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ABSTRACT OF DOCTORAL THESIS

PROGNOSTIC IMPLICATIONS OF NEW ECHOCARDIOGRAPHIC TECHNIQUES AND CARDIAC MAGNETIC RESONANCE IN DILATED CARDIOMYOPATHY

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The doctoral thesis comprises 162 pages, has an iconography consisting of 49 figures and 49 tables.

The thesis is structured in three main parts: the general part, which includes the current state of knowledge, the special part, which includes personal contributions and the bibliography

The bibliography includes a number of 309 bibliographic references.

Key words: non-ischemic and ischemic dilated cardiomyopathy, heart failure, prognostic, ejection fraction, global longitudinal and circumferential strain, left ventricular basal and apical rotation, left ventricular twist, left ventricular diastolic dysfunction, E/e', E/Vp, ventricular asynchronism, late gadolinium enhancement, fatty metaplasia

LIST OF ABREVIATIONS

AAV – atrio-ventricular asynchrony

AF – atrial fibrillation

APT – aortic pre-ejection time

AUC – area under curve

BNP – brain natriuretic peptide

CMR – cardiac magnetic resonance

CI – cardiac index

CO – cardiac output

CRP – C-reactive protein

CRT– cardiac resynchronization therapy

CVASIC - Center for Invasive and Non-invasive Research in the Field of Cardiac and Vascular Pathology in Adults

DANISH - Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

DAPA-HF - Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction

DCM – dilated cardiomyopathy

ECV – extracellular volume

EF- ejection fraction

EROA – effective regurgitant orifice area

FAC – fractional area change

GCS – global circumferential strain

GLS – global longitudinal strain

HF – heart failure

HFSS – Heart Failure Survival Score

hs-CRP – high-sensitive C-reactive protein

IMIV - interventricular mechanical interval

LA – left atrium

LBB – left bundle block

LDL – low density lipoprotein

LGE – late gadolinium enhancement

LS AP2C – longitudinal strain in 2 chamber apical view

LS AP3C - longitudinal strain in 3 chamber apical view

LS AP4C - longitudinal strain in 3 chamber apical view

LV – left ventricle

LVEF – left ventricle ejection fraction

LV- EDD – left ventricle end-diastolic diameter

LV- EDV – left ventricle end-diastolic volume

LV-ESV – left ventricle end-systolic volume

MAPSE – mitral annular plane systolic excursion

MRI – magnetic resonance imaging

NT-proBNP – N-terminal fraction of brain natriuretic peptide

NYHA – New York Heart Association

PAP -pulmonary arterial pressure

PARADIGM-HF - Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure

PISA – proximal isovelocity surface area

PPT – pulmonary pre-ejection time

PsAxL – parasternal long axis view

RA – right atrium

RF – regurgitant fraction

RV – right ventricle

RVEF – right ventricle ejection fraction

RVol – regurgitant volume

SCD – sudden cardiac death

Se - sensibility

SGLT2 - sodium-glucose co-transporter 2

SHFM – Seattle Heart Failure Mode

Sp -specificity

SPWMD – septal to posterior wall motion delay

STAR – Speckle Tracking and Resynchronization

6MWT – six minute walking test

TAPSE – tricuspid annular plane systolic excursion

VC – vena contracta

Vp – flow propagation velocity at the level of the mitral valve

VPN – negative predictive value

VPP – positive predictive value

VT – ventricular tachycardia

V1- visit 1

V2- visit 2

V3 – visit 3

INTRODUCTION

The term dilated cardiomyopathy (DCM) includes a heterogeneous group of myocardial pathology, characterized by left ventricular (LV) dilation and LV systolic dysfunction, with normal LV wall thickness, changes present in the absence of pressure or volume overload (hypertension, heart disease valvular) and coronary heart disease (1) Various causes such as genetic mutations, infections, autoimmune triggers, toxic, nutritional deficiencies and endocrine abnormalities can lead to the final common change of ventricular dilatation with impaired systolic function (2-4).

DCM causes progressive heart failure (HF), arrhythmias of supraventricular origin or ventricular origin, conduction disturbances, thromboembolic events and death. DCM is the third leading cause of HF and the leading cause of cardiac transplantation (1,5).

The prognosis of patients with DCM shows great variability, the etiology representing an important element that significantly affects the evolution of these patients (3). In 20-30% of DCM cases, the cause is not identified, suggesting unidentified genetic or environmental factors as etiological agents (6). For these cases, classified as idiopathic DCM, giving targeted and specific etiological treatment becomes impossible.

Estimating the prognosis for morbidity, disability and death in patients with HF helps patients and clinicians to decide the appropriate type and timing of therapies (in particular the decision on rapid transition to advanced therapies). Numerous prognostic markers for mortality and/or decompensation with the need for HF hospitalization have been identified in patients with HF. However, their applicability in clinical practice is low and accurate risk stratification in HF remains challenging (7). In the last decades, a series of multiparametric prognostic scores have been proposed for different populations of patients with HF (8-13). Multiparametric prognostic scores are used to predict death in groups of subjects with HF, but have less utility in predicting the need for subsequent HF hospitalizations (9-10). Systematic review of the current literature revealed a number of prognostic models (Rahimi et al evaluated 64 such models in a systematic review (9), Ouwerkerk et al meta-regression analyzed 117 such models (10)), which were found to have moderate accuracy for predicting mortality, while models predicting the combined endpoint of death and hospitalization or hospitalization alone had even less predictive power (7).

The 5-year survival of patients with dilated cardiomyopathy ranges from 30% to 80% (2,3). There is currently no specific risk prediction model for DCM. Validated risk prediction models for heart failure apply to these patients. In 2016, the International Society of Heart and Pulmonary Transplantation redefined the criteria for including patients on heart transplant lists. Heart failure prognostic scores should be performed in conjunction with cardiopulmonary exercise testing to determine prognosis and guide placement on outpatient transplant lists. An estimated 1-year survival <80% calculated with the Seattle Heart Failure Model (SHFM) or a high/intermediate risk estimated by the Heart Failure Survival Score (HFSS) are considered reasonable cut-offs for enrollment on cardiac transplant lists (class IIb indication, level of evidence C) (14). The only imaging parameter included in these scores is the left ventricular ejection fraction.

CHAPTER 1

1. CURRENT STATE OF KNOWLEDGE

1.1. DCM – DEFINITION

The term dilated cardiomyopathy (DCM) includes a heterogeneous group of myocardial pathology, characterized by left ventricular (LV) dilatation and LV systolic dysfunction, with normal LV wall thickness, changes present in the absence of pressure or volume overload (hypertension, heart disease valvular) and coronary heart disease (1). Right ventricular dilatation and dysfunction may also be found, but these elements are not mandatory for establishing a positive diagnosis (3). LV dilatation is defined as an LV end-diastolic diameter or volume >2x standard deviation according to nomograms in use corrected for body surface area and age or body surface area and sex (3).

1.2. DCM – CLASSIFICATION AND ETIOLOGY

One of the most common classifications of DCM uses the etiological criterion to discriminate the different forms. Thus, DCM is divided into 2 large categories: the familial form and the non-familial form (3,4).

Familial DCM is defined as follows: when one or more individuals (first or second degree relatives) have defined diagnostic criteria for dilated cardiomyopathy or hypokinetic nondilated cardiomyopathy, and in the absence of an index patient meeting the diagnostic criteria for dilated cardiomyopathy or hypokinetic nondilated cardiomyopathy when sudden death has been documented in one first-degree relative under the age of 50 and at autopsy DCM was detected (3,15).

The transmission mode of the genetic defect in familial DCM is mainly autosomal-dominant, but the X-linked, autosomal-recessive and mitochondrial pathways have also been identified, to a lesser extent compared to the autosomal-dominant one (3). The genetics of DCM is complex and is characterized by incomplete penetrance, variable expressivity, unclear association between DCM-specific genotypes and phenotypes (6). Non-familial (non-genetic or sporadic) DCM has inflammatory or autoimmune mechanisms as its etiopathogenetic substrate. Studies by Felker et al and the Myocarditis Treatment Trial reported myocarditis as the cause of idiopathic DCM in 9% and 10% of patients, respectively (16, 18). However, in half of the patients studied, the etiology remained undefined. Inflammatory DCM is the late complication of the complex interaction between an infectious agent, most commonly viral, and the (auto)-immunological response that develops primarily in susceptible individuals (corresponding to a genetic factor) (17, 18).

1.3. EPIDEMIOLOGY

The actual prevalence of DCM in the general population is unknown, being estimated at 1:2500 and the incidence at 7/100,000/year. This pathology can appear at any age (incidence in children being 0.57/100000/year), without any differences in relation to the sex or ethnicity of the patient. In both adults and children, DCM has a higher frequency in males compared to females (3,19). The age of presentation is variable, with a predominance in the third and fourth

decade of life (1,5). It is estimated that two-thirds of DCM cases in children are actually idiopathic DCM (3,19).

1.4. PATHOLOGICAL ANATOMY AND PATHOPHYSIOLOGY

1.4.1 Pathological anatomy

Macroscopic evaluation reveals dilated cardiac cavities and increased parietal thickness secondary to myocyte hypertrophy and fibrosis that occur in this pathology. Heart valves are usually normal in appearance, but their function is frequently affected by the dilatation of the valve annulus that accompanies cavitary dilatation. Intracavitary thrombosis, especially at the LV apex, is common. Coronary arteries are in most cases of normal appearance, but in some cases coronary stenoses are identified below the limit of angiographic significance (the presence of stenotic lesions at the level of epicardial coronary arteries greater than 70%, defines the ischemic etiology of ventricular dilatation - ischemic heart disease in the dilatative stage) (3,4).

Microscopic evaluation reveals two associated imported changes to varying degrees: cardiomyocyte hypertrophy and interstitial fibrosis (3,4).

1.4.2 Pathophysiology

The main pathophysiological characteristics of DCM are the following: decrease in LV contractility, decrease in stroke volume, cardiac output and cardiac index, increase in end-diastolic pressures at LV level, thus resulting in alteration of both components of left ventricular dynamics: systolic contraction and diastolic relaxation (3). A number of factors are involved in cardiac myocyte apoptosis: parietal stress, activation of the catecholaminergic neuroendocrine system with β-adrenergic signaling and the release of angiotensin II, nitric oxide, reactive oxygen species and inflammatory cytokines. The optimal medical therapy used for HF antagonizes these pathogenic factors, being able to determine the regression of the pathological myocardial remodeling (3,20).

1.5. CLINICAL PICTURE

The clinical picture of patients with DCM is superimposed with that of patients with HF of any etiology. The initial stages of the disease are pauci-symptomatic, with patients reporting a slight limitation of exercise capacity after a careful anamnesis.

Pinto et al summarized the clinical spectrum of DCM, emphasizing the importance of the pre-clinical period. DCM can be classified as ND or D (non-dilated/dilated) or NH or H (non-hypokinetic/hypokinetic) or mut+ (mutation carrier) or AHA+ (anti-heart antibody positive) or A/CD (arrhythmia/conduction defect) (15).

Specific HF symptoms and signs are found in DCM patients with variable degrees and severity, related to the disease stage.

1.6. PARACLINICAL INVESTIGATIONS

Laboratory tests performed on patients with idiopathic dilated cardiomyopathy are as follows (21):

- blood count and inflammatory status
- metabolic tests
- thyroid function assessment
- cardiac biomarkers and natriuretic peptides
- biological markers that can suggest specific etiologies (3)

1.6.1 Blood count and inflammatory status

The complete blood count is of interest in patients with DCM mainly to detect the presence of anemia (21). Also, certain indicators such as mean platelet volume, neutrophil/lymphocyte ratio, platelet/lymphocyte are of interest in these patients as markers of possible underlying inflammation. Complementary to these inflammatory changes, the analysis of C-reactive protein (CRP) and especially high-sensitive C-reactive protein (hs-CRP) should be associated.

CRP correlates well with the severity and prognosis of heart failure and with the treatment response of these patients. Regardless of the etiology of heart failure (ischemic heart disease, idiopathic dilated cardiomyopathy, valvular heart disease), an increased concentration of hs-CRP has been shown to be associated with a faster negative evolution of the disease, a reduced left ventricular ejection fraction (EF), a lower quality life and lower therapeutic effect, higher New York Heart Association classes, higher levels of activated neurohormones (B-type natriuretic peptide, noradrenaline, aldosterone), higher readmission rates for cardiac decompensation, and in case of acute heart failure – admission to intensive care units, higher in-hospital and long-term mortality (22, 23).

1.6.2 Metabolic tests

In DCM, metabolic analyzes (21) are performed, investigations necessary for risk stratification and therapy follow-up such as:

- hyponatremia is independently associated with adverse clinical events in HF patients (24, 27).
- increased creatinine levels and a reduced creatinine clearance signify kidney damage in heart failure causing renal failure by pre-renal mechanism (hypovolemia)
- metabolic alkalosis can be secondary to diuretic therapy
- liver tests: the hepatic cytolysis syndrome occurs in heart failure due to liver stasis and liver failure may occur in patients with long-term evolution of the disease or in patients with severe cardiac decompensation that is difficult to reverse or is refractory to treatment
- hyperuricemia is related to symptoms, exercise tolerance, aggravation of diastolic dysfunction and long-term evolution (28, 29). Anker et al highlighted that the value of 9.5 mg/dL may be the cut-off value for predicting mortality (30).

1.6.3 Thyroid function assessment

Thyroid function assessment is of interest in view of the presence or absence of hyper- or hypothyroidism, which can be causes of left ventricular dilatation; on the other hand, thyroid dysfunction established after the onset of DCM confers a negative prognosis on these patients according to recent studies (21). Low triiodothyronine levels have been associated with myocardial fibrosis and perfusion/metabolism abnormalities in patients with idiopathic DCM. The combination of triiodothyronine levels and myocardial fibrosis assessed by cardiac magnetic resonance provides useful information regarding the prognostic evaluation of patients with idiopathic DCM (31).

1.6.4 Cardiac biomarkers and natriuretic peptides

Myocardial cytolytic enzymes (myoglobin, MB fraction of creatine phosphokinase, and troponin T and I) are important in the assessment of acute or recent myocardial injury, their serum levels being elevated in acute myocarditis. Moreover, recent research shows that patients with elevated levels of these enzymes have more severe heart failure and increased mortality compared to those with normal levels (32, 33). Plasma levels of natriuretic peptides are determined in the context of symptoms suggestive of HF with the aim of initial diagnosis of HF. Elevated concentrations support the diagnosis of HF, have a role in prognostic stratification (34), and may guide further cardiac investigations (35).

Several studies have correlated BNP and the N-terminal fraction of BNP (NT-proBNP) with worse prognosis (29). In the PARADIGM-HF trial that included patients with HF and reduced left ventricular EF, the decrease in NT-proBNP levels was clinically correlated with the decrease in mortality (13.3% versus 16.5%) (21). In DAPA-HF trial, Dapagliflozin significantly reduced NT proBNP by 300 pg/mL after 8 months of treatment compared with placebo and also reduced the risk of HF worsening and death (36). BNP and NT-pro BNP have both diagnostic and prognostic roles and they are also important for monitoring treatment effect (37)

1.6.5 Biological markers that can suggest specific etiologies

Certain abnormalities of some biological markers may be useful in identifying a specific etiology of DCM (3, 37):

- persistent increase in plasma levels of creatine kinase suggests neuromuscular diseases
- lactic acidosis, myoglobinuria are identified in mitochondrial diseases
- increased serum ferritin and transferrin binding capacity are found in hemochromatosis
- leukopenia has been detected in mitochondrial diseases (TAZ gene/Barth syndrome)
- autoimmune investigations

1.7. ELECTROCARDIOGRAM

The electrocardiogram shows no specific changes for DCM positive diagnosis. It can record heart rate and rhythm disorders (sinus tachycardia, atrial fibrillation, ventricular extrasystoles with varying degrees of systematization), atrioventricular conduction disorders (these may indicate laminopathy or neuromuscular diseases), intraventricular conduction delay from hemiblock to block left branch (LBB). The LBB is a marker of a long-term evolution of the disease, its presence having therapeutic implications (criterion associated with NYHA functional class and LV ejection fraction for the decision of cardiac resynchronization) and prognostic role (3, 37). Reduced amplitude of the R wave and its slow progression in the precordial leads, Q waves in various territories in the absence of necrosis or coronary lesions are associated with a high degree of myocardial fibrosis (3, 37).

Certain electrocardiographic elements have a prognostic role, being considered predictive factors of mortality: reduction of heart rate variability, prolonged QT interval and non-sustained ventricular tachycardia associated with left ventricular systolic dysfunction. To the same extent, it has been observed that atrial fibrillation in DCM patients is associated with increased mortality or HF progression (3).

1.8. ECHOCARDIOGRAPHY

Echocardiography plays an essential role in the DCM diagnosis. In the presence of HF, echocardiography is essential not only to evaluate LV function but also to guide the management of patients and exclude alternative causes of HF (valvular disease, restrictive cardiomyopathy, constrictive pericarditis). Typically, DCM is characterized by LV dilatation (increased end-diastolic and end-systolic dimensions) with impaired global contractility and reduced systolic function. As the disease progresses, the LV becomes more spherical (38, 39).

The exponential growth of echocardiographic technologies and performance in recent years has resulted in improved diagnostic accuracy, stratification, management and follow-up of patients with DCM (40).

1.8.1 Echocardiographic diagnostic criteria

DCM has long been defined by the presence of LV ejection fraction (LVEF) less than 45% and/or a shortening fraction less than 25% and LV end-diastolic diameter (LV-EDD) greater than 112% of the predicted value depending on age and body surface area (38, 41). The equation used to predict LV-EDD (mm) corrected for age (years) and body surface area (m^2) was defined by Henry WL et al (67): corrected LV-EDD = [(45.3xbody surface area$^{0.3}$)-0.03xage)-7.2] ±12%. A more conservative cut-off value of 117% for LV dilatation has been proposed to increase specificity in familial screening studies for DCM (42).

The 2023 European Society of Cardiology cardiomyopathies guideline updates the definition of DCM as LV dilatation with LV end-diastolic dimensions or volumes > 2 Z-scores above population mean values corrected for body surface area, sex and/or age. For adults these are an LV end-diastolic diameter >58 mm in men and >52 mm in women and an indexed LV end-diastolic volume ≥75 mL/m2 in men and ≥62 mL/m2 in women. Global LV systolic dysfunction in DCM, a clinical entity that could also include non-dilated and arrhythmogenic forms, is defined as ejection fraction < 50% (15, 40, 43-45).

1.8.2 Left ventricular systolic function

Several echocardiographic parameters are used to assess LV systolic function: EF, shortening fraction, dP/dT, cardiac output that are dependent on volume or pressure load, and myocardial velocities at the level of the mitral annulus determined by tissue doppler and myocardial strain imaging by the speckle tracking technique, techniques that are less dependent on volume or pressure load (38, 46). LVEF is the most widely used expression of LV systolic function. It is the main determinant of symptoms, functional class and prognosis (47). Mitral annulus myocardial velocities obtained by Tissue Doppler and myocardial deformation by speckle tracking performed in 2D and more recently 3D echocardiography are less dependent on overload and are decreased in patients with LV systolic dysfunction. They provide diagnostic and prognostic information and are useful in the early diagnosis of systolic dysfunction in patients with various cardiomyopathies (38, 48).

1.8.3 Left ventricular diastolic function

Diastolic dysfunction is associated with hemodynamic alteration, advanced symptoms, and poor prognosis (38, 39). Different echocardiographic parameters of diastolic dysfunction are available and all have been studied in patients with DCM. Among them, the most studied is the trans-mitral diastolic flow pattern. E-wave deceleration time <150 ms, increased E/A ratio (>2), and increased E-wave velocity (>50 cm/sec) are associated with increased LV filling pressures and poorer prognosis. M-mode trans-mitral flow propagation velocity (Vp) has low values in most patients with impaired LVEF, with an E/Vp ratio >2.5 indicating elevated

pulmonary capillary pressures (38, 49). Early diastolic myocardial velocity at the level of the mitral annulus measured by Tissue Doppler (TDI) (e') and relationship with early diastolic filling (E/e') are used to estimate increased filling pressures due to their accuracy. In DCM an increased E/e' ratio is associated with increased filling pressures and worse prognosis (38, 49).

Left atrial (LA) dilation as a marker of diastolic dysfunction should be used with caution in this population, since many patients have left atrial dilatation with normal LV filling pressures (38, 49).

1.8.4 Right ventricular (RV) function and dimensions

RV dilatation and dysfunction are commonly seen in patients with DCM. These changes are usually caused by LV dysfunction or biventricular involvement rather than significant pulmonary hypertension (38, 39). The prevalence of RV dysfunction ranges from 63% to 76% and correlates with the degree of LV dysfunction. RV dysfunction has prognostic significance and its evaluation should be performed in all cases (38, 50). Fractional area change (FAC), TAPSE, tricuspid annulus systolic myocardial velocity on Tissue Doppler, and RV myocardial performance index have been widely studied in patients with DCM (38, 51). Tissue Doppler imaging and speckle tracking with analysis of RV strain and strain rate has shown promise in evaluating RV systolic function under certain conditions (63, 83). On the other hand, the lack of reference values, reproducibility problems and paucity of clinical data limit their application in current practice (38, 49).

1.8.5 The role of stress echocardiography in DCM

Stress echocardiography has a potential role in the initial but also advanced stages of the disease: in the initial stages, with normal LV function, the reduced inotropic reserve can unmask the initial changes, and in the advanced stages, stress echocardiography is complementary to resting echocardiography, being able to identify a heterogeneous prognosis profile that can guide therapeutic strategies (38, 53).

1.8.6 Associated changes

Mitral regurgitation in DCM is functional and related to LV dilatation and dysfunction. Secondary mitral regurgitation, found in both DCM and coronary artery disease in dilated stage, results from an imbalance between closing and tractional forces secondary to altered LV and LA geometry and function (54-56). The severity of mitral regurgitation is associated with a negative prognosis in patients with dilated cardiomyopathy (56).

The incidence of *intracavitary thrombi* in DCM has been reported to be between 4% and 16% (57). Spontaneous ultrasound contrast and LV thrombi can develop in the presence of severe LV dysfunction and dilatation. Specifically, LV ejection fraction is the major factor associated with LV thrombus formation in DCM (58) and the risk of systemic thromboembolism increases with LV ejection fraction less than 20% (57). Interestingly, it has been shown that the presence of severe mitral regurgitation may have a protective role against the formation of LV thrombi (58).

Functional tricuspid regurgitation and pulmonary hypertension are common in DCM, particularly in the presence of RV dilatation and dysfunction (59). While the severity of LV systolic dysfunction did not show an independent relationship with pulmonary hypertension, the severity of functional mitral regurgitation and diastolic dysfunction were strongly correlated with pulmonary hypertension (60).

Cardiac mechanical asynchrony has negative effects on cardiac function causing a decrease in stroke volume and cardiac output secondary to changes generated in myocardial and valvular kinetics: asynchronous and ineffective contraction, delayed and ineffective relaxation, reduction of diastolic filling time, mitral regurgitation with end-diastolic component (61- 63).

Mechanical LV asynchrony in DCM patients with HF with severe LV systolic dysfunction and left bundle branch block has been shown to have independent predictive value for response to cardiac resynchronization device therapy (CRT) and long-term survival (64).

Speckle-tracking strain imaging can provide a more accurate assessment of asynchrony by calculating the time differences between the peak strain of opposite LV segments (usually the anteroseptal and posterolateral walls of the LV) (65). The Speckle Tracking and Resynchronization (STAR) study revealed that LV radial and transverse strain were significantly associated with response and long-term prognosis after CRT (66).

Despite the multitude of imaging parameters studied to predict the response to CRT (67) and therefore for their appropriate selection for this therapy, the only validated imaging parameter is still the LV ejection fraction, the other parameters needing further studies to show their utility in appropriate patient selection (68).

1.8.7 Risk stratification (LV systolic function, LV filling pattern, RV function).

Several echocardiographic parameters measured at baseline and at follow-up are valuable for the prognostic stratification of patients with DCM (38).

The degree of LV dilatation is correlated with disease severity and prognosis (69). On the other hand, low LVEF and severely increased LV dimensions (LV end-diastolic diameter ≥38 mm/m^2) are predictors of sudden cardiac death in patients with DCM (70, 71). Indications for primary prophylaxis of sudden cardiac death by defibrillator implantation in patients with DCM include LV ejection fraction as an echocardiographic parameter to consider (LV ejection fraction ≤35% - class IA indication in case of HF of ischemic etiology, class IIa A indication in HF of non-ischemic etiology) in association with NYHA functional class II or III, after 3 or more months of optimal medical therapy (109).

LV reverse remodeling, documented at follow-up of patients under optimal pharmacological therapy, is an independent prognostic factor for favorable long-term prognosis, reflecting less myocardial damage at baseline and a greater likelihood of improvement after treatment (72). Reverse LV remodeling is characterized by decreased ventricular volumes and normalization of LV shape associated with improved LV systolic and diastolic function (73). Initial predictors of reverse remodeling were higher systolic blood pressure and absence of left bundle branch block (72).

Although LV ejection fraction is universally used as an indicator of systolic dysfunction, it is too simplistic to capture the full spectrum of myocardial abnormalities accompanying myocardial dysfunction. Furthermore, LVEF correlates more closely with radial myocardial performance ignoring the contribution of longitudinal strain and contraction; it is important to bear in mind that the systolic mechanics unfolds in 3 directions: circumferential, radial and longitudinal (74, 75).

Global longitudinal strain (GLS) is one of the most studied parameters of myocardial deformation. (76). Stanon et al studied the prognostic value of GLS beyond conventional parameters in 546 patients with HF. GLS provided incremental value in the subgroup of patients with LV ejection fraction >35% and in those without segmental kinetic disorder. A value of GLS ≥ -12% has been shown to have a prognostic role (77).

In the Penn Heart Failure trial, the utility of strain was studied in 416 HF patients with low LV ejection fraction (76% of them of non-ischemic etiology). Reduced strain correlated with higher NYHA class, higher NT-proBNP levels, and larger chamber sizes. Strain in all 3 directions (longitudinal, circumferential, radial) was independently associated with an increased risk of major cardiovascular events in multivariate models adjusted for clinical variables. (74).

GLS has been shown to be a prognostic parameter for reverse LV remodeling. The higher the GLS (in absolute value) the more it is associated with better reverse remodeling, even at a similar LV ejection fraction. A GLS value more negative than -10%, which is reported as the cut-off, is correlated with better reverse remodeling and consequently with a better long-term prognosis (78, 79).

Speckle-tracking echocardiography has been proposed and validated as a feasible method for measuring LV rotation and torsion (80-82). Reversed apical rotation and loss of LV torsion in patients with DCM is associated with significant LV remodeling, impaired ventricular geometry, increased electrical asynchrony, reduced systolic function, and increased LV filling pressures. These changes identified a subgroup of patients with more advanced disease (80).

Assessment of LV diastolic function adds additional prognostic information in patients with DCM. The restrictive pattern (grade 3 diastolic dysfunction) of LV filling reflects a more advanced clinical stage of the disease, being generally accompanied by severe LV dilatation and systolic dysfunction, dilated LA, RV involvement and functional mitral regurgitation, and is a strong marker of increased risk of death and the need for cardiac transplantation (83). Moreover, grade 2 and 3 diastolic dysfunction, as well as E/e'>15 have been shown to be significant prognostic factors, independent of LV ejection fraction, in patients with DCM (84). Systolic velocity at the level of the mitral lateral annulus less than 5 cm/sec associated with a value of E/e'>15 in patients with DCM has been shown to be strongly related to the negative prognosis (85).

RV dysfunction has been recognized as a negative prognostic factor in DCM and is associated with more advanced LV dysfunction and considerably poorer functional class and prognosis. A TAPSE value of less than 14 mm has been shown to have a negative prognostic value in patients with DCM (86). Additionally, reduced values of RV strain and 3D RV ejection fraction have been related to decreased exercise capacity in this population (87-88).

In addition, bi-ventricular dilatation is known to carry a more reserved prognosis compared to isolated LV dilatation (89). To the same extent, dilatation of the left atrium is an unfavorable prognostic element in elderly patients with DCM, over 70 years old (90).

Functional mitral regurgitation is another negative prognostic marker (72), and higher degrees of mitral regurgitation are related to worse clinical status and reduced survival (91). Several studies have demonstrated the negative prognostic value of mitral regurgitation using a cut-off value of regurgitation area greater than 0.2 cm2 (92). Pulmonary hypertension and tricuspid regurgitation are also predictors of morbidity and mortality in DCM (59).

1.9. CARDIAC MAGNETIC RESONANCE

Cardiac magnetic resonance (CMR) is a valuable investigation for the evaluation of patients with DCM with an continuous increasing impact on diagnosis and therapeutic management. The ability of CMR to characterize the myocardium, using different imaging parameters, provides us with information regarding the DCM etiology and its prognosis. CMR is widely accepted as the reference standard for quantifying cardiac chamber dimensions and LVEF and right ventricular EF. In addition, tissue characterization techniques such as late gadolinium enhancement (LGE) and other quantitative parameters such as T1-mapping, both native and with extracellular volume measurement, T2-mapping and T2-* mapping were validated against the histologically examination in a wide range of clinical scenarios (93).

1.9.1 The cine sequences

CMR cine sequences are used to assess cardiac function and morphology by reconstructing gated ECG images (74). Cine sequences are the reference technique to quantify cardiac cavity dimensions, ventricular function and mass, to assess parietal thickness and segmental function, and to calculate the parietal thickness/cardiac cavity radius ratio. Typically, the left ventricle (and right – not in all patients) shows moderate to severe dilatation with moderate or very low EF. The atria can be dilated, but usually the dilation is less pronounced than the ventricular one. Ventricular stroke volumes are usually within normal limits or only modestly reduced due to ventricular dilatation. Particular attention should be paid in the

situation of the concomitant existence of valvular regurgitation, when stroke volumes must be corrected (94).

Regarding parietal kinetics, severe hypokinesia or dyskinesia with varying degrees of asynchrony is detected (asynchrony frequently associated with bundle branch block and related to the degree of myocardial fibrosis (94).

1.9.2 Assessment of myocardial fibrosis

In view of the histopathological changes described in DCM, there has been an increased interest in evaluating the role of myocardial fibrosis as a biomarker to guide the management of patients and to determine their prognosis. Currently, it is known that fibrosis can occur in 2 forms that can be detected by CMR (93): irreversible replacement fibrosis that corresponds to late gadolinium enhancement (LGE) and diffuse interstitial fibrosis that corresponds better to changes detected on T1 sequences -mapping (95). This is where the most attractive clinical potential of contrast-enhanced MRI sequences emerges: the possibility of providing a non-invasive histological assessment and thus helping to identify specific etiologies of cardiomyopathies, without the need for endomyocardial biopsy (74).

1.9.2.1 Late gadolinium enhancement – LGE

LGE is of great help in making the differential diagnosis between left ventricular dilatation secondary to coronary artery disease and left ventricular dilatation without underlying coronary disease, a differentiation important for subsequent therapeutic strategy. Ischemic heart disease in the dilated stage typically shows subendocardial or transmural contrast uptake (representing the myocardial scar) in a coronary perfusion territory, whereas patients with idiopathic dilated cardiomyopathy may show no contrast uptake or linear or focal contrast uptake in the middle portion of the ventricular myocardium (contrast uptake that does not respect a coronary territory and not necessarily limited to the left ventricle, may also involve the right ventricle). Myocardial contrast uptake reflects segmental fibrosis in patients with idiopathic dilated cardiomyopathy (94). Myocardial fibrosis identified by LGE is most commonly present in the middle portion of the interventricular septum and can be identified in approximately 30% of patients with DCM (93, 96).

The presence of LGE identifies a cohort of patients who do not respond well to optimal medical therapy, a finding independent of other standard clinical parameters such as QRS duration and N-terminal fraction levels of natriuretic peptide. The amount of LGE is independently and inversely associated with changes in ejection fraction (the phenomenon of reverse remodeling defined as the decrease in the dimensions of the left ventricle and the improvement of its systolic function) that occurs secondary to medical therapy (93). The presence of LGE is a predictor of mortality, arrhythmic ventricular events, including sudden cardiac death, tachycardia or ventricular fibrillation, or appropriate defibrillator-initiated therapy, and for the risk of rehospitalization for heart failure (97).

Bogun et al (97) used LGE to map and plan the appropriate ablation strategy in a small group of patients with dilated cardiomyopathy. The location of the scar (endo vs. epicardial) was important in determining the optimal ablation approach. Moreover, transcatheter ablation has been shown to be ineffective in patients with predominantly intramural scars. Heart failure patients without myocardial scarring at LGE have a more favorable response to beta-blocker therapy by functional improvement and reverse ventricular remodeling compared with those with myocardial scarring (94).

Similar to arrhythmic risk assessment, LGE may be useful in predicting response to cardiac resynchronization therapy (93). Patients without LGE did significantly better after resynchronization therapy compared with those with LGE or those who underwent this therapy non-LGE guided (98).

1.9.2.2 T1-mapping technique

Myocardial pathology affects the myocardium in a rather uniform manner and with a global distribution in the form of inflammation, fibrosis, hypertrophy and diffuse myocardial infiltration, aspects that cannot be detected by LGE (99). The disadvantage of LGE is that it does not detect diffuse myocardial fibrosis because this technique is optimized to detect focal myocardial pathology. This explains the normal appearance of LGE in most patients with dilated cardiomyopathy (94, 100). T1 mapping, however, is a new technique that allows us to diagnose these diffuse conditions by measuring T1 values. T1-mapping measurements provide us with important indices of clinical significance and also allow us to estimate the extracellular space by calculating the extracellular volume fraction (ECV) (101).

The most important causes for increased T1 time are edema (increased tissue water for example in acute myocardial infarction or inflammation) and increased interstitial space (for example in fibrosis or infarct-scars, or cardiomyopathy or amyloid deposition). The most important determinants of low native T1 values are lipid overload (Anderson-Fabry disease, lipomatous metaplasia in old, chronic myocardial infarction) and iron overload (102).

Extracellular volume (ECV) is increased in case of amyloid deposition and excessive collagen deposition, thus being a more robust measure of myocardial fibrosis. VEC is decreased in thrombi and fat/lipomatous metaplasia. VEC can be calculated for myocardial regions of interest or visualized as ECV maps (102).

Native T1 values are increased in DCM and correlate with ventricular wall thickness (102). Increased ECV reflects the high amount of myocardial collagen in patients with DCM and may serve as a non-invasive imaging biomarker to monitor response to therapy and help stratify risk at different stages of the disease (103). ECV in DCM was shown to have values similar to those of patients with hypertrophic cardiomyopathy (28±0.4% - 1.5 T) (103).

Both in the acute and chronic phase of myocardial infarction, native T1 and ECV values are higher than in intact myocardium (in the acute phase the values are significantly higher than in the chronic phase) (104). In the acute phase of myocardial infarction, microvascular obstruction in the center of the infarcted area (no-reflow phenomenon) results in a pseudo-normalization of T1 values in this area (105, 106). Due to the accumulation of methemoglobin (T1 time shortening effect) the T1 time may even be decreased in case of intramyocardial hemorrhage (102). T1 mapping can reveal areas of lipomatous metaplasia in chronic myocardial infarction: these areas affect the electrical properties of the myocardium and may play an important role in the occurrence of post myocardial infarction arrhythmias (107). Fat has very low T1 values (230-350 ms at 1.5T) (108), and the area of fatty replacement in the central portion of the infarcted area causes significant decreases in T1 time (106).

1.10. THERAPEUTIC STRATEGIES IN DCM

The management of DCM is partially overlapping with that of HF with reduced LVEF (<40%) and mildly reduced LVEF (41-49%), to which is associated the management of cardiac arrhythmias and conduction disorders (atrial fibrillation, ventricular rhythm disorders of varying degrees of severity, atrioventricular blocks, left bundle branch block) and the management of thromboembolic complications (intracavitary thrombosis and/or systemic embolism) that may occur at the time of diagnosis or during the course of the disease. Treatment indications for asymptomatic left ventricular dilatation and/or dysfunction are insufficient, these situations representing real diagnostic challenges in terms of establishing a possible genetic etiology (43, 109).

1.10.1 Therapeutic management of DCM with reduced LV systolic function (≤40%)

The therapeutic strategy for HF with reduced LVEF should include the four therapeutic classes that have been shown to be effective by reducing mortality in randomized clinical trials: converting enzyme inhibitors/neprilysin receptor inhibitors, beta-blockers, mineralocorticoids receptor antagonists and sodium-glucose co-transporter 2 (SGLT2) inhibitors (109).

Associated with drug therapy, pacing device therapy, cardiac resynchronization and/or defibrillator implant, has an important role in the management of HF patients with reduced LVEF. The cut-off value of LVEF ≤ 35% is necessary to establish the indication for defibrillator implant, and for cardiac resynchronization therapy the criterion of QRS complex duration ≥ 130 ms should be added (109).

Secondary prevention by implantable defibrillator to increase survival is reserved for survivors of cardiac arrest and for cases with documented symptomatic sustained ventricular arrhythmias with hemodynamic alteration (110); the decision of such an implant must take into account the patient's opinion and his quality of life, as well as the association of no other pathologies that could cause death in less than a year (43).

The primary prevention of sudden cardiac death (SCD) is still a controversial subject requiring additional trials to complete the existing data (43).

A recent meta-analysis of studies evaluating defibrillator therapy in patients with DCM observed a survival benefit, although the effect was modest compared with patients with coronary artery disease with LVEF≤35% (111). Although LVEF ≤35% has been reported as an independent risk factor for global and cardiac mortality in DCM patients, it has modest discriminatory power in identifying DCM patients at increased risk of SCD, thus suggesting the need for additional factors that should be considered for the defibrillator implant decision for a pathology with significant etiological heterogeneity (43).

Recent studies suggest that genotype plays an important role in SCD risk, with patients carrying different variants of the PLN, DSP, LMNA, FLNC, TMEM43, and RBM20 genes having a substantially higher rate of major arrhythmic events than other causes of DCM, regardless of FEVS (43, 112-120). In patients without a high-risk genotype for SCD and LVEF≥35%, the presence and extent of myocardial scar as determined by LGE on cardiac magnetic resonance may help for risk stratification in patients with DCM (43, 121, 122). Additional risk factors such as syncope or the presence of unsustain ventricular tachycardia or the arrhythmic burden of ventricular ectopy may also guide the implantation of a defibrillator. At present, there is insufficient data for a threshold value of the arrhythmic burden of ventricular ectopy, the importance of which depends on the underlying genotype and other clinical factors (43, 113, 117, 123).

1.10.2 Therapeutic management of DCM with mildly decreased systolic function (LVEF 41-49%)

Therapeutic management of HF with mildly reduced LVEF (LVEF 41-49%) includes the 4 drug classes use in HF with low LVEF (≤40%) and diuretic therapy as appropriate, the indication classes being partially different (109).

1.10.3 Management of patients with advanced heart failure

Many HF patients progress to the advanced HF stage, characterized by persistent symptoms despite maximal therapy (124-126). Prognosis remains poor at this stage of the disease, with 1-year mortality ranging from 25% to 75% (124-126). The fourth universal definition of advanced HF was updated by the HF Association of the European Society of Cardiology in 2018 (125). A severely reduced LVEF is common but not mandatory for the diagnosis of advanced HF, as it can also develop in patients with preserved LVEF. In addition to the reported criteria, extra-cardiac organ dysfunction due to HF (eg, cardiac cachexia, renal

or hepatic dysfunction) or type II pulmonary hypertension may be present, but are not mandatory elements for the fourth definition of advanced HF (125).

In patients with advanced HF, pharmacological therapy and short-term mechanical circulatory support may be necessary until long-term mechanical circulatory support devices are implanted or until cardiac transplantation is possible (109).

CHAPTER 2

2. PERSONAL CONTRIBUTIONS

2.1 GENERAL OBJECTIVES

In addressing the issue of the proposed doctoral theme, the following specific objectives are established:

- O1: evaluation of patients by conventional two-dimensional echocardiography and by new echocardiographic methods – Tissue Doppler Imaging, speckle-tracking and identification of echocardiographic parameters with the most important prognostic impact
- O2: evaluation of patients by cardiac magnetic resonance and identification of the parameters with the most important prognostic impact
- O3: correlation of echocardiographic and cardiac magnetic resonance data in order to establish a protocol for prognostic assessment of patients

The primary endpoint is cardiovascular and all-cause death, and the *secondary endpoints* are the assessment of cardiovascular causes of death and the assessment of the number of hospitalizations for decompensated heart failure or severe arrhythmic events or thromboembolic events with cardiovascular starting point.

Creating an evaluation protocol with a prognostic purpose for patients with dilated cardiomyopathy, using the parameters obtained during the biological, electrocardiographic, echocardiographic and cardiac magnetic resonance evaluation, can be useful to the clinician in practice for establishing the severity of the pathology, for choosing an appropriate therapy and prioritizing the therapeutic strategies according to the degree of risk (pharmacotherapy, therapy with devices – pacemaker, defibrillator, resynchronization therapy or heart transplant) and to establish a follow-up plan for patients with dynamic assessments at different time intervals to capture on time the aggravating elements.

2.2 GENERAL METHODOLOGY

The studies included in the current work, enrolled and followed prospectively in the period 2017-2021 patients with DCM of non-ischemic (idiopathic) etiology (30 patients) and ischemic (30 patients) who were evaluated within the Center for Invasive and Non-invasive Research in the Field of Cardiac and Vascular Pathology in Adults (CVASIC) of the Sibiu County Emergency Hospital. They were examined clinically, biologically, electrocardiographically, echocardiographic with the help of a Philips CX50 ultrasound machine (equipped with specific cardiac applications, including Tissue Doppler Imaging and speckle tracking with the possibility of evaluating longitudinal and circumferential strain and parameters derived from this), invasive by coronary angiography with Philips Alura Clarity FD20 monoplane angiographic system (equipped with specific software for angiography and percutaneous treatment of angiographically significant coronary lesions) and by cardiac magnetic resonance with Phillips Ingenia 3T device (native cardiac evaluation and evaluation after gadolinium administration as contrast substance).

All patients presented optimal medical therapy that included the 4 drug classes recommended by the European Society of Cardiology for heart failure in the period 2017-2021: beta-blockers, converting enzyme inhibitors or angiotensin and neprilysin receptor inhibitor, mineralocorticoids receptor antagonist and SGLT2 receptor inhibitors were associated during the final follow-up period, as they were recommended as therapy in the 2021 European Society

of Cardiology guidelines for heart failure. Drug doses were adjusted according to the clinical and biological profile of each individual patient.

Antiplatelet therapy and lipid-lowering therapy were associated in patients who had significant coronary artery disease as a cause of left ventricular dilatation. Patients with angiographically significant coronary artery disease benefited from specific endovascular treatment with existing devices in the Angiography and Cardiac Catheterization Laboratory.

Therapy with pacemaker, defibrillator or cardiac resynchronization therapy was performed to all patients who presented an indication for these therapies according to the guideline recommendations of the European Society of Cardiology at that time.

Patients were dynamically followed with evaluations every one year for a period of 3 years: visit V1 – evaluation at 1 year, visit V2 – evaluation at 2 years and visit V3 – evaluation at 3 years.

Clinical (including the 6-minute walking test), electrocardiographic (12-lead electrocardiography and 24-hour ambulatory electrocardiographic monitoring), biological, echocardiographic and cardiac magnetic resonance data were collected according to a follow-up protocol during the 3 visits and recorded in the form of a database. Cardiac magnetic resonance was performed at the time of patient enrollment without being repeated during the follow-up period.

The obtained data were statistically processed in the SPSS Statistics 29.1.0 program, IBM, USA and presented in the form of tables and graphs. Statistical significance (p) was set at a threshold value of less than 0.05 (two-tailed).

2.3 STUDY I: THE PROGNOSTIC ROLE OF LEFT VENTRICULAR SYSTOLIC FUNCTION ASSESSED BY ECHOCARDIOGRAPHY IN DILATED CARDIOMYOPATHY

2.3.1 INTRODUCTION

Echocardiography plays an essential role in the diagnosis and long-term follow-up of patients with CM, also having a prognostic role, by evaluating structural abnormalities, systolic and diastolic dysfunction of the left and right ventricle, and the severity of valvular regurgitation. Different echocardiographic parameters were evaluated for prognostic purposes in heart failure patient populations, and ischemic and non-ischemic DCM were the main study groups.

Certain echocardiographic parameters evaluated, both at the time of diagnosis and in dynamics, are important for the prognostic stratification of patients with DCM (63). The degree of LV dilatation is correlated with disease severity and prognosis (69). Moreover, low LVEF and severely increased LV dimensions (end-diastolic diameter ≥38 mm/m2) are predictors of sudden cardiac death in patients with DCM (70, 71).

Although LVEF is universally used as an indicator of systolic dysfunction (2) (LVEF ≤35% after 3 months of optimal medical therapy being one of the essential criteria for cardiac resynchronization therapy and defibrillator implantation as primary prevention of sudden cardiac death (109)), is a too simplistic parameter to encompass the entire spectrum of abnormalities accompanying myocardial dysfunction. Moreover, LVEF correlates more strongly with LV radial myocardial performance, ignoring the contribution of longitudinal and circumferential strain (74, 75).

Systolic velocity at the level of the mitral annulus is a marker of LV systolic performance. Lateral mitral annulus systolic velocity less than 5 cm/sec in patients with DCM has been shown to be strongly related to a poor prognosis (85).

Global longitudinal strain is one of the most studied parameters of myocardial deformation. Some studies have shown that GLS provided incremental prognostic value in the subgroup of patients with LVEF>35% and in those without segmental kinetic disorders. A value of GLS ≥ -12% has been shown to have a prognostic role (77). The GLS is also a predictor of

LV reverse remodeling. The higher the GLS in absolute value, the more strongly it is associated with greater reverse remodeling, even at the same value of LVEF. A GLS value more negative than -10%, reported as a cut-off value, is correlated with better reverse remodeling and, consequently, with a better long-term prognosis (78, 79).

Reversed apical rotation and loss of LV torsion in patients with DCM are associated with significant negative LV remodeling with important change in ventricular geometry, increased electrical asynchrony, decreased systolic function, and increased values of LV filling pressures. These changes identified a subgroup of patients with more advanced disease (80).

2.3.2 MATERIAL AND METHOD

We evaluated 60 patients with heart failure, 30 with non-ischemic (idiopathic) DCM and 30 with ischemic DCM; all patients had optimal medical therapy. Patients were followed dynamically with evaluations every one year for a period of 3 years (Visits V1 – evaluation at 1 year, V2 – evaluation at 2 years and V3 – evaluation at 3 years). The patients were evaluated clinically, biologically, electrocardiographically – electrocardiogram in 12 leads and by two-dimensional echocardiography; all patients were evaluated by coronary angiography – patients with significant coronary lesions (greater than 70% or previous coronary angioplasty) as well as single vessel disease (significant stenosis in the anterior descending artery) or multivessel disease (significant stenosis greater than 50% in the common trunk of the left coronary artery or bivascular involvement - any two of the anterior descending artery, circumflex artery and right coronary artery - or significant concomitant stenoses of the 3 coronary arteries) were included in the ischemic DCM study group.

The inclusion criteria were the following:

- Age older than 18 years
- Left ventricular end-diastolic diameter measured by 2D echocardiography >112% relative to age and body surface area and an end-diastolic volume ≥ 75 mL/m2 in men and ≥62 mL/m2 in women (dimensions measured by two-dimensional echocardiography)
- LVEF ≤ 45% (determined by the Simpson bi-plane method) of ischemic or non-ischemic etiology

The exclusion criteria were the following:

- Age less than 18 years
- Other causes of ventricular dilatation such as: significant primary valvular disease (mitral regurgitation, aortic regurgitation, aortic stenosis), congenital heart diseases, other cardiomyopathies (hypertrophic, restrictive, arrhythmogenic cardiomyopathy) or any other conditions such as: endocrinopathies, connective tissue diseases, infiltrative diseases – sarcoidosis, amyloidosis, toxic and/or drug induced cardiomyopathy, tachyarrhythmic cardiomyopathy
- severe renal dysfunction defined by a creatinine clearance calculated by the Cockroft Gault formula of less than 30 ml/min/1.73m2

The objectives of the study were:

1. the primary objective: death from cardiovascular causes and from any cause – its correlation with echocardiographic parameters of LV systolic function
2. secondary objectives related to echocardiographic parameters of LV systolic function
   - evaluation of the number of hospitalizations determined by decompensated heart failure or severe arrhythmic events or thromboembolic events with a cardiovascular starting point
   - assessment of the causes of cardiovascular death

Refractory heart failure was defined as persistence or worsening of heart failure symptoms (including persistence of signs of systemic and/or pulmonary congestion requiring

increased doses of intravenous diuretic therapy, dependence on positive inotropic or vasoactive therapy, malignant ventricular arrhythmias refractory to antiarrhythmic therapy) in the context of the existence of optimal medical therapy and/or with different devices (defibrillator and/or cardiac resynchronization therapy).

Statistical analysis was performed in SPSS Statistics 29.1.0, IBM, USA. Quantitative variables were expressed as median ± standard deviation and were analyzed using Student's t test. Qualitative variables were expressed as a percentage and were analyzed using the Chi-square test. The prognostic value of statistically significant variables was analyzed using the ROC curve, an AUC (area under curve) value > 0.8 being considered as an excellent discriminative level (Hosmer and Lemeshow, 2000). Variables that showed a favorable AUC were subsequently analyzed by binomial logistic regression. Statistical significance (p) was set at a threshold value of less than 0.05 (two-tailed).

2.3.3 RESULTS

2.3.3.1 Comparative analysis non-ischemic group - ischemic group

With regard to the primary objective, the death rate was higher in patients with ischemic DCM (21.66%) compared to non-ischemic DCM (13.33%), but without reaching the threshold of statistical significance (p 0.714).

Regarding secondary endpoints, the main cause of death in both groups was refractory HF. The rate of SCD was the same in both groups, and in the ischemic DCM group the rate of refractory HF and fatal ischemic stroke was higher compared to the non-ischemic DCM group, but without reaching the threshold of statistical significance (p 0.685).

The HF hospitalization rate was significantly higher ($p<0.001$) in the ischemic group compared to the non-ischemic group, and hospitalizations for HF requiring vasoactive support had a significantly higher rate ($p<0.001$) in the ischemic group.

There were no statistically significant gender differences between the two analyzed groups. In terms of age, patients with non-ischemic DCM were significantly younger compared to patients with ischemic DCM (<0.001). Symptomatically, there were no differences in NYHA class at initial assessments (V1, V2) between the ischemic and non-ischemic groups. At the 3-year assessment (V3) in the non-ischemic CM group NYHA class II was significantly better represented compared to the ischemic group where NYHA classes III and IV were more frequent.

Also, there were no statistically significant differences ($p>0.05$) between the distance covered in the 6-minute walking test, in the ischemic group a steeper decrease in the walking distance was observed in the dynamic evaluations.

The analyzed biological parameters - NT-proBNP, serum creatinine, sodium, serum uric acid level, serum hemoglobin, liver cytolysis enzymes analyzed by determining TGP and LDH, total cholesterol, LDL-cholesterol and CRP as a marker of inflammation - showed no differences statistically significant between patients with ischemic versus non-ischemic DCM.

Analyzing the electrocardiographic parameters – the presence of sinus rhythm (SR) or atrial fibrillation (AF), QRS duration, QTc value, resting heart rate (HR), episodes of unsustain ventricular tachycardia, the presence of resuscitated cardiac arrest – no statistically significant differences were detected between non-ischemic DCM and ischemic DCM group. The duration of the QRS complex was longer in the non-ischemic group compared to the ischemic group, but without reaching the threshold of statistical significance.

From an echocardiographic point of view, no statistically significant differences were detected regarding the LV dimensions (as LD-EDD and LV-ESS) between the ischemic and non-ischemic group. Among the evaluation parameters of LV systolic function, LVEF, MAPSE, S' velocity expressed as the average of the values determined at the medial and lateral mitral annulus, GCS and LV FAC did not show statistically significant differences between the non-

ischemic and ischemic groups. In the ischemic group, the S velocity at the level of the mitral annulus decreased over time from the assessment of V1 to V3, while in the non-ischemic group the mitral S was relatively stationary in dynamics.

The dp/dt ratio had significantly lower values in the non-ischemic group compared to the ischemic group

The GLS did not present significant differences at the initial evaluations (V1, V2), but in dynamics at the V3 evaluation, it had significantly more impaired values in the ischemic group compared to the non-ischemic one. Moreover, following the dynamics on the 3 evaluations (V1-V3), both the GLS and the GCS registered a trend of improvement in the values in the non-ischemic group compared to the ischemic group where the GLS and GCS- ul have depreciated over time.

Basal and apical rotation of LV, LV torsion and twist, had significantly more impaired values in the non-ischemic group compared to the ischemic group, changes consistent with a longer QRS duration in the non-ischemic group compared to the ischemic group. Reversed apical rotation (clockwise) was significantly more frequent in the non-ischemic group compared to the ischemic group.

2.3.3.2 Comparative analysis deceased group – non-deceased group

The primary endpoint was achieved by 21 patients (35%) of the 60 evaluated. Overall mortality was higher in the ischemic group (n=13, 21.66%) versus non-ischemic (n=8, 13.33%). Regarding the gender and age of the evaluated patients, there were no statistically significant differences between the deceased versus non-deceased group.

Regarding secondary endpoints, the main cause of death was refractory HF, followed in order by SCD and fatal ischemic stroke. The rate of hospitalizations for HF and hospitalizations requiring vasoactive support was significantly higher (p 0.001) in the deceased group compared to the non-deceased group.

Clinically, patients who died had more advanced NYHA class, consistent with higher NT-proBNP values, more severe degrees of anemia, renal dysfunction, hyponatremia, liver cytolysis, higher uric acid values, and LDH and more pronounced inflammation assessed by determining C-reactive protein.

In the deceased group, in terms of electrocardiographic changes, the patients were more tachycardic, had a higher frequency of atrial fibrillation and a longer corrected QT interval. QRS complex duration did not show statistically significant differences between the deceased versus non-deceased group. No significant differences were found for documented episodes of ventricular tachycardia and history of resuscitated SCR between the deceased and non-deceased groups.

From an echocardiographic point of view, in the group of deceased patients, significantly more dilated LV was observed as diameter and end-diastolic volume, compared to the group of non-deceased patients. The classic parameters for evaluating LV systolic function - LV ejection fraction (LVEF), MAPSE, dp/dt - showed statistically significant differences between the two groups of patients both at the initial determination (V1) and at the subsequent evaluations (V2, V3), with lower values in patients from the deceased group.

Myocardial systolic velocity at the level of the mitral annulus (as the average of measurements at the medial and lateral levels) was significantly lower in the deceased group compared to the non-deceased group, with lower values at V3 assessment in the ischemic group versus the non-ischemic group -ischemic (4.96±1.33 versus 5.56±1.20) but without reaching the threshold of statistical significance (p 0.069).

Global longitudinal strain (GLS) and circumferential strain (GCS) did not show significant differences at the initial assessment (V1), but had statistically significantly more impaired values (closer to zero) in the deceased group compared to the non-deceased group in dynamics (at follow-up visits – V2, V3). Moreover, the GLS and its components (LS AP 2C,

LS AP 3C, LS AP 4C) and the GCS and its components (CS basal, CS medial, CS apical) were found to be independent predictors of mortality with an area under the curve (AUC) in ROC analysis greater than 0.8. The GLS at the V3 visit was significantly (p 0.034) lower in the ischemic group (-7.80±4.09) compared to the non-ischemic group (-9.92±3.43), while FEV did not show statistically significant differences between the ischemic group and non-ischemic both at initial assessment and at follow-up. In the non-ischemic DCM group, there was a significantly higher rate of LVEF improvement compared to the ischemic DCM group (20% versus 6.67%) (p 0.037).

Basal LV rotation, LV torsion, and twist were also significantly lower in the deceased group compared to the non-deceased group. LV apical rotation was more impaired in the deceased group compared to the non-deceased group, but without reaching the threshold of statistical significance (p 0.328).

For evaluating the effects of GLS LS AP 2C, LS AP 3C, LS AP 4C, GCS, basal CS, medium CS, apical CS over death probability in DCM patients, regardless of ischemic versus non-ischemic etiology, we performed a binomial logistic regression analysis. The logistic regression model was statistically significant $\chi2(8) = 44.203$, $p < 0.001$. This model explained 73.1% (Nagelkerke R2) of the variation and correctly classified 90% of the cases. The sensitivity of the regression model was 88.23%, and the specificity 95.12%, the positive predictive value 90.69% and the negative predictive value 88.23%. Only 3 of the 98 predictor variables were statistically significant: LA AP 2C, LS AP 3C, and basal CS. Increasing LS AP 2C, LS AP 3C and basal CS (values closer to zero) were associated with an increased probability of dying.

2.3.4 DISCUTIONS

Dilated cardiomyopathy is associated with an increased risk of heart failure and malignant ventricular arrhythmias including sudden cardiac death, being the most common cause of heart transplantation (1,5).

LV systolic dysfunction remains the main prognostic determinant of patients with DCM, and the 35% LVEF threshold stratifies patients for optimal medical therapy versus optimal medical therapy and cardiac device therapy (cardiac resynchronization therapy and/or defibrillator implant) (109). The importance of LVEF as a prognostic factor was also emphasized in the present study, with LVEF having lower values in the deceased group compared to the non-deceased group at 3 years of follow-up, without having statistically significant differences between the ischemic versus non-ischemic group. The mortality rate in the presented study was higher in patients with DCM of ischemic etiology compared to non-ischemic etiology; these data are consistent with data from current guidelines and studies.

In parallel with the LVEF deterioration, in the group of deceased patients there was a more important dilation of the LV in terms of diameter and LV end-diastolic volume. The importance of these data has been emphasized in the current literature, as it is well known that low LVEF and severely increased LV dimensions (LV end-diastolic diameter ≥ 38 mm/m2) are predictors of sudden cardiac death in patients with DCM (70, 127).

In addition to LVEF, the other classical parameters of LV systolic function (dp/dt, MAPSE) were found to have lower values in the group of deceased patients. These low values are consistent with low LVEF values. MAPSE values less than 8 mm have a sensitivity of 98% and a specificity of 82% for identifying patients with LVEF less than 50% (128). Dp/dt < 1000 mmHg/s signifies systolic dysfunction, and dp/dt < 600 mmHg/s signifies severe systolic dysfunction and has independent prognostic value (128). In our study, in the deceased group, MAPSE had a mean value lower than 8 mm and dp/dt had a value slightly higher than 600 mmHg/s at the initial evaluations (V1, V3), and at 3-year evaluation the value falls below the threshold value of 600 mmHg.

The systolic velocity at the level of the mitral annulus evaluated by Tissue Doppler had significantly lower values in the deceased group compared to the non-deceased group. This value was below 5 mm/s, the threshold value confirmed by current studies to have a negative prognostic impact (85), but no statistically significant difference was observed between the ischemic versus non-ischemic group.

The parameters derived from speckle tracking imaging, GLS and GCS, proved in our study to be independent prognostic factors of mortality, having good discriminative power for predicting death. Both GLS and GCS had more impaired values in the deceased group compared to the non-deceased group. In several studies in the current literature, the GLS value greater than -10 % (closer to zero) was considered the threshold value that was shown to be associated with a negative long-term prognosis (78, 79). In the present study the GLS had values greater than -10% (closer to zero) in patients who had died since the initial assessment, with further deterioration at subsequent evaluations despite maximal therapy administered. Patients in the non-deceased group had GLS values greater than -10% (closer to zero) at the initial visits, so that at the 3-year assessment the GLS value becomes lower (further from zero) than the threshold value of -10%, in parallel with keeping LVEF relatively constant from one assessment to another.

Moreover, the GLS had lower values in the case of ischemic versus non-ischemic etiology, this result being consistent with the higher mortality rate in the ischemic group.

Taking strain from all LV segments together as a binomial logistic regression, increased longitudinal strain (closer to zero) in apical 2-chamber and 3-chamber incidences (LA AP 2C, LS AP 3C) and increased basal circumferential strain (closer to zero) had the highest predictive power of death in DCM patients assessed, regardless of ischemic or non-ischemic etiology.

Apical systolic rotation (normally counterclockwise) is the main determinant of LV systolic torsion (81, 82). In our study, LV apical rotation had lower values in the deceased versus non-deceased group, but without reaching the threshold of statistical significance. In contrast, basal LV rotation, torsion and LV twist were significantly lower in the deceased group compared to the non-deceased group.

Regarding ischemic versus non-ischemic etiology, basal and apical LV rotation, LV torsion and twist, had significantly more impaired values in the non-ischemic group compared to the ischemic group, changes consistent with a longer QRS duration in the non-ischemic group compared to the ischemic group. Reversed apical rotation (clockwise) was significantly more frequent in the non-ischemic group compared to the ischemic group. This result is discordant with the higher mortality in the ischemic group compared to the non-ischemic group, thus suggesting that more mechanisms are involved in the impairment of LV apical and basal rotation, and consequently of twist and torsion than the impairment of LV systolic function evaluated in the present study by LVEF GLS and GCS. Experimental studies have demonstrated that epicardial fibers have a mechanical advantage in dominating the general direction of rotation. Taber et al demonstrated that the dilatation and thinning of the LV walls present in DCM equalizes the radii of the subepicardial and subendocardial layers (132, 133); as a result, the mechanical advantage of subepicardial myofibers (the main determinant of ventricular twist under physiological conditions) is reduced (134). In LV dilatation of ischemic etiology, the greatest suffering and replacement scar fibrosis is found in the subendocardial layers, and the subepicardial layers are the last to be affected, while in LV dilation of non-ischemic etiology, the replacement fibrosis is located in the thickness of the LV myocardium (middle-wall) or subepicardial with the presence of varying degrees of reactive interstitial fibrosis that affects the interaction of myocardial fibers. This explains why in non-ischemic DCM the basal and apical rotation of the LV and consequently the twist and torsion have reduced values compared to patients with non-ischemic DCM. Although they represent essential elements of LV mechanics, twist and torsion have a weaker correlation with LVEF compared to GLS (135). The question arises of a better correlation of basal and apical LV rotation, LV twist and torsion with radial strain, in the context in which the Speckle Tracking and Resynchronization (STAR) Study revealed that LV radial and transverse strain were significantly associated with response and

long-term prognosis after CRT (66). Patients responding to CRT (reduction of LV-EDD by more than 10%) had an improvement in twist (66).

2.3.5 CONCLUSIONS

LV systolic performance is the main determinant of the evolution of patients with DCM, with the different echocardiographic parameters used providing complementary prognostic information.

The following were observed in our studied group:

- Approximately one-third of patients with non-ischemic and ischemic DCM died at 3 years of follow-up.
- Overall mortality is higher in patients with ischemic DCM compared to patients with non-ischemic DCM
- The main cause of death in both groups is refractory heart failure, followed by sudden cardiac death and ischemic stroke
- The classical parameters for evaluating LV systolic function – LVEF, MAPSE, dp/dt, and S velocity at the level of the mitral annulus had significantly lower values in deceased patients compared to non-deceased patients, but without being significantly different in relation to the etiology non-ischemic versus ischemic
- Myocardial deformation parameters, GLS and GCS had significantly more impaired values in deceased patients compared to non-deceased patients, proving to be independent prognostic factors for mortality, having a good discriminative level for predicting death.
- The GLS had values significantly more impaired in dynamics in patients with ischemic DCM compared to patients with non-ischemic DCM, at relatively similar values of LVEF and NT-proBNP.
- LV basal rotation, torsion and twist had more impaired values in deceased patients compared to non-deceased patients. Apical rotation had lower values in the deceased group compared to the non-deceased group without reaching the threshold of statistical significance.
- LV Basal, apical rotation, torsion and twist, had significantly more impaired values in the non-ischemic group compared to the ischemic group, changes consistent with a longer QRS duration in the non-ischemic group compared to the ischemic group. Reversed apical rotation (clockwise) was significantly more frequent in the non-ischemic group compared to the ischemic group.
- Higher values (closer to zero) of longitudinal strain in 2 and 3 chambers, respectively, and higher values of circumferential strain in the LV basal segments had the greatest power to predict death in the whole group of study, regardless of ischemic or non-ischemic etiology.

2.3.6 STUDY LIMITATIONS

The main limitations of the study are represented by the small group of patients, as it is necessary to evaluate larger groups of patients to be able to extrapolate the results obtained, the relatively short follow-up period (3 years), the impossibility of determining the LV ejection fraction by 3D echocardiography, the impossibility determination of radial strain and calculation of mechanical dispersion parameters derived from myocardial strain imaging.

2.4 STUDY II: THE PROGNOSTIC ROLE OF THE DIASTOLIC FUNCTION OF THE LEFT VENTRICLE ASSESSED BY ECHOCARDIOGRAPHY IN DILATED CARDIOMYOPATHY

2.4.1 INTRODUCTION

Echocardiography is an important method for evaluating patients with dilated cardiomyopathy, both for diagnostic purposes and for long-term dynamic evaluation. Dilation of cardiac cavities, left and right ventricular systolic and diastolic dysfunction, and valvular regurgitation are frequently described elements in DCM, with varying degrees of severity.

Different echocardiographic parameters were studied for prognostic evaluation in heart failure patient populations - focusing on left ventricular systolic function, and patients with ischemic and non-ischemic DCM were the main study groups.

LV dilatation and impaired LV systolic function (assessed mainly by low LV ejection fraction and reduced global longitudinal strain) are the two main determinants of negative prognosis in patients with DCM. LV diastolic function has been less studied as a prognostic factor compared to LV systolic function.

Assessment of LV diastolic function provides additional prognostic information in patients with DCM. The restrictive pattern (grade III diastolic dysfunction) of LV filling reflects a more advanced clinical stage of the disease, being generally accompanied by severe LV dilatation and LV systolic dysfunction, dilated left atrium, right ventricular dysfunction and functional mitral regurgitation, being a marker strongly associated with increased risk of death and need for cardiac transplantation. The LV filling pattern assessed during invasive treatment indicated that the reversibility of the restrictive pattern correlates with a better long-term prognosis. Moreover, grade 2 and 3 diastolic dysfunction as well as an E/e' ratio >15 was found to be significant prognostic factors, independent of LV ejection fraction in patients with DCM (84).

2.4.2 MATERIAL AND METHOD

We evaluated 60 patients with heart failure, 30 with non-ischemic DCM and 30 with ischemic DCM; all patients had optimal medical therapy. Patients were followed dynamically with evaluations every one year for a period of 3 years (Visits V1 – evaluation at 1 year, V2 – evaluation at 2 years and V3 – evaluation at 3 years). The patients were evaluated clinically, biologically, electrocardiographically – electrocardiogram in 12 leads and by two-dimensional echocardiography; all patients were evaluated by coronary angiography – patients with significant coronary lesions (greater than 70% or previous coronary angioplasty) as well as single vessel disease (significant stenosis in the anterior descending artery) or multivessel disease (significant stenosis in the common trunk of the coronary artery left or bivascular involvement - any two of the anterior descending artery, circumflex artery and right coronary artery - or significant concomitant stenoses of the 3 coronary arteries) were included in the ischemic DCM study group.

The inclusion criteria were the following:

- Age older than 18 years
- Left ventricular end-diastolic diameter measured by 2D echocardiography >112% relative to age and body surface area and an end-diastolic volume ≥ 75 mL/m2 in men and ≥62 mL/m2 in women (dimensions measured by two-dimensional echocardiography)
- LVEF ≤ 45% (determined by the Simpson bi-plane method) of ischemic or non-ischemic etiology

The exclusion criteria were the following:

- Age less than 18 years

- Other causes of ventricular dilatation such as: significant primary valvular disease (mitral regurgitation, aortic regurgitation, aortic stenosis), congenital heart diseases, other cardiomyopathies (hypertrophic, restrictive, arrhythmogenic cardiomyopathy) or any other conditions such as: endocrinopathies, connective tissue diseases, infiltrative diseases – sarcoidosis, amyloidosis, toxic and/or drug induced cardiomyopathy, tachyarrhythmic cardiomyopathy
- severe renal dysfunction defined by a creatinine clearance calculated by the Cockroft Gault formula of less than 30 ml/min/1.73m2

The objectives of the study were:

1. primary objective: death from cardiovascular causes and from any cause – its correlation with echocardiographic parameters of LV diastolic function
2. secondary objectives related to echocardiographic parameters of LV diastolic function
   - evaluation of the number of hospitalizations determined by decompensated heart failure or severe arrhythmic events or thromboembolic events with a cardiovascular starting point
   - assessment of the causes of cardiovascular death

Statistical analysis was performed in SPSS Statistics 29.1.0, IBM, USA. Quantitative variables were expressed as median ± standard deviation and were analyzed using Student's t test. Qualitative variables were expressed as a percentage and were analyzed using the Chi-square test. The prognostic value of statistically significant variables was analyzed using the ROC curve, an AUC (area under curve) value > 0.8 being considered as an excellent discriminative level (Hosmer and Lemeshow, 2000). The Pearson correlation was used in the situations that allowed its use, a value of the coefficient r >0.5 signifying a strong correlation. Statistical significance (p) was set at a threshold value of less than 0.05 (two-tailed).

2.4.3 RESULTS

2.4.3.1 Comparative analysis non-ischemic group - ischemic group

The mortality rate was higher in the ischemic group (21.66%) versus the non-ischemic group, but without reaching the threshold of statistical significance (p 0.174). The main causes of death in both groups were refractory heart failure (HF), sudden cardiac death (SCD) and ischemic stroke, with an equal rate of SCD in the two groups and a higher rate of refractory HF and ischemic stroke in the ischemic group – but without reaching the threshold of statistical significance. The rate of hospitalization for HF was significantly higher ($p<0.001$) in the ischemic group compared to the non-ischemic group, and hospitalizations for HF requiring vasoactive support had a significantly higher rate ($p<0.001$) in the ischemic group.

Comparing patients with ischemic DCM versus non-ischemic DCM, no statistically significant differences were found regarding NT-proBNP and LVEF during the patients' follow-up period. On the other hand, patients with ischemic DCM presented more frequently NYHA class III and IV at the 3-year evaluation and more impaired GLS. There were no statistically significant differences between the two groups of patients regarding the degree of diastolic dysfunction, but the E/e' ratio and estimated systolic pressure at the level of the pulmonary artery had significantly higher values in the ischemic group compared to the non-ischemic group. The indexed LA volume and the E/Vp ratio were higher in the ischemic group compared to the non-ischemic group, but without reaching the threshold of statistical significance.

2.4.3.2 Comparative analysis deceased group - non-deceased group

The mortality rate in the studied group was 35% (21 patients) and was higher in the group with ischemic DCM (21.66%) versus non-ischemic DCM (13.33%), but without reaching the threshold of statistical significance. Regarding the gender and age of the evaluated patients, there were no statistically significant differences between the deceased versus non-deceased group.

Regarding the primary endpoint, the 21 patients (35%) who died had a significantly higher incidence of atrial fibrillation, more advanced NYHA class (III and IV), higher values of NT-proBNP, more dilated LV and LA, LVEF and GLS more impaired compared to the non-deceased group.

Regarding secondary endpoints, the main cause of death was refractory HF, followed in order by SCD and fatal ischemic stroke. The rate of HF hospitalizations and HF hospitalizations requiring vasoactive support was significantly higher in the deceased group compared to the non-deceased group.

Analyzing LV diastolic function, the deceased group had higher degrees of diastolic dysfunction (grade 2 and 3) with lower values of E-wave deceleration time (TDE) and mitral valve flow velocity (Vp) , higher values of E/e' and E/Vp ratios, tricuspid regurgitation velocity and estimated pulmonary artery pressures (PAP). During the follow-up period, the E/e' ratio and the PAP value had an increasing trend in the deceased group, while in the non-deceased group they were relatively stationary or even improved slightly.

NT-proBNP and E/e' ratio at 3-year follow-up and E/Vp were found to be independent predictors of mortality with an area under the curve (AUC) greater than 0.8.

Assessing whether there is a correlation between structural and functional changes, in the present study a strong positive correlation was registered between the E/Vp ratio and the indexed LA volume at 3 years of follow-up ($r=0.576$, $p<0.001$) and the end-systolic volume of the LV (LV-ESV) at 3 years of follow-up ($r=0.512$, $p<0.001$) (Figure 31). The E/Vp ratio showed a moderate negative correlation with LVEF ($r=-0.484$, $p<0.001$) and a moderate positive correlation with GLS ($r=0.439$, $p<0.001$).

The E/e' ratio showed a strong positive correlation ($r>0.5$) with LA volume ($r=0.623$, $p<0.001$), LV-EDV ($r=0.697$, $p<0.001$)) and GLS ($r=0.704$, $p<0.001$) and a strong negative correlation with LVEF ($r=0.731$, $p<0.001$), the strongest correlation being with LVEF, closely followed by GLS.

2.4.4 DISCUTIONS

Dilated cardiomyopathy carries an increased risk of heart failure and malignant ventricular arrhythmias, including sudden cardiac death, and is the most common cause of heart transplantation (6,7).

Recent studies have shown the importance of diastolic dysfunction for risk stratification in patients with DCM.

Indexed LA volume is an independent predictor of cardiovascular events including atrial fibrillation and cardiovascular mortality (136, 137). Moreover, LA indexed volume is a marker of diastolic dysfunction, and unlike LVEF, correlates well with NYHA functional class and global exercise capacity (138, 139). Indexed LA volume correlates with the E/e' ratio and may serve as a predictor of increased LV filling pressures during exercise (140). In the present study, indexed LA volume was significantly greater in the deceased versus non-deceased group, with no significant differences by ischemic or non-ischemic etiology, and strongly correlated with E/e' and E/Vp.

In a study of 12421 stage B and C heart failure patients with LVEF < 50%, Benfari et al showed that an increased E/e' ratio at diagnosis is associated with more advanced heart failure,

and is also related with reduced short-term survival and increased long-term mortality, independent of heart failure presentation, and thus should be incorporated into heart failure risk assessment. An E/e' value >14 was used as a threshold value for short- and long-term reserved prognosis, with a significantly worse prognosis at a value >20 (19).

In the present study the E/e' ratio proved to be an independent prognostic factor for mortality in patients with DCM of ischemic and non-ischemic etiology (AUC > 0.8), with higher values in the ischemic group, the group in which mortality was recorded bigger. Moreover, in the ischemic group at the dynamic evaluation over successive years, the E/e' ratio had an increasing evolution so that at the last evaluation it exceeded the cut-off value of 14, and in the deceased group the E/e' ratio has had a higher value of 14 since the first evaluation, with an upward trend in dynamics.

The increase in the E/e' ratio may be induced by volume overload in decompensated HF (18) and has been hypothesized to be unrelated to myocardial stiffness. However, studies have shown that after adjusting the E/e' ratio for "hemodynamic" parameters such as LVEF, PAP, glomerular filtration rate, it remains independently associated with short- and long-term prognosis (19, 20, 141). Thus, the persistence of increased values of the E/e' ratio after pharmacological decongestion of patients gives an even more reserved prognosis.

In summary, E/e' ratio ≥14 and indexed LA volume ≥34 ml/min are important markers of diastolic dysfunction and correlate with invasively measured LV filling pressures. Furthermore, in contrast to LVEF, indexed LA volume, E/e' ratio, and tricuspid regurgitation velocity correlate better with exercise capacity (142).

The E/Vp ratio reflects increased values of LV filling pressures, similar to the E/e' ratio, and in the present study proved to be a good predictor of mortality (AUC > 0.8), but without statistically significantly differentiating between etiology ischemic and non-ischemic. Studies have shown that E/Vp ratio >2.7 in HF patients with low LVEF predicted death, cardiac transplantation, and HF hospitalizations (143).

Biologically, in patients with HF, NT-proBNP determination is a surrogate for clinically evident dyspnea, with clearly demonstrated correlations between NT-proBNP values and NYHA class. NT-proBNP is released from myocardial cells in patients with HF, having a diagnostic role, a role for monitoring the effectiveness of treatment as well as a prognostic role. Studies have shown that elevated plasma levels of NT-proBNP correlate strongly with the decline in diastolic myocardial velocities e' at the level of the mitral annulus, but have a weak correlation with the E/e' ratio in patients with HF (109). In the present study NT-proBNP was a good discriminator for overall mortality (AUC > 0.8 at V2, V3 assessment), consistent with increased values of E/e' and E/Vp ratios and higher values of PAP estimated by echocardiography.

The functional changes expressed by the E/e' and E/Vp ratios appear in the context of structural changes such as ventricular and atrial cavity dilatation. In the present study, the existence of correlations between the functional and morphological elements was also evaluated and the existence of a strong positive correlation (r > 0.5) between the E/Vp ratio and the indexed LA volume and the LV end-systolic volume (LV-ESV) at 3 years of follow-up was revealed. and a moderated correlation with LVEF and GLS. Increased E/e' ratio strongly correlates with increased LA volume and LV end-diastolic volume, increased GLS (GLS values closer to zero), and decreased LVEF.

2.4.5 CONCLUSIONS

LV diastolic dysfunction plays an important role for the evolution of patients with DCM, being correlated with clinical status - NYHA class and their prognosis.

The following were observed on the studied lot:

- LA expressed as indexed volume was significantly more dilated in the deceased versus non-deceased group without statistically significant differences being recorded in relation to ischemic versus non-ischemic etiology
- E/e' and E/Vp ratios proved to be the diastolic function parameters with the greatest prognostic impact, along with NT-proBNP, being independent predictors of mortality, regardless of ischemic or non-ischemic etiology.
- Comparing ischemic and non-ischemic etiology, the E/e' ratio had significantly higher values in the ischemic group - the group with a higher mortality rate - while LVEF did not show statistically significant differences, and GLS had more impaired values in the ischemic group compared to the non-ischemic group;
- In the ischemic group, at the dynamic evaluation over successive years, the E/e' ratio had an increasing evolution so that at the 3-year evaluation it exceeded the cut-off value of 14, and in the deceased group the E/e' ratio was had since the first assessment a higher value of 14, with an upward trend in dynamics.
- The E/Vp ratio did not show statistically significant differences between the ischemic group and the non-ischemic group
- Increasing E/Vp ratio strongly correlates with increasing indexed LA volume and LV end-systolic volume (LV-ESV) at 3-year follow-up. The increase in E/e' ratio strongly correlates with LA volume, LV end-diastolic volume.
- Increasing E/e' ratio strongly correlates with increasing GLS (values of GLS closer to zero) and decreasing FEV. Increasing E/Vp ratio moderately correlates with increasing GLS (GLS values closer to zero) and with decreasing LVEF.

In conclusion, the imaging evaluation of DCM should include, in addition to the assessment of LV systolic function, the systematic definition of the LV diastolic profile and especially the E/e' and E/Vp ratios, which should be considered for risk stratification.

2.4.6 STUDY LIMITATIONS

The main limitations of the study are represented by the small group of patients, being necessary to evaluate larger groups of patients to be able to extrapolate the results obtained, the relatively short follow-up period (3 years), the impossibility of performing LA strain that brings complementary information in the evaluation LV diastolic dysfunction.

2.5 STUDY III - EVALUATION OF VALVULAR REGURGITATION (MITRAL AND TRICUSPID REGURGITATION AND SECONDARY PULMONARY HYPERTENSION), LV ASYNCHRONISM AND RIGHT VENTRICLE

2.5.1 INTRODUCTION

Mitral regurgitation in DCM is functional and related to LV dilatation and dysfunction. Secondary mitral regurgitation found in both idiopathic DCM and coronary heart disease in dilate stage results from the imbalance between closing and tractional forces secondary to altered LV and LA geometry and function (54-56).

Functional mitral regurgitation is a negative prognostic marker in DCM (72) and higher degrees of mitral regurgitation are related to worse clinical status and reduced survival (91). Several studies have demonstrated the negative prognostic value of mitral regurgitation using a threshold value of regurgitant orifice area greater than 0.2 cm2 (92).

Functional *tricuspid regurgitation* and pulmonary hypertension are common in DCM, particularly in the presence of RV dilatation and dysfunction (59). While the severity of LV systolic dysfunction did not show an independent relationship with pulmonary hypertension, the severity of functional mitral regurgitation and diastolic dysfunction were strongly correlated with pulmonary hypertension (60). Pulmonary hypertension and tricuspid regurgitation are also predictors of morbidity and mortality in DCM (59).

RV dilatation and dysfunction are commonly seen in patients with DCM. These changes are usually caused by LV dysfunction or biventricular involvement rather than significant pulmonary hypertension (38,39). RV dysfunction has prognostic significance and its evaluation should be performed in all cases (38, 50).

RV dysfunction has been recognized as a negative prognostic factor in DCM and is associated with more advanced LV dysfunction and considerably poorer functional class and prognosis. A TAPSE value of less than 14 mm has been shown to have a negative prognostic value in patients with DCM (86). Additionally, reduced values of RV strain and 3D RV ejection fraction have been related to decreased exercise capacity in this population (87, 88).

In addition, bi-ventricular dilatation is known to carry a more reserved prognosis compared to isolated LV dilatation (89). To the same extent, left atrial dilatation is a negative prognostic factor in DCM patients older than 70 years (90).

Cardiac mechanical asynchrony has negative effects on cardiac function causing a decrease in stroke volume and cardiac output secondary to changes generated in myocardial and valvular kinetics: asynchronous and ineffective contraction, delayed and ineffective relaxation, reduction of diastolic filling time, mitral regurgitation with end-diastolic component (61- 63). The assessment of cardiac asynchrony is challenging and should consider several parameters for the assessment of atrioventricular, interventricular and intraventricular asynchrony.

Mechanical LV asynchrony in DCM patients with HF with severe LV systolic dysfunction and left bundle branch block has been shown to have independent predictive value for response to cardiac resynchronization therapy (CRT) and long-term survival (64).

Speckle-tracking strain imaging can provide a more accurate assessment of asynchrony by calculating the time differences between the peak strain of opposite LV segments (usually the anteroseptal and posterolateral walls of the LV) (65). The Speckle Tracking and Resynchronization (STAR) study revealed that LV radial and transverse strain were significantly associated with response and long-term prognosis after CRT (66).

Moreover, interventricular asynchrony assessed by interventricular mechanical interval (IMIV) should be evaluated in patients with DCM, as significant interventricular asynchrony has been shown to be associated with a higher probability of favorable response to CRT (144).

Significant (moderate to severe) secondary mitral regurgitation is common among patients who are candidates for CRT and has been shown to affect long-term survival and response to therapy (145-146). CRT can improve mitral regurgitation in up to 40% of patients (145). However, in 60% of patients' significant mitral regurgitation is not corrected (147-148). Edge-

to-edge transcatheter mitral valve repair has been shown to improve response to CRT in registries (147-148), but not maintain the same response in randomized clinical trials despite optimal medical therapy (151).

Despite the multitude of imaging parameters studied to predict the response to CRT (67) and therefore for their appropriate selection for this therapy, the only validated imaging parameter is still the LV ejection fraction, while other elements such as the extent of the myocardial scar, the presence of mitral regurgitation or RV systolic function are important to identify potential non-responders who may need additional treatments (for example mitral valve interventions) (68).

2.5.2 MATERIAL AND METHOD

We evaluated 60 patients with heart failure, 30 with non-ischemic DCM and 30 with ischemic DCM; all patients had optimal medical therapy. Patients were followed dynamically with evaluations every one year for a period of 3 years (Visits V1 – evaluation at 1 year, V2 – evaluation at 2 years and V3 – evaluation at 3 years). The patients were evaluated clinically, biologically, electrocardiographically – electrocardiogram in 12 leads and by two-dimensional echocardiography; all patients were evaluated by coronary angiography – patients with significant coronary lesions (greater than 70% or previous stenting) as well as single vessel disease (significant stenosis of the anterior descending artery) or multivessel disease (significant stenosis of the common trunk artery left coronary artery or bivascular involvement - any two of the anterior descending artery, circumflex artery and right coronary artery - or significant concomitant stenoses of the 3 coronary arteries) were included in the ischemic cm study group.

The inclusion criteria were the following:

- Age older than 18 years
- Left ventricular end-diastolic diameter measured by 2D echocardiography >112% relative to age and body surface area and an end-diastolic volume ≥ 75 mL/m2 in men and ≥62 mL/m2 in women (dimensions measured by two-dimensional echocardiography)
- LVEF ≤ 45% (determined by the Simpson bi-plane method) of ischemic or non-ischemic etiology

The exclusion criteria were the following:

- Age less than 18 years
- Other causes of ventricular dilatation such as: significant primary valvular disease (mitral regurgitation, aortic regurgitation, aortic stenosis), congenital heart diseases, other cardiomyopathies (hypertrophic, restrictive, arrhythmogenic cardiomyopathy) or any other conditions such as: endocrinopathies, connective tissue diseases, infiltrative diseases – sarcoidosis, amyloidosis, toxic and/or drug induced cardiomyopathy, tachyarrhythmic cardiomyopathy
- severe renal dysfunction defined by a creatinine clearance calculated by the Cockroft Gault formula of less than 30 ml/min/1.73m2

The patients were evaluated by two-dimensional echocardiography with the determination of valvular regurgitation parameters according to the recommendations of the ESC guidelines for valvular disease, with the morphological and functional analysis of the RV and the analysis of atrio-ventricular, interventricular and intraventricular asynchrony parameters:

- mitral regurgitation: morphological criteria (mitral annulus, tenting area, coaptation distance, sphericity index), semiquantitative criteria (vena contracta -VC) and quantitative criteria (PISA parameters – regurgitant volume and regurgitant orifice area).

- tricuspid regurgitation (vena contracta - VC) and estimated pulmonary artery pressures based on tricuspid regurgitation velocity
- analysis of the right cavities: RA area, RV dimensions in the parasternal long axis incidence and in the apical incidence adjusted for the RV (RV basal, RV medium and RV apex-base length), systolic function parameters: TAPSE, S' RV , fractional area change (FAC)
- analysis of asynchrony parameters:
  - atrio-ventricular (AAV = mitral filling duration/cardiac cycle duration),
  - interventricular (Interventricular Mechanical Interval (IMIV) (ms) = aortic pre-ejection time (APT) – pulmonary pre-ejection time (PPT))
  - intraventricular (septal to posterior wall motion delay - SPWMD - by M Tissue Doppler mode, aortic pre-ejection time)
  - elements of basal, apical rotation, torsion and LV twist obtained by myocardial deformation imaging (circumferential strain)

The objectives of the study were:

1. the primary objective: death from cardiovascular causes and from any cause – its correlation with echocardiographic parameters for the assessment of mitral, tricuspid regurgitation, asynchrony parameters and RV function
2. secondary objectives related to the echocardiographic parameters for evaluating mitral and tricuspid regurgitation, asynchrony parameters and RV function:
   - evaluation of the number of hospitalizations determined by decompensated heart failure or severe arrhythmic events or thromboembolic events with a cardiovascular starting point
   - assessment of the causes of cardiovascular death

Statistical analysis was performed in SPSS Statistics 29.1.0, IBM, USA. Quantitative variables were expressed as median ± standard deviation and were analyzed using Student's t test. Qualitative variables were expressed as a percentage and were analyzed using the Chi-square test. The prognostic value of statistically significant variables was analyzed using the ROC curve, an AUC (area under curve) value > 0.8 being considered as an excellent discriminative level (Hosmer and Lemeshow, 2000). Variables that showed a favorable AUC were subsequently analyzed by binomial logistic regression. Statistical significance (p) was set at a threshold value of less than 0.05 (two-tailed).

2.5.3 ASSESSMENT OF THE IMPACT OF MITRAL REGURGITATION IN THE ISCHEMIC VERSUS NON-ISCHEMIC GROUP AND IN THE DECEASED VERSUS NON-DECEASED GROUP

Comparatively analyzing the ischemic group versus the non-ischemic group, it was observed that there are no statistically significant differences regarding the severity of mitral regurgitation evaluated by VC and PISA method (RVol, EROA) throughout the whole follow-up period. During the follow-up evaluation, an increase in the proportion of severe mitral regurgitation was observed in both ischemic and non-ischemic groups, with a higher incidence of severe mitral regurgitation at 3 years of follow-up in the ischemic group. Structurally, the mitral coaptation distance was significantly higher in the non-ischemic group compared to the ischemic group. Tenting area and mitral annulus were larger in the non-ischemic group compared to the ischemic group, but without reaching the threshold of statistical significance.

On the other hand, in deceased patients, a significantly higher incidence of moderate and severe mitral regurgitation was observed, with values of VC, RVol, EROA, mitral annulus, tenting area and mitral coaptation distance significantly higher in the deceased group compared to the non- deceased. No statistically significant differences were detected regarding the sphericity index between the deceased versus non-deceased group.

Moreover, in the ROC analysis, the morphological parameters of mitral valve deformation that appear secondary to its traction (tenting area and coaptation distance), the vena

contracta (VC) of mitral regurgitation and the PISA parameters of mitral regurgitation (RVol, EROA) are proved to be independent predictors of mortality, VC having excellent predictive power (AUC 0.845), followed in order by AOR (AUC 0.741), coaptation distance (AUC 0.740), tenting area (AUC 0.739) and RVol (AUC 0.689). Further statistical analysis using binary logistic regression was performed to see if the values of VC, EROA, RVol, mitral tenting area, mitral coaptation distance, and LV basal rotation had an impact on the probability of a patient dying. The logistic regression model was statistically significant, $\chi 2(6) = 38.442$, $p<0.001$. The model explained 65.2% (Nagelkerke R2) of the variation in deceased and non-deceased patients in the cohort and correctly classified 86.7% of patients. The sensitivity was 76.2% and the specificity was 92.3%. The positive predictive value was 87.80% and the negative predictive value was 84.21%. Of the 6 predictors, only VC, RVol, mitral tenting area, coaptation distance, and basal rotation were predictors of death.

2.5.4 ASSESSMENT OF THE IMPACT OF ELECTRICAL AND MECHANICAL LV ASYNCHRONISM IN THE ISCHEMIC VERSUS NON-ISCHEMIC GROUP AND IN THE DECEASED VERSUS NON-DECEASED GROUP, RESPECTIVELY

Comparing the non-ischemic group versus the ischemic group, a significantly higher incidence of complete left bundle branch block was observed in the non-ischemic group at the initial V1, V2 assessments, while in the ischemic group the conduction disorder of the anterior-superior or posterior-inferior hemiblock type was more frequent. At the 3-year evaluation, there were no more significant differences in terms of intraventricular conduction disorder. The QRS complex duration was longer in the non-ischemic group compared to the ischemic group without reaching the threshold of statistical significance.

Regarding mechanical asynchrony, there were no statistically significant differences in atrioventricular asynchrony between the non-ischemic and the ischemic group at baseline and at follow-up evaluations. The interventricular asynchrony evaluated by IMIV was significantly higher in the non-ischemic group compared to the ischemic group. Intraventricular asynchrony assessed by APT and SPWMD was significantly higher at the initial assessment (V1) in the non-ischemic group, so that at the 3-year assessment the difference was no longer statistically significant.

LV apical and basal rotation, LV torsion and twist had more impaired values in the non-ischemic group compared to the ischemic group. Moreover, reversed LV apical rotation had a significantly higher incidence in the non-ischemic group compared to the ischemic group.

Analyzing the deceased versus non-deceased group, no statistically significant differences were detected regarding QRS duration, the presence of left bundle branch block or anterior-superior or anterior-inferior hemiblock conduction disturbances at the initial assessments (V1, V2, while at the 3-year evaluation in the non-deceased group there were more patients without intraventricular conduction disorders. QRS duration was longer in the deceased group than in the non-deceased group, but without reaching the threshold of statistical significance.

Regarding mechanical asynchrony, at follow-up evaluations V2 and V3 , atrioventricular asynchrony was significantly more accentuated in the deceased versus non-deceased group. Interventricular (IMIV) and intraventricular (APT and SPWMD) asynchrony parameters had higher values at 3 years of follow-up in the deceased versus non-deceased group. LV basal rotation, torsion, and twist were significantly more impaired in the deceased versus non-deceased group. LV apical rotation was more impaired in the deceased group compared to the non-deceased group, but without reaching the threshold of statistical significance.

Among the asynchrony parameters evaluated, SPWMD, APT and LV basal rotation were found to be moderate independent predictors of mortality, with basal rotation having the highest prognostic value (AUC 0.743), followed by SPWMD (AUC 0.734) and APT (AUC 0.660). LV twist and torsion did not emerge as independent predictors of mortality.

2.5.5 EVALUATION OF THE IMPACT OF RV AND RA DILATION, RV SYSTOLIC DYSFUNCTION AND ESTIMATED SYSTOLIC PRESSURE IN THE PULMONARY ARTERY IN THE ISCHEMIC VERSUS NON-ISCHEMIC GROUP, AND IN THE DECEASED VERSUS NON-DECEASED GROUP, RESPECTIVELY

Comparing the non-ischemic group versus the ischemic group, it was observed that there were no statistically significant differences between the dimensions of the RV and RA. The RV was more dilated in the non-ischemic group compared to the ischemic group, but without reaching the threshold of statistical significance. From the point of view of RV systolic function, there were no statistically significant differences between TAPSE, S' RV and FAC between the non-ischemic versus ischemic group. Functional tricuspid regurgitation was minor or moderate in both groups with no statistically significant differences throughout the follow-up period (V1, V2, V3) between the non-ischemic versus the ischemic group. If at the initial evaluations (V1, V2) the estimated PAP did not show significant differences between the 2 groups, at the 3-year evaluation (V3) the estimated PAP was significantly higher in the ischemic group compared to the non-ischemic group.

Analyzing the deceased group versus the non-deceased group, it was observed that the RV and RA were dilated in the deceased group, while in the non-deceased group the dimensions of the RV, RA were located towards the upper limit of normal. RV and RA were significantly more dilated in the deceased versus non-deceased group. RV size measured in the parasternal long-axis view (proximal RV ejection tract) was found to be a moderate independent predictor of mortality (AUC 0.793, p 0.002).

In terms of RV systolic function, both TAPSE and S' RV were significantly lower in the deceased group compared to the non-deceased group at the 2- and 3-year follow-up assessments, respectively (V2, V3). FAC was significantly lower in the deceased group versus the non-deceased group throughout the follow-up period (V1, V2, V3). In the deceased group, moderate tricuspid regurgitation had a significantly higher incidence than in the non-deceased group, with significantly higher estimated PAP values in the deceased group. Elevated PAP values were found to be moderate independent predictors of mortality at 1 year follow-up (AUC 0.688, p 0.017), so that at 2 and 3 years follow-up, elevated PAP values proved to be strong independent predictors of mortality (AUC 0.897, $p < 0.001$, versus AUC 0.894, $p < 0.001$)

2.5.6 DISCUTIONS

Secondary mitral regurgitation found in both idiopathic DCM and dilated ischemic heart disease results from the imbalance between closing and tractional forces secondary to altered LV and LA geometry and function (54-56). In this context, the more pronounced the deformation of the mitral valve, the greater the severity of the mitral regurgitation, negatively influencing the possibility of valve repair. In the current study, there were no statistically significant differences between the non-ischemic group and the ischemic group regarding mitral tenting area; instead, the coaptation distance was significantly higher in the ischemic group (the group with higher mortality), having a value exceeding the threshold value of 1 cm (considered unfavorable for valvular repair techniques). Regarding the main objective of global mortality, both the tenting area and the coaptation distance had significantly higher values in the deceased group compared to the non-deceased group, exceeding the threshold of 2.5 cm^2 for the tenting area and 1 cm for the coaptation distance – threshold values considered as cut-off values for the significantly reduced probability of valvular repair; moreover, mitral tenting area, coaptation distance, VC, RVol and EROA were found to be independent predictors of mortality. Analyzed together in binomial regression, only VC, RVol, mitral tenting area, coaptation distance, and basal rotation were predictors of death with satisfactory sensitivity, specificity, positive predictive value, and negative predictive value. The interest in evaluating morphological changes of the mitral valve derives from the fact that repair techniques in functional mitral regurgitation are still associated with suboptimal results. Stumm et al showed in a study of 240 patients with functional mitral

regurgitation who underwent the mitral annuloplasty procedure that a preoperative tenting area ≥2.4 cm2 was associated with a lower 5-year survival rate and a higher risk increased adverse cardiac events (150).

The severity of mitral regurgitation is assessed semiquantitative by the vena contracta (VC) and quantitatively by the PISA parameters: regurgitant volume (RVol) and effective regurgitant orifice area (EROA). Functional mitral regurgitation is a negative prognostic marker in CM (72) and higher degrees of mitral regurgitation are related to worse clinical status and reduced survival (91). Several studies have demonstrated the negative prognostic value of mitral regurgitation using a threshold value of regurgitant orifice area greater than 0.2 cm2 (92). In the present study there were no significant differences regarding VC, EROA, RVol between ischemic versus non-ischemic etiology of LV dilatation; but relative to mortality, all three parameters were found to be independent predictors of mortality, with VC having the highest predictive power, followed in order by EROA and RVol. In the deceased group, VC had a value greater than 4.5 mm, EROA greater than 0.2 cm2 and RVol greater than 30 ml, suggesting that not only severe mitral regurgitation according to the criteria of the 2021 guideline of valvular disease of the European Society of Cardiology, confers negative prognosis but also moderate mitral regurgitation. In the studied group, the deceased patients presented predominantly moderate and severe mitral regurgitation. The importance of correct assessment of mitral regurgitation derives from the need to establish the appropriate timing for interventional therapy of edge-to-edge transcatheter repair in severe and moderately severe mitral regurgitation (151-153).

Cardiac mechanical asynchrony has negative effects on cardiac function causing a decrease in stroke volume and cardiac output secondary to changes generated in myocardial and valvular kinetics: asynchronous and ineffective contraction, delayed and ineffective relaxation, reduction of diastolic filling time, mitral regurgitation with end-diastolic component (61- 63). The assessment of cardiac asynchrony includes parameters for the assessment of atrioventricular, interventricular and intraventricular asynchrony and is performed in parallel with the assessment of electrical asynchrony on the electrocardiogram. In the present study the elements of electrical asynchrony (the presence of LBB and the duration of the QRS complex) as well as the elements of intraventricular mechanical asynchrony of the APT, SPWMD were more accentuated in the non-ischemic DCM group at the initial visits, than at the 3-year assessment these differences disappear. This is because some patients were referred to CRT, responding favorably to this therapy. Apical, basal rotation, LV torsion and twist had more impaired values in the non-ischemic group compared to the ischemic group.

Moreover, reversed LV apical rotation had a significantly higher incidence in the non-ischemic group compared to the ischemic group. Interventricular asynchrony assessed by IMIV was significantly higher in the non-ischemic group compared to the ischemic group; no statistically significant differences were detected regarding atrioventricular asynchrony between the non-ischemic and the ischemic group. Practically, both intraventricular and interventricular asynchrony tend to be more accentuated in the non-ischemic group compared to the ischemic one, a discordant result with the higher mortality rate in the ischemic group. This could be explained by the fact that in advanced forms of DCM with extensive areas of akinesia, these markers have low feasibility and reproducibility (38).

Globally analyzing all 60 patients regarding the primary endpoint of mortality, in the deceased group the presence of both atrio-ventricular asynchrony (AAV < 40%) and interventricular (IMIV > 40 ms) and intraventricular (ATP>140 ms, SPWMD >130 mm) asynchrony were observed at the 3-year evaluation, while in the non-deceased group these parameters did not reach these threshold values considered as elements of disease severity. The importance of this derives from the fact that mechanical LV asynchrony in DCM patients with HF with severe LV systolic dysfunction and left bundle branch block has been shown to have independent predictive value for response to cardiac resynchronization therapy (CRT) and long-term survival (64).

LV basal and apical rotation, twist and torsion - which can be appreciated both as elements of LV systolic function and as elements of intraventricular asynchrony, had more depreciated

values in deceased patients compared to non-deceased ones. Moreover, the impairment of basal rotation proved to be a moderate predictor (AUC between 0.6-0.8) of mortality in patients with both ischemic and non-ischemic DCM. Popescu and collaborators highlighted that impaired apical rotation (even reversed – clockwise) and impairment to loss of LV torsion in a group of 50 patients with DCM is associated with significant negative LV remodeling, increased electrical asynchrony, low LV systolic function, increased LV filling pressures, being indicators of a more advanced stage of the disease (80).

RV dilatation and dysfunction are commonly seen in patients with DCM. These changes are usually caused by LV dysfunction or biventricular involvement rather than significant pulmonary hypertension (38, 39).

In our study, the RV and RA were significantly more dilated in the deceased versus non-deceased group, with no significant differences between the ischemic group compared to the non-ischemic group. The importance of this observation derives from the fact that bi-ventricular dilatation is known to carry a more negative prognosis compared to isolated LV dilatation (89). Moreover, in the present study, proximal RV ejection tract size (measured in parasternal long-axis view) was found to be a moderate independent predictor of mortality (AUC between 0.6–0.8).

The prevalence of RV dysfunction ranges from 63% to 76% and correlates with the degree of LV dysfunction. RV dysfunction has prognostic significance and its evaluation should be performed in all cases (38, 50). In the present study, in terms of RV systolic function, both TAPSE and S' RV were significantly lower in the deceased group compared to the non-deceased group at the 2- and 3-year follow-up assessments, respectively (V2, V3). FAC was significantly lower in the deceased group versus the non-deceased group throughout the whole follow-up period (V1, V2, V3). RV dysfunction has been recognized as a negative prognostic factor in DCM and is associated with more advanced LV dysfunction and considerably poorer functional class and prognosis. A TAPSE value of less than 14 mm has been shown to have negative prognostic value in patients with DCM (86). In our study, the RV did not present severe longitudinal systolic dysfunction, with TAPSE values above 14 mm in all 60 patients followed dynamically, which could be explained by their relatively short follow-up period (3 years) and strengthens the prognostic value negative of RV systolic dysfunction even from its slightly low values.

Functional tricuspid regurgitation and *pulmonary hypertension* are common in DCM, particularly in the presence of RV dilatation and dysfunction (59).

In the deceased group of the 60 patients evaluated, moderate tricuspid regurgitation had a significantly higher incidence than in the non-deceased group, with significantly higher estimated PAP values in the deceased group; also the estimated PAP value was significantly higher in the ischemic group, the group with a higher mortality rate, compared to the non-ischemic group. Increased values of PAP proved to be initially moderate independent predictors of mortality (AUC between 0.6-0.8), so that during the evolution (V3) the increase of PAP became a strong independent predictor of mortality.

While the severity of LV systolic dysfunction did not show an independent relationship with pulmonary hypertension, the severity of functional mitral regurgitation and diastolic dysfunction were strongly correlated with pulmonary hypertension (60). Moreover, it was shown that patients with a restrictive or pseudo normal trans mitral flow pattern had higher pulmonary artery pressures, and the improvement of the trans mitral flow appearance towards the altered relaxation pattern was accompanied by a significant reduction in pulmonary artery pressure (154). Pulmonary hypertension and tricuspid regurgitation are also predictors of morbidity and mortality in DCM (59).

2.5.7 CONCLUSIONS

Secondary mitral regurgitation, LV intraventricular asynchrony and RV dilatation and dysfunction play an important role in the evolution of DCM patients, being correlated with the clinical status – NYHA class and their prognosis.

In the studied group, the following were observed:

- Secondary mitral regurgitation tends to worsen over time in both ischemic and non-ischemic LV dilatation
- Severe and moderate-to-severe secondary mitral regurgitation is associated with poor patient prognosis, regardless of ischemic or non-ischemic etiology.
- VC, EROA, RVol, mitral tenting area and coaptation distance were significantly increased in deceased versus non-deceased group. Regarding ischemic or non-ischemic etiology, only the coaptation distance was significantly higher in the ischemic group, the group with the higher mortality rate.
- Both from the point of view of mitral valve deformation, evaluated by the coaptation distance and the tenting area, and from the point of view of the severity of mitral regurgitation evaluated semiquantitative by VC and quantitatively by PISA parameters (RVol, EROA), moderate to severe and severe secondary mitral regurgitation is a moderate independent predictor of mortality. Analyzed all these parameters together in binomial regression, only VC, RVol, mitral tenting area, coaptation distance and basal rotation were predictors for death with satisfactory sensitivity, specificity, positive predictive value and negative predictive value
- RVol ≥ 20 ml and EROA ≥ 30 mm2 seem to be the threshold values from which secondary mitral regurgitation causes a negative evolution, being associated with an unfavorable prognosis, and can be considered as criteria for the indication of percutaneous edge-to-catheter repair edge
- LV electrical asynchrony, assessed by QRS duration, did not show significant differences between the non-ischemic versus ischemic group, nor between the deceased versus non-deceased group.
- Interventricular mechanical asynchrony assessed by IMIV and intraventricular assessed by SPWMD and APT and LV basal and apical rotation, LV twist and torsion was more accentuated in the deceased versus non-deceased group and also in the non-ischemic group compared to ischemic group.
- SPWMD, APT and LV basal rotation were found to be independent predictors of mortality regardless of ischemic or non-ischemic etiology
- RV dilatation, longitudinal and circumferential systolic dysfunction of the RV (TAPSE, S' RV, FAC) are more pronounced in the deceased group compared to the non-deceased group, without significant differences between the ischemic versus non-ischemic group
- Estimated pulmonary arterial systolic pressure was significantly higher in the deceased versus non-deceased group, with significantly higher values at follow-up in the ischemic group (higher mortality group) versus non-ischemic
- RV dilatation, assessed by measuring the proximal RV ejection tract in parasternal long-axis view, and estimated PAP are independent predictors of mortality.

2.5.8 STUDY LIMITATIONS

The main limitations of the study are represented by the small group of patients, as it is necessary to evaluate larger groups of patients to be able to extrapolate the results obtained, the relatively short follow-up period (3 years), the impossibility of 3D evaluation of the mitral valve for more accurate volume and the regurgitant area quantification, the impossibility of evaluating ventricular asynchrony through radial strain and the 3D method, as well as the impossibility of

evaluating RV systolic function through the 3D ejection fraction and global longitudinal strain or at the level of the free wall.

2.6 STUDIUL IV: THE PROGNOSTIC ROLE OF CARDIAC MAGNETIC RESONANCE IN DILATED CARDIOMYOPATHY

2.6.1 INTRODUTION

Dilated cardiomyopathy has an increased risk of heart failure, malignant ventricular arrhythmias, including sudden cardiac death, being the most common cause of heart transplantation. In clinical practice DCM should not be a final diagnosis but a starting point for further ethio-pathogenetic investigations. This explains the complexity of DCM patients' assessment: laboratory tests, electrocardiogram, 12-hour ambulatory electrocardiographic examination, cardiopulmonary stress test, imaging investigations (echocardiography, cardiac magnetic resonance) and invasive diagnostic techniques (coronary angiography, endomyocardial biopsy).

Given that the most common cause of left ventricular dilatation is coronary artery disease, DCM is frequently classified as ischemic or non-ischemic.

Cardiac magnetic resonance has an ever-increasing impact for the evaluation of DCM in terms of etiology, risk stratification, and therapeutic approach (93), providing complementary information to that obtained by echocardiography.

Cardiac magnetic resonance is the globally recognized imaging technique as the gold standard method for quantifying cardiac dimensions and evaluating the systolic function, through the ejection fraction, of the left and right ventricle; the main advantage of cardiac magnetic resonance is the possibility of tissue characterization, being able to highlight replacement myocardial fibrosis (through the late gadolinium enhancement - LGE technique) and reactive interstitial and perivascular fibrosis (mapping techniques - T1-mapping, T2-mapping, T2 * mapping). Both LGE and mapping techniques have been validated by comparative studies with histological evaluation for a significant number of clinical scenarios (93).

Many studies have shown important correlations between various changes identified by cardiac magnetic resonance and cardiovascular morbidity and mortality. Some parameters are independent predictors for malignant ventricular arrhythmias, with risk of sudden cardiac death, or for non-responder status to cardiac resynchronization therapy. Thus, the pattern of myocardial fibrosis helps to establish the etiology of DCM and has prognostic and therapeutic implications, the presence of LGE being associated with a weaker therapeutic response and an increased risk of complex ventricular arrhythmias. At the same time, the absence of LGE associated with the presence of reactive fibrosis quantified by mapping techniques, especially by the increase in extracellular volume, identifies patients with a potentially favorable response to optimal medical and cardiac resynchronization therapy (93, 97, 155-157).

2.6.2 MATERIAL AND METHOD

We evaluated 60 patients with heart failure, 30 with non-ischemic DCM and 30 with ischemic DCM; all patients had optimal medical therapy. Patients were followed dynamically with evaluations every one year for a period of 3 years (Visits V1 – evaluation at 1 year, V2 – evaluation at 2 years and V3 – evaluation at 3 years). Patients were evaluated clinically, biologically, electrocardiographically – 12-lead electrocardiogram, with 2D echocardiography and contrast enhanced cardiac magnetic resonance; all patients were evaluated by coronary angiography – patients with significant coronary lesions (greater than 70% or prior stenting) as well as single vessle disease (significant stenosis in the anterior descending artery) or multivessel disease (significant stenosis in the common trunk artery left coronary artery or

bivascular involvement - any two of the anterior descending artery, circumflex artery and right coronary artery - or significant concomitant stenoses of the 3 coronary arteries) were included in the ischemic DCM study group.

Cardiac MRI included the following acquisitions:

- Cine sequences (SSFP-cine) used to evaluate cardiac function and morphology with ECG gating
- Cardiac morphology sequences: T1 (including T1w black blood SA, T1w black blood image with fat suppression SA), T2w
- Sequences after administration of contrast substance (gadolinium): perfusion sequences, early post-contrast T1 sequences 1 minute after administration of contrast substance and late evaluation 10-12 minutes after administration of contrast substance that allows assessment of myocardial scars under form of late gadolinium enhancement (LGE); in the case of ischemic etiology, the LGE is located subendocardial and the degree of transmurality greater than 50% defines a non-viable territory, and less than 50% defines a viable territory. Fatty metaplasia is defined on cine sequences as a thinned and akinetic parietal segment, on T1w black blood sequences as hypersignal in the previously observed thinned parietal segment indicating lipomatous metaplasia, on T1w black blood image sequences with fat suppression as hyposignal in the same area, on the LGE sequences as a hyposignal zone interspersed with the hypersignal zone.
- Flow sequences (phase contrast - flow velocity encoded mapping) at the root of the aorta and pulmonary artery

The severity of mitral and tricuspid regurgitation was assessed by the indirect method of evaluating the regurgitant volume (RVol = stroke volume resulting from the planimetric method of calculating LVEF/RVEF - stroke volume (antegrade aortic/pulmonary flow resulting from flow analysis at the level of the aortic root /pulmonary artery) and the derived regurgitant fraction (RF = RVol/ stroke volume resulting from the planimetric method of calculating LVEF/RVEF). Regurgitation is considered mild if RF <30%, moderate if RF is between 30% and 50% and severe if RF>50%.

The inclusion criteria were the following:

- Age older than 18 years
- Left ventricular end-diastolic diameter measured by cardiac magnetic resonance >112% relative to age and body surface area and an end-diastolic volume ≥ 81 mL/m^2 in men and ≥76 mL/m^2 in women (dimensions measured by cardiac magnetic resonance)
- LVEF ≤ 45% (determined by cardiac magnetic resonance) of ischemic or non-ischemic etiology

The exclusion criteria were the following:

- Age less than 18 years
- Other causes of ventricular dilatation such as: significant primary valvular disease (mitral regurgitation, aortic regurgitation, aortic stenosis), congenital heart diseases or any other conditions such as: endocrinopathies, connective tissue diseases, infiltrative diseases - sarcoidosis, amyloidosis, toxic-induced cardiomyopathy and/or drugs, tachyarrhythmic cardiomyopathy
- severe renal dysfunction defined by a creatinine clearance calculated by the Cockroft Gault formula of less than 30 ml/min/1.73m^2

The study objectives were:

1. the primary objective: death from cardiovascular causes and from any cause – its correlation with the morphological, functional and structural parameters identified by magnetic resonance
2. secondary objectives related to the morphological, functional and structural parameters identified by magnetic resonance:
    - evaluation of the number of hospitalizations determined by decompensated heart failure or severe arrhythmic events or thromboembolic events with a cardiovascular starting point
    - assessment of cardiovascular death causes

Statistical analysis was performed in SPSS Statistics 29.1.0, IBM, USA. Quantitative variables were expressed as median ± standard deviation and were analyzed using Student's t test. Qualitative variables were expressed as a percentage and were analyzed using the Chi-square test. The prognostic value of statistically significant variables was analyzed using the ROC curve, an AUC (area under curve) value > 0.8 being considered as an excellent discriminative level (Hosmer and Lemeshow, 2000). Statistical significance (p) was set at a threshold value of less than 0.05 (two-tailed).

2.6.3 RESULTS

2.6.3.1 Comparative analysis non-ischemic group - ischemic group

Analyzing the ischemic versus non-ischemic group, no statistically significant differences were recorded regarding LV, RV, LA, RA cavity dimensions and LV mass. Also, there were no significant differences between LV and RV ejection fractions, between cardiac output (CO) and indexed cardiac output (CI) between the ischemic and non-ischemic groups. Regarding the LV stroke volume measured by the aortic flow sequence, it was significantly lower (p 0.042) in the ischemic versus non-ischemic group.

Intracavitary thrombosis was more frequent in the ischemic group compared to the non-ischemic group, but without reaching the threshold of statistical significance (p 0.197).

Regarding the severity of mitral regurgitation, it was more severe in the ischemic group, with moderate and severe mitral regurgitation being predominant, while in the non-ischemic group minor mitral regurgitation had a higher frequency. The regurgitant volume did not show significant differences between the two groups, but the regurgitant fraction was higher in the ischemic versus non-ischemic group (p 0.003).

Evaluating tricuspid regurgitation, it was observed to be significantly more severe in the ischemic versus non-ischemic group, with higher regurgitant volume and regurgitant fraction in the ischemic versus non-ischemic group (p 0.0012 and $p<0.001$, respectively).

Regarding the assessment of myocardial scars by the presence of LGE, it was observed that all patients with DCM of ischemic etiology presented LGE at the LV level with sub-endocardial pattern that had various degrees of transmurality. LGE transmurality over 50% of the parietal thickness, which defines non-viable myocardial territory, was detected in 76.67% of the patients with ischemic DCM, only 23.33% of them also presenting viable territories (with degree of transmurality below 50%). Moreover, secondary to the myocardial remodeling process, in addition to the classic scar secondary to myocardial infarction represented by myocardial fibrosis identified by LGE, 33.33% of patients presented areas of fatty metaplasia at the level of the myocardial scar. Patients with fatty metaplasia had a higher incidence of sustained/unsustained ventricular tachycardia and a higher rate of defibrillator implantation compared with patients without fatty metaplasia. The cause of death in patients with fatty metaplasia was sudden cardiac death, whereas in patients without fatty metaplasia the causes of death were refractory heart failure or ischemic stroke.

In the non-ischemic group half of the patients presented LGE localized in the thickness of the LV walls (mid-wall pattern). The most common localization was at the level of the medio-

basal interventricular septum, followed by the localization at the level of the lateral wall and then the association of localization at the level of the interventricular septum and the LV lateral wall. LGE was present at the interventricular septum level in 43.33% of patients in the non-ischemic group.

Regarding the primary endpoint, patients who presented LGE had a higher rate of death compared to those without LGE. Moreover, the presence of LGE was associated with a higher percentage of SCD, unsustained VT, defibrillator implant compared to patients who did not present LGE. The incidence of sustained VT and resuscitated cardiorespiratory arrest was the same in patients with and without LGE. Cardiac resynchronization therapy indicated in patients with LVEF less than 35% and QRS duration greater than 130 ms with LBB-type morphology, had a higher frequency in patients without LGE compared to patients with LGE.

2.6.3.2 Comparative analysis deceased group – non-deceased-group

Analyzing the deceased versus non-deceased group from a morphological point of view, it was observed that LV, RV, LA, RA were significantly more dilated in the deceased group. LV mass was also greater in deceased patients compared to non-deceased patients.

Regarding the LV systolic function, the deceased patients had a significantly lower LVEF compared to the non-deceased (22.80±8.29 versus 33.10±7.73, $p<0.001$), while there were no statistically significant differences for cardiac output and indexed cardiac output between the two groups. In contrast, stroke volume was significantly lower in deceased group versus non-deceased group. The absence of myocardial scar assessed by LGE was significantly more frequent in non-deceased patients compared to deceased patients (p 0.008).

LV end-diastolic diameter, indexed LV end-diastolic and end-systolic volumes were found to be strong independent predictors of mortality with AUC greater than 0.8 in ROC analysis (LV-EDD AUC 0.835, p 0.003, indexed LV-EDV AUC 0.911, p 0.002, indexed LV-ESV AUC 0.934, p 0.002).

LV mass, LA and RA indexed areas proved to be moderate independent predictors of mortality with AUC between 0.7 – 0.8 in ROC analysis (LV mass AUC 0.723, $p<0.001$, LA indexed area AUC 0.735, $p<0.001$, RA indexed area AUC 0.734, $p<0.001$).

Mitral regurgitation and tricuspid regurgitation were more severe in the deceased versus non-deceased group, with moderate regurgitation being more frequent in the deceased group. For both mitral regurgitation and tricuspid regurgitation, the regurgitant volume is higher in the deceased versus non-deceased group without reaching the threshold of statistical significance. Mitral and tricuspid regurgitation fractions were found to be modest predictors of mortality in ROC analysis with AUC between 0.6-0.7 (MR regurgitant fraction AUC 0.689, $p<0.001$, TR regurgitant fraction AUC 0.642, $p<0.001$).

2.6.4 DISCUTIONS

Typically, in patients with DCM the left ventricle (and right – not in all patients) shows moderate to severe dilatation with moderate or very low EF (94), a fact also observed in the present study where the LV was more dilated (both as LV-EDD, as well as LV-EDV and LV-ESV) in the deceased group compared to the non-deceased group, without being significantly different related to ischemic versus non-ischemic etiology. LV dilatation is associated over time with deterioration of LV systolic function, assessed by EF determination. Moreover, in the present study, LV dilatation expressed as end-diastolic diameter or as end-diastolic or end-systolic volume proved to be strong independent predictors of mortality regardless of ischemic or non-ischemic etiology.

The importance of LVEF has been emphasized in multiple studies, including in the European and American Cardiology guidelines, the cut-off value of less than 35% being an important criterion for selecting patients for device-therapy such as defibrillator implant or cardiac resynchronization therapy (109). In the present study, LVEF was significantly lower in the deceased versus non-deceased group, with no significant differences between ischemic and non-ischemic etiology.

Ventricular stroke volumes are usually within normal limits or only modestly reduced due to ventricular dilatation (94), a situation also encountered in the present work. Particular attention should be paid in the situation of the concomitant existence of valvular regurgitation, when stroke volumes must be corrected (94). In the present analysis of the 60 patients with dcm, LV stroke volume was observed to have lower values in the deceased versus non-deceased group, with also lower values in the ischemic group (higher mortality rate group) versus the non-ischemic group. In the present study, the assessment of stroke volume was performed by the flow sequence at the level of the aortic root, in order to eliminate the error that could be caused by mitral regurgitation.

The atria may be dilated, but usually the dilatation is less pronounced than the ventricular one (94). In the present work LA and RA expressed as area and indexed area, respectively, were more dilated in deceased versus non-deceased patients, and proved to be moderate independent predictors for mortality regardless of ischemic versus non-ischemic etiology.

The assessment of mitral and tricuspid regurgitation severity by CMR is still an intensively evaluated subject. Grading of the severity of functional mitral regurgitation remains controversial despite the adverse prognosis and rapidly evolving interventions. Moreover, it is still unclear whether quantitative assessment by CMR can have an incremental role in risk stratification for patients with ischemic or non-ischemic DCM in terms of regurgitant fraction and LGE. A 5% increase in regurgitant fraction was associated with the primary end point, with relatively similar hazard ratio in ischemic versus non-ischemic etiology. The optimal regurgitant fraction threshold for mitral regurgitation was ≥25% for moderate MR and ≥35% for severe MR in both ischemic and non-ischemic groups, threshold values set from the prediction of the primary endpoint (158). In our study the regurgitant fraction of both mitral regurgitation and tricuspid regurgitation were significantly higher in the deceased versus non-deceased group, with higher values in the ischemic group with higher morality compared to the non-ischemic group; regurgitant fractions of MR and TR proved to be modest independent predictors of mortality, regardless of ischemic or non-ischemic etiology.

LGE is of great help in making the differential diagnosis between left ventricular dilatation secondary to coronary artery disease and left ventricular dilatation without underlying coronary disease, a differentiation important for subsequent therapeutic strategy. Ischemic heart disease in the dilated stage typically shows subendocardial or transmural contrast enhancemet (representing the myocardial scar) in a coronary perfusion territory, whereas patients with idiopathic dilated cardiomyopathy may show no contrast or linear or focal contrast enhancement in the middle portion of the ventricular myocardium (contrast enhancememt that does not respect a coronary territory and not necessarily limited to the left ventricle, may also involve the right ventricle). Myocardial contrast enhancement reflects segmental fibrosis in patients with idiopathic dilated cardiomyopathy (94). Myocardial fibrosis identified by LGE is most commonly present in the middle portion of the interventricular septum and can be identified in approximately 30% of patients with DCM (93, 96). In the present study, half of the patients with non-ischemic DCM presented LGE with mid-wall pattern, the most frequent location being at the level of the interventricular septum, followed by the location at the level of the LV lateral wall, and was associated with a higher frequency of death, SCD, non-sustained ventricular tachycardia and defibrillator implant. In the ischemic group, all patients presented LGE with a subendocardial disposition, two thirds of them with territories interpreted as non-viable (LGE transmurality>50%).

In the overall analysis of evaluated patients, the absence of LGE was significantly associated with better survival. The presence of LGE is a predictor of mortality, arrhythmic

ventricular events, including sudden cardiac death, tachycardia or ventricular fibrillation, or appropriate defibrillator-initiated therapy, and for the risk of rehospitalization for heart failure (97).

A risk calculator has been developed that, unlike other risk scores, also incorporates the presence of LGE on cardiac MRI, although this has not yet been validated (159). There are currently ongoing trials for defibrillator implant based on the presence of myocardial scarring on cardiac magnetic resonance, including patients with DCM, but the authors of the European cardiomyopathy's guideline believe that the current evidence can support the use of LGE to guide defibrillator therapy in subgroups of patients with DCM (43). Thus, the 2023 European guideline for cardiomyopathies states the importance of LGE considered as an additional risk factor in patients with certain genotypes: LMNA, FLNC- truncated variants, PLN, DSP, RBM20 (43).

Associated with LGE in patients with ischemic DCM, the presence of fatty metaplasia was also identified in 1/3 of patients, and it was associated with a higher incidence of sustained/unsustained ventricular tachycardia, SCD, defibrillator implant compared to patients without fatty metaplasia. The prevalence of fatty metaplasia is low in patients with chronic ischemia, intermediate in post-infarct patients with an incidence between 22 and 68%, and high in patients with a history of myocardial infarction and ventricular tachycardia, with an incidence between 64 and 100%. The incidence of fatty metaplasia appears to be closely associated with disease severity, but its quantification can often be challenging with different CMR techniques. Fatty metaplasia is more commonly seen in old infarcts and in infarcts involving large myocardial territories. Fatty metaplasia is associated with regional parietal thinning and impaired localized parietal kinetics. Ventricular aneurysms are also closely associated with fatty metaplasia (160).

Similar to arrhythmic risk assessment, LGE may be useful in predicting response to cardiac resynchronization therapy (93). In a study of 599 patients with both ischemic heart disease and non-ischemic DCM (161), guidance of biventricular pacemaker implantation by LGE was associated with significantly improved identification of patients most likely to benefit from this therapy. Patients without LGE did significantly better after resynchronization therapy compared with those with LGE or those who underwent non-LGE guided CRT. Regardless of the ability to predict which patients will or will not respond to resynchronization therapy, the presence of LGE in the middle portion of the interventricular septum was an independent predictor of morbidity and mortality in patients undergoing this therapy (98). In our study, cardiac resynchronization therapy in the non-ischemic group was more frequent in patients without LGE compared to patients with LGE, suggesting that not only LGE contributes to the increase in QRS duration, other morpho-functional factors being probably also incriminated.

2.6.5 CONCLUSIONS

Cardiac magnetic resonance has an important role in DCM patients' evaluation, both for diagnostic purposes (which also includes targeting some specific etiologies) and for prognostic and therapeutic purposes.

On the studied group, the following were observed:

- LV, RV, LA, RA were significantly more dilated in the deceased versus non-deceased group, with no statistically significant differences between the ischemic versus non-ischemic group. LV mass was significantly greater in the deceased versus non-deceased group
- LV-EDD, indexed LV-EDV and indexed LV-ESV were shown to be strong independent predictors of mortality
- LV mass, indexed areas of LA and RA were found to be moderate independent predictors of mortality

- LVEF was significantly lower in the deceased group compared to the non-deceased group, without significant differences between ischemic and non-ischemic etiology
- Cardiac output and indexed cardiac output did not show significant differences between the deceased versus non-deceased group, nor between ischemic and non-ischemic etiology. Stroke volume, on the other hand, was significantly lower in patients in the deceased versus non-deceased group, and was also lower in patients in the ischemic group, the group with higher mortality
- Mitral regurgitation and tricuspid regurgitation were more severe in the deceased versus non-deceased group, with moderate regurgitation being more frequent in the deceased group. Mitral and tricuspid regurgitation fractions were found to be modest independent predictors of mortality, being higher in the ischemic group (higher mortality group) versus non-ischemic.
- Absence of myocardial scar assessed by LGE was associated with better survival
- In patients with non-ischemic DCM, the presence of mid-wall LGE was associated with a higher percentage of SCD, unsustained VT, defibrillator implant compared to patients who did not present LGE. The incidence of sustained VT and resuscitated cardiorespiratory arrest was the same in patients with and without LGE. Cardiac resynchronization therapy had a higher frequency in patients without LGE compared to patients with LGE. LGE was most frequently located at the level of the medio-basal interventricular septum
- In patients with ischemic DCM, it was observed that all patients presented LGE at the LV level of sub-endocardial type with various degrees of transmurality. LGE transmurality over 50% of the parietal thickness, which defines non-viable myocardial territory, was detected in three-quarters of patients with ischemic DCM, only a quarter of them also presented viable territories (with a degree of transmurality below 50%)
- Fatty metaplasia was present in one third of patients with ischemic DCM.
- Patients with fatty metaplasia had a higher incidence of sustained/unsustained ventricular tachycardia and a higher rate of defibrillator implantation compared to patients without fatty metaplasia. The cause of death in patients with fatty metaplasia was sudden cardiac death, whereas in patients without fatty metaplasia the causes of death were refractory heart failure or ischemic stroke.

2.6.6 STUDY LIMITATIONS

The study limits are represented by the absence of the possibility of quantitative measuring of LGE burden and the absence of the possibility of evaluating reactive fibrosis through mapping techniques and in particular T1 mapping, for the evaluation of native T1 times and extracellular volume. Another important limitation was represented by the impossibility of genetic testing of patients with non-ischemic DCM, in order to correlate the imaging phenotype from cardiac magnetic resonance and from echocardiography with the genotype identified in order to increase the accuracy of the prognostic assessment.

2.7 ESTABLISHING A PROGNOSTIC ALGORITHM IN DCM BASED ON ECHOCARDIOGRAPHIC AND CARDIAC MAGNETIC RESONANCE ASSESSMENT

Estimating the prognosis for morbidity and mortality in patients with HF helps clinicians to decide on the appropriate type and timing of therapies (in particular the decision on rapid transition to advanced therapies). Numerous prognostic markers for mortality and/or decompensation with the need for HF hospitalization have been identified in patients with HF. However, their applicability in clinical practice is low and accurate risk stratification in HF remains challenging (7). Systematic review of the current literature revealed a number of prognostic models (Rahimi et al evaluated 64 such models in a systematic review (9), Ouwerkerk et al analyzed 117 such models as a meta-regression (10)) , which were found to have moderate accuracy for predicting mortality, while models predicting the combined endpoint of death and hospitalization or hospitalization alone had even less predictive power (7). The parameters most consistently reported as predictors of mortality and/or hospitalization for heart failure were age, renal function, blood pressure, serum sodium, left ventricular ejection fraction, sex, BNP, NYHA functional class, diabetes, weight and body mass index and exercise capacity (9)

The 5-year survival of patients with dilated cardiomyopathy ranges from 30% to 80% (2,3). There is currently no specific risk prediction model for DCM. Validated risk prediction models for heart failure apply to these patients. In 2016, the International Society of Heart and Lung Transplantation redefined the criteria for including patients on heart transplant lists. Heart failure prognostic scores should be performed in conjunction with cardiopulmonary exercise testing to determine prognosis and guide placement on outpatient transplant lists. An estimated 1-year survival <80% as calculated by the Seattle Heart Failure Model (SHFM) or a high/intermediate risk as estimated by the Heart Failure Survival Score (HFSS) are considered reasonable cut-offs for enrollment on transplant cardiac lists (class IIb indication, level of evidence C) (14). The only imaging parameter included in these scores is the left ventricular ejection fraction.

The 2022 guideline of the International Society of Heart and Lung Transplantation no longer refers to these two scores for pretransplant assessment, emphasizing instead the importance of invasive assessment of pulmonary arterial pressure, with lowering of the mean pulmonary arterial pressure threshold from 25 to 20 mmHg, since it has been observed that patients with mean pulmonary artery pressure values between 21 and 25 mmHg have an increased risk of having an unfavorable evolution after transplantation (162).

The present work evaluated for prognostic purposes a series of clinical, biological, electrocardiographic and imaging parameters (derived from echocardiography and cardiac magnetic resonance), following over a period of 3 years patients with non-ischemic DCM versus ischemic DCM, having as primary endpoint overall mortality.

Summarizing all the analyzed data, the present work proposes a step-by-step evaluation algorithm of patients with DCM (figure 1) in order to place the patient in the appropriate risk class from the time of diagnosis. The presence or absence of severity elements in clinical, electrocardiographic, echocardiographic and magnetic resonance evaluation are important for initiation of optimal therapy and afterwords for establishing the periodicity of controls during the follow-up period:

- at 1 month in case of an episode of heart failure that required hospitalization,
- after 3 months of optimal medical therapy;
    - ✓ in the presence of symptomatic heart failure with LVEF ≤ 35%, the patient is referred for an ICD implant for SCD primary prophylaxis - in this context, the presence of LGE, unsustained VT during Holter EKG monitoring, history of syncope are elements that support the indication of the primary prophylaxis of MSC; the association of QRS duration ≥130 ms establishes the indication of CRT-D

- ✓ in the context of FEVS > 35% - the medication is up-titrated up to the maximum tolerated doses with the active screening of negative prognostic elements: their absence allows establishing the next control at 6 months, and their presence may require re-evaluation at 3 months.

- Thereafter, at 6 months -1 year depending on the clinical and biological evolution

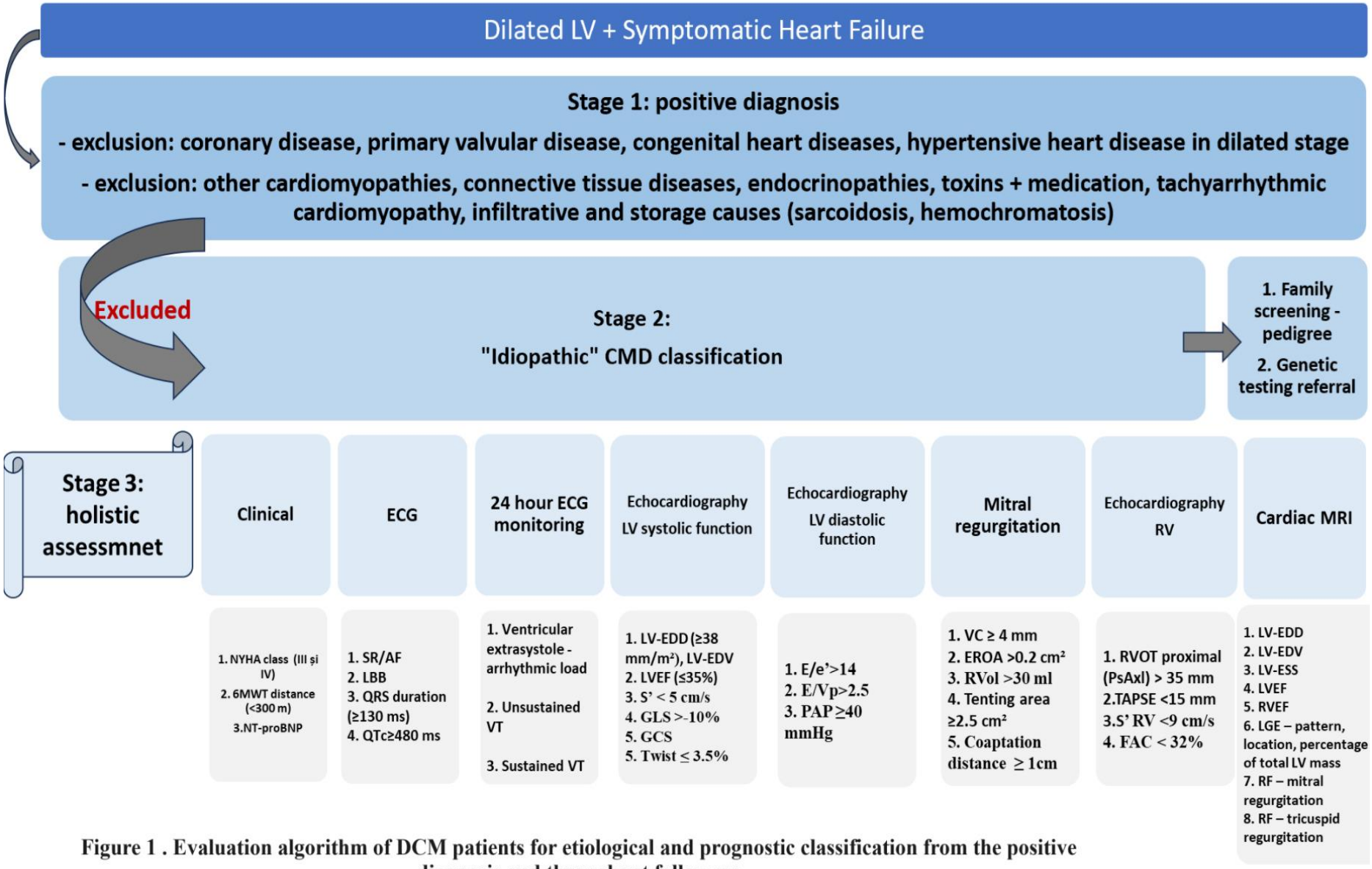

Figure 1 . Evaluation algorithm of DCM patients for etiological and prognostic classification from the positive diagnosis and throughout follow-up

2.8 GENERAL DISCUTIONS

Dilated cardiomyopathy is associated with an increased risk of heart failure and malignant ventricular arrhythmias including sudden cardiac death, being the most common cause of heart transplantation (1,5).

LV systolic dysfunction remains the main prognostic determinant of patients with DCM, and the 35% LVEF threshold stratifies patients for optimal medical therapy versus optimal medical therapy and cardiac device therapy (cardiac resynchronization therapy and/or defibrillator implant) (109). The importance of LVEF as a prognostic factor was also emphasized in the present study, with LVEF having lower values in the deceased group compared to the non-deceased group at 3 years of follow-up, without having statistically significant differences between the ischemic versus non-ischemic group. The mortality rate in the presented study was higher in patients with DCM of ischemic etiology compared to non-ischemic etiology; these data are consistent with data from current guidelines and studies.

In parallel with the LVEF deterioration, in the group of deceased patients there was a more important dilation of the LV in terms of diameter and LV end-diastolic volume. The importance of these data has been emphasized in the current literature, as it is well known that low LVEF and severely increased LV dimensions (LV end-diastolic diameter ≥ 38 mm/m2) are predictors of sudden cardiac death in patients with DCM (70, 127).

In addition to LVEF, the other classical parameters of LV systolic function (dp/dt, MAPSE) were found to have lower values in the group of deceased patients. These low values are consistent with low LVEF values. MAPSE values less than 8 mm have a sensitivity of 98% and a specificity of 82% for identifying patients with LVEF less than 50% (128). Dp/dt < 1000 mmHg/s signifies systolic dysfunction, and dp/dt < 600 mmHg/s signifies severe systolic dysfunction and has independent prognostic value (128). In our study, in the deceased group, MAPSE had a mean value lower than 8 mm and dp/dt had a value slightly higher than 600 mmHg/s at the initial evaluations (V1, V3), and at 3-year evaluation the value falls below the threshold value of 600 mmHg.

The systolic velocity at the level of the mitral annulus evaluated by Tissue Doppler had significantly lower values in the deceased group compared to the non-deceased group. This value was below 5 mm/s, the threshold value confirmed by current studies to have a negative prognostic impact (85), but no statistically significant difference was observed between the ischemic versus non-ischemic group.

The parameters derived from speckle tracking imaging, GLS and GCS, proved in our study to be independent prognostic factors of mortality, having good discriminative power for predicting death. Both GLS and GCS had more impaired values in the deceased group compared to the non-deceased group. In several studies in the current literature, the GLS value greater than -10 % (closer to zero) was considered the threshold value that was shown to be associated with a negative long-term prognosis (78, 79). In the present study the GLS had values greater than -10% (closer to zero) in patients who had died since the initial assessment, with further deterioration at subsequent evaluations despite maximal therapy administered. Patients in the non-deceased group had GLS values greater than -10% (closer to zero) at the initial visits, so that at the 3-year assessment the GLS value becomes lower (further from zero) than the threshold value of -10%, in parallel with keeping LVEF relatively constant from one assessment to another. Moreover, the GLS had lower values in the case of ischemic versus non-ischemic etiology, this result being consistent with the higher mortality rate in the ischemic group.

Taking strain from all LV segments together as a binomial logistic regression, increased longitudinal strain (closer to zero) in apical 2-chamber and 3-chamber incidences (LA AP 2C, LS AP 3C) and increased basal circumferential strain (closer to zero) had the highest predictive power of death in DCM patients assessed, regardless of ischemic or non-ischemic etiology.

Apical systolic rotation (normally counterclockwise) is the main determinant of LV systolic torsion (81, 82). In our study, LV apical rotation had lower values in the deceased versus non-deceased group, but without reaching the threshold of statistical significance. In contrast,

basal LV rotation, torsion and LV twist were significantly lower in the deceased group compared to the non-deceased group.

Regarding ischemic versus non-ischemic etiology, basal and apical LV rotation, LV torsion and twist, had significantly more impaired values in the non-ischemic group compared to the ischemic group, changes consistent with a longer QRS duration in the non-ischemic group compared to the ischemic group. Reversed apical rotation (clockwise) was significantly more frequent in the non-ischemic group compared to the ischemic group. This result is discordant with the higher mortality in the ischemic group compared to the non-ischemic group, thus suggesting that more mechanisms are involved in the impairment of LV apical and basal rotation, and consequently of twist and torsion than the impairment of LV systolic function evaluated in the present study by LVEF GLS and GCS. Experimental studies have demonstrated that epicardial fibers have a mechanical advantage in dominating the general direction of rotation. Taber et al demonstrated that the dilatation and thinning of the LV walls present in DCM equalizes the radii of the subepicardial and subendocardial layers (132, 133); as a result, the mechanical advantage of subepicardial myofibers (the main determinant of ventricular twist under physiological conditions) is reduced (134). In LV dilatation of ischemic etiology, the greatest suffering and replacement scar fibrosis is found in the subendocardial layers, and the subepicardial layers are the last to be affected, while in LV dilation of non-ischemic etiology, the replacement fibrosis is located in the thickness of the LV myocardium (middle-wall) or subepicardial with the presence of varying degrees of reactive interstitial fibrosis that affects the interaction of myocardial fibers. This explains why in non-ischemic DCM the basal and apical rotation of the LV and consequently the twist and torsion have reduced values compared to patients with non-ischemic DCM. Although they represent essential elements of LV mechanics, twist and torsion have a weaker correlation with LVEF compared to GLS (135). The question arises of a better correlation of basal and apical LV rotation, LV twist and torsion with radial strain, in the context in which the Speckle Tracking and Resynchronization (STAR) Study revealed that LV radial and transverse strain were significantly associated with response and long-term prognosis after CRT (66). Patients responding to CRT (reduction of LV-EDD by more than 10%) had an improvement in twist (66).

Recent studies have shown the importance of diastolic dysfunction for risk stratification in patients with DCM.

Indexed LA volume is an independent predictor of cardiovascular events including atrial fibrillation and cardiovascular mortality (136, 137). Moreover, LA indexed volume is a marker of diastolic dysfunction, and unlike LVEF, correlates well with NYHA functional class and global exercise capacity (138, 139). Indexed LA volume correlates with the E/e' ratio and may serve as a predictor of increased LV filling pressures during exercise (140). In the present study, indexed LA volume was significantly greater in the deceased versus non-deceased group, with no significant differences by ischemic or non-ischemic etiology, and strongly correlated with E/e' and E/Vp.

In a study of 12421 stage B and C heart failure patients with LVEF < 50%, Benfari et al showed that an increased E/e' ratio at diagnosis is associated with more advanced heart failure, and is also related with reduced short-term survival and increased long-term mortality, independent of heart failure presentation, and thus should be incorporated into heart failure risk assessment. An E/e' value >14 was used as a threshold value for short- and long-term reserved prognosis, with a significantly worse prognosis at a value >20 (19).

In the present study the E/e' ratio proved to be an independent prognostic factor for mortality in patients with DCM of ischemic and non-ischemic etiology (AUC > 0.8), with higher values in the ischemic group, the group in which mortality was recorded bigger. Moreover, in the ischemic group at the dynamic evaluation over successive years, the E/e' ratio had an increasing evolution so that at the last evaluation it exceeded the cut-off value of 14, and in the deceased group the E/e' ratio has had a higher value of 14 since the first evaluation, with an upward trend in dynamics.

The increase in the E/e' ratio may be induced by volume overload in decompensated HF (18) and has been hypothesized to be unrelated to myocardial stiffness. However, studies have shown that after adjusting the E/e' ratio for "hemodynamic" parameters such as LVEF, PAP, glomerular filtration rate, it remains independently associated with short- and long-term prognosis (19, 20, 141). Thus, the persistence of increased values of the E/e' ratio after pharmacological decongestion of patients gives an even more reserved prognosis.

In summary, E/e' ratio ≥14 and indexed LA volume ≥34 ml/min are important markers of diastolic dysfunction and correlate with invasively measured LV filling pressures. Furthermore, in contrast to LVEF, indexed LA volume, E/e' ratio, and tricuspid regurgitation velocity correlate better with exercise capacity (142).

The E/Vp ratio reflects increased values of LV filling pressures, similar to the E/e' ratio, and in the present study proved to be a good predictor of mortality (AUC > 0.8), but without statistically significantly differentiating between etiology ischemic and non-ischemic. Studies have shown that E/Vp ratio >2.7 in HF patients with low LVEF predicted death, cardiac transplantation, and HF hospitalizations (143).

Biologically, in patients with HF, NT-proBNP determination is a surrogate for clinically evident dyspnea, with clearly demonstrated correlations between NT-proBNP values and NYHA class. NT-proBNP is released from myocardial cells in patients with HF, having a diagnostic role, a role for monitoring the effectiveness of treatment as well as a prognostic role. Studies have shown that elevated plasma levels of NT-proBNP correlate strongly with the decline in diastolic myocardial velocities e' at the level of the mitral annulus, but have a weak correlation with the E/e' ratio in patients with HF (109). In the present study NT-proBNP was a good discriminator for overall mortality (AUC > 0.8 at V2, V3 assessment), consistent with increased values of E/e' and E/Vp ratios and higher values of PAP estimated by echocardiography.

The functional changes expressed by the E/e' and E/Vp ratios appear in the context of structural changes such as ventricular and atrial cavity dilatation. In the present study, the existence of correlations between the functional and morphological elements was also evaluated and the existence of a strong positive correlation (r > 0.5) between the E/Vp ratio and the indexed LA volume and the LV end-systolic volume (LV-ESV) at 3 years of follow-up was revealed. and a moderated correlation with LVEF and GLS. Increased E/e' ratio strongly correlates with increased LA volume and LV end-diastolic volume, increased GLS (GLS values closer to zero), and decreased LVEF.

Secondary mitral regurgitation found in both idiopathic DCM and dilated ischemic heart disease results from the imbalance between closing and tractional forces secondary to altered LV and LA geometry and function (54-56). In this context, the more pronounced the deformation of the mitral valve, the greater the severity of the mitral regurgitation, negatively influencing the possibility of valve repair. In the current study, there were no statistically significant differences between the non-ischemic group and the ischemic group regarding mitral tenting area; instead, the coaptation distance was significantly higher in the ischemic group (the group with higher mortality), having a value exceeding the threshold value of 1 cm (considered unfavorable for valvular repair techniques). Regarding the main objective of global mortality, both the tenting area and the coaptation distance had significantly higher values in the deceased group compared to the non-deceased group, exceeding the threshold of 2.5 cm^2 for the tenting area and 1 cm for the coaptation distance – threshold values considered as cut-off values for the significantly reduced probability of valvular repair; moreover, mitral tenting area, coaptation distance, VC, RVol and EROA were found to be independent predictors of mortality. Analyzed together in binomial regression, only VC, RVol, mitral tenting area, coaptation distance, and basal rotation were predictors of death with satisfactory sensitivity, specificity, positive predictive value, and negative predictive value. The interest in evaluating morphological changes of the mitral valve derives from the fact that repair techniques in functional mitral regurgitation are still associated with suboptimal results. Stumm et al showed in a study of 240 patients with functional mitral regurgitation who underwent the mitral annuloplasty procedure that a preoperative tenting area

≥2.4 cm2 was associated with a lower 5-year survival rate and a higher risk increased adverse cardiac events (150).

The severity of mitral regurgitation is assessed semiquantitative by the vena contracta (VC) and quantitatively by the PISA parameters: regurgitant volume (RVol) and effective regurgitant orifice area (EROA). Functional mitral regurgitation is a negative prognostic marker in CM (72) and higher degrees of mitral regurgitation are related to worse clinical status and reduced survival (91). Several studies have demonstrated the negative prognostic value of mitral regurgitation using a threshold value of regurgitant orifice area greater than 0.2 cm2 (92). In the present study there were no significant differences regarding VC, EROA, RVol between ischemic versus non-ischemic etiology of LV dilatation; but relative to mortality, all three parameters were found to be independent predictors of mortality, with VC having the highest predictive power, followed in order by EROA and RVol. In the deceased group, VC had a value greater than 4.5 mm, EROA greater than 0.2 cm2 and RVol greater than 30 ml, suggesting that not only severe mitral regurgitation according to the criteria of the 2021 guideline of valvular disease of the European Society of Cardiology, confers negative prognosis but also moderate mitral regurgitation. In the studied group, the deceased patients presented predominantly moderate and severe mitral regurgitation. The importance of correct assessment of mitral regurgitation derives from the need to establish the appropriate timing for interventional therapy of edge-to-edge transcatheter repair in severe and moderately severe mitral regurgitation (151-153).

Cardiac mechanical asynchrony has negative effects on cardiac function causing a decrease in stroke volume and cardiac output secondary to changes generated in myocardial and valvular kinetics: asynchronous and ineffective contraction, delayed and ineffective relaxation, reduction of diastolic filling time, mitral regurgitation with end-diastolic component (61- 63). The assessment of cardiac asynchrony includes parameters for the assessment of atrioventricular, interventricular and intraventricular asynchrony and is performed in parallel with the assessment of electrical asynchrony on the electrocardiogram. In the present study the elements of electrical asynchrony (the presence of LBB and the duration of the QRS complex) as well as the elements of intraventricular mechanical asynchrony of the APT, SPWMD were more accentuated in the non-ischemic DCM group at the initial visits, than at the 3-year assessment these differences disappear. This is because some patients were referred to CRT, responding favorably to this therapy. Apical, basal rotation, LV torsion and twist had more impaired values in the non-ischemic group compared to the ischemic group.

Moreover, reversed LV apical rotation had a significantly higher incidence in the non-ischemic group compared to the ischemic group. Interventricular asynchrony assessed by IMIV was significantly higher in the non-ischemic group compared to the ischemic group; no statistically significant differences were detected regarding atrioventricular asynchrony between the non-ischemic and the ischemic group. Practically, both intraventricular and interventricular asynchrony tend to be more accentuated in the non-ischemic group compared to the ischemic one, a discordant result with the higher mortality rate in the ischemic group. This could be explained by the fact that in advanced forms of DCM with extensive areas of akinesia, these markers have low feasibility and reproducibility (38).

Globally analyzing all 60 patients regarding the primary endpoint of mortality, in the deceased group the presence of both atrio-ventricular asynchrony (AAV < 40%) and interventricular (IMIV > 40 ms) and intraventricular (ATP>140 ms, SPWMD >130 mm) asynchrony were observed at the 3-year evaluation, while in the non-deceased group these parameters did not reach these threshold values considered as elements of disease severity. The importance of this derives from the fact that mechanical LV asynchrony in DCM patients with HF with severe LV systolic dysfunction and left bundle branch block has been shown to have independent predictive value for response to cardiac resynchronization therapy (CRT) and long-term survival (64).

LV basal and apical rotation, twist and torsion - which can be appreciated both as elements of LV systolic function and as elements of intraventricular asynchrony, had more depreciated values in deceased patients compared to non-deceased ones. Moreover, the impairment of basal

rotation proved to be a moderate predictor (AUC between 0.6-0.8) of mortality in patients with both ischemic and non-ischemic DCM. Popescu and collaborators highlighted that impaired apical rotation (even reversed – clockwise) and impairment to loss of LV torsion in a group of 50 patients with DCM is associated with significant negative LV remodeling, increased electrical asynchrony, low LV systolic function, increased LV filling pressures, being indicators of a more advanced stage of the disease (80).

RV dilatation and dysfunction are commonly seen in patients with DCM. These changes are usually caused by LV dysfunction or biventricular involvement rather than significant pulmonary hypertension (38, 39).

In our study, the RV and RA were significantly more dilated in the deceased versus non-deceased group, with no significant differences between the ischemic group compared to the non-ischemic group. The importance of this observation derives from the fact that bi-ventricular dilatation is known to carry a more negative prognosis compared to isolated LV dilatation (89). Moreover, in the present study, proximal RV ejection tract size (measured in parasternal long-axis view) was found to be a moderate independent predictor of mortality (AUC between 0.6–0.8).

The prevalence of RV dysfunction ranges from 63% to 76% and correlates with the degree of LV dysfunction. RV dysfunction has prognostic significance and its evaluation should be performed in all cases (38, 50). In the present study, in terms of RV systolic function, both TAPSE and S' RV were significantly lower in the deceased group compared to the non-deceased group at the 2- and 3-year follow-up assessments, respectively (V2, V3). FAC was significantly lower in the deceased group versus the non-deceased group throughout the whole follow-up period (V1, V2, V3). RV dysfunction has been recognized as a negative prognostic factor in DCM and is associated with more advanced LV dysfunction and considerably poorer functional class and prognosis. A TAPSE value of less than 14 mm has been shown to have negative prognostic value in patients with DCM (86). In our study, the RV did not present severe longitudinal systolic dysfunction, with TAPSE values above 14 mm in all 60 patients followed dynamically, which could be explained by their relatively short follow-up period (3 years) and strengthens the prognostic value negative of RV systolic dysfunction even from its slightly low values.

Functional tricuspid regurgitation and *pulmonary hypertension* are common in DCM, particularly in the presence of RV dilatation and dysfunction (59).

In the deceased group of the 60 patients evaluated, moderate tricuspid regurgitation had a significantly higher incidence than in the non-deceased group, with significantly higher estimated PAP values in the deceased group; also the estimated PAP value was significantly higher in the ischemic group, the group with a higher mortality rate, compared to the non-ischemic group. Increased values of PAP proved to be initially moderate independent predictors of mortality (AUC between 0.6-0.8), so that during the evolution (V3) the increase of PAP became a strong independent predictor of mortality.

While the severity of LV systolic dysfunction did not show an independent relationship with pulmonary hypertension, the severity of functional mitral regurgitation and diastolic dysfunction were strongly correlated with pulmonary hypertension (60). Moreover, it was shown that patients with a restrictive or pseudo normal trans mitral flow pattern had higher pulmonary artery pressures, and the improvement of the trans mitral flow appearance towards the altered relaxation pattern was accompanied by a significant reduction in pulmonary artery pressure (154). Pulmonary hypertension and tricuspid regurgitation are also predictors of morbidity and mortality in DCM (59).

Cardiac magnetic resonance in DCM patients provides complementary information to that of echocardiography.

As in the echocardiographic assessment, in the present study the LV was more dilated (both LV-EDD, and LV-EDV and LV-ESV) in the deceased group compared to the non-deceased group, without being significantly different regarding ischemic versus non- ischemic etiology. Moreover, in the present study, LV dilatation expressed as end-diastolic diameter or

as end-diastolic or end-systolic volume was shown to be a strong independent predictor of mortality regardless of ischemic or non-ischemic etiology.

The importance of LVEF has been emphasized in multiple studies, including in the European and American Cardiology guidelines, the cut-off value of less than 35% being an important criterion for selecting patients for device-therapy such as defibrillator implant or cardiac resynchronization therapy (109). In the present study, LVEF was significantly lower in the deceased versus non-deceased group, with no significant differences between ischemic and non-ischemic etiology.

Ventricular stroke volumes are usually within normal limits or only modestly reduced due to ventricular dilatation (94), a situation also encountered in the present work. Particular attention should be paid in the situation of the concomitant existence of valvular regurgitation, when stroke volumes must be corrected (94). In the present analysis of the 60 patients with dcm, LV stroke volume was observed to have lower values in the deceased versus non-deceased group, with also lower values in the ischemic group (higher mortality rate group) versus the non-ischemic group. In the present study, the assessment of stroke volume was performed by the flow sequence at the level of the aortic root, in order to eliminate the error that could be caused by mitral regurgitation.

The atria may be dilated, but usually the dilatation is less pronounced than the ventricular one (94). In the present work LA and RA expressed as area and indexed area, respectively, were more dilated in deceased versus non-deceased patients, and proved to be moderate independent predictors for mortality regardless of ischemic versus non-ischemic etiology.

The assessment of mitral and tricuspid regurgitation severity by CMR is still an intensively evaluated subject. Grading of the severity of functional mitral regurgitation remains controversial despite the adverse prognosis and rapidly evolving interventions. Moreover, it is still unclear whether quantitative assessment by CMR can have an incremental role in risk stratification for patients with ischemic or non-ischemic DCM in terms of regurgitant fraction and LGE. A 5% increase in regurgitant fraction was associated with the primary end point, with relatively similar hazard ratio in ischemic versus non-ischemic etiology. The optimal regurgitant fraction threshold for mitral regurgitation was ≥25% for moderate MR and ≥35% for severe MR in both ischemic and non-ischemic groups, threshold values set from the prediction of the primary endpoint (158). In our study the regurgitant fraction of both mitral regurgitation and tricuspid regurgitation were significantly higher in the deceased versus non-deceased group, with higher values in the ischemic group with higher morality compared to the non-ischemic group; regurgitant fractions of MR and TR proved to be modest independent predictors of mortality, regardless of ischemic or non-ischemic etiology.

LGE is of great help in making the differential diagnosis between left ventricular dilatation secondary to coronary artery disease and left ventricular dilatation without underlying coronary disease, a differentiation important for subsequent therapeutic strategy. Ischemic heart disease in the dilated stage typically shows subendocardial or transmural contrast enhancemet (representing the myocardial scar) in a coronary perfusion territory, whereas patients with idiopathic dilated cardiomyopathy may show no contrast or linear or focal contrast enhancement in the middle portion of the ventricular myocardium (contrast enhancememt that does not respect a coronary territory and not necessarily limited to the left ventricle, may also involve the right ventricle). Myocardial contrast enhancement reflects segmental fibrosis in patients with idiopathic dilated cardiomyopathy (94). Myocardial fibrosis identified by LGE is most commonly present in the middle portion of the interventricular septum and can be identified in approximately 30% of patients with DCM (93, 96). In the present study, half of the patients with non-ischemic DCM presented LGE with mid-wall pattern, the most frequent location being at the level of the interventricular septum, followed by the location at the level of the LV lateral wall, and was associated with a higher frequency of death, SCD, non-sustained ventricular tachycardia and defibrillator implant. In the ischemic group, all patients presented LGE with a subendocardial disposition, two thirds of them with territories interpreted as non-viable (LGE transmurality>50%).

In the overall analysis of evaluated patients, the absence of LGE was significantly associated with better survival. The presence of LGE is a predictor of mortality, arrhythmic ventricular events, including sudden cardiac death, tachycardia or ventricular fibrillation, or appropriate defibrillator-initiated therapy, and for the risk of rehospitalization for heart failure (97).

A risk calculator has been developed that, unlike other risk scores, also incorporates the presence of LGE on cardiac MRI, although this has not yet been validated (159). There are currently ongoing trials for defibrillator implant based on the presence of myocardial scarring on cardiac magnetic resonance, including patients with DCM, but the authors of the European cardiomyopathy's guideline believe that the current evidence can support the use of LGE to guide defibrillator therapy in subgroups of patients with DCM (43). Thus, the 2023 European guideline for cardiomyopathies states the importance of LGE considered as an additional risk factor in patients with certain genotypes: LMNA, FLNC- truncated variants, PLN, DSP, RBM20 (43).

Associated with LGE in patients with ischemic DCM, the presence of fatty metaplasia was also identified in 1/3 of patients, and it was associated with a higher incidence of sustained/unsustained ventricular tachycardia, SCD, defibrillator implant compared to patients without fatty metaplasia. The prevalence of fatty metaplasia is low in patients with chronic ischemia, intermediate in post-infarct patients with an incidence between 22 and 68%, and high in patients with a history of myocardial infarction and ventricular tachycardia, with an incidence between 64 and 100%. The incidence of fatty metaplasia appears to be closely associated with disease severity, but its quantification can often be challenging with different CMR techniques. Fatty metaplasia is more commonly seen in old infarcts and in infarcts involving large myocardial territories. Fatty metaplasia is associated with regional parietal thinning and impaired localized parietal kinetics. Ventricular aneurysms are also closely associated with fatty metaplasia (160).

Similar to arrhythmic risk assessment, LGE may be useful in predicting response to cardiac resynchronization therapy (93). In a study of 599 patients with both ischemic heart disease and non-ischemic DCM (161), guidance of biventricular pacemaker implantation by LGE was associated with significantly improved identification of patients most likely to benefit from this therapy. Patients without LGE did significantly better after resynchronization therapy compared with those with LGE or those who underwent non-LGE guided CRT. Regardless of the ability to predict which patients will or will not respond to resynchronization therapy, the presence of LGE in the middle portion of the interventricular septum was an independent predictor of morbidity and mortality in patients undergoing this therapy (98). In our study, cardiac resynchronization therapy in the non-ischemic group was more frequent in patients without LGE compared to patients with LGE, suggesting that not only LGE contributes to the increase in QRS duration, other morpho-functional factors being probably also incriminated.

2.9 GENERAL CONCLUSIONS

LV systolic performance is the main determinant of the evolution of patients with DCM, with the different echocardiographic parameters used providing complementary prognostic information.

The following were observed in our studied group:

1. Approximately one-third of patients with non-ischemic and ischemic DCM died at 3 years of follow-up. Overall mortality is higher in patients with ischemic DCM compared to patients with non-ischemic DCM
2. The main cause of death in both groups is refractory heart failure, followed by sudden cardiac death and ischemic stroke
3. The classical parameters for evaluating LV systolic function – LVEF, MAPSE, dp/dt, and S velocity at the level of the mitral annulus had significantly lower values

in deceased patients compared to non-deceased patients, but without being significantly different in relation to the etiology non-ischemic versus ischemic

4. Myocardial deformation parameters, GLS and GCS had significantly more impaired values in deceased patients compared to non-deceased patients, proving to be independent prognostic factors for mortality, having a good discriminative level for predicting death. The GLS had values significantly more impaired in dynamics in patients with ischemic DCM compared to patients with non-ischemic DCM, at relatively similar values of LVEF and NT-proBNP. Both in the ischemic group and in the non-ischemic group the GLS had a median value higher than the threshold value of -10% cited in the literature as a negative prognostic factor, but in the ischemic group with higher mortality the GLS deteriorated over time, while in the non-ischemic group the GLS improved from one evaluation to another.
5. LV basal rotation, torsion and twist had more impaired values in deceased patients compared to non-deceased patients. Apical rotation had lower values in the deceased group compared to the non-deceased group without reaching the threshold of statistical significance. LV basal, apical rotation, torsion and twist, had significantly more impaired values in the non-ischemic group compared to the ischemic group, changes consistent with a longer QRS duration in the non-ischemic group compared to the ischemic group. Reversed apical rotation (clockwise) was significantly more frequent in the non-ischemic group compared to the ischemic group.
6. Higher values (closer to zero) of longitudinal strain in 2 and 3 chambers, respectively, and higher values of circumferential strain in the LV basal segments had the greatest power to predict death in the whole group of study, regardless of ischemic or non-ischemic etiology.

LV diastolic dysfunction plays an important role for the evolution of patients with DCM, being correlated with clinical status - NYHA class and their prognosis.

The following were observed on the studied lot:

1. LA expressed as indexed volume was significantly more dilated in the deceased versus non-deceased group without statistically significant differences being recorded in relation to ischemic versus non-ischemic etiology
2. E/e' and E/Vp ratios proved to be the diastolic function parameters with the greatest prognostic impact, along with NT-proBNP, being independent predictors of mortality, regardless of ischemic or non-ischemic etiology.
3. Comparing ischemic and non-ischemic etiology, the E/e' ratio had significantly higher values in the ischemic group - the group with a higher mortality rate - while LVEF did not show statistically significant differences, and GLS had more impaired values in the ischemic group compared to the non-ischemic group;
4. In the ischemic group, at the dynamic evaluation over successive years, the E/e' ratio had an increasing evolution so that at the 3-year evaluation it exceeded the cut-off value of 14, and in the deceased group the E/e' ratio was had since the first assessment a higher value of 14, with an upward trend in dynamics. The E/Vp ratio did not show statistically significant differences between the ischemic group and the non-ischemic group
5. Increasing E/Vp ratio strongly correlates with increasing indexed LA volume and LV end-systolic volume (LV-ESV) at 3-year follow-up. The increase in E/e' ratio strongly correlates with LA volume, LV end-diastolic volume.
6. Increasing E/e' ratio strongly correlates with increasing GLS (values of GLS closer to zero) and decreasing FEV. Increasing E/Vp ratio moderately correlates with increasing GLS (GLS values closer to zero) and with decreasing LVEF.

In conclusion, the imaging evaluation of DCM should include, in addition to the assessment of LV systolic function, the systematic definition of the LV diastolic profile and especially the E/e' and E/Vp ratios, which should be considered for risk stratification.

Secondary mitral regurgitation, LV intraventricular asynchrony and RV dilatation and dysfunction play an important role in the evolution of DCM patients, being correlated with the clinical status – NYHA class and their prognosis.

In the studied group, the following were observed:

1. Severe and moderate-to-severe secondary mitral regurgitation is associated with poor patient prognosis, regardless of ischemic or non-ischemic etiology.
2. VC, EROA, RVol, mitral tenting area and coaptation distance were significantly increased in deceased versus non-deceased group. Regarding ischemic or non-ischemic etiology, only the coaptation distance was significantly higher in the ischemic group, the group with the higher mortality rate.
3. Both from the point of view of mitral valve deformation, evaluated by the coaptation distance and the tenting area, and from the point of view of the severity of mitral regurgitation evaluated semiquantitative by VC and quantitatively by PISA parameters (RVol, EROA), moderate to severe and severe secondary mitral regurgitation is a moderate independent predictor of mortality.
4. Analyzed all these parameters together in binomial regression, only VC, RVol, mitral tenting area, coaptation distance and basal rotation were predictors for death with satisfactory sensitivity, specificity, positive predictive value and negative predictive value
5. LV electrical asynchrony, assessed by QRS duration, did not show significant differences between the non-ischemic versus ischemic group, nor between the deceased versus non-deceased group.
6. Interventricular mechanical asynchrony assessed by IMIV and intraventricular assessed by SPWMD and APT and LV basal and apical rotation, LV twist and torsion was more accentuated in the deceased versus non-deceased group and also in the non-ischemic group compared to ischemic group. SPWMD, APT and LV basal rotation were found to be independent predictors of mortality regardless of ischemic or non-ischemic etiology
7. RV dilatation, longitudinal and circumferential systolic dysfunction of the RV (TAPSE, S' RV, FAC) are more pronounced in the deceased group compared to the non-deceased group, without significant differences between the ischemic versus non-ischemic group
8. Estimated pulmonary arterial systolic pressure was significantly higher in the deceased versus non-deceased group, with significantly higher values at follow-up in the ischemic group (higher mortality group) versus non-ischemic
9. RV dilatation, assessed by measuring the proximal RV ejection tract in parasternal long-axis view, and estimated PAP are independent predictors of mortality.

Cardiac magnetic resonance has an important role in DCM patients' evaluation, both for diagnostic purposes (which also includes targeting some specific etiologies) and for prognostic and therapeutic purposes.

On the studied group, the following were observed:

1. LV, RV, LA, RA were significantly more dilated in the deceased versus non-deceased group, with no statistically significant differences between the ischemic versus non-ischemic group. LV mass was significantly greater in the deceased versus non-deceased group

2. LV-EDD, indexed LV-EDV and indexed LV-ESV were shown to be strong independent predictors of mortality. LV mass, indexed areas of LA and RA were found to be moderate independent predictors of mortality
3. LVEF was significantly lower in the deceased group compared to the non-deceased group, without significant differences between ischemic and non-ischemic etiology. Cardiac output and indexed cardiac output did not show significant differences between the deceased versus non-deceased group, nor between ischemic and non-ischemic etiology. Stroke volume, on the other hand, was significantly lower in patients in the deceased versus non-deceased group, and was also lower in patients in the ischemic group, the group with higher mortality
4. Mitral regurgitation and tricuspid regurgitation were more severe in the deceased versus non-deceased group, with moderate regurgitation being more frequent in the deceased group.
5. Mitral and tricuspid regurgitation fractions were found to be modest independent predictors of mortality, being higher in the ischemic group (higher mortality group) versus non-ischemic.
6. Absence of myocardial scar assessed by LGE was associated with better survival
7. In patients with non-ischemic DCM, the presence of mid-wall LGE was associated with a higher percentage of SCD, unsustained VT, defibrillator implant compared to patients who did not present LGE. The incidence of sustained VT and resuscitated cardiorespiratory arrest was the same in patients with and without LGE. Cardiac resynchronization therapy had a higher frequency in patients without LGE compared to patients with LGE. LGE was most frequently located at the level of the medio-basal interventricular septum
8. In patients with ischemic DCM, it was observed that all patients presented LGE at the LV level of sub-endocardial type with various degrees of transmurality. LGE transmurality over 50% of the parietal thickness, which defines non-viable myocardial territory, was detected in three-quarters of patients with ischemic DCM, only a quarter of them also presented viable territories (with a degree of transmurality below 50%)
9. Fatty metaplasia was present in one third of patients with ischemic DCM. Patients with fatty metaplasia had a higher incidence of sustained/unsustained ventricular tachycardia and a higher rate of defibrillator implantation compared to patients without fatty metaplasia. The cause of death in patients with fatty metaplasia was sudden cardiac death, whereas in patients without fatty metaplasia the causes of death were refractory heart failure or ischemic stroke.

2.10 ORIGINALITY AND INNOVATIVE CONTRIBUTIONS OF THE THESIS

Dilated cardiomyopathy represents a challenge for the clinician both from a diagnostic point of view, including the etiological classification, and from the point of view of prognostic stratification and effective staging of different therapeutic strategies. Through an individualized treatment - medical, interventional with various devices such as CRT, ICD, Mitra Clip or even surgical in selected cases - it is possible to "save" the patient with major benefits for the patient and the community.

The evaluation of the elements that determine a negative prognosis in DCM is important precisely for the most accurate selection of patients who can benefit early from advanced therapies in order to increase not only survival but also the quality of life in parallel with the increase in life expectancy.

The present work aimed to evaluate the prognostic impact of the imaging elements derived from echocardiography with an emphasis on the new echocardiographic techniques (Tissue Doppler imaging and speckle tracking imaging) and cardiac magnetic resonance, beyond the impairment of the left ventricular ejection fraction.

The patients were evaluated based on a staged diagnostic algorithm, thus creating a holistic picture of the patient with DCM (clinical, biological, electrocardiographic, echocardiographic and by cardiac magnetic resonance) and following the analysis of the data, certain prognostic factors were individualized which can draw attention to the probability of a negative evolution, requiring the patient to be reassessed at shorter time intervals and referred to advanced therapies. Imaging elements with the highest prognostic power should be included in the routine evaluation of all patients with DCM.

The prognosis of dilated cardiomyopathy, although intensively studied, is still a current topic in the specialized literature, not exhausted from the point of view of attempts to identify the imaging parameters, both echocardiographic and cardiac magnetic resonance, which allow the stratification of patients into risk groups and thus allow their justified referral to different therapies. In this sense, the present paper proposed an evaluation algorithm to help the clinician in the diagnostic, etiological and prognostic approach.

One of the important aspects of the present work is the fact that it highlighted that from a certain point in the disease evolution the influence of ischemic or non-ischemic etiology on the prognosis decreases, being only a few imaging elements that emphasize the more negative evolution of ischemic DCM compared to non-ischemic DCM at similar values of cavity dimensions and LV ejection fraction, namely: (a) GLS value more impaired in the ischemic group, (b) E/e' value more increased in the ischemic group, (c)higher estimated pulmonary artery pressures in the ischemic group versus non- ischemic, (d) mitral valve coaptation distance measured in echocardiography and (e) severity of mitral and tricuspid regurgitation assessed by regurgitation fraction on CMR which are higher in the ischemic group, and (f) stroke volume measured directly by CMR at the level of the aortic root on flow sequences which has lower values in the ischemic group. These parameters have the advantage that they can be relatively easy to determine in clinical practice, in the context of increasing access in current practice to techniques such as Tissue Doppler, speckle tracking imaging and cardiac magnetic resonance.

The results of analyzing interventricular and intraventricular asynchrony parameters, including the quantification of LV basal and apical rotation, were more heterogeneous, proving to be independent predictors of global mortality, but with more impaired values in the non-ischemic group that had lower mortality than the ischemic group. This suggests that further research is needed to more accurately quantify the prognostic role of these parameters and how they influence the evolution of patients; a complementary role in this regard could be the analysis of the asynchrony between the different ventricular segments by assessing the mechanical dispersion at the LV level through speckle tracking.

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