities in patients with HF. Improvements in primary prevention and pharmacological treatment of cardiovascular risk factors result in a lower risk of cardiovascular events and fewer deaths(3).

As a result, the age at which people have their first cardiovascular event would shift to a later age, and patients would survive longer after the onset of cardiovascular disease. Today, more patients with CVD have longer life expectancy and are increasingly experiencing comorbidities, making this population of particular interest to research groups involved in comorbidity analysis(4, 5).

Comorbidity could lead to poorer performance status, lower quality of life, and even increased mortality(6-8). In addition to the effects on patients, having multiple chronic diseases also poses a challenge for health systems, especially primary care, as it has traditionally been centered around individual diseases.

In addition to better understanding the profile of an inpatient with cardiac conditions, this study may also help in the management of patients admitted to non-profile hospitals receiving cases with cardiac pathology. Knowing the main comorbidities and their proportion in patients, both in those analysed here and in others to be analysed, efficiency in hospitals could be increased through the formation of teams of doctors specialised in comorbidities, more efficient allocation of hospital resources such as equipment, or human resources.

After analysing the comorbidities of patients admitted for CVD symptoms, we can draw several conclusions relevant to the management of these complex cases.

Firstly, the study revealed the significant prevalence of comorbidities such as hypertension, diabetes mellitus, obesity, hyperlipidaemia and metabolic syndrome among patients with CVD. These conditions demonstrated a major influence on clinical outcomes, highlighting the complexity of managing these cases. However, the specific impact of these comorbidities on the clinical course and management of patients with established CVD remains uncertain and requires further investigation.

Secondly, implementation of behavioural change and effective management of comorbidities were identified as significant challenges in the care of patients with CVD. Even with lifestyle changes and medical treatment initiated, prevention and effective treatment of hypertension, diabetes, and obesity were found to be persistent challenges. This finding underscores the crucial importance of prevention strategies in reducing the overall impact of CVD.

Thirdly, the use of ML technologies, in particular the k-means method for grouping patients into clusters, has brought new insight into the analysis of comorbidities. The classification of patients according to their comorbid characteristics revealed three main patterns, with significant implications for tailoring the therapeutic approach. This method provides a useful framework for a deeper understanding of case diversity and can guide management efforts tailored to the specific needs of each patient group.

STUDY 3. IMPACT OF COMORBIDITIES AND DEMOGRAPHIC FACTORS ON EJECTION FRACTION

The primary objective of this study was to conduct a comprehensive analysis comparing differences in HF between men and women, taking into account relevant demographic variables such as gender and education, as well as relevant comorbidities including valvular heart disease, ischaemia, smoking, obesity, high cholesterol and diabetes. Research has demonstrated substantial disparities in ejection fraction values, both between genders and at different levels of education, with male patients showing considerably lower ejection fraction levels.

Significantly noticeable differences were observed in terms of education level, where individuals with a lower level of education showed markedly reduced ejection fraction levels. It is assumed that this discrepancy stems from the tendency of those with a higher level of education to prioritise preventive measures. Patient education has emerged as a key factor in HF management, serving as a catalyst to provide patients with essential self-care knowledge and skills. Furthermore, education contributes to improving patient quality of life by promoting self-management skills and encouraging a sense of control over their condition. Patients who are knowledgeable about HF and its management are better equipped to actively participate in their own care, leading to better physical and emotional well-being. In addition, patient education tends to aid prevention, and prevention would also bring

economic benefits to the healthcare system. Unfortunately, we do not have data on patient income. It would have been interesting to study income in this context of health and education. Also, education probably brings a good income, which could lead to a healthier lifestyle.

This study highlights the critical role of patient education in increasing compliance, self-efficacy and overall quality of life among HF patients, while mitigating healthcare expenditures. Patient education encompasses vital issues such as medication adherence, dietary changes, fluid restriction, symptom recognition, adherence to exercise guidelines, and the importance of regular appointments with the primary care physician. By conveying this crucial information, healthcare providers can equip patients with the tools they need to effectively manage their condition, thereby promoting improved health outcomes and reducing the burden on healthcare resources.

Comorbidities such as hypertension, dyslipidaemia, obesity and smoking exert a significant influence on LVEF, a crucial parameter in assessing cardiac function. ETS imposes an overload on the left ventricle, which can culminate in left ventricular hypertrophy and compromised ventricular relaxation. Both alterations can lead to reduced ejection fraction(9, 10).

Obesity, recognized as a precursor to many cardiovascular risk factors including hypertension, dyslipidemia and insulin resistance, induces left ventricular remodeling, impairs diastolic function and decreases ejection fraction (11, 12). Smoking, a substantial cardiovascular risk factor, causes endothelial dysfunction, inflammation, oxidative stress and vasoconstriction, all of which contribute to the development of atherosclerosis. Smoking-related coronary artery disease can lead to myocardial infarction, subsequently affecting left ventricular function.

Elevated LDL cholesterol levels and low HDL cholesterol levels promote atherosclerosis, inducing ischemia and myocardial damage, thus impacting ejection fraction(13, 14).

Valvulopathies encompass a spectrum of heart valve diseases and abnormalities. Several echocardiographic parameters change with age and are influenced by physical

activity. The severity of valvulopathies significantly affects LVEF ejection fraction, mainly classified into stenosis and regurgitation(15).

Valvular stenosis, which occurs in the aortic, mitral, pulmonary or tricuspid valves, obstructs efficient ejection of blood from the left ventricle, increasing ventricular pressure during contraction. Prolonged stenosis can lead to ventricular hypertrophy and reduce LVEF. Valvular regurgitation, found in the aortic, mitral, pulmonary or tricuspid valves, results in increased volume overload within the left ventricle due to retrograde blood flow during contraction. This condition can cause ventricular dilatation and decreased LVEF (16).

Diabetes is a widely recognized risk factor in the progression and occurrence of CAD complications. In individuals with both diabetes and CAD, compromised flow can result in myocardial injury, impairing left ventricular function and consequently causing a decrease in LVEF.

However, in people with diabetes who do not have significant CAD, the impact on LVEF may be less clear. Some studies have suggested that diabetes itself may have a direct effect on left ventricular function independent of CAD. Diabetes may contribute to structural changes in cardiac muscle, such as left ventricular hypertrophy and fibrosis, which can affect systolic function and lead to a reduction in LVEF. It is important to note that research results on the association between diabetes and LVEF have been inconsistent. Some studies have reported a significant reduction in LVEF among diabetics compared to non-diabetics, while others have not found a significant difference. Variation in study findings may be attributed to differences in study populations, methodology, duration of diabetes, control of other risk factors, and presence or absence of CAD.

Overall, the impact of diabetes on left ventricular systolic function, especially LVEF, may depend on various factors, including the presence of CAD. While diabetes is associated with an increased risk of cardiac complications, the exact relationship with LVEF is not yet fully elucidated and further studies are needed to better understand the underlying mechanisms.

Through a meticulous analysis of the aforementioned factors and their impact on HF, this study attempts to provide an in-depth insight into the distinctive requirements and

nuances essential for the prevention, diagnosis and effective management of HF in both men and women.

By comprehensively understanding gender-specific variations in HF, this research strives to contribute to the formulation of precise interventions and individualized treatment strategies. Such tailored approaches are key to improving outcomes among people of different genders, marking a significant advance in cardiac healthcare.

The main limitations of this study are the small size and low diversity of patients analysed. Although it was sufficient to find significant results, it would have been interesting to see how these influences of comorbidities manifest themselves on different groups of people, taking into account age, gender, lifestyle, etc., which would have required much more data.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

The aim of this thesis, divided into three independent studies, is to investigate the influence of demographic factors and co-morbidities on LVEF in HF. These factors include gender, education and comorbidities such as hypertension, diabetes, obesity and hyperlipidemia are prevalent in HF patients and can strongly influence clinical outcomes.

In study no. 1 we found that behavioral factors significantly influence the likelihood of LVEF values. Smoking had the greatest impact, significantly reducing LVEF values. Obesity has an impact, but smaller compared to smoking, and the absence of obesity has similar benefits to non-smoking status. Alcoholism seems to be related, but not very obvious.

Also in the same study, we found that social variables such as poor education, low income, female gender and rural background have a significant influence on the likelihood of having LVEF over 50. Poor education has the highest negative impact, while, paradoxically, low income has a protective impact. Female gender has a slight advantage and rural background seems to have minimal influence. These findings are supported by both the Shapley values and the logistic regression coefficients.

The results of study no. 2 indicated that smoking and obesity are the most harmful behavioral factors. In contrast, diabetes controlled by diet or drug therapy does not seem to significantly affect LVEF. In terms of social factors, poor education seems to have a statistically significant negative impact on LVEF, in contradiction to the results obtained in the first study.

Thus, study 2 highlights the importance of appropriate monitoring and management of comorbidities, as these can have cumulative effects on cardiac function and LVEF. In addition, research on gender differences in HF progression is needed to develop personalized strategies for treatment and prevention of the disease.

The results of Study no.3 suggest that demographic factors and education significantly influence LVEF. Apparently, LVEF was lower in men and those with poor education. These findings may be related to male-specific neurohormonal balance and the importance of education in the prevention and management of cardiovascular diseases (CVD).

Comorbidities such as hypertension, dyslipidemia, obesity, smoking and other cardiac conditions can affect LVEF, leading to left ventricular hypertrophy, diastolic dysfunction and other structural changes. Patients with these comorbidities should receive appropriate monitoring and management to prevent deterioration of ventricular function and LVEF.

The use of ML technologies, such as the K-means method, is of significant importance in the field of HF detection and monitoring. By analyzing clinical data and risk factors, these techniques can identify specific types of patients, such as those with moderate or severe comorbidities, helping to develop personalized treatment plans.

The development of large group studies covering different geographical areas can also make significant contributions to the field of HF research. This complex heart condition is a major topic of interest in the medical field, and large and diversified investigations can have a significant impact on understanding and improving HF prevention and treatment.

Another innovative approach with major potential in HF is the use of real-time data from sensors and monitoring devices. These data can provide detailed information on cardiac function, physical activity, physiological parameters and other aspects relevant to the health status of patients. This real-time monitoring can provide a more accurate and up-to-date picture of HF progression and response to treatment and can be successfully integrated into ML techniques.

PERSONAL CONTRIBUTIONS

Critical analysis of modifiable risk factors and certain comorbidities in order to improve the prognosis of patients with IC. (**Subchapter 5.1**)

Identification of the main factors of IC, subsequently used to estimate disease progression and survival of patients. (**Subchapter 5.2**)

Analysis of the impact of behavioral factors on LVEF values, focusing on smoking, obesity and alcoholism. (**Subchapter 5.1**)

Critical analysis of social variables (poor education, low income, female sex, rural environment) and their influence on the likelihood of having LVEF above 50%, supported by Shapley values and logistical regression coefficients. (**Subchapter 5.1**)

Investigation of the impact of dietary or drug-controlled diabetes on LVEF, with additional observations on the influence of precarious education on LVEF in the context of social factors. (**Subchapter 5.3**)

Emphasizing the importance of proper monitoring and management of comorbidities in the context of cumulative effects on heart function and LVEF. (**Subchapter 5.1**)

Highlighting the need for research on gender differences in the evolution of HFs for the development of tailor-made treatment and prevention strategies. (**Subchapter 5.2**)

Analysis of the influence of demographic factors and education on LVEF, with emphasis on reducing LVEF in men and those with poor education. (**Subchapter 5.2**)

Clarification of the impact of comorbidities (hypertension, dyslipidemia, obesity, smoking, other heart diseases) on LVEF, emphasizing the need for adequate monitoring and management to prevent ventricular function and LVEF deterioration. (**Subchapter 5.3**)

Demonstration of the importance of using ML technologies, including the K-means method, in IC detection and monitoring through analysis of clinical data and risk factors, to identify specific types of patients and develop personalized treatment plans. (**Subchapter 5.2**)

LIST OF PUBLISHED SCIENTIFIC PAPERS

1. **Soysaler C.A.**, Andrei C.L., Ceban O., Sinescu C.J. The Relationship of Behavioral, Social and Diabetes Factors with LVEF Measured Using Machine Learning Techniques. Applied Sciences. 2022 Sep 21;12(19):9474. **(ISI Web of Science indexed journal, IF-2.838) [MAIN AUTHOR]** [link] **(subchapter 5.1)**

2. Soysaler C.A., Andrei C.L., Ceban O., Sinescu C.J. Comorbidity Patterns in Patients at Cardiovascular Hospital Admission. Medicines. 2023 Mar 28;10(4):26. **(BDI B+ PUBMED indexed journal) [MAIN AUTHOR]** [link] **(subchapter 5.2)**

3. **Soysaler, C. A.**, Andrei, C. L., Ceban, O., & Sinescu, C. J. (2023). The Impact of Comorbidities and Demographic Factors on Ejection Fraction. *Medicines*, *11*(1), 1. **(BDI B+ PUBMED indexed journal) [MAIN AUTHOR]** [link] **(subchapter 5.3)**

REFERENCES

1. Cook C, Cole G, Asaria P, Jabbour R, Francis DP. The annual global economic burden of heart failure. Int J Cardiol. 2014;171(3):368-76.

2. Jones NR, Roalfe AK, Adoki I, Hobbs FDR, Taylor CJ. Survival of patients with chronic heart failure in the community: a systematic review and meta-analysis. Eur J Heart Fail. 2019;21(11):1306-25.

3. O'Flaherty M, Buchan I, Capewell S. Contributions of treatment and lifestyle to declining CVD mortality: why have CVD mortality rates declined so much since the 1960s? Heart. 2013;99(3):159-62.

4. Hoogwerf BJ. Prediabetes, Atrial Fibrillation, and Heart Failure: An Intersection of Comorbidities. Diabetes Care. 2023;46(1):9-10.

5. Screever EM, van der Wal MHL, van Veldhuisen DJ, Jaarsma T, Koops A, van Dijk KS, et al. Comorbidities complicating heart failure: changes over the last 15 years. Clin Res Cardiol. 2023;112(1):123-33.

6. Coste J, Valderas JM, Carcaillon-Bentata L. The epidemiology of multimorbidity in France: Variations by gender, age and socioeconomic factors, and implications for surveillance and prevention. PLoS One. 2022;17(4):e0265842.

7. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;380(9836):37-43.

8. Quinones AR, Hwang J, Heintzman J, Huguet N, Lucas JA, Schmidt TD, et al. Trajectories of Chronic Disease and Multimorbidity Among Middle-aged and Older Patients at Community Health Centers. JAMA Netw Open. 2023;6(4):e237497.

9. Tadic M, Cuspidi C, Ilic I, Suzic-Lazic J, Zivanovic V, Jozika L, et al. The relationship between blood pressure variability, obesity and left atrial phasic function in hypertensive population. Int J Cardiovasc Imaging. 2016;32(4):603-12.

10. Alpert MA, Karthikeyan K, Abdullah O, Ghadban R. Obesity and Cardiac Remodeling in Adults: Mechanisms and Clinical Implications. Prog Cardiovasc Dis. 2018;61(2):114-23.

11. Mendoza MF, Kachur SM, Lavie CJ. Hypertension in obesity. Curr Opin Cardiol. 2020;35(4):389-96.

12. Li M, Chi X, Wang Y, Setrerrahmane S, Xie W, Xu H. Trends in insulin resistance: insights into mechanisms and therapeutic strategy. Signal Transduct Target Ther. 2022;7(1):216.

13. Li N, Fu J, Koonen DP, Kuivenhoven JA, Snieder H, Hofker MH. Are hypertriglyceridemia and low HDL causal factors in the development of insulin resistance? Atherosclerosis. 2014;233(1):130-8.

14. Marciniak A, Glover K, Sharma R. Cohort profile: prevalence of valvular heart disease in community patients with suspected heart failure in UK. BMJ Open. 2017;7(1):e012240.

15. Lancellotti P, Tribouilloy C, Hagendorff A, Popescu BA, Edvardsen T, Pierard LA, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging. 2013;14(7):611-44.

16. Neeland IJ, Poirier P, Despres JP. Cardiovascular and Metabolic Heterogeneity of Obesity: Clinical Challenges and Implications for Management. Circulation. 2018;137(13):1391-406.